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Numerical Simulation of the Hemodynamic Response to Hemodialysis-Induced Hypovolemia

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Abstract: To provide a framework for analyzing cardiovascular response to hemodialysis-induced hypovolemia, we developed a computer model which simulates arterial pressure changes caused by loss of blood volume. The model includes arterial and venous systemic circulation, Starling's law and inotropic regulation of heart, arterial and cardiopulmonary baroreflex control of capacitance, and resistance vessels. The performance of this model was assessed by analyzing the hemodynamic responses recorded in 12 patients undergoing chronic hemodialysis, 6 classified as hypotension resistant (stable group) and 6 as hypotension prone (unstable group). Arterial pressure, heart rate, and blood volume were recorded during regular hemodialysis. Blood volume and heart rate were used as inputs to the simulator whereas the arterial pressure response obtained by simulation was fitted to the measured data by tuning simulator parameters relative to the capacitance and resistance controls. Although analyzed pressure responses exhibited a wide variety of time patterns, for each one it was possible to identify an optimal set of parameters allowing the recorded pressure data to be accurately reproduced by the model. Sensitivity analysis performed with the model indicated that pressure response strongly depends on the parameter K_v accounting for the capability to control vascular capacitance. According to these results, the parameter K_v in the stable group was 9 times that of the unstable group, thereby suggesting a possible cause of their different hemodynamic behavior. **Key Words:** Hemodialysis—Cardiovascular system—Computer simulator—Hypotension—Baroreflex regulation.

During hemodialysis, plasma water depletion causes a significant reduction in circulatory blood volume (about 15%). This hypovolemic state may trigger the sudden, dramatic decrease in arterial pressure that has been recognized to be one of the most serious complications of hemodialysis. Acute hypotension often degenerates into cardiocirculatory collapse thus requiring abrupt termination of the treatment. This event may occur in up to one-third of dialysis sessions, and critical patients have up to 60% of their dialysis complicated by acute hypotension (1,2). Therefore, it seems important to introduce novel approaches aimed at obtaining more information from the recording usually performed during therapy, also in order to prevent serious complications.

Physiopathological mechanisms underlying hemodialysis-induced acute hypotension still deserve more thorough elucidation. However, there is evidence supporting the hypothesis that as impaired autonomic regulation of cardiovascular functions is unable to provide efficient compensatory response to hypovolemia it could play a pivotal role in the onset of this phenomenon (3–6).

Physiological autonomic compensatory response to acute hypovolemia includes three principal mechanisms: a decrease in venous vessel capacity to maintain cardiac filling; an increase in vascular resistance to ensure perfusion of critical organs; and an increase in cardiac contractility and rate to optimize heart activity.

Decreased venous capacity is directly involved in compensating changes in circulatory blood volume (7). Capacitance vessels such as splanchnic and cutaneous circulations have a variable blood-storage function. Both active and passive mechanisms participate in capacity changes of these peripheral circulatory beds. Active venoconstriction due to an increase in vasomotor tone tends to raise central

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venous pressure. Conversely, passive venoconstriction, due to a decreased regional inflow or refilling, corresponds to decreased venous pressure. Active constriction of a capacitance vessel appears to be the major component of compensation during hypovolemia (8).

Increased peripheral resistance during hypovolemia has two main effects: to reduce inflow to splanchnic, cutaneous, skeletal and renal vascular beds with redistribution of cardiac output to vital circulatory districts, and to increase pressure in the proximal arterial circulation. Finally, if cardiac filling is adequate, increased ventricular contractility and heart rate cause an increase in cardiac output.

Through the effectiveness of these three compensatory mechanisms, in healthy subjects, cardiovascular homeostasis is maintained during hypovolemia, and systemic arterial pressure does not exhibit significant decreases. Although arterial pressure remains stable, baroreflex increase in sympathetic activity is fundamental: after a ganglionic blockade, only a small hemorrhage causes a dangerous hypotension (9).

Two principal baroreflex arcs affect vascular tone and heart activity during hypovolemia. One originates in the cardiopulmonary baroreceptor sites (located in the atria and in the main pulmonary veins), the other in arterial baroreceptors (located in the aortic arch and carotid sinus). Both sets of receptors with afferent vagal fibers exert autonomic inhibition of sympathetic outflow to resistance and capacitance vessels as well as to the heart. Arterial baroreceptors provide one input, and cardiopulmonary receptors are likely contributors, but the relative importance of these two ways is still not well established. However, several pieces of evidence support the hypothesis that low-pressure receptors play an important role in eliciting an efficient compensatory response to hypovolemia (8,10).

When the cardiovascular system is stressed with such a loss of blood volume as occurs during mild hemorrhage or hemodialysis, cardiopulmonary and arterial baroreceptor discharge leads to reflex-sympathetic excitation and parasympathetic inhibition. A result of this regulatory reflex is that capacitance and resistance vessels constrict and heart inotropic activity increases, thereby compensating for the reduction in arterial and venous pressure. The efficiency of the whole regulation process from receptors to actuators is, of course, essential to prevent hypotension during hypovolemia.

In order to gain a deeper understanding of the role that autonomic-mediated regulation plays in the genesis of hemodialysis-induced acute hypotension, we implemented a computer model to simulate the changes in arterial pressure that occur when the cardiovascular system is stressed by a loss of blood volume. In accordance with the physiological knowledge outlined above, the model includes a simple mathematical description of the cardiovascular system and baroreflex regulation of venous capacity and vascular resistance. Using this model, we analyzed the hemodynamic responses recorded during hemodialysis in patients with and without a history of acute hypotension. In this paper, the main aspects of the model are described, and some relevant results are shown.

METHODS

Mathematical model

Because the hemodynamic response under study involves much slower dynamics than the heart period, the cardiovascular system was modeled considering the mean values of the hemodynamic quantities over the cardiac cycle, hence neglecting the pulsatile nature of the cardiac pump.

