APPARATUS FOR EXTRACORPOREAL TREATMENT OF BLOOD AND PROCESS OF CALCULATING SET FLOW RATES IN A MEDICAL APPARATUS FOR EXTRACORPOREAL TREATMENT OF BLOOD

Abstract

A CRRT apparatus comprising a control unit configured to execute a flow-rate setup procedure by receiving a patient prescription comprising clinical prescription parameters, by allowing entry of a set value for a prescribed dialysis dose (D_{set}) to be delivered, and of a target value for a parameter ($nNBL$; Cp_{HCO3_PAT}) indicative of a steady state acid-base balance in the blood of the patient who has to undergo a CRRT blood treatment, and by determining operating parameters calculating a set value of relevant fluid flow rates including one or more of a fluid flow rate (Q_{cit}) through the anticoagulant infusion line, a fluid flow rate (Q_{PBP}) through the PBP infusion line, a fluid flow rate ($Q_{rep.pre}$) through the pre-dilution infusion line, a fluid flow rate ($Q_{rep.post}$) through the post-dilution infusion line, a fluid flow rate (Q_{HCO3}) through the post-dilution bicarbonate infusion line, a fluid flow rate (Q_{ca}) through the ion balancing infusion line, a blood fluid flow rate (Q_b) through the extracorporeal blood circuit, a fluid flow rate (Q_{dial}) through the dialysis liquid supply line, and a fluid flow rate (Q_{eff}) through the effluent fluid line, wherein calculating the set value of the fluid flow rates is based at least on the set value of the prescribed dialysis dose (D_{set}) and on the target value for the parameter ($nNBL$; Cp_{HCO3_PAT}) indicative of a steady state acid-base balance in the blood.

Background/Summary

TECHNICAL FIELD
[0001] The present invention relates to a medical apparatus for extracorporeal treatment of blood. The present invention also relates to a process of calculating set flow rates in a medical apparatus for extracorporeal fluid processing.
[0002] In more detail, the present invention is applicable in the context of continuous renal replacement therapies (CRRT) with or without anticoagulation, for example CRRT with or without systemic anticoagulation (e.g., heparin)/with or without regional anticoagulation (e.g., citrate). In particular, the present invention may be advantageously used for administering regional citrate anticoagulation (RCA) during continuous renal replacement therapies (CRRT).
Background of the Invention
[0003] The kidneys fulfil many functions, including the removal of water, the excretion of catabolites (or waste from the metabolism, for example urea and creatinine), the regulation of the concentration of the electrolytes in the blood (e.g. sodium, potassium, magnesium, calcium, bicarbonates, phosphates, chlorides) and the regulation of the acid/base equilibrium within the body, which is obtained in particular by the removal of weak acids and by the production of ammonium salts. In individuals who have lost (temporarily or permanently) the use of their kidneys, since these excretion

and regulation mechanisms no longer work, the body accumulates water and waste from the metabolism and exhibits an excess of electrolytes, as well as, in general, acidosis, the pH of the blood plasma shifting downwards, below 7.35 (the blood pH normally varies within narrow limits of between 7.35 and 7.45). As mentioned, in order to overcome renal dysfunction, resort is conventionally made to a blood treatment involving extracorporeal circulation through an exchanger having a semipermeable membrane (dialyzer) in which the patient's blood is circulated on one side of the membrane and a dialysis liquid, comprising the main electrolytes of the blood in concentrations close to those in the blood of a healthy subject, is circulated on the other side. Furthermore, a pressure difference is created between the two compartments of the dialyzer which are delimited by the semipermeable membrane, so that a fraction of the plasma fluid passes by ultrafiltration through the membrane into the compartment containing the dialysis liquid. The blood treatment which takes place in a dialyzer as regards waste from the metabolism and electrolytes results from two mechanisms of molecular transport through the membrane. On the one hand, the molecules migrate from the liquid where their concentration is higher to the liquid where their concentration is lower. This is diffusive transport. On the other hand, certain catabolites and certain electrolytes are entrained by the plasma fluid which filters through the membrane under the effect of the pressure difference created between the two compartments of the exchanger. This is convective transport. Three of the abovementioned functions of the kidney, namely the removal of water, the excretion of catabolites and the regulation of the electrolytic concentration of the blood, are therefore performed in a conventional blood treatment device by the combination of dialysis and blood filtration (this combination is referred to as hemodiafiltration). To perform one or more of the above described treatments, extracorporeal blood treatment equipment may comprise a plurality of lines for delivering fluid directly to the patient or into the extracorporeal blood circuit.

[0004] When setting up the machine, an operator usually imposes the blood pump flow rate, the individual flow rates for each of the infusion lines, the flow rate for the dialysis line and for the effluent line (in reality this latter may alternatively be calculated based on the set patient fluid removal rate). The set values for the flow rates on each line are used to control respective pumps: in other words, a plurality of pumps are used where each pump draws fluid from or supplies fluid to a respective fluid container according to the set flow rate value for the respective line. Setting up of the machine is therefore cumbersome as it entails the definition and entry on the part of the operator of a relatively high number of flow rates. Moreover, the independent setting of each one of the flow rates does not provide the operator with intuitive information in terms of medically relevant prescription parameters. Finally, the need for independently setting a plurality of parameters may be source of errors and does not allow to optimize fluid consumption.

[0005] WO 2013/030642 deals with a blood treatment apparatus and a process of setting up a medical apparatus for the delivery or collection of fluids, wherein a control unit is configured calculate set values of two or more of the fluid flow rates based on a fluid flow rate set by the operator and on a prescribed dose value. However, WO 2013/030642 does not focus on the acid-base balance management aspects and does not specifically address the issue of acid base balance in regional anticoagulation in the context of CRRT.

[0006] As regards the regulation of the acid/base equilibrium inside the body, the approach adopted to overcome renal deficiency is to act on a mechanism by which the acid/base equilibrium inside the body is regulated, this mechanism consisting of the buffer systems of the blood, the main one of which comprises carbonic acid, as a weak acid, associated with its alkali salt, bicarbonate. This is why, in order to correct acidosis in a patient suffering from renal insufficiency, he/she is administered with bicarbonate via the vascular route, directly or indirectly, during a hemodialysis session. In the field of renal treatment, continuous renal replacement therapy (CRRT) has been widely used in critically ill patients with acute kidney injury and anticoagulation of the extracorporeal blood is necessary to maintain the patency of the circuit. In recent decades, different anticoagulation strategies have been used in clinical settings and heparin is the most commonly used anticoagulant. Although heparin has the advantages of low cost, easy monitoring and simple reversal, it may increase bleeding. Additionally, there is the risk of heparin-induced thrombocytopenia type II that can result in life-threatening complications. Regional citrate anticoagulation (RCA), which was first introduced into clinical use in the early 1980s, has been recommended as the most suitable form of CRRT regional circuit anticoagulation and has been safely used even in patients with severe liver dysfunction. However, citrate infusion in critically ill patients impacts a variety of metabolic systems, which can lead to metabolic alkalosis, hypocalcaemia and citrate excessive load/toxicity. These potential disturbances may be partially resolved by careful monitoring, adherence to treatment protocols, and oversight by trained staff in clinical practice. Notwithstanding the above criticalities, citrate anticoagulation has become the preferred anticoagulation choice for continuous renal replacement therapies (CRRT) as minimizing patient bleeding risks (regional anticoagulation effect) and increasing extracorporeal blood circuit life time. While RCA has some limitations with respect to compatibility with 'large' blood flow rates, this is not a problem in CRRT where efficiency is primarily driven by the fluid exchange rate and where the vast majority of treatments are delivered at blood flow rate below 200 ml/min. Fast metabolism of the citrate infused to the patient is part of the key mechanisms making RCA successful. Citrate metabolism produces energy, as well as bicarbonate and CO_2 while releasing complexed calcium. In the situation where large amounts of citrate are infused to the patient, large amounts of bicarbonate are produced, up to the point where metabolic alkalosis is generated. Citrate accumulation matches with the scenario where systemic citrate concentration is significantly increased. It can develop in two circumstances 'normal' citrate load combined to poor citrate metabolism, and 'normal' citrate metabolism combined to large citrate load. The first scenario is likely to lead to metabolic acidosis due to a low production rate of bicarbonate from citrate. The second scenario is considered and addressed in the present application, specifically in respect to CRRT therapies in the RCA context. Consequence of citrate accumulation is a need to increase total calcium concentration as to keep (systemic) ionised calcium within the physiological range. This can be achieved by increasing the calcium infusion rate. This problem is a transitory problem during initiation of the therapy, as a safe steady state can be reached after stabilization of systemic citrate concentration (6-8 hours). Discontinuation of the therapy may however lead to an episode of hypercalcemia (as citrate is metabolized and complex-bound calcium is released). In the clinical setting, citrate accumulation is diagnosed via the monitoring of total to ionised systemic calcium ratio (ratio >2.5 indicating probable citrate accumulation). Further, once citrate enters the patient systemic circulation, it is metabolized to bicarbonate on a 1:3 basis; thus, 1 mmol citrate yields 3 mmol bicarbonate. In presence of high citrate load, large amounts of bicarbonate are produced with the risk of metabolic alkalosis. Therefore, though regional anticoagulation may highly alleviate the adverse effects of heparin, RCA imposes the need of proper monitoring the acid-base balance in the patient blood, to avoid severe risks of alkalosis.

[0007] EP0678301 relates to an artificial kidney for intensive care particularly adapted to treating people suffering temporarily from kidney failure following an accident or a surgical operation. As clarified in the prior art document, in addition to purifying plasma wastes (e.g. urea) and to remove excess water, the kidneys play an important role in maintaining the acid-base equilibrium of the blood. Since the final concentration of bicarbonate in the blood depends on the concentration of bicarbonate in the perfusion solution or in the dialysis liquid, on the respective flow rates thereof, and on the flow rate of the patient's blood through the membrane exchanger, the main problem at the basis of document EP0678301 is that the concentration of bicarbonate in the blood of the patient corresponds rarely exactly to the desired concentration. EP0678301 describes a blood treatment device including a dialyzer with two chambers separated by a membrane. A dialysis liquid container (that does not contain any bicarbonate) is connected to a fluid pump via a duct which runs to the second chamber of the dialyzer. Electromagnetic clamps are provided for connecting the container to either the dialyzer or to the blood circuit. A bubble trap is provided in the return line of the blood circuit. The bubble trap is linked to an infusion container containing a solution of bicarbonate. In accordance with EP0678301, the flow rate Q_{HCO3} of the circulation pump is controlled as a function of the flow rate Q_{OUT} of the dialysate pump regardless of the type of treatment being delivered to the patient either by the equation:

[00001] $Q_{HCO3} = Q_{OUT} * [HCO_3]_{DES} / [HCO_3]_{SOL}$

or by the equation:

[00002] $Q_{HCO3} = CI * [HCO_3]_{DES} / [HCO_3]_{SOL}$

wherein: [0008] Q.sub.HHCO3 is flow rate of the circulation pump; [0009] Q.sub.OUT is the flow rate Q.sub.OUT of the dialysate pump; [0010] [HCO.sub.3].sub.DES is the desired concentration of bicarbonate in the blood of the patient; [0011] [HCO.sub.3].sub.SOL is the concentration of the

solution in the container; [0012] Cl is the clearance of the dialyzer for bicarbonate.

[0013] Notably, this prior art is directed to proper adjustment of patient blood acid-base equilibrium, by using a specific control of post infusion of bicarbonate solution based on clearance/dialysate flow rate which exclusively works in the following dialysis machine configurations: HF with post dilution and HD(F) with post dilution. Therefore, the problem of proper acid-base management in configuration wherein citrate is infused pre-blood pump (e.g., regional anticoagulation systems) and/or bicarbonate containing solution is pre-infused remains unsolved.

[0014] As to adapting to specific patient condition, protocols may (by far not systematically) include guidelines for adjusting citrate infusion or dialysis fluid/replacement flow rates in case patient monitoring data evidence alkalosis or acidosis problems. When present, these guidelines appear largely empirical. In the case of acidosis, some literature report for the infusion of bicarbonate 'bolus'. Although some published protocols are derived from some upstream modelling, no parameter representative of the expected buffer balance from the therapy is made explicitly available, whatever 'original' protocol parameters are used or after these have been tuned further to patient monitoring data. As to date, anticipation and control of acid base-balance during CRRT, particularly when using regional citrate anticoagulation (RCA) remains a difficult question especially when intending to use non-proven prescriptions.

SUMMARY

[0015] In this situation, it is a general object of the present embodiments to offer a technical solution capable overcoming one or more of the above drawbacks.

[0016] More in detail, it is an object of the present embodiments to render available a CRRT medical apparatus for the extracorporeal treatment of blood and a process configured for providing assisted prescription, at the same time taking into consideration the proper acid-base blood balance, particularly in the context of regional anticoagulation. In detail, it is an aim of the present embodiments to allow for acid-balance control/management, wherein the system is also designed to vary buffer balance of the extracorporeal blood circuit in an easy, but safe and controlled way.

[0017] It is an aim to provide an apparatus and a method allowing to properly calculate set flow rates keeping an eye towards a proper buffer balance and capable of reducing as much possible the actions required for setting up the apparatus. Is a further object of aspects of the invention to define an apparatus and a process allowing the operator to set up a CRRT blood treatment apparatus using medically meaningful parameters, which may result in an easier to use user interface. In particular, it is an aim to provide an assisted prescription in a situation where prescription includes a parameter specifying a steady state acid-base balance target, parameter which is of specific importance in the case of citrate anticoagulation

[0018] It is an auxiliary object of the invention to offer a medical apparatus for the treatment of fluid and a process for calculating set flow rates in said apparatus which may facilitate flow rate setting before and during the treatment- and optimize the consumption of fluid with respect to the prescription target and the system constraints.

[0019] Another auxiliary object is an apparatus capable of controlling operating parameters in a safe manner.

[0020] At least one of the above objects is substantially reached by an apparatus according to one or more of the appended apparatus claims. One or more of the above objects is also substantially reached by a process according to any one of the appended process claims.

[0021] Apparatus and processes according to aspects of the invention are here below described.

[0022] A 1.sup.st independent aspect concerns a Continuous Renal Replacement Therapy (CRRT) apparatus comprising: [0023] a filtration unit (**2**) having a primary chamber (**3**) and a secondary chamber (**4**) separated by a semi-permeable membrane (**5**); [0024] an extracorporeal blood circuit (**17**) having a blood withdrawal line (**6**) connected to an inlet of the primary chamber (**3**), and a blood return line (**7**) connected to an outlet of the primary chamber (**3**), said extracorporeal blood circuit (**17**) being configured for connection to a patient cardiovascular system; [0025] a blood pump (**21**) configured to control the flow of blood through the extracorporeal blood circuit (**17**); an effluent fluid line (**13**) connected to an outlet of the secondary chamber (**4**); [0026] one or more of further fluid lines selected in the group comprising: [0027] a pre-dilution infusion line (**29**) connected at one end thereof to the blood withdrawal line (**6**), [0028] a post-dilution infusion line (**63**) connected at one end thereof to the blood return line (**7**), [0029] a post-dilution bicarbonate infusion line (**23**) connected at one end thereof to the blood return line (**7**), [0030] a ion balancing infusion line (**74**) connected at one end thereof either to the blood return line (**7**) or to a patient catheter, [0031] a dialysis liquid supply line (**8**) connected at one end thereof to the inlet of the secondary chamber (**4**), [0032] a pre-blood pump—PBP—infusion line (**52**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), [0033] an anticoagulant infusion line (**51**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), and [0034] a syringe fluid line (**22**) connected at one end thereof to the blood withdrawal line, [0035] actuators for regulating the flow of fluid (**24**, **25**, **26**, **31**, **53**, **54**, **65**, **75**) through said fluid lines (**23**, **8**, **13**, **29**, **52**, **51**, **63**, **74**); [0036] a memory (**16**) storing one or more mathematical relations; and [0037] a control unit (**12**) connected to the memory (**16**) and to the actuators, the control unit being configured to execute a flow-rate setup procedure comprising: [0038] receiving a patient prescription comprising clinical prescription parameters, the receiving step including: [0039] allowing entry of a target value for a parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient who has to undergo a CRRT blood treatment, [0040] determining one or more operating parameters using said one or more mathematical relations, the determining of the operating parameters comprises calculating a set value of one or more fluid flow rates selected in the group including: [0041] a fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), [0042] a fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**), [0043] a fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**), [0044] a fluid flow rate (Q.sub.rep.post) through the post-dilution infusion line (**63**), [0045] a fluid flow rate (Q.sub.HCO3) through the post-dilution bicarbonate infusion line (**23**), [0046] a fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**), [0047] a blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**), [0048] a fluid flow rate (Q.sub.syr) through a syringe fluid line (**22**), [0049] a fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**), and [0050] a fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**), [0051] wherein calculating the set value of one or more fluid flow rates is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0052] In an aspect according to the previous aspect, receiving a patient prescription comprises allowing entry of a set value for a prescribed dialysis dose (D.sub.set) to be delivered, and determining one or more operating parameters comprises determining at least two operating parameters, the determining of the operating parameters comprises calculating a set value of at least two fluid flow rates selected in the group, calculating the set value of at least two fluid flow rates is based at least on said set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0053] A further independent aspect is directed to a process of setting up a Continuous Renal Replacement Therapy (CRRT) apparatus, the apparatus comprising: [0054] a filtration unit (**2**) having a primary chamber (**3**) and a secondary chamber (**4**) separated by a semi-permeable membrane (**5**); [0055] an extracorporeal blood circuit (**17**) having a blood withdrawal line (**6**) connected to an inlet of the primary chamber (**3**), and a blood return line (**7**) connected to an outlet of the primary chamber (**3**), said extracorporeal blood circuit (**17**) being configured for connection to a patient cardiovascular system; [0056] a blood pump (**21**) configured to control the flow of blood through the extracorporeal blood circuit (**17**); an effluent fluid line (**13**) connected to an outlet of the secondary chamber (**4**); [0057] one or more of further fluid lines selected in the group comprising: [0058] a pre-dilution infusion line (**29**) connected at one end thereof to the blood withdrawal line (**6**), [0059] a post-dilution infusion line (**63**) connected at one end thereof to the blood return line (**7**), [0060] a post-dilution bicarbonate infusion line (**23**) connected at one end thereof to the blood return line (**7**), [0061] a ion balancing infusion line (**74**) connected at one end thereof either to the blood return line (**7**) or to a patient catheter, [0062] a dialysis liquid supply line (**8**) connected at one end thereof to the inlet of the secondary chamber (**4**), [0063] a pre-blood pump—PBP—infusion line (**52**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood

pump (**21**), [0064] an anticoagulant infusion line (**51**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), and [0065] a syringe fluid line (**22**) connected at one end thereof to the blood withdrawal line, [0066] actuators for regulating the flow of fluid (**24**, **25**, **26**, **31**, **53**, **54**, **65**, **75**) through said fluid lines (**23**, **8**, **13**, **29**, **52**, **51**, **63**, **74**); [0067] a memory (**16**) storing one or more mathematical relations; and [0068] a control unit (**12**) connected to the memory (**16**) and to the actuators, [0069] the method comprising the following steps executable by the control unit: [0070] receiving a patient prescription comprising clinical prescription parameters, the receiving step including: [0071] allowing entry of a set value for a prescribed dialysis dose (D.sub.set) to be delivered, [0072] allowing entry of a target value for a parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient who has to undergo a CRRT blood treatment, [0073] determining operating parameters using said one or more mathematical relations, the determining of the operating parameters comprises calculating a set value at least two fluid flow rates selected in the group including: [0074] a fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), [0075] a fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**), [0076] a fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**), [0077] a fluid flow rate (Q.sub.rep.post) through the post-dilution infusion line (**63**), [0078] a fluid flow rate (Q.sub.HCO3) through the post-dilution bicarbonate infusion line (**23**), [0079] a fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**), [0080] a blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**), [0081] a fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**), and [0082] a fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**), [0083] wherein calculating the set value of at least two fluid flow rates is based at least on said set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0084] In another independent aspect, a Continuous Renal Replacement Therapy (CRRT) apparatus is provided comprising: a filtration unit (**2**) having a primary chamber (**3**) and a secondary chamber (**4**) separated by a semi-permeable membrane (**5**); [0085] an extracorporeal blood circuit (**17**) having a blood withdrawal line (**6**) connected to an inlet of the primary chamber (**3**), and a blood return line (**7**) connected to an outlet of the primary chamber (**3**), said extracorporeal blood circuit (**17**) being configured for connection to a patient cardiovascular system; [0086] a blood pump (**21**) configured to control the flow of blood through the extracorporeal blood circuit (**17**); [0087] an effluent fluid line (**13**) connected to an outlet of the secondary chamber (**4**); [0088] one or more of further fluid lines selected in the group comprising: [0089] a pre-dilution infusion line (**29**) connected at one end thereof to the blood withdrawal line (**6**), [0090] a post-dilution infusion line (**63**) connected at one end thereof to the blood return line (**7**), [0091] a post-dilution bicarbonate infusion line (**23**) connected at one end thereof to the blood return line (**7**), [0092] a ion balancing infusion line (**74**) connected at one end thereof either to the blood return line (**7**) or to a patient catheter, [0093] a dialysis liquid supply line (**8**) connected at one end thereof to the inlet of the secondary chamber (**4**), [0094] a pre-blood pump—PBP—infusion line (**52**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), [0095] an anticoagulant infusion line (**51**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), and [0096] a syringe fluid line (**22**) connected at one end thereof to the blood withdrawal line, [0097] actuators for regulating the flow of fluid (**24**, **25**, **26**, **31**, **53**, **54**, **65**, **75**) through said fluid lines (**23**, **8**, **13**, **29**, **52**, **51**, **63**, **74**); [0098] a memory (**16**) storing one or more mathematical relations; and [0099] a control unit (**12**) connected to the memory (**16**) and to the actuators, the control unit being configured to execute a flow-rate setup procedure comprising: [0100] receiving a patient prescription comprising clinical prescription parameters, the receiving step including: [0101] allowing entry of a set value for a prescribed dialysis dose (D.sub.set) to be delivered, [0102] allowing entry of a target value for a parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient who has to undergo a CRRT blood treatment, [0103] determining operating parameters using said one or more mathematical relations, the determining of the operating parameters comprises calculating a set value at least two fluid flow rates selected in the group including: [0104] a fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), [0105] a fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**), [0106] a fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**), [0107] a fluid flow rate (Q.sub.rep.post) through the post-dilution infusion line (**63**), [0108] a fluid flow rate (Q.sub.HCO3) through the post-dilution bicarbonate infusion line (**23**), [0109] a fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**), [0110] a blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**), [0111] a fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**), and [0112] a fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**), [0113] wherein calculating the set value of at least two fluid flow rates is based at least on said set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0114] Notably and in accordance with the previous aspects, calculating each set value of the at least two fluid flow rates is based at least on both said set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood. For example, a first fluid flow rate from the list (e.g., the fluid flow rate (Q.sub.rep.post) through the post-dilution infusion line (**63**)) is calculated based on both the set value of the prescribed dialysis dose (D.sub.set) and on the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and a second fluid flow rate from the list (e.g., the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**)) is calculated based on both the set value of the prescribed dialysis dose (D.sub.set) and on the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0115] In a further independent aspect, a Continuous Renal Replacement Therapy (CRRT) apparatus is provided comprising: a filtration unit (**2**) having a primary chamber (**3**) and a secondary chamber (**4**) separated by a semi-permeable membrane (**5**); [0116] an extracorporeal blood circuit (**17**) having a blood withdrawal line (**6**) connected to an inlet of the primary chamber (**3**), and a blood return line (**7**) connected to an outlet of the primary chamber (**3**), said extracorporeal blood circuit (**17**) being configured for connection to a patient cardiovascular system; [0117] a blood pump (**21**) configured to control the flow of blood through the extracorporeal blood circuit (**17**); an effluent fluid line (**13**) connected to an outlet of the secondary chamber (**4**); [0118] one or more of further fluid lines selected in the group comprising: [0119] a pre-dilution infusion line (**29**) connected at one end thereof to the blood withdrawal line (**6**), [0120] a post-dilution infusion line (**63**) connected at one end thereof to the blood return line (**7**), [0121] a post-dilution bicarbonate infusion line (**23**) connected at one end thereof to the blood return line (**7**), [0122] a ion balancing infusion line (**74**) connected at one end thereof either to the blood return line (**7**) or to a patient catheter, [0123] a dialysis liquid supply line (**8**) connected at one end thereof to the inlet of the secondary chamber (**4**), [0124] a pre-blood pump—PBP—infusion line (**52**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), [0125] an anticoagulant infusion line (**51**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), and [0126] a syringe fluid line (**22**) connected at one end thereof to the blood withdrawal line, [0127] actuators for regulating the flow of fluid (**24**, **25**, **26**, **31**, **53**, **54**, **65**, **75**) through said fluid lines (**23**, **8**, **13**, **29**, **52**, **51**, **63**, **74**); [0128] a memory (**16**) storing one or more mathematical relations; and [0129] a control unit (**12**) connected to the memory (**16**) and to the actuators, the control unit being configured to execute a flow-rate setup procedure comprising: [0130] receiving a patient prescription comprising clinical prescription parameters, the receiving step including: [0131] allowing entry of a set value for a prescribed dialysis dose (D.sub.set) to be delivered, [0132] allowing entry of a target value for a parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient who has to undergo a CRRT blood treatment, [0133] determining one or more operating parameters using said one or more mathematical relations, the determining of the operating parameters comprises calculating a set value of at least two fluid flow rates selected in the group including: [0134] a fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), [0135] a fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**), [0136] a fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**), [0137] a fluid flow rate (Q.sub.rep.post) through the post-dilution infusion line (**63**), [0138] a fluid flow rate (Q.sub.HCO3) through the post-dilution bicarbonate infusion line (**23**), [0139] a fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**), [0140] a blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**), [0141] a fluid flow rate (Q.sub.syr) through a syringe fluid line (**22**), [0142] a fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**), and [0143] a fluid flow

rate (Q.sub.eff) through the effluent fluid line (**13**), [0144] wherein calculating the set value of either: [0145] the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), [0146] the fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**), [0147] the fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**), [0148] is based at least on both said set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood (it is noted that this flow rate is one of the at least two flow rates mentioned in previous aspects), and [0149] wherein calculating the set value of at least another fluid flow rate is based at least on both said set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0150] In a further aspect in accordance with any one of the previous aspects, said at least another fluid flow rate (or one of the at least two flow rates) is either: [0151] the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**); or [0152] the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**),

and wherein calculating the set value of said another fluid flow rate is based at least on both said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and on said set value of the prescribed dialysis dose (D.sub.set).

[0153] In a 2.sup.nd aspect according to any one of the previous aspects the anticoagulant infusion line (**51**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**) and an anticoagulant source (**10**) connected at an opposite end of the anticoagulant infusion line (**51**), wherein receiving a patient prescription further comprises allowing entry of a set value for a regional anticoagulation dose (D.sub.cit), in particular a citrate dose, indicative of an intensity of the regional anticoagulation.

[0154] In a 3.sup.rd aspect according to the preceding aspect, the regional anticoagulation dose (D.sub.cit) has the same unit as a concentration and is in more detail the injected amount of anticoagulant per liter of treated blood (mmol/L blood).

[0155] In a 4.sup.th aspect according to the preceding two aspects, the control unit (**12**) is configured to mathematically relate, using a citrate flow rate mathematical relation, the set value for the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**) with the set value for the regional anticoagulation dose (D.sub.cit), in particular to calculate the set value for the fluid flow rate (Q.sub.cit) as a function of the set value for the regional anticoagulation dose (D.sub.cit).

[0156] In a 5.sup.th aspect according to any one of the preceding three aspects, the control unit (**12**) is configured to mathematically relate, using a citrate flow rate mathematical relation, the set value for the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**) with a blood flow rate (Q.sub.b) and/or with an anticoagulant, particularly citrate, concentration in the anticoagulant source (**10**), in particular to calculate the set value for the fluid flow rate (Q.sub.cit) as a function of the blood flow rate (Q.sub.b) and/or the anticoagulant, particularly citrate, concentration in the anticoagulant source (**10**).

[0157] In a 6.sup.th aspect according to any one of the preceding four aspects, said one or more mathematical relations include a citrate flow rate mathematical relation and the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**) is calculated based on the citrate flow rate mathematical relation stored in said memory (**16**):

[00003]$Q_{\mathrm{cit}} = \frac{D_{\mathrm{cit}}}{C_{\mathrm{cit\_PBP}}}$ .Math. Q_b [0158] wherein the significance of the denotations is given in the Glossary.

[0159] In a 7.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is configured to drive an anticoagulant pump (**54**) to infuse anticoagulant in the blood withdrawal line at the calculated fluid flow rate (Q.sub.cit) for the anticoagulant.

[0160] In a 8.sup.th aspect according to any one of the preceding aspects 2 or 3, the regional anticoagulation dose (D.sub.cit) is the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**).

[0161] In a 9.sup.th aspect according to any one of the preceding seven aspects, calculating the set value comprises calculating at least three fluid flow rates and is further based at least on said set value of the regional anticoagulation dose (D.sub.cit), in particular using at least one of said one or more mathematical relations.

[0162] In a 10.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus comprises the ion balancing infusion line (**74**) connected at one end thereof either to the blood return line (**7**) or to a patient catheter and a source of ion balancing solution (**11**) connected at an opposite end of ion balancing infusion line (**74**), wherein receiving a patient prescription further comprises allowing entry of a set value for an ion re-establishing solution parameter (CaComp; D.sub.ca), in particular a calcium compensating parameter, indicative of the intensity of ion balancing, in particular of calcium ions balancing.

[0163] In an 11.sup.th aspect according to the preceding aspect, the ion re-establishing solution parameter (CaComp) represents a compensation value or compensation percentage of the calcium removed in the filtration unit (**2**), for example included between 0.05 and 2 or between 5% and 200%.

[0164] In a 12.sup.th aspect according to the preceding aspect 10, the ion re-establishing solution parameter (D.sub.ca) is a, e.g. calcium, dose in terms of an ion, e.g., calcium, concentration, in particular the calcium dose being total calcium concentration in the effluent.

[0165] In a 13.sup.th aspect according to any one of the preceding three aspects, the control unit (**12**) is configured to mathematically relate, using a calcium flow rate mathematical relation, the set value for the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**) with the set value for the ion re-establishing solution parameter (CaComp; D.sub.ca), in particular to calculate the set value for the fluid flow rate (Q.sub.ca) as a function of the set value for the ion re-establishing solution parameter (CaComp; D.sub.ca).

[0166] In a 14.sup.th aspect according to any one of the preceding four aspects, the control unit (**12**) is configured to mathematically relate, using a calcium flow rate mathematical relation, the set value for the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**) with an effluent flow rate (Q.sub.eff), in particular to calculate the set value for the fluid flow rate (Q.sub.ca) as a function of the effluent flow rate (Q.sub.eff).

[0167] In a 15.sup.th aspect according to any one of the preceding five aspects, the control unit (**12**) is configured to mathematically relate, using a calcium flow rate mathematical relation, the set value for the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**) with a calcium concentration (C.sub.ca) in a source of ion balancing solution (**11**) and/or with a calcium concentration (C.sub.da.sub.rep.post) in an auxiliary container (**64**) connected to the post-dilution infusion line (**63**), and/or with a calcium concentration (C.sub.ca.sub.HCO3) in a bicarbonate container (**28**) connected to the post-dilution bicarbonate infusion line (**23**), in particular to calculate the set value for the fluid flow rate (Q.sub.ca) as a function of the calcium concentration (C.sub.ca) in the source of ion balancing solution (**11**) and/or as a function of the calcium concentration (C.sub.da.sub.rep.post) in the auxiliary container (**64**) connected to the post-dilution infusion line (**63**) and/or as a function of the calcium concentration (C.sub.ca.sub.HCO3) in a bicarbonate container (**28**) connected to the post-dilution bicarbonate infusion line (**23**).

[0168] In a 16.sup.th aspect according to any one of the preceding six aspects, said one or more mathematical relations include a calcium flow rate mathematical relation and wherein the set value for the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**) is calculated based on the calcium flow rate mathematical relation stored in the memory (**16**):

[00004]$Q_{\mathrm{ca}} = \frac{\mathrm{CaComp} \,.\mathrm{Math.}\, J_{\mathrm{Ca}}}{C_{\mathrm{ca}}} - \frac{Q_{\mathrm{rep.post}} \,.\mathrm{Math.}\, C_{\mathrm{ca_{rep.post}}}}{C_{\mathrm{ca}}} - \frac{Q_{\mathrm{HCO3}} \,.\mathrm{Math.}\, C_{\mathrm{ca_{HCO3}}}}{C_{\mathrm{ca}}}$ [0169] wherein the significance of the denotations is given in the Glossary.

[0170] In a 17.sup.th aspect according to the preceding aspect 12, said one or more mathematical relations include a calcium flow rate mathematical relation and wherein the set value for the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**) is calculated based on the calcium flow rate mathematical relation stored in the memory (**16**):

[00005]$Q_{\mathrm{ca}} = \frac{D_{\mathrm{ca}} \,.\mathrm{Math.}\, Q_{\mathrm{eff}}}{C_{\mathrm{ca}}} - \frac{Q_{\mathrm{rep.post}} \,.\mathrm{Math.}\, C_{\mathrm{ca_{rep.post}}}}{C_{\mathrm{ca}}} - \frac{Q_{\mathrm{HCO3}} \,.\mathrm{Math.}\, C_{\mathrm{ca_{HCO3}}}}{C_{\mathrm{ca}}}$ [0171] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0172] In a 18.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is configured to drive an ion balancing pump (**75**) to infuse an ion re-establishing solution in the blood return line (**7**) or into the patient (P) at the calculated fluid flow rate (Q.sub.ca) for ion re-

establishing solution.

[0173] In a 19.sup.th aspect according to any one of the preceding nine aspects, calculating the set value comprises calculating at least three fluid flow rates and is further based at least on said set value for the ion re-establishing solution parameter (CaComp; D.sub.ca), in particular using at least one of said one or more mathematical relations.

[0174] In a 20.sup.th aspect according to any one of the preceding aspects, receiving a patient prescription further comprises allowing entry of a set value for the blood flow rate (Q.sub.b) and calculating the set value comprises calculating at least three fluid flow rates and calculating one or more (two or all) set values out of the at least three fluid flow rates is further based at least on said set value for the blood flow rate (Q.sub.b), in particular using at least one of said one or more mathematical relations.

[0175] In a 21.sup.st aspect according to any one of the preceding aspects, receiving a patient prescription further comprises allowing entry of a set value for at least a fluid removal rate (Q.sub.PFR) from the patient and calculating the set value comprises calculating at least three fluid flow rates and calculating one or more (two or all) set values out of the at least three fluid flow rates is further based at least on said set value for the fluid removal rate (Q.sub.PFR) from the patient, in particular using at least one of said one or more mathematical relations.

[0176] In a 22.sup.nd aspect according to any one of the preceding aspects, the control unit (**12**) is configured to mathematically relate, using an effluent flow rate mathematical relation, the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**) with the set value for the fluid removal rate (Q.sub.PFR), in particular to calculate the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**) based on the set value for the fluid removal rate (Q.sub.PFR).

[0177] In a 23.sup.rd aspect according to any one of the preceding two aspects, the control unit (**12**) is configured to mathematically relate, in particular to calculate, the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**) based on an effluent flow rate mathematical relation comprised in said one or more mathematical relations:

[00006]$$Q_{eff} = Q_{PBP} + Q_{cit} + Q_{syr} + Q_{dial} + Q_{rep.pre} + Q_{rep.post} + Q_{HCO3} + Q_{PFR} + Q_{ca}$$ [0178] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines or the dialysis liquid supply line is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0179] In a 24.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus comprises a fluid source of a solution supplying fluid to one of said one or more further fluid lines, said solution comprising at least one buffer agent in the form of bicarbonate or bicarbonate precursor.

[0180] In a 25.sup.th aspect according to the preceding aspect, the bicarbonate precursor includes citrate, lactate and/or acetate.

[0181] In a 26.sup.th aspect according to any one of the preceding aspects, the parameter (nNBL) indicative of a steady state acid-base balance in the blood of the patient undergoing a CRRT treatment is a parameter function of a net buffer load (NBL) in the patient expected at a steady state, wherein the net buffer load is a sum of bicarbonate generation from bicarbonate precursor metabolism, such as citrate or lactate metabolism, bicarbonate balance in the extracorporeal blood circuit (**17**) and/or of bicarbonate infusions into the patient and/or of acid infusion in the extracorporeal blood circuit (**17**), such as citric acid infusion.

[0182] In a 27.sup.th aspect according to the preceding aspect, the net buffer load is a normalized net buffer (nNBL) load in the patient expected at a steady state, particularly normalized over a patient body weight (BW), in more detail the parameter (nNBL) indicative of a steady state acid-base balance in the blood of the patient undergoing a CRRT treatment being the net buffer load (NBL) or the normalized net buffer load (nNBL):

[00007]$$\frac{J_{buffer\_load}}{BW} = nNBL = \frac{NBL}{BW}$$

[0183] In a 28.sup.th aspect according to any one of the preceding aspects, the parameter (nNBL) indicative of a steady state acid-base balance in the blood of the patient is based on one or more of, and in particular the four of: [0184] an estimation of an amount per unit of time of bicarbonate generated from metabolism of the bicarbonate precursor infused to the patient, in particular of citrate (J.sub.met_cit) and/or lactate (J.sub.met_lact); [0185] a bicarbonate balance (J.sub.HCO3_bal) from the CRRT blood treatment to be delivered in terms of an amount per unit of time; [0186] a lactate balance (J.sub.lact_bal) from the CRRT blood treatment to be delivered in terms of an amount per unit of time; [0187] an acid infusion (J.sub.H+) from citric acid contained in the fluid source in terms of an amount per unit of time.

[0188] In a 29.sup.th aspect according to the preceding aspect, the parameter (nNBL) indicative of a steady state acid-base balance in the blood of the patient is an algebraic sum of the estimation of bicarbonate form precursor metabolism (J.sub.met_cit; J.sub.lact), the bicarbonate balance (J.sub.HCO3_bal), and the acid infusion (J.sub.H+), in particular the acid infusion (J.sub.H+) being a negative term providing a loss in patient buffer.

[0189] In a 30.sup.th aspect according to the preceding aspect, the parameter (nNBL) indicative of a steady state acid-base balance in the blood of the patient is defined as follows:

[00008]$$nNBL = \frac{J_{buffer\_load}}{BW} = \frac{J_{met\_cit} + J_{HCO3\_bal} - J_{H+}}{BW}$$

alternatively, when also lactate balance is considered, the parameter (nNBL) indicative of a steady state acid-base balance in the blood of the patient is defined as follows:

[00009]$$nNBL = \frac{J_{buffer\_load}}{BW} = \frac{J_{met\_cit} + J_{HCO3\_bal} + J_{lact\_bal} - J_{H+}}{BW}$$

[0190] In a 31.sup.st aspect according to any one of the preceding aspects, the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient is based on an acid infusion (J.sub.H+) from citric acid contained in the fluid source in terms of an amount per unit of time, wherein the acid infusion (J.sub.H+) is a function of a citric acid concentration (C.sub.citric_pbp) and of an infusion rate (Q.sub.cit) of citric acid, in particular the acid infusion (J.sub.H+) being equal to 3 times the citric acid concentration (C.sub.citric_pbp) times the infusion rate (Q.sub.cit) of citric acid.

