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Research Article

The relationship between plasma viscosity and endotel markers in patients with ascending aortic aneurysms: A pilot study

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Abstract

Objectives: An ascending aortic aneurysm (AsAA) is fundamentally defined as the "ballooning" of the aorta at its exit site from the heart. The role of plasma viscosity (PV) and endothelial markers in AsAA is unknown. This study was designed to investigate AsAA in association with PV and the endothelial markers of fibrinogen, nitric oxide (NOx), and asymmetric dimethylarginine (ADMA).

Methods: This study group consisted of 23 patients who underwent surgical repair for AsAA and 30 controls without diabetes, hypo- or hyperlipidemia, or heart disease. Several parameters, including plasma viscosity (PV), fibrinogen, NOx, and ADMA were assayed in both groups.

Results: The preoperative PV in the patient group was significantly higher than that measured on postoperative day 7 and that of the control group ($p<0.05$). Fibrinogen and ADMA values were significantly higher in the control group than the preoperative values ($p<0.001$). Postoperative NOx results were lower than preoperative NOx ($p<0.05$).

Conclusion: An increase in PV may cause an increase in permeability and glomerular capillary pressure. The fibrinogen level may have been lower in the preoperative AsAA group as a result of impaired production or increased consumption due to intravascular coagulation. The decrease in ADMA is associated with increased NOx, which is a potent inhibitor of platelet aggregation and adhesion to the vessel wall. A high preoperative level of NOx can be accounted for by impaired blood flow. Our results suggest that PV and oxidative stress parameters may play a crucial role in the diagnosis, treatment, and follow-up of patients with AsAA.

Keywords: Ascending aortic aneurysm, asymmetric dimethylarginine, fibrinogen, nitric oxide, plasma viscosity

Aortic aneurysms represent a leading cause of cardiovascular mortality and morbidity worldwide [1]. An aneurysm is defined as an irreversible dilation of a blood vessel accompanied by weakening of the vessel wall [2]. Ascending aortic aneurysms (AsAAs) are a well-known surgical entity, most commonly involving the ascending part of the aorta, and are morphologically defined as progressive dilatation of an aortic segment by more than 50% of its normal diameter [3]. Dilatation is associated with a propensity for dissection, rupture, and aortic valve insufficiency. Although most AsAAs are of unknown etiology, underlying physiological circumstances, such as the individual's age and body surface area are among the main determinants of the size of the ascending aorta [4, 5]. Aortic aneurysms are also associated with vascular remodeling, decreased capillary density, and increased left ventricular end-diastolic pressure, which may cause perfusion abnormalities and may result in an impairment of coronary flow hemodynamics [6].

Hemorheological parameters, such as blood and plasma viscosity (PV), and hematocrit (Hct) and fibrinogen values, which are in a continuous interplay with each other, have critical effects in

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terms of tissue perfusion. Alterations in these hemorheological parameters directly affect endothelial function through an alternating shear force profile on the endothelial wall [7]. Furthermore, blood viscosity is known to be a function of shear rate and has an impact on wall shear stress [8], which has been reported to be strongly associated with aneurysm formation, progression, and risk of rupture [9]. PV is an important contributing factor to whole blood viscosity [10]. Since endothelial cells are in a state of constant contact with shear stress and plasma, plasma components have a major role in endothelial changes occurring due to PV [11]. Plasma is the blood component remaining once red and white blood cells, as well as other cellular elements, have been removed. Macromolecular components and water content play a role in the viscosity of plasma, which is a concentrated protein solution. The molecular structure and weight of a protein such as fibrinogen affect PV. Greater molecular weight and aggregating capacity, and less spheroid formation contribute to greater PV [12].

Nitric oxide (NO), released by vascular endothelial cells, is also believed to play a role in aneurysm formation [13]. Asymmetric dimethylarginine (ADMA), a potential marker of endothelial dysfunction, is an endogenous inhibitor of both endothelial and inducible nitric oxide synthase (NOS), and has been associated with mortality in several acute and chronic vascular conditions [14, 15].

The aim of this study was to investigate change in PV and the endothelial markers of fibrinogen, nitrite and NOx, and ADMA before and after AsAA surgery and to compare the results with those of healthy patients.

