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Title

The Effect of Whole Blood Viscosity on Intraoperative Graft Flow during Coronary Artery Bypass Graft Surgery: An Observational Pilot Study

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Running title

Effect of blood viscosity on intraoperative graft flow

Abstract

Background: Transit-time flow measurement (TTFM) is frequently used to evaluate intraoperative quality control during coronary artery bypass grafting (CABG). Although TTFM has the ability to assess graft failure intraoperatively, the perioperative factors affecting TTFM during CABG surgery remain poorly understood.

Methods: Patients who underwent CABG surgery at a single institution between July 2016 and May 2018 were prospectively evaluated. Patients' demographic characteristics, previous medical history, Euroscore, the results of preoperative blood tests, and intraoperative data were recorded. TTFM and blood viscosity were measured hemodynamically, and mean flow (mL/min) and pulsatility index (PI) were recorded. Arterial blood gas was analyzed immediately after anastomosis of the left internal mammary artery (LIMA) to the left descending artery (LAD) and before sternal closure. Factors associated with TTFM were assessed by multiple linear regression analysis.

Results: Of the 62 patients who underwent CABG surgery during the study period, 57 were evaluated, including 49 who underwent off-pump and eight who underwent on-pump surgery. Blood viscosity was not significantly associated with TTFM ($p > 0.05$). However, TTFM was significantly associated with body mass index (BMI), systolic blood pressure, and cardiac index ($p < 0.05$ each).

Conclusions: Blood viscosity was not significantly associated with intraoperative graft flow. Blood flow of graft vessels, however, was significantly associated with BMI, systolic blood pressure, and cardiac index.

Keywords

Blood viscosity, Transit-time flow measurement, Coronary artery bypass surgery

Introduction

Ischemic heart disease(IHD) is the global leading cause of death, according to the World Health Organization (WHO) survey from 2000 to 2016[1]. The mortality rate in IHD is gradually lowering in Western countries due to the development of diagnostic and therapeutic techniques for IHD, whereas in developing countries, it is gradually increasing in westernized lifestyles[2]. Coronary artery bypass grafting (CABG) surgery is still an important and preferred treatment despite the development of various interventions in IHD. In CABG surgery, early detection of postoperative graft failure during surgery is very important to prevent postoperative complications such as refractory angina, myocardial infarction, arrhythmias,and even mortality[3].

Transit-time flow measurement (TTFM), which utilizes ultrasound to measure flow velocity in blood vessels, is frequently used for intraoperative assessment of graft quality in patients undergoing coronary artery bypass graft (CABG) surgery [3-8]. TTFM is a noninvasive, easy-to-use method of measuring graft flow velocity in real time, does not require complex equipment, and provides numerical results [9,10]. Moreover, graft flow velocity measured by this method was shown to be accurate and reproducible [11,12]. Blood viscosity, an indicator of the stickiness of blood, can be measured as the degree of blood resistance to flow [13]. The most important factors influencing blood viscosity are hematocrit, red blood cell deformability, red blood cell aggregation, and plasma viscosity [14,15], with hematocrit being the strongest factor affecting whole blood viscosity [14]. Plasma viscosity is a function of water content and macromolecular components, including the types and concentrations of plasma proteins [14,16]. Blood viscosity varies with shear rate, with blood being less viscous at high shear rates and more viscous at low shear rates, resulting from increased vessel diameter or low flow rate [17]. Blood viscosity is expected to change continuously during surgery, as a result of intraoperative hemorrhage and subsequent fluid administration and transfusion.