[0191] In a 32.sup.nd aspect according to any one of the preceding aspects, the parameter (nNBL) indicative of a steady state acid-base balance in the blood of the patient undergoing a CRRT treatment is a parameter defined assuming a constant value for patient plasma bicarbonate concentration (Cp.sub.HCO3_pat0), said constant value being for example 25 mM.

[0192] In a 33.sup.rd aspect according to any one of the preceding aspects, the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient is based on an estimated net buffer load (J.sub.buffer_load/BW) indicative of a steady state acid-base balance in the blood of the patient.

[0193] In a further aspect according to any one of the preceding aspects, the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient is defined imposing a constant value for a normalized net buffer load (NBL) for the patient at steady state, said constant value being for example NBL=nNBL0.Math.BW=0.1 mmol/h/kg.

[0194] In a 34.sup.th aspect according to any one of the preceding aspects, the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient is defined imposing a constant value for the normalized net buffer load (NBL) for the patient at steady state, said constant value being for example nNBL0.Math.BW=0.1 mmol/h/kg.

[0195] In a 35.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include steady state bicarbonate indicator mathematical relations, and wherein the steady state bicarbonate indicator mathematical relations links the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient with said at least two flow rates in the group.

[0196] In a 36.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include steady state bicarbonate indicator mathematical relations, and wherein the steady state bicarbonate indicator mathematical relations links the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient with one or more of the fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**), the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**), the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), the fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**), in particular links the parameter

(Cp.sub.HCO3_pat) with the fluid flow rate (Q.sub.rep.pre; Q.sub.dial; Q.sub.cit; Q.sub.PBP) times the respective bicarbonate concentration (C.sub.HCO3rep.pre; C.sub.HCO3.sub.dial; C.sub.HCO3.sub.cit; C.sub.HCO3.sub.PBP) in the fluid flowing in the respective line.

[0197] In a 37.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include steady state bicarbonate indicator mathematical relations, and wherein the steady state bicarbonate indicator mathematical relations links the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient with the blood flow rate (Q.sub.b), in particular a blood water flow rate (Q.sub.bw) and/or a blood water flow rate (Q.sub.bw_inlet) at the inlet of the filtration unit (**2**).

[0198] In a 38.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include steady state bicarbonate indicator mathematical relations, and wherein the steady state bicarbonate indicator mathematical relations links the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient with a bicarbonate concentration (C.sub.HCO3.sub.dial) in a fluid flowing in the dialysis liquid supply line (**8**) and/or with a bicarbonate clearance (K.sub.HCO3) of the filtration unit (**2**).

[0199] In a 39.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include steady state bicarbonate indicator mathematical relations, and wherein the steady state bicarbonate indicator mathematical relations links the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient with a bicarbonate plasma water concentration Cpw.sub.HCO3_inlet at filtration unit inlet.

[0200] In a 40.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include steady state bicarbonate indicator mathematical relations, and wherein the steady state bicarbonate indicator mathematical relations links the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient with an ultrafiltration flow rate (Q.sub.fil) in the filtration unit (**2**), in particular with the ultrafiltration flow rate (Q.sub.fil) times a bicarbonate concentration (C.sub.HCO3.sub.dial) in the fluid flowing in the dialysis liquid supply line (**8**).

[0201] In a 41.sup.st aspect according to any one of the preceding aspects, said one or more mathematical relations include steady state bicarbonate indicator mathematical relations, and wherein the steady state bicarbonate indicator mathematical relations links the parameter (Cp.sub.HCO3_pat) indicative of a steady state bicarbonate concentration in the blood of the patient with a bicarbonate removal (J.sub.HCO3_eff) into spent dialysate flowing in the effluent line (**13**).

[0202] In a 42.sup.nd aspect according to any one of the preceding aspects, said one or more mathematical relations include steady state bicarbonate indicator mathematical relations, and wherein the steady state bicarbonate indicator mathematical relations are the following:

$$[00010] Cp_{HCO3\_pat} = \frac{Fp}{Qbw} .Math. (Cpw_{HCO3_{inlet}} .Math. Qbw_{inlet} - Q_{rep.pre} .Math. C_{HCO3rep.pre} - Q_{cit} .Math. C_{HCO3_{cit}} - Q_{PBP} .Math. C_{HCO3_{PBP}})$$

$$Cpw_{HCO3\_inlet} = C_{HCO3\_dial} + \frac{J_{HCO3\_eff} - Q_{dial} \times C_{HCO3_{dial}} - Q_{fil} \times C_{HCO3\_dial}}{K_{HCO3}} J_{HCO3\_eff} = J_{HCO3\_inf} - J_{HCO3_{bal}} = J_{HCO3\_inf} + J_{met\_cit} - J_{H+} - J_{buffer\_load}$$

$J_{buffer\_load} = nNBL \times BW$ [0203] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines or the dialysis liquid supply line is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0204] Note that if Cp.sub.HCO3_pat is taken as the parameter indicative of a steady state acid-base balance in the blood of the patient, then nNBL will have to be (implicitly) taken as a constant, namely nNBL0; if vice versa, nNBL is taken as the parameter indicative of a steady state acid-base balance in the blood of the patient, then Cp.sub.HCO3_pat will have to be (implicitly) taken as a constant, namely Cp.sub.HCO3_pat0.

[0205] In a 43.sup.rd aspect according to any one of the preceding aspects, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient affects the set value of the fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**), the set value of the fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**) being an operating parameter calculated by the control unit (**12**). In particular, this is one of the at least two flow rates calculated based on the set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0206] In a 44.sup.th aspect, according to any one of the preceding aspects, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient affects the set value of the fluid flow rate (Q.sub.rep.post) through the post-dilution infusion line (**63**), affects the set value of the fluid flow rate (Q.sub.rep.post) through the post-dilution infusion line (**63**) being an operating parameter calculated by the control unit (**12**). In particular, this is one of the at least two flow rates calculated based on the set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0207] In a 45.sup.th aspect according to any one of the preceding aspects, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient affects the set value of the fluid flow rate (Q.sub.HCO3) through the post-dilution bicarbonate infusion line (**23**), the set value of the fluid flow rate (Q.sub.HCO3) through the post-dilution bicarbonate infusion line (**23**) being an operating parameter calculated by the control unit (**12**). In particular, this is one of the at least two flow rates calculated based on the set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0208] In a 46.sup.th aspect according to any one of the preceding aspects, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient affects the set value of the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**), the set value of the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**) being an operating parameter calculated by the control unit (**12**). In particular, this is one of the at least two flow rates calculated based on the set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0209] In a 47.sup.th aspect according to any one of the preceding aspects, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient affects the set value of the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**), the set value of the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**) being an operating parameter calculated by the control unit (**12**). In particular, this is one of the at least two flow rates calculated based on the set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0210] In a 48.sup.th aspect according to any one of the preceding aspects, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient affects the set value of the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), particularly in case the set value for the blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**) is determined by the control unit (**12**) as an operating parameter, [0211] the set value of the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**) being an operating parameter calculated by the control unit (**12**). In particular, this is one of the at least two flow rates calculated based on the set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0212] In a 49.sup.th aspect according to any one of the preceding aspects, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient affects the set value of the fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**), the set value of the fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**) being an operating parameter calculated by the control unit (**12**). In particular, this is one of the at least two flow rates calculated based on the set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0213] In a 50.sup.th aspect according to any one of the preceding aspects, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient affects the set value of the blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**), the set value of the blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**) being an operating parameter

calculated by the control unit (**12**). In particular, this is one of the at least two flow rates calculated based on the set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0214] In a 51.sup.st aspect according to any one of the preceding aspects, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient affects the set value of the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**), the set value of the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**) being an operating parameter calculated by the control unit (**12**). In particular, this is one of the at least two flow rates calculated based on the set value of the prescribed dialysis dose (D.sub.set) and on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood.

[0215] Notably, the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient is used for the calculation of the majority and specifically all the above indicated fluid flow rates, when relevant (i.e., if the lines is present and the applied treatment requires use of the line with a set flow rate different from zero).

[0216] In a 52.sup.nd aspect according to any one of the preceding aspects, at least a number of said one or more mathematical relations correlates the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient who has to undergo a CRRT blood treatment with the at least two fluid flow rates selected in said group.

[0217] In a 53.sup.rd aspect according to any one of the preceding aspects, calculating the set value of the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**) is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and/or on said set value of the prescribed dialysis dose (D.sub.set), particularly in case the set value for the blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**) is determined by the control unit (**12**) as an operating parameter, [0218] in particular wherein the control unit (**12**) calculates the set value of the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**) using said mathematical relations.

[0219] In a 54.sup.th aspect according to any one of the preceding aspects, calculating the set value of the fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**) is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and/or on said set value of the prescribed dialysis dose (D.sub.set), in particular wherein the control unit (**12**) calculates the set value of the fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**) using said mathematical relations.

[0220] In a 55.sup.th aspect according to any one of the preceding aspects, calculating the set value of the fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**) is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and/or on said set value of the prescribed dialysis dose (D.sub.set), in particular wherein the control unit (**12**) calculates the set value of the fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**) using said mathematical relations.

[0221] In a 56.sup.th aspect according to any one of the preceding aspects, calculating the set value of the fluid flow rate (Q.sub.rep.post) through the post-dilution infusion line (**63**) is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and/or on said set value of the prescribed dialysis dose (D.sub.set), in particular wherein the control unit (**12**) calculates the set value of the fluid flow rate (Q.sub.rep.post) through the post-dilution infusion line (**63**) using said mathematical relations.

[0222] In a 57.sup.th aspect according to any one of the preceding aspects, calculating the set value of the fluid flow rate (Q.sub.HCO3) through the post-dilution bicarbonate infusion line (**23**) is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and/or on said set value of the prescribed dialysis dose (D.sub.set), in particular wherein the control unit (**12**) calculates the set value of the fluid flow rate (Q.sub.HCO3) through the post-dilution bicarbonate infusion line (**23**) using said mathematical relations.

[0223] In a 58.sup.th aspect according to any one of the preceding aspects, calculating the set value of the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**) is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and/or on said set value of the prescribed dialysis dose (D.sub.set), in particular wherein the control unit (**12**) calculates the set value of the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**) using said mathematical relations.

[0224] In a 59.sup.th aspect according to any one of the preceding aspects, calculating the set value of the blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**) is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and/or on said set value of the prescribed dialysis dose (D.sub.set), in particular wherein the control unit (**12**) calculates the set value of the fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**) using said mathematical relations.

[0225] In a 60.sup.th aspect according to any one of the preceding aspects, calculating the set value of the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**) is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and/or on said set value of the prescribed dialysis dose (D.sub.set), in particular wherein the control unit (**12**) calculates the set value of the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**) using said mathematical relations.

[0226] In a 61.sup.st aspect according to any one of the preceding aspects, calculating the set value of the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**) is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood and/or on said set value of the prescribed dialysis dose (D.sub.set), in particular wherein the control unit (**12**) calculates the set value of the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**) using said mathematical relations.

[0227] In a 62.sup.nd aspect according to any one of the preceding aspects, wherein said one or more mathematical relations include a net buffer load mathematical relation linking the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood with at least one, and particularly all, of: [0228] a bicarbonate balance (J.sub.HCO3_bal), [0229] a bicarbonate generated from metabolism of citrate (J.sub.met_cit), or a citrate load (J.sub.cit_load), in particular wherein the metabolism of citrate load leads to 3 moles of bicarbonate per mole of citrate at steady state, namely J.sub.met_cit=3.Math.J.sub.cit_load, [0230] a bicarbonate generated from metabolism of lactate (J.sub.met_lact), or a lactate balance (J.sub.lact_bal), in particular wherein the metabolism of lactate leads to 1 mole of bicarbonate per mole of lactate at steady state, namely J.sub.met_lact=J.sub.lact_bal, [0231] an acid infusion J.sub.H+,
wherein optionally the net buffer load mathematical relation is:

[00011] $J_{\text{buffer\_load}} = J_{\text{met\_cit}} + J_{\text{HCO3}_{\text{bal}}} + J_{\text{met\_lact}} - J_{H+}$ [0232] wherein the significance of the denotations is given in the Glossary; if any of the mass transfer rate is missing, the corresponding mass transfer term is absent from the mathematical relation, or the corresponding value is set to zero.

[0233] In a 63.sup.rd aspect according to any one of the preceding aspects, said one or more mathematical relations include a bicarbonate balance mathematical relation based on a bicarbonate balance (J.sub.HCO3_bal) from the CRRT blood treatment to be delivered in terms of an amount per unit of time, in particular wherein the bicarbonate balance (J.sub.HCO3_bal) is the difference between a bicarbonate infusion rate from the dialysis liquid supply line (**8**) and/or the infusion lines (J.sub.HCO3_inf) and the bicarbonate removal into dialysate (J.sub.HCO3_dial), in particular the bicarbonate balance mathematical relation is:

[00012] $J_{\text{HCO3\_bal}} = J_{\text{HCO3\_inf}} - J_{\text{HCO3\_eff}}$ [0234] wherein the significance of the denotations is given in the Glossary; if any of the mass transfer rate is missing, the corresponding mass transfer term is absent from the mathematical relation, or the corresponding value is set to zero.

[0235] In a 64.sup.th aspect according to the preceding aspect, bicarbonate infusion rate (J.sub.HCO3_inf) from the dialysis liquid supply line (**8**) is a function of the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**) and bicarbonate concentration (C.sub.HCO3.sub.dial) in the dialysis fluid flowing in the dialysis liquid supply line (**8**), in particular the fluid flow rate (Q.sub.dial) times the bicarbonate concentration (C.sub.HCO3.sub.dial).

[0236] In a 65.sup.th aspect according to any one of the preceding two aspects, bicarbonate infusion rate (J.sub.HCO3_inf) from the infusion lines is a function of the fluid flow rate/s (Q.sub.rep.pre; Q.sub.rep.post; Q.sub.cit; Q.sub.PBP; Q.sub.HCO3; Q.sub.ca) and the respective bicarbonate

concentration (C.sub.HCO3.sub.rep.pre; C.sub.HCO3.sub.rep.post; C.sub.HCO3.sub.cit; C.sub.HCO3.sub.pp; C.sub.HCO3.sub.HCO3; C.sub.HCO3.sub.ca), in particular the fluid flow rate/s (Q.sub.rep.pre; Q.sub.rep.post; Q.sub.cit; Q.sub.PBP; Q.sub.HCO3; Q.sub.ca) times the respective bicarbonate concentration (C.sub.HCO3.sub.rep.pre; C.sub.HCO3.sub.rep.post; C.sub.HCO3.sub.cit; C.sub.HCO3.sub.pp; C.sub.HCO3.sub.HCO3; C.sub.HCO3.sub.ca).

[0237] In a 66.sup.th aspect according to any one of the preceding three aspects, said one or more mathematical relations include a bicarbonate infusion mathematical relation and wherein the bicarbonate infusion rate from the dialysis liquid supply line (**8**) and the infusion lines (J.sub.HCO3_inf) is particularly according to the bicarbonate infusion mathematical relation:

[00013]
$$J_{HCO3\_inf} = Q_{dial} \cdot C_{HCO3_{dial}} + Q_{rep.pre} \cdot C_{HCO3_{rep.pre}} + Q_{rep.post} \cdot C_{HCO3_{rep.post}} + Q_{HCO3} \cdot C_{HCO3_{HCO3post}} + Q_{cit} \cdot C_{HCO3_{cit}} + Q_{PBP} \cdot$$

[0238] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines or the dialysis liquid supply line is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0239] In a 67.sup.th aspect according to any one of the preceding four aspects, the bicarbonate removal into spent dialysate (J.sub.HCO3_eff) in the effluent line (**13**) is a function of the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**) and bicarbonate concentration (C.sub.HCO3.sub.dial) in the dialysis fluid flowing in the dialysis liquid supply line (**8**), in particular the fluid flow rate (Q.sub.dial) times the bicarbonate concentration (C.sub.HCO3.sub.dial).

[0240] In a 68.sup.th aspect according to any one of the preceding five aspects, the bicarbonate removal into spent dialysate (J.sub.HCO3_eff) in the effluent line (**13**) is a function of bicarbonate concentration in the dialysis fluid (C.sub.HCO3_dial), in particular as a function of a difference between bicarbonate plasma water concentration at filter inlet (Cpw.sub.HCO3_inlet) and bicarbonate concentration in the dialysis fluid (C.sub.HCO3_dial).

[0241] In a 69.sup.th aspect according to any one of the preceding six aspects, the bicarbonate removal into spent dialysate (J.sub.HCO3_eff) in the effluent line (**13**) is a function of an ultrafiltration flow rate (Q.sub.fil) in the filtration unit (**2**) and bicarbonate concentration (C.sub.HCO3.sub.dial) in the dialysis fluid flowing in the dialysis liquid supply line (**8**), in particular the ultrafiltration flow rate (Q.sub.fil) times the bicarbonate concentration (C.sub.HCO3.sub.dial).

[0242] In a 70.sup.th aspect according to any one of the preceding seven aspects, the bicarbonate removal into spent dialysate (J.sub.HCO3_eff) in the effluent line (**13**) is a function of a bicarbonate clearance (K.sub.HCO3).

[0243] In a 71.sup.st aspect according to any one of the preceding eight aspects, the bicarbonate removal into spent dialysate (J.sub.HCO3_eff) in the effluent line (**13**) is a function of the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**), in particular wherein a bicarbonate clearance (K.sub.HCO3) is estimated equal to said effluent fluid flow rate (Q.sub.eff).

[0244] In a 72.sup.nd aspect according to any one of the preceding aspects, the bicarbonate removal into spent dialysate (J.sub.HCO3_eff) in the effluent line (**13**) is a function of a bicarbonate clearance (K.sub.HCO3) and the bicarbonate clearance (K.sub.HCO3) is a function of one or more flow rates, particularly including one or more of the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**), an ultrafiltration rate (Q.sub.fil) in filtration unit (**2**), and a blood water flow rate (Qbw.sub.inlet).

[0245] In a 73.sup.rd aspect according to the preceding aspect, the bicarbonate clearance (K.sub.HCO3) is a function of the filtration unit (**2**) intended for CRRT treatment, in particular as a function of a sieving coefficient (SC.sub.HCO3) for bicarbonate and/or a ratio of filtration unit surface area to diffusive mass transfer resistance (S/RT.sub.HCO3) for bicarbonate.

[0246] In a 74.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include bicarbonate clearance mathematical relations as follows:

[00014]
$$K_{HCO3} = \frac{Qbw_{inlet} \cdot Q_{dial} - f_{HCO3} \cdot (Qbw_{inlet} - SC_{HCO3} \cdot Q_{fil}) \cdot (Q_{dial} + SC_{HCO3} \cdot Q_{fil})}{Q_{dial} - f_{HCO3} \cdot (Qbw_{inlet} - SC_{HCO3} \cdot Q_{fil})} \quad f_{HCO3} = (\frac{Qbw_{inlet} - SC_{HCO3} \cdot Q_{fil}}{Qbw_{inlet}} \cdot \frac{Q_{dial} + SC_{HCO3} \cdot Q_{fil}}{Q_{dial}})^{-\frac{1}{HCO_3}}$$

$$_{HCO3} = e^{(\frac{SC_{HCO3} \cdot Q_{fil}}{(\frac{S}{RT})_{HCO3}})} - 1$$

[0247] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines or the dialysis liquid supply line is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0248] It is noted that above equations do not work with Q.sub.dial=0 or Q.sub.fil=0; in such situations it is possible to remove the infinite value by (artificially) replacing 0 value for either or both Q.sub.dial and/or Q.sub.fil by e.g., 1 or 0.1 ml/h. Otherwise specific equations for pure CVVHD or pure CVVH may be alternatively used.

[0249] In a 75.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include an ultrafiltration flow rate mathematical relation linking an ultrafiltration flow rate (Q.sub.fil) through the filtration unit (**2**) with a fluid removal rate (Q.sub.PFR) from the patient and infusion flow rate/s (Q.sub.PBP, Q.sub.cit, Q.sub.rep.pre, Q.sub.rep.post, Q.sub.HCO3, Q.sub.ca) in the extracorporeal blood circuit (**17**), in particular according to:

[00015]
$$Q_{fil} = Q_{PBP} + Q_{cit} + Q_{syr} + Q_{rep.pre} + Q_{rep.post} + Q_{HCO3} + Q_{PFR} + Q_{ca}$$

[0250] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0251] In a 76.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include a blood water flow rate mathematical relation linking a blood water flow rate (Q.sub.bw) to the blood fluid flow rate (Q.sub.b) and haematocrit (Hct), in particular according to:

[00016]
$$Qbw = Q_b \cdot [(1 - Hct) \cdot F_p + Hct \cdot Frbc]$$

[0252] wherein the significance of the denotations is given in the Glossary.

[0253] In a 77.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include a blood water flow rate at filtration unit inlet mathematical relation linking blood water flow rate Qbw.sub.inlet at the filtration unit inlet to one or more of a blood water flow rate (Q.sub.bw), the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), the fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**), and the fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**), in particular blood water flow rate at filtration unit inlet mathematical relation being as follows:

[00017]
$$Qbw_{inlet} = Q_{bw} + Q_{cit} + Q_{PBP} + Q_{rep,pre} + Q_{syr}$$
$$= Q_b \cdot [(1 - Hct) \cdot Fp + Hct \cdot Frbc] + Q_{cit} + Q_{PBP} + Q_{rep,pre} + Q_{syr}$$

[0254] wherein the significance of the denotations is given in the Glossary.

[0255] In a 78.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include a bicarbonate removal mathematical relation, in particular wherein the bicarbonate removal mathematical relation is:

[00018]
$$J_{HCO3\_eff} = Q_{dial} \cdot C_{HCO3\_dial} + K_{HCO3} \cdot (Cpw_{HCO3\_inlet} - C_{HCO3\_dial}) + Q_{fil} \cdot C_{HCO3\_dial}$$

[0256] wherein the significance of the denotations is given in the Glossary.

[0257] In a 79.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include a plasma water concentration at filter inlet mathematical relation correlating the bicarbonate plasma water concentration at filter inlet (Cpw.sub.HCO3_inlet) as a function of flow rates including one or more of blood water flow rate (Q.sub.bw), blood water flow rate at filter inlet (Qbw.sub.inlet), the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), the fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**) and the fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**) and/or as a function of bicarbonate concentrations (C.sub.HCO3.sub.cit;

C.sub.HCO3.sub.PBP; C.sub.HCO3.sub.rep.pre) in the fluid flowing in the corresponding infusion lines and patient plasma bicarbonate concentration (Cp.sub.HCO3.sub.pat).

[0258] In an 80.sup.th aspect according to the preceding aspect, said plasma water concentration at filter inlet mathematical relation is:

[00019]$Cpw_{HCO3\_inlet} = \dfrac{Q_{bw} \,.Math. \frac{Cp_{HCO3_{pat}}}{Fp} + Q_{cit} \,.Math. \, C_{HCO3_{cit}} + Q_{PBP} \,.Math. \, C_{HCO3_{PBP}} + Q_{rep,pre} \,.Math. \, C_{HCO3_{rep,pre}}}{Qbw_{inlet}}$ [0259] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0260] In an 81.sup.st aspect according to any one of the preceding aspects, said one or more mathematical relations include a bicarbonate balance mathematical relation based on a bicarbonate balance (J.sub.HCO3_bal) from the CRRT blood treatment to be delivered in terms of an amount per unit of time, in particular the bicarbonate balance mathematical relation is:

[00020]
$J_{HCO3\_bal} = Q_{rep,pre} \,.Math. \, C_{HCO3_{rep,pre}} + Q_{cit} \,.Math. \, C_{HCO3_{cit}} + Q_{PBP} \,.Math. \, C_{HCO3_{PBP}} + Q_{rep,post} \,.Math. \, C_{HCO3_{rep,post}} + Q_{HCO3} \,.Math. \, C_{HCO3_{HCO3post}} - K_{HCO3} \,.$

[0261] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines or the dialysis liquid supply line is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0262] Note that the above equation assumes that no bicarbonate is present in the ion replacement (Ca) solution.

[0263] In an 82.sup.nd aspect according to any one of the preceding aspects, the net buffer load mathematical relation of aspect 62 and the bicarbonate balance mathematical relation of aspect 81 (or alternatively aspects 63+66+78) link the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood with the at least two fluid flow rates selected in the group, the control unit (**12**) using the net buffer load mathematical relation of aspect 62 and the bicarbonate balance mathematical relation of aspect 81 (or alternatively aspects 63+66+78) to calculate the set value of said at least two fluid flow rates.

[0264] In an 83rd aspect according to the preceding aspect, the mathematical relations of aspects 75, 76, 77 and 78 are further used by the control unit (**12**) to calculate the set value of said at least two flow rates.

[0265] In an 84.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include a citrate load mathematical relation based on a citrate load (J.sub.cit_load) to the patient in terms of an amount per unit of time, in particular wherein the citrate load (J.sub.cit_load) is the difference between a citrate infusion rate (J.sub.cit_PBP) through the anticoagulant infusion line (**51**) and a citrate removal rate to effluent (J.sub.cit_dial) in the effluent line (**13**), in particular the citrate load mathematical relation is:

[00021]$J_{citrate\_load} = J_{cit\_PBP} - J_{cit\_dial}$ [0266] wherein the significance of the denotations is given in the Glossary; if any of the mass transfer rate is missing, the corresponding mass transfer term is absent from the mathematical relation, or the corresponding value is set to zero.

[0267] In an 85.sup.th aspect according to the preceding aspect, the citrate load (J.sub.cit_load), in particular the citrate removal rate to effluent (J.sub.cit_dial), is a function of patient citrate metabolic clearance (K.sub.cit_met), in particular the metabolic clearance being based on, e.g., directly proportional to, a patient body weight (BW), for example being determined as follows:

[00022]$K_{cit\_met} = 700 \,.Math. \frac{BW}{72}$ [0268] wherein patient citrate metabolic clearance (K.sub.cit_met) is measured as [ml/min] and body weight (BW) is measured as [kg].

[0269] In an 86.sup.th aspect according to any one of the preceding two aspects, the citrate load (J.sub.cit_load) is a function of citrate clearance (K.sub.cit).

[0270] An 87.sup.th aspect according to any one of the preceding three aspects, the citrate load (J.sub.cit_load) is a function of the fluid flow rate (Q.sub.eff) through the effluent fluid line (**13**), in particular wherein a citrate clearance (K.sub.cit) is estimated equal to said effluent fluid flow rate (Q.sub.eff).

[0271] In an 88.sup.th aspect according to any one of the preceding aspects, the citrate load (J.sub.cit_load) is a function of a citrate clearance (K.sub.cit) and, according to citrate clearance mathematical relations of said one or more mathematical relations, the citrate clearance (K.sub.cit) is a function of one or more flow rates, particularly including one or more of the fluid flow rate (Q.sub.dial) through the dialysis liquid supply line (**8**), an ultrafiltration rate (Q.sub.fil) in filtration unit (**2**), and a plasma water flow rate (Qpw.sub.inlet) at the filtration unit inlet.

[0272] In an 89.sup.th aspect according to the preceding aspect, the citrate load (J.sub.cit_load) is a function of the filtration unit (**2**) intended for CRRT treatment, in particular as a function of a sieving coefficient (SC.sub.cit) for citrate and/or a ratio of filtration unit surface area to diffusive mass transfer resistance (S/RT.sub.cit) for citrate.

[0273] In a 90.sup.th aspect according to the one of the preceding aspects, said one or more mathematical relations include citrate clearance mathematical relations as follows:

[00023]$K_{cit} = \dfrac{Qpw_{inlet} \,.Math. \, Q_{dial} - f_{cit} \,.Math. \, (Qpw_{inlet} - SC_{cit} \,.Math. \, Q_{fil}) \,.Math. \, (Q_{dial} + SC_{cit} \,.Math. \, Q_{fil})}{Q_{dial} - f_{cit} \,.Math. \, (Qpw_{inlet} - SC_{cit} \,.Math. \, Q_{fil})} \quad f_{cit} = (\dfrac{Qpw_{inlet} - SC_{cit} \,.Math. \, Q_{fil}}{Qpw_{inlet}} \,.Math. \, \dfrac{Q_{dial} + SC_{cit} \,.Math. \, Q_{fil}}{Q_{dial}})^{\frac{1}{cit}}$

$_{cit} = e(\frac{SC_{cit} \,.Math. \, Q_{fil}}{\frac{S}{RT_{cit}}}) - 1$ [0274] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines or the dialysis liquid supply line is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0275] In a 91.sup.st aspect according to any one of the preceding aspects, said one or more mathematical relations include a plasma flow rate mathematical relation linking a plasma flow rate (Q.sub.p) to the blood fluid flow rate (Q.sub.b) and haematocrit (Hct), in particular according to:
[00024]$Qp = Q_b \,.Math. \, (1 - Hct)$ [0276] wherein the significance of the denotations is given in the Glossary.

[0277] In a 92.sup.nd aspect according to any one of the preceding aspects, said one or more mathematical relations include a plasma water flow rate mathematical relation linking a plasma water flow rate (Q.sub.pw) to the blood fluid flow rate (Q.sub.b) and haematocrit (Hct), in particular according to:
[00025]$Qpw = Q_b \,.Math. \, (1 - Hct) \,.Math. \, F_p$ [0278] wherein the significance of the denotations is given in the Glossary.

[0279] In a 93.sup.rd aspect according to any one of the preceding aspects, said one or more mathematical relations include a plasma water flow rate at filtration unit inlet mathematical relation linking plasma water flow rate Qpw.sub.inlet at the filtration unit inlet to one or more of a plasma water flow rate (Q.sub.pw), the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**), the fluid flow rate (Q.sub.PBP) through the PBP infusion line (**52**), and the fluid flow rate (Q.sub.rep.pre) through the pre-dilution infusion line (**29**), in particular blood water flow rate at filtration unit inlet mathematical relation being as follows:

[00026] $\begin{aligned} Qpw_{inlet} &= Qpw + Q_{cit} + Q_{syr} + Q_{PBP} + Q_{rep,pre} \\ &= Q_b \,.Math. \, (1 - Hct) \,.Math. \, Fp + Q_{cit} + Q_{PBP} + Q_{rep,pre} \end{aligned}$ [0280] wherein the significance of the denotations is given in the Glossary; if any of the infusion lines or the dialysis liquid supply line is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

[0281] In a 94.sup.th aspect according to any one of the preceding aspects, a citrate load (J.sub.cit_load) is alternatively a function of a citrate dose (D.sub.cit) and the blood flow (Q.sub.b), namely according to D.sub.cit.Math.Q.sub.b, or a function of the citrate flow rate (Q.sub.cit) in the anticoagulant line (**51**) and a total citrate concentration (C.sub.cit_pbp), namely according to Q.sub.cit.Math.C.sub.cit.sub.PBP.

[0282] In a 95.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations include a citrate load mathematical relation linking a citrate load (J.sub.cit_load) with a citrate dose (D.sub.cit) and/or the blood flow rate (Q.sub.b) and/or a citrate clearance (K.sub.cit) and/or plasma water flow rate (Q.sub.pw_inlet) at the inlet of the filtration unit (**2**), in particular wherein the citrate load

mathematical relation is either:

[00027] $J_{\text{citrate\_load}} = D_{\text{cit}}$ .Math. Q_b .Math. $(1 - \frac{K_{\text{cit}}}{\text{Qpw}_{\text{inlet}}})$ .Math. $(1 - \frac{1}{1 + \frac{K_{\text{cit\_met}}}{K_{\text{cit}}} \cdot \text{Math.} \frac{\text{Qpw}_{\text{inlet}}}{\text{Qp}}})$ or: $J_{\text{citrate\_load}} = D_{\text{cit}} \times Qb \times (1 - \frac{K_{\text{cit}}}{\text{Qpw}_{\text{inlet}}})$ [0283] wherein the

significance of the denotations is given in the Glossary.

[0284] In a 96.sup.th aspect according to any one of the preceding aspects, the net buffer load mathematical relation of aspect 67 and the citrate load mathematical relation of aspect 95 link the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood with the at least two fluid flow rates selected in the group, the control unit (**12**) uses the net buffer load mathematical relation of aspect 67 and the citrate load mathematical relation of aspect 95 to calculate the set value of said at least two fluid flow rates.

[0285] In a 97.sup.th aspect according to the preceding aspect, the mathematical relations of aspects 85, 90, 91, 92 and 83 are further used by the control unit (**12**) to calculate the set value of said at least two fluid flow rates.

[0286] In a 98.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is configured to calculate two or more fluid flow rates selected in the group.

[0287] In a 99.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is configured to calculate three or more fluid flow rates selected in the group.

[0288] In a 100.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is configured to calculate four or more fluid flow rates selected in the group.

[0289] In a 101.sup.st aspect according to any one of the preceding aspects, the control unit (**12**) is configured to receive a number 'n' of clinical prescription parameters and to calculate a plurality 'm' of fluid flow rates selected in the group, wherein the plurality of fluid flow rates is higher or equal to the number clinical prescription parameters, namely m≥n.

[0290] In a 102.sup.nd aspect according to any one of the preceding aspects, the control unit (**12**) is configured to receive a number 'n' of clinical prescription parameters comprising said prescribed dialysis dose (D.sub.set) and said parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient and one or more of: [0291] a regional anticoagulation, e.g., citrate, dose (D.sub.cit) plus a ion, e.g., calcium, re-establishing solution parameter (CaComp; D.sub.ca); [0292] a fluid removal rate (Q.sub.pfr) from the patient; and [0293] a blood flow rate (Q.sub.b);

wherein the control unit (**12**) is further configured to calculate a plurality 'm' of fluid flow rates selected in the group, wherein the plurality of fluid flow rates is higher or equal to the number clinical prescription parameters, namely m≥n.

[0294] In a 103.sup.rd aspect according to any one of the preceding two aspects, if m>n, the control unit (**12**) provides for additional therapy configuration parameters to be selectable, said additional therapy configuration parameters adding further mathematical relations to be used for calculating the 'm' fluid flow rates, in particular, if m=n+1, one additional therapy configuration parameter is selectable, if m=n+2, two additional therapy configuration parameters are selectable.

[0295] In a 104.sup.th aspect according to any one of the preceding aspects, said further mathematical relations include one or more of a convection-diffusion relation, a blood pre-dilution relation, and a pre-post infusion relation.

[0296] In a 105.sup.th aspect according to any one of the preceding aspects, the apparatus is configured for performing regional anticoagulation treatments and comprises: [0297] the anticoagulant infusion line (**51**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**); [0298] a source of regional anticoagulant (**10**) providing an anticoagulant to the anticoagulant infusion line (**51**), said source including in particular citrate; [0299] the ion balancing infusion line (**74**) connected at one end thereof either to the blood return line (**7**) or to the patient catheter, and [0300] a source of ion balancing solution (**11**) providing an ion balancing solution to the ion balancing infusion line (**74**), said source including in particular calcium ions;

wherein the control unit (**12**) is configured to execute the flow-rate setup procedure comprising: [0301] receiving the patient prescription, the receiving step further including: [0302] allowing entry of a set value for a prescribed anticoagulant dose (D.sub.cit) to be delivered, [0303] determining of the operating parameters comprising calculating the at least two fluid flow rates, the set value for at least the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**) and the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**) using said one or more mathematical relations.

[0304] In a 106.sup.th aspect according to the preceding aspect, calculating the set value for at least the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**) and/or the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**), is based at least on said set value of the prescribed dialysis dose (D.sub.set), particularly in case the set value for the blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**) is determined by the control unit (**12**) as an operating parameter.

[0305] In a 107.sup.th aspect according to the preceding aspect, calculating the set value for at least the fluid flow rate (Q.sub.cit) through the anticoagulant infusion line (**51**) and/or the fluid flow rate (Q.sub.ca) through the ion balancing infusion line (**74**), is based at least on said target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood, particularly when the set value for the blood fluid flow rate (Q.sub.b) through the extracorporeal blood circuit (**17**) is determined by the control unit (**12**) as an operating parameter.

[0306] In a 108.sup.th aspect according to any one of the preceding aspects, one or more of said mathematical relations correlate the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient to on an estimation of an amount per unit of time of bicarbonate generated from metabolism of citrate (J.sub.met_cit) infused to the patient, in particular wherein the metabolism of citrate load leads to 3 moles of bicarbonate per mole of citrate at steady state, namely:

[00028] $J_{\text{met\_cit}} = 3$ .Math. $J_{\text{cit\_load}}$.

[0307] In a 109.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is further configured to control said actuators for regulating the flow of fluid based on said set value and calculated value/s of the fluid flow rates.

[0308] In a 110.sup.th aspect according to any one of the preceding aspects, the actuators for regulating the flow of fluid (**24**, **25**, **26**, **31**, **53**, **54**, **65**, **75**) comprises pumps, e.g., rotational and/or peristaltic pumps, and/or valves.

[0309] In a 111.sup.th aspect according to any one of the preceding aspects, said one or more mathematical relations correlates the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient who has to undergo a CRRT blood treatment with the at least two fluid flow rates selected in said group.

[0310] In a 112.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is further configured to calculate the set values of the at least two fluid flow rates by applying said prescribed dose value (D.sub.set) and the target value for the parameter indicative of a steady state acid-base balance in the blood to said mathematical relations.

[0311] In a 113.sup.th aspect according to any one of the preceding two aspects, the control unit (**12**) is further configured to calculate the set values of the at least two fluid flow rates by applying the clinical prescription parameters to said mathematical relations.

[0312] In a 114.sup.th aspect according to any one of the preceding three aspects, the clinical prescription parameters further comprises a fluid removal rate (Q.sub.pfr) from the patient to said mathematical relations.

[0313] In a 115.sup.th aspect according to any one of the preceding four aspects, the clinical prescription parameters further comprises a blood flow rate (Q.sub.b) in the extracorporeal blood circuit (**17**).

[0314] In a 116.sup.th aspect according to any one of the preceding five aspects, the clinical prescription parameters further comprises the prescribed dialysis dose (D.sub.set) and the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient.

[0315] In a 117.sup.th aspect according to any one of the preceding six aspects, the clinical prescription parameters further comprises the regional

anticoagulation dose (D.sub.cit) and/or the ion re-establishing solution parameter (CaComp; D.sub.ca).

[0316] In a 118.sup.th aspect according to any one of the preceding aspects, the memory (**16**) stores a plurality of further mathematical relations correlating the at least two fluid flow rates selected in said group with each other.

[0317] In a 119.sup.th aspect according to the preceding aspect, the CRRT apparatus comprises—a preset number of pre-dilution lines selected in the group including said pre-dilution infusion line (**29**) connected at one end thereof to the blood withdrawal line (**6**), said pre-blood pump—PBP—infusion line (**52**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), and said anticoagulant infusion line (**51**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**); [0318] a preset number of post-dilution lines selected in the group including said post-dilution infusion line (**63**) connected at one end thereof to the blood return line (**7**), said post-dilution bicarbonate infusion line (**23**) connected at one end thereof to the blood return line (**7**), and said ion balancing infusion line (**74**) connected at one end thereof either to the blood return line (**7**) or to a patient catheter; wherein said further mathematical relations stored in said memory comprise one or more of the following: [0319] a convection-diffusion relation, relating the total fluid flow rate (Q.sub.rep.pre+Q.sub.rep.post+Q.sub.pbp+Q.sub.HCO3+Q.sub.ca+Q.sub.cit) through said preset number of pre- and post-dilution lines with the fluid flow rate (Q.sub.dial) through said dialysis liquid supply line (**8**), [0320] a blood pre-dilution relation, relating the flow rate of blood (Q.sub.b) or of plasma (Q.sub.p) and a total fluid flow rate (Q.sub.rep.pre+Q.sub.pbp+Q.sub.cit) infused in the blood withdrawal line through said preset number of pre-dilution lines, [0321] a pre-post relation, relating a total fluid flow rate (Q.sub.rep.pre+Q.sub.pbp+Q.sub.cit) through said preset number of pre-dilution lines with a total fluid flow rate (Q.sub.rep.post+Q.sub.HCO3+Q.sub.ca) through said preset number of post-dilution lines.