Materials and Methods

Subjects and study design

The study group included a total of 23 patients who underwent surgical repair for AsAA (mean age: 63±8 years), and the control group consisted of 30 healthy patients without diabetes, hypo- or hyperlipidemia, or heart disease (mean age: 72±10 years). The mean ascending aorta diameter was 3.60±0.20 cm in the control group. The mean diameter of the ascending aorta in the study group was 6.00±1.80 cm. The exclusion criteria included the presence of congenital valve disease (bicuspid, unicuspid, or quadricuspid aortic valve, etc.), a hereditary connective tissue disorder (Marfan, Ehlers-Danlos, Loeys-Dietz syndromes, etc.), reoperation, or a dissecting aortic aneurysm. The plasma creatinine and glycated hemoglobin levels were within normal limits in all of the control and study group patients.

In the study group, 17 patients had been diagnosed with hypertension and were on metoprolol 50 mg once daily. Eight patients were current tobacco smokers (1 packet/day). All of the operations in the study group were elective procedures.

The study protocol was approved by the Republic of Turkey Ministry of Health, Public Hospitals Administration of Turkey, Kartal Koşuyolu High Specialization Training and Research Hospital, Date: 27.03.2013 Number of Approval: 2013.1/21. Oral and written informed consent were obtained from all of the participants.

Surgical procedure

Surgical treatment was initiated under general anesthesia following general preparations for surgery. A Bentall-De Bono procedure (replacement of the ascending aorta and aortic valve using a mechanical valve prosthesis) was performed in 6 cases, and a David procedure (reimplantation of the aortic valve within a vascular graft) was performed in 3 patients. A tubular graft was interposed in the ascending aorta in the remaining 14 patients. All of the patients were monitored in the intensive care unit during the anesthesia recovery period.

Assessments

Patient blood samples were obtained preoperatively and at postoperative day 7 for plasma evaluation. In the control group, a single sample was obtained for comparison. The collected blood samples were drawn into vacutainers containing potassium ethylenediaminetetraacetic acid as an anticoagulant. The plasma was separated using centrifugation at 3000 x g for 15 minutes in order to analyze the biochemical parameters. All of the parameters were analyzed at the central laboratory of Kartal Kosuyolu Research and Training Hospital. The Hct, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) levels were determined with enzymatic methods using commercial kits (Roche/Hitachi Modular Analytics System; Roche Diagnostics Corp., Indianapolis, IN, USA). The intra-assay and inter-assay coefficients of variation were 2.8% and 3.2%, respectively, for TC; 3.9% and 4.7%, respectively, for HDL-C; 4.1% and 4.8%, respectively, for LDL-C; and 2.9% and 3.6%, respectively, for TG. Biochemical parameters were analyzed using a biochemical assay analyzer (Cobas 8000 c 702 module; Roche Diagnostics, Corp., Indianapolis, IN, USA). Once the biochemical assays were completed, the remaining plasma was sent to the Department of Biophysics, Istanbul University-Cerrahpasa. The samples were stored at -80oC for 2 weeks for PV, fibrinogen, NOx, and ADMA analysis. PV was measured using a Coulter Harkness capillary viscometer (Serial Number 6083; Beckman Coulter, Inc., Brea, CA, USA) at 37oC. The intra- and inter-assay coefficients of variation for PV were 3.8% and 4.0%, respectively. Plasma fibrinogen levels were measured using the clotting Clauss method with Multifibren U (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) commercial kits and the data were expressed as g/L [8]. NOx was determined according to the concentration of nitrate plus nitrite in the serum using a colorimetric method with a Griess reagent (Cayman Chemical Corp., Ann Arbor, MI, USA). Spectrophotometric quantification of nitrite using the Griess reagent is a straightforward method, and nicotinamide adenine dinucleotide-dependent enzyme nitrate reductase was used to convert the nitrate to nitrite prior to quantification with the Griess reagent. The intra- and inter-assay coefficients of variation for NOx were 4.9% and 5.1%, respectively, and the data were expressed as µmol/L.

Plasma ADMA concentrations were determined with a competitive enzyme-linked immunosorbent assay (ADMA ELISA kit; Diagnostika GmbH, Hamburg. Germany). The intra- and inter-assay coefficients of variation were 3.4% and 4.5%, respectively, and the results were expressed as mmol/L.

Statistical analysis

The results were expressed as mean±SD. The statistical analyses were performed using SPSS Statistics for Windows, Version 17.0 (SPSS, Inc., Chicago, IL, USA). An independent t-test was applied to analyze the significance of the difference between the control and study groups, and a paired sample t-test was applied to analyze the significance of the difference between the study groups. A Wilcoxon signed-rank test was used to analyze intra-group variation. A probability level of 0.05 was used as the criterion of significance in all analyses.

Results

The biochemical parameters and endothelial dysfunction markers observed in the control subjects and in the AsAA patients (pre- and postoperative) are demonstrated in the figures, as described.

The preoperative PV measured in the AsAA patients was higher than that of the controls ($p<0.05$) (Fig. 1). At postoperative day 7, the PV was significantly lower and the fibrinogen was significantly higher in comparison with preoperative baseline values in the AsAA patients ($p<0.05$). Both the pre- and postoperative fibrinogen values observed in the study subjects were significantly lower than in controls ($p<0.001$) (Fig. 2). Preoperatively, NOx was higher in AsAA patients than that seen in the controls, although the difference was not significant. A significant decrease in NOx was found in the AsAA patients postoperatively ($p<0.05$) (Fig. 3). Both preop and postop ADMA levels in AsAA patients were significantly lower than those seen in the controls ($p<0.001$ and $p<0.01$, respectively) (Fig. 4) (Table 1).

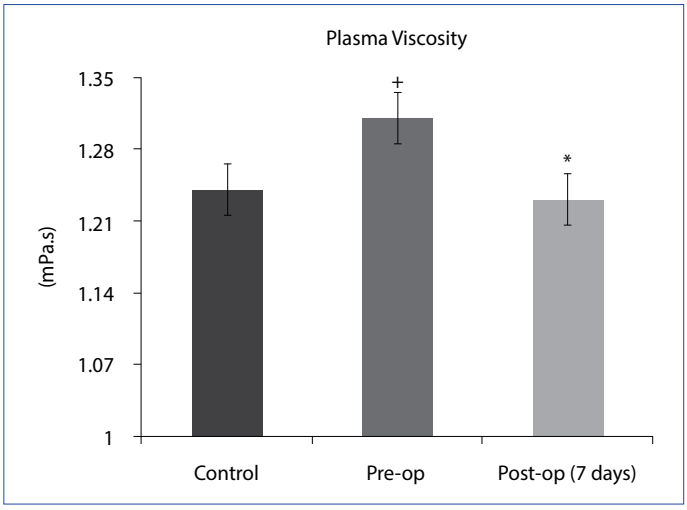

Figure 1. Plasma viscosity level of the control and ascending aortic aneurysm patients.

+: $p<0.05$; Compared with the control group; *: $p<0.05$; Compared with the pre-op group.

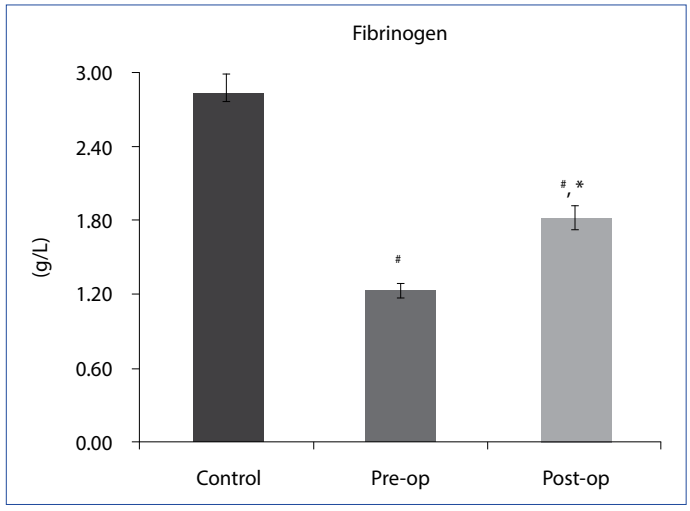

Figure 2. Fibrinogen level of the control and ascending aortic aneurysm patients.

*: $p<0.05$; Compared with the pre-op group; #: $p<0.001$; Compared with the control group.

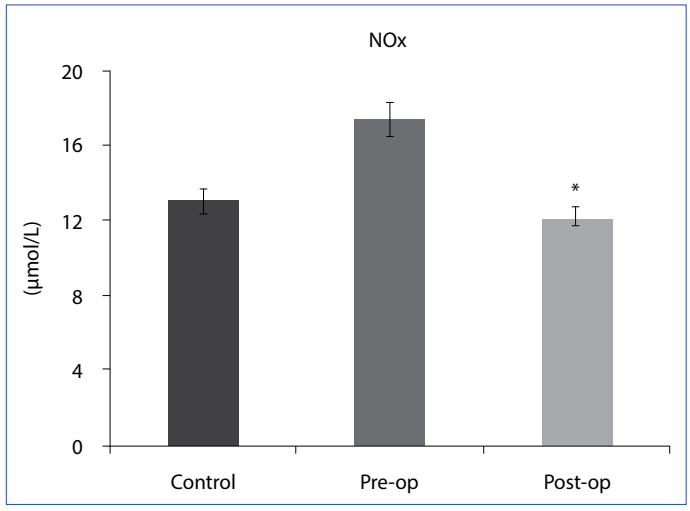

Figure 3. Nitric oxide (NOx) level of the control and ascending aortic aneurysm patients.

*: $p<0.05$; Compared with the pre-op group.

Age and biochemistry results obtained in the controls and the AsAA patients are shown in Table 2. There were no significant differences in age, Hct, TC, LDL-C, or HDL-C levels between the groups. Only the TG value was statistically higher in the AsAA patients compared with the controls ($p<0.05$). In the control group, PV correlated positively with TC ($r=0.516$*; $p<0.05$), TC correlated positively with LDL-C ($r=0.509$*; $p<0.05$), LDL-C correlated positively with Hct ($r=0.507$*; $p<0.05$), and ADMA correlated positively with age ($r=0.698$*; $p<0.05$). Similarly, PV correlated positively with TC ($r=0.640$**; $p<0.01$), TC correlated positively with LDL-C ($r=0.697$**; $p<0.01$), LDL-C correlated

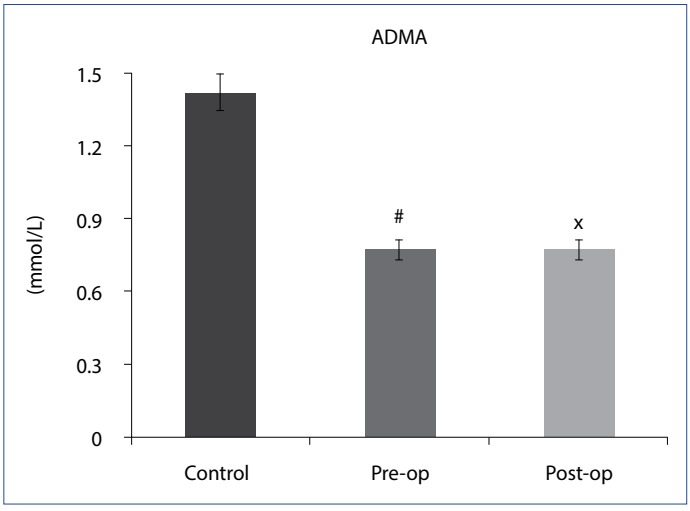

Figure 4. Asymmetric dimethylarginine (ADMA) level of the control and ascending aortic aneurysm patients.
[x]: p<0.01; Compared with the control group; [#]: p<0.001; Compared with the control group.

Table 1. Plasma viscosity, fibrinogen, nitric oxide, and ADMA parameters in the control and study groups

Parameters	Control group (n=30) mean±SD	AsAA group (n=23) mean±SD	
		Pre-op	Post-op
Plasma viscosity (mPa.s)	1.24±0.08	1.31±0.15	1.23±0.08
Fibrinogen (g/L)	2.83±0.52	1.22±0.42[#]	1.81±0.46[#,*]
NOx (µmol/L)	13.02±2.70	17.37±6.95	12.05±3.50*
ADMA (mmol/L)	1.42±0.83	0.77±0.07[#]	0.77±0.16[x]

[+]: p<0.05; Compared with the control group; *: p<0.05; Compared with the pre-op group; [x]: p<0.01; Compared with the control group; [#]: p<0.001; Compared with the control group; ADMA: Asymmetric dimethylarginine; NOx: Nitric oxide.

positively with Hct (r=0.454*; p<0.05), and ADMA correlated positively with age (r=0.425*; p<0.05) postoperatively in the AsAA patients. PV correlated with age (r=0.523**; p<0.01); fibrinogen correlated negatively with Hct (r=-0.632**; p<0.01) and ADMA (r=-0.558*; p<0.05); ADMA correlated negatively with TG (r=-0.371*; p<0.05), TC (r=-0.514**; p<0.01) and LDL-C (r=-0.415*; p<0.01); TG correlated positively with TC (r=0.459*; p<0.01) and HDL-C (r=-0.447*; p<0.01); and TC correlated positively with LDL-C (r=0.863**; p<0.001) preoperatively among the AsAA patients.

Discussion

To the best of our knowledge, this study represents the first published research to show a possible association between PV and AsAA development by demonstrating a significantly increased PV in untreated AsAA patients compared with controls. Variations in aneurysmal geometry and the properties of a flow diverter are among many determinants of aneurysmal hemodynamics [16]. Altered vessel diameter impedes microcirculation with subsequent impairment of capillary perfusion [7, 17]. Reduced blood flow in the expanded segment of the vessel can initiate thrombosis and lead to the formation of clots, ultimately leading to an elevated PV [2, 18].

Table 2. Baseline characteristics and biochemical parameters in the control and study groups

Parameters	Control group (n=30) Mean±SD	AsAA group (n=23) Mean±SD
Age (years)	72±10	63±8
Male gender (%)	50	57
AAOD (cm)	3.60±0.20	6.00±1.80
Hct (%)	37.75±3.01	39.13±4.63
TG (mg/dL)	76.8±16.53	156.95±56.38[+]
TC (mg/dL)	213.6±48.92	196.78±38.52
LDL-C (mg/dL)	136.8±46.20	140.62±23.05
HDL-C (mg/dL)	61.4±14.57	42.64±8.38
Arterial pressure (mmHg) (systolic/diastolic)	112.6±9/70±11	133.1±17/85±12[#]
DM (%)	0	17[+]
Smoker (%)	0	35[#]

[+]: p<0.05; Compared with the control group; [#]: p<0.001; Compared with the control group; AAOD: Ascending aortic diameter; AsAA: Ascending aortic aneurysm; DM: Diabetes mellitus; Hct: Hematocrit; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglyceride.

Enlargement of vessel diameter leads to turbulent flow, and increased turbulence may contribute significantly to elevated pressure and the magnitude of wall stress in aortic aneurysms [19, 20]. Irregular wall shear stress weakens the wall tissue. As the wall tissue loses integrity, a positive feedback loop is initiated, leading to further aneurysmal dilatation [9, 14]. As a result of turbulent flow, high shear stress can lead to increased viscosity and rupture of the aneurysm. Viscosity may also increase with decreasing shear rate.

We found that there was a positive correlation between PV and TC in the preoperative AsAA group. Also, the TG level was significantly higher in the preoperative AsAA group than in the control patients. Significant associations between TC and aortic aneurysm risk have been observed previously in some prospective studies, and a higher TC has been associated with a greater risk of aortic aneurysm [10–14]. A high level of TG and TC can induce damage to the arterial wall through various mechanisms. It has been recognized that very high levels of TG are supported by an increase in the circulation of macromolecular complexes and chylomicrons, which are capable of considerably affecting the physical properties of plasma. It has been hypothesized that blood lipids may result in an alteration of plasma or blood viscosity. An elevated PV with lipid profile deteriorations may cause endothelial dysfunction in cardiovascular diseases. Small

increases in TG levels have not been observed to be very important and, as in our results, probably have a negligible influence. Similarly, in vitro studies have demonstrated that the addition of lipoproteins to plasma led to an increase in viscosity, but it remained relatively low. Several studies have demonstrated an association between the rheological properties of blood and serum lipid levels [2, 5, 9, 17, 21, 22]. Nevertheless, the data are not clear and are often difficult to interpret.

Our results demonstrated an high PV and a low fibrinogen level preoperatively in AsAA patients. PV correlated positively with TC, TC correlated positively with LDL-C, and LDL-C correlated positively with Hct in both the control and AsAA groups. That may be explained by the rheological effects of macromolecules. As the number and size of macromolecules increases, the plasma become more viscous. PV an indicator of a deterioration of microcirculatory flow, which limits tissue perfusion and is the main determinant of flow through the microcirculation. These mechