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Electric properties of blood and impedance cardiography

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CHAPTER 7

SUMMARY, DISCUSSION AND CONCLUSIONS

INTRODUCTION

Impedance cardiography is a non-invasive method for the estimation of stroke volume, in which the electric impedance of the thorax between two electrodes is measured in the longitudinal direction. The heart-synchronous variations and the first derivative with respect to time of the absolute value of the thoracic impedance are recorded (chapter 1, figure 2) while the mean absolute value of the thoracic impedance (Z_m) is displayed [17]. The variations of the thoracic impedance related to the respiration are disregarded, mostly by making the recordings during end-expiratory breath holding.

The assumptions, underlying the calculation of stroke volume in impedance cardiography, are:

- a. the thoracic impedance is considered to be a parallel connection of a tissue impedance and a blood resistor ("parallel conductor model");
- b. the resistivity of the blood is constant;
- c. the blood resistor is considered to be an electrically conducting tube of uniform diameter, or a parallel connection of such tubes regarded as one;
- d. the electric current distribution in this tube is homogeneous;
- e. the volume variations due to variations in diameter of the blood resistor are the only cause of the heart-synchronous impedance variations;
- f. although impedance is a complex quantity, characterised by a modulus or absolute value and an argument or phase angle, phase angles can be neglected;
- g. a correction for the outflow of blood from the blood resistor can be made through an extrapolation procedure as proposed by Patterson [30].

The resistivity of blood is not only a function of the resistivities of erythrocytes and plasma, and of the haematocrit (or volume fraction of cells), but also, because of their biconcave shape, of the orientation and shape of the erythrocytes [11]. The resistivity or conductivity of flowing blood is found to be a function of the shear rate (velocity gradient) profile, because the orientation of the erythrocytes is influenced by the viscous forces of plasma.

In this thesis four papers [chapters 2-5] are included which all deal, in a direct or indirect way, with the assumed constancy of the resistivity (or electric conductivity) of blood in relation to impedance cardiography. A fifth paper [chapter 6] gives an application of the insight which had been gained from studying the relation between the electric properties of blood and impedance cardiography as described in the preceding four pa-

pers.

In questioning the assumed constancy of the resistivity of blood, two aspects are of importance:

1. how does the resistivity of blood vary *in vitro*?
2. what is the importance of these variations for the heart-synchronous thoracic impedance variations *in vivo*?

The first aspect has been investigated by measuring the flow rate and the resistance in the longitudinal direction of blood flowing through a rigid circular tube [chapter 2 and 3]. The second aspect has been investigated by measuring the complex thoracic impedance and the absolute value of its heart-synchronous variations in dogs in which the blood is gradually replaced by a stroma free haemoglobin solution [chapters 4 and 5]. In the fifth paper a theoretical foundation is given for the determination of systolic time intervals by impedance cardiography [chapter 6].

RESISTIVITY OF BLOOD

Blood is considered as a suspension of particles (erythrocytes or red blood cells) with a high resistivity in a conducting fluid (plasma). Other cells and the platelets are of no importance for the electric properties of blood, because they are too small in size or in number.

The theory relating the resistivity of a particle suspension to the resistivities of suspending medium and suspended particles is due to Fricke [11]. He calculated the resistivity of a suspension of homogeneous ellipsoids in a homogeneous conducting medium when the distances between the ellipsoids were large enough to consider the disturbance of the current produced by each of the ellipsoids as independent of each other. This led to a theory which takes the shape and orientation of the particles into account, in addition to the resistivities of medium and particles, and the fraction of particles.

The erythrocytes are approximated by oblate ellipsoids with a short axis with length a (axis of symmetry) and two long axes with equal length b . When a particle is rotated on its axis of symmetry its orientation does not change. Therefore, the orientation of an erythrocyte is described as the orientation of its axis of symmetry with respect to the direction of the electric field. This theory is generally accepted to describe the resistivity of blood at low frequencies (<1 MHz) [9, 38] and was used throughout this thesis.

For most mammals, including humans, the resistivity of erythrocytes is large compared to that of plasma. Application of Fricke's theory then leads to

$$\frac{\rho_b}{\rho_p} = 1 + \frac{H}{1-H} C \quad (1)$$

where ρ_b and ρ_p are the resistivities of blood and plasma, H is the hematocrit and C is a constant. Or

$$\frac{\sigma_b}{\sigma_p} = \frac{1}{1 + \frac{H}{1-H} C} \quad (2)$$

where σ_b and σ_p are the conductivities of blood and plasma.