[0322] In a 120.sup.th aspect according to the preceding aspect, the convection-diffusion relation defines a first split between the total fluid flow rate (Q.sub.rep.pre+Q.sub.rep.post+Q.sub.pbp+Q.sub.HCO3+Q.sub.ca+Q.sub.cit) through said preset number of pre- and post-dilution lines and the fluid flow rate (Q.sub.dial) through said dialysis liquid supply line (**8**), in particular the convection-diffusion relation defines a first percentage split or a first ratio R**1** dividing the total fluid flow rate (Q.sub.rep.pre+Q.sub.rep.post+Q.sub.pbp+Q.sub.HCO3+Q.sub.ca+Q.sub.cit) through said preset number of pre- and post-dilution lines by the fluid flow rate (Q.sub.dial) through said dialysis liquid supply line (**8**).

[0323] In a 121.sup.st aspect according to any one of the preceding two aspects, the blood pre-dilution relation defines a second ratio R**2** dividing the total fluid flow rate (Q.sub.rep.pre+Q.sub.pbp+Q.sub.cit) infused in the blood withdrawal line (**6**) through said preset number of pre-dilution lines by the flow rate of blood (Q.sub.b) or of plasma (Q.sub.p).

[0324] In a 122.sup.nd aspect according to any one of the preceding three aspects, the pre-post relation defines a third split between the total fluid flow rate (Q.sub.rep.pre+Q.sub.pbp+Q.sub.cit) through said preset number of pre-dilution lines and total fluid flow rate (Q.sub.rep.post+Q.sub.HCO3+Q.sub.ca) through said preset number of post-dilution lines, in particular the pre-post relation defines a third percentage split or a third ratio R**3** dividing the total fluid flow rate (Q.sub.rep.pre+Q.sub.pbp+Q.sub.cit) through said preset number of pre-dilution lines by total fluid flow rate (Q.sub.rep.post+Q.sub.HCO3+Q.sub.ca) through said preset number of post-dilution lines.

[0325] In a 123.sup.rd aspect according to any one of the preceding three aspects, the control (**12**) unit is further configured to: store a preset value or preset range for each one of said first, second and third splits/ratios R**1**, R**2**, R**3**.

[0326] In a 124.sup.th aspect according to any one of the preceding four aspects, the control unit (**12**) is further configured to allow entry by an operator of a set value or a set range for each one of said first, second and third splits/ratios R**1**, R**2**, R**3**.

[0327] In a 125.sup.th aspect according to any one of the preceding seven aspects, the control unit (**12**) is further configured to allow the user to select one or more therapy configurations, said therapy configurations comprising at least one of said further mathematical relations, and optionally two or three of said further mathematical relations, and to calculate the set values of at least two of said fluid flow rates by applying the set value of the prescribed dose (D.sub.set) and the target value of the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient entered by the operator to both the mathematical relations and the further mathematical relation/s selected by the user.

[0328] In a 126.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is further configured to allow the user to select one or more therapy configurations, wherein selecting said therapy configurations comprises choosing the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient who has to undergo a CRRT blood treatment between a net buffer load (nNBL; NBL) and a steady state patient bicarbonate (Cp.sub.HCO3_pat).

[0329] In a 127.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is further configured to allow the user to select one or more therapy configurations, wherein selecting said therapy configurations comprises choosing a definition for the prescribed dialysis dose (D.sub.set).

[0330] In a 128.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is further configured to allow the user to select one or more therapy configurations, wherein selecting said therapy configurations comprises choosing blood flow rate as clinical prescription parameter or as operating parameter.

[0331] In a 129.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is further configured to allow the user to enter treatment configuration values including receiving entries for one or more of: [0332] patient body weight (BW); [0333] patient hematocrit (Hct); [0334] filtration unit parameters, such as filter mass transfer coefficient by surface area (K0.A), sieving coefficient (SC), solute clearance (K.sub.sol), filtration unit surface (S), diffusive mass transfer resistance (RT) or any combination thereof; [0335] substance concentration for one or more containers feeding said lines (**29**, **63**, **23**, **74**, **8**, **52**, **51**), in particular bicarbonate concentration and/or lactate concentration and/or citrate concentration and/or calcium concentration.

[0336] In a 130.sup.th aspect according to the preceding aspect, the control unit (**12**) is further configured to calculate the set values of the at least two fluid flow rates by applying the treatment configuration values to said mathematical relations.

[0337] In a 131.sup.st aspect according to any one of the preceding two aspects, said substance concentration for one or more containers is entered by an operator for each respective container through a user interface (**15**) connected to the control unit (**12**), and/or said substance concentration in the fluid is determined by the control unit (**12**) associating an identification code on each respective container to a respective substance concentration.

[0338] In a 132.sup.nd aspect according to any one of the preceding three aspects, said filtration unit parameters for the filtration unit are entered by an operator, and/or said filtration unit parameters are determined by the control unit (**12**) associating an identification code on the filtration unit (**2**) to said filtration unit parameters.

[0339] In a 133.sup.rd aspect according to any one of the preceding aspects, the apparatus comprises the dialysis liquid supply line (**8**) connected to the inlet of the secondary chamber, wherein the control unit is configured to calculate the set value for the fluid flow rate (Q.sub.dial) in the dialysis liquid supply line (**8**), which is not set by the operator, based on at least a part of the clinical prescription parameters, in particular the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance set by the operator and/or on said prescribed dialysis dose value (D.sub.set).

[0340] In a 134.sup.th aspect according to any one of the preceding aspects, the apparatus comprises the pre-dilution infusion line (**29**) connected at one end thereof to the blood withdrawal line (**6**), in particular the blood pump (**21**) being active in correspondence of a segment of the blood withdrawal line (**6**) and the pre-dilution infusion line (**29**) being connected to the blood withdrawal line (**6**) downstream the blood pump (**21**), wherein the control unit is configured to calculate the set value for the fluid flow rate (Q.sub.rep.pre) in the pre-dilution infusion line (**29**), which is not set by the operator, based on at least a part of the clinical prescription parameters, in particular the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance set by the operator and/or on said prescribed dialysis dose value (D.sub.set).

[0341] In a 135.sup.th aspect according to any one of the preceding aspects, the apparatus comprises the post-dilution infusion line (**63**) connected at one end thereof to the blood return line (**7**), wherein the control unit is configured to calculate the set value for the fluid flow rate (Q.sub.rep.post) in the post-dilution infusion line (**63**), which is not set by the operator, based on at least a part of the clinical prescription parameters, in particular the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance set by the operator and/or on said prescribed dialysis dose value (D.sub.set).

[0342] In a 136.sup.th aspect according to any one of the preceding aspects, the apparatus comprises the post-dilution bicarbonate infusion line (**23**) connected at one end thereof to the blood return line (**7**), wherein the control unit is configured to calculate the set value for the fluid flow rate (Q.sub.HCO3) in the post-dilution bicarbonate infusion line (**23**), which is not set by the operator, based on at least a part of the clinical prescription parameters, in particular the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance set by the operator and/or on said prescribed dialysis dose value (D.sub.set).

[0343] In a 137.sup.th aspect according to any one of the preceding aspects, the apparatus comprises the ion balancing infusion line (**74**) connected at one end thereof either to the blood return line (**7**) or to a patient catheter, wherein the control unit is configured to calculate the set value for the fluid flow rate (Q.sub.ca) in the ion balancing infusion line (**74**), which is not set by the operator, based on at least a part of the clinical prescription parameters, in particular the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance set by the operator and/or on said prescribed dialysis dose value (D.sub.set).

[0344] In a 138.sup.th aspect according to any one of the preceding aspects, the apparatus comprises the pre-blood pump—PBP [0345] infusion line (**52**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), in particular the blood pump (**21**) being active in correspondence of a segment of the blood withdrawal line (**6**), wherein the control unit is configured to calculate the set value for the fluid flow rate (Q.sub.PBP) in the pre-blood pump—PBP—infusion line (**52**), which is not set by the operator, based on at least a part of the clinical prescription parameters, in particular the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance set by the operator and/or on said prescribed dialysis dose value (D.sub.set).

[0346] In a 139.sup.th aspect according to any one of the preceding aspects, the apparatus comprises the anticoagulant infusion line (**51**) connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump (**21**), in particular the blood pump (**21**) being active in correspondence of a segment of the blood withdrawal line (**6**), wherein the control unit is configured to calculate the set value for the fluid flow rate (Q.sub.cit) in the anticoagulant infusion line (**51**), which is not set by the operator, based on at least a part of the clinical prescription parameters, in particular the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance set by the operator and/or on said prescribed dialysis dose value (D.sub.set).

[0347] In a 140.sup.th aspect according to any one of the preceding aspects, the operating parameters further comprises a blood flow rate (Q.sub.b) in the extracorporeal blood circuit (**17**), wherein the control unit is configured to calculate the set value for the blood flow rate (Q.sub.b) in the extracorporeal blood circuit (**17**), which is not set by the operator, based on at least a part of the clinical prescription parameters, in particular the target value for the parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance set by the operator and/or on said prescribed dialysis dose value (D.sub.set).

[0348] In a 141.sup.st aspect according to any one of the preceding aspects, the control unit (**12**) is configured to calculate three or more, and in particular four or more, set values of the fluid flow rates selected in the group.

[0349] In a 142.sup.nd aspect according to any one of the preceding aspects, the control unit (**12**) is configured to calculate the set value for a patient fluid removal rate (Q.sub.PFR) from the patient.

[0350] In a 143.sup.rd aspect according to any one of the preceding aspects, said prescribed dialysis dose value (D.sub.set) comprises a prescribed value for a flow rate or a combination of flow rates.

[0351] In a 144.sup.th aspect according to any one of the preceding aspects, said prescribed dialysis dose value (D.sub.set) comprises a prescribed value for one selected in the group including: [0352] an effluent dose flow rate (D.sub.eff_set), which is the prescribed value of the flow rate through the effluent line (**13**), [0353] a convective dose flow rate (D.sub.conv_set), which is the prescribed value of the sum of the flow rates through all infusion lines (Q.sub.rep.pre, Q.sub.rep.post, Q.sub.PBP, Q.sub.cit, Q.sub.ca, Q.sub.HCO3) and the patient fluid removal rate (Q.sub.pfr), optionally wherein the prescribed convective dose flow rate value is corrected for predilution, [0354] a diffusive dose flow rate (D.sub.dial_set), which is the prescribed value of the flow rate through the dialysis fluid line (Q.sub.dial), [0355] an urea dose (D.sub.urea_set), which is a prescribed value for an estimated urea clearance, [0356] a clearance dose (K.sub.solute_set), which is a prescribed value for an estimated clearance for a given solute.

[0357] In a 145.sup.th aspect according to the preceding aspect, the control unit (**12**) is configured to correct the selected one of the above defined doses to take into account a predilution effect, when a infusion line (**29**; **51**; **52**) is present and delivers fluid upstream from the treatment unit (**2**), by multiplying the dose value times a dilution factor (F.sub.dilution), which is <then 1, as per the following formula:

[00029] $\mathrm{Dose}_{\mathrm{corr\_xxx}} = F_{\mathrm{dilution}} \times \mathrm{Dose}_{\mathrm{\_xxx}} (\mathrm{with} \, xxx = \mathrm{eff}, \mathrm{conv}, \mathrm{dial})$.

[0358] In a 146.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is configured to control the blood pump (**21**) using either the entered or the calculated set value for the blood flow (Q.sub.b).

[0359] In a 147.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus further comprises a graphic user interface (**15**) connected to said control unit (**12**), said control unit being configured to: [0360] display on the graphic user interface an indicium prompting a user to enter or select the set value for said prescribed dialysis dose (D.sub.set), [0361] display on the graphic user interface an indicium prompting a user to enter or select the target value for said parameter (nNBL; Cp.sub.HCO3_pat) indicative of a steady state acid-base balance in the blood of the patient, [0362] display on the graphic user interface an indicium allowing selection of one or more further mathematical relations the user intends to select, including displaying an indicium allowing a user to enter or select a set value for the mathematical relation/s, in particular to enter or select one or more of said first, second and third ratios, [0363] detecting selection of the further mathematical relation, and [0364] using said further mathematical relation to calculate the set value of the at least two fluid flow rates selected in the group.

[0365] In a 148.sup.th aspect according to any one of the preceding aspects, the actuators for regulating the flow of fluid through said fluid lines comprises a pre-infusion pump (**31**) for regulating the flow through said pre-dilution infusion line (**29**) and/or a post-infusion pump (**65**) for regulating the flow through said post-dilution infusion line (**63**).

[0366] In a 149.sup.th aspect according to any one of the preceding aspects, a dialysis liquid supply line (**8**) is connected to the inlet of the secondary chamber (**4**), and the actuators for regulating the flow of fluid through said fluid lines comprises at least a dialysis fluid pump (**25**) for regulating the flow through said dialysis liquid supply line (**8**).

[0367] In a 150.sup.th aspect according to any one of the preceding aspects, the actuators for regulating the flow of fluid through said fluid lines comprises PBP infusion pump (**53**) for regulating the flow through said pre-blood pump—PBP—infusion line (**52**) and/or an anticoagulant pump (**54**) for regulating the flow through said anticoagulant infusion line (**51**).

[0368] In a 151.sup.st aspect according to any one of the preceding aspects, the actuators for regulating the flow of fluid through said fluid lines comprises a bicarbonate pump (**24**) for regulating the flow through said post-dilution bicarbonate infusion line (**23**) and/or an ion balancing pump (**75**) for regulating the flow through said ion balancing infusion line (**74**).

[0369] In a 152.sup.nd aspect according to any one of the preceding aspects, the CRRT apparatus further comprises a collection container (**62**) connected to an end of the effluent fluid line (**13**) to collect spent dialysate.

[0370] In a 153.sup.rd aspect according to any one of the preceding aspects, the CRRT apparatus further comprises a replacement container (**30**) of fresh fluid connected to an end of the pre-dilution infusion line (**29**)), in particular said container (**30**) being a bag containing a replacement solution.

[0371] In a 154.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus further comprises an auxiliary container (**64**) of fresh fluid connected to an end of the post-infusion line (**63**), in particular said container (**64**) being a bag containing a replacement solution.

[0372] In a 155.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus further comprises a liquid container (**14**) of fresh fluid connected to an end of the dialysis liquid supply line (**8**), in particular said container (**14**) being a bag containing fresh dialysis fluid.

[0373] In a 156.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus further comprises a PBP container (**18**) of fresh fluid connected to an end of the pre-blood pump infusion line (**52**), in particular said container (**18**) being a bag containing a replacement solution.

[0374] In a 157.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus further comprises a container (**10**) for regional anticoagulant connected to an end of the anticoagulant infusion line (**51**), in particular wherein said container (**10**) is a bag and contains citrate, and optionally citric acid.

[0375] In a 158.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus further comprises a bicarbonate container (**24**) connected to an end of the post-dilution bicarbonate infusion line (**23**), in particular said container (**24**) being a bag containing a bicarbonate solution, optionally a concentrated bicarbonate solution.

[0376] In a 159.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus further comprises an ion balancing solution container (**11**) connected to an end of the ion balancing infusion line (**74**), in particular said container (**11**) being a bag or a syringe containing a calcium concentrated solution.

[0377] In a 160.sup.th aspect according to any one of the preceding aspects, the CRRT apparatus further comprises one or more scales weighing one or more of said containers, in particular the apparatus comprising a corresponding scale for each respective of said containers, said one or more scales being connected to the control unit and sending to the control unit corresponding weight signals.

[0378] In a 161.sup.st aspect according to any one of the preceding aspects, the memory (**16**) stores one or a plurality of optimization criteria, said control unit (**12**) being configured to calculate the set value for the fluid flow rate/s by applying the optimization criteria.

[0379] In a 162.sup.nd aspect according to the preceding aspect, the optimization criteria comprises a first optimization criterion imposing that an emptying time of at least one among the containers (**10**; **18**; **30**; **64**; **28**; **11**; **14**) of fresh fluid and/or a filling time of the collection container (**62**) is substantially same as or multiple of the emptying time of one or more of the other containers of fresh fluid.

[0380] In a 163.sup.rd aspect according to any one of the preceding two aspects, the optimization criteria comprises a second optimization criterion imposing that fluid consumption through said fluid lines is minimized.

[0381] In a 164.sup.th aspect according to any one of the preceding three aspects, the optimization criteria comprises a third optimization criterion imposing that a life time of said filtration unit (**2**) is maximized.

[0382] In a 165.sup.th aspect according to any one of the preceding four aspects, the optimization criteria comprises a fourth optimization criterion imposes that urea clearance or dialysance of a given solute is maximized.

[0383] In a 166.sup.th aspect according to any one of the preceding five aspects, the control unit (**12**) is configured to allow the user selecting one or more of said criteria and calculate said at least one flow rate using said selected criteria.

[0384] In a 167.sup.th aspect according to any one of the preceding six aspects, the control unit (**12**) is configured to allow the user selecting one or more of said criteria and one or more of said further mathematical relations and to calculate at least three or more flow rates using said selected criteria and said selected further mathematical relations.

[0385] In a 168.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is configured to determine if said selected further mathematical relations are compatible or conflicting with each other and then: [0386] in case the selected further mathematical relations are compatible, calculate the flow rate/s based on the selected further mathematical relations and the clinical prescription parameters, [0387] in case one or more of the selected further mathematical relations are conflicting with each other, execute one or more of the following sub-steps: [0388] inform the user, [0389] allow the user to assign a priority to each of the selected further mathematical relations, [0390] assign a priority ranking to the selected further mathematical relations, said priority ranking being either predetermined or user adjustable, and then ignore further mathematical relations as soon as flow rates have been calculated from the prioritized further mathematical relations, [0391] define a compromise between further mathematical relations using preset rules.

[0392] In a 169.sup.th aspect according to any one of the preceding aspects, the control unit (**12**) is configured to store in the memory (**16**) the volume or weight of fluid which is contained in each container (**10**; **18**; **30**; **64**; **28**; **11**; **14**) of fresh fluid and optionally in the collection container (**62**).

[0393] In a 170.sup.th aspect according to the preceding aspect, said volume or weight of fluid is detected by a sensor associated to each respective container and connected to the control unit (**12**).

[0394] In a 171.sup.st aspect according to the preceding aspect, wherein said volume of fluid is detected based on signals associated to the corresponding pump acting on the infusion line fluidly connected to the respective container, for example based on signals from a Hall sensor associated to a peristaltic pump or based on plunger position in a syringe pump.

[0395] In a 172.sup.nd aspect according to the preceding aspect, wherein said volume of fluid is detected based on signals associated to the corresponding pump in one or more of: [0396] the ion balancing infusion line (**74**); [0397] the syringe fluid line (**22**); [0398] the anticoagulant infusion line (**51**).

[0399] In a 173.sup.rd aspect according to the preceding aspect 170, wherein said sensor is a weight scale weighing at least one of said containers.

[0400] In a 174.sup.th aspect according to the preceding aspect 170, wherein said sensor is a droplet counter determining weight and/or volume based on drops count.

[0401] In a 175.sup.th aspect according to any one of the preceding aspects, a data carrier is provided comprising instructions which when executed by the control unit of an apparatus according to any one of the preceding apparatus aspects render said control unit configured to execute the respective steps described in the preceding aspects.

Description

DESCRIPTION OF THE DRAWINGS

[0402] Aspects of the invention are shown in the attached drawings, which are provided by way of non-limiting example, wherein:

[0403] FIG. **1** shows a CRRT extracorporeal blood treatment apparatus according to aspects of the disclosure;

[0404] FIGS. **2-6** show schematic representations of blood treatment apparatuses according to aspects of the disclosure;

[0405] FIG. **7** is a flowchart showing calculation of set flow rates in a CRRT extracorporeal blood treatment apparatus, e.g. of the type of FIGS. **1-6**, according to aspects of the invention.

DETAILED DESCRIPTION

[0406] As mentioned, extracorporeal blood treatment (dialysis) may be used in patients with rapidly developing loss of kidney function, called acute renal failure or slowly worsening kidney function, called Stage **5** chronic kidney disease (or end-stage renal disease). In the following description, some embodiments of extracorporeal blood treatment apparatuses will be firstly described being suitable, or designed, principally for intensive care treatments. Citrate regional anticoagulation will be thereafter introduced followed by definition of steady state acid-base balance parameter/s. The methods to simplify and/or assist CRRT prescription on the basis of meaningful clinical parameters are thereafter described and may be implemented in any of the described embodiments as it is apparent from the following description.

Definitions

[0407] Unless defined otherwise, all technical and scientific terms used have the same meaning as commonly understood by one of ordinary skill in the art.

[0408] The term "downstream" refers to a position of a first component in a flow path relative to a second component wherein fluid will pass by the second component prior to the first component during normal operation. The first component can be said to be "downstream" of the second component, while the second component is "upstream" of the first component. FIG. **1** shows the fluid circulation directions (indicated with reference **200**) during normal operation of the apparatus **1**.

[0409] We define the "dialysis fluid" as the treatment fluid introduced to the second chamber of the filtration unit **2**. The dialysis fluid may be on-line prepared or pre-packaged in sterile bags. Usually in CRRT apparatuses/applications the dialysis fluid, but also the replacement fluids (possibly also regional anticoagulant fluid and/or ion re-establishing solution fluid) are contained in (disposable) bags.

[0410] We define the "dialysate" or "effluent" as the fluid from the outlet from the second chamber of the filtration unit **2**. Dialysate or effluent is the spent dialysis fluid, comprising the uremic toxins removed from the blood and may include ultrafiltrate fluid.

[0411] We define "regional anticoagulant" as a substance which, once mixed with extracorporeal blood, substantially prevents blood coagulation in the extracorporeal blood circuit and which is quickly metabolized by the patient, thus avoiding systemic anticoagulation.

[0412] We define "net buffer load" during the extracorporeal blood treatment (e.g., CRRT) the combination of bicarbonate generated from the metabolism of bicarbonate precursors, such as citrate and/or lactate infused into the patient (J.sub.met_cit; J.sub.met_lact), bicarbonate balance from the extracorporeal blood therapy (J.sub.HCO3_bal) which may match with net loss or net gain for the patient, and acid infusion, e.g., from citric acid content of the anticoagulant solution, when relevant. From the mathematical point of view, the general definition of net buffer load (mmol/h) used hereinafter is:

[00030] $J_{\text{buffer\_load}} = J_{\text{met\_cit}} + J_{\text{HCO3\_bal}} + J_{\text{met\_lact}} - J_{H+}$

[0413] We define "citrate dose" as the injected amount of citrate per liter of blood treated (mmol/L blood); it defines the intensity of citrate anticoagulation.

[0414] We define patient "citrate load" as the rate at which citrate is returned to the patient (mmol/h).

[00031] $J_{\text{citrate\_load}} = J_{\text{cit\_PBP}} - J_{\text{cit\_eff}}$

[0415] We define "bicarbonate balance" as the net infusion or loss rate of bicarbonate in the extracorporeal blood treatment matching with the difference between the infusion rate from the dialysate and/or replacement fluids and the bicarbonate removal rate into dialysate.

[00032] $J_{\text{HCO3\_bal}} = J_{\text{HCO3\_inf}} - J_{\text{HCO3\_eff}}$

[0416] We define "calcium compensation" (or calcium compensation parameter) as the relative dosage of calcium infusion to compensate for the estimated calcium loss in dialysate, expressed in percentage.

[0417] We define "total calcium concentration", particularly in the effluent as the total amount of calcium per unit of liquid volume in the effluent, including both ionized and bound calcium.

[0418] We define "K.sub.0A" as the mass transfer-area coefficient of a filtration unit, wherein K.sub.0 is the clearance at infinite blood and dialysis fluid flow rates and A is the filtration unit surface area. "K.sub.0A" is specific of a given solute and thereby changes according to the solute which is specifically considered.

[0419] In this application the term "citrate" means that the component is in form of a salt of citric acid, such as sodium, magnesium, calcium, or potassium salt thereof. The citric acid (denoted C.sub.6H.sub.8O.sub.7) is deprotonated stepwise, therefore the "citrate" include all the different forms, citrate (denoted C.sub.6H.sub.5O.sub.7.sup.3−), hydrogen citrate (denoted C.sub.6H.sub.6O.sub.7.sup.2−), and dihydrogen citrate (denoted C.sub.6H.sub.7O.sup.7−).

[0420] The term "citrate" or "total citrate" means the total amount of citric acid and any salts thereof, such as its sodium, magnesium, calcium, or potassium salt thereof. In other terms, "total citrate" is the sum of free citrate ions and citrate containing complexes and ion pairs.

[0421] The term "buffer agent" means bicarbonate or bicarbonate precursors such as lactate, citrate or acetate.

[0422] We define "number of degrees of freedom" as the difference between the numbers of operating flow rates to be computed minus the number of prescription parameters.

Glossary

[0423] The following terms/parameters are consistently used throughout the equations provided in the following description of the detailed working of the extracorporeal blood treatment apparatus.

TABLE-US-00001 Parameters BW patient body weight (kg) C solute concentration (mM) C.sub.cit.sub.—.sub.PBP total citrate concentration in citrate anticoagulation solution (sodium citrate + citric acid) - (mM) C.sub.ca calcium concentration of the ion balancing solution (mmol/l) C.sub.ca.sub.rep.post calcium concentration of the replacement solution in post-dilution (mmol/l) C.sub.ca.sub.HCO3 calcium concentration in the bicarbonate container/infusion line (mmol/l) C.sub.p plasma concentration (mM) C.sub.pw plasma water concentration (mM) Cpw.sub.cit.sub. —.sub.inlet citrate concentration in plasma water at the filter inlet (mM) Cp.sub.cit.sub.—.sub.pat patient systemic citrate concentration (mM) C.sub.HCO3.sub.cit bicarbonate concentration in citrate solution (mM) C.sub.HCO3.sub.PBP bicarbonate concentration in PBP solution (mM) C.sub.HCO3.sub.dial bicarbonate concentration in dialysis fluid (mM) C.sub.HCO3.sub.rep.pre bicarbonate concentration in pre-dilution line (mM) C.sub.HCO3.sub.rep.post bicarbonate concentration in post-dilution line (mM) C.sub.HCO3.sub.HCO3post bicarbonate concentration in bicarbonate post-dilution line (mM) Cp.sub.HCO3.sub.—.sub.pat patient systemic bicarbonate plasma concentration (mM) (.Math. [HCO.sub.3.sup. −].sub.pat.eq) Cpw.sub.HCO3.sub.—.sub.pat patient systemic bicarbonate plasma water concentration (mM) Cpw.sub.HCO3.sub.—.sub.inlet bicarbonate plasma water concentration at filter inlet (mM) C.sub.lact.sub.—.sub.dial lactate concentration in dialysis fluid (mM) C.sub.lact.sub.rep.pre lactate concentration in pre-dilution line (mM) C.sub.lact.sub.rep.post lactate concentration in post-dilution line (mM) Cp.sub.lact.sub.—.sub.pat patient systemic lactate plasma concentration (mM) Cpw.sub.lact.sub.—.sub.inlet lactate plasma water concentration at filter inlet (mM) D.sub.CRRT CRRT dialysis dose (ml/h) D.sub.eff Effluent dose (ml/h) D.sub.conv convective dose (ml/h) D.sub.dial diffusive dose (ml/h) D.sub.urea urea dose (ml/h) D.sub.sol clearance dose (ml/h) NDose.sub.xxx Normalized dose (ml/kg/h) D.sub.cit citrate dose (mmol/L of blood) D.sub.ca calcium dose; calcium concentration in the effluent (mmol/l) Hct haematocrit (dimensionless, ∈ [0; 1]) J.sub.xxx mass transfer rate of 'xxx' solute (amount per unit of time) - (mmol/h) J.sub.HCO3.sub.—.sub.bal Bicarbonate balance from the extracorporeal blood therapy - (mmol/h) J.sub.HCO3.sub.—.sub.inf Bicarbonate infusion rate from the dialysis and/or all replacement fluids - (mmol/h) J.sub.HCO3.sub.—.sub.eff Bicarbonate removal rate into effluent - (mmol/h) J.sub.H+ Acid infusion in the extracorporeal blood therapy - (mmol/h) J.sub.citrate.sub.—.sub.load Citrate load or the net infusion rate of citrate to the patient - (mmol/h) J.sub.cit.sub.—.sub.PBP Citrate infusion rate from the pre-blood-pump anticoagulant circuit - (mmol/h) J.sub.cit.sub.—.sub.dial Citrate losses in the effluent - (mmol/h) J.sub.met.sub.—.sub.cit Bicarbonate generated from the metabolism of citrate infused to the patient - (mmol/h) J.sub.lact.sub.—.sub.bal Lactate balance from the extracorporeal blood therapy - (mmol/h) J.sub.lact.sub.—.sub.inf Lactate infusion rate from the dialysis and/or all replacement fluids - (mmol/h) J.sub.lact.sub.—.sub.eff Lactate removal rate into effluent - (mmol/h) J.sub.met.sub.—.sub.lact Bicarbonate generated from the metabolism of lactate infused to the patient - (mmol/h) J.sub.buffer.sub.—.sub.load Net buffer load during extracorporeal therapies - (mmol/h) SC.sub.urea filter sieving coefficient for urea SC.sub.cit filter sieving coefficient for citrate SC.sub.HCO3 filter sieving coefficient for bicarbonate PRE pre-infusion ratio of replacement fluid flow (dimensionless, ∈ [0; 1]) Q flow rate (ml/min) Q.sub.b blood flow rate (ml/min) Q.sub.PBP Pre-Blood-Pump flow rate (ml/min) Q.sub.cit citrate solution flow rate (ml/min) Q.sub.HCO3 bicarbonate post infusion solution flow rate (ml/min) Q.sub.rep.pre replacement flow rate/pre-filter (ml/min) Q.sub.rep.post replacement flow rate/post-filter (ml/min) Q.sub.PFR Patient Fluid Removal (PFR) rate (ml/min) Q.sub.rep total

replacement flow rate ($Q_{rep.pre}$ + $Q_{rep.post}$) (ml/min) Q_{pre} total predilution infusion flow rate (ml/min) Q_{syr} syringe flow rate (ml/min) Q_{bw} blood water flow rate (ml/min) $Q_{bw\text{-}inlet}$ blood water flow rate at the filter inlet (ml/min) Q_p plasma flow rate (ml/min) Q_{pw} plasma water flow rate (ml/min) $Q_{pw\text{-}inlet}$ plasma water flow rate at filter inlet (ml/min) Q_{eff} effluent flow rate (ml/min) Q_{fil} ultrafiltration rate in CRRT filter (ml/min) Q_{dial} dialysis flow rate (ml/min) Q_{ca} calcium solution flow rate (ml/min) S/RT_{xxx} ratio of filter surface area to diffusive mass transfer resistance (ml/min) for solute 'xxx' ($.Math.'K0.A_{xxx}'$) CaComp calcium compensation parameter (dimensionless, $\in$ [5%; 200%]) $F_{dilution_{blood}}$ blood dilution factor (dimensionless) $F_{dilution_{plasma}}$ plasma dilution factor (dimensionless) $F_{dilution_{pw}}$ plasma water dilution factor (dimensionless) Indices cit citrate HCO_3 bicarbonate lact lactate Ca calcium inlet filter blood inlet PBP Pre Blood-Pump dial dialysis fluid rep replacement rep.pre pre-dilution replacement infusion rep.post post-dilution replacement infusion eff Effluent or dialysate Constants Below indicated fixed value may be changed based on specific needs CP_{HCO30} = 25 mM patient plasma bicarbonate concentration (mM) Cp_{lact0} = 1.5 mM patient plasma lactate concentration (mM) $nNBL0$ = 0.1 mmol/h/kg Set normalized net buffer load at patient steady state F_{cal}^* = 0.92 fraction of patient plasma total calcium made available in plasma for transfer through filter membrane after citrate infusion (dimensionless) F_p = 0.95 plasma water volume fraction F_{rbc} = 0.85 intra erythrocyte water volume fraction F_{cal} = F_{cal}^*/F_p fraction of patient plasma total calcium made available in plasma water for transfer through filter membrane after citrate infusion (dimensionless)

[0424] It is noted that values for the above constants are exemplificative. For example, patient plasma bicarbonate concentration may be set at a different level based on medical staff decision e.g., 27 mM; the same occurs with normalized net buffer load that may assume different values such as 0.15 mmol/h/kg. Further, other constants may be more (or less) precisely estimated without affecting the other part of the present description.

Extracorporeal Blood Treatment Apparatus Particularly for CRRT Treatments

[0425] With reference to FIG. **1**, the numeral **1** globally refers to the extracorporeal blood treatment apparatus, in particular for intensive care therapies. The extracorporeal blood treatment apparatus **1** is designed for delivering any one of treatments like hemodialysis, hemofiltration, hemodiafiltration, ultrafiltration. The apparatus according to FIG. **1** is particularly designed for continuous renal replacement therapies (CRRT). CRRT systems are configured for delivering very specific treatments designed for patients versing in acute states of illness and who have temporarily lost their kidney function in its entirety. In this respect, CRRT systems may be structurally and/or operationally different from extracorporeal blood treatment systems designed for chronic patient care. In contrast to chronic patients, acute patients temporarily experience complete loss of their kidney function typically due to a contemporaneous state of severe injury or during recovery from surgery. Consequently, acute patients are often extremely weak and typically not in a condition to be submitted to regular dialysis treatment, which could further deteriorate their state and lead to serious and possibly life-threatening complications. Under circumstances as described, CRRT systems are designed to individually treat a patient exhibiting very poor health, without inducing further stress to the patient body, in particular without allowing vital parameters pertaining to the patient's blood to deviate from ideal or near-ideal values. Within the scope of this document CRRT systems are, thus, inherently characterized by one or more of the following features. CRRT involves renal replacement therapy, meaning an adjuvant therapy aimed firstly at facilitating continuous fluid removal in diuretic-resistant or acute renal failure patients. Therefore, CRRT systems inherently require a continuous net fluid removal from the patient. In other words, a CRRT system requires a fluid balance control system, such as a weight loss control system, configured to generate a continuous net weight loss rate (as opposed to merely controlling parameters to enable achieving a desired target weight loss as typically found in chronic patient care). Furthermore, acute patients experience extravascular fluid overload, which cannot be safely removed within a short period of time (e.g. within a few hours of chronic treatment) without causing potentially severe consequences (e.g. hypovolemic shock, arrhythmia, hypoxemia, hypoventilation, etc.). Therefore, a CRRT system must inherently include a much more accurate control over system parameters, in particular flow rates, in order to ensure that the required low flow rates of both blood circulating extra-corporeally and of treatment fluid (infused in the extracorporeal circuit or diffused through the dialyzer) are used. Moreover, CRRT treatment is performed continuously (e.g. for days or even weeks, without interruption/with minimal interruptions e.g., downtimes to change bags). Therefore, treatment settings in CRRT are based on flow rate settings, rather than settings pertaining to some specified treatment time (which would be unknown as acute patients may require treatment for an unknown time). Consequently, operation of CRRT systems cannot be based on some pre-defined absolute weight loss to be achieved, but rather on a meticulously controlled fluid balance in the patient, requiring continuous adjustments to a number of operating parameters, which have to be controlled and maintained during the entire (and a priori unknown) treatment time, based on a set weight-loss rate. Additionally, CRRT renal replacement therapy involves therapy substituting kidney functions for a relatively long time period and, thus, a CRRT system further requires at least either fresh dialysis liquid exchange in the dialyzer (in order to remove unwanted substances from blood and to add desired substances to the blood by diffusion) and/or fresh infusion fluid in combination with ultrafiltration (in order to remove unwanted substances from blood and to add desired substances to the blood by convection).

[0426] At least for the reasons set forth above, CRRT systems need to exhibit specific technical features enabling the system to: [0427] Allow setting of a weight loss rate, [0428] Continuously remove excess water in accordance with a set weight loss rate, [0429] Operate continuously at comparably low flow rates compatible with CRRT, and [0430] Balance ion equilibrium by means of proper dialysis being performed and/or by means of substitution fluid continuously being delivered at controlled flow rates.

[0431] Finally, in order to ready a CRRT apparatus as soon as possible given the acute situation of a patient requiring a treatment and given the absence of advance notice of the emergency situation requiring treatment, the CRRT machine is dressed using an integrated disposable set, wherein all the lines and the filtration unit are grouped together and already properly connected in the disposable set. Further, all the fluids are contained in pre-packaged bags (dialysis fluid or replacement fluids in bags of e.g., 2, 5 or 10 litres each) or pre-packaged syringes (heparin and/or concentrated calcium replacement solution).

[0432] The apparatus **1** of FIG. **1** has an extracorporeal blood circuit **17**, which takes blood from a patient P, for instance by means of a needle or a catheter or an implanted port or other access device (not shown), introduced into a vein or artery of said patient, and through the blood withdrawal line **6** takes said blood, for instance continuously, to the filtration unit **2**. The filtration unit **2** having a primary chamber **3** and a secondary chamber **4** separated by a semi-permeable membrane **5**; depending upon the treatment the membrane of the filtration unit may be selected to have different properties and performances.

[0433] The blood passes through the primary chamber **3** of the filtration unit **2** and, through the blood return line **7**, the treated blood is carried back to the patient. In the example of FIG. **1**, the connection with an anticoagulant line **51** is provided immediately downstream from the blood collecting zone on the blood withdrawal line **6**. In particular, the machine is equipped with source of regional anticoagulant **10**, such as at least a secondary fluid container or bag for supplying the anticoagulant line **51**; by using corresponding actuator/s for conveying fluid, in the example shown comprising an anticoagulant pump **54**, for instance a peristaltic pump, it is possible to control the fluid flow within said line by introducing the regional anticoagulant directly into the blood with a direct connection to the blood withdrawal line **6**. After defining a direction of fluid (blood) circulation **200** (during normal use of the apparatus) from the blood withdrawal line **6** towards the filtration unit **2** and from the latter through the blood return line **7** towards the patient P, a known blood pressure sensor **48**, which shall not be described in further detail, is placed immediately downstream the anticoagulant line **51**. The blood circuit **17** comprises actuator/s for conveying fluid, i.e. in this particular case at least a blood pump **21** for controlling and managing the suitable blood flow Q_b in the circuit. Also the blood pump **21** is generally a peristaltic pump acting either on the blood withdrawal line (as shown e.g. in FIG. **1**) or on the blood return line. An operator may enter a set value for the blood flow rate Q_b through a user interface **15** and the control unit **12**, during treatment, is configured to control the blood pump based on the set blood flow rate. Note that, alternatively, the blood pump **21** may be automatically controlled with no need of user input/prescription: in that case control unit **12** may control the blood pump **21** at a prefixed flow rate or at a flow rate calculated based on other parameters such as, for instance, other flow rates and

constraints set by the medical operator (as apparent from the following description). In addition, or alternatively, the blood pump may also be controlled based on pressure; if the blood pump **21** is controlled based on the pressure signal detected upstream the blood pump then a pressure sensor **48** is present in the tract of bloodline upstream the blood pump **21**: for instance the control unit **12** may be designed to drive the blood pump in a manner to keep the pressure detected by pressure sensor **48** within a prefixed range, or below a prefixed threshold. Following the direction of blood circulation, a gas exchanger **46** for removing CO_2 from circulating blood may be connected to the blood circuit. The gas exchanger **46** is in fluid communication with the blood circuit **17** to receive extracorporeal blood, allow CO_2 removal from blood and returning blood to the blood circuit at a downstream point. FIG. **1** shows a gas exchanger **46** placed upstream the filtration unit **2**; however, the gas exchanger may be alternatively positioned downstream the filtration unit along blood circulation direction. As mentioned, blood circulation direction during normal use of the apparatus is indicated in FIG. **1** with an arrow **200** which also represent the blood flow rate Q_b direction during treatment. The gas exchanger **46** is connected in series with the filtration unit **2** and is placed downstream the injection point **50** where the regional anticoagulation solution is delivered to extracorporeal blood. The gas exchanger **46** has a blood chamber and a gas chamber separated by a membrane permeable to gases, in particular CO_2; the gas exchanger comprise a gas inlet, which can be connected to a gas source, such as the medical gas supply system in a hospital to receive pressurized air or oxygen for example, and a gas outlet in fluid communication with the gas chamber to discharge exhausted gas having removed CO_2 from extracorporeal blood. The blood inlet and the blood outlet put the extracorporeal blood circuit **17** in fluid communication with the gas exchanger blood chamber.