The patency of a coronary artery bypass depends on several factors, including the nature of the coronary vessel, the quality and type of the grafts, the collateral flow through the native coronary vessel, and the construction of the anastomosis [18-20]. Slower TTFM during CABG surgery has been reported to be associated with a greater likelihood of graft failure after surgery [21]. Therefore, the velocity of blood flow through the graft vessels measured during surgery can affect patient prognosis, making it necessary to determine factors affecting blood flow velocity, especially those than can be controlled [3,22-24]. To our knowledge, however, factors affecting blood flow velocity of graft vessels, including those affecting changes in viscosity during surgery, have not yet been determined. The present study therefore investigated the effects of blood viscosity on the velocity of blood flow through graft vessels measured during surgery in patients undergoing CABG surgery.

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Methods

Study population

The protocol of this observational study was approved by the Institutional Review Board of Asan Medical Center, and the study was registered at the Korean Clinical Trials Registry (KCT0002047). Written informed consent was obtained prospectively from each patient. Patients were prospectively included if they underwent on-pump CABG or off-pump coronary artery bypass (OPCAB) surgery at a single institution between July 2016 and May 2018. Patients were excluded if they underwent emergency surgery; had poor systolic function of the left ventricle, defined as preoperative ejection fraction <40, on preoperative echocardiogram; had undergone any type of anastomosis other than anastomosis from the left internal mammary artery (LIMA) to the left anterior descending artery (LAD); had preoperative arrhythmias such as atrial fibrillation; or refused participation. All clinical data were obtained from the electronic medical records system of our institution.

Anesthesia and perioperative management

General anesthesia was induced with a bolus IV injection of 0.1 mg/kg midazolam, followed by 0.8 mg/kg rocuronium to facilitate orotracheal intubation, and was maintained by continuous infusion of remifentanil and propofol using a target controlled infusion pump (Orchestra Base Primea; Fresenius Kabi, Brezins, France). Although cardiac preload was maintained with crystalloids or colloids, patients who showed reductions in mean arterial pressure and/or cardiac index during surgery were administered inotropic agents, such as dobutamine; or norepinephrine and a vasopressor such as phenylephrine. Packed red blood cells were transfused when hemoglobin concentration was below 8 g/dL. A cell salvage device (AUTOLOG, Medtronic Inc., Minneapolis, MN) was used in all patients, and salvaged blood was reinfused before the end of surgery. Throughout surgery, all patients were continuously administered an isosorbide dinitrate and a calcium channel blocker such as diltiazem.

All surgical procedures were performed by five cardiac surgeons highly experienced in on-pump CABG or OPCAB. All patients underwent median sternotomy and received volume-controlled ventilation with 50% inspired oxygen during surgery, with tidal volume set at 8 mL/kg of ideal body weight without positive or expiratory pressure.

After surgery, all patients were transferred to the intensive care unit (ICU) and discharged from the ICU to the general ward when their clinical status became stabilized, and further ICU monitoring and care were not required.

Clinical variables and perioperative variables

Demographic variables recorded included patient age, sex, weight, height, and body mass index (BMI). Preoperative variables included previous medical history, including medications, Euroscore (II, logistic), and ejection fraction of the left ventricle on preoperative echocardiography. Laboratory data included hemoglobin concentration; hematocrit; and serum concentrations of blood urea nitrogen (BUN), creatinine, albumin, cholesterol, triglycerides, high density lipids, low density lipids, creatine kinase-MB (CK-MB), and troponin I. Intraoperative data included anesthesia time; surgery time; size of the graft vessel; intraoperative total fluid volume including transfusions; and hemodynamic parameters, including heart rate, mean arterial blood pressure, pulse oximetry, central venous pressure, cerebral oximetry, pulmonary artery pressure, cardiac index, systemic vascular resistance index, and arterial blood gas analysis. Postoperative variables included duration of mechanical ventilation, length of ICU stay, length of hospital stay, and postoperative complications. Postoperative complications included myocardial infarction, atrial fibrillation, wound complication, acute kidney injury, and death.