In this case (large resistivity of erythrocytes) C is only a function of a/b (shape) and of the distribution of the orientations of the erythrocytes with respect to the electric field. There are only two well-defined states of orientation of the erythrocytes: random orientation and parallel orientation (all erythrocytes parallel to each other). In case of random orientation, C is exclusively a function of a/b ; for parallel orientation, C is a function of a/b and of the direction of the axis of symmetry with respect to the direction of the electric field. Random orientation can be attained in stationary blood; parallel orientation can be approximated in flowing blood. Randomness of orientation is maintained through the influence of Brownian motion; but other forces (e.g. gravity, viscous forces in flowing blood) disturb the randomness. It is possible to calculate the resistivity at parallel orientation from the resistivity at random orientation and vice versa.

STATIONARY BLOOD

Changes in the resistivity of flowing blood should obviously be related to the resistivity of stationary blood as reference value. However, in stationary blood the orientation of erythrocytes also influences the magnitude of the resistivity since the erythrocytes tend to orient themselves with their axes of symmetry in the vertical direction under the influence of gravity. This tendency can be countered by vibrating or shaking the blood. If there is randomness of orientation, the conductivities of blood in the horizontal and vertical directions are equal. Therefore, the resistivity of stationary blood was measured in a cell which was vibrated in order to attain random orientation of the erythrocytes. The random orientation was checked by measuring the resistivity in both the horizontal and vertical directions. A measurement was accepted only when the two measurements gave equal results. This requirement for accurately measuring the resistivity of stationary blood has generally been neglected [chapter 3].

The resistivity of human plasma (ρ_p) was measured to be $0.637 \Omega m$ at $37^\circ C$; this corresponds with $1.57 S/m$ for the conductivity of plasma

(σ_p) . The resistivity of stationary human blood (ρ_b) with different haematocrit values (H) was measured at 37°C. H varied from 0.046 to 0.787. With equation 1, C for random orientation (C_r) was estimated to be 1.91 ± 0.09 (mean \pm sd; n=25) from these measurements (chapter 3, figure 3). For $H=0.45$, ρ_b was $1.63 \Omega \text{m}$. From C_r , a/b was calculated to be 0.22. Through variation in orientation of erythrocytes, C varies between 1.17 (all erythrocytes with their axis of symmetry perpendicular to the field) and 3.38 (all erythrocytes with their axis of symmetry parallel to the field). These values of C generate two curves in the H- σ_b plane (equation 2), between which all possible values of σ_b for undeformed erythrocytes are situated (chapter 3, figure 3).

FLOWING BLOOD

Because of the influence of the orientation of the erythrocytes, blood is electrically anisotropic. The electric conductivity is not a scalar but a symmetric second-order tensor with six components. Blood is only isotropic when the erythrocytes are homogeneously distributed and in random orientation. In homogeneous one-dimensional situations it is possible to designate a single (scalar) value of the conductivity of blood. In one-dimensional situations with unknown orientation it is possible to define an effective conductivity. For axisymmetric flow through a cylindrical tube and with a uniform electric field in the longitudinal direction only, we deal with such a situation. The effective conductivity ($\langle \sigma_{zz} \rangle$) is

$$\langle \sigma_{zz} \rangle = \frac{\int_0^R \sigma_{zz} 2\pi r dr}{S} \quad (3)$$

where σ_{zz} is the principal component of the conductivity tensor in the longitudinal (z) direction, r is the radial coordinate, R the radius of the tube and S the cross-sectional area. Analogous to the effective conductivity, an effective resistivity can be defined. By using the so defined quantities, conductivity and resistivity can be treated as if they were scalars. For reasons of simplicity they are indicated as σ and ρ [chapter 2].

Under axisymmetric conditions the shear rate profile, which determines the orientation of the erythrocytes and hence the resistivity of flowing blood, are a function of a single parameter: the average velocity divided by the radius of the tube. This parameter is called the reduced average velocity and has the dimension of a shear rate. By describing the resistivity of flowing blood as a function of the reduced average velocity (instead of the average velocity), not only a more general description is obtained, but also one that clearly indicates that changes in both velocity and radius of an elastic tube (blood vessel) influence the resistivity but in

opposite directions.

The effective resistivity (or conductivity) of human blood was investigated while the blood was in laminar flow in a rigid circular tube (i.d. 4 mm) at 10 different constant flow rates for three haematocrit values (53.7, 47.5 and 36.4 %) at 37 °C. The change in effective resistivity ($\Delta \rho_b$) as a percentage of the resistivity of stationary blood (ρ_b) is given by the following empirical relationship

$$\frac{\Delta \rho_b}{\rho_b} = -0.45H \left(1 - \exp \left(-0.26 \left| \frac{\langle v \rangle}{R} \right|^{0.39} \right) \right) \quad (4)$$

where H is the haematocrit (in % if $\Delta \rho_b/\rho_b$ is expressed in %) and $|\langle v \rangle/R|$ is the absolute value of the reduced average velocity in s^{-1} (chapter 2, figure 3). The change in effective conductivity ($\Delta \sigma_b$) as a percentage of the conductivity of stationary blood (σ_b) is given by (chapter 3, figure 3)

$$\frac{\Delta \sigma_b}{\sigma_b} = 0.58H \left(1 - \exp \left(-0.20 \left| \frac{\langle v \rangle}{R} \right|^{0.41} \right) \right) \quad (5)$$

From equation 5, maximal conductivity of flowing blood in the direction of flow ($(\sigma_b)_{max}$) was estimated to be

$$(\sigma_b)_{max} = (1 + 0.58H)\sigma_b \quad (6)$$

which is obtained for velocity values approaching infinity. Such a maximum value was considered to correspond with the conductivity when all the erythrocytes are oriented with their axes of symmetry perpendicular to the field and are maximally deformed. The value of a/b for the maximal conductivity is about 0.4, indicating deformation of the erythrocytes. If we compare the maximum conductivity that can be attained by undeformed cells with those that can be attained by deformed cells, it is clear that these large deformations have little influence on the conductivity (chapter 3, figure 3).

During acceleration of flow the resistivity change is synchronous with the change in flow rate, but during deceleration of flow there is an exponential decay characterized by a relaxation time τ (chapter 2, figure 2). For haematocrit values of 36.4 % and 47.5 %, τ was estimated to be 0.21 s; for a haematocrit of 53.7 %, τ was estimated to be 0.29 s [chapter 2].

DISCUSSION

The theory of Fricke is only exact for dilute suspensions. It can be

shown that it is a first order approximation in the variable H [9]. However, it can also be shown that higher order terms can be neglected for the case in which the conductivity of the medium is high in comparison with the conductivity of the particles. As this is the case for blood, application of the theory of Fricke is also allowed for more concentrated suspensions (as long as $H \leq 0.8$) [9]. On experimental evidence Dellimore and Gosling [6] estimated the applicability of the theory to be limited to $H < 0.6-0.65$. The erythrocytes are approximated by oblate ellipsoids. This form is chosen because it represents two attributes of importance: the axis of symmetry and the discoid shape of the erythrocytes. The excellent fit of the data of stationary blood ($r = -0.999$, $n = 25$) shows the correctness of this simplification (chapter 3, figure 3).

Many different equations have been presented in the literature for the relation between the electric conductivity (or resistivity) of stationary blood and the haematocrit [12, 15, 16, 26, 27, 33, 41-43]. The equations vary from straight lines [15, 16, 27] to exponential functions [12, 26, 33, 42, 43] and equations similar to equation 1 [12, 41]. These differences are, at least partly, explained by the fact that in the measurement of the conductivity of blood the orientation of the erythrocytes is generally neglected. Random orientation is the only well-defined state of orientation of the erythrocytes that can be attained in stationary blood. But it is mandatory to check this condition by measuring the conductivity in the horizontal and vertical directions.

The magnitude of the resistivity changes in flowing blood due to changes in orientation of the erythrocytes ("orientation effect") can be as large as 30 % for normal haematocrit values and flow rates in the physiological range in tubes with dimensions of the main arterial branches or larger. Other phenomena (i.e. rouleaux formation, cell-free zone at the wall of the tube, particle migration perpendicular to the direction of flow due to non-uniform shear, and deformation of cells) may also cause conductivity changes in flowing blood, but with the flow rates and tube diameters considered here, they are of little or no importance [chapters 2 and 3].

All investigators who conducted comparable experiments [4, 5, 8, 21-23, 35, 39] found a similar relation between the changes in resistivity (or conductivity) and the average velocity as the one presented here (equation 4 and 5; figures 3 in chapters 2 and 3). It is difficult to obtain exact values for the resistivity changes from the literature, because results are usually given in the form of a graph. The order of magnitude found in literature agrees with our findings, but there are differences. Part of an explanation may be found in the differences in setup: the use of two electrodes or four electrodes, flow through a circular or non-circular tube or Couette flow, influence or no influence of entrance effect, and in different kinds of blood used at different temperatures and with different haematocrit values. An important factor undoubtedly is the value of the resistivity of stationary blood used as a reference; none of the authors clearly states which resistivity values were used and whether or

how randomness of the orientation of the cells in stationary blood was ascertained. Another reference value for the resistivity should lead to different values for the constants in equations 4 and 5. Those authors who used different haematocrit values also found the magnitude of the decrease in resistivity increasing with increasing haematocrit values [8, 13, 31, 35, 39]. For a constant reduced average velocity we found the relative changes in resistivity to be linearly related to the haematocrit (equation 4). Theory does not predict this linearity [11], but for a small range of haematocrit values linearity may be valid. Davis [5] and Dellimore and Gosling [7] reported that the resistivity change in flowing blood is proportional to $\langle v \rangle^{1/3}$. If we expand our expression (equation 4) into powers of $\langle v \rangle$ the first term has the power 0.39, which is close to 1/3. The proportionality of the resistivity change to some fractional power of $\langle v \rangle$ can only be correct for low velocities, because at high velocities the resistivity should have a finite limiting value because both erythrocyte orientation and deformation are finite.

In the literature, little attention is given to the difference in resistivity change between acceleration and deceleration of flow. Dellimore and Gosling [7] reported this difference and mentioned a time constant between 40 and 50 s ($0.40 < H < 0.45$), but they neither defined the term time constant nor reported how it was determined. As a consequence of the decay during deceleration of flow, the magnitude of the resistivity variations in pulsatile flow decreases with increasing frequency; this has been mentioned by some authors [13, 20, 22, 23, 35].

Blood flow in large intrathoracic blood vessels is pulsatile. In our experiments we have used rectangular flow pulses. This may be too simple a model to mimic the real flow pulses. It must be realized that the orientation effect is a highly non-linear phenomenon, so an exact description for real flow pulses, under all conditions of interest, is difficult. All measurements were performed in laminar flow. However, in the aorta turbulent flow may occur [25].

If fluid flows from a reservoir into a tube, the velocity profile changes in the first part of the tube (entrance effect) [25, 37]. The length of this part is called inlet length. For the calculation of the inlet length a flat velocity profile is assumed at the entrance of the tube. To calculate the inlet length, we used an approximation for a Newtonian fluid in constant laminar flow. Blood is a non-Newtonian fluid. As a consequence of this, the velocity profile is more flattened [25], so the real inlet length may be shorter. The inlet length in pulsatile flow differs from the inlet length at constant flow [1, 25]. All measurements were made in a part of the tube with a constant velocity profile (developed flow). Consequently, the entrance effect has not influenced our results. As the blood flow in the relevant region of many vessels clearly occurs within their inlet length its influence should be considered because the entrance effect has influence on the magnitude of the orientation effect [44]. All the above-mentioned factors: non-Newtonian viscosity and pulsatile flow, which both influence the actual inlet length and the

entrance effect itself which influence the actual magnitude of the orientation effect, make an assessment of the influence of the inlet length on the orientation effect very complicated.

The results of our experiments clearly indicate that significant resistivity variations due to variations in the orientation of the erythrocytes may occur in the large intrathoracic blood vessels. Consequently, these variations may be an additional cause of the heart-synchronous variations of the thoracic impedance as found in impedance cardiography. However, complicating factors such as the pulsatile nature of blood flow, the possibility of turbulence, and the influence of the entrance effect, make *in vivo* experiments necessary for a realistic estimate of the importance of the orientation effect in impedance cardiography.

EXCHANGE TRANSFUSION EXPERIMENTS

To investigate the importance of the resistivity variations due to variations in erythrocyte orientation for the measurement of thoracic impedance variations *in vivo*, experiments were carried out on four adult splenectomized mongrel dogs in which blood was gradually replaced by a stroma free haemoglobin solution. This is a haemoglobin solution with the same pH, electrolyte concentrations and colloid osmotic pressure as canine plasma but without cells, platelets or cell remains. Its resistivity is comparable to that of plasma. It has a sufficient O₂ and CO₂ carrying capacity. The exchange transfusion was accomplished in such a way that the volume of the circulating fluid and the volumes of the other fluid compartments of the body remained constant.

The haematocrit and resistivity at body temperature of every volume of removed circulating fluid were measured. Just before each exchange the real and imaginary parts of the thoracic impedance and the modulus of the heart-synchronous impedance variations were measured. The haematocrit decreased exponentially with the number of exchanges. This indicates that the circulating fluid volume remained constant during the exchange transfusion and allowed to make an estimate of the circulating fluid volume. Its estimated values were within the expected physiological range for splenectomized dogs.

PARALLEL CONDUCTOR MODEL

To investigate the importance of the orientation effect, a model of the thorax is necessary. Therefore the parallel conductor model (parallel connection of a tissue impedance and a blood resistor or a parallel connection of a tissue admittance and a blood conductor) was investigated first; admittance is the reciprocal value of impedance. The decrease in haematocrit during the exchange transfusion caused a decrease in the resistivity of blood which caused a decrease in the blood resistance, while the tissue impedance remained constant. During the exchange transfusion the mean decrease in resistivity of the circulating fluid was 54 %. Be-

cause of the parallel connection, all calculations were based on admittance. The real and imaginary parts of the thoracic admittance were calculated from the measured values of the real and imaginary parts of the thoracic impedance. The real part (thoracic conductance) increased linearly with the conductivity of the circulating fluid, whereas the imaginary part (thoracic susceptance) remained constant. This is in agreement with the model. The components of the model were estimated from the values of the thoracic conductance and susceptance. For a haematocrit of 40 % the mean values of the tissue impedance, the blood resistance, and the transthoracic impedance were 46, 712, and 43Ω , respectively. The mean values of the arguments (phase angles) of tissue impedance and thoracic impedance were 12.4° and 11.8° , respectively [chapter 4].

SIGNIFICANCE OF RESISTIVITY VARIATIONS IN VIVO

The decrease in haematocrit during the exchange transfusion not only caused a decrease in the resistivity of blood, but also a cell volume-related gradual disappearance of the orientation effect, while the volume variations of the large intrathoracic blood vessels were kept as constant as possible. This decrease in orientation effect was used to determine its contribution to the heart-synchronous thoracic impedance variations, using an extended form of the parallel conductor model of the thorax.

The parallel conductor model was extended to account for the influence on the blood conductor G_b of haematocrit and orientation of the erythrocytes. Applying this extended model, the average magnitude of the variations in G_b at a haematocrit of 40 % were estimated to be 7.46 %: 3.03 % due to volume variations and 4.43 % due to orientation effect. After further extending the model to account for the influence of small changes in mean and pulse (or pulsatile part of) blood pressures and heart rate, the average magnitude of the volume variations was estimated to range from 2.8 % to 3.3 % and the average magnitude of the orientation effect from 4.1 % to 4.7 % at a haematocrit of 40 % [chapter 5].

DISCUSSION

The parallel conductor model for the thorax is a very simple one; it gives quite a general representation of the electrical properties of the thorax. The same holds for the measurement technique in impedance cardiography. If the electrical properties are measured in more detail a more sophisticated model is needed for the interpretation of the experimental results. Apparently, in this case a simple model is sufficient, because the results of our experiments are in accordance with the model [chapter 4]. Moreover, our experiments enabled us to estimate the magnitudes of the components of the model (chapter 4, table 6).

Our results agree with those of other experiments designed to validate the parallel conductor model [29, 30, 40]. These investigators measured absolute impedance values instead of moduli and arguments or real

and imaginary values. If the variations ΔY_o due to the action of the heart are caused only by variations in the blood conductance G_b , then the magnitude of ΔY_o (or $-\Delta Z_o/Z_o^2$) does not change through the addition of an external parallel resistor. This fact was used by Nyboer *et al.* [29] to test the model on the human leg and by Patterson [30] to test the model on the human thorax. The results of their experiments allowed both authors to confirm the suitability of the parallel conductor model for their application, but they were unable to estimate the magnitude of the components of the model. Shimazu *et al.* measured the admittance of the human arm before and after venous occlusion [40]. During the measurements the limb was submerged in a fluid the conductivity of which was changed. The total volume of limb and fluid was kept constant. The conductivity of the blood in the limb was compared with the conductivity of the surrounding fluid in a situation in which a volume change due to venous occlusion did not result in a change in admittance. From these experiments they confirmed the validity of the parallel conductor model in this situation. Their kind of experiment cannot be performed on the thorax unless with great difficulty in an animal model.

Our investigations have shown that contributions to the heart-synchronous thoracic impedance variations of variations in blood conductivity due to variations in orientation of the erythrocytes and due to volume variations are of comparable magnitude. The contribution of the volume variations is the sum of the volume variations in the contributing intrathoracic vessels. The effects of variations in orientation are added up in proportion to the relative volumes of the contributing vessels. The extensions of the parallel conductor model brought out all factors contributing to the magnitude of the heart-synchronous thoracic impedance variations. These are factors related to heart action and circulation:

- heart rate,
 - pulse and mean flows in all contributing blood vessels,
 - pulse and mean pressures in all contributing blood vessels, and
 - compliances of all contributing blood vessels;
- and factors related to blood:
- haematocrit,
 - the relations between orientation effect and flow velocity for all contributing blood vessels,
 - the relations between orientation effect and vascular volume for all contributing blood vessels, and
 - the relation between orientation effect and heart rate for all contributing blood vessels.

A first order approximation for the influences of these factors has been derived (chapter 5, equations 12 and 19-25).

The estimated magnitude of the orientation effect is comparable with the values reported in the literature [4, 7, 8, 13, 20-23, 28, 31-36, 39, 41, 45-48]. However, these determinations, were all done *in vitro* with one exception. Gollan and Namon [13] perfused the head and hind leg of dogs with blood, diluted with physiological saline solution, but

they did not take into account the effect of the dilution on the electric conductivity of the circulating fluid. By neglecting this, they arrived at a conclusion opposite to ours.

SYSTOLIC TIME INTERVALS

The dZ/dt signal has many distinct peaks and notches that can be related to events in the cardiac cycle as, for instance, the opening and closing of the aortic valve. From these the left ventricular ejection time can be measured and from simultaneous recordings of ECG and dZ/dt the pre-ejection period. These quantities are the systolic time intervals [chapter 6].

The basis of determining the left ventricular ejection time from the dZ/dt signal is entirely empirical [3, 10, 14, 18, 19, 24]. A theoretical foundation for this determination is presented in chapter 6.

The thoracic admittance is the sum of a constant tissue admittance and a time-varying blood conductor G_b [chapter 4]. dZ/dt reflects the changes in G_b . The notches corresponding with opening and closing of the aortic valve are due to conductivity changes of blood caused by changes in orientation of erythrocytes; near zero-velocity the first derivative of these conductivity changes approaches infinity. Therefore, these notches coincide with the actual opening and closing of the valve, although different vessels contribute to dZ/dt .

Comparison of ejection times, simultaneously measured by impedance cardiography and by aortic pressure recording, showed excellent agreement up to a heart rate of about 140 min^{-1} ($n=70$, $r=0.986$) [chapter 6].

The reasoning behind the conclusion about the origin of the notches corresponding with opening and closing of the aortic valve involves several steps. The last step but one is that for the synchronized occurrence of a peak or notch in dZ/dt with the event in a individual vessel from which its originates, the derivative with respect to time of the conductance of that vessel must approach infinity at the occurrence of the event. The last step is that this is true for resistivity changes due to changes in orientation of the erythrocytes near zero velocity. The faithful recordings of the internal cross-sectional area of the aorta in the dog by Baan *et al.* [2] show that the changes in the area closely resemble the changes in pressure in the aorta, also during the opening and closing of the aortic valve, revealing sharp notches at opening and closing of the aortic valve. Consequently, the same will be true for the volume changes of a small segment of the aorta. Therefore the volume changes in the aorta corresponding with the opening and closing of the aortic valve may also satisfy the requirements to coincide with their representation in dZ/dt .

CONCLUSIONS

In investigating the relation between the electric properties of blood and impedance cardiography, the essential assumptions underlying the calculation of stroke volume have been reviewed. Assumption a (page 74) has been proved correct, but assumptions b and e (as formulated on page 74) have been proved false and should be reformulated as follows:

- the parallel conductor model appears to give an adequate description of the human thorax for use in impedance cardiography.
- the resistivity of blood is definitely not constant, because the resistivity changes due to changes in orientation of the erythrocytes. Blood is electrically anisotropic and the resistivity of flowing blood is non-homogeneous; the meaning of resistivity of flowing blood is ambiguous.

Therefore:

- the volume variations due to variations in diameter of the blood resistor are certainly not the only cause of the heart-synchronous impedance variations.

Because the original assumptions b and e have been falsified, the calculation of stroke volume as proposed by Kubicek *et al.* [17] and Patterson [30] is not correct. So the assumptions f and g (page 74) are irrelevant, as well as the practice to interpret the calculated volume change as originating solely from the left ventricle.

We investigated the contribution of the volume effect and the orientation effect to ΔZ . However, in impedance cardiography dZ/dt is considered. dZ/dt represents the changes in the blood conductance G_b (dG_b/dt); G_b is the sum of the blood conductances of the contributing blood vessels [chapter 6, equations 1 and 3]. In every dG_{bi}/dt , the first derivative of the blood conductance of the contributing blood vessel with number i, a contribution of the volume effect and of the orientation effect can be distinguished

$$\frac{dG_{bi}}{dt} = \frac{1}{l^2} \left(\sigma_{bi} \frac{dV_i}{dt} + V_i \frac{d\sigma_{bi}}{dt} \right) \quad (7)$$

l is the distance between the measuring electrodes, V_i the volume of the vessel and σ_{bi} the conductivity of the blood in the vessel. The orientation effect is a function of the reduced average velocity. Therefore, we can write for the contribution of the orientation effect

$$\frac{d\sigma_{bi}}{dt} = \frac{\langle v_i \rangle}{R_i} \frac{d\sigma_{bi}}{d\left(\frac{\langle v_i \rangle}{R_i}\right)} \left(\frac{1}{\langle v_i \rangle} \frac{d\langle v_i \rangle}{dt} - \frac{1}{R_i} \frac{dR_i}{dt} \right) \quad (8)$$

R_i is the radius of the vessel and $\langle v_i \rangle$ is the average velocity of the blood in the vessel. $(1/\langle v \rangle)d\langle v \rangle/dt$ and $(1/R)dR/dt$ are the momentary relative changes in average velocity and radius, respectively.

During most of the cardiac cycle both terms have the same sign. Consequently, the contribution of the orientation effect to dG_{bi}/dt may be small in comparison with the contribution of the volume effect if the relative changes in average velocity and radius are of comparable magnitude. The same holds true for dG_b/dt or for dZ/dt , because

$$\frac{-1}{Z_o^2} \frac{dZ}{dt} = \frac{dG_b}{dt} = \sum_i \frac{dG_{bi}}{dt} \quad (9)$$

[chapter 6, equations 1 and 3]. Thus although the contributions of the volume effect and the orientation effect to the magnitude of ΔZ are comparable (3.0 % and 4.4 %, respectively; page 82), the changes in these effects during the cardiac cycle may be of quite different magnitude; it may even be possible that dZ/dt is largely determined by the volume effect.

In impedance cardiography a signal is obtained in a very simple way. This signal is related to the mechanical activity of the heart. Its shape can be related to the events of the cardiac cycle. However, the estimation of stroke volume is an empirical method of questionable validity.

The investigations described above necessarily lead to a more realistic, but also to a more complicated theoretical understanding of impedance cardiography. This may hopefully lead to a better foundation of any application, while on the other hand unjustified claims should be rejected. Moreover, it is hoped that a better understanding may indicate areas of future research, not only related to impedance cardiography, but also to other applications of bio-electric impedance measurement in which flowing blood plays a part.

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