[0434] Then, the blood passes through another pressure sensor **49** controlling the correct flow within the blood circuit. After passing through the primary chamber **3** of the filtration unit **2**, where the suitable exchanges of substances, molecules and fluids occur by means of a semipermeable membrane, the treated blood enters the blood return line **7**, first passing through the air separator **19**, commonly known as "bubble trap", designed so as to ensure the detection and removal of air bubbles present in the blood. The treated blood getting out of the air separator **19**, before being returned to the patient P passes through an air bubble sensor **55** verifying the absence of said dangerous formations within the treated blood that has to be re-introduced in the patient's blood circulation. Immediately downstream from the bubble sensor **55**, the safety valve **20** (or venous clamp) is placed which, in case of alarm, can block the blood flow towards the patient. In particular, should the bubble sensor **55** detect the presence of anomalies in the blood flow, the machine through safety valve **20** would be able to block immediately the passage of blood so as to avoid any consequence to the patient. A corresponding safety valve **27** (or arterial clamp) is present on the blood withdrawal line close the patient vascular access to fully isolate the patient from the extracorporeal blood circuit in case of need. Downstream from the safety valve **20**, the treated blood is then carried back to the patient P undergoing therapy. The extracorporeal blood treatment apparatus of FIG. **1** is equipped with a dialysis fluid circuit **32**, which is also provided with at least a dialysis supply line **8** leading into the filtration unit **2** and with an effluent (or dialysate) line **13** from the filtration unit. At least a primary fluid container, defining said dialysis liquid source **14**, is designed to supply the supply line **8** of the dialysis fluid circuit **32** (generally the primary fluid container shall consist of one or more bags containing a suitable dialysis liquid). The supply line **8** includes actuator/s for conveying fluid such as at least a dialysis fluid pump **25** (in the embodiment of FIG. **1** a peristaltic pump) for controlling the flow rate Q_{dial} of dialysis liquid from the bag and for defining a direction **200** of dialysis fluid circulation. Downstream from the dialysis fluid pump **25** in the direction of circulation **200** there is a branching **56** splitting the dialysis supply line **8** up into an intake branch **57** and an infusion branch **58**. In particular, the infusion branch **58** is connected to the blood return line **7** of the blood circuit **17**. In other words, by means of said infusion branch **58** it is possible to obtain a post-infusion directly in the blood line **17** using the content of the primary fluid container. Conversely, the intake branch **57** conveys the fluid directly to the filtration unit **2** and in particular to the secondary chamber of said unit. The dialysis fluid circuit **32** is further equipped with a selector **59** for determining the percentages of fluid flow within the infusion branch **58** and the intake branch **57**. Generally said selector **59**, usually placed near the branching **56**, can be positioned at least between a first operating condition in which it allows the passage of fluid in the intake branch **57** and blocks the passage in the infusion branch **58**, and a second operating condition in which it allows the passage of fluid in the infusion branch **58** and blocks the passage in the intake branch **57**. In other words, said selector **59** may consist of a valve element operating on the dialysis fluid circuit **32** by alternatively blocking the passage of fluid in either branch. Suitable selectors may be alternatively provided, which are able to establish a priori the amount of liquid that has to pass through both branches simultaneously. It will also be possible to vary the percentages of fluid in either branch as a function of time and of the pre-established therapies. The dialysis liquid through the intake branch **57** gets into the secondary chamber **4** of the filtration unit **2**. In particular, the primary chamber **3** through which the blood flow passes is separated from the secondary chamber **4** through which the dialysis liquid passes by means of the semipermeable membrane **5** ensuring the suitable passage of the dangerous substances/molecules and of fluid from the blood towards the dialysis liquid mainly by means of convection and diffusion processes, and also ensuring through the same principles the passage of substances/molecules from the dialysis liquid towards the blood. The dialysis fluid then gets into the effluent line **13** and passes through a suitable effluent pressure sensor **60**. An actuator is provided for conveying fluid, for instance a dialysate pump **26** controlling the flow rate Q_{eff} in the effluent line **13** within the fluid circuit **32**. Also said pump will generally be a peristaltic pump. The fluid to be eliminated then passes through a blood detector **61** and is conveyed into a collection container or bag **62**. The hydraulic circuit of the apparatus according to FIG. **1** includes at least another infusion line **63** for feeding fluid into the blood return line **7** of the blood circuit **17**. In particular, the infusion fluid is taken from at least an auxiliary container **64** and is sent directly to the blood return line **7** of the blood circuit **17** through actuator/s for conveying fluid, generally an infusion pump **65** (in the example a peristaltic pump) controlling its flow rate Q_{rep}−total replacement flow rate. In particular, the infusion liquid can be introduced directly into the air separator **19**. As can also be inferred, the infusion branch **58** of the dialysis fluid circuit **32** and the infusion line **63** are equipped with a common end length **66** letting fluid to enter into the blood circuit **17**. Said intake end length **66** is placed downstream from the infusion pump **65** with respect to a direction of infusion and carries the fluid directly into the air separator **19**. Further, referring to the diagram in FIG. **1**, the infusion line **63** comprises at least a pre-infusion branch **67** connected to the blood withdrawal line **6** of the blood circuit **17**. In further detail, downstream from the infusion pump **65** with respect to the direction of infusion, there is an infusion branching **68** splitting the infusion line **63** up into the pre-infusion branch **67** and post-infusion branch **69**. The pre-infusion branch **67**, in particular, carries the fluid taken from the bag **64** into the blood withdrawal line **6** of the blood circuit **17** downstream from the blood pump **21** and downstream the gas exchanger **46** with respect to the direction of blood circulation. Conversely, the post-infusion branch **69** is connected directly to the common end length **66**. The infusion line **63** further comprises a selector **70** for determining the percentage of liquid flow to be sent to the post-infusion branch **69** and to the pre-infusion branch **67**. The selector **70** placed near the branching **68** may be switched between at least a first operating condition in which it allows the passage of fluid in the pre-infusion branch **67** and blocks the passage in the post-infusion branch **69**, and at least a second operating condition in which it allows the passage of fluid in the post-infusion branch **69** and blocks the passage in the pre-infusion branch **67**. Obviously, as in the case of the selector **59** present on the dialysis fluid circuit **32**, also the other selector **70** will be able to determine the percentage of fluid that has to pass in each of the two branches and to possibly vary it in time in accordance with the planned therapies. Moreover, the selector **59** and the other selector **70** will generally, though not necessarily, be of the same nature. Notably, the flow rate through the pre-infusion branch/line **67** may be determined by proper control of the infusion pump **65** and other selector **70**; the control unit **12** may receive a pre-infusion ratio of replacement fluid flow PRE (a value between 0 and 1) and determine the pre-infusion flow rate $Q_{rep.pre}$ based on the pre-infusion ratio PRE and on total replacement flow rate Q_{rep}. In particular, $Q_{rep.pre}=PRE.Math.Q_{rep}$. Alternatively, post-infusion ratio may be used symmetrically, or a ratio between pre- and pos-infusion rate may be used as well ($R3=Q_{re.pre}/Q_{rep.post}$).

[0435] The apparatus is equipped with means **71** for determining at least the weight of the primary fluid container **14** and/or of the auxiliary fluid container **64** and/or of the regional anticoagulant container **10** and/or of the collection container **62**. In particular, said means **71** comprises weight sensors, for instance respective scales A, B, C, D and E (for example at least an independent sensor for each fluid bag associated to the machine). In particular, there will be at least four of said scales, each pair being independent from the other, and each one measuring the respective weight of a

bag. It should then be pointed out that there is a control unit or CPU **12** active (at least) on the blood circuit **17** and in particular active on the pressure sensor **48** for reading pressure values, on the blood pump **21**, on the gas exchanger **46**, on the other pressure sensor **49**, and on the device for detecting the presence of air bubbles **55** and on the respective safety valves **20**, **27**. The control unit **12** has also to control the dialysis fluid circuit **32** and, in particular, shall be input with the data detected by the scales A, B, C, D and (possibly) E and, concerning the weight of the bag **14**, and shall act on the pump **25**, on the selector **59**, on the pressure sensor **60**, then on the dialysate pump **26** and shall eventually receive the data detected by the scale A whose function is to determine the weight of the collection container **62**. The control unit **12** shall also act on the infusion line **63** checking the weight of the auxiliary container **64** (checked by the scale C) and will be able to control both the infusion pump **65** and the other selector **70**. The control unit **12** shall also act on the anticoagulant line **51** detecting the weight of the anticoagulant fluid container **10** by means of the scale B and suitably controlling the anticoagulant pump **54** according to the treatments to be carried out as below detailed and explained. As apparent, a regional anticoagulation system is implemented in the apparatus **1** of FIG. **1** to provide anticoagulation restricted to the extracorporeal blood circuit **17**. The regional anticoagulation system is described in detail in the respective description paragraph. However, the apparatus of FIG. **1** may be alternatively (or additionally) provided with a systemic anticoagulation system, such as a syringe pump **9** for injecting heparin downstream the blood pump **21**. Indeed, the algorithm of embodiments the invention as described in the subsequent detailed description works both in CRRT treatment configurations with RCA and in CRRT treatment configurations with systemic (or no) anticoagulation without RCA.

[0436] The control unit **12** is also connected to a memory **16** and to user interface **15**, for instance a graphic user interface, which receives operator's inputs and displays the apparatus outputs. For instance, the graphic user interface **15** may include a touch screen, a display screen and/or hard keys for entering user's inputs or a combination thereof.

The Regional Anticoagulation System

[0437] A regional anticoagulation system comprises a source of regional anticoagulant **10**, e.g., a container or a bag containing at least a substance having an anticoagulant effect. For example, citrate, in the form of pure sodium citrate (Na.sub.3citrate) or mixture of sodium citrate and citric acid are used for blood anticoagulation purpose. Alternatively pure citric acid may be used as anticoagulant. Indeed, citrate has a high affinity for calcium in creating complexes and several steps of the coagulation cascade are dependent on blood (ionized) calcium. A proper decrease of ionized calcium concentration in the presence of citrate inactivates the coagulation cascade.

[0438] Normal plasma includes about 1.1 to 1.3 mmol/l of ionized calcium, 0.1-0.2 mmol/l of complexed calcium and 0.9 to 1.2 mmol/l of protein-bound calcium. In order to achieve proper anticoagulation effects, general guidelines are to adjust citrate amount/dose as to reach an ionized calcium concentration of 0.20 to 0.35 mmol/l in the extracorporeal blood circuit after citrate infusion. Plasma with citrate addition for anticoagulation purposes would include (as an average) about 0.3 mmol/l of ionized calcium, 1.8 mmol/l of complexed calcium (mainly Ca.sub.3citrate.sub.2) and 0.2 mmol/l of protein-bound calcium. During RCA, intensity of anticoagulation can be adjusted via the amount of infused citrate. Post-filtration unit ionized calcium concentration is commonly used as key parameter (target in the 0.20-0.35 mmol/l range) and is measured e.g., with blood gas analyzer.

[0439] The regional anticoagulation system is arranged to deliver the regional anticoagulant at a delivery point **50** in the extracorporeal blood circuit **17**. Citrate infusion is preferably administered close to an access end of the blood withdrawal line **6** to get full anticoagulation of the extracorporeal blood circuit **17**. In general the delivery point **50** is located upstream the blood pump **21**; however, it is not excluded that the delivery point **50** is located in the blood withdrawal line **6** downstream the blood pump. Alternatively, or in combination, the delivery point **50** for citrate may be the inlet of the filtration unit **2**. In this latter configuration, the dialysis fluid contains citrate in an amount sufficient to achieve ionized calcium level around 0.25-0.35 mmol/l in blood circuit downstream the dialyzer. Citrate may be added to the treatment fluid flowing along the supply line **8** using a corresponding concentrate bag/container in case the dialysis fluid is on-line prepared as in current apparatuses for chronic treatment. Alternatively, particularly in case of CRRT apparatuses, the source **14** for dialysis fluid is a container/bag including the proper citrate concentration or content.

[0440] Commercial citrate solutions are generally packed in respective plastic bags (sources **10**) and can be split between physiologic and concentrated solutions. Physiologic citrate solutions are solutions having sodium concentration about 140 mmol/l, such as Baxter PrismoCitrate 10/2 (with 10 mmol/l Nacitrate and 2 mmol/l citric acid) and Baxter RegioCit 18/0 (with 18 mmol/l Nacitrate). Concentrated citrate solutions are for example, ACD-A (Anticoagulant Citrate Dextrose Solution) from Biomet: mix of sodium citrate (75 mmol/l), citric acid (38 mmol/l) and glucose; and Citrate 4% from Fresenius: citrate 136 mmol/l.

[0441] When citrate is infused into the blood withdrawal line **6** close to the patient vascular access, blood pump speed is automatically adjusted as to take the operator set blood flow rate from access site (blood pump speed=k*(Q.sub.b+Q.sub.cit), wherein Q.sub.b is the set (or calculated) blood flow rate—desired at the access site and Q.sub.cit is the citrate infusion flow rate). Citrate amount is prescribed through the 'Citrate Dose' parameter (D.sub.citrate) which is the amount of citrate per liter of blood treated (mmol/l blood). Notably, citrate dose does not match with citrate concentration in the diluted blood reaching the filtration unit. The concept is rather to provide for an amount of citrate in proportion to the amount of calcium to be chelated. The set of the citrate pump **54** is:

[00033] $Q_{cit} = \frac{D_{cit}}{C_{cit,PBP}}$ .Math. Q_b (Eq. 1) [0442] wherein [0443] Q.sub.cit is the citrate infusion flow rate; [0444] Q.sub.b is the set blood flow rate; [0445] D.sub.cit is the citrate dose; and [0446] C.sub.cit_pbp is the citrate concentration in the anticoagulant source. This is the citrate flow rate mathematical relation which is stored in the memory **16** of the control unit **12** and used to determine the citrate infusion flow rate Q.sub.cit given the citrate dose D.sub.cit and citrate concentration in the anticoagulant source **10** as input. Blood flow can be either an input value (prescription parameter) or a calculated value (operating parameter) that the control unit determines based on the system configuration and prescription parameters (see the following detailed description).

[0447] Citrate infusion is delivered with a dosage aimed to maintain ionized calcium level around 0.25-0.35 mmol/l in blood circuit downstream the dialyzer. Typically, citrate dose is included in the range 1.5 to 6.0 mmol/l-of-blood. The most common range is 2 to 4 mmol/L-of-blood. Citrate dose guideline of 3.0 mmol/L-of-blood is globally followed.

[0448] Ionized calcium and citrate complexes are rather small molecules which are easily transferred through the filtration unit **2**. Loss rates are basically dependent on flow rates, filter efficiency with respect to small molecules and solute concentrations. While about half of the total calcium is not available to mass transfer during standard anticoagulation (since it is protein-bound), about 90% of total calcium becomes available during citrate anticoagulation. Therefore, citrate regional anticoagulation combined with the use of calcium free dialysis and/or replacement fluids implies significant calcium losses to dialysate. In extracorporeal blood treatments with RCA, calcium infusion is required to balance calcium losses to dialysate. During RCA, calcium infusion is adjusted to keep patient systemic ionized calcium in the normal range (e.g., 1.0-1.2 mmol/l).

[0449] Therefore, the regional anticoagulation system of the apparatus **1** includes a source of ion balancing solution **11**, which is reinfused in the blood, either in the return line **7**, in particular close to the venous vascular access, or directly into the patient P (infusion into central catheter, which is recommended). The ion balancing solution **11** is contained in a vessel e.g., a syringe, a container or a bag; the regional anticoagulation system of the apparatus **1** comprises a ion replacement infusion line **74** and a corresponding ion replacement pump **75** to drive delivery of a proper ion replacement infusion rate Q.sub.ca. FIG. **1** shows a line **74** directly infuse in the blood return line **7**, possibly close to the venous access. Of course, line **74** may alternatively directly infusing into the patient P. In the example of FIG. **1**, the syringe pump **9** usually used to deliver heparin may be alternatively used to deliver the ion balancing solution either directly into the patient or alternatively in the blood return line. The ion balancing solution includes ionized (concentrated) calcium and its infusion is performed to restore patient systemic ionized calcium at normal level. Notably, ion balancing solution may include also ionized magnesium and its infusion is performed to restore patient systemic ionized magnesium at normal level since also magnesium removal in dialysate is increased during RCA. The ion replacement infusion rate Q.sub.ca may be adjusted based on the revealed patient

ionized calcium concentration in blood or an automatic control may be implemented, such as the one described in patent publication U.S. Pat. No. 8,668,825B2 (which is here incorporated by reference).

[0450] In an implementation, the ion balancing solution flow rate is kept proportional to the estimated calcium loss rate in dialysate. For example it is computed by the apparatus control unit through the equation (calcium flow rate mathematical relation):

[00034] $$Q_{ca} = \frac{CaComp \cdot J_{Ca}}{C_{ca}} - \frac{Q_{rep.post} \cdot C_{ca_{rep.post}}}{C_{ca}} - \frac{Q_{HCO3} \cdot C_{ca_{HCO3}}}{C_{ca}} \quad (Eq.\, 2)$$

[0451] Where CaComp is a calcium compensation parameter, Q_{ca} is the ion balancing solution flow rate (ml/h), J_{ca} is the estimated calcium loss rate in the dialysate (mmol/h), C_{ca} is calcium concentration of the ion balancing solution (mmol/l), $Q_{rep.post}$ is the post-dilution replacement flow rate (ml/h), $C_{ca\_rep.post}$ is calcium concentration of the replacement solution in post-dilution (mmol/l), Q_{HCO3} is the fluid flow rate (ml/h) through the post-dilution bicarbonate infusion line **23**, and C_{ca_HCO3} is the calcium concentration in the bicarbonate container. Calcium compensation is the user-controllable setting, which might be set by the operator generally in a range between 5% and 200%.

[0452] Notably the above equation takes into account a post replacement solution including calcium, as well as bicarbonate infusion also including calcium. In case no calcium is in the post replacement solution (or no replacement solution is used) the second term of the equation should be disregarded (equal to zero). In case no calcium is in the bicarbonate replacement solution (or no bicarbonate solution is used) the third term of the equation should be disregarded (equal to zero).

[0453] The calcium flow rate mathematical relation is also used by the control unit **12** to determine the ion re-establishing flow rate Q_{ca} based on known (input) calcium concentration in the various post infused solutions. Further, it is assumed that no calcium is infused upstream the filtration unit **2** to avoid undesired coagulation effects (in this respect the anticoagulant solution does not contain any calcium and the pre-dilution infusion line **67** is absent or the replacement solution pre-infused is calcium free). Further, the ion compensating parameter is part of the prescription as well. The post infusion flow rates, namely $Q_{rep.post}$ and Q_{HCO3} are operating parameter and the control unit **12** determines them based on the prescription parameters and apparatus configuration. Also J_{ca} is estimated, for example as disclosed in the mentioned U.S. Pat. No. 8,668,825B2 application.

[0454] Alternatively, the medical staff may provide a 'calcium dose' D_{ca} in terms of calcium concentration in the effluent (mmol/l). The ion balancing solution flow rate Q_{ca} is calculated based on the set calcium dose taking into account calcium concentration of the ion balancing solution, calcium concentration of the replacement solution and estimated calcium concentration in blood at the outlet of the filtration unit **2**.

[0455] Indeed, as to dialysis fluid (and replacement solution), they are generally calcium free to prevent transferring ionized calcium to blood. Moreover, the dialysis and/or replacement fluids may have adapted buffer content due to citrate metabolism and adapted sodium if concentrated citrate solution (hypertonic) is used.

[0456] As to the buffer agent, since RCA has complex impact on acid-base balance equilibrium due to a significant fraction of citrate returned to patient (citrate is metabolized into bicarbonate), when assisting prescription, the control unit **12** would require input of a steady state acid-base balance target to be achieved. Indeed, blood returned to the patient contains a significant concentration of citrate-calcium complexes. These complexes are (quickly) metabolized in liver, skeletal muscles, kidney releasing calcium in the blood stream, thus preventing systemic anticoagulation to develop; the citrate metabolism produces bicarbonate (3 moles HCO_3 for 1 mole citrate).

[0457] In this respect, the dialysis fluid may contain no buffer agent, e.g., no bicarbonate. A buffer agent from a source/container/bag **64** may be infused into the blood return line **7** via a suitable buffer agent supply line **63**, **69**, **66** and the corresponding buffer agent pump **65**. Alternatively or in combination, to allow for acid-balance additional control, the apparatus **1** might also be designed to vary buffer balance of the extracorporeal blood circuit in an easy and controlled way via the possibility to set dialysis fluid (low) buffer concentration and/or to use source bags **14**, **64** with different buffer concentration, e.g., in the range 15 to 25 mmol/l (and up to 40 mmol/l and/or down to 0 mmol/l) for bicarbonate. As described, a specifically designed bicarbonate solution may be post-infused to allow for acid-base balance additional control (see e.g., FIGS. **4** to **6**).

[0458] As mentioned, citrate accumulation in the patient may correlate with hypocalcemia, metabolic acidosis (low bicarbonate production due to poor metabolism) or metabolic alkalosis (excessive bicarbonate production subsequent to high citrate load). As citrate measurement is not commonly available at the hospital, ratio of total calcium to ionized calcium is used as indicator, namely values below 2.5 are considered as normal (normal value below 2.0) and values above 2.5 indicate low ionized calcium concentration with respect to total calcium, possibly due to the presence of a significant systemic concentration of citrate. However, this monitoring is considered an insufficient measure, particularly in treatment involving relevant risks of acid/base unbalance, such as in RCA with 'large' flow rates, such as certain SCUF treatments.

SPECIFIC EMBODIMENTS

[0459] The embodiment of FIGS. **2** and **3** show different configurations of the apparatus **1** shown in FIG. **1**, where the same components described for the embodiment of FIG. **1** are also present and are identified by same reference numerals and thus not described again in detail.

[0460] The embodiment of FIG. **2** refers to a CRRT configuration with no or systemic anticoagulation. In particular, in case systemic anticoagulation is used, a heparin container (e.g., a syringe **9**) is used to inject boluses of anticoagulant into the withdrawal line **6** via a heparin line **22** usually infusing downstream the blood pump **21**. The embodiment includes a pre-blood-pump (PBP) line **52** for infusing a replacement solution (no citrate) contained in a PBP container **18** with a PBP pump **53** generating a pre-blood-pump infusion flow rate Q_{PBP}. Further, a post-infusion line is present for post-infusing a replacement solution contained in auxiliary container **64**. A dialysis liquid source **14** is also included to provide a dialysis fluid flow rate Q_{dial} to the second chamber **4** of the filtration unit **2**; an effluent fluid flow rate Q_{eff} is directed to the collection container **62** by means of the dialysate pump **26**. If we compare the embodiment of FIGS. **1** and **2**, we note that the embodiment of FIG. **2** lacks any ion balancing infusion line **74** (no regional anticoagulation is provided), that the fluid from liquid source **14** is directed to the dialyzer (selector **59** is configured to prevent any fluid to route to post-infusion) and that the replacement liquid from auxiliary container **64** is exclusively routed in post dilution (additional selector **70** is configured to prevent any fluid to route to pre-infusion).

[0461] Embodiment of FIG. **3** differs from the embodiment of FIG. **2** since it refers to a CRRT configuration with regional anticoagulation. No heparin syringe **9** is used. The container **10** is a source of regional anticoagulant (citrate) and the anticoagulant pump **54** generates a citrate infusion flow rate Q_{cit}. A corresponding ion balancing infusion line **74** and ion balancing pump **75** are included to infuse a calcium concentrated solution from the source of ion balancing solution **11** at a calcium infusion flow rate Q_{ca}.

[0462] The embodiment of FIG. **4** includes the same dialysis fluid circuit of embodiments 2 and 3. As already shown in embodiment 2, the embodiment of FIG. **4** refers to a CRRT configuration with no or systemic anticoagulation. Differently, a pre-infusion line, downstream the blood pump **21**, for infusing a replacement solution in pre-dilution is included. The pre-infusion line may be the infusion line **63** of FIG. **1**, wherein the other selector **70** is configured to direct all the replacement fluid coming from auxiliary container **63** in pre-dilution through pre-infusion branch **67**. Alternatively, a pre-dilution infusion line **29** delivering the replacement fluid contained in replacement source **30** is provided. The infusion pump **31** generates a pre-infusion replacement flow rate $Q_{rep.pre}$. Additionally, also a post-dilution bicarbonate infusion line **23** for concentrate bicarbonate solution is included. A bicarbonate pump **24** injects a bicarbonate concentrate solution from a bicarbonate container **28** at a bicarbonate concentrate post-infusion flow rate Q_{HCO3}.

[0463] The embodiment of FIG. **5** refers to a CRRT configuration with regional anticoagulation. No heparin syringe **9** is used. The container **10** is a source of regional anticoagulant (citrate) and the anticoagulant pump **54** generates a citrate infusion flow rate Q_{cit}. A corresponding ion balancing infusion line **74** and ion balancing pump **75** are included to infuse a calcium concentrated solution from the source of ion balancing solution **11** at a calcium infusion flow rate Q_{ca}. Further, a post-infusion line **63** is present for post-infusing a replacement solution contained in

auxiliary container **64**. Additionally, also a post-infusion line **23** for concentrate bicarbonate solution is included. A bicarbonate pump **24** injects a bicarbonate concentrate solution from a bicarbonate container **28** at a bicarbonate concentrate post-infusion flow rate Q.sub.HCO3.

[0464] FIG. **6** is another embodiment, wherein the apparatus includes all possible infusion lines, namely two separate pre-blood-pump infusion lines: one anticoagulant line **51** for citrate infusion (flow rate: Q.sub.cit), and one PBP infusion line **52** for pre-blood-pump replacement fluid infusion (flow rate: Q.sub.PBP), one pre-dilution infusion line **29** infusing replacement fluid from a replacement source **30** (e.g., a pre-packaged container) by means of a respective pre-infusion pump **31** (flow rate: Q.sub.rep.pre), one post-dilution infusion line **63** infusing from an auxiliary container **64** including a replacement solution (flow rate: Q.sub.rep.post), one post-dilution bicarbonate infusion line **23** (flow rate: Q.sub.HCO3), one ion balancing infusion line **74** for infusing a calcium concentrate solution (flow rate: Q.sub.ca), one dialysis supply line **8** for directing fresh dialysis fluid to the filtration unit (flow rate: Q.sub.dial) and one effluent line **13** for sending spent dialysate to a collection container **62** (flow rate: Q.sub.eff). In the embodiment of FIG. **6** the pre-infusion post-blood-pump line **29** and the post-infusion line **63** are shown as separate and independent lines; alternatively, the two lines **29**, **63** may be merged together as in the embodiment of FIG. **1**, wherein one single bag **64** provides the same replacement fluid to two branches one directing the fluid in pre-dilution, the other in post-dilution. The respective infusion fluid flow rates Q.sub.rep.post and Q.sub.rep.pre are obtained by properly driving the infusion pump **65** and the selector **70**: the flow from the single pump **65** is alternatively directed either to pre-infusion or to post-infusion via selector **70** over time; the control of the time spent in each of the two states allows to control the split of the flows between pre and post infusion. The desired flow values are obtained as average values over a certain period of time, which must naturally be long enough, i.e. at least several minutes.

[0465] Further, the two infusion lines **51** and **52** infusing fluids pre-blood-pump, may be substituted by a single line, used for citrate in case of regional anticoagulation, or for PBP replacement fluid in case of no or system anticoagulation.

[0466] Finally, it is noted that in case any line is missing in a specific circuit configuration, the corresponding flow rate may be omitted in any of the following formula/mathematical relations (or its value set to zero).

Equations for Flow Rates

[0467] The following equations for flow rates express the relations between the flow rates which are used in the detailed description. These equations are stored in the memory **16** of the apparatus. When necessary, the control unit **12** makes use of the following equations to determine the operative parameters (as explained in the following sections).

[0468] The plasma flow rate is function of blood flow rate as follows:

[00035] $Qp = Q_b$ .Math. $(1 - \text{Hct})$ (Eq. 3)

[0469] The plasma water flow rate is function of blood flow rate as follows:

[00036] $\text{Qpw} = \text{Qp}$ .Math. $F_p = Q_b$ .Math. $(1 - \text{Hct})$ .Math. F_p (Eq. 4)

[0470] The plasma water flow rate at the filter inlet is:

[00037] $\text{Qpw}_{inlet} = Qpw + Q_{cit} + Q_{syr} + Q_{PBP} + Q_{\text{rep .Math. pre}} = Q_b$ .Math. $(1 - \text{Hct})$ .Math. $\text{Fp} + Q_{cit} + Q_{PBP} + Q_{\text{rep .Math. pre}}$ (Eq. 5)

[0471] The blood water flow rate is function of blood flow rate as follows:

[00038] $Qbw = Q_b$ .Math. $[(1 - H\text{ct})$ .Math. $F_p + \text{Hct}$ .Math. $\text{Frbc}]$ (Eq. 6)

[0472] The blood water flow rate at the filter inlet is:

[00039]
$Qbw_{inlet} = Q_{bw} + Q_{cit} + Q_{syr} + Q_{PBP} + Q_{\text{rep .Math. pre}} = Q_b$ .Math. $[(1 - H\text{ct})$ .Math. $\text{Fp} + \text{Hct}$ .Math. $\text{Frbc}] + Q_{cit} + Q_{PBP} + Q_{\text{rep .Math. pre}}$ (Eq. 7)

[0473] The ultrafiltration rate in the filtration unit is:

[00040] $Q_{\text{fil}} = Q_{PBP} + Q_{cit} + Q_{syr} + Q_{\text{rep .Math. pre}} + Q_{\text{rep .Math. post}} + Q_{HCO3} + Q_{PFR} + Q_{ca}$ (Eq. 8)

[0474] In case one single infusion line **63** (as in FIG. **1**) is used, the pre-infusion rate of replacement fluid may be calculated based on the (total) replacement flow rate (Q.sub.rep) delivered by infusion pump **65** times a pre-replacement fluid flow factor (PRE) is:

[00041] $Q_{\text{rep .Math. pre}} = \text{PRE}$ .Math. $Q_{rep} \quad Q_{rep} = (Q_{\text{rep .Math. pre}} + Q_{\text{rep .Math. post}})$ (Eq. 9)

[0475] The effluent flow rate is:

[00042] $Q_{\text{eff}} = Q_{PBP} + Q_{cit} + Q_{syr} + Q_{dial} + Q_{\text{rep .Math. pre}} + Q_{\text{rep .Math. post}} + Q_{HCO3} + Q_{PFR} + Q_{ca} = Q_{dial} + Q_{\text{fil}}$ (Eq. 10)

Clinical Prescription Parameters

[0476] Clinical prescription parameters are the parameters that the CRRT apparatus requires from the medical staff when initiating or updating treatment prescription on a specific patient. The apparatus may either request the physician to input the prescription parameter or provide a suggested value to be confirmed or updated. Prescription parameters to be confirmed/updated may be read from patient cards or similar supports.

[0477] Purpose of the 'assisted prescription' process is to operate from prescription parameters being fully meaningful from the clinical perspective; selected prescription parameters of interest are listed in next table.

TABLE-US-00002

Symbol	Parameter name	Clinical aspect
D.sub.CRRT	CRRT dose (ml/kg/h)	Defines intensity of the RRT treatment
D.sub.cit	Citrate dose (mmol/L)	Intensity of citrate anticoagulation (RCA)
CaComp	Calcium compensation (%)	Intensity of calcium balancing (RCA)
D.sub.ca	Calcium dose (mmol/l)	
C.sub.p.sub.HCO3.sub.—.sub.pat	Steady patient bicarbonate (mM)	Steady state acid-base balance target
nNBL	Normalized Net Buffer Load (mmol/h/kg)	(either C.sub.p.sub.HCO3.sub.—.sub.pat or nNBL)
Q.sub.PFR	Patient Fluid Removal rate (ml/h)	Patient fluid balance
Q.sub.b	Blood flow rate (ml/min)	Optional; see below

[0478] Not all the above mentioned clinical prescription parameters are necessary/required, but their relevance depends on selected treatment options and medical staff preferences.

[0479] For example, blood flow rate listed in the table may be used as prescription parameter (set by medical staff) or as operating parameters (set by the system algorithm) according to the customer preference as hereinafter described.

[0480] Citrate dose and calcium compensation are relevant in case of regional anticoagulation treatments and not necessary in case of no or systemic anticoagulation.

[0481] Patient fluid removal rate may be entered as a prescription or, alternatively, may be calculated by the control unit.

[0482] In general, CRRT dose is the 'running' dose which has to be derived from the clinical target (20 to 25 ml/kg/h according to KDIGO guidelines) corrected for system down times; this leads to a recommended running dose in the 25-30 ml/kg/h range. The CRRT dose is further explained in the following paragraph.

[0483] As previously indicated, citrate dose controls the intensity of anticoagulation; it should be adjusted as to decrease ionized calcium concentration in the extracorporeal blood circuit down to the 0.2-0.35 mM range. In parallel, calcium compensation controls the balancing level of calcium losses relatively to a computed default loss rate; alternatively to a percentage, calcium balancing may be prescribed as a concentration of calcium in effluent (calcium dose D.sub.ca). Steady state acid-base balance target is either defined as a steady state patient bicarbonate concentration (requiring an assumption on nNBL), or as normalized Net Buffer Load (requiring an assumption on bicarbonate concentration). Second option is normally preferred. At steady state, nNBL is expected to balance the protons (H+) generation rate from patient metabolism. The steady state acid-base balance target is further discussed in the following paragraphs. Patient fluid removal prescription directly derives from the analysis of the patient fluid balance, considering all patient's fluid inputs and outputs, as well as the desired correction of patient's fluid status. It is clear that setting

the patient fluid removal rate may be preferred; however, the setting of another fluid flow rate may allow to determine patient fluid removal rate as a consequence (e.g., setting effluent flow rate and using Eq. 10 having knowledge of the infusion flow rates and dialysis flow rate).

[0484] Blood flow rate is not expected to have any strong clinical background aside some technical considerations on the patient's vascular access. If chosen as prescription parameter, the medical prescription may either provide a desired set value or simply define lower and/or upper limit(s) of the blood flow rate setting range.

CRRT Dose Definitions

[0485] In the present specification, CRRT dose refers primarily to a flow rate or to a combination of flow rates (expressed then in ml/h). It is however noted that an additional definition of treatment dose in CRRT is expressed in ml/kg/h, meaning the normalisation of a flow rate (or combination of flow rates) to patient body weight (BW). Particularly for infants, literature CRRT dose also refers to a treatment dose normalised to patient Body Surface Area (BSA).

[0486] Dose (aside from its 'normalisation' to patient size) can be defined as a combination of the flow rates in the most general way, with following examples: [0487] effluent dose (D.sub.eff): Q.sub.eff as perfect typical (and simple) example of field practice, [0488] convective dose (D.sub.conv): sum of all infusion flow rates to blood circuit or patient plus patient fluid removal rate, [0489] diffusive dose (D.sub.dial): dialysis flow rate Q.sub.dial, [0490] all above doses corrected for blood (or plasma) pre-dilution upstream the filter [0491] urea dose (D.sub.urea): estimated urea clearance, [0492] clearance dose (D.sub.sol): any dose computed on the basis of an estimated clearance of a given solute (=>expression function of all flow settings and of dialyzer/filter related parameters).

Formulae for CRRT Dialysis Dose

[0493] All below expressions of Dose are not normalised to patient size (body weight BW or patient surface area PA); expressions of normalised dose (NDose) can be directly expressed as:

NDose=Dose/BW; or

NDose=Dose/BSA×1.73 (when normalised to a 1.73 m.sup.2 surface area patient−Body Surface Area; see paediatric literature)

For example, one of the following magnitudes may be used as dose: [0494] effluent dose (D.sub.eff): the flow rate across the effluent line, namely D.sub.eff=Q.sub.eff; [0495] convective dose (D.sub.conv): the sum of the flow rates through the infusion line or lines connected directly to the patient or connected to the blood circuit and of the patient fluid removal rate, namely

$$[00043] D_{conv} = Q_{PBP} + Q_{cit} + Q_{syr} + Q_{rep\,.Math.\,pre} + Q_{rep\,.Math.\,post} + Q_{PFR} + Q_{ca} + Q_{HCO3}, or\, D_{conv} = Q_{fil}$$

[0496] of course, in case one or more lines are absent, the corresponding flow rate term/s may be absent from the definition or the value/s set to 0; [0497] diffusive dose (D.sub.dial): the flow rate of fluid supplied to the filtration unit secondary chamber, namely D.sub.dial=Q.sub.dial. [0498] urea dose (D.sub.urea): estimated urea clearance (K.sub.urea); note that in CRRT conditions, a first approximated expression assumes that filter urea clearance is more or less identical to effluent flow rate Q.sub.eff; in a further alternative, an estimate of urea clearance more accurate than Q.sub.eff, especially when operating with large flow rates or small filters (paediatric conditions), may be provided by the following equations: [0499] a) For purely diffusive mode (where there is no infusion of replacement fluid and where the patient fluid removal rate is zero or substantially zero) and counter-courant flow configuration (fluids in the chambers of the filtration unit **2** are counter-current):

$$[00044]\ Z = \frac{Q_{bw_{inlet}}}{Q_{dial}} NT = \frac{(\frac{S}{RT})urea}{Q_{bw_{inlet}}}\ (Eq.11)\ D_{urea}(Q_{bw_{inlet}}; Q_{dial}) = K_{urea} = Q_{bw_{inlet}}\,.Math.\,\frac{e^{[NT\,.Math.\,(1-Z)]}-1}{e^{[NT\,.Math.\,(1-Z)]}-Z} if Z \neq 1$$

$$D_{urea}(Q_{bw_{inlet}}; Q_{dial}) = K_{urea} = Q_{bw_{inlet}}\,.Math.\,\frac{NT}{NT+1} if Z = 1$$

[0500] where: S (effective filter surface area) is dependent on the hemodialyzer (i.e. the filtration unit **2)** in use; RT is total mass transfer resistance dependent of the hemodialyzer in use (membrane properties, filter design) and the solute of interest, in this case urea; note that S/RT is also the mass transfer property of the filtration unit, namely K0.A (ml/min) and Qbw.sub.inlet is the blood water flow rate at the inlet of the filtration unit **2**, [0501] b) In case of presence of both dialysis fluid flow rate, Q.sub.dial, and of one or more infusions of fluid, then:

$$[00045]\ = e^{\frac{SC_{urea}\,.Math.\,Q_{fil}}{(S/RT)_{urea}} - 1}\ (Eq.12)\ f_{urea} = (\frac{Q_{bw_{inlet}} - SC_{urea}\,.Math.\,Q_{fil}}{Q_{bw_{inlet}}}\,.Math.\,\frac{Q_{dial} - SC_{urea}\,.Math.\,Q_{fil}}{Q_{dial}})^{1}$$

$$D_{urea}(Q_{bw_{inlet}}; Q_{dial}; Q_{fil}) = K_{urea} = \frac{Q_{bw_{inlet}}\,.Math.\,Q_{dial} - f_{urea}\,.Math.\,(Q_{bw_{inlet}} - SC_{urea}\,.Math.\,Q_{fil})\,.Math.\,(Q_{dial} - SC_{urea}\,.Math.\,Q_{fil})}{Q_{dial} - f_{urea}\,.Math.\,(Q_{bw_{inlet}} - SC_{urea}\,.Math.\,Q_{fil})}$$

[0502] where: S (effective filter surface area) is dependent on the hemodialyzer in use; RT is total mass transfer resistance dependent of the hemodialyzer in use (membrane properties, filter design) and the solute of interest, in this case urea; Q.sub.fil is the ultrafiltration rate in CRRT filter; and Qbw.sub.inlet is the blood water flow rate at the inlet of the filtration unit **2**. SC.sub.urea is the sieving coefficient for urea (dependent of selected filtration unit). [0503] clearance dose: an estimated clearance for a given solute; for certain solutes a first approximated expression assumes that filter solute clearance is more or less identical to effluent flow rate Q.sub.eff; alternatively solute clearance may be estimated as function of all flow settings and of dialyzer/filter related parameters; alternatively appropriate sensors could be placed to measure conductivity or concentration and thereby allow calculation of an actual clearance for a given solute (e.g. sodium), for instance using one of the methods described in EP patent n. 0547025 or EP patent n. 0658352 or EP patent n. 0920887 (which are here in incorporated by reference). In a further alternative the equations of above paragraphs a) and b) as described for the urea clearance could be used with RT (K0.A) and SC.sub.xxx adapted to take into account the specific solute 'xxx'.