Transit-time flow measurement

The primary outcome of this study was TTFM, an ultrasound measure of the velocity of blood flow through the blood vessel. TTFM is based on the measured difference in time required for blood flow between two ultrasonic signals emitted by a probe [4,25,26] and is expressed as milliliters per minute

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(mL/min) [27]. TTFM in this study was measured twice, immediately after LIMA to LAD anastomosis and before sterna closure, using a VeriQ Flowmeter (Medistim ASA, Oslo, Norway). Mean blood flow (mL/min) and pulsatility index (PI) were recorded.

Viscosity of graft flow measurements

Blood viscosity, measured as systolic and diastolic blood viscosity, is dependent on blood pressure, which changes with every cardiac cycle [28-30]. Systolic blood viscosity is dependent on hematocrit and plasma viscosity, and is highly affected by the volume of intraoperative fluid infusion [28,29]. By contrast, diastolic blood viscosity is affected by many factors, including platelet counts and concentrations of immune complexes, triglycerides, and cholesterol [28,29]. TTFM and blood viscosity were measured at the same time. Immediately after measuring the velocity of blood flow through the graft vessel, 3 mL blood was collected in an EDTA container and refrigerated at 4°C, and systolic and diastolic blood viscosity were measured using Hemovistor™.

Sample size and clinical data

The absence of previous studies or data from pilot studies prevented a calculation of correct sample size. Assuming a first type error (α) of 0.05 and a second type error (β) of 20%, the power would be 80% when the expected effect size (f) was set at 0.15 and the prediction factor at 5. Thus, 91 subjects were regarded as adequate; assuming 10% dropout rate, a total of 100 subjects was estimated as sufficient.

Statistical analysis

Categorical variables were expressed as numbers and percentages, and continuous variables as means and standard deviations. Categorical variables were compared using the Pearson χ^2 test or Fisher's exact test, whereas continuous variables were compared using Student's *t*-test or the Mann–Whitney *U*-test. Univariate logistic regression analysis was performed to investigate the associations between clinical

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variables, including blood viscosity, with TTFM. Variables with $p < 0.1$ on univariate analyses and clinically meaningful variables were entered into multivariate logistic regression analysis, with backward elimination procedures used to determine the independent variables associated with TTFM. Multivariate logistic or linear regression analyses were used to assess β coefficients with 95% confidence intervals (CIs) of the relationships between clinical variables and TTFM. All measured variables at both measurement times were included in the analysis because of the small cohort size. A random effects model for regression analysis was used to control for unobserved heterogeneity when heterogeneity was constant over time. All statistical analyses were performed using “R” statistical software (R ver. 3.5.1.), with p-values <0.05 considered statistically significant.

Results

Of the 100 patients who underwent CABG between July 2016 and May 2018, 38 who met the exclusion criteria were excluded, as were an additional two patients in whom blood viscosity was not measured. Because blood flow <20 mL/min combined with PI >5 indicates technically inadequate grafts [31], three additional patients with PI >5 were also excluded. Thus, this study included 57 patients, 45 men and 12 women, of mean ± SD age 64.3 ± 8.3 years (Fig. 1). Of these 57 patients, 49 (86.0%) underwent off-pump and eight (14.0%) underwent on-pump CABG. The baseline demographic and clinical characteristics of the study patients are shown in Table 1.

Intraoperative data are shown in Table 2 and hemodynamic findings in Figure 2. Mean blood pressure, diastolic blood pressure, central venous pressure, and mean pulmonary arterial pressure increased after LIMA to LAD anastomosis rather than immediately after induction, but then decreased before sternal closure (Fig. 2). Conversely, systolic blood pressure and cardiac index decreased after anastomosis rather than immediately after induction, but increased before sternal closure. The average ICU stay was 40 hours, the average hospital stay was about 9 days, and the mean mechanical ventilation time was approximately 10 hours. Nine patients experienced postoperative complications, including six with atrial fibrillation, one with wound complications, and two with acute kidney injury . Postoperative outcomes are summarized in Table 3.