The heart was treated as a continuous pump which moves blood from venous return directly into the systemic arterial circulation, bypassing pulmonary circulation, in accordance with the heart function curve as reported by Guyton et al. (9). Briefly, as the ventricle fills to higher atrial pressure, within physiological limits, the strength of cardiac contraction rises causing the heart to pump increased quantities of blood into the arterial circulation, the so-called Starling's law. However, ventricle capacity is limited, and when filling atrial pressure (P_{RA}) rises in value, cardiac output (CO) exhibits saturation (Fig. 1). Therefore, the relationship between cardiac output

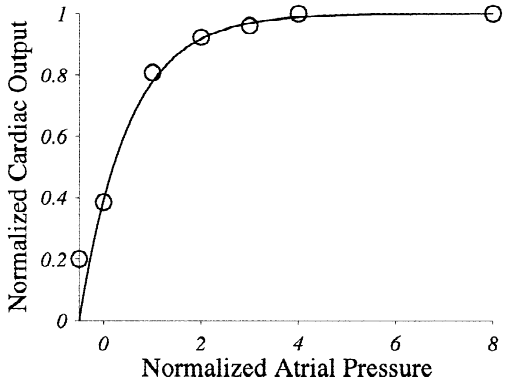

FIG. 1. The cardiac output versus right atrial pressure is shown. Equation 1 was used to fit experimental data (4) after normalization of cardiac output with respect to the saturation value (C_{sat}) and atrial pressure with respect to P_{RAN}.

and atrial pressure was expressed in the model by an exponential curve with a saturation level (CO_{sat}):

$$CO = CO_{sat}\left(1 - e^{-\frac{P_{RA} - P_{RAZ}}{P_{RAN}}}\right) \quad (1)$$

where the parameters P_{RAZ} and P_{RAN} set the intercept and the slope of the cardiac output atrial pressure curve.

In physiological conditions, as long as cardiac filling is adequate, changes in inotropic heart activity produce considerable changes in cardiac output. In the model, cardiac inotropism was taken indirectly into account by the modulation of cardiac output function, Eq. 1, through the heart rate, which is one of the inputs to the model, which well reflects the cardiac inotropic state. Within physiological limits, at any given right atrial pressure, cardiac output increases as sympathetic stimulation increases and decreases as the latter is inhibited (11). This behavior was modeled by a sigmoid function of the heart rate (HR) which modulates the saturation level of the cardiac output curve:

$$CO_{sat} = CO_M\,(1 + \Delta_{co}\tanh\,(K_{co}(HR - \overline{HR}))) \quad (2)$$

where $\overline{HR}$ indicates the initial heart rate, i.e. the heart rate at the beginning of dialysis (time equals zero) and CO_M the corresponding cardiac output, Δ_{co} is the amplitude of the sigmoid and K_{co} the slope.

In physiological conditions, regulation of the heart's inotropic state provides cardiac output with a negligible sensitivity to fairly wide variations in atrial pressure. Decreased atrial pressure (P_{RA}) causes a baroreflex increase in inotropic heart activity which tends to compensate for the reduction in cardiac output due to decreased atrial filling. However, during hypovolemia, cardiac output is determined primarily by the amount of cardiac filling whereas adrenergic changes in heart rate and in cardiac contractility have been shown to have no significant role (12). The sigmoid curve takes into account this behavior making cardiac output sensitivity to atrial pressure dependent on heart rate.

The circulatory system was broken down into 4 compartments arranged in series: 3 for arterial, peripheral and venous circulations, and one for the right atrium (Fig. 2). Each compartment was modeled in accordance with the classical Windkessel theory, which accounts for the capacitive and resistive properties of circulation. Therefore, each compartment was similar to an elastic chamber exchanging flow with the downstream and the upstream compartments through hydraulic resistances from which we can deduce the following:

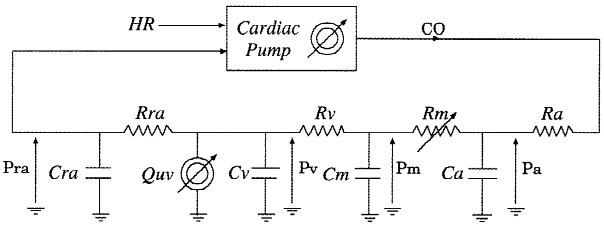

FIG. 2. The electrical equivalent of the systemic circulation model is illustrated. Four circulatory compartments are arranged in series: arterial, peripheral, venous, and atrial. R_a, R_p, R_v, and R_{ra} represent the circulatory resistance respectively of arterial, peripheral, venous and atrial compartments whereas C_a, C_p, C_v, and C_{ra} represent the relevant compliance; flow source Q_{uv} simulates the unstressed volume variations; CO is the cardiac output; and P_A and P_{RA} represent arterial and atrial pressures. Arrows indicate time-varying quantities under regulation.

$$Q = \frac{\Delta P}{R} \quad (3)$$

where ΔP is the pressure drop between 2 compartments and Q is the flow through the resistance R which links them. According to the mass preservation equation, time variation of blood volume in each compartment is equal to the difference between inflow and outflow. According to the scheme in Fig. 2, one can write

$$\frac{dV_A}{dt} = CO - \frac{P_A - P_M}{R_M} \quad (4)$$

$$\frac{dV_M}{dt} = \frac{P_A - P_M}{R_M} - \frac{P_M - P_V}{R_V} \quad (5)$$

$$\frac{dV_{RA}}{dt} = \frac{P_V - P_{RA}}{R_{RA}} - CO \quad (6)$$

where the state variables V_A, V_M, and V_{RA} are the blood volumes in the arterial, peripheral, and right atrial circulatory compartments, respectively; P_A, P_M, and P_{RA} the corresponding pressure; and P_V the pressure in the venous compartment.

Because the total circulatory blood volume (V_{BT}), which is the second input to the model, is distributed throughout the 4 compartments, the venous blood volume (V_V) can be calculated as

$$V_V = V_{BT} - (V_M + V_A + V_{RA}) \quad (7)$$

The volume of each compartment was expressed as the sum of two contributions: the unstressed volume, that is the volume for null transmural pressure, and the stressed volume that accounts for elastic deformation. For each compartment, pressure was then calculated as a linear function of the volume

$$P_A = \frac{V_A - V_{AU}}{C_A} \quad (8)$$

$$P_M = \frac{V_M - V_{MU}}{C_M} \quad (9)$$

$$P_V = \frac{V_V - V_{VU}}{C_V} \quad (10)$$

$$P_{RA} = \frac{V_{RA} - V_{RAU}}{C_{RA}} \quad (11)$$

with V_{AU}, V_{MU}, V_{VU}, V_{RAU} the unstressed volumes of four compartments and C_A, C_M, C_V, C_{RA} the corresponding compliances. Arterial pressure (P_A) is the model output, which was fitted to the mean arterial pressure measured in the brachial artery.