[0504] In the course of the following description reference will be made to the above dose definitions which are relating to doses not normalized to patient body weight (BW) or patient surface area (BSA). Of course the same principles and formulas below described could be normalized to body weight or patient surface area by dividing the dose value by either body weight BW or surface area BSA. The examples at the end of the description comprise normalized CRRT doses and the patient weight.

[0505] Furthermore, the above defined doses could be corrected to take into account the predilution effect, when a fluid replacement line is present upstream the treatment unit, such as lines **51** and **67** in the enclosed drawings. Each of the above defined doses could be corrected multiplying the dose value times a dilution factor F.sub.dilution:

$$[00046] Dose_{corr\_xxx} = F_{dilution}\,.Math.\,D_{xxx}\ (with xxx = eff, conv, dial, etc);$$

[0506] The dilution factor F.sub.dilution may be defined according to one of the following:

$$[00047]\ Blood\,dilution\,factor: F_{dilution_{blood}} = \frac{Q_b}{Q_b + Q_{rep\,.Math.\,pre} + Q_{PBP} + Q_{cit} + Q_{syr}}\ (Eq.13)$$

$$Plasma\,dilution\,factor: F_{dilution_{plasma}} = \frac{Q_p}{Q_p + Q_{rep\,.Math.\,pre} + Q_{PBP} + Q_{cit} + Q_{syr}}\ (Eq.14)$$

$$Plasma\,water\,dilution\,factor: F_{dilution_{pw}} = \frac{Q_{pw}}{Q_{pw} + Q_{rep\,.Math.\,pre} + Q_{PBP} + Q_{cit} + Q_{syr}}\ (Eq.15)$$

$$Blood\,water\,dilution\,factor: F_{dilution_{bw}} = \frac{Q_{bw}}{Q_{bw} + Q_{rep\,.Math.\,pre} + Q_{PBP} + Q_{cit} + Q_{syr}}\ (Eq.15')$$

[0507] Where Q.sub.cit and/or Q.sub.PBP and/or Q.sub.rep.pre and/or Q.sub.syr in above equations is absent or negligible, the corresponding term may be cancelled (or set to 0). In the entire application, whenever a term in a formula is negligible (usually this applies to syringe flow rate, but not exclusively to it, the term may be neglected, i.e., its value considered 0 or the term removed. In practice, the effluent dose corrected for the predilution effect would be: Dose.sub.corr_eff=F.sub.diluition×D.sub.eff.

[0508] F.sub.dilution factor shall be selected according to the solute distribution and ability to move through red blood cells membrane (example: creatinine with slow diffusion through red blood cells=>plasma dilution factor).

[0509] For example, in case the urea dose (D.sub.urea) is assumed to be more or less identical to effluent flow rate and as urea is distributed in whole blood and can transfer quickly through the red blood cells membrane, the correction factor to consider for predilution shall refer to whole blood. Accordingly:

[00048] $D_{urea\_corr} = F_{\text{dilution}_{blood}}$ .Math. $K_{urea} = \dfrac{Q_b}{Q_b + Q_{rep.Math.\,pre} + Q_{PBP} + Q_{cit} + Q_{syr}}$ .Math. Q_{eff} (Eq. 16)

[0510] More sophisticated equations can provide for a more accurate estimate of urea clearance (K.sub.urea) than Q.sub.eff (as previously indicated in Eq. 11 and 12), especially when operating with large flow rates or small filters (paediatric conditions).

Buffer Load Definition

[0511] Net buffer load during extracorporeal therapies (J.sub.buffer_load) is defined as the combination of (one or more of): [0512] Bicarbonate generated from the metabolism of citrate infused to the patient (J.sub.met_cit) and/or of lactate infused to the patient (J.sub.met_lact)—more in general generated from metabolism of all bicarbonate precursors, [0513] Bicarbonate balance from the extracorporeal blood therapy (J.sub.HCO3_bal) which may match with net loss or net gain for the patient, [0514] Acid infusion from e.g., citric acid content of the anticoagulant solution (J.sub.H+), when relevant.

[0515] From the mathematical point of view, the general definition of net buffer load is:

[00049] $J_{\text{buffer\_load}} = J_{met\_cit} + J_{HCO3_{bal}} (+J_{met\_lact}) - J_{H+}$ (Eq. 17)

[0516] By convention, net buffer load is positive in the case extracorporeal blood therapy provides for a net gain in buffer/bicarbonate to the patient, and negative in the case of loss in buffer.

[0517] From a physiologic perspective, the extracorporeal blood therapy is expected to provide for a net buffer gain to the patient, as to balance the metabolic production of protons (proteins metabolism). However, a net buffer loss may be desirable in the scenario where the patient initiates the therapy in the situation of (severe) metabolic alkalosis.

[0518] Buffer balance parameter is derived from a modelling of one or more of: [0519] citrate infusion rate to patient (citrate load), [0520] balance of bicarbonate and other buffers (e.g. lactate), [0521] assumption on citrate metabolism (1 mole citrate metabolized in 3 moles of bicarbonate), [0522] assumptions on patient systemic concentration for citrate, bicarbonate and other buffers (can be fixed values or computed from other sub-models).

[0523] Set buffer balance target does not match with the current buffer balance of the CRRT running therapy (which would require specific knowledge of current patient levels for citrate and bicarbonate), but with the (normalized) Net Buffer Load expected at a steady state where patient bicarbonate would stabilize at e.g., 25 mM.

[0524] Acid-base steady state is established slowly and measurable changes are commonly present after 24 hours; two days appear as a reasonable minimum to consider that acid-base status is reaching steady state in the context of CRRT.

[0525] In the framework of the buffer balance analysis here introduced, acid-base balance steady state is reached when: [0526] Patient systemic citrate concentration has stabilized across all the body compartments, thus leading to constant citrate load and bicarbonate generation, [0527] Patient bicarbonate concentration has stabilized across all the body compartments as a result of Net Buffer Load balancing the metabolic proton generation rate G.sub.H+.

Citrate Load

[0528] Citrate load is defined as the net infusion rate of citrate to the patient and it matches with the difference between the citrate infusion rate from the pre-blood-pump anticoagulant circuit (J.sub.cit_PBP) and the citrate removal rate into dialysate (J.sub.cit_dial), namely with the difference between citrate infusion in the blood circuit and citrate losses through dialyzer/dialysate.

[0529] From the mathematical point of view, below equations are directed to the computation of the amount of citrate returned to the patient (citrate load) which is relevant to the acid-base balance prescription during RCA.

[0530] The definition of patient citrate load is:

[00050] $J_{citrate\_\text{load}} = J_{cit\_PBP} - J_{cit\_\text{dial}}$ (Eq. 18)

[0531] Computation of citrate infusion can be expressed in two ways, according to the definition of citrate dose (D.sub.cit).

[0532] From the mathematical point of view, the definition of citrate infusion rate is:

[00051] $J_{cit\_PBP} = Q_{cit}$ .Math. $C_{cit\_PBP} = D_{cit}$ .Math. Q_b (Eq. 19)

[0533] Citric acid and citrate forms are considered in the same way in this approach.

[0534] Removal rate of citrate into the dialysate is expressed from the definition of filter clearance for the citrate-calcium complexes (K.sub.cit) and the citrate concentration (in plasma water) at the filter inlet.

[0535] From the mathematical point of view, the definition of citrate removal to effluent is:

[00052] $J_{cir\_\text{dial}} = K_{cit}$ .Math. Cpw_{cit_inlet} (Eq. 20)

Citrate Load (Main Variant)

[0536] The hypotheses for modelling the citrate mass transfer in the extracorporeal blood circuit includes the assumptions that citrate is distributed in plasma (and not in red blood cells), that CRRT filter citrate clearance is computed also based on citrate concentration in plasma water for mass transfer computations, that consideration is taken of patient citrate metabolism and non-zero steady state citrate concentration at blood access and that patient citrate clearance is proportional to body weight.

[0537] The definition of plasma water flow rate at filter inlet is the following:

[00053]

$Q_{pw_{inlet}} = Q_{pw} + Q_{cit}(+Q_{syr} + Q_{PBP}) + Q_{rep.Math.\,pre} = Q_b$ .Math. $(1 - Hct)$ .Math. $Fp + Q_{cit}(+Q_{syr} + Q_{PBP}) + Q_{PBP} + Q_{rep.Math.\,pre}$ (Eq. 5)

[0538] Here (and in the following) it is assumed that no pre-blood-pump infusion line other than (citrate) anticoagulant line **51** is present and that no heparin is used/injected since RCA is provided (i.e., no PBP replacement fluid and no syringe flow rate are considered—the terms are included between brackets for the explained reason).

[0539] The equations (equations 21) for computation of citrate clearance in CRRT with non-zero dialysis fluid and filtration flow rates are as follows:

[00054] $K_{cit} = \dfrac{Qpw_{inlet} \,.\text{Math.}\, Q_{dial} - f_{cit} \,.\text{Math.}\, (Qpw_{inlet} - SC_{cit} \,.\text{Math.}\, Q_{fil}) \,.\text{Math.}\, (Q_{dial} + SC_{cit} \,.\text{Math.}\, Q_{fil})}{Q_{dial} - f_{cit} \,.\text{Math.}\, (Qpw_{inlet} - SC_{cit} \,.\text{Math.}\, Q_{fil})}$ (Eq. 21)

$f_{cit} = (\dfrac{Qpw_{inlet} - SC_{cit} \,.\text{Math.}\, Q_{fil}}{Qpw_{inlet}} \,.\text{Math.}\, \dfrac{Q_{dial} + SC_{cit} \,.\text{Math.}\, Q_{fil}}{Q_{dial}})^{\frac{1}{cit}}_{\,cit} = e^{(\frac{SC_{cit} Q_{fil}}{R_{cit}})} - 1$

[0540] It is noted that citrate mass transfer parameters used for computation of above removal rate are known and constant values depending on the selected dialyzer.

[0541] For example, the following table reports the values for some used Baxter Prismaflex sets:

TABLE-US-00003 Prismaflex set S/RT.sub.cit ml/h SC.sub.cit M100 7500 1.0

[0542] Simpler equations might be used with lower accuracy. For example, K.sub.cit may be assumed equivalent to effluent flow rate Q.sub.eff.

[0543] Plasma water citrate concentration at filter inlet (Cpw.sub.cit_inlet) can be defined considering or not an increase of patient citrate concentration.

[0544] Simple and rough estimate will consider that patient citrate concentration remains negligible all along the therapy (see next paragraph), however, more accurate approach needs to estimate the increase of patient systemic citrate concentration (Cp.sub.cit_pat) via an estimate of the patient citrate metabolic clearance (K.sub.cit_met)—see below. Indeed, during an RCA treatment, citrate concentration at the blood access is never zero as some citrate accumulates in the patient.

[0545] This accumulation should be taken into consideration to avoid bias of about 10% (in case of neglecting). It requires the knowledge of the citrate metabolism rate (K.sub.cit_met) in liver and muscles of the patient that can vary in a wide range and significantly bias the final estimation. However it could be relevant to consider a 'minimum' accumulation that occurs for a patient having a 'normal' citrate metabolism. In this respect, patient citrate concentration is computed at steady state, assuming a typical metabolic clearance value of (about) 700 ml/min (from literature). Although not described in literature, patient citrate clearance is assumed as proportional to body weight.

[0546] The expression of patient systemic citrate concentration at steady state is the following:

[00055] $Cp_{cit.pat} = \frac{J_{citrate\_load}}{K_{cit.met}}$ (Eq. 22)

[0547] According to the above, estimation of patient citrate metabolic clearance (ml/min) is:

[00056] $K_{cit.met} = 700 \cdot Math. \frac{BW}{72}$ (Eq. 23)

[0548] The expression of citrate plasma water concentration at filter inlet is as follows:

[00057] $Qp \cdot Math. Cp_{cit_{pat}} + J_{cit_{PBP}} = Qpw_{inlet} \cdot Math. Cpw_{cit\_inlet}$ (Eq. 24)

[0549] Combination of above Equation 18, Equation 20, Equation 22 and Equation 24 allows eliminating citrate concentration parameters and expressing patient citrate load as a function of flow rates and clearances.

[00058] $J_{citrate\_load} = D_{cit} \cdot Math. Q_b \cdot Math. (1 - \frac{K_{cit}}{Qpw_{inlet}}) \cdot Math. (1 - \frac{1}{1 + \frac{K_{cit.met}}{K_{cit}} \cdot Math. \frac{Qpw_{inlet}}{Qp}})$ (Eq. 25)

[0550] The above citrate load mathematical relation is used in the context of the present application to relate the buffer load parameter (which depends on citrate load) with the citrate dose, the blood flow, the metabolic clearance and citrate clearance (depending on respective flow rates), as well as plasma flow rate and plasma water flow rate at filtration unit inlet.

Citrate Load (Simplified Variant)

[0551] According to previously described main variant, the increase of patient systemic citrate concentration (Cp.sub.cit_pat) subsequent to citrate anticoagulation is considered and estimated through the equations 22 and 23. This choice leads to the above reported equation 25 for citrate load.

[0552] A simpler alternative to this formulation, is to neglect changes in the patient systemic citrate concentration and to take it as a constant, for example zero. Equation 22 and Equation 23 are consequently not used according to this alternative.

[0553] In the case where patient citrate systemic concentration is assumed as zero (Cp.sub.cit_pat=0), Equation 24 and Equation 25 turn into following equations Equation 24′ and Equation 25′:

[00059] $J_{cit\_PBP} = Qpw_{inlet} \times Cpw_{cit\_inlet}$ (Eq. 24′) $J_{citrate\_load} = D_{cit} \times Qb \times (1 - \frac{K_{cit}}{Qpw_{inlet}})$ (Eq. 25′)

Bicarbonate Balance in Extracorporeal Blood Circuit

[0554] Bicarbonate balance is defined as the net infusion or loss rate of bicarbonate in the extracorporeal blood treatment; it matches with the difference between the infusion rate from the dialysis and/or all replacement fluids (J.sub.HCO3_inf) and the bicarbonate removal rate into effluent (J.sub.HCO3_effl).

[0555] The definition of bicarbonate balance rate is the following:

[00060] $J_{HCO3.bal} = J_{HCO3\_inf} - J_{HCO3.eff}$ (Eq. 26)

[0556] The hypotheses for modelling the bicarbonate mass transfer in the extracorporeal blood circuit includes the assumptions that bicarbonate is distributed in both plasma and red blood cells, that bicarbonate concentration at blood access Cp.sub.HCO3_pat0 is fixed (e.g., equal to 25 mM); of course, a different (fixed) value for bicarbonate concentration at blood access may be used.

[0557] Other assumptions include that the citrate solution is bicarbonate free and no other pre-blood-pump infusion with bicarbonate is present (in the reverse case, the bicarbonate content/concentration is to be taken into consideration in the bicarbonate balance, namely Q.sub.cit.Math.C.sub.HCO3.sub.cit and/or Q.sub.PBP.Math.C.sub.HCO3.sub.PBP), that CRRT filtration unit bicarbonate clearance is identical to urea clearance, and that bicarbonate removal in dialysate is computed according to similar equations as for citrate and consideration of bicarbonate concentration in plasma water for mass transfer computations. Computation of bicarbonate infusion rate is based on knowledge of the fluids composition (i.e. known bicarbonate concentration).

[00061]

$J_{HCO3\_inf} = Q_{dial} \cdot Math. C_{HCO3_{dial}} + Q_{cit} \cdot Math. C_{HCO3_{cit}} + Q_{PBP} \cdot Math. C_{HCO3_{PBP}} + Q_{rep.Math. pre} \cdot Math. C_{HCO3_{rep.Math. pre}} + Q_{rep.Math. post} \cdot Math. C_{HCO3_{rep.Mat}}$

[0558] In case bicarbonate is in the calcium replacement infusion line **74** (unlikely due to potential risks of precipitation), then a term Q.sub.ca.Math.C.sub.HCO3.sub.ca is to be added to equation 27. Fluid composition (i.e., bicarbonate concentration and/or replacement fluid prescription) may be entered by the physician (upon request from the dialysis apparatus) or read through e.g., a reader of the dialysis apparatus, for example by associating a product name with its bicarbonate content/concentration.

[0559] Equations of bicarbonate removal to dialysate are very similar to those of citrate; however, they differ for the fact that bicarbonate is present in the dialysis fluid, that the value of mass transfer parameter (K.sub.0A) is different and that a fixed value is considered for patient systemic bicarbonate. Clearly, in case citrate was present in the dialysis fluid, the corresponding citrate load/balance may take into consideration such dialysis fluid citrate concentration in the corresponding equations for citrate and in the same way as below indicated for bicarbonate.

[0560] The definition of bicarbonate removal to dialysate is the following:

[00062] $J_{HCO3\_eff} = Q_{dial} \cdot Math. C_{HCO3_{dial}} + K_{HCO3} \cdot Math. (Cpw_{HCO3\_inlet} - C_{HCO3\_dial}) + Q_{fil} \cdot Math. C_{HCO3\_dial}$ (Eq. 28)

[0561] Opposite to citrate, bicarbonate is easily transferred between red blood cells and plasma; whole blood water is thus considered for the computation of mass transfer to dialysate. Moreover, CRRT filter diffusive mass transfer coefficient of bicarbonate is taken identical to urea on the basis of their respective molecular weight (61 vs 60 g/mole). Sieving coefficient is taken as 1.

[0562] A constant physiological value of bicarbonate at blood access is considered.

[0563] The definition of blood water flow rate at filter inlet is as follows:

[00063]

$Qbw_{inlet} = Q_{bw} + Q_{cit} + Q_{syr} + Q_{PBP + Q_{rep.pre}} = Q_b \cdot Math. [(1 - Hct) \cdot Math. Fp + Hct \cdot Math. Frbc] + Q_{cit} + Q_{syr} + Q_{PBP} + Q_{rep.pre}$ (Eq. 7)

[0564] The equations for computation of bicarbonate clearance in CRRT with non-zero dialysis fluid and filtration rates are similar to those for citrate; however, for the reasons above stated, mass transfer coefficients SC and K.sub.0A are different and the flow rate considered on the blood circuit is whole blood water flow (Qbw), instead of plasma water flow (Qpw). Indeed, bicarbonate is distributed in both plasma and red blood cells with the assumption of non-hindered transfer leading to the consideration of total blood water flow rate for the clearance estimate. The equations (equations 29) for computation of citrate clearance in CRRT with non-zero dialysis fluid and filtration rates are as follows:

[00064]
$$K_{HCO3} = \cfrac{Qbw_{inlet} \cdot Math. \cdot Q_{dial} - f_{HCO3} \cdot Math. \cdot (Obw_{inlet} - SC_{HCO3} \cdot Math. \cdot Q_{fil}) \cdot Math. \cdot (Q_{dial} + SC_{HCO3} \cdot Math. \cdot Q_{fil})}{Q_{dial} - f_{HCO3} \cdot Math. \cdot (Obs_{inlet} - SC_{HCO3} \cdot Math. \cdot Q_{fil})} \quad \text{(Eq. 29)}$$

$$f_{HCO3} = \left(\frac{Qbw_{inlet} - SC_{HCO3} \cdot Math. \cdot Q_{fil}}{Qbw_{inlet}} \cdot Math. \cdot \frac{Q_{dial} + SC_{HCO3} \cdot Math. \cdot Q_{fil}}{Q_{dial}} \right)^{-\frac{1}{-HCO3}} \qquad HCO3 = e^{\left(\frac{SC_{HCO3} \cdot Math. \cdot Q_{fil}}{(\frac{2}{E})_{HCO3}} \right)} - 1$$

[0565] It is noted that bicarbonate mass transfer parameters used for computation of above removal rate are known and constant values depending on the selected dialyzer.

[0566] For example, the following table reports the values for some used Baxter Prismaflex sets:

TABLE-US-00004 Prismaflex set S/RT.sub.bic ml/h SC.sub.bic M100 17000 1.0

[0567] Alternatively to the complexity of the above equations (Eq. 29), a reasonable approximation of bicarbonate clearance in most circumstances is given by below equation for simplified estimate of filter bicarbonate clearance:

[00065] $K_{HCO3} = Q_{eff}$ (Eq. 30)

[0568] The plasma water concentration at filter inlet is derived from the set of below equations 31, namely:

[00066] $Cpw_{HCO3\_pat} = \frac{Cp_{HCO3\_pat}}{Fp}$ (Eq. 31)

$$Q_{bw} \cdot Math. \cdot Cpw_{HCO3_{pat}} + Q_{cit} \cdot Math. \cdot C_{HCO3_{cit}} + Q_{PBP} \cdot Math. \cdot C_{HCO3_{PBP}} + Q_{rep.pre} \cdot Math. \cdot C_{HCO3_{rep.pre}} = Qbw_{inlet} \cdot Math. \cdot Cpw_{HCO3\_inlet}$$

[0569] From above equations, the expression of bicarbonate plasma water concentration at filter inlet is:

[00067]
$$Cpw_{HCO3\_inlet} = \cfrac{Q_{bw} \cdot Math. \cdot \frac{Cp_{HCO3_{pat}}}{Fp} + Q_{cit} \cdot Math. \cdot C_{HCO3_{cit}} + Q_{PBP} \cdot Math. \cdot C_{HCO3_{PBP}} + Q_{rep.pre} \cdot Math. \cdot C_{HCO3_{rep.pre}}}{Qbw_{inlet}} \quad \text{(Eq. 32)}$$

Lactate Balance in Extracorporeal Blood Circuit (Optional)

[0570] Lactate balance is defined as the net infusion or loss rate of lactate in the extracorporeal blood treatment; it matches with the difference between the infusion rate from the dialysate and/or replacement fluids (J.sub.lact_inf) and the lactate removal rate into dialysate (J.sub.lact_dial).

[0571] Lactate can be used as an alternative buffer to bicarbonate with the benefit of getting more stable solutions. Lactate based dialysis fluid is well known in dialysis; for example, it is used in the home dialysis version of the System One device from NxStage. Furthermore, lactate is also present in a certain number of bicarbonate solutions in the form of lactic acid as to control pH and solution stability. This is the case for the Baxter Hemosol/PrismaSol CRRT solutions range having 3 mM lactic acid. Similarly to citrate, lactate is quickly metabolized into bicarbonate when infused to the patient, with a mole per mole conversion rate. Lactate may be modelled in the very same way as bicarbonate, assuming the patient steady state plasma lactate concentration is about 1.5 mM.

[0572] Lactate clearance may be assumed identical to urea clearance, even though lactate molecular weight is about double of urea (112 vs 60 g/mole). However, clearance estimate error is minimal in the CRRT context where flow rates are the primary limiting factor. Of course, a more accurate estimate might be used, e.g. using the power dependence of K.sub.0A on solute molecular weight (meaning possible to derive K.sub.0A lactate from known K.sub.0A on Urea, creatinine, vitamin B12, inulin).

[0573] The hypotheses for modelling of lactate mass transfer in the extracorporeal blood circuit include the assumptions that lactate is distributed in plasma and red blood cells and that CRRT filtration unit lactate clearance is identical to urea clearance. Further, patient steady state plasma lactate concentration at blood access is assumed fixed at 1.5 mM; obviously a different fixed value may be assumed and used. Lactate mass balance in the extracorporeal blood circuit is computed with similar equations to bicarbonate considering metabolism of lactate load leading to 1 mole of bicarbonate per mole of lactate.

[0574] Mass transfer equations for lactate are as follows. The definition of lactate balance rate is the following:

[00068] $J_{lact\_bal} = J_{lact\_inf} - J_{lact\_eff}$ (Eq. 33)

[0575] Computation of lactate infusion rate is based on knowledge of the fluid composition (i.e. known lactate concentration); here it is assumed that no bicarbonate concentrate solution is infused/no lactate is present in the bicarbonate concentrate solution (otherwise, the terms Q.sub.HCO3.Math.C.sub.lact.HCO3 is to be considered); the same occurs for pre-blood-pump infusions.

[00069] $J_{tact\_inf} = Q_{dial} \cdot Math. \cdot C_{lact\_dial} + Q_{rep.pre} \cdot Math. \cdot C_{lact_{rep.pre}} + Q_{rep.post} \cdot Math. \cdot C_{lact_{rep.post}}$ (Eq. 34)

[0576] Fluid composition (i.e., lactate concentration and/or replacement fluid prescription) may be entered by the physician or read through e.g., a reader of the dialysis apparatus.

[0577] The definition of lactate removal to dialysate is the following:

[00070] $J_{lact\_eff} = Q_{dial} \cdot Math. \cdot C_{lact\_dial} + K_{lact} \cdot Math. \cdot (Cpw_{lact\_inlet} - C_{lact\_dial}) + Q_{fil} \cdot Math. \cdot C_{lact\_dial}$ (Eq. 35)

[0578] Lactate is easily transferred between red blood cells and plasma; whole blood water is thus considered for the computation of mass transfer to dialysate. Moreover, CRRT filter diffusive mass transfer coefficient of bicarbonate is taken identical to urea. Sieving coefficient is taken as 1.

[0579] Lactate clearance (K.sub.lact) is considered equal to bicarbonate clearance (K.sub.HCO3) and therefore the control unit calculates it in the same way with same equations previously presented. The expression of lactate plasma water concentration at filter inlet is:

[00071] $Cpw_{lact\_inlet} = \frac{Q_{bw} \cdot Math. \cdot \frac{Cp_{lact\_pat}}{Fp} + Q_{rep.pre} \cdot Math. \cdot C_{lact_{rep.pre}}}{Qbw_{inlet}}$ (Eq. 36)

Net Patient Buffer Load

[0580] Net patient buffer load is defined in relation to citrate infusion rate to patient (namely, citrate load) and bicarbonate generation. To achieve this target, the hypotheses on citrate metabolism include the following assumptions: metabolism of citrate load leads to 3 moles of bicarbonate per mole of citrate and Net Buffer Load (NBL) may be reduced by the rate of acid infusion, such as citric acid. The expression of bicarbonate generation rate from citrate metabolism (at steady state) is the following:

[00072] $J_{met\_cit} = 3 \cdot Math. \cdot J_{cit\_load}$ (Eq. 37)

[0581] The expression referring to acid infusion rate is as follows:

[00073] $J_{H+} = 3 \cdot Math. \cdot J_{citric\_acid} = 3 \cdot Math. \cdot Q_{cit} \cdot Math. \cdot C_{cit\_PBP}$ (Eq. 38)

[0582] Combination of Equation 17, Equation 37 and Equation 38 leads to the expression for net buffer load as a function of citrate load and bicarbonate balance:

[00074] $J_{buffer\_load} = 3 \cdot Math. \cdot J_{cit\_load} + J_{HCO3\_bal} - 3 \cdot Math. \cdot J_{citric\_acid}$ (Eq. 39)

[0583] It is remarked that the expression of J.sub.citrate_load is given in Equation 25 (or simplified Eq. 25′), while full expression of J.sub.HCO3_bal is to be derived from Equation 26, Equation 27, Equation 28, Equation 29 (or simplified Eq. 30) and Equation 32. J.sub.citric_acid is to be derived from Equation 38.

[0584] From a therapy perspective, net buffer load should be positive as to neutralize the proton (H.sup.+) generation rate G.sub.H+ from metabolism. Literature report typical G.sub.H+ values of about 1 mmol/day/kg, or 0.04 mmol/h/kg. Production of protons from metabolism is however strongly dependent on protein catabolism.

[0585] In case lactate is taken into consideration (optional), the expression for the net buffer load as a function of citrate load, lactate balance and bicarbonate balance becomes:

[00075] $J_{\text{buffer\_load}} = 3 \cdot \text{Math.} J_{\text{cit\_load}} + J_{\text{HCO3\_bal}} + J_{\text{lact\_bal}} - 3 \cdot \text{Math.} J_{\text{citric\_acid}}$ (Eq. 40)

[0586] In this case, in addition to mentioned equations for J.sub.citrate_load, J.sub.HCO3_bal and J.sub.citric_acid, the equations for J.sub.lact_bal are required, namely Equation 33, Equation 34, Equation 35, Equation 29—if lactate clearance K.sub.lact is considered equal to bicarbonate clearance K.sub.HCO3.sub.− (or corresponding equation for lactate clearance, or simplification K.sub.lact=Q.sub.eff) and Equation 36.

Steady State Acid-Base Balance Prescription

[0587] The apparatus control unit is configured to receive a steady state acid-base balance target, namely a steady state acid-base balance prescription set value before the start of the treatment. This additional prescription value influences various flow rates to be determined by the control unit **12**. Indeed, the definition for the steady state acid-base balance target depends on almost all operating parameters and other prescription parameters (as well as on system configuration).

[0588] As previously indicated, the steady state acid-base balance prescription may be specified either as: [0589] A) a steady state patient bicarbonate concentration (requiring an assumption on nNBL, namely nNBL0), or as [0590] B) normalized Net Buffer Load or nNBL (requiring an assumption on bicarbonate concentration, namely (Cp.sub.HCO3_pat0)).

[0591] At steady state, nNBL is expected to balance the protons (H+) generation rate from patient metabolism.

nNBL

[0592] The control unit **12** of the apparatus for extracorporeal blood treatment allow the operator to enter a parameter (J.sub.buffer_load/BW) indicative of a steady state acid-base (or buffer) balance in the blood of the patient who has to undergo the CRRT blood treatment. This parameter defines a quantitative information on the intensity of the therapy with respect to the net patient buffer (bicarbonate) gain or loss. This parameter is of high and peculiar interest in the complex cases of citrate anticoagulation, but it remains also relevant to any extracorporeal dialysis therapy (run with systemic or no anticoagulation). In more detail, the control unit **12** receives the net buffer load at the apparatus setting (i.e., before the CRRT treatment is started).

[0593] The definition of normalized net buffer load (nNBL) is the following:

[00076] $\text{nNBL} = \frac{J_{\text{buffer\_load}}}{\text{BW}}$ (Eq. 41)

nNBL is chosen as the indicative parameter of acid-base balance level at steady state, and is expressed as amount of buffer infused per unit of time and per patient kg (mmol/h/kg).

[0594] In this respect, it is noted that J.sub.buffer_load is linked to several other flow rates through the equations previously indicated. Indeed, J.sub.buffer_load and consequently NBL or nNBL, is defined based on equations 17, 26, 27, 28 (or 26′ combination of Eq. 26, 27 and 28), 29 (or 30), 32, 38; in case lactate is present definition is additionally based on equations 29 (or 30), 33, 34, 35 and 36. All these equations are function of one or more other flow rates of the CRRT apparatus configuration. Therefore, imposing a set value for the steady state acid base balance prescription generate a constraint between the various fluid flow rates and consequently influences the operating flow rates of the apparatus. By solving the mentioned equations, the apparatus control unit **12** may derive corresponding flow rates of operating parameters matching with the prescription (as apparent from the following detailed description).

[0595] Notably, review of published clinical data on CRRT with RCA at steady state has shown good correlation of this nNBL parameter with both steady state patient bicarbonate and base excess. Therefore, instead of using the (normalized) net buffer load as above defined, the buffer balance parameter could be expressed as the steady state bicarbonate concentration, once assuming a 'default' value for the normalized net buffer load (nNBL); see further paragraph in this respect.

[0596] In the previously described embodiment, nNBL matches with the value of buffer balance when the patient reaches the assumed bicarbonate level (e.g; 25 mM)=>nNBL.sub.25). If nNBL.sub.25 matches with the protons generation rate (G), then steady state is reached and patient will stabilize at the assumed HCO.sub.3 level (25 mM). Alternatively, if nNBL.sub.25 is larger than the protons generation rate, patient bicarbonate will increase up to Ceq such as nNBL.sub.Ceq matches with the (current) protons generation rate. In case nNBL.sub.25 is lower than G.sub.H+, then patient bicarbonate will stabilize at a lower value than the assumed level.

[0597] Though the parameter indicative of a steady state acid-base (or buffer) balance in the blood of the patient has been described as normalized over patient weigh, it is also possible to normalize the parameter over patient surface or over another patient-related variable. Of course, and even if it is not considered the best approach, the control unit **12** may also receive the Net Buffer Load (mmol/h) without any normalization.

Variant with Steady State HCO.sub.3 Indicator—Cp.sub.HCO3_pat

[0598] Patient bicarbonate concentration (Cp.sub.HCO3_pat) could be alternatively taken as the indicative parameter of steady state acid-base equilibrium, providing that the (desirable/targeted) nNBL level has been chosen. In this scenario, previous equations may be re-arranged as to express the patient steady state bicarbonate concentration as a function of a predefined nNBL level, for example nNBL0=0.1 mmol/h/kg. Citrate equations, namely equations 18-25, 24′ and 25′, remain unchanged.

[0599] Differently, bicarbonate equations require some rearrangement. In more detail, expression of steady state patient bicarbonate (rearrangement of Equation 31) is the following:

[00077]

$$Cp_{\text{HCO3\_pat}} = \frac{\text{Fp}}{\text{Qbw}} \cdot \text{Math.} (Cpw_{\text{HCO3}_{\text{inlet}}} \cdot \text{Math. Qbw}_{\text{inlet}} - Q_{\text{rep .Math. pre}} \cdot \text{Math.} C_{\text{HCO3rep .Math. pre}} - Q_{\text{cit}} \cdot \text{Math.} C_{\text{HCO3}_{\text{cit}}} - Q_{\text{PBP}} \cdot \text{Math.} C_{\text{HCO3}_{\text{PBP}}})$$ (Eq. 42)

[0600] The expression of plasma water bicarbonate concentration at filter inlet (rearrangement of Equation 28) becomes:

[00078] $Cpw_{\text{HCO3\_inlet}} = C_{\text{HCO3\_dial}} + \frac{J_{\text{HCO3\_eff}} - Q_{\text{dial}} \times C_{\text{HCO3}_{\text{dial}}} - Q_{\text{fil}} \times C_{\text{HCO3\_dial}}}{K_{\text{HCO3}}}$ (Eq. 43)

[0601] Merging equations 42 and 43 provides the following expression for steady state patient bicarbonate:

[00079]

$$Cp_{\text{HCO3\_pat}} = \frac{\text{Fp}}{\text{Qbw}} \cdot \text{Math.} (C_{\text{HCO3\_dial}} + \frac{J_{\text{HCO3\_eff}} - Q_{\text{dial}} \times C_{\text{HCO3}_{\text{dial}}} - Q_{\text{fil}} \times C_{\text{HCO3\_dial}}}{K_{\text{HCO3}}} \cdot \text{Math. Qbw}_{\text{inlet}} - Q_{\text{rep .Math. pre}} \cdot \text{Math.} C_{\text{HCO3rep .Math. pre}} - Q_{\text{cit}} \cdot \text{Math.} C_{\text{HCO3}_{\text{cit}}} - Q_{\text{PBP}}$$

[0602] The expression of bicarbonate losses to effluent (from equations 17 and 26):

[00080] $J_{\text{HCO3\_eff}} = J_{\text{HCO3\_inf}} - J_{\text{HCO3}_{\text{bal}}} = J_{\text{HCO3\_inf}} + J_{\text{met\_cit}} - J_{H+} - J_{\text{buffer\_load}}$ (Eq. 44)

[0603] The relation between chosen/set nNBL0 and J.sub.buffer_load is as follows:

[00081] $J_{\text{buffer\_load}} = \text{nNBL0} \times \text{BW}$ (Eq. 45)

[0604] Therefore, equation 44 may be expressed as follows:

[00082] $J_{\text{HCO3\_eff}} = J_{\text{HCO3\_inf}} + J_{\text{met\_cit}} - J_{H+} - \text{nNBL0} \times \text{BW}$ (Eq. 44′)

[0605] J.sub.buffer_load from equation 45, J.sub.H+ from equation 38, J.sub.met_cit from equation 37 and equation 25 or 25′ and J.sub.HCO3_inf from equation 27 are input to equation 44; the latter is then combined with equation 43 so that all terms of the this combined expression are known. Cpw.sub.HCO3_inlet is finally introduced in equation 42 to derive an expression of variables defining the value of steady state patient bicarbonate which is the parameter to be set by the medical staff, which influences almost all fluid flow rates to be set.

[0606] As apparent, this solution provides an alternative parameter, namely the steady state patient bicarbonate concentration (which is again a parameter indicative of the steady state acid-base balance in the blood of the patient who has to undergo to a CRRT blood treatment), with respect to

the normalized buffer load parameter, allowing medical staff to set a proper value and the control unit **12** to maintain a proper acid-base balance during the CRRT treatment.

Therapy Configuration Parameters

[0607] Therapy configuration parameters are user settings that can be set in the system as to configure the CRRT modality according to local protocols and/or some customer preferences. Though it is possible to set the therapy configuration parameters any time it is needed, these user settings are generally set once for all at a certain customer place and then used for all treated patients.

TABLE-US-00005 Parameter Configuration purpose CRRT Dose Selection of the formula to be used for CRRT dose/see detailed paragraph Steady state acid-base Selection of the prescription balance target parameter: C.sub.p.sub.HCO3.sub.—.sub.pat or nNBL Blood flow rate Selection as prescription parameter or not Convection/diffusion Parameters used to configure the CRRT split therapy with respect to the relative Predilution ratio proportion of diffusion (dialysate flow) Pre/post infusion and convection (all infusion fluids), as ratio well as distribution of infusion fluids pre or post filter/see next paragraphs for a more complete list and a detailed description of possible CRRT parameters

[0608] Other default therapy configuration parameters may come from the system technical constraints and/or manufacturer choices. These constraints are embedded in the system and not user selectable. Examples of such parameters are flow operating ranges of the fluid circuits (e.g. calcium infusion in RCA), or mandatory relations between specific flow rates related to safety or technical considerations (e.g. maximum PBP or citrate flow rate versus blood flow rate.