Factors associated with TTFM are shown in Table 4. Univariate linear regression showed that female sex, BMI, ejection fraction on preoperative echocardiogram, volumes of total fluid and packed red blood cells infused intraoperatively, heart rate, systolic blood pressure, mean blood pressure, oxygen saturation on pulse oximetry, and cardiac index were significantly associated with TTFM ($p < 0.1$ each). These variables were used to construct a multiple linear regression model, which found that BMI ($p = 0.008$), systolic blood pressure ($p = 0.023$), and cardiac index ($p = 0.039$) were independently associated with TFFM. Volume of total fluid infused intraoperatively tended to be significantly associated with TFFM ($p = 0.081$). By contrast, TTFM was not associated with blood viscosity (Figure 3).

Discussion

TTFM has been reported as important for determining the success of grafts during surgery [22] and for predicting the risk of graft failure after surgery [21], making TTFM the most widely used method of intraoperative graft quality control in patients undergoing CABG surgery [3-8]. Prior to this study, however, the perioperative factors affecting TTFM during CABG surgery had not been determined, making this study one of the first to assess perioperative factors affecting flow measurements in graft vessels.

Although this study was designed to determine the association between blood viscosity and TTFM, no. such significant association was observed. Because blood is a non-Newtonian fluid, its viscosity is affected by shear rate[17]. Blood viscocity is higher at low shear rates, while being lower at high shear rates[17]. Coronary artery blood flow is not at steady-state, making its viscosity inconstant. Furthermore, previous studies have reported a significant increase in blood viscosity during cardiac surgery and after surgery[32]. Cardiac surgery can cause abnormal blood rheological characteristics that may be associated with lung dysfunction and endothelial damage[33]. In addition, blood viscosity changes due to systemic inflammatory and thrombotic responses during cardiac surgery[32]. Although the blood viscosity was measured twice during surgery and was divided into systolic and diastolic viscosity, blood viscosity changes according to the blood flow with continuous change during the surgery, making it difficult to determine the real-time relationship between viscosity and TTFM. Despite the limitations of measuring methods, blood viscosity plays an important role in hemodynamics, thrombosis, and inflammation, as well as affects the diagnosis and treatment of cardiovascular diseases [34-39]. Because we were unable to determine how blood viscosity affects postoperative clinical outcomes including postoperative graft failure, further studies are needed.

Interestingly, we found that BMI was significantly associated with TTFM, in agreement with findings showing that high BMI or obesity is associated with coronary endothelial dysfunction, an early stage of coronary atherosclerosis that may involve the epicardial and/or resistance vessels [40,41]. The negative

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effects of obesity on coronary circulation include immediate changes in coronary arterial vasomotor responsiveness and the development of occlusive coronary artery disease [42,43], as well as the generation of adipocyte-derived adipokines [44,45]. Several diseases in obese patients caused by coronary microvascular inflammation have been associated with cellular mechanisms that control the secretion of adipokines and proinflammatory cytokines from adipose tissue [46]. This association between BMI and TTFM indicates that metabolic dysfunction associated with obesity also affects coronary blood flow.

Factors significantly associated with TTFM in the present study included systolic blood pressure, and cardiac index, suggesting that hemodynamic status is an important determinant of TTFM. This study, however, was unable to determine the contribution or effect of each factor.

We expected that diastolic blood pressure would more likely affect TTFM than systolic blood pressure because coronary perfusion pressure is determined by the difference between aortic diastolic pressure and left ventricular end-diastolic pressure (LVEDP) [47]. Surprisingly, however, we found that systolic blood pressure was associated with TTFM, whereas diastolic blood pressure was not. TTFM was more affected by blood flow through engrafted vessels than through native coronary vessels due to obstruction of the latter. As expected, cardiac index was associated with TTFM because cardiac output is an important determinant of both coronary blood flow and blood flow through the engrafted vessel.