To simulate baroreflex regulation of the vasomotor activity, two distinct afferent pathways were considered: one for arterial and the other for cardiopulmonary baroreceptors. Changes in the arterial and atrial pressure drive, changes in peripheral resistance (R_M) and unstressed venous volume (V_{VU}) according to the block diagram are shown in Fig. 3.

Receptors in the cardiopulmonary region restrain adrenergic outflow to resistance and capacitance vessels, which in turn depends on arterial receptor input. Static interaction between these 2 afferent pathways was modeled (Fig. 3) with a linear superimposition characterized by a reciprocal "balance-like" relationship between the sensitivity of arterial and cardiopulmonary baroreceptors as

$$T_B = (1 - K_{aff}) \frac{P_A - \overline{P}_A}{\overline{P}_A} + (1 + K_{aff}) \frac{P_{RA} - \overline{P}_{RA}}{\overline{P}_{RA}} \quad (12)$$

where $\overline{P}_A$ and $\overline{P}_{RA}$ are arterial and atrial pressure at the beginning of dialysis, when the cardiovascular system is assumed to be in equilibrium and $T_B = 0$. Thus, cardiopulmonary and arterial baroreceptors may interact through reciprocal inhibition when the activity of either is enhanced, according to experimental evidence (13). Indeed, by changing the parameter K_{aff} from –1 to 1, it was possible to assign a different relative weight to the afferences: when K_{aff} is positive, the compensatory reflex starting from the low-pressure receptors tends to prevail with respect to the reflex starting from the arterial receptors, the contrary occurs when K_{aff} is negative. In particular, when $K_{aff} = 1$, the arterial pathway is completely inhibited whereas when $K_{aff} = -1$, the cardiopulmonary pathway is inhibited.

Efferent static regulations were modeled by sigmoid curves suitable for obtaining linear behavior for small pressure perturbations and the typical saturation effects for large pressure changes

$$R_M = \overline{R}_M (1 - K_r \tanh 2T_B) \quad (13)$$

$$V_{VU} = \overline{V}_{VU} (1 + K_v \tanh 2T_B) \quad (14)$$

with $\overline{V}_{VU}$ and $\overline{R}_M$ the unstressed venous volume and the peripheral resistance at the beginning of dialysis when $T_B = 0$. The parameters K_r and K_v were assumed within the range from 0 to 1. When they were equal to 1, the corresponding regulatory pathway was maximally activated. Conversely, when they were null, no regulation took place. The balance K_{aff} of the afferent pathways and the gains K_V and K_r of the efferences express the efficiency in the overall regulation of the vasoconstriction state.

Patients and data acquisition

Twelve patients with end-stage renal failure undergoing hemodialysis treatment 3 times/week were selected. These subjects were already included in a previous study where their autonomic nervous system function was investigated (3). Six patients were classified as hypotension-resistant (stable group) and 6 as hypotension-prone (unstable group), according to their history of hemodialysis-induced cardiovascular collapses. Patients of the stable group never collapsed during the latest 12 treatments whereas the unstable group included patients whose latest 12 treatments were complicated by at least 2 episodes of cardiovascular collapse. Nevertheless, none of the sessions analyzed in this study ended with a collapse episode. The duration of each session ranged from 160 to 270 min. The ultrafiltration rate, normalized with respect to body weight, was similar in the 2 groups.

During the entire session, hemoglobin concentration was measured by an optical probe in the arterial line of the extracorporeal circuit (Hemoscan, Hospal-Dsaco S.p.A., Medolla, Italy), and the per-

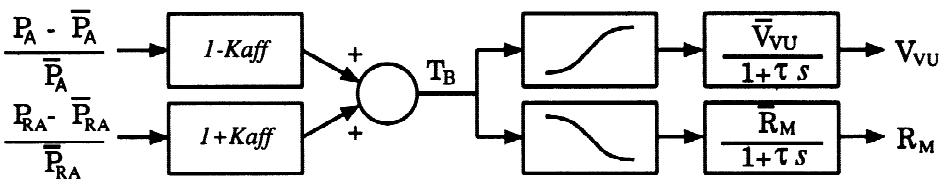

FIG. 3. A schematic representation of the short-term baroreflex is shown. Arterial (P_A) and atrial (P_{RA}) pressures drive the vasomotor center through afferent arterial and atrial baroreceptor activity. Vasomotor efferent tone (T) affects the vasoconstriction state through peripheral resistance (R_m) and unstressed venous volume (V_{VU}) modulation.

centage changes in blood volume were estimated as the ratio between current and initial hemoglobin concentration. Sampling frequency of the blood volume was 0.1 Hz. ECG was recorded continuously (Cardiette, Elettronica Trentina S.p.A., Cavareno, Italy), and an array containing the beat-to-beat heart rate was extracted from the R–R time series. To remove high-frequency variability, blood volume and heart rate time series were low-pass filtered with a digital Butterworth filter. Mean arterial blood pressure was measured every 10 min by an oscillometric automatic blood pressure device (BPM, Hospal-Dasco S.p.A., Medolla, Italy) integrated in the artificial kidney.

Blood volume and heart rate were used as inputs to the simulator whereas mean arterial pressure was used as data to compare the simulation output with.

Parameter and initial value assignment

Although the model has a very simple structure, it involves a number of parameters: 5 for heart curves, 12 for circulation, and 3 for baroreflex control. To numerically simulate pressure response to hemodialysis-induced hypovolemia for each patient, an overall criterion for assigning a value to model parameters was established. Heart and circulatory parameters were assigned "a priori" whereas baroreflex control parameters were identified for each patient in order to obtain the best fit for simulated pressure response to measured pressure data.