Treatment Configuration Parameters

[0609] The treatment configuration parameters are variables specific of the patient to be treated and of the composition of prescribed fluids (which are also part of the medical prescription).

TABLE-US-00006 Symbol Parameter name Comment BW Patient body weight (kg) Generally required for prescription from D.sub.CRRT Hct Hematocrit (%) Not required in some simple variants of assisted prescription Filtration unit CRRT filter type Not required in the simplest approaches C.sub.cit Composition of citrate solution in sodium Generally required for prescription from D.sub.cit C.sub.citr.sub.—.sub.acid citrate and citric acid with 1 RCA (concentrations) C.sub.HCO3.xxx Bicarbonate concentration of used solution Generally required for prescription of steady 'xxx' (dialysate, replacement, PBP . . .) state acid-base balance target C.sub.lact.xxx Lactate concentration of used solution 'xxx' Generally required for prescription of steady (dialysate, replacement, PBP . . .) state acid-base balance target in case lactate is considered C.sub.ca.xxx Calcium concentration of used solution 'xxx' Required with RCA only (dialysate, replacement, PBP . . .) C.sub.ca.bal Calcium concentration in the solution used to balance Ca losses

[0610] Notably, hematocrit may alternatively be directly measured by the apparatus and on-line monitored.

[0611] Multiple default treatment configuration parameters may come together from the filter type, such as flow operating ranges and/or mass transfer coefficient(s). These are not user selectable and originate from the manufacturer. Of course, instead of providing the filter type to the apparatus (either by reading with a reader a filtration unit code or by inputting/selecting onto the user interface the used filtration unit), the relevant parameter values may be manually entered. As apparent from the following description, in the simplest approaches where clearance of small solutes is estimated identical to effluent flow rate, identification of the filter is not required. This type of approach becomes inaccurate in the scenario where dialysate and blood flow become similar, like in pediatrics application or high volume CRRT.

Operating Parameters

[0612] Operating parameters are the CRRT monitor treatment parameters computed by the assisted prescription algorithm (here below illustrated) as a function of: [0613] Prescription parameters [0614] Therapy configuration parameters [0615] Treatment configuration parameters.

[0616] All the operating parameters are flow rates. The list of operating parameters is dependent on the anticoagulation method, as well as on the CRRT system capabilities and configuration.

[0617] In certain embodiments, calcium infusion may not be directly controlled by the CRRT system during RCA and infusion may be performed by a separate infusion pump. In this situation, the calculated prescribed value should be input in the external ion balancing infusion pump **75** and the control unit **12** may not verify or insure assisted prescription compliance. The same applies to anticoagulant infusion during systemic anticoagulation (usually a syringe boluses infusion).

[0618] The CRRT system may have a variable number of pumps available for fluid infusion at different locations along the extracorporeal blood circuit. See the examples of FIGS. **2** to **6** having a different number of infusion lines and/or pumps.

[0619] The following table identifies operating parameters (associated to respective pumps) which will be considered in the examples. While this list refers to a maximum of 7 pumps (including the blood pump), systems including more pumps and infusion lines could be considered as well.

[0620] PBP and citrate flow rates are both indicated in the table, although they are typically delivered by the same pump in alternative configurations. PBP flow rate is specific of therapies not using citrate anticoagulation. Note that embodiment of FIG. **6** provides for two different pre-blood-pump infusion lines, namely an anticoagulant (citrate) infusion line **51** and a separate PBP infusion line **52**.

TABLE-US-00007 Symbol Parameter name Comment Q.sub.cit Citrate solution infusion Parameters specific of flow rate in RCA citrate anticoagulation Q.sub.Ca Calcium solution infusion flow rate in RCA Q.sub.dial Dialysis flow rate If applicable Q.sub.PBP Pre blood pump infusion If applicable flow rate Q.sub.rep.pre Pre filter replacement If applicable solution infusion flow rate Q.sub.rep.post Post filter replacement If applicable solution infusion flow rate Q.sub.HCO3 Post-filter bicarbonate Specific to 'Bicarbonate Post infusion flow rate Infusion' system configuration Q.sub.eff Effluent flow rate Control CRRT fluid balance process Q.sub.b Blood flow rate In case blood flow is not a prescription parameter

Assisted Prescription with No/Systemic Anticoagulation

[0621] In the context of systemic anticoagulation, a concentrated anticoagulant solution is infused in the extracorporeal blood circuit. While this prescription is clinically important, heparin infusion is not particularly relevant with respect to the CRRT prescription and calculation of flow rates since (heparin) infusion flow rate is very low, typically less than 5 ml/h matching with about 0.1% of all the fluid infusion rates, thus not impacting CRRT dosage measurably, and used anticoagulant does not interfere with acid-base equilibrium. Due to these characteristics, anticoagulation prescription in systemic anticoagulation during RRT can be seen as fully independent from the RRT prescription in itself and will not be treated in the next section which can thus address simultaneously all prescriptions using no or systemic anticoagulation.

[0622] When no or systemic anticoagulation is used, the CRRT prescription can be built from the following: [0623] 1. CRRT dose, [0624] 2. Steady-state acid-base equilibrium target, [0625] 3. Patient fluid removal rate (PFR), [0626] 4. Optionally, blood flow rate.

[0627] Anticoagulant prescription could be listed as well in the case of systemic anticoagulation; it however does not interfere measurably with any of the other prescription parameters and can be addressed independently.

[0628] In a system with 3 fluid infusion pumps and one effluent pump, 4 fluid flow rates are to be defined from the above 3 first prescription parameters. There is thus one degree of freedom, which may allow to consider one additional setting from the therapy configuration in the definition of operating flow rate parameters. If one additional infusion pump is added, then two degrees of freedom are available and two further settings might be selected to allow the control unit to propose corresponding flow rates matching prescription and settings. With one infusion pump less, the 3 first prescription parameter are sufficient to define the fluid flow rates for the therapy configuration.

Qualitative Dependence of Operating Parameters

[0629] Next table provides an indication for the interdependence between operating and prescription parameters in no or systemic anticoagulation; notably, this dependence is conditional to the definition given to/selection of the CRRT dose.

TABLE-US-00008 Prescription parameter Operating Acid-base parameter CRRT dose equilibrium PFR Blood flow Q.sub.dial X1 X3 — —

Q.sub.PBP X1 X3 — — Q.sub.rep.pre X1 X3 — — — Q.sub.rep.post X1 X3 — — — Q.sub.HCO3 X1 X3 — — — Q.sub.eff X1 X3 X4 — Q.sub.b X2 X3 — X5 [0630] X1: contribution of flow rates to the CRRT dose is dependent on the definition given to it (see previous paragraph). Most relevant definitions make use of all flow rates (whatever simply referring to Q.sub.eff or to an estimated clearance). [0631] X2: contribution of blood rate to CRRT dose is also dependent on the chosen dose definition. Blood flow is relevant as soon as predilution effects are considered (which is not the case when simply referring the effluent flow rate as CRRT dose). [0632] X3: all infusion fluids or dialysis fluid contribute to the acid-base balance according to the fluid composition associated to each infused solution. Blood flow rate impacts predilution and concentration of buffer solutes at the CRRT filter inlet. [0633] X4: patient fluid removal rate prescription is directly controlled by the definition of effluent flow rate versus all the other infusion flow rates of the dialysis system, including the anticoagulant flow rate if relevant. [0634] X5: when blood flow is defined as one prescription parameter, there is a loss of one degree of freedom in the definition of operating flow rates, meaning that less constraints from the therapy configuration parameters can be used. Number of degrees of freedom is defined as the difference between the numbers of operating flow rates to be computed minus the number of prescription parameters.

The Control Unit and the Assisted Prescription Algorithm

[0635] The control unit **12** is connected to the various sensors, to the actuators for regulating the flow rate through the various lines (in the above examples these actuators comprise the pumps active on the lines and the switch valves) and to the user interface. The control unit **12** may comprise a digital processor (CPU) and necessary memory (or memories) such as memory **16**, an analogical type circuit, or a combination thereof. In the course of the present description it is indicated that the control unit is "configured" or "programmed" to execute certain steps: this may be achieved in practice by any means which allow configuring or programming the control unit. For instance, in case of a control unit comprising one or more CPUs, a program may be stored in an appropriate memory containing instructions which, when executed by the control unit, cause the control unit to execute the steps herein described. Alternatively, if the control unit is of an analogical type, then the circuitry of the control unit may be designed to include circuitry configured in use to execute the steps herein disclosed. The steps in the method aspects are generally performed by the control unit unless differently indicated by the circumstances.

[0636] In the examples of FIGS. **1** to **6**, the control unit **12** is configured to execute a flow-rate setup procedure as described here below. Starting from the embodiment of FIG. **2**, there are five pumps to be set, that define (or generate) five flow rates in total; the flow rates should be either received by the medical staff or calculated by the control unit **12**.

[0637] This flow-rate setup procedure comprises to initially set (or accept or maintain) the therapy configuration. Indeed, the control unit **12** is configured to allow the user to select one or more therapy configurations. Therapy configurations available are exemplificatively disclosed in the previous paragraph of the present description. The CRRT dialysis dose is to be selected among the described (or additional) possibilities. For example, CRRT dose as effluent dose D.sub.eff may be selected; alternatively, urea dose D.sub.urea or any different dose type may be selected. The acid base balance parameter is selected to, e.g., between (normalized) net buffer load (n)NBL or patient systemic bicarbonate plasma concentration. Blood flow rate may be decided as prescription parameter or as operating parameter. Finally, depending on the number of degrees of freedom (namely on the number of flow rates to be set by the control unit **12** minus the prescription parameters), none, one, two or more of a convection-diffusion relation, blood pre-dilution relation and pre-post relation may be selected as additional constraints (see step **100** in FIG. **7**).

[0638] After setting/accepting the therapy configuration, the necessary treatment configuration is to be provided. See step **101** in FIG. **7**. In particular, patient specific values and apparatus or disposable or solutions specific values have to be provided. Typically, patient body weight BW (or equivalent, for CRRT dose—body surface BSA depending on parameter normalization) needs to be provided. This is requested if any one of the patient prescription is normalized over patient weight as per the examples at the end of the present disclosure. Depending on apparatus configuration haematocrit Hct is required. If the specific apparatus configuration and mathematical relations to calculate the operating parameters so require, concentration of certain solutes contained in the relevant bags is to be provided as well. In particular, all solutes contributing to acid-base balance requires their concentration and specific location to be provided. For example, all bicarbonate solutions are generally requested, as well as citrate and calcium concentrations in the various bags; lactate and other bicarbonate precursors, such as acetate may be necessary, too. Finally, filtration unit data, such as K0.A of one or more solutes, might be requested. As already indicated, data may be entered manually or automatically acquired e.g., via a reader. For example, the apparatus memory may include data associated to a product code (a solution bag code or a filtration unit code, for example). Of course, the apparatus input system (graphic user interface) may prompt entering only necessary values/parameters or, alternatively, request all data and thereafter the control unit **12** exclusively makes use of the necessary ones.

[0639] After the above steps, the apparatus is ready for receiving the prescription parameters, whose values are entered by the operator (see step **102** in FIG. **7**). Once acquired, the control unit **12** uses one or more of the previously mentioned mathematical relations together with the entered treatment configuration data and the prescription parameters to determine the operating parameters consisting of the various requested flow rates. In this respect, the control unit **12** uses the mathematical relations that links the treatment configuration data, the prescription parameters and the operating parameters as a system of equations that, once solved, provides all the relevant flow rates to be proposed or set. At the end of step **103**, the control unit **12** stores the calculated operating parameters to the memory **16** and provides the calculated values to the user interface for displaying to the user. In general, the control unit **12** waits for acceptance of the proposed values before driving the corresponding actuators (pumps) and achieving the calculated flow rates in the respective lines. In another embodiment, the control unit **12** automatically set the pumps to achieve the flow rates in the respective lines once the flow rates are available.

[0640] In case the imposed conditions are conflicting, namely there is no solution to the flow rate system given the therapy and treatment configurations, the imposed and existing constraints and the prescription parameters, an alert to the user is provided. Possibly, one or more solutions in terms of proposed operating flow rates close to the imposed conditions are provided to the user via the user interface. For example, the further mathematical relations (convection-diffusion relation, blood pre-dilution relation and pre-post relation) are given lower priority with respect to other main mathematical relations linking the input prescription parameters. A rank may also be imposed to said convection-diffusion relation, blood pre-dilution relation and pre-post relation. Alternatively, in case blood flow rate is selected as prescription parameter, the blood flow is moved to operating parameter and its value is calculated, rather than received. In other terms, the control unit **12** may be configured to manage conflicting situations with different protocols of intervention. Optionally, more than one set of solutions for the operating flow rates is provided for the user selection. Moving to the example of FIG. **2**, only PBP infusion line and post dilution infusion line are used for replacement fluid. There are five flow rates to be set, namely blood flow rate Q.sub.b, dialysis fluid flow rate Q.sub.dial, PBP flow rate Q.sub.PBP, post-dilution flow rate Q.sub.rep.post, and effluent flow rate Q.sub.eff. As previously indicated, once the therapy configuration is received, the treatment configuration has to be provided. If effluent dose is selected among available dose types (meaning that blood predilution does not influence the CRRT dialysis dose) and assumption is accepted that filtration unit clearance for small solutes can be taken sufficiently equal to effluent flow rate, no filter data are necessary. Body weight, haematocrit and bicarbonate concentration have to be entered into the memory via user interface. The control unit waits then to receive a prescribed dose value D.sub.set, a prescribed value for the fluid removal rate Q.sub.pf from the patient, a steady state acid-base balance parameter target and a setting for the blood flow rate Q.sub.b (see step **102** in FIG. **7**).

[0641] The memory **16** associated with or connected to the control unit **12** stores the plurality of mathematical relations correlating the fluid flow rates Q.sub.PBP, Q.sub.rep.post, Q.sub.eff, Q.sub.b, Q.sub.PFR, and Q.sub.dial. Since we have four prescription parameters and five flow rates to be set, an additional constraint is selectable. In this respect, there are additional mathematical relations stored in said memory, which may be the following: [0642] a convection-diffusion relation, relating the total fluid flow rate through said infusion lines+patient fluid removal rate Q.sub.PBP+Q.sub.rep.post+Q.sub.PFR with the fluid flow rate through said dialysis fluid line Q.sub.dial; the convection-diffusion relation may define in practice a first ratio R.sub.1=(Q.sub.PBP+Q.sub.rep.post+Q.sub.PFR)/(Q.sub.dial), [0643] a blood pre-dilution relation, relating the flow

rate of blood or of plasma Q.sub.b or Q.sub.p and the fluid flow rate infused in the blood withdrawal line Q.sub.PBP through said pre-dilution infusion line **52**; the blood pre-dilution relation may define a second ratio R.sub.2=Q.sub.b/(Q.sub.PBP) or R.sub.2=Q.sub.p/(Q.sub.PBP); [0644] a pre-post relation, relating the fluid flow rates Q.sub.PBP through pre-dilution infusion line with the fluid flow rate through the post-dilution infusion line Q.sub.rep.post; the pre-post relation may define in practice a third ratio R.sub.3=(Q.sub.PBP)/(Q.sub.rep.post).

[0645] The control unit **12** allows the user, e.g. through user interface **12**, to select one of said relations and then may calculate the set values of all flow rates Q.sub.PBP, Q.sub.rep.post, Q.sub.eff, and Q.sub.dial (step **103** in FIG. **7**) by applying the set value of the dose D.sub.set, the target value for the steady state acid-base balance, the set blood flow rate Q.sub.b and the set value of fluid removal rate Q.sub.pfr entered by the operator to the mathematical relations previously discussed that links the steady state acid-base balance parameters to the various flow rates and the further mathematical relation above identified and selected by the user (and the fluid balance equation which needs to be satisfied in order to maintain the fluid balance in line with the prescription: Q.sub.PBP+Q.sub.rep.post+Q.sub.dial+Q.sub.pfr=Q.sub.eff; FBE—fluid balance equation).

[0646] In case a syringe pump is also present/considered for injecting an auxiliary fluid, e.g. heparin, in the blood withdrawal line, then the above equation may be modified accordingly to account for the syringe flow rate.

[0647] Note that preset values for each one of said first, second and third ratios R.sub.1, R.sub.2, R.sub.3 may be pre-stored in the memory or that the control unit may allow entry by an operator of a set value or a set range for each one of said first, second and third ratios R.sub.1, R.sub.2, R.sub.3, e.g. via the user interface **12**.

[0648] In one alternative, the memory **16** of the apparatus of FIG. **1** may (further) store a plurality of optimization criteria, which the control unit **12** may use to calculate the set values for the relevant operating flow rates in alternative or in combination with the above ratios R.sub.1, R.sub.2, R.sub.3.

[0649] For instance, optimization criteria stored in memory **16** may comprise a first optimization criterion imposing that an emptying time of at least one among the containers of fresh fluid **14**, **64**, **10**, **11** and/or a filling time of the waste container **62** is substantially same as, or multiple of, or proportional to the emptying time of one or more of the other containers of fresh fluid. A second optimization criterion stored in the memory **16** may impose that fluid consumption through the fluid lines is minimized. A third optimization criterion stored in memory **16** may impose that a life time of filtration unit **2** is maximized. A fourth optimization criterion stored in the memory **16** may impose that urea clearance or dialysance of a given solute is maximized.

[0650] In practice, if optimization criteria are stored in memory **16**, the control unit **12** may be configured to allow the user to select (step **100**), e.g. via the user interface **12**, the criteria he wants to have satisfied and may be further configured to calculate the set values for the relevant operating flow rates based on the mathematical relations previously discussed that links the steady state acid-base balance parameters to the various flow rates and the selected optimization criteria and on the above mentioned fluid balance equation (FBE).

[0651] In case the selected mathematical relations (and eventually the selected criteria) are compatible, then the set flow rates are calculated based on the selected mathematical relations (and eventually optimization criteria). On the other hand, in case selected mathematical relations (and/or the selected criteria) are conflicting, the control unit **12** may be configured to execute one or more of the following sub-steps: [0652] inform the user; the user has then the power to re-enter compatible selections; [0653] assign a priority ranking to the mathematical relations (and/or selected criteria); the priority ranking is either predetermined or user adjustable: in any case the control unit is configured to ignore criteria or mathematical relations as soon as flow rates have been calculated from the prioritized criteria/mathematical relations; [0654] define a compromise between conflicting mathematical relations and/or criteria using preset rules.

[0655] In accordance with a variant, the control unit may use the flow-rate setup procedure to initially calculate the flow rates set values through the various lines and during a first interval in the treatment control the actuators for regulating using said calculated set values. Then, after a certain time interval or upon detection of a user input, the control unit may recalculate the set values for the flow rates through the various lines exclusively based on one or more different prescription value and/or differently selected (or modified in value) further mathematical relation and, apply the newly calculated set values during a second time period subsequent to the first time period. For instance the flow-rate setup procedure may allow setting of the flow rates such that a certain delivered dose is attained. On the other hand, if at a certain point the user wants to privilege bag-emptying synchronization he may select to impose the first optimization criteria so that the control unit may recalculate the set values of the flow-rates allowing to synchronize as possible the emptying of the fluid bags.

[0656] FIG. **3** shows a different configuration of the CRRT apparatus, wherein regional anticoagulation protocol is used. In this second example, there are six flow rates to be set, namely Q.sub.cit, Q.sub.rep.post, Q.sub.eff, Q.sub.b, Q.sub.ca, and Q.sub.dial. However, regional anticoagulation requires a citrate dose and a calcium compensation parameter to be provided as patient prescription parameters. Therefore, the CRRT apparatus control unit **12** requires the medical staff to enter, CRRT dialysis dose, acid-base balance parameter, patient fluid removal rate, citrate dose and calcium compensation parameter. If blood flow rate is selected as prescription parameters, there are no more degrees of freedom. Therefore, once the physician has entered the requested info, no further mathematical equation may be selected. The control unit **12** calculates the operating parameter through the equation system of the relevant mathematical relations. Of course, based on the different system configuration (namely the additional post-infusion of calcium) and the different content of the used bags (e.g., citrate in the bag **10**), the relevant mathematical relations that the control unit **12** uses are different with respect to the example of FIG. **2** (as apparent form the detailed examples here-below reported). The equation system defines some constraints, mainly due to citrate infusion and the need to keep the imposed acid-base parameter target that may leads to a system with no solutions for the flow rates. Again, one or more of the approaches above defined may be taken is such a situation. Again, the detailed examples clarify this situation.

[0657] The configuration of FIG. **4** provides for an HDF configuration, wherein a pre-dilution line and a bicarbonate post-dilution line are used. In particular, the post-dilution line infuses a replacement solution with high bicarbonate concentration. This configuration allows some more freedom to regulate acid-base balance. Also in this configuration, the control unit **12** makes use of the relevant mathematical relations based on CRRT apparatus design, on decided prescription parameters type/nature, the treatment configuration parameters, the imposed values for the prescription parameters and the corresponding relevant mathematical relations.

[0658] FIG. **5** is directed to another embodiment of the CRRT apparatus: HDF configuration with regional anticoagulation including a post-dilution replacement solution and a post-dilution bicarbonate solution in addition to the calcium reinfusion line. There are seven flow rates to be set and usually six prescription parameters, namely blood flow rate, acid-base balance target, CRRT dialysis dose, citrate dose and calcium reinfusion parameter value. Therefore, once again it is possible for the user to additionally select one among the convection/diffusion split, the pre-dilution ratio and the pre-post infusion ratio. The configuration of FIG. **5** requires the control unit **12** to use many of the mathematical relations to properly take into account the interactions of the various fluids, particularly in terms of acid-base balance.

EXAMPLES

[0659] In the present section, some examples are provided to better explain working of the CRRT apparatus.

[0660] In the context of CRRT with no or systemic anticoagulation, the possibility to adjust the steady state acid-base balance equilibrium when using fluids having all similar bicarbonate content appears limited. Some possibilities exist when using simultaneously one fluid with low bicarbonate content (e.g. below 25 mM) and one with a higher content (e.g. higher than 40 mM).

[0661] Reference is made to the apparatus as shown in FIG. **2**, provided with 4 fluid pumps (dialysis fluid pump **25**, effluent pump **26**, PBP infusion pump **53** and post-dilution infusion pump **65**) and thus capable of running an HDF therapy.

TABLE-US-00009 Fluid circuit/pump Symbol Present dialysis fluid pump/supply line dial X PBP infusion pump/line PBP X pre-dilution infusion pump/line rep.pre absent or no use post-dilution infusion pump/line rep.post absent or no use post-dilution bicarbonate infusion HCO.sub.3 absent or

no use line/pump effluent pump/line eff X blood pump b X

[0662] Next examples S1-S5 (S stands for systemic anticoagulation or no anticoagulation) are based on the above circuit configuration and on FIG. **2.**

Example S1

[0663] Effluent dose is selected as CRRT dose, therefore blood predilution does not influence dose and equations are simpler to solve. In this context of simple approach, filter clearance of small solutes (like bicarbonate) is taken equal to effluent flow rate as well; consequently no information is required on the filter type/performances.

[0664] Further, steady state bicarbonate is selected as the acid-base balance prescription parameter (when selecting steady state bicarbonate, the apparatus control unit assumes that nNBL0 is equal to 0.1 mmol/h/kg); blood flow rate is also selected among prescription parameters (reducing the degrees of freedom of the configuration). Five pumps are available and four prescription values are entered. Therefore, the system has one degree of freedom and one therapy configuration constrain may be further selected to obtain a calculation of all operating flow rate parameters.

[0665] Among therapy configurations, any of convection/diffusion split, predilution ratio and pre/post infusion ratio may be selected. Predefined (modifiable) values for these relations are also included in the memory and presented to the user. Further, necessary treatment configuration values are also entered by the operator or acquired by the control unit **12**.

TABLE-US-00010 Therapy configuration CRRT Dose Effluent Acid-base balance target C.sub.p.sub.HCO3.sub.—.sub.pat (nNBL0 = 0.1 mmol/h/kg) Blood flow rate Prescription Convection/diffusion split 50-50 or R1 = 1 ⬛custom-character ⬛custom-character ⬛custom-character ⬛custom-character

TABLE-US-00011 Treatment configuration BW (kg) 75 Hct (%) 32 Filter No data C.sub.HCO3.sub.dial (mM) 32 C.sub.HCO3.sub.PBP (mM) 30 C.sub.HCO3.sub.rep.post (mM) 32

[0666] It is assumed that the following prescription is entered by the user via user interface **12**: [0667] Patient: BW (body weight)=75 kg [0668] Hct (%)=32 [0669] CRRT dose D.sub.eff=28 ml/kg/h, where the dose is an 'effluent dose' per kg [0670] steady state bicarbonate target value: Cp.sub.HCO3_pat=25 mmol/l [0671] patient fluid removal rate: Q.sub.PFR=120 ml/h [0672] blood flow rate: Q.sub.b=200 ml/min

TABLE-US-00012 Prescription unit D.sub.CRRT 28 ml/kg/h C.sub.p.sub.HCO3.sub.—.sub.pat 25 mmol/L Q.sub.PFR 120 ml/h Q.sub.b 200 ml/min Degrees of freedom 5 − 4 = 1 —

[0673] There are a number of additional constrains stored in the in memory **16**, particularly in terms of min/max flow rates; for example: dialysate flow rate (Q.sub.dial): 0 to 6000 ml/h and replacement flow rate (Q.sub.rep.post): 0 to 4000 ml/h.

[0674] The operator selects (or has previously configured): [0675] diffusion/convection split: 50-50, namely a ratio: R.sub.1=1.0

[0676] The control unit **12** then computes the operating parameters, namely the various flow rates as follows:

TABLE-US-00013 Operating flow rate parameters (ml/h) Q.sub.dial (ml/h) 990 Q.sub.PBP (ml/h) 220 Q.sub.rep.post (ml/h) 770 Q.sub.eff (ml/h) 2100 Q.sub.b (ml/min) 200

[0677] In particular:

[0678] Effluent flow rate is determined from the CRRT dialysis dose and body weight as follows: Q.sub.eff=28×75=2100 ml/h, [0679] Q.sub.dial, Q.sub.PBP, Q.sub.rep.post, and Q.sub.eff, are defined through below equation set, explicitly indicated:

[00083]$R_1 = Q_{dial} / (Q_{rep.Math.post} + Q_{PBP}) = 1. Q_{dial} + Q_{PBP} + Q_{rep.Math.post} + Q_{PFR} = Q_{eff} = 2100$

[0680] With the above two equations, Q.sub.dial can be directly calculated and set to 990 ml/h; further Q.sub.PBP+Q.sub.rep.post is equal to 990 ml/h.

[0681] Q.sub.PBP is then—arbitrarily—chosen as the remaining unknown parameter to compute in the next steps.

[0682] Q.sub.fil is calculated based on Eq. 8 that relates it to PBP flow rate, post-dilution flow rate and patient fluid removal rate:

[00084]$Q_{fil} = Q_{PBP} + Q_{rep.Math.post} + Q_{PFR} = 990 + 120 = 1110 ml/h$

[0683] Then, patient steady state bicarbonate concentration (Cpw.sub.HCO3.sub.pat) is defined through the following mathematical relations, namely Eq. 42, Eq. 43 (with the assumption that K.sub.HCO3 is equal to Q.sub.eff—see Eq. 30), which relates the various flow rates generating a further fluid flow rate constrain (in below equations, the terms referred to missing fluid lines have been removed from the general formulation provided in Eq. 42 and 43):

[00085]$Cp_{HCO3\_pat} = \frac{Fp}{Qbw} .Math. (Cpw_{HCO3_{inlet}} .Math. Qbw_{inlet} - Q_{PBP} .Math. C_{HCO3_{PBP}})$

$Cpw_{HCO3\_inlet} = C_{HCO3\_dial} + \frac{J_{HCO3\_eff} - Q_{dial} \times C_{HCO3_{dial}} - Q_{fil} \times C_{HCO3\_dial}}{Q_{eff}}$

[0684] All the terms of above two equations can be either computed or expressed as a function of Q.sub.PBP, as shown below.

[0685] Q.sub.bw and Q.sub.bw_inlet are determined using Eq. 6 and Eq. 7:

[00086]$Qbw = Q_b .Math. [(1 - Hct) .Math. F_p + Hct .Math. Frbc] = 200 .Math. [(1 - 0.32) .Math. 0.95 + 0.32 .Math. 0.85] .Math. 60 = 11016 ml/h$

$Qbw_{inlet} = Q_{bw} + Q_{PBP} = 11016 + Q_{PBP}$

[0686] J.sub.HCO3_eff is determined based on Eq. 44:

[00087]$J_{HCO3\_eff} = J_{HCO3\_inf} - J_{HCO3_{bal}} = J_{HCO3\_inf} - J_{buffer\_load}$

[0687] J.sub.buffer_load is determined based on Eq. 45 (with assumed nNBL0=0.1):

[00088]$J_{buffer\_load} = nNBL0 \times BW = 7,5 mmol/h$

[0688] J.sub.HCO3_inf is determined based on Eq. 27, referencing J.sub.HCO3_inf in mmol/h and Q.sub.PBP in ml/h:

[00089]$J_{HCO3\_inf} = Q_{dial} .Math. C_{HCO3_{dial}} + Q_{rep.Math.post} .Math. C_{HCO3_{rep.Math.post}} + Q_{PBP} .Math. C_{HCO3_{PBP}}$

$J_{HCO3\_inf} = \frac{990}{1000} .Math. 32 + (\frac{990 - Q_{PBP}}{1000}) .Math. 32 + \frac{Q_{PBP}}{1000} .Math. 30 = 63.36 - \frac{Q_{PBP}}{1000} .Math. 2$

[0689] With the above expressions of bicarbonate rates, following expression of plasma water concentration of bicarbonate at filter inlet can be derived:

[00090]$Cpw_{HCO3\_inlet} = 32 + \frac{63.36 - 7.5 - 0.002 .Math. Q_{PBP} - 31.68 - 35.52}{\frac{2100}{1000}} = 26.6 - 0.000952 .Math. Q_{PBP}$

[0690] Expression of steady state patient plasma bicarbonate thus becomes:

[00091]$Cp_{HCO3\_pat} = 25 = \frac{0.95}{11016} .Math. ((26.6 - 0.000952 .Math. Q_{PBP}) .Math. (11016 + Q_{PBP}) - Q_{PBP} .Math. 30)$

$25 .Math. \frac{11016}{0.95} = 289894 = 293026 + (26.6 - 10.49 - 30) .Math. Q_{PBP} - 0.000952 .Math. Q_{PBP}^2$ $3132 - 13.89 .Math. Q_{PBP} - 0.000952 .Math. Q_{PBP}^2 = 0$

[0691] One single solution to above equation is positive and matches with the expected PBP flow rate:

[00092]$Q_{PBP} = \frac{13.89 - \sqrt{13.89^2 - 4 .Math. (-0.000952) .Math. 3123}}{2 .Math. (-0.000952)} = \frac{-13.89 + 14.31}{2 .Math. 0.000952} = 222 ml/h$

[0692] Post-replacement flow rate is then easily derived as:

[00093]$Q_{rep.post} = 990 - Q_{PBP} = 768 ml/h$

[0693] The flow rate values are finally rounded.

Example S2

[0694] Similarly to previous example S1, effluent dose is selected as CRRT dose (blood predilution does not influence dose), filter clearance of small solutes (like bicarbonate) is considered equal to effluent flow rate, too.

[0695] Vice versa, normalized net buffer load nNBL is selected as acid-base balance prescription (when nNBL, the apparatus control unit assumes

that Cp.sub.HCO3_pat0 is equal to 25 mM); blood flow rate is also selected among prescription parameters (reducing the degrees of freedom of the configuration). As in the previous example, five pumps are available and four prescription values are entered. Therefore, the system has one degree of freedom and one therapy configuration constrain may be further selected to obtain a calculation of all operating flow rate parameters. Among therapy configurations, any of convection/diffusion split, predilution ratio and pre/post infusion ratio may be selected. Predefined (modifiable) values for these relations are also included in the memory and presented to the user. Further, necessary treatment configuration values are also entered by the operator or acquired by the control unit **12**. Changed values are identified with different background shading.

TABLE-US-00014 Therapy configuration CRRT Dose Effluent Acid-base balance target nNBL (C.sub.p.sub.HCO3.sub.—.sub.pat = 25 mM) Blood flow rate Prescription ![custom-character] ![custom-character] ![custom-character] ![custom-character] Pre/post infusion ratio 33-67

TABLE-US-00015 Treatment configuration BW (kg) 75 Hct (%) 32 Filter No data C.sub.HCO3.sub.dial (mM) 32 C.sub.HCO3.sub.PBP (mM) 22 C.sub.HCO3.sub.rep.post (mM) 40

[0696] Note that acid-base balance prescription is switched to nNBL and solutions with low and high bicarbonate concentrations are used to provide for some possibilities of adjustment of acid-base balance.

[0697] It is assumed that the following prescription is entered by the user via user interface **12**: [0698] Patient: BW (body weight)=75 kg [0699] Hct (%)=32 [0700] CRRT dose D.sub.eff=28 ml/kg/h, where the dose is an 'effluent dose' per kg [0701] normalized net buffer load nNBL target value: nNBL=0.15 mmol/h/kg [0702] patient fluid removal rate: Q.sub.PFR=120 ml/h [0703] blood flow rate: Q.sub.b=200 ml/min

TABLE-US-00016 Prescription unit D.sub.CRRT 28 ml/kg/h nNBL 0.15 mmol/h/kg Q.sub.PFR 120 ml/h Q.sub.b 200 ml/min Degrees of freedom 5 − 4 = 1 —

[0704] This time, the operator selects: [0705] Pre/post infusion ratio 33%-67%, namely a ratio: R.sub.2=0.5

[0706] The control unit **12** then computes the operating parameters, namely the various flow rates as follows:

TABLE-US-00017 Operating flow rate parameters (ml/h) Q.sub.dial (ml/h) 600 Q.sub.PBP (ml/h) 460 Q.sub.rep.post (ml/h) 920 Q.sub.eff (ml/h) 2100 Q.sub.b (ml/min) 200

[0707] In particular:

[0708] Effluent flow rate is determined as follows: Q.sub.eff=28×75=2100 ml/h, [0709] Q.sub.dial, Q.sub.PBP, Q.sub.rep.post, and Q.sub.eff, are defined through below equation set explicitly indicated:

[00094] $R_{2=} Q_{PBP} / Q_{rep.post} = 0.5 Q_{dial} + Q_{PBP} + Q_{rep.post} + Q_{PFR} = Q_{eff} = 2100$

[0710] Then, normalized net buffer balance (nNBL) is defined on the following mathematical relations, namely Eq. 41, Eq. 26, Eq. 27, Eq. 28, which relates the various flow rates generating a further fluid flow rate constrain (the terms relating to missing fluid lines have been removed from the relevant equations):

[00095] $nNBL = \frac{J_{buffer\_load}}{BW} = \frac{J_{HCO3\_bal}}{BW}$

$J_{HCO3\_bal} = J_{HCO3\_inf} - J_{HCO3\_eff} = Q_{dial}$ .Math. $C_{HCO3_{dial}}$ .Math. $Q_{rep.post} + C_{HCO3_{rep.post}} + Q_{PBP}$ .Math. $C_{HCO3_{PBP}} -$ [Q_{dial} .Math. $C_{HCO3_{dial}} + K_{HCO3}$ .Ma

[0711] According to assumption K.sub.HCO3 is approximated with the effluent flow rate (see Eq. 30):

[00096] $J_{HCO3\_bal} = Q_{rep.post} + C_{HCO3_{rep.post}} + Q_{PBP}$ .Math. $C_{HCO3_{PBP}} -$ [Q_{eff} .Math. $(Cpw_{HCO3_{inlet}} - C_{HCO3_{dial}}) + Q_{fil}$ .Math. $C_{HCO3_{dial}}$]

[0712] Q.sub.fil is calculated based on Eq. 8:

[00097] $Q_{fil} = Q_{PBP} + Q_{rep.post} + Q_{PFR}$

[0713] Cpw.sub.HCO3.sub.inlet is determined based on Eq. 32, with the assumption that patient plasma bicarbonate concentration in the patient is imposed at 25 mM:

[00098] $Cpw_{HCO3\_inlet} = \frac{Q_{bw} .Math. \frac{Cp_{HCO3pat}0}{Fp} + Q_{PBP} .Math. C_{HCO3PBP}}{Qbw_{inlet}}$

[0714] Q.sub.bw and Q.sub.bw_inlet are determined using Eq. 6 and Eq. 7:

[00099] $Qbw = [Q_b$ .Math. $(1 - Hct)$ .Math. $F_p + Hct$ .Math. $Frbc]$

$Qbw_{inlet} = Q_{bw} + Q_{PBP} = Q_b$ .Math. $[(1 - Hct)$ .Math. $Fp + Hct$ .Math. $Frbc] + Q_{PBP}$

[0715] Leading to Q.sub.dial=600 ml/h, Q.sub.rep.post=920 ml/h, Q.sub.PBP=460 ml/h

Example S3

[0716] Similarly to previous example S2, effluent dose is selected as CRRT dose, filter clearance of small solutes (like bicarbonate) is considered equal to effluent flow rate, normalized net buffer load nNBL is selected as acid-base balance prescription (when nNBL, the apparatus control unit assumes that Cp.sub.HCO3_pat is equal to 25 mM), too.

[0717] Vice versa, blood flow rate is removed from prescription parameters (increasing the degrees of freedom of the configuration). Now, five pumps are available and three prescription values are entered. Therefore, the system has two degrees of freedom and two therapy configuration constrains may be further selected to obtain a calculation of all operating flow rate parameters.

[0718] Among therapy configurations, any of convection/diffusion split, predilution ratio and pre/post infusion ratio may be selected. Predefined (modifiable) values for these relations are also included in the memory and presented to the user. Further, necessary treatment configuration values are also entered by the operator or acquired by the control unit **12**. Changed values are identified with different background shading.

TABLE-US-00018 Therapy configuration CRRT Dose Effluent Acid-base balance target nNBL (Cp.sub.HCO3.sub.—.sub.pat = 25mM) Blood flow rate Operating par. Convection/diffusion split 50-50 ![custom-character] ![custom-character] Pre/post infusion ratio 33-67

TABLE-US-00019 Treatment configuration BW (kg) 75 Hct (%) 32 Filter No data C.sub.HCO3.sub.dial(mM) 32 C.sub.HCO3.sub.PBP(mM) 22 C.sub.HCO3.sub.rep.post(mM) 40

[0719] Note that acid-base balance prescription is switched to nNBL and solutions with low and high bicarbonate concentrations are used to provide for some possibilities of adjustment of acid-base balance.

[0720] It is assumed that the following prescription is entered by the user via user interface **12**: [0721] Patient: BW (body weight)=75 kg [0722] Hct (%)=32 [0723] CRRT dose D.sub.eff=28 ml/kg/h, where the dose is an 'effluent dose' per kg [0724] normalized net buffer load nNBL target value: nNBL=0.15 mmol/h/kg [0725] patient fluid removal rate: Q.sub.PFR=120 ml/h

TABLE-US-00020 Prescription unit D.sub.CRRT 28 ml/kg/h nNBL 0.15 mmol/h/kg Q.sub.PFR 120 ml/h ![custom-character] ![custom-character] Degrees of freedom 5 − 3 = 2 —

[0726] The operator selects: [0727] Diffusion/convection split: 50-50, namely a ratio: R.sub.1=1.0 [0728] Pre/post infusion ratio 33-67, namely a ratio: R.sub.2=0.5 Since Q.sub.b is an operating parameter to be calculated, the convection diffusion further mathematical relation is added to the previous equations/mathematical relations used for example S2.

[0729] The control unit **12** then tries to compute the operating parameters, namely the various flow rates. The additional degree of freedom provided by the blood flow setting left to the control unit calculation allows to select the additional equation imposing the pre/post infusion ratio. The other used equations are the same used for the previous example S2; however, in the present case, the equation system has no solution with the imposed settings.

TABLE-US-00021 With the imposed flow With pre/post Operating parameters configuration constraints ratio 33-67 Q.sub.dial (ml/h) No solution 720 600 Q.sub.PBP (ml/h) 420 460 Q.sub.rep.post (ml/h) 840 920 Q.sub.eff (ml/h) 2100 2100 Q.sub.b* (ml/min) 100 200 Convection/diffusion split 50-50 66-34 71-29 *Q.sub.b: 100 ml/min is assumed as minimum acceptable value

[0730] In examples S1 and S2, it is possible to find operating parameters exactly matching with all prescription parameters, as well as to the CRRT

flow configuration constraint. In the example S3, with one additional degree of freedom (blood flow), it is not possible to meet all the prescription parameters simultaneously to the two CRRT flow configuration constraints; in this case, the system should choose one out of the two flow configuration constraints (possibly from a predefined prioritization ranking) as to offer for operating flow rates meeting all prescription parameters, but the second constraint.

[0731] In the same example S3, once considering only one of the two therapy flow configuration constraints, multiple solutions exist. The system can either report the solution which is the closest to the 'dropped' flow constraint (in example S3, the set of parameters with Q_b=100 ml/min, wherein the convection diffusion split is 66%-34% instead of 67%-33%), or to offer several options to the operator. In the example, operating parameters with one larger blood flow rate (Q_b=200 ml/min) is suggested in addition to the closest solution.

[0732] Next examples S4 and S5 include the same system configuration as in previous series of examples is considered; moreover, examples S4 and S5 are identical to examples S1 and S2 except for the chosen definition of CRRT dose; in below examples S4 and S5, CRRT dose refers to urea clearance, and thus considers the effect of predilution.

[0733] In this context, more complex equations are used for the estimation of the clearances of urea (CRRT dose—see Eq. 12) and bicarbonate (acid-base balance analysis); mass transfer properties (K0.A) of the filter must be known.

Example S4

[0734] This example is identical to example S1, but for the chosen definition of CRRT dose.

TABLE-US-00022 Therapy configuration CRRT Dose Urea clearance Acid-base balance target $Cp_{HCO3,pat}$ (nNBL = 0.1 mmol/h/kg) Blood flow rate Prescription Convection/diffusion split 50-50 custom-character custom-character custom-character custom-character

TABLE-US-00023 Treatment configuration BW (kg) 75 Hct (%) 32 K0.A (ml/min) 240 $C_{HCO3,dial}$(mM) 32 $C_{HCO3,PBP}$(mM) 30 $C_{HCO3,rep.post}$(mM) 32

TABLE-US-00024 Prescription unit D_{CRRT} 28 ml/kg/h $Cp_{HCO3,—,pat}$ 25 mmol/L Q_{PFR} 120 ml/h Q_b 200 ml/min Degrees of freedom 5 − 4 = 1 —

[0735] With the above prescription data and selected constrain, the control unit may propose to the user the following operating flow rate parameters:

TABLE-US-00025 Operating flow rate parameters (ml/h) Qdial (ml/h) 1030 Q_{PBP} (ml/h) 400 Qrep.post (ml/h) 630 Qeff (ml/h) 2180 Qb (ml/min) 200

Example S5

[0736] This example is identical to example S2, but for the chosen definition of CRRT dose.

TABLE-US-00026 Therapy configuration CRRT Dose Urea Acid-base balance target nNBL ($Cp_{HCO3,—,pat0}$ = 25 mM) Blood flow rate Prescription custom-character custom-character custom-character custom-character Pre/post infusion ratio 33-67

TABLE-US-00027 Treatment configuration BW (kg) 75 Hct (%) 32 K0.A (ml/min) 240 $C_{HCO3,dial}$(mM) 32 $C_{HCO3,PBP}$(mM) 22 $C_{HCO3,rep.post}$(mM) 40

TABLE-US-00028 Prescription unit D_{CRRT} 28 ml/kg/h nNBL 0.15 mmol/h/kg Q_{PFR} 120 ml/h Q_b 200 ml/min Degrees of freedom 5 − 4 = 1 —

[0737] With the above prescription data and selected constrain, the control unit may propose to the user the following operating flow rate parameters:

TABLE-US-00029 Operating flow rate parameters (ml/h) Q_{dial} (ml/h) 870 Q_{PBP} (ml/h) 395 $Q_{rep.post}$ (ml/h) 870 Q_{eff} (ml/h) 2175 Q_b (ml/min) 200

[0738] K0.A parameter relates to the type of CRRT filter in use and specifies the diffusive mass transfer performance for bicarbonate or urea, which are assumed to be identical in these examples; this assumption relies of the similar molecular weight to the 2 species (60 g/mole for urea, 61 g/mole for HCO_3).

[0739] As expected with the use of a CRRT dose integrating the effect of predilution, higher effluent flow rates are computed in examples S4 and S5 when compared to examples S1 and S2.

Assisted Prescription with Citrate Anticoagulation

[0740] In the context of citrate anticoagulation and as previously described, a citrate solution is infused in the access line of the extracorporeal circuit, particularly next to the patient vascular access, upstream from the blood pump. Simultaneously, a calcium solution for re-establishing the ion content in the blood is infused directly into the patient or into the return line of the circuit as to balance calcium (and possibly other ions) losses to effluent.

[0741] Flow rates of the two infusions relate to the anticoagulation prescription (amount of citrate titrated to reach a certain level of ionised calcium in the extracorporeal blood circuit) and CRRT dose prescription (for the calcium losses), as well as to the concentrations of the respective citrate and calcium solutions.

[0742] Even in the context of 'concentrated' solutions (e.g. 110-140 mM of citrate, >500 mM calcium), the combined flow rate of citrate and calcium infusions has a measurable contribution to the CRRT dose (in the 5 to 10% range).

[0743] In addition, a fraction of infused citrate returns to the patient and is metabolized, leading to the release of calcium and production of bicarbonate impacting on the acid-base balance equilibrium.

[0744] Accordingly, at the opposite of systemic anticoagulation, citrate anticoagulation prescription has complex interactions with both CRRT dose and acid-base balance management. These interactions introduce significant level of complexity in the prescription of CRRT with citrate anticoagulation.

Prescription

[0745] When citrate anticoagulation is used, the CRRT patient prescription may be built from following clinical prescription parameters, all of which have a clear meaning for the medical staff dealing with CRRT treatments): [0746] 1. CRRT dose, [0747] 2. Steady-state acid-base equilibrium target, [0748] 3. Anticoagulant (Citrate) dose, [0749] 4. Ion (Calcium) balancing, [0750] 5. Patient fluid removal rate (PFR), [0751] 6. Optionally, blood flow rate.

[0752] In a system with 4 fluid pumps (dialysis+infusion pumps) and one effluent pump, 5 fluid flow rates are to be defined from the above 5 first prescription parameters. There is thus no degree of freedom left, and no option to consider additional setting from the therapy configuration (unless defining blood flow as operating parameter).

Qualitative Dependence of Operating Parameters

[0753] Next table provides for the interdependence between operating and prescription parameters; importantly this dependence can be conditional to the definition given to the CRRT dose.

TABLE-US-00030

Operating parameter	CRRT dose	Acid-base equilibrium	Citrate dose	Calcium balancing	PFR	Blood flow
Q_{dial}	X1	X3	—	—	—	—
Q_{cit}	X1	X3	X6	—	—	—
Q_{Ca}	X1	X3		X7		
$Q_{rep. pre}$	X1	X3	—	—	—	—
$Q_{rep. post}$	X1	X3	—	—	—	—
Q_{HCO3}	X1	X3	—	—	—	—
Q_{eff}	X1	X3	X7	X4	—	
Q_b	X2	X3	X6	—	—	X5rca

[0754] X1: contribution of flow rates to the CRRT dose is dependent on the definition given to it (see previous paragraph). Most relevant definitions make use of all flow rates (whatever simply referring to Q_{eff} or to an estimated clearance). [0755] X2: contribution of blood rate to CRRT dose is dependent on the chosen dose definition. In the context of RCA, where citrate infusion is proportional to blood flow, blood flow rate will interfere with virtually all expressions of CRRT dose practically used. [0756] X3: all fluid infusions or dialysate contribute to the acid-base balance according to the fluid composition associated to it. Impact of blood flow rate is more significant than in no or systemic anticoagulation as it defines the amount of citrate returned to the patient—and related bicarbonate generation—on top of the predilution effect. Contribution of calcium infusion is marginal when associated to very low infusion

flow rates (<20 ml/h). [0757] X4: patient fluid removal rate prescription is directly controlled by the definition of effluent flow rate versus all the other infusion flow rates of the dialysis system, including the anticoagulant flow rate if relevant. [0758] X5rca: when blood flow defined as prescription parameter, there is a loss of one degree of freedom in the definition of operating flow rates, meaning that less constraints from the therapy configuration parameters can be used. In most of current CRRT systems with RCA, no degree of freedom is left when selecting blood flow as prescription parameter and intending to prescribe acid-base balance equilibrium. [0759] X6: citrate infusion flow rate in RCA is typically prescribed to be proportional to the blood flow, via a prescribed citrate dose coefficient. The resulting flow rate is typically infused pre-blood pump and matches with the PBP flow rate of systemic anticoagulation. [0760] X7: calcium infusion is defined in relation to estimate losses to effluent. These losses are dependent on the clearance of citrate-calcium complexes, and thus on all operating flow rates, as well as on filter mass transfer characteristics. Basic systems may assume calcium losses proportional to effluent flow rate.

EXAMPLES

[0761] Although simplified expressions may be considered, the complexity of interactions between the mass transfer of citrate complexes and bicarbonate in the CRRT filter justifies the use of more accurate estimates of filter clearance, requiring access to the mass transfer properties of the filter in use. In this context, all examples will include these parameters. Examples will illustrate use of 'concentrated' or 'diluted' citrate solutions, as commonly used in the clinical practice. In all the following examples, calcium concentration of the citrate and dialysate solutions is assumed to be zero. Presence of calcium in the post-infusion fluid will be considered in some examples.

[0762] All flow rates are rounded to the next ten, except when less than 100 ml/h.

[0763] The system configuration used throughout the next examples is comparable to the system configuration considered in examples S1 to S5, but for the addition of one pump for calcium infusion. Of course the pre-blood-pump infusion line infuses citrate, rather than a replacement solution as in previous examples S1 to S5. Though the pre-blood-pump infusion line can be physically the same used in the previous examples (see FIG. **1**), a notation 'cit' is used to identify the respective flow rate and container concentration of citrate and different reference numbers are used (see FIG. **3** vs FIG. **2**). The system for RCA includes 5 fluid pumps and the blood pump.

[0764] CRRT system definition for the examples C1 to C6 is indicated in the following table.

TABLE-US-00031 Fluid circuit/pump Symbol Present dialysis fluid pump/supply line Dial X anticoagulant pump/infusion line (citrate) Cit X ion balancing pump/infusion line (calcium) Cal X pre-dilution infusion pump/fluid line rep.pre absent or no use post-dilution infusion pump/fluid line rep.post X post-dilution bicarbonate infusion HCO.sub.3 absent or pump/fluid line no use Effluent pump/line Eff X Blood pump B X

[0765] Next examples C1 to C5 are based on the above circuit configuration and on FIG. **3**.

Examples with Effluent Dose as CRRT Dose

[0766] In this first series of examples, CRRT dose is referred to effluent rate without correction for predilution. Parameters changed in the consecutive examples of this section are identified in coloured cells.

Example C1

[0767] The first reference example is built using normalized Net Buffer Load as acid-base balance prescription, use of diluted citrate solution and blood flow rate as clinical prescription parameters.

[0768] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00032 Therapy configuration CRRT Dose Effluent Acid-base balance target nNBL (Cp.sub.HCO3.sub.—.sub.pat0 = 25 mM) Blood flow rate Prescription custom-character custom-character custom-character custom-character custom-character custom-character

TABLE-US-00033 Treatment configuration BW (kg) 85 Hct (%) 27 K0.A.sub.HCO3 (ml/min) 240 K0.A.sub.cit (ml/min) 109 C.sub.cit.sub.—.sub.PBP (mM) 18 C.sub.ca (mM) 350 C.sub.HCO3.sub.dial(mM) 22 C.sub.HCO3.sub.rep.post(mM) 30 C.sub.ca.sub.rep.post(mM) 0

[0769] As indicated the following clinical prescription parameters are input by the medical staff:

TABLE-US-00034 Prescription unit D.sub.CRRT 30 ml/kg/h nNBL 0.15 mmol/h/kg D.sub.cit 3.1 mmol/L CaComp 110 % Q.sub.PFR 90 ml/h Q.sub.b 130 ml/min Degrees of freedom 6 − 6 = 0 —

[0770] Since the prescription parameter provides for 6 constraints, there is no degree of freedom available to further set additional therapy configurations.

[0771] With the above apparatus set, the control unit determines the following operating flow rates (Q.sub.b is indicated, but it is a prescription parameter already set to 130 ml/min).

TABLE-US-00035 Operating flow rate parameters (ml/h) Q.sub.dial (ml/h) 970 Q.sub.cit (ml/h) 1343 Q.sub.ca (ml/h) 13.3 Q.sub.rep.post (ml/h) 130 Q.sub.eff (ml/h) 2550 custom-character custom-character

[0772] In particular, effluent flow rate Q.sub.eff is determined based on CRRT dose and patient weight:

[00100] $Q_{\text{eff}} = 30 \text{ .Math. } 85 = 2550 ml/h$

[0773] Anticoagulant flow rate Q.sub.cit is related to blood flow rate by the citrate flow rate mathematical relation (Eq. 1):

[00101] $Q_{cit} = \frac{D_{\text{cit}}}{C_{\text{cit\_PBP}}} \text{ .Math. } Q_b = 1343 ml/h$

[0774] Since blood flow rate Q.sub.b and citrate dose D.sub.cit are imposed and citrate concentration is known, Q.sub.cit is immediately derived from above equation.

[0775] Calcium flow rate derives from calcium flow rate mathematical relation (Eq. 2); missing flow rates and terms equal to zero, or negligible have been removed from the general formulation of the description:

[00102] $Q_{ca} = \frac{\text{CaComp .Math. } J_{\text{Ca}}}{C_{ca}}$

[0776] As indicated in the previous examples, the effluent flow rate should respect the fluid balance (see equation 10):

[00103] $Q_{\text{eff}} = Q_{cit} + Q_{\text{dial}} + Q_{\text{rep.post}} + Q_{PFR} + Q_{ca}$

[0777] The last but more complex constraint is based on the normalized net buffer load parameter target nNBL due to its interaction with all flow rates and effects of buffer balance from bicarbonate and bicarbonate precursors, i.e., citrate. Net buffer load mathematical relations links the parameter with the citrate load and bicarbonate balance (Eq. 40 and Eq. 41):

[00104] $J_{buffer\_load} = 3 \text{ .Math. } J_{\text{cit\_load}} + J_{\text{HCO3\_bal}}$ nNBL $= \frac{J_{buffer\_load}}{BW}$

[0778] The citrate load is determined based on citrate load mathematical relation (Eq. 25) that takes into account for citrate metabolic clearance:

[00105] $J_{\text{citrate\_load}} = D_{cit} \text{ .Math. } Q_b \text{ .Math. } (1 - \frac{K_{cit}}{\text{Qpw}_{inlet}}) \text{ .Math. } (1 - \frac{1}{1 + \frac{K_{cit\_met}}{K_{cit}} \text{ .Math. } \frac{\text{Qpw}_{inlet}}{Qp}})$

[0779] Citrate clearance K.sub.t derives from Eq. 21 (with SC.sub.cit=1):

[00106] $K_{cit} = \frac{\text{Qpw}_{inlet} \text{ .Math. } Q_{\text{dial}} - f_{cit} \text{ .Math. } (\text{Qpw}_{inlet} - Q_{\text{fil}}) \text{ .Math. } (Q_{\text{dial}} + Q_{\text{fil}})}{Q_{\text{dial}} - f_{cit} \text{ .Math. } (\text{Qpw}_{inlet} - Q_{\text{fil}})}$ $f_{cit} = (\frac{\text{Qpw}_{inlet} - Q_{\text{fil}}}{\text{Qpw}_{inlet}} \text{ .Math. } \frac{Q_{\text{dial}} + Q_{\text{fil}}}{Q_{\text{dial}}})^{\frac{1}{cit}}$ $cit = e^{(\frac{Q_{\text{fil}}}{K0.A})} - 1$

[0780] Wherein the plasma water flow rate Qpw.sub.inlet at the filtration unit inlet comes from Eq. 5:

[00107] $Qpw_{inlet} = Q_b \text{ .Math. } (1 - \text{Hct}) \text{ .Math. } Fp + Q_{cit}$

[0781] And plasma water flow rate Q.sub.pw is calculated from Eq. 4:

[00108] $Qpw = Q_b \text{ .Math. } (1 - Hct) \text{ .Math. } F_p$

[0782] Ultrafiltration flow rate through the filtration unit **2** is (Eq. 8):

[00109] $Q_{\text{fil}} = Q_{cit} + Q_{\text{rep.post}} + Q_{PFR} + Q_{ca}$

[0783] Metabolic clearance for citrate is estimated with Eq. 22:

[00110] $K_{cit\_met} = 700 \cdot Math. \frac{BW}{72}$

[0784] Vice versa, second term of the net buffer load, namely the bicarbonate balance J.sub.HCO3_bal, comes from e.g., Eq. 26′:

[00111] $J_{HCO3\_bal} = Q_{rep.post} \cdot Math. \, C_{HCO3_{rep.post}} - K_{HCO3} \cdot Math. \, (Cpw_{HCO3_{inlet}} - C_{HCO3_{dial}}) - Q_{fil} \cdot Math. \, C_{HCO3\_dial}$

[0785] Bicarbonate clearance is more precisely estimated through bicarbonate clearance mathematical relations (Eq. 29);

[00112] $SC_{HCO3} = 1: \, K_{HCO3} = \dfrac{Qbw_{inlet} \cdot Math. \, Q_{dial} - f_{HCO3} \cdot Math. \, (Qbw_{inlet} - Q_{fil}) \cdot Math. \, (Q_{dial} + Q_{fil})}{Q_{dial} - f_{HCO3} \cdot Math. \, (Qbw_{inlet} - Q_{fil})}$

$f_{HCO3} = (\dfrac{Qbw_{inlet} - Q_{fil}}{Qbw_{inlet}} \cdot Math. \, \dfrac{Q_{dial} + Q_{fil}}{Q_{dial}})^{\frac{1}{HCO3}}$ $HCO3 = e^{(\frac{Q_{fil}}{(\frac{\ }{\ })_{HCO3}})} - 1$

[0786] Blood water flow rate Qbw.sub.inlet at filtration unit inlet comes from Eq. 7:

[00113] $Qbw_{inlet} = Q_b \cdot Math. \, [(1 - Hct) \cdot Math. \, Fp + Hct \cdot Math. \, Frbc] + Q_{cit}$

[0787] Blood water flow rate is derived from Eq. 6:

[00114] $Qbw = Q_b \cdot Math. \, [(1 - Hct) \cdot Math. \, F_p + Hct \cdot Math. \, Frbc]$

[0788] Finally, required plasma water bicarbonate concentration Cpw.sub.HCO3_inlet at filter inlet from Eq. 32 is:

[00115] $Cpw_{HCO3\_inlet} = \dfrac{Q_{bw} \cdot Math. \, \frac{Cp_{HCO3_{pat}} 0}{Fp}}{Qbw_{inlet}}$

[0789] Wherein bicarbonate concentration in the patient plasma at steady state is fixed and assumed constant (e.g., 25 mM). Using all the above mathematical relations, the control unit **12** determines all the operative prescription parameters.

Example C2

[0790] Second example is using previous example C1 as reference and illustrates the changes in flow rates required further to a change of citrate dose prescription, which could be required to keep blood circuit ionized calcium within recommended levels (e.g. in the 0.25-0.35 mM range).

[0791] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00036 Therapy configuration CRRT Dose Effluent Acid-base balance target nNBL (Cp.sub.HCO3.sub.—.sub.pat0 = 25 mM) Blood flow rate Prescription custom-character custom-character custom-character custom-character custom-character custom-character

TABLE-US-00037 Treatment configuration BW (kg) 85 Hct (%) 27 K0.A.sub.HCO3 (ml/min) 240 K0.A.sub.cit (ml/min) 109 C.sub.cit.sub.—.sub.PBP (mM) 18 C.sub.ca (mM) 350 C.sub.HCO3.sub.dial(mM) 22 C.sub.HCO3.sub.rep.post(mM) 30 C.sub.ca.sub.rep.post(mM) 0

TABLE-US-00038 Prescription unit D.sub.CRRT 30 ml/kg/h nNBL 0.15 mmol/h/kg D.sub.cit 2.8 mmol/L CaComp 110 % Q.sub.PFR 90 ml/h Qb 130 ml/min Degrees of freedom 6 − 6 = 0 —

[0792] Since the prescription parameter provides for 6 constraints, there is no degree of freedom available to further set additional therapy configurations.

[0793] With the above apparatus set, the control unit determines the following operating flow rates (Q.sub.b is indicated, but it is a prescription parameter already set to 130 ml/min). As can be seen, all operating flow rates are significantly affected by the citrate dose change, but the effluent flow rate.

TABLE-US-00039 Operating flow rate parameters (ml/h) Q.sub.dial (ml/h) 720 Q.sub.cit (ml/h) 1213 Q.sub.cal (ml/h) 13.7 Q.sub.rep.post (ml/h) 510 Q.sub.eff (ml/h) 2550 custom-character custom-character

Example C3

[0794] In the continuation of the two previous examples, example C3 illustrates changes required further to an increase of citrate dose.

[0795] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00040 Therapy configuration CRRT Dose Effluent Acid-base balance target nNBL (Cp.sub.HCO3.sub.—.sub.pat0 = 25 mM) Blood flow rate Prescription custom-character custom-character custom-character custom-character custom-character custom-character

TABLE-US-00041 Treatment configuration BW (kg) 85 Hct (%) 27 K0.A.sub.HCO3 (ml/min) 240 K0.A.sub.cit (ml/min) 109 C.sub.cit.sub.—.sub.PBP (mM) 18 C.sub.ca (mM) 350 C.sub.HCO3.sub.dial(mM) 22 C.sub.HCO3.sub.rep.post(mM) 30 C.sub.ca.sub.rep.post(mM) 0

TABLE-US-00042 Prescription unit D.sub.CRRT 30 ml/kg/h nNBL 0.15 mmol/h/kg D.sub.cit 3.5 mmol/L CaComp 110 % Q.sub.PFR 90 ml/h Q.sub.b 130 ml/min Degrees of freedom 6 − 6 = 0 —

[0796] Since the prescription parameter provides for 6 constraints, there is no degree of freedom available to further set additional therapy configurations.

[0797] With the above apparatus set, the control unit tries to determine the operating flow rates (in the second column, Q.sub.b is indicated, but it is a prescription parameter already set to 130 ml/min). As can be seen, there is no solution to the equation system compatible with the prescription.

[0798] All operating flow rates are significantly affected by the citrate dose change, but the effluent flow rate and it is not possible to achieve the desired targets. Third column provides a proposed solution considering Q.sub.b as an operating parameter (that may vary within prescribes limit values).

TABLE-US-00043 Operating flow rate With Qb as parameters (ml/h) operating parameter Q.sub.dial (ml/h) No solution 940 Q.sub.cit (ml/h) 1400 Q.sub.cal (ml/h) 13.0 Q.sub.rep.post (ml/h) 110 Q.sub.eff (ml/h) 2550 2550 Q.sub.b (ml/min) custom-character 120

Example C4

[0799] The example C4 is based on C1 reference with the replacement of the diluted citrate solution with a 'concentrated' one; calcium solution is changed as well with a less concentrated one.

[0800] Highlighted changes are those in reference to C1 example.

[0801] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00044 Therapy configuration CRRT Dose Effluent Acid-base balance target nNBL (Cp.sub.HCO3.sub.—.sub.pat0 = 25 mM) Blood flow rate Prescription custom-character custom-character custom-character custom-character custom-character custom-character

TABLE-US-00045 Treatment configuration BW (kg) 85 Hct (%) 27 K0.A.sub.HCO3 (ml/min) 240 K0.A.sub.cit (ml/min) 109 C.sub.cit.sub.—.sub.PBP (mM) 136 C.sub.ca (mM) 100 C.sub.HCO3.sub.dial(mM) 22 C.sub.HCO3.sub.rep.post(mM) 30 C.sub.ca.sub.rep.post(mM) 0

TABLE-US-00046 Prescription unit D.sub.CRRT 30 ml/kg/h nNBL 0.15 mmol/h/kg D.sub.cit 3.1 mmol/L CaComp 110 % Q.sub.PFR 90 ml/h Qb 130 ml/min Degrees of freedom 6 − 6 = 0 —

[0802] Since the prescription parameter provides for 6 constraints, there is no degree of freedom available to further set additional therapy configurations.

[0803] With the above apparatus set, the control unit tries to determine the operating flow rates (in the second column, Q.sub.b is indicated, but it is a prescription parameter already set to 130 ml/min). As can be seen, there is no solution to the equation system compatible with the prescription.

[0804] All operating flow rates are significantly affected by the citrate dose change, but the effluent flow rate and it is not possible to achieve the desired targets. Third column provides a proposed solution considering Q.sub.b as an operating parameter (that may vary within prescribes limit values).

TABLE-US-00047 Operating flow rate With Qb as parameters (ml/h) operating parameter Q.sub.dial (ml/h) No solution 1960 Q.sub.cit (ml/h) 137

Q.sub.cal (ml/h) 52.7 Q.sub.rep.post (ml/h) 310 Q.sub.eff (ml/h) 2550 2550 Q.sub.b (ml/min) custom-character 100

[0805] Above examples C1 to C4 illustrates the importance of blood flow rate during citrate anticoagulation for the definition of adequate acid-base balance when having fixed bicarbonate composition of the fluids.

Examples with Urea Clearance Dose as CRRT Dose

[0806] Similarly to the series of example provided in no or systemic anticoagulation, next examples are provided in the context of RCA, where CRRT dose includes a factor for predilution, for example where referring to Urea clearance dose.

[0807] Same system configuration is the same used for examples C1 to C4 (see FIG. **3**). The used mathematical relations are basically the same used for example C1, but the CRRT dialysis dose is determined using Eq. 12.

Example C5

[0808] This example is built in reference to example C1, replacing effluent CRRT dose with urea clearance dose (see relevant paragraph). Changes are highlighted in reference to example C1.

[0809] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00048 Therapy configuration CRRT Dose Urea clearance Acid-base balance target nNBL (Cp.sub.HCO3.sub.—.sub.pat0 = 25 mM) Blood flow rate Prescription custom-character custom-character custom-character custom-character custom-character custom-character

TABLE-US-00049 Treatment configuration BW (kg) 85 Hct (%) 27 K0.A.sub.HCO3 (ml/min) 240 K0.A.sub.cit (ml/min) 109 C.sub.cit.sub.—.sub.PBP (mM) 18 C.sub.ca (mM) 350 C.sub.HCO3.sub.dial(mM) 22 C.sub.HCO3.sub.rep.post(mM) 30 C.sub.ca.sub.rep.post(mM) 0

TABLE-US-00050 Prescription unit D.sub.CRRT 30 ml/kg/h nNBL 0.15 mmol/h/kg D.sub.cit 3.1 mmol/L CaComp 110 % Q.sub.PFR 90 ml/h Qb 130 ml/min Degrees of freedom 6 − 6 = 0 —

[0810] Since the prescription parameter provides for 6 constraints, there is no degree of freedom available to further set additional therapy configurations.

[0811] With the above apparatus set, the control unit determines the following operating flow rates (Q.sub.b is indicated, but it is a prescription parameter already set to 130 ml/min).

TABLE-US-00051 Operating flow rate parameters (ml/h) Q.sub.dial (ml/h) 780 Q.sub.cit (ml/h) 1343 Q.sub.cal (ml/h) 15.9 Q.sub.rep.post (ml/h) 800 Q.sub.eff (ml/h) 3030 custom-character

Example C6

[0812] Similar simulation as done between examples C2 and C1 is repeated here between C6 and C5.

[0813] Changes between C6 and C5 are those highlighted in next table.

[0814] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00052 Therapy configuration CRRT Dose Urea clearance Acid-base balance target nNBL (Cp.sub.HCO3.sub.—.sub.pat0 = 25 mM) Blood flow rate Prescription custom-character custom-character custom-character custom-character custom-character custom-character

TABLE-US-00053 Treatment configuration BW (kg) 85 Hct (%) 27 K0.A.sub.HCO3 (ml/min) 240 K0.A.sub.cit (ml/min) 109 C.sub.cit.sub.—.sub.PBP (mM) 18 C.sub.ca (mM) 350 C.sub.HCO3.sub.dial(mM) 22 C.sub.HCO3.sub.rep.post(mM) 30 C.sub.ca.sub.rep.post(mM) 0

TABLE-US-00054 Prescription unit D.sub.CRRT 30 ml/kg/h nNBL 0.15 mmol/h/kg D.sub.cit 2.8 mmol/L CaComp 110 % Q.sub.PFR 90 ml/h Q.sub.b 130 ml/min Degrees of freedom 6 − 6 = 0 —

[0815] Since the prescription parameter provides for 6 constraints, there is no degree of freedom available to further set additional therapy configurations.

[0816] With the above apparatus set, the control unit determines the following operating flow rates (Q.sub.b is indicated, but it is a prescription parameter already set to 130 ml/min).

TABLE-US-00055 Operating flow rate parameters (ml/h) Q.sub.dial (ml/h) 570 Q.sub.cit (ml/h) 1213 Q.sub.cal (ml/h) 16.1 Q.sub.rep.post (ml/h) 1090 Q.sub.eff (ml/h) 2980 custom-character

[0817] Examples C5 and C6 shows the major impact of blood predilution when using 'diluted' citrate solutions and referring to a CRRT dose integrating the impact of predilution, like urea clearance dose. Effluent flow rate is significantly increased between examples C5-C6 and C1-C2 (about 400 to 500 ml/h).

[0818] In parallel, these examples show the major adjustments of dialysate and post-replacement flow rates required to maintain the desired acid-base balance while increasing the CRRT dose.

Bicarbonate Post-Infusion System Configuration

[0819] This section provides for assisted prescription examples in the context of a system where a concentrated bicarbonate solution is infused post filter and contributes to a major part of all bicarbonate infused through the CRRT therapy (via all fluids including dialysate). Ideally, this major part is more than 50% and may reached 100%; in the latter case, this means that all fluids are bicarbonate free, except the concentrated bicarbonate infusion.

[0820] Purpose of the system configuration is to decouple as much as possible acid-base balance prescription from CRRT dose and/or citrate dose prescriptions, providing thus for more freedom in varying these parameters independently.

[0821] All examples provided in this section are built using a CRRT dose based on urea clearance, and thus factoring the impact of predilution.

Examples in No or Systemic Anticoagulation

[0822] The system configuration used throughout the next examples is comparable to the system configuration considered in examples S1 to S5 for the number of fluid pumps (n=4) and the presence of one infusion circuit in pre-dilution and one in post-dilution; it however includes several changes as reported in next table.

[0823] The CRRT system definition referred to examples BS1 to BS2 (BS stands for bicarbonate+systemic or no anticoagulation) is shown in the following table and also shown in FIG. **4**.

TABLE-US-00056 Fluid circuit/pump Symbol Present dialysis fluid pump/supply line Dial X PBP infusion pump/line PBP absent or no use pre-dilution infusion pump/line rep.pre X post-dilution infusion pump/line rep.post absent or no use post-dilution bicarbonate infusion HCO3 X line/pump effluent pump/line eff X blood pump b X

Example BS1

[0824] This example is comparable to example S5, but for the composition of fluids and the therapy configuration parameter. Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00057 Therapy configuration CRRT Dose Urea clearance Acid-base balance target nNBL (Cp.sub.HCO3.sub.—.sub.pat0 = 25 mM) Blood flow rate Prescription Convection/diffusion split 50-50 custom-character custom-character custom-character custom-character

TABLE-US-00058 Treatment configuration BW (kg) 75 Hct (%) 32 K0.A (ml/min) 240 C.sub.HCO3.sub.dial(mM) 0 C.sub.HCO3.sub.rep.pre(mM) 22 C.sub.HCO3.sub.HCO3post(mM) 140

TABLE-US-00059 Prescription unit D.sub.CRRT 28 ml/kg/h nNBL 0.15 mmol/L Q.sub.PFR 120 ml/h Q.sub.b 200 ml/min Degrees of freedom 5 − 4 = 1 —

[0825] Since one degree of freedom is available, one additional constraint may be selected, in the present example, convention diffusion split (or ratio) is selected and set to 50%-50% or R**1**=1.

[0826] Given the above clinical prescription parameters and the additional user selection of therapy configuration, the control unit **12** determines the following operating parameters (Q_b being part of the prescription):

TABLE-US-00060 Operating flow rate parameters (ml/h) Q_{dial} (ml/h) 1050 $Q_{rep.pre}$ (ml/h) 660 Q_{HCO3} (ml/h) 390 Q_{eff} (ml/h) 2220

Example BS2

[0827] This example is comparable to previous and targets a much higher net buffer load. Changes from previous example BS1 are highlighted with backgrounded cells.

[0828] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00061 Therapy configuration CRRT Dose Urea clearance Acid-base balance target nNBL ($Cp_{HCO3^-,pat0}$ = 25 mM) Blood flow rate Prescription Convection/diffusion split 50-50

TABLE-US-00062 Treatment configuration BW (kg) 75 Hct (%) 32 K0.A (ml/min) 240 $C_{HCO3.dial}$(mM) 0 $C_{HCO3.rep.pre}$(mM) 22 $C_{HCO3.HCO3post}$(mM) 140

[0829] The clinical prescription parameters are the same as in the previous example BS1, but the nNBL is changed from 0.15 to a sensibly higher 0.25 value.

TABLE-US-00063 Prescription unit D_{CRRT} 28 ml/kg/h nNBL 0.25 mmol/L Q_{PFR} 120 ml/h Q_b 200 ml/min Degrees of freedom 5 − 4 = 1 —

[0830] The calculated flow rates for the remaining operating parameters are as follows (Q_b being still part of the prescription):

TABLE-US-00064 Operating flow rate parameters (ml/h) Q_{dial} (ml/h) 1050 $Q_{rep.pre}$ (ml/h) 595 Q_{HCO3} (ml/h) 455 Q_{eff} (ml/h) 2220

[0831] In the context of a system having only bicarbonate infusion as post-infusion, it is not relevant/possible to include therapy parameters such pre-post infusion ratio, as the post infusion rate is dictated by the acid-base balance prescription. In other terms, selection of pre-post infusion ratio would have caused the control unit to return no solution to the equation system. Therefore, selection of convection/diffusion ratio appears to be the exclusively reasonable selection among therapy additional constraints.

[0832] Comparison of examples BS1 and BS2 illustrates the strong and direct dependence of acid-base balance equilibrium on the bicarbonate post infusion flow rate, in a configuration where more than 80% of total bicarbonate infusion comes from a single source.

[0833] Notably, the 'high' nNBL level prescription of example BS2 cannot be provided in the conventional system and bicarbonate fluid configurations of examples S4-S5, unless using extremely high CRRT prescribed dialysis dose (e.g. about 50 ml/kg/h).

Examples in Citrate Anticoagulation

[0834] The concept of bicarbonate infusion is further illustrated in the context of citrate anticoagulation (RCA).

[0835] Selected system configuration is comparable to the configuration of examples C1-C6 with the addition of a bicarbonate post-infusion pump. This system is thus including six fluid pumps and one blood pump (see the example of FIG. **5**). CRRT system definition for examples BC1 to BC3 (BC stands for bicarbonate+citrate anticoagulation) is indicated in the following table:

TABLE-US-00065 Fluid circuit/pump Symbol Present dialysis fluid pump/supply line Dial X anticoagulant pump/infusion line (citrate) Cit X ion balancing pump/infusion line (calcium) Cal X pre-dilution infusion pump/fluid line rep.pre Absent - no use post-dilution infusion pump/fluid line rep.post X post-dilution bicarbonate infusion HCO_3 X pump/fluid line Effluent pump/line Eff X Blood pump b X

[0836] See FIG. **5** for reference to the used circuit configuration.

Example BC1

[0837] This example is similar to previous example CC, but for the addition of the bicarbonate post infusion and the use of buffer-free dialysate.

[0838] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00066 Therapy configuration CRRT Dose Urea clearance Acid-base balance target nNBL ($Cp_{HCO3^-,pat0}$ = 25 mM) Blood flow rate Prescription Convection/diffusion split 50-50

TABLE-US-00067 Treatment configuration BW (kg) 85 Hct (%) 27 $K0.A_{HCO3}$ (ml/min) 240 $K0.A_{cit}$ (ml/min) 109 $C_{cit,^-,PBP}$ (mM) 18 C_{ca} (mM) 350 $C_{HCO3.dial}$(mM) 0 $C_{HCO3.rep.post}$(mM) 30 $C_{ca.rep.post}$(mM) 0 $C_{HCO3.HCO3post}$(mM) 140

[0839] As below indicated, Q_b is still a prescription parameter in addition to the prescribed dialysis dose (D_{set}—urea clearance) to be delivered, to the normalized net buffer load, to the patient fluid removal rate (Q_{PFR}) and the RCA prescriptions:

TABLE-US-00068 Prescription unit D_{CRRT} 30 ml/kg/h nNBL 0.15 mmol/h/kg D_{cit} 3.1 mmol/L CaComp 110 % Q_{PFR} 90 ml/h Q_b 130 ml/min Degrees of freedom 7 − 6 = 1 —

[0840] There is one remaining degree of freedom based on the six prescription parameters and the seven flow rates to be determined. However, the selected convection-diffusion split cannot be reached given the system configuration and the clinical prescription parameters:

TABLE-US-00069 Closest to With Qb as Operating flow rate convection/diffusion operating parameters (ml/h) target parameter Q_{dial} (ml/h) No 1300 1520 Q_{cit} (ml/h) solution 1343 1033 Q_{cal} (ml/h) 15.2 14.8 $Q_{rep.post}$ (ml/h) 0 0 Q_{HCO3} (ml/h) 287 394 Q_{eff} (ml/h) 3036 3052 Qb (ml/min) 130 100 Convection- N/A 57-43 50-50 diffusion split

[0841] The control unit **12** provides for the solution relating to flow rates for the operating parameter which is closest to the convection diffusion ratio selected. In the present case the convection diffusion ratio is 57%-43% (R**1**=1.33). As an alternative, Q_b is moved from prescription parameter to operating parameter and the convection diffusion ratio is kept at 50%-50% as originally set. Resulting blood flow rate is reduced to 100 ml/min.

Example BC2

[0842] BC2 example is similar to BC1 with a change of the citrate solution towards a higher concentration. Changes from BC1 are highlighted.