This study had several limitations, including its small cohort size. Nevertheless, these findings represent an important first step in evaluating perioperative factors affecting the measurement of blood flow through graft vessels. Studies of factors affecting TTFM in larger numbers of patients are needed to determine the extent of their effects on TTFM. Another limitation of this study was that operations were performed by five different surgeons, which may have affected TTFM.

Conclusion

This study found no significant relationship between blood viscosity and intraoperative graft flow. By contrast, BMI, systolic blood pressure, and cardiac index were significantly associated with blood flow through graft vessels. Additional studies are needed to determine the extent to which individual factors affect TTFM, and how factors related to TTFM affect clinical outcomes.

Figure 1. Flow diagram of the study. TTFM, transit-time flow measurement; PI, pulsatility index.

Figure 2. Intraoperative and hemodynamic findings. T1, after induction of anesthesia. T2, after anastomosis of the left internal mammary artery (LIMA) to the left anterior descending artery (LAD). T3, before sternal closure. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; CVP, central venous pressure; mPAP, mean pulmonary artery pressure; CI, cardiac index; SVRI, systemic vascular resistance index; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; Hb, hemoglobin; Hct, hematocrit.

Figure 3. Scatter plot of TTFM and viscosity. TTFM, transit-time flow measurement. Viscosity S, systolic blood viscosity; Viscosity D, diastolic blood viscosity.

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Authors' contributions

Study concept/design: all authors

Study conduct: all authors

Data analysis: S-W.L.,W-J.K, D-K.C. C-I.C.

Writing paper: S-W.L., D-K.C.

Revising paper: all authors

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Declaration of interests

None declared.

References

1. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Availabe online: http://www.who.int/healthinfo/global_burden_disease/estimates/en/ (accessed on
2. Nowbar, A.N.; Gitto, M.; Howard, J.P.; Francis, D.P.; Al-Lamee, R. Mortality From Ischemic Heart Disease. *Circ Cardiovasc Qual Outcomes* **2019**, *12*, e005375, doi:10.1161/CIRCOUTCOMES.118.005375.
3. Leong, D.K.; Ashok, V.; Nishkantha, A.; Shan, Y.H.; Sim, E.K. Transit-time flow measurement is essential in coronary artery bypass grafting. *Ann Thorac Surg* **2005**, *79*, 854-857; discussion 857-858, doi:10.1016/j.athoracsur.2004.06.010.
4. Beldi, G.; Bosshard, A.; Hess, O.M.; Althaus, U.; Walpoth, B.H. Transit time flow measurement: experimental validation and comparison of three different systems. *Ann Thorac Surg* **2000**, *70*, 212-217, doi:10.1016/s0003-4975(00)01246-7.
5. Hirotani, T.; Kameda, T.; Shirota, S.; Nakao, Y. An evaluation of the intraoperative transit time measurements of coronary bypass flow. *Eur J Cardiothorac Surg* **2001**, *19*, 848-852, doi:10.1016/s1010-7940(01)00700-x.
6. Kjaergard, H.K.; Irmukhamedov, A.; Christensen, J.B.; Schmidt, T.A. Flow in coronary bypass conduits on-pump and off-pump. *Ann Thorac Surg* **2004**, *78*, 2054-2056, doi:10.1016/j.athoracsur.2004.06.009.
7. Onorati, F.; Pezzo, F.; Esposito, A.; Impiombato, B.; Comi, M.C.; Polistina, M.; Renzulli, A. Single versus sequential saphenous vein grafting of the circumflex system: a flowmetric study. *Scand Cardiovasc J* **2007**, *41*, 265-271, doi:10.1080/14017430701283864.
8. Nordgaard, H.; Vitale, N.; Haaverstad, R. Transit-time blood flow measurements in sequential saphenous coronary artery bypass grafts. *Ann Thorac Surg* **2009**, *87*, 1409-1415, doi:10.1016/j.athoracsur.2009.02.018.
9. Takami, Y.; Takagi, Y. Roles of Transit-Time Flow Measurement for Coronary Artery Bypass Surgery. *Thorac Cardiovasc Surg* **2018**, *66*, 426-433, doi:10.1055/s-0037-1618575.
10. D'Ancona, G.; Karamanoukian, H.L.; Ricci, M.; Bergsland, J.; Salerno, T.A. Graft patency verification in coronary artery bypass grafting: principles and clinical applications of transit time flow measurement. *Angiology* **2000**, *51*, 725-731, doi:10.1177/000331970005100904.
11. Dean, D.A.; Jia, C.X.; Cabreriza, S.E.; D'Alessandro, D.A.; Dickstein, M.L.; Sardo, M.J.; Chalik, N.; Spotnitz, H.M. Validation study of a new transit time ultrasonic flow probe for continuous great vessel measurements. *ASAIO J* **1996**, *42*, M671-676.
12. Matre, K.; Birkeland, S.; Hessevik, I.; Segadal, L. Comparison of transit-time and Doppler ultrasound methods for measurement of flow in aortocoronary bypass grafts during cardiac surgery. *Thorac Cardiovasc Surg* **1994**, *42*, 170-174, doi:10.1055/s-2007-1016481.

