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On-line blood viscosity monitoring in vivo with a central venous catheter, using electrical impedance technique

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ABSTRACT

Blood viscosity is an important determinant of microvascular hemodynamics and also reflects systemic inflammation. Viscosity of blood strongly depends on the shear rate and can be characterized by a two parameter power-law model. Other major determinants of blood viscosity are hematocrit, level of inflammatory proteins and temperature. In-vitro studies have shown that these major parameters are related to the electrical impedance of blood. A special central venous catheter was developed to measure electrical impedance of blood in-vivo in the right atrium. Considering that blood viscosity plays an important role in cerebral blood flow, we investigated the feasibility to monitor blood viscosity by electrical bioimpedance in 10 patients during the first 3 days after successful resuscitation from a cardiac arrest. The blood viscosity–shear rate relationship was obtained from arterial blood samples analyzed using a standard viscosity meter. Non-linear regression analysis resulted in the following equation to estimate in-vivo blood viscosity ($Viscosity_{imp}$) from plasma resistance (R_p), intracellular resistance (R_i) and blood temperature (T) as obtained from right atrium impedance measurements:

$Viscosity_{imp}=(-15.574+15.576R_pT)SR^{(-.138R_pT-.290R_i)}$. This model explains 89.2% ($R^2=.892$) of the blood viscosity–shear rate relationship. The explained variance was similar for the non-linear regression model estimating blood viscosity from its major determinants hematocrit and the level of fibrinogen and C-reactive protein ($R^2=.884$). Bland–Altman analysis showed a bias between the in-vitro viscosity measurement and the in-vivo impedance model of .04 mPa s at a shear rate of 5.5 s^{-1} with limits of agreement between −1.69 mPa s and 1.78 mPa s. In conclusion, this study demonstrates the proof of principle to monitor blood viscosity continuously in the human right atrium by a dedicated central venous catheter equipped with an impedance measuring device. No safety problems occurred and there was good agreement with in-vitro measurements of blood viscosity.

1. Introduction

Blood is a concentrated suspension of blood cells in plasma and it exhibits a range of non-Newtonian properties (Gijsen et al., 1999; Chien et al., 1987). These properties are mainly due to deformation and aggregation of red blood cells, with the consequence that the viscosity of blood is not constant but is strongly dependent on shear rate. The widely used two parameter power-law model is a generalized Newtonian model that can be used to describe the shear rate dependence of blood viscosity (Gijsen et al., 1999).

At a particular shear rate the resistance (R) of blood flow is determined by a vascular and a viscous component such as expressed in the Hagen–Poisseuille equation: $R=8l\eta/\pi r^4$, in which r is vessel radius, l is vessel length and η is blood viscosity. The shear rate dependency of blood viscosity has a great impact on areas within the circulation that exhibit a low shear rate such as the microcirculation. With increasing viscosity, plugging of the capillary bed might occur followed by arterio-venous shunting and diminished tissue perfusion (Chien et al., 1987). Blood viscosity increases during inflammation due to aggregating forces

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of acute phase proteins on blood cells (Lowe et al., 1981; Koenig and Ernst, 1992; Woodward et al., 1999). Inflammation is one of the major responses of the body to internal and external stimuli. Numerous studies in the last decades have demonstrated that atherosclerosis is also a chronic inflammatory disorder (Ross, 1999; Libby and Ridker 1999; Libby et al., 2002). Increased blood viscosity has been shown to predict worse cardiovascular short-term and long-term outcome (Ridker et al., 2000).

Since the eighteenth century electrical impedance measurements have been used to examine the bulk electrical properties of tissues (Fricke and Morse, 1925; Pribush et al., 1999; Pribush et al., 2000). In 1925, Fricke described the electrical characteristics of whole blood in a three-element model, in which R_p (plasma resistance) is placed parallel with C_m (membrane capacitance), which is in series with R_i (total intracellular resistance). Several studies with this model confirmed the close relationship between hematocrit (*Ht*) and the electrical resistivity at low frequencies (20–100 kHz; Hill and Thompson, 1975; Fricke, 1953). Other studies have shown the relationship of blood flow and the fibrinogen level with the electrical characteristics of blood at higher frequencies (100–1500 kHz, Zhao and Jacobson, 1997; Beving et al., 1994). Considering that hematocrit, flow and fibrinogen are important determinants of blood viscosity, our group demonstrated in 2003 that blood electrical impedance closely matches whole blood viscosity as a parameter of hemorheology and inflammation (Pop et al., 2003). This in-vitro study was followed by an in-vivo study in animals, in which catheter-based impedance measurements in the right atrium were shown to be feasible and allowed continuous measurement of hematocrit and blood viscosity (Pop et al., 2004).