[0843] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00070 Therapy configuration CRRT Dose Urea clearance Acid-base balance target nNBL ($Cp_{HCO3^-,pat0}$ = 25 mM) Blood flow rate Prescription Convection/diffusion split 50-50

TABLE-US-00071 Treatment configuration BW (kg) 85 Hct (%) 27 $K0.A_{HCO3}$ (ml/min) 240 $K0.A_{cit}$ (ml/min) 109 $C_{cit,^-,PBP}$ (mM) 50 C_{ca} (mM) 350 $C_{HCO3.dial}$(mM) 0 $C_{HCO3.rep.post}$(mM) 30 $C_{ca.rep.post}$(mM) 0 $C_{HCO3.HCO3post}$(mM) 140

[0844] Clinical prescription parameters are unaltered with respect to example BC1:

TABLE-US-00072 Prescription unit D_{CRRT} 30 ml/kg/h nNBL 0.15 mmol/h/kg D_{cit} 3.1 mmol/L CaComp 110 % Q_{PFR} 90 ml/h Q_b 130 ml/min Degrees of freedom 7 − 6 = 1 —

[0845] With the change(increase) in anticoagulant bag concentration for citrate, the control unit **12** finds a solution for the operating flow rates without the need to change the set blood flow rate and/or changing the convection/diffusion split:

TABLE-US-00073 Operating flow rate parameters (ml/h) Q_{dial} (ml/h) 1365 Q_{cit} (ml/h) 484 Q_{cal} (ml/h) 15.7 $Q_{rep.post}$ (ml/h) 615 Q_{HCO3} (ml/h) 161 Q_{eff} (ml/h) 2730

Example BC3

[0846] BC3 illustrates the changes in flow rates when changing citrate dose prescription given in example BC2.

[0847] Changes from BC2 are highlighted.

[0848] Therapy configuration is set as per the following table. Treatment configuration data are requested and entered according to the second table below reported.

TABLE-US-00074 Therapy configuration CRRT Dose Urea clearance Acid-base balance target nNBL (Cp.sub.HCO3.sub.—.sub.pat0 = 25 mM) Blood flow rate Prescription Convection/diffusion split 50-50 ![custom-character] ![custom-character] ![custom-character] ![custom-character]

TABLE-US-00075 Treatment configuration BW (kg) 85 Hct (%) 27 K0.A.sub.HCO3 (ml/min) 240 K0.A.sub.cit (ml/min) 109 C.sub.cit.sub.—.sub.PBP (mM) 50 C.sub.ca (mM) 350 C.sub.HCO3.sub.dial(mM) 0 C.sub.HCO3.sub.rep.post(mM) 30 C.sub.ca.sub.rep.post(mM) 0 C.sub.HCO3.sub.HCO3post(mM) 140

[0849] As below indicated, citrate dose is raised from 3.1 to 3.5 mmol/L:

TABLE-US-00076 Prescription unit D.sub.CRRT 30 ml/kg/h nNBL 0.15 mmol/h/kg D.sub.cit 3.5 mmol/L CaComp 110 % Q.sub.PFR 90 ml/h Qb 130 ml/min Degrees of freedom 7 − 6 = 1 —

[0850] The calculated operating parameters are as follows (blood flow rate being a prescription parameter):

TABLE-US-00077 Operating flow rate parameters (ml/h) Q.sub.dial (ml/h) 1375 Q.sub.cit (ml/h) 546 Q.sub.cal (ml/h) 15.7 Q.sub.rep.post (ml/h) 595 Q.sub.HCO3 (ml/h) 128 Q.sub.eff (ml/h) 2750 ![custom-character]

[0851] Addition of the bicarbonate post-infusion pump adds one degree of freedom and enables to consider one therapy configuration constraint in example BC1 (when compared to C5). However use of a 'diluted' citrate solution drives for significant convective flow and makes difficult to achieve an HDF prescription with equal convection and diffusion flow rates.

[0852] Example BC2 documents the benefit of more concentrated citrate solution when targeting a CRRT therapy configuration with significant dialysis/diffusion contribution, further to the decrease of citrate solution flow rate (which contributes to convective fluid exchange).

[0853] Example BC3 indicates that changes in citrate dose (for the purpose of anticoagulation intensity adjustment) can be easily balanced via adjustment of the bicarbonate post-infusion rate in order to keep the same acid-base equilibrium target.

Compatibility with Other System Features

[0854] High level interactions exist between the assisted prescription feature and optional features and an advanced CRRT system.

[0855] Blood flow rate management: in the configuration where the system is equipped with a module optimising automatically the blood pump speed as a function of vascular access performance, the system should operate with blood flow defined as operating parameter, rather than prescription parameter. A maximum blood flow rate value should however be offered as an operator settable constraint. In these conditions, the control unit shall re-compute automatically the various flow settings each time the blood flow rate is adjusted by the 'blood pump management' module.

[0856] TMP monitoring/convection: in the configuration where the system is equipped with a module optimising automatically the convective flow rate as a function of TMP (or other pressure parameters), the assisted prescription system, namely the control unit shall re-compute automatically the various flow settings each time the convective flow rates are adjusted.

[0857] Dose Control: Assisted prescription module provides for the computation of flow rate settings, while the Dose Control system monitors the 'instantaneous' CRRT dose requirements along the therapy in order to achieve an overall CRRT dose clinical target over several days of treatment. The assisted prescription enhancement brought with the inclusion of acid-base balance prescription parameter makes the Dose Control system applicable to citrate anticoagulation in a safe and practical way.

Mathematical Relations

[0858] Here below the main mathematical relations that the control unit **12** uses to link patient prescription parameters, treatment configuration parameters and operating parameters are reported. The mathematical relations are already described in detail in the previous sections of the present application. When the necessary and/or selected patient prescription parameters and treatment configuration parameters are received, the control unit **12** is configured to use the relevant mathematical equations to calculate the set flow rates of fluid in the lines for the operating parameters.

[0859] The control unit **12** may then output the set and calculated flow rates for acceptance to a user and, after acceptance, drive the various actuators (pumps) to obtain the set and calculated flow rates in the relevant lines. Alternatively, the control unit **12** may automatically set the actuators to achieve the set and calculated flow rates.

Eq. 1—Citrate Flow Rate Mathematical Relation

[00116] $Q_{cit} = \frac{D_{cit}}{C_{cit\_PBP}}$ .Math. Q_b

Eq. 2—Calcium Flow Rate Mathematical Relation

[00117] $Q_{ca} = \frac{CaComp \,.Math.\, J_{Ca}}{C_{ca}} - \frac{Q_{rep.post} \,.Math.\, C_{ca_{rep.post}}}{C_{ca}} - \frac{Q_{HCO3} \,.Math.\, C_{ca_{HCO3}}}{C_{ca}}$

Eq. 3—Plasma Flow Rate Mathematical Relation

[00118] $Qp = Q_b$ .Math. $(1 - Hct)$

Eq. 4—Plasma Water Flow Rate Mathematical Relation

[00119] $Qpw = Qp$ .Math. $F_p = Q_b$ .Math. $(1 - Hct)$ .Math. F_p

Eq. 5—Plasma Water Flow Rate at Filtration Unit Inlet Mathematical Relation

[00120] $Qpw_{inlet} = Qpw + Q_{cit} + Q_{syr} + Q_{PBP} + Q_{rep.pre} = Q_b$ .Math. $(1 - Hct)$ .Math. $Fp + Q_{cit} + Q_{syr} + Q_{PBP} + Q_{rep.pre}$

Eq. 6—Blood Water Flow Rate Mathematical Relation

[00121] $Qbw = Q_b$ .Math. $[(1 - Hct)$ .Math. $F_p + Hct$ .Math. $Frbc]$

Eq. 7—Blood Water Flow Rate at Filtration Unit Inlet Mathematical Relation

[00122] $$Qbw_{inlet} = Q_{bw} + Q_{cit} + Q_{syr} + Q_{PBP} + Q_{rep.pre}$$
$$= Q_b \,.Math.\, [(1 - Hct) \,.Math.\, Fp + Hct \,.Math.\, Frbc] + Q_{cit} + Q_{syr} + Q_{PBP} + Q_{rep.pre}$$

Eq. 8—Ultrafiltration Flow Rate Mathematical Relation

[00123] $Q_{fil} = Q_{PBP} + Q_{cit} + Q_{syr} + Q_{rep.pre} + Q_{rep.post} + Q_{HCO3} + Q_{PFR} + Q_{ca}$

Eq. 9—Pre-Post Split

[00124] $Q_{rep.pre} = PRE$ .Math. $Q_{rep}\ Q_{rep} = (Q_{rep.pre} + Q_{rep.post})$

Eq. 10—Effluent Flow Rate Mathematical Relation

[00125] $Q_{eff} = Q_{PBP} + Q_{cit} + Q_{syr} + Q_{dial} + Q_{rep.pre} + Q_{rep.post} + Q_{HCO3} + Q_{PFR} + Q_{ca}$

Eq. 11—Urea Clearance (Purely Diffusive Mode)

[00126] $Z = \frac{Q_{pw_{inlet}}}{Q_{dial}}\ NT = \frac{S/RT}{Q_{pw_{inlet}}}\ D_{urea}(Q_{pw_{inlet}}; Q_{dial}) = K_{urea} = Q_{pw_{inlet}}$ .Math. $\frac{e^{[NT \,.Math.\, (1-Z)]} - 1}{e^{[NT \,.Math.\, (1-Z)]} - Z}\ if Z \neq 1$

$D_{urea}(Q_{pw_{inlet}}; Q_{dial}) = K_{urea} = Q_{pw_{inlet}}$ .Math. $\frac{NT}{NT+1}\ if Z = 1$

Eq. 12—Urea Clearance (Diffusive and/or Convective Mode)

$$D_{\text{urea}}(Q_{\text{pw}_{\text{inlet}}}; Q_{\text{dial}}; Q_{\text{fil}}) = K_{\text{urea}}$$

[00127] $= e^{\frac{SC_{\text{urea}} \cdot \text{Math.} \, Q_{\text{fil}}}{(S/RT)_{\text{urea}}}} - 1 f_{\text{urea}} = (\frac{Q_{\text{pw}_{\text{inlet}}} - SC_{\text{urea}} \cdot \text{Math.} \, Q_{\text{fil}}}{Q_{\text{pw}_{\text{inlet}}}} \cdot \text{Math.} \, \frac{Q_{\text{dial}} + SC_{\text{urea}} \cdot \text{Math.} \, Q_{\text{fil}}}{Q_{\text{dial}}})^{1}$

$Q_{\text{pw}_{\text{inlet}}} \cdot \text{Math.} \, Q_{\text{dial}} - f_{\text{urea}} \cdot \text{Math.} \, (Q_{\text{pw}_{\text{inlet}}} - SC_{\text{urea}} \cdot \text{Math.} \, Q_{\text{fil}}) \cdot \text{Math.}$

$= \dfrac{(Q_{\text{dial}} + SC_{\text{urea}} \cdot \text{Math.} \, Q_{\text{fil}})}{Q_{\text{dial}} - f_{\text{urea}} \cdot \text{Math.} \, (Q_{\text{pw}_{\text{inlet}}} - SC_{\text{urea}} \cdot \text{Math.} \, Q_{\text{fil}})}$

Eq. 13/14/15/15′—Dilution Factors

[00128] $F_{\text{dilution}_{\text{blood}}} = \frac{Q_b}{Q_b + Q_{\text{rep.pre}} + Q_{PBP} + Q_{cit} + Q_{syr}} F_{\text{dilution}_{\text{plasma}}} = \frac{Q_p}{Q_p + Q_{\text{rep.pre}} + Q_{PBP} + Q_{cit} + Q_{syr}} F_{\text{dilution}_{pw}} = \frac{Q_{pw}}{Q_{pw} + Q_{\text{rep.pre}} + Q_{PBP} + Q_{cit} + Q_{syr}}$

$F_{\text{dilution}_{bw}} = \frac{Q_{bw}}{Q_{bw} + Q_{\text{rep.pre}} + Q_{PBP} + Q_{cit} + Q_{syr}}$

Eq. 16—Urea Dose (Corrected for Pre-Dilution)

[00129] $D_{\text{urea\_corr}} = F_{\text{dilution}_{\text{blood}}} \cdot \text{Math.} \, K_{\text{urea}} = \frac{Q_b}{Q_b + Q_{\text{rep.pre}} + Q_{PBP} + Q_{cit} + Q_{syr}} \cdot \text{Math.} \, Q_{\text{eff}}$

Eq. 17—Net Buffer Load Mathematical Relation

[00130] $J_{\text{buffer\_loud}} = J_{\text{met\_cit}} + J_{\text{HCO3}_{bal}} + J_{\text{met\_lact}} - J_{H+}$

Eq. 18/19/20—Citrate Load Mathematical Relations

[00131] $J_{\text{citrate\_load}} = J_{\text{cit\_PBP}} - J_{\text{cit\_dial}} J_{\text{cit\_PBP}} = Q_{cit} \cdot \text{Math.} \, C_{\text{cit\_PBP}} = D_{cit} \cdot \text{Math.} \, Q_b J_{\text{cit\_dial}} = K_{cit} \cdot \text{Math.} \, \text{Cpw}_{\text{cit\_inlet}}$

Eq. 21/22/23/24/24′—Citrate Clearance and Inlet Concentration Mathematical Relations

[00132] $K_{cit} = \frac{\text{Qpw}_{\text{inlet}} \cdot \text{Math.} \, Q_{\text{dial}} - f_{cit} \cdot \text{Math.} \, (\text{Qpw}_{\text{inlet}} - SC_{cit} \cdot \text{Math.} \, Q_{\text{fil}}) \cdot \text{Math.} \, (Q_{\text{dial}} + SC_{cit} \cdot \text{Math.} \, Q_{\text{fil}})}{Q_{\text{dial}} - f_{cit} \cdot \text{Math.} \, (\text{Qpw}_{\text{inlet}} - SC_{cit} \cdot \text{Math.} \, Q_{\text{fil}})} f_{cit} = (\frac{\text{Qpw}_{\text{inlet}} - SC_{cit} \cdot \text{Math.} \, Q_{\text{fil}}}{\text{Qpw}_{\text{inlet}}} \cdot \text{Math.} \, \frac{Q_{\text{dial}} + SC_{cit} \cdot \text{Math.} \, Q_{\text{fil}}}{Q_{\text{dial}}})^{\frac{1}{cit}}$

$cit = e^{(\frac{SC_{cit} \cdot \text{Math.} \, Q_{\text{fil}}}{\frac{S}{RT}_{cit}})} - 1 \text{Cp}_{\text{cit\_pat}} = \frac{J_{\text{citrate\_load}}}{K_{\text{cit\_met}}} K_{\text{cit\_met}} = 700 \cdot \text{Math.} \, \frac{BW}{72} \text{Qp} \cdot \text{Math.} \, \text{Cp}_{\text{cit}_{pat}} + J_{cit_{PBP}} = \text{Qpw}_{\text{inlet}} \cdot \text{Math.} \, \text{Cpw}_{\text{cit\_inlet}}$

$J_{\text{cit\_PBP}} = \text{Qpw}_{\text{inlet}} \times \text{Cpw}_{\text{cit\_inlet}}$

Eq. 25/25′—Citrate Load Mathematical Relation/s

[00133] $J_{\text{citrate\_load}} = D_{cit} \cdot \text{Math.} \, Q_{cit} \cdot \text{Math.} \, (1 - \frac{K_{cit}}{\text{Qpw}_{\text{inlet}}}) \cdot \text{Math.} \, (1 - \frac{1}{1 + \frac{K_{\text{met\_cit}}}{K_{cit}} \cdot \text{Math.} \, \frac{\text{Qpw}_{\text{inlet}}}{\text{Qp}}}) J_{\text{citrate\_load}} = D_{cit} \times Qb \times (1 - \frac{K_{cit}}{\text{Qpw}_{\text{inlet}}})$

Eq. 26/26′—Bicarbonate Balance Mathematical Relations

[00134] $J_{\text{HCO3\_ba}l} = J_{\text{HCO3\_inf}} - J_{\text{HCO3\_eff}}$

$J_{\text{HCO3\_bal}} = Q_{\text{rep.pre}} \cdot \text{Math.} \, C_{\text{HCO3}_{\text{rep.pre}}} + Q_{\text{rep.post}} \cdot \text{Math.} \, C_{\text{HCO3}_{\text{rep.post}}} + Q_{\text{HCO3}} \cdot \text{Math.} \, C_{\text{HCO3}_{\text{HCO3post}}} + Q_{cit} \cdot \text{Math.} \, C_{\text{HCO3}_{cit}} + Q_{PBP} \cdot \text{Math.} \, C_{\text{HCO3}_{PBP}} - K_{\text{HCO3}}$

Eq. 27—Bicarbonate Infusion Mathematical Relation

[00135]

$J_{\text{HCO3\_inf}} = Q_{\text{dial}} \cdot \text{Math.} \, C_{\text{HCO3}_{\text{dial}}} + Q_{cit} \cdot \text{Math.} \, C_{\text{HCO3}_{cit}} + Q_{PBP} \cdot \text{Math.} \, C_{\text{HCO3}_{PBP}} + Q_{\text{rep.pre}} \cdot \text{Math.} \, C_{\text{HCO3}_{\text{rep.pre}}} + Q_{\text{rep.post}} \cdot \text{Math.} \, C_{\text{HCO3}_{\text{rep.post}}} + Q_{\text{HCO3}} \cdot \text{Mat}$

Eq. 28—Bicarbonate Removal Mathematical Relation

[00136] $J_{\text{HCO3\_eff}} = Q_{\text{dial}} \cdot \text{Math.} \, C_{\text{HCO3}_{\text{dial}}} + K_{\text{HCO3}} \cdot \text{Math.} \, (\text{Cpw}_{\text{HCO3\_inlet}} - C_{\text{HCO3\_dial}}) + Q_{\text{fil}} \cdot \text{Math.} \, C_{\text{HCO3\_dial}}$

Eq. 29/30—Bicarbonate Clearance Mathematical Relations

[00137] $K_{\text{HCO3}} = \frac{\text{Qbw}_{\text{inlet}} \cdot \text{Math.} \, Q_{\text{dial}} - f_{\text{HCO3}} \cdot \text{Math.} \, (\text{Qbw}_{\text{inlet}} - SC_{\text{HCO3}} \cdot \text{Math.} \, Q_{\text{fil}}) \cdot \text{Math.} \, (Q_{\text{dial}} + SC_{\text{HCO3}} \cdot \text{Math.} \, Q_{\text{fil}})}{Q_{\text{dial}} - f_{\text{HCO3}} \cdot \text{Math.} \, (\text{Qbw}_{\text{inlet}} - SC_{\text{HCO3}} \cdot \text{Math.} \, Q_{\text{fil}})} f_{\text{HCO3}} = (\frac{\text{Qbw}_{\text{inlet}} - SC_{\text{HCO3}} \cdot \text{Math.} \, Q_{\text{fil}}}{\text{Qbw}_{\text{inlet}}} \cdot \text{Math.} \, \frac{Q_{\text{dial}} + SC_{\text{HCO3}} \cdot \text{Math.} \, Q_{\text{fil}}}{Q_{\text{dial}}})^{\frac{1}{\text{HCO3}}}$

$\text{HCO3} = e^{(\frac{SC_{\text{HCO3}} \cdot \text{Math.} \, Q_{\text{fil}}}{(\frac{S}{RT})_{\text{HCO3}}})} - 1 K_{\text{HCO3}} = \text{Qeff}$

Eq. 31—Plasma Water Bicarbonate Concentration Equations

[00138] $\text{Cpw}_{\text{HCO3\_pat}} = \frac{\text{Cp}_{\text{HCO3\_pat}}}{\text{Fp}}$

$Q_{\text{bw}} \cdot \text{Math.} \, \text{Cpw}_{\text{HCO3}_{\text{pat}}} + Q_{cit} \cdot \text{Math.} \, C_{\text{HCO3}_{cit}} + Q_{PBP} \cdot \text{Math.} \, C_{\text{HCO3}_{PBP}} + Q_{\text{rep.Math.pre}} \cdot \text{Math.} \, C_{\text{HCO3}_{\text{rep.Math.pre}}} = \text{Qbw}_{\text{inlet}} \cdot \text{Math.} \, \text{Cpw}_{\text{HCO3\_inlet}}$

Eq. 32—Plasma Water Bicarbonate Concentration at Filter Inlet Mathematical Relation

[00139] $\text{Cpw}_{\text{HCO3\_inlet}} = \dfrac{Q_{\text{bw}} \cdot \text{Math.} \, \frac{\text{Cp}_{\text{HCO3}_{\text{pat}}}}{\text{Fp}} + Q_{cit} \cdot \text{Math.} \, C_{\text{HCO3}_{cit}} + Q_{PBP} \cdot \text{Math.} \, C_{\text{HCO3}_{PBP}} + Q_{\text{rep.Math.pre}} \cdot \text{Math.} \, C_{\text{HCO3}_{\text{rep.Math.pre}}}}{\text{Qbw}_{\text{inlet}}}$

Eq. 33/34/35/36—Mathematical Relations for Lactate

[00140] $J_{\text{lact\_bal}} = J_{\text{lact\_inf}} - J_{\text{lact\_eff}}$

$J_{\text{lact\_inf}} = Q_{\text{dial}} \cdot \text{Math.} \, C_{\text{lact\_dial}} + Q_{cit} \cdot \text{Math.} \, C_{\text{lact}_{cit}} + Q_{PBP} \cdot \text{Math.} \, C_{\text{lact}_{PBP}} + Q_{\text{rep.Math.pre}} \cdot \text{Math.} \, C_{\text{lact}_{\text{rep.Math.pre}}} + Q_{\text{rep.Math.post}} \cdot \text{Math.} \, C_{\text{lact}_{\text{rep.Math.post}}}$

$J_{\text{lact\_eff}} = Q_{\text{dial}} \cdot \text{Math.} \, C_{\text{lact\_dial}} + K_{\text{lact}} \cdot \text{Math.} \, (\text{Cpw}_{\text{lact\_inlet}} - C_{\text{lact\_dial}}) + Q_{\text{fil}} \cdot \text{Math.} \, C_{\text{lact\_dial}} \text{Cpw}_{\text{lact\_inlet}} = \dfrac{Q_{\text{bw}} \cdot \text{Math.} \, \frac{\text{Cp}_{\text{lact\_pat}}}{\text{Fp}} + Q_{\text{rep.Math.pre}} \cdot \text{Math.} \, C_{\text{lact}_{\text{rep.Math.pre}}} + Q_{cit} \cdot \text{Math.} \, C_{\text{lact}_{cit}} + Q_{PBP} \cdot \text{Math.} \, C_{\text{lact}_{PBP}}}{\text{Qbw}_{\text{inlet}}}$

Eq. 37—Patient Citrate Metabolic Clearance

[00141] $J_{\text{met\_cit}} = 3 \cdot \text{Math.} \, J_{\text{cit\_load}}$

Eq. 38—Acid Infusion Equation

[00142] $J_{H+} = 3 \cdot \text{Math.} \, J_{\text{citric\_acid}} = 3 \cdot \text{Math.} \, Q_{cit} \cdot \text{Math.} \, C_{\text{cit\_PBP}}$

Eq. 39/40/41—Net Buffer Load Mathematical Relations

[00143] $J_{\text{buffer\_load}} = 3 \cdot \text{Math.} \, J_{\text{cit\_load}} + J_{\text{HCO3\_bal}} - 3 \cdot \text{Math.} \, J_{\text{citric\_acid}} J_{\text{buffer\_load}} = 3 \cdot \text{Math.} \, J_{\text{cit\_load}} + J_{\text{HCO3\_bal}} + J_{\text{lact\_bal}} - 3 \cdot \text{Math.} \, J_{\text{citric\_acid}}$

$\text{nNBL} = \frac{J_{\text{buffer\_load}}}{\text{BW}}$

Eq. 42/43/44/45/42′/44′—Steady State Acid Base Balance Indicator Mathematical Relations

[00144]

$\text{Cp}_{\text{HCO3\_pat}} = \frac{\text{Fb}}{\text{Qbw}} \cdot \text{Math.} \, (\text{Cpw}_{\text{HCO3}_{\text{inlet}}} \cdot \text{Math.} \, \text{Qbw}_{\text{inlet}} - Q_{\text{rep.Math.pre}} \cdot \text{Math.} \, C_{\text{HCO3rep.Math.pre}} - Q_{cit} \cdot \text{Math.} \, C_{\text{HCO3}_{cit}} - Q_{PBP} \cdot \text{Math.} \, C_{\text{HCO3}_{PBP}})$

$\text{Cpw}_{\text{HCO3\_inlet}} = C_{\text{HCO3\_dial}} + \frac{J_{\text{HCO3\_eff}} - Q_{\text{dial}} \times C_{\text{HCO3\_dial}} - Q_{\text{fil}} \times C_{\text{HCO3\_dial}}}{K_{\text{HCO3}}} J_{\text{HCO3\_eff}} = J_{\text{HCO3\_inf}} - J_{\text{HCO3\_bal}} = J_{\text{HCO3\_inf}} + J_{\text{met\_cit}} - J_{H+} - J_{\text{buffer\_load}}$

$J_{\text{buffer\_load}} = \text{nNBL} \times \text{BW}$

$\text{Cp}_{\text{HCO3\_pat}} = \frac{\text{Fp}}{\text{Qbw}} \cdot \text{Math.} \, (C_{\text{HCO3\_dial}} + \frac{J_{\text{HCO3\_eff}} - Q_{\text{dial}} \times C_{\text{HCO3\_dial}} - Q_{\text{fil}} \times C_{\text{HCO3\_dial}}}{K_{\text{HCO3}}} \cdot \text{Math.} \, \text{Qbw}_{\text{inlet}} - Q_{\text{rep.Math.pre}} \cdot \text{Math.} \, C_{\text{HCO3rep.Math.pre}} - Q_{cit} \cdot \text{Math.} \, C_{\text{HCO3}_{cit}} - Q_{PBP}$

$J_{\text{HCO3\_eff}} = J_{\text{HCO3\_inf}} + J_{\text{met\_cit}} - J_{H+} - \text{nNBL0} \times \text{BW} \quad (\text{Eq.} \, 44')$

Claims

1-23. (canceled)
24. A Continuous Renal Replacement Therapy (CRRT) apparatus configured to perform regional anticoagulation treatments, the CRRT apparatus

comprising: a filtration unit having a primary chamber and a secondary chamber separated by a semi-permeable membrane; an extracorporeal blood circuit having a blood withdrawal line connected to an inlet of the primary chamber, and a blood return line connected to an outlet of the primary chamber, said extracorporeal blood circuit being configured to connect to a patient cardiovascular system; a blood pump configured to control the flow of blood through the extracorporeal blood circuit; an effluent fluid line connected to an outlet of the secondary chamber; an anticoagulant infusion line having one end connected to the blood withdrawal line in a region of the blood withdrawal line positioned in use upstream from the blood pump, a source of regional anticoagulant operably connected to the anticoagulant infusion line; one or more further fluid lines selected from a fluid line group comprising: a pre-dilution infusion line connected at one end thereof to the blood withdrawal line, a post-dilution infusion line connected at one end thereof to the blood return line, a post-dilution bicarbonate infusion line connected at one end thereof to the blood return line, an ion balancing infusion line connected at one end thereof either to the blood return line or to a patient catheter, a dialysis liquid supply line connected at one end thereof to the inlet of the secondary chamber, a pre-blood pump (PBP) infusion line connected at one end thereof to the blood withdrawal line in a region of the blood withdrawal line which is positioned in use upstream from the blood pump, and a syringe fluid line connected at one end thereof to the blood withdrawal line; one or more actuators for regulating the flow of fluid through said one or more further fluid lines; and a control unit connected to memory storing one or more mathematical relations and to the one or more actuators, the control unit configured to execute a flow-rate setup procedure comprising: receiving a patient prescription comprising clinical prescription parameters, the receiving including: allowing entry of a set value for a prescribed dialysis dose to be delivered, allowing entry of a target value for a parameter indicative of a steady state acid-base balance in the blood of a patient, and allowing entry of a set value for a prescribed anticoagulant dose to be delivered; determining one or more operating parameters using said one or more mathematical relations, the determining of the one or more operating parameters comprising calculating a set value of three or more fluid flow rates selected from a flow rate group comprising: a fluid flow rate through the anticoagulant infusion line, a fluid flow rate through the PBP infusion line when the one or more further fluid lines includes the PBP infusion line, a fluid flow rate through the pre-dilution infusion line when the one or more further fluid lines includes the pre-dilution infusion line, a fluid flow rate through the post-dilution infusion line when the one or more further fluid lines includes the post-dilution infusion line, a fluid flow rate through the post-dilution bicarbonate infusion line when the one or more further fluid lines includes the post-dilution bicarbonate infusion line, a fluid flow rate through the ion balancing infusion line when the one or more further fluid lines includes the ion balancing infusion line, a blood fluid flow rate through the extracorporeal blood circuit, a fluid flow rate through the syringe fluid line when the one or more further fluid lines includes the syringe fluid line, a fluid flow rate through the dialysis liquid supply line when the one or more further fluid lines includes the dialysis liquid supply line, and a fluid flow rate through the effluent fluid line; wherein calculating each set value of the three or more fluid flow rates is based at least on: said set value of the prescribed dialysis dose, said target value for the parameter indicative of a steady state acid-base balance in blood, and said set value for the prescribed anticoagulant dose.

25. The CRRT apparatus of claim 24, wherein the target value for the parameter indicative of a steady state acid-base balance in the blood of the patient affects the set value of the fluid flow rate through the anticoagulant infusion line when the set value for the blood fluid flow rate through the extracorporeal blood circuit is determined by the control unit as one of the one or more operating parameters, the set value of the fluid flow rate through the anticoagulant infusion line being one of the one or more operating parameters calculated by the control unit.

26. The CRRT apparatus of claim 24, wherein calculating the set value of three or more fluid flow rates comprises determining of the operating parameters comprising calculating the set value for the fluid flow rate through the anticoagulant infusion line, wherein the regional anticoagulation dose is a citrate dose indicative of the intensity of the regional anticoagulation.

27. The CRRT apparatus of claim 24, wherein the regional anticoagulation dose has the same units as a concentration and is the injected amount of anticoagulant per liter of treated blood (mmol/L blood).

28. The CRRT apparatus of claim 24, wherein the control unit is configured to calculate, using a citrate flow rate mathematical relation, the set value for the fluid flow rate through the anticoagulant infusion line as a function of one or more of: the set value for the regional anticoagulation dose, the set value for the fluid flow rate through the anticoagulant infusion line with a blood flow rate; and an anticoagulant concentration in the anticoagulant source.

29. The CRRT apparatus of claim 24, wherein said one or more mathematical relations include a citrate flow rate mathematical relation and the fluid flow rate through the anticoagulant infusion line is calculated based on the citrate flow rate mathematical relation stored in said memory: $? \frac{?}{?} ?$?indicates text missing or illegible when filed wherein the significance of the denotations is given in the Glossary.

30. The CRRT apparatus of claim 24, wherein the control unit is configured to control an anticoagulant pump to infuse anticoagulant in the blood withdrawal line at the calculated fluid flow rate for the anticoagulant.

31. The CRRT apparatus of claim 24, comprising the ion balancing infusion line having one end connected either to the blood return line or to a patient catheter and a source of ion balancing solution connected at an opposite end of the ion balancing infusion line, wherein receiving a patient prescription further comprises allowing entry of a set value for an ion re-establishing solution parameter indicative of the intensity of ion balancing, wherein calculating the set value of three or more fluid flow rates comprises calculating the set value of four or more fluid flow rates and determining of the operating parameters comprises calculating the set value for at least the fluid flow rate through the ion balancing infusion line.

32. The CRRT apparatus of claim 31, wherein the ion re-establishing solution parameter is either: a compensation value or compensation percentage of the calcium removed in the filtration unit; or a calcium dose in terms of an ion concentration, the calcium dose being calcium concentration in the effluent.

33. The CRRT apparatus of claim 31, wherein the control unit is configured to calculate, using a calcium flow rate mathematical relation, the set value for the fluid flow rate through the ion balancing infusion line as a function of one or more of: the set value for the ion re-establishing solution parameter; an effluent flow rate; a calcium concentration in a source of ion balancing solution; a calcium concentration in an auxiliary container connected to the post-dilution infusion line; a calcium concentration in a bicarbonate container connected to the post-dilution bicarbonate infusion line.

34. The CRRT apparatus of claim 31, wherein said one or more mathematical relations include a calcium flow rate mathematical relation and wherein the set value for the fluid flow rate through the ion balancing infusion line is calculated based on the calcium flow rate mathematical relation stored in the memory, said mathematical relation being either: $? = \frac{CaComp \cdot Math. \, ?}{C_{ca}} - \frac{?.Math.?}{C_{ca}} - \frac{?.Math.?}{C_{ca}}$ or $? = \frac{D_{ca} \cdot Math. \, Q_{eff}}{C_{ca}} - \frac{?.Math.?}{C_{ca}} - \frac{?.Math.?}{C_{ca}}$?indicates text missing or illegible when filed wherein the significance of the denotations is given in the Glossary and when any of the infusion lines is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

35. The CRRT apparatus of claim 24, wherein calculating the set value of the fluid flow rate through the ion balancing infusion line is based at least on said target value for the parameter indicative of a steady state acid-base balance in the blood and on said set value of the prescribed dialysis dose, wherein the control unit calculates the set value of the fluid flow rate through the ion balancing infusion line using said mathematical relations.

36. The CRRT apparatus of claim 24, wherein the control unit is configured to control an ion balancing pump to infuse an ion re-establishing solution in the blood return line or into the patient at the fluid flow rate calculated for the ion re-establishing solution.

37. The CRRT apparatus of claim 24, wherein said one or more mathematical relations include a net buffer load mathematical relation linking the parameter indicative of a steady state acid-base balance in the blood with at least one of: a bicarbonate balance, a bicarbonate generated from metabolism of citrate, or a citrate load, wherein the metabolism of citrate load leads to 3 moles of bicarbonate per mole of citrate at steady state, namely J.sub.met_cit=3.Math.J.sub.cit_load, a bicarbonate generated from metabolism of lactate, or a lactate balance, wherein the metabolism of lactate leads to 1 mole of bicarbonate per mole of lactate at steady state, namely J.sub.met_lact=J.sub.lact_bal, an acid infusion.

38. The CRRT apparatus of claim 37, wherein the net buffer load mathematical relation is: $? + ? + ? - J_{H+}$?indicates text missing or illegible when filed wherein the

significance of the denotations is given in the Glossary; when any of the mass transfer rate is missing, the corresponding mass transfer term is absent from the mathematical relation, or the corresponding value is set to zero.

39. The CRRT apparatus of claim 24, wherein said one or more mathematical relations include a citrate load mathematical relation based on a citrate load to the patient in terms of an amount per unit of time, wherein the citrate load is the difference between a citrate infusion rate through the anticoagulant infusion line and a citrate removal rate to effluent in the eluent line.

40. The CRRT apparatus of claim 39, wherein the citrate load mathematical relation is: $?-?$ $?_{\text{indicates text missing or illegible when filed}}$ wherein the significance of the denotations is given in the Glossary; when any of the mass transfer rate is missing, the corresponding mass transfer term is absent from the mathematical relation, or the corresponding value is set to zero.

41. The CRRT apparatus of claim 39, wherein the citrate removal rate to effluent, is a function of one or more of: patient citrate metabolic clearance, the metabolic clearance being directly proportional to a patient body weight, for example being determined as follows: $K_{\text{cit\_met}} = 700$ .Math. $\frac{BW}{72}$ wherein patient citrate metabolic clearance is measured as [ml/min] and body weight is measured as [kg]; fluid flow rate through the effluent fluid line, wherein a citrate clearance is estimated equal to said effluent fluid flow rate, a citrate clearance and, according to citrate clearance mathematical relations of said one or more mathematical relations, the citrate clearance is a function of one or more of the fluid flow rate through the dialysis liquid supply line, an ultrafiltration rate in filtration unit, and a plasma water flow rate at the filtration unit inlet.

42. The CRRT apparatus of claim 24, wherein said one or more mathematical relations include citrate clearance mathematical relations as follows:
$? = \frac{Qpw_{\text{inlet}} \text{ .Math. } Q_{\text{dial}} - ? \text{ .Math. } (Qpw_{\text{inlet}} - ? \text{ .Math. } Q_{\text{fil}}) \text{ .Math. } (Q_{\text{dial}} + ? \text{ .Math. } Q_{\text{fil}})}{Q_{\text{dial}} - ? \text{ .Math. } (Qpw_{\text{inlet}} - ? \text{ .Math. } Q_{\text{fil}})}$ $? = (\frac{Qpw_{\text{inlet}} - ? \text{ .Math. } Q_{\text{fil}}}{Qpw_{\text{inlet}}}$ .Math. $\frac{Q_{\text{dial}} + ? \text{ .Math. } Q_{\text{fil}}}{Q_{\text{dial}}}? ? = ? - 1$ $?_{\text{indicates text missing or illegible when filed}}$ wherein the significance of the denotations is given in the Glossary; when any of the infusion lines or the dialysis liquid supply line is missing, the corresponding flow rate is absent from the mathematical relation, or the corresponding flow rate is set to zero.

43. The CRRT apparatus of claim 24, wherein a citrate load is alternatively a function of a citrate dose and the blood flow, according to D.sub.cit.Math.Q.sub.b, or a function of the citrate flow rate in the anticoagulant line and a total citrate concentration, according to Q.sub.cit.Math.C.sub.cit.sub.PBP.

44. The CRRT apparatus of claim 24, wherein said one or more mathematical relations include a citrate load mathematical relation linking a citrate load with one or more of a citrate dose, the blood flow rate, a citrate clearance, and plasma water flow rate at the inlet of the filtration unit.

45. The CRRT apparatus of claim 44, wherein the citrate load mathematical relation is either:
$? - ?$ .Math. $?$ .Math. $(1 - \frac{?}{Qpw_{\text{inlet}}})$ .Math. $(1 - \frac{1}{1 + \frac{?}{?} \text{ .Math. } \frac{Qpw_{\text{inlet}}}{Qp}})$ or: $?Qb?(1 - \frac{?}{Qpw_{\text{inlet}}})$ $?_{\text{indicates text missing or illegible when filed}}$ wherein the significance of the denotations is given in the Glossary.

46. The CRRT apparatus of claim 24, wherein calculating the set value for at least the fluid flow rate through the anticoagulant infusion line and/or the fluid flow rate through the ion balancing infusion line, is based on said set value of the prescribed dialysis dose, in case the set value for the blood fluid flow rate through the extracorporeal blood circuit is determined by the control unit as an operating parameter.

47. The CRRT apparatus of claim 24, wherein calculating the set value for at least the fluid flow rate through the anticoagulant infusion line and/or the fluid flow rate through the ion balancing infusion line, is based at least on said target value for the parameter indicative of a steady state acid-base balance in the blood, when the set value for the blood fluid flow rate through the extracorporeal blood circuit is determined by the control unit as an operating parameter.

48. The CRRT apparatus of claim 24, wherein the parameter indicative of a steady state acid-base balance in the blood of the patient undergoing a CRRT treatment is a parameter function of a net buffer load in the patient expected at a steady state, wherein the net buffer load is a sum of bicarbonate generation from bicarbonate precursor metabolism, bicarbonate balance in the extracorporeal blood circuit, bicarbonate infusions into the patient and acid infusion in the extracorporeal blood circuit.

49. The CRRT apparatus of claim 24, wherein the parameter indicative of a steady state bicarbonate concentration in the blood of the patient is defined imposing a constant value for a normalized net buffer load for the patient at steady state.