13. Cinar, Y.; Senyol, A.M.; Duman, K. Blood viscosity and blood pressure: role of temperature and hyperglycemia. *Am J Hypertens* **2001**, *14*, 433-438, doi:10.1016/s0895-7061(00)01260-7.
14. Nader, E.; Skinner, S.; Romana, M.; Fort, R.; Lemonne, N.; Guillot, N.; Gauthier, A.; Antoine-Jonville, S.; Renoux, C.; Hardy-Dessources, M.D., et al. Blood Rheology: Key Parameters, Impact on Blood Flow, Role in Sickle Cell Disease and Effects of Exercise. *Front Physiol* **2019**, *10*, 1329, doi:10.3389/fphys.2019.01329.
15. Baskurt, O.K.; Meiselman, H.J. Blood rheology and hemodynamics. *Semin Thromb Hemost* **2003**, *29*, 435-450, doi:10.1055/s-2003-44551.
16. Kesmarky, G.; Kenyeres, P.; Rabai, M.; Toth, K. Plasma viscosity: a forgotten variable. *Clin Hemorheol Microcirc* **2008**, *39*, 243-246.
17. Cokelet, G.R., and Meiselman, H. J. *Handbook of Hemorheology and Hemodynamics*; IOS Press: Amsterdam, 2007.
18. Amin, S.; Pinho-Gomes, A.C.; Taggart, D.P. Relationship of Intraoperative Transit Time Flowmetry Findings to Angiographic Graft Patency at Follow-Up. *Ann Thorac Surg* **2016**, *101*, 1996-2006, doi:10.1016/j.athoracsur.2015.10.101.
19. Head, S.J.; Borgermann, J.; Osnabrugge, R.L.; Kieser, T.M.; Falk, V.; Taggart, D.P.; Puskas, J.D.; Gummert, J.F.; Kappetein, A.P. Coronary artery bypass grafting: Part 2--optimizing outcomes and future prospects. *Eur Heart J* **2013**, *34*, 2873-2886, doi:10.1093/eurheartj/eht284.
20. Head, S.J.; Kieser, T.M.; Falk, V.; Huysmans, H.A.; Kappetein, A.P. Coronary artery bypass grafting: Part 1--the evolution over the first 50 years. *Eur Heart J* **2013**, *34*, 2862-2872, doi:10.1093/eurheartj/eht330.
21. Lehnert, P.; Moller, C.H.; Damgaard, S.; Gerds, T.A.; Steinbruchel, D.A. Transit-time flow measurement as a predictor of coronary bypass graft failure at one year angiographic follow-up. *J Card Surg* **2015**, *30*, 47-52, doi:10.1111/jocs.12471.
22. D'Ancona, G.; Karamanoukian, H.L.; Ricci, M.; Schmid, S.; Bergsland, J.; Salerno, T.A. Graft revision after transit time flow measurement in off-pump coronary artery bypass grafting. *Eur J Cardiothorac Surg* **2000**, *17*, 287-293.
23. Walpoth, B.H.; Bosshard, A.; Genyk, I.; Kipfer, B.; Berdat, P.A.; Hess, O.M.; Althaus, U.; Carrel, T.P. Transit-time flow measurement for detection of early graft failure during myocardial revascularization. *Ann Thorac Surg* **1998**, *66*, 1097-1100, doi:10.1016/s0003-4975(98)00653-5.
24. Di Giammarco, G.; Pano, M.; Cirmeni, S.; Pelini, P.; Vitolla, G.; Di Mauro, M. Predictive value of intraoperative transit-time flow measurement for short-term graft patency in coronary surgery. *J Thorac Cardiovasc Surg* **2006**, *132*, 468-474, doi:10.1016/j.jtcvs.2006.02.014.
25. Plass, K.G. A new ultrasonic flowmeter for intravascular application. *IEEE Trans Biomed Eng* **1964**, *11*, 154-156, doi:10.1109/tbme.1964.4502325.
26. Bland, J.M.; Altman, D.G. Statistical methods for assessing agreement between two methods of

clinical measurement. *Lancet* **1986**, *1*, 307-310.

27. Mack, M.J. Intraoperative coronary graft assessment. *Curr Opin Cardiol* **2008**, *23*, 568-572, doi:10.1097/HCO.0b013e3283121cbf.
28. Letcher, R.L.; Chien, S.; Pickering, T.G.; Sealey, J.E.; Laragh, J.H. Direct relationship between blood pressure and blood viscosity in normal and hypertensive subjects. Role of fibrinogen and concentration. *Am J Med* **1981**, *70*, 1195-1202, doi:10.1016/0002-9343(81)90827-5.
29. Fowkes, F.G.; Lowe, G.D.; Rumley, A.; Lennie, S.E.; Smith, F.B.; Donnan, P.T. The relationship between blood viscosity and blood pressure in a random sample of the population aged 55 to 74 years. *Eur Heart J* **1993**, *14*, 597-601, doi:10.1093/eurheartj/14.5.597.
30. Gori, T.; Wild, P.S.; Schnabel, R.; Schulz, A.; Pfeiffer, N.; Blettner, M.; Beutel, M.E.; Forconi, S.; Jung, F.; Lackner, K.J., et al. The distribution of whole blood viscosity, its determinants and relationship with arterial blood pressure in the community: cross-sectional analysis from the Gutenberg Health Study. *Ther Adv Cardiovasc Dis* **2015**, *9*, 354-365, doi:10.1177/1753944715589887.
31. Task Force on Myocardial Revascularization of the European Society of, C.; the European Association for Cardio-Thoracic, S.; European Association for Percutaneous Cardiovascular, I.; Wijns, W.; Kolh, P.; Danchin, N.; Di Mario, C.; Falk, V.; Folliguet, T.; Garg, S., et al. Guidelines on myocardial revascularization. *Eur Heart J* **2010**, *31*, 2501-2555, doi:10.1093/eurheartj/ehq277.
32. Wu, Y.F.; Hsu, P.S.; Tsai, C.S.; Pan, P.C.; Chen, Y.L. Significantly increased low shear rate viscosity, blood elastic modulus, and RBC aggregation in adults following cardiac surgery. *Sci Rep* **2018**, *8*, 7173, doi:10.1038/s41598-018-25317-8.
33. Asimakopoulos, G.; Smith, P.L.; Ratnatunga, C.P.; Taylor, K.M. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. *Ann Thorac Surg* **1999**, *68*, 1107-1115, doi:10.1016/s0003-4975(99)00781-x.
34. Lowe, G.D. Blood viscosity and cardiovascular disease. *Thromb Haemost* **1992**, *67*, 494-498.
35. Becker, R.C. The role of blood viscosity in the development and progression of coronary artery disease. *Cleve Clin J Med* **1993**, *60*, 353-358, doi:10.3949/ccjm.60.5.353.
36. Kesmarky, G.; Toth, K.; Habon, L.; Vajda, G.; Juricskay, I. Hemorheological parameters in coronary artery disease. *Clin Hemorheol Microcirc* **1998**, *18*, 245-251.
37. Yarnell, J.W.; Patterson, C.C.; Sweetnam, P.M.; Lowe, G.D. Haemostatic/inflammatory markers predict 10-year risk of IHD at least as well as lipids: the Caerphilly collaborative studies. *Eur Heart J* **2004**, *25*, 1049-1056, doi:10.1016/j.ehj.2004.04.011.
38. Jeong, S.K.; Cho, Y.I.; Duey, M.; Rosenson, R.S. Cardiovascular risks of anemia correction with erythrocyte stimulating agents: should blood viscosity be monitored for risk assessment? *Cardiovasc Drugs Ther* **2010**, *24*, 151-160, doi:10.1007/s10557-010-6239-7.
39. Sloop, G.; Holsworth, R.E., Jr.; Weidman, J.J.; St Cyr, J.A. The role of chronic hyperviscosity in