Heart curve parameters (Table 1) were assigned in order to reproduce, with Eqs. 1 and 2, data drawn from physiological literature (Fig. 1) (9). This set of parameters was the same for all patients.

Moreover, compliance values (Table 2) were patient-independent and were assigned in accordance with human physiological data similar to those used in previous simulation studies (7). However, it was verified that, within physiological limits, the differences in these parameters had no significant influence on the results of this study.

The initial blood volumes and circulatory resistances were assigned taking into account an inter-individual differentiation depending on patient body weight, arterial pressure, and heart rate at the beginning of dialysis. Systemic blood volume normalized with respect to patient body weight was 52 (ml/Kg). The percentage distribution of the systemic blood volume in the 4 compartments (Table 3) was assumed to be the same for all patients, thus assigning the initial values of compartment volumes.

The unstressed volume of the arterial compartment (V_{AU}) was calculated on the basis of the initial arterial pressure ($\overline{P}_A$) according to Eq. 8. Unstressed volume in the peripheral compartment (V_{MU}) was 4.5 (ml/Kg). Unstressed atrial volume (V_{RAU}) was calculated by using Eq. 11, and establishing atrial pressure in accordance with the cardiac curve Eq. 1 for an initial stroke volume of 1.14 (ml/Kg). Finally, the initial value of unstressed venous volume ($\overline{V}_{VU}$) was calculated using the balance equation 7.

The resistance values were obtained by imposing the equilibrium condition of the model at the beginning of dialysis.

It was verified for all patients that the parameter values assigned according to the above-mentioned criterion were within human physiological range.

Simulation and parameter identification

Model equations were numerically integrated over time using the Adams-Bashforth method with constant time step. Blood volume and heart rate measured in each session were used as inputs to the simulator whereas arterial pressure response obtained by simulation was compared with the measured values.

All cardiocirculatory parameters were kept constant throughout the simulations, and only the parameters concerning baroreflex regulation (K_{aff}, K_v, K_r) were identified. An iterative procedure was used to determine the optimal value of the 3 parameters giving the best fit of the measured pressure data. A

TABLE 1. *Heart pump parameters*

Parameter	Unit	Value
P_{RAZ}	mm Hg	−0.5
P_{RAN}	mm Hg	3
CO_M	ml/s	240
Δ_{CO}		0.7
K_{CO}	s	0.5

TABLE 2. *Compliances of the four circulatory compartments*

Parameter	Unit	Value
C_A	ml/mm Hg	1.0
C_M	ml/mm Hg	8.9
C_V	ml/mm Hg	95.0
C_{RA}	ml/mm Hg	32.1

TABLE 3. *Blood volume percentage distribution*

Compartment	%
Arterial	18
Peripheral	10
Venous	59
Atrial	13

cost function was defined as the root mean square error between measured and simulated pressure data. The Nelder-Mead simplex algorithm was used to find the cost function minimum with respect to the above mentioned parameters (14).

Statistical analysis

To characterize stable and unstable groups, the mean and standard deviations were used. Mean values were compared by using one-way analysis of variance (ANOVA), and differences were considered significant at $p < 0.05$.

RESULTS

Patient hemodynamic profiles

At the beginning of hemodialysis, heart rate ($\overline{HR}$), blood volume ($\overline{V}_{BT}$), and arterial pressure ($\overline{P}_A$) were similar in the stable and unstable groups (Table 4). To establish a standard value for these quantities, the mean values over the whole population were also calculated.

Hemodialysis treatment induced similar hypovolemia in all patients, and no significant differences in the percentage reduction in blood volume over time between stable and unstable groups were observed. At the end of the third hour of dialysis, the blood volume was 83 ± 3.4% with respect to the initial value in the stable group and 86 ± 3.2% in the unstable group. In this sense, the hemodynamic perturbation induced by hemodialysis was considered similar in the 2 groups.

Regulatory parameter identification

Although the 12 examined sections exhibited a very large variability in heart rate, blood volume, and arterial pressure time course, identification of regulatory parameters enabled good simulation of all pressure responses. Representative examples of simulations of 2 stable and 2 unstable patients compared with data collected during dialysis are shown in Fig. 4 and in Fig. 5. These figures also show the corresponding blood volume and heart rate changes that were used as simulation inputs.

In the hypotension-resistant patients (Fig. 4), arterial pressure tended to remain stable during dialysis, especially in the initial stage of the session, with no significant deviation from the initial value. Conversely, in some hypotension-prone patients (Fig. 5), hypovolemia elicited pressure responses with large variations.

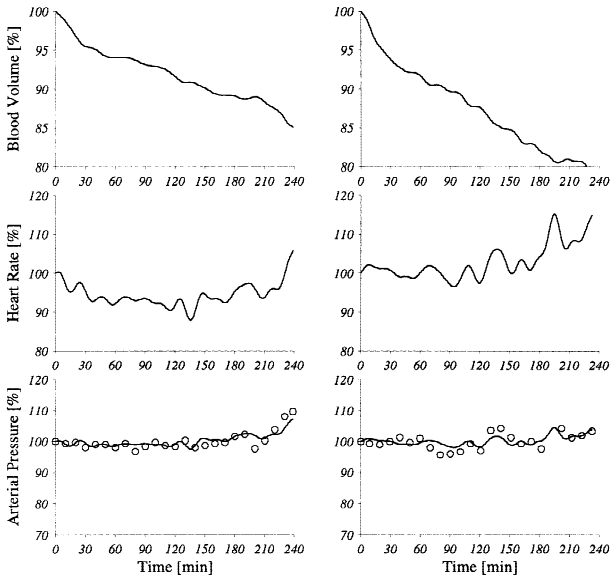

FIG. 4. Examples of hemodynamic responses for two hypotension-resistant patients are shown. Blood volume and heart rate percentage changes used as inputs to the model are shown in the upper panels. Simulated (continuous lines) and measured arterial pressure (circles) are shown in the bottom panels.

In all the analyzed sessions, fitting of pressure data obtained by tuning the baroreceptor balance-parameter, K_{aff}, and the vasoconstriction gains K_v and K_r, was satisfactory and comparable to those shown in Figs. 4 and 5. Root mean square error, normalized with respect to initial pressure, ranged between 2% and 5% and was similar to the accuracy of the device used to measure the pressure.