Since viscosity is a major determinant of blood flow, continuous in-vivo measurement may yield continuous in-vivo information on determinants of flow and inflammation and may guide therapy. The present pilot-study in humans was undertaken to investigate the feasibility of on-line measurement of blood viscosity using a central venous impedance catheter. We investigated this in patients during the first 3 days after successful resuscitation from out-of-hospital cardiac arrest. In these patients, the post-resuscitation period is characterized by changes in macrovascular and microvascular cerebral blood flow (Holzer et al., 2005; Ristagno et al., 2008). In addition, the ischemia–reperfusion injury in these patients is associated with a systemic inflammatory response (Adrie et al., 2004). Whole blood viscosity is a major determinant of macro- and microvascular flow and at the same time viscosity is dynamically influenced by inflammation; therefore, continuous monitoring of blood viscosity may be clinically relevant in these patients. The aims of the study were (I) to measure the electrical impedance of blood in the right atrium of the heart; (II) to establish a mathematical equation to determine blood viscosity from on-line electrical impedance measurements in the right atrium and blood temperature by non-linear regression of the in-vitro blood viscosity measurements as obtained with a Contraves LS 300; (III) using the same non-linear regression analysis to establish a mathematical equation to estimate blood viscosity from the major determinants of blood viscosity: hematocrit and the acute phase proteins fibrinogen and CRP in addition to blood temperature; and (IV) to compare the in-vitro blood viscosity measurements with the Contraves and the two models of indirect viscosity estimation by Bland–Altman analysis.

2. Methods

2.1. Study population

We performed a prospective observational study in 10 comatose patients successfully resuscitated from an out-of-hospital cardiac arrest treated with mild therapeutic hypothermia. The local Institutional Review Board approved the protocol and written informed consent was obtained from the nearest relative. All patients of 18 years or older were eligible for the study if they were comatose (Glasgow Coma Scale score <6) after return of spontaneous circulation. Patients were excluded if they were pregnant, received thrombolytic therapy, had refractory cardiogenic shock, or had a life expectancy of <24 h.

2.2. Patient management

All patients were admitted to the ICU of our tertiary care university hospital in Nijmegen, The Netherlands. If necessary, a coronary angiogram and a percutaneous coronary intervention were performed before admission to the ICU. According to our standard protocol, patients were cooled to 32–34 °C by rapid infusion of 30 ml/kg body weight of cold Ringer's lactate at 4 °C followed by external cooling using two water-circulating blankets (Blanketroll II Cincinatti Subzero, The Surgical Company, Amersfoort, The Netherlands). Temperature was measured continuously with a rectal temperature probe (YSI Incorporated 401, van de Putte Medical, Nieuwegein, The Netherlands) and maintained at 32–34 °C for 24 h, followed by passive rewarming to normothermia (defined as 36.5 °C). All patients were intubated and mechanically ventilated aiming at an arterial oxygen partial pressure (PaO_2) $>$ 75 mmHg and arterial carbon dioxide pressure ($PaCO_2$) between 34 and 42 mmHg. Alpha-stat was used for pH maintenance. The radial or femoral artery was cannulated for monitoring of blood pressure; the intra-arterial line was also used for periodic sampling of blood for measurement of hematocrit, fibrinogen, CRP and viscosity. The HemoCard Vision catheter was introduced into the right atrium via the right internal jugular vein using a Seldinger technique (Fig. S1, Supplement on-line). According to our local protocol, mean arterial blood pressure (MAP) was maintained between 80 and 100 mmHg with a dieresis $>.5$ ml/kg/h. If necessary, patients were treated with volume infusion and dobutamine and/or (nor)epinephrine. Serum concentrations of sodium, potassium, magnesium and phosphate were maintained within the normal range. All patients were treated with continuous insulin infusion therapy to keep blood glucose levels between 6.0 and 8.0 mmol/l. Hemoglobin concentration was kept ≥ 6.0 mmol/l.

2.3. In-vivo right atrium impedance measurement

The HemoCard Vision catheter is a dedicated 8.25 French, 30 cm, 3-lumen central venous catheter of polyurethane of 30 cm length (Fig. S2, Supplement on-line). A fourth lumen is used for co-axial insulated cables, which are connected to four different electrodes at the tip. In order to satisfy the electro-magnetic emission requirements of the IEC60601 norm, the actively-guarded cables are enveloped by a second grounded shield. An excitation current of 10 μA_{rms} is applied to the outer excitation electrodes and the whole-blood complex–impedance is measured between the inner sensing electrodes by applying a sinusoidal excitation signal at four frequencies: 100 kHz, 200 kHz, 625 kHz and 1.25 MHz. The frequencies are applied each for 10 ms at a time. An intracavitary ECG signal is also separately extracted from the two inner electrodes. Furthermore, a thermistor incorporated at the catheter's tip allows central blood temperature measurement. Impedance, temperature and ECG signals are extracted at 10 min intervals for 18 s.

The ECG, blood complex impedance and temperature readings are processed by an electronic interface (Fig. S2, Supplement on-line) and sent wirelessly to an external monitor. The entire catheter has a heparin-based hydrophilic coating to enhance hemocompatibility and to prevent the formation of a biofilm or thrombus. The tip of the catheter is introduced up to the middle