vascular disease. *Ther Adv Cardiovasc Dis* **2015**, *9*, 19-25, doi:10.1177/1753944714553226.

40. Al Suwaidi, J.; Higano, S.T.; Holmes, D.R., Jr.; Lennon, R.; Lerman, A. Obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries. *J Am Coll Cardiol* **2001**, *37*, 1523-1528.
41. Ziccardi, P.; Nappo, F.; Giugliano, G.; Esposito, K.; Marfella, R.; Cioffi, M.; D'Andrea, F.; Molinari, A.M.; Giugliano, D. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* **2002**, *105*, 804-809.
42. Csige, I.; Ujvarosy, D.; Szabo, Z.; Lorincz, I.; Paragh, G.; Harangi, M.; Somodi, S. The Impact of Obesity on the Cardiovascular System. *J Diabetes Res* **2018**, *2018*, 3407306, doi:10.1155/2018/3407306.
43. Poirier, P.; Giles, T.D.; Bray, G.A.; Hong, Y.; Stern, J.S.; Pi-Sunyer, F.X.; Eckel, R.H.; American Heart, A.; Obesity Committee of the Council on Nutrition, P.A.; Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* **2006**, *113*, 898-918, doi:10.1161/CIRCULATIONAHA.106.171016.
44. Halberg, N.; Khan, T.; Trujillo, M.E.; Wernstedt-Asterholm, I.; Attie, A.D.; Sherwani, S.; Wang, Z.V.; Landskroner-Eiger, S.; Dineen, S.; Magalang, U.J., et al. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. *Mol Cell Biol* **2009**, *29*, 4467-4483, doi:10.1128/MCB.00192-09.
45. Kadowaki, T.; Yamauchi, T.; Kubota, N.; Hara, K.; Ueki, K.; Tobe, K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* **2006**, *116*, 1784-1792, doi:10.1172/JCI29126.
46. Bagi, Z.; Broskova, Z.; Feher, A. Obesity and coronary microvascular disease - implications for adipose tissue-mediated remote inflammatory response. *Curr Vasc Pharmacol* **2014**, *12*, 453-461.
47. McEvoy, J.W.; Chen, Y.; Rawlings, A.; Hoogeveen, R.C.; Ballantyne, C.M.; Blumenthal, R.S.; Coresh, J.; Selvin, E. Diastolic Blood Pressure, Subclinical Myocardial Damage, and Cardiac Events: Implications for Blood Pressure Control. *J Am Coll Cardiol* **2016**, *68*, 1713-1722, doi:10.1016/j.jacc.2016.07.754.