The balance K_{aff} and the gains K_v and K_r as estimated for stable and unstable groups are summarized in Table 5, which also reports the mean over the whole population of parameters, which were considered typical of a standard response. It is worth noting that for the standard set K_r and K_v correspond to the mid-point of their prefixed range (from 0 to 1), K_{aff} was only slightly shifted towards the cardiopulmonary side.

Stable groups reveal major dominance of low-pressure reflex in the compensatory response. In fact, the median value of K_{aff} was equal to 0.8 de-

TABLE 4. *Blood volume ($\overline{V_{BS}}$), mean arterial pressure ($\overline{P_A}$), and heart rate ($\overline{HR}$) at the beginning of dialysis*

	Stable (n = 6) (Mean ± SD)	Unstable (n = 6) (Mean ± SD)	ANOVA	Standard (Mean ± SD)
$\overline{V_{BS}}$ (l)	3.7 ± 0.5	3.5 ± 0.3	NS	3.6 ± 0.4
$\overline{P_A}$ (mm Hg)	100 ± 9	89 ± 9	NS	93 ± 12
$\overline{HR}$ (bpm)	72 ± 11	74 ± 15	NS	73 ± 13

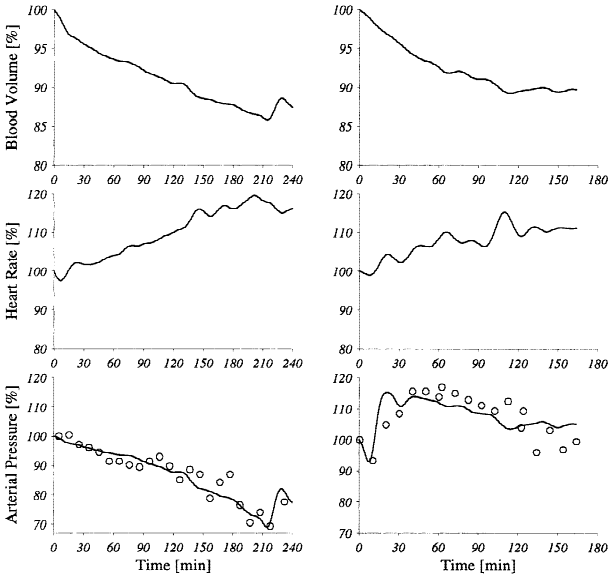

FIG. 5. Examples of hemodynamic responses for 2 hypotension-prone patients are shown. Blood volume and heart rate percentage changes used as inputs to the model are shown in the upper panels. Simulated (continuous lines) and measured arterial pressure (circles) are shown in the bottom panels.

noting a strong prevalence of cardiopulmonary afferences in the vasoconstraint process. Only in one patient was K_{aff} negative (–0.8) whereas in the remaining 5 stable cases, it was greater than 0.2. Conversely, for the unstable group, the shift toward 1 of the 2 afferent pathways was not so evident. Indeed, K_{aff} was negative in 4 cases out of 6, with a median value equal to –0.2. However, the limited number of unstable cases makes this result inconclusive. Moreover, in both groups this parameter was characterized by high variance, and the difference between mean values in stable and unstable groups was not statistically significant.

Significant differences were instead found on comparing stable and unstable groups with respect to parameters K_r and K_v. This result indicates a different capability in the vasoconstriction for both peripheral resistance and unstressed venous volume. Stable patients exhibited a significantly higher K_v and a lower K_r than unstable patients (Table 5). In particular, the parameter K_v, which expresses the capability of reducing venous vessel capacity to maintain adequate cardiac filling, was 9 times higher in the stable than in the unstable group.

Simulation of pressure response to hypovolemia

We considered the mean parameters which were estimated in a stable group, in an unstable group and in the whole population (Table 5), respectively representative of a stable, of an unstable and of a standard case. Then, by using these sets of mean parameters we performed some comparative simulations in order to show the effect of different sets on the pressure-response to hypovolemia.

The relevance of baroreflex vasoconstriction to compensate for acute hypovolemia was shown by comparing the pressure response simulated in the standard parameter-set case with the lack-of-regulation case, i.e. $K_v = 0$ and $K_r = 0$ (Fig. 6). In both simulations heart rate was kept to a constant value ($HR = 72$ [bpm]) in order to emphasize solely the role of vasoconstriction, without including heart inotropic regulation. Unlike the standard parameter-set case, for which the pressure response did not exhibit evident changes, in the complete lack-of-regulation case, arterial pressure dramatically fell as soon as the circulatory blood volume was reduced (Fig. 6). In particular, in the latter case a small volume reduction (6%) was sufficient to induce acute hypotension.

A similar difference was observed between the simulated pressure responses for the mean parameters of stable and unstable groups (Fig. 7). In the stable group, pressure tended to remain constant with no changes for a 20% of blood volume reduction, which is similar to those occurring during hemodialysis. In the case of the unstable parameter-set, arterial pressure exhibited a small increase for mild blood volume reductions and then an abrupt drop when the reduction in blood volume exceeded a threshold of about 10%, thereby manifesting the typical pressure instability of these patients.

The effects of changes in the balance-parameter K_{aff} on the pressure responses to hypovolemia were assessed by considering the standard values for K_v and K_r (Fig. 8). When baroreflex regulation was mediated by cardiopulmonary receptors only ($K_{aff} = 1$), arterial pressure overcomes the response simulated with the standard parameter-set. This extreme condition exhibited a paradoxical hyper-efficient regulation to hypovolemia because the limiting factor due to arterial baroreflex, which generally opposes arterial pressure increases, is in this case completely inhibited. On the contrary, when vasoconstriction control is completely mediated by arterial baroreceptors ($K_{aff} = -1$), low-pressure baroreflex does not take place and arterial pressure slowly decreases during hypovolemia. Even though, in this case, regulation to hypovolemia appeared to be much less efficient compared to standard response, arterial pressure did not overcome the threshold of acute hypotension (75%). Moreover, the slope of the pressure response, indicating sensitivity of pressure to volume changes, was lower than the response for the unstable parameter-set (Figs. 7

TABLE 5. *Mean and standard deviation (SD) of regulatory parameters after model identification in stable and unstable groups*

Parameter	Stable (n = 6) (Mean ± SD)	Unstable (n = 6) (Mean ± SD)	ANOVA	Standard (Mean ± SD)
K_{AFF}	0.5 ± 0.7	0.1 ± 0.7	NS	0.3 ± 0.7
K_V	0.9 ± 0.2	0.1 ± 0.1	$p < 0.05$	0.5 ± 0.4
K_R	0.4 ± 0.4	0.7 ± 0.4	$p < 0.05$	0.5 ± 0.4

and 8) even though the cardiopulmonary reflex was not operative.

Changes in gain K_r seemed to have a similar effect on the pressure response to changes in K_{aff} (Fig. 9). Maximum efficiency in peripheral resistance regulation ($K_r = 1$) allowed an increase in arterial pressure during hypovolemia. On the contrary, when peripheral resistance was not regulated ($K_r = 0$) arterial pressure decreased toward critical values, thereby demonstrating the importance of this kind of regulation for sustaining pressure during hypovolemia (15).

Pressure response exhibited the greatest sensitivity to changes in the K_v parameter (Fig. 10). Indeed, when this regulatory mechanism did not take part in the control process ($K_v = 0$), arterial pressure dramatically fell to hypotension levels. On the contrary, hyper-activation of venous capacity regulation ($K_v = 1$) became evident only for large blood volume losses when pressure response was further stabilized with respect to the standard case.

DISCUSSION

In this paper we propose a novel approach for analyzing pressure response to hemodialysis-induced hypovolemia. It is based on computer simulation and endeavors to combine a time-series of cardiovascular data recorded during conventional hemodialysis, with a simple model of the cardiovascular system for better understanding of patient hemodynamic behavior. With such an approach, the computer model may help to systematize and extract more information from recordings as well as to test possible consequences or implications of different hypotheses. From this point of view, a modeling approach like the present one could have particular importance in patient monitoring, especially in preventing acute hypotension during hemodialysis.

A notable comprehensive model of the hemodynamic response to hemodialysis was already published by Ursino and Innocenti (16). They used a computer model to investigate the complex interaction between hemodynamic and osmotic factors in the development of symptomatic hypotension (17). This model also included solute and water kinetics for estimating blood volume. In our model, blood volume and heart rate were both considered as inputs, thereby greatly simplifying the model structure.

Similarly to the Ursino and Innocenti model (16), we described the cardiovascular system by using Guyton's classical models (9,18,19). In this kind of model, the distributed properties of circulation are lumped in a few compartments, distinguishing only the relevance of the main circulatory districts. This approach is consistent with the aim of this study because the cardiovascular model is used here essen-

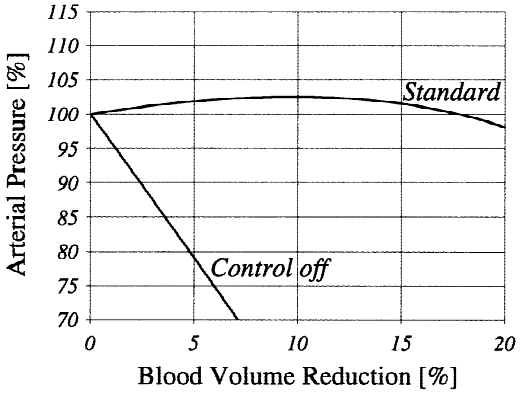

FIG. 6. Simulated pressure response to hypovolemia for the standard set of parameters (Tables 4 and 5) is compared to the lack-of-regulation case ($K_v = K_r = 0$). In both cases, heart rate was kept constant.

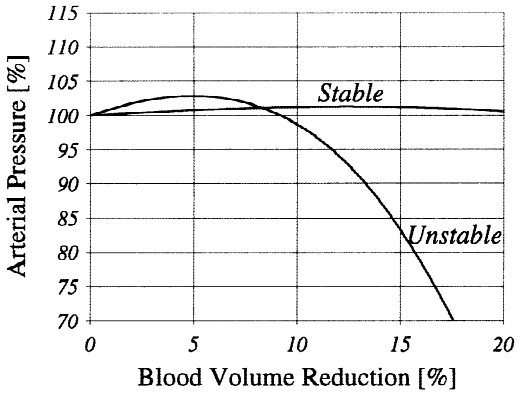

FIG. 7. Comparison of pressure responses obtained with the simulator by assigning the mean values of regulatory parameters as estimated, respectively, for the stable and unstable group (Table 5) is illustrated. In both cases, heart rate was kept constant.

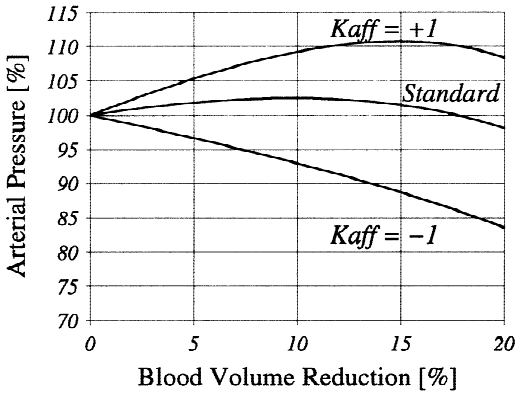

FIG. 8. The effects of changes in the balance-parameter K_{aff} on the pressure response are shown. Parameters K_v and K_r were kept to standard values (Table 5), while K_{aff} was equal to minimum, standard, and maximum values.

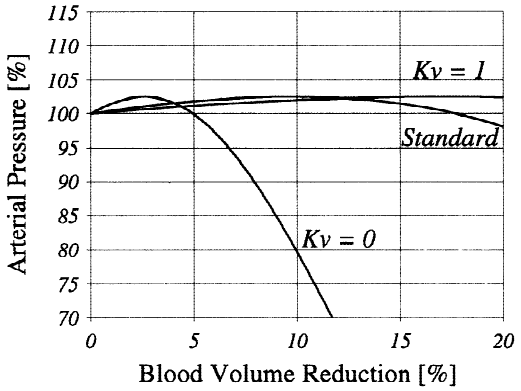

FIG. 10. The effects of changes in parameter K_v on the pressure response are shown. Parameters K_{aff} and K_r were set to standard values (Table 5) whereas K_r was equal to minimum, standard, and maximum values.

tially to estimate blood distribution between venous and arterial compartments and to calculate the high and low pressure levels driving baroreflex regulation of vasomotor activity.

A critical task was to describe afferent baroreflex regulation by using a simple model. Although much information is on hand regarding the efferent mechanisms involved in the physiological compensatory response to acute hypovolemia (7), understanding of the interaction between low- and high-pressure receptors in the control of the vasoconstraint state still requires further investigation. In agreement with the Ursino and Innocenti model (16), we assumed a linear superimposition between arterial and cardiopulmonary baroreceptor outflows. Then we used a "balance-like" relationship characterizing the relative weight of 2 afferent pathways with just one parameter (K_{aff}).

According to current physiological knowledge (7,20–22), in the model the mechanisms compensating for the pressure perturbations operate on venous unstressed volume and peripheral resistance. Each mechanism was modeled with a sigmoid gain and was characterized by only one parameter expressing the effectiveness of the mechanism. The balance K_{aff} of the afferent pathways and gains K_v and K_r of the effectors determine the effectiveness of the vasoconstriction state. This simple structure of the regulatory feedback, with only 3 parameters to be estimated, avoids redundancy in the parameter identification procedure.

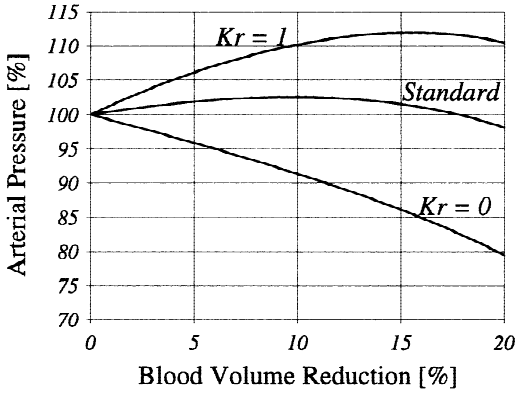

FIG. 9. The effects of changes in parameter K_r on the pressure response are illustrated. Parameters K_{aff} and K_v were set to standard values (Table 5) whereas K_r was equal to minimum, standard, and maximum values.

In spite of the model's simplicity, it displays a remarkable ability to fit the measured pressure data, starting from the blood volume and heart rate time courses. In fact, by tuning only 3 parameters (K_{aff}, K_v, and K_r), all the pressure responses were well reproduced, despite showing significantly different time patterns.

We tested the performance of the model by selecting 2 groups of patients (6 + 6) whose hemodynamic behavior was easily distinguished according to their history of hemodynamic-induced acute hypotension. The same criterion had already been used in a previous study (3), and therefore, under the implicit assumption that a deficiency in autonomic regulation may play a pivotal role in hemodynamic-induced hypotension (1,5,6,20), we identified the model parameters related to baroreflex control.

It is worth noting that the pressure responses of the stable and unstable groups considered in this study were not significantly different. In fact, pressure responses only partially reflected the classification of patients as hypotension-prone and hypotension-resistant because acute hypotension did not occur in the analyzed sessions. In spite of this fact, the results of parameter identification are consistent with patient preclassification, and a clear distinction

between the 2 groups was possible on the basis of the estimated parameters in particular considering K_v. This result agrees with the hypothesis that hypotension-prone and hypotension-resistant patients have autonomic-mediated regulatory mechanisms of different strength. In particular, stable patients exhibit a sustained effectiveness in vasoconstriction, which is able to compensate for hemodialysis-induced hypovolemia. Conversely, unstable patients show a low reflex regulatory capability. This is the most significant difference we found between the 2 groups, which could be the main cause of their different hemodynamic behavior.

By the model, we also simulated the changes in cardiac output in the course of dialysis. A significant reduction of cardiac output (20 ± 10%) was computed in the case of the unstable group whereas cardiac output remained unchanged (differences less than 10%) in the case of stable patients. This model prediction closely agrees with the results of Nakamura et al. which observed a stable cardiac index in 7 patients whose pressure response to hemodialysis was stable whereas the cardiac index fell in a group of 10 patients with hypotension response (23).

Once parameter sets representative of 2 groups of patients were identified, we used the model to perform a sensitivity analysis in order to show how pressure response depends on the effectiveness of regulatory mechanisms.

This analysis significantly revealed that pressure response had the greatest sensitivity to changes in parameter K_v (Fig. 10). When active capacitance vessel constriction did not participate in the regulatory process ($K_v = 0$), the pressure response exhibited a dramatic fall to acute hypotension. Instead, when peripheral resistance regulation was off (Fig. 9), the pressure decrease was limited as long as compensation in venous volume was adequate. This result is in accordance with the hypothesis that the control of capacitance vessels is the major component of hypovolemia compensation (8). Further, Nakamura et al. suggest that hypotension following dialysis is mainly due to the fall in cardiac output, in which increases in venous distensibility play a pivotal role (23).

Ursino and Innocenti focused the role of peripheral arterioles regulation, and they suggested that the progressive arterial pressure decrease observed late in hemodialysis may, in some instances, be caused by an impairment of such mechanism (16). Actually, they analyzed with the model only responses of stable dialysis patients. The data that they qualitatively reproduced with the model were related to dialysis in which blood pressure decreased (less than 20%) because total peripheral vascular resistance did not increase, despite the hemodynamic stability of the patients. Therefore, their conclusion could be strictly influenced by the particular set of data they analyzed. However, in the sensitivity analysis they found that the control acting on venous unstressed volume had a comparable role to systemic resistance control (17). Moreover, according to our results, they also asserted the prevalence of cardiopulmonary over arterial baroreflex control.

When we simulated the case of control completely mediated by arterial baroreceptors ($K_{aff} = -1$) (Fig. 8), regulation to hypovolemia appeared to be much less efficient than in the standard case, proving the importance of cardiopulmonary baroreflex in keeping arterial pressure high. Nevertheless, our simulation predicts that even if regulation of the low-pressure side is leaked, arterial baroreflex alone is sufficient to prevent acute hypotension.

On the basis of model identification, in hypotension-resistant patients, the main regulation appears to be effected through the cardiopulmonary baroreflex ($K_{aff} = 0.5$). This reflex is able to cope with hypovolemia through a strong sympathetic vasoconstriction, which causes a significant decrease in venous unstressed volume ($K_v = 0.9$). It is worth noting that an hyper-efficient regulatory action can even lead to an increase in arterial pressure (Fig. 8). In this condition, the loading of arterial baroreceptors contributes to limit the hypertensive effects of cardiopulmonary baroreceptors regulation, and the two systems operate in a competitive way, maintaining arterial pressure stable. By contrast, in hypotension-prone patients, arterial pressure tends to decrease, thus causing unloading of the arterial baroreceptor. In this case, arterial and cardiopulmonary baroreceptors cooperate to sustain arterial pressure.

The paradoxical increase in arterial pressure that was observed in some unstable patients during the first stage of hypovolemia could be due to a hyper-efficient peripheral resistance regulation as simulated in Fig. 9.

In the case shown in Fig. 5 (left panels), the pressure tended to decrease significantly, and in order to prevent a vasovagal syncope, a plasma expander infusion at about $t = 215$ min was necessary. It is worth noting that, in this case too, the model accurately reproduced the consequent pressure recovery.

The results obtained in this study, besides demonstrating the validity of the model "in se" indicates that model-based computer simulation may be a useful tool to analyze the hemodynamic response conventionally recorded during hemodialysis. An important prerogative of this approach is that starting from three distinct sources of information (blood

volume, heart rate, and arterial pressure), one can obtain 3 single values that synthesize the hemodynamic behavior of the patient. In a longer prospective, the computer simulation could be also applied on-line to provide real-time prediction of short-term pressure response.

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REFERENCES

1. Henrich WL. Hemodynamic instability during haemodialysis. *Kidney Int* 1986;30:605–12.
2. Rostand SG, Brunzell JD, Cannon RO, III, Victor RG. Cardiovascular complications in renal failure. *J Am Soc Nephrol* 1992;2:1053–1062.
3. Cavalcanti S, Severi S, Enzmann G. Analysis of oscillatory components of short-term heart rate variability in hemodinamically stable and unstable patients during hemodialysis. *Artif Organs* 1998;22:98–106.
4. Heber ME, Lahiri A, Thompson D, Raftery EB. Baroreceptor, not left ventricular, dysfunction is the cause of haemodialysis hypotension. *Clin Nephrol* 1989;32:79–86.
5. Kersh ES, Kronfield SJ, Unger A, Popper RW, Cantor S, Cohn K. Autonomic insufficiency in uremia as a cause of haemodialysis-induced hypotension. *N Engl J Med* 1974;290: 650–65.
6. Zoccali C, Ciccarelli M, Maggiore Q. Effective reflex control of heart rate in dialysis patients: Evidence for an afferent autonomic lesion. *Clin Sci* 1982;63:285–92.
7. Rothe CH. Reflex control of veins and vascular capacitance. *Physiol Rev* 1983;63:1281–1342.
8. Rowell LB, Detry JMR, Blackmon JR, Wyss C. Importance of the splanchnic vascular bed in human blood pressure regulation. *J Appl Physiol* 1972;32:213–20.
9. Guyton AC, Jones CE, Coleman TG. *Circulatory physiology: cardiac outpout and its regulation.* Philadelphia: W.B. Saunders Co., 1973.
10. Johnson JM, Rowell LB, Niederberger M, Eisman MM. Human splanchnic and forearm vasoconstrictor responses to reductions of right atrial and aortic pressures. *Circ Res* 1974;34: 515–24.
11. Melbin J, Detweiler DK, Riffle A, Noordergraaf A. Coherence of cardiac output with rate changes. *Am J Physiol* 1982; 243:H499–H504.
12. Ushioda E, Nuwayhid B, Kleinman G, Tabsh K, Brinkman CR, Assali NS. The contribution of the beta-adrenergic system to the cardiovascular response to hypovolemia. *Am J Obstet Gynecol* 1983;147:423–429.
13. Mark AL, Mancia G. Cardiopulmonary baroreflexes in humans. In: Shepherd JT, Abboud FM, eds. *Handbook of Physiology,* Sec. 2, Vol. III. Bethesda, MD: American Physiological Society, 1983:453–96.
14. Nelder JA, Maead R. A simplex method for function minimization. *Comp J* 1965;7:308–13.
15. Sagawa K. Baroreflex control of systemic arterial pressure and vascular bed. In: Shepherd JT, Abboud FM, eds. *Handbook of Physiology,* Sec. 2, Vol III. Bethesda, MD: American Physiological Society, 1983:453–496.
16. Ursino M, Innocenti M. Modeling arterial hypotension during hemodialysis. *Artif Organs* 1997;21:873–90.
17. Ursino M, Innocenti M. Mathematical investigation of some physiological factors involved in hemodialysis hypotension. *Artif Organs* 1997;21:891–902.
18. Coleman TG, Bower JD, Guyton AC. Chronic hemodialysis and circulatory function. *Simulation* 1970;15:222–8.
19. Guyton AC, Cowley AW, Jr., Young DB, Coleman TG, Hall JE, DeClue JW. Integration and control of circulatory function. *Int Rev Physiol* 1976;9:341–85.
20. Daugirdas JT. Dialysis hypotension: a hemodynamic analysis. *Kidney Int* 1991;39:233–46.
21. Guyton AC. *Textbook of medical physiology.* 7th ed. Philadelphia: W.B. Saunders Co., 1986.
22. Guyton AC, Coleman TG, Fourcade JC, Navar LG. Physiologic control of arterial pressure. *Bull NY Acad Med* 1969; 45:811–30.
23. Nakamura Y, Ikeda T, Takata S, Yokoi H, Hirono M, Abe T, Takaza-kura E, Kobayashi K. The role of peripheral capacitance and resistance vessels in hypotension following hemodialysis. *Am Heart J* 1991;121:1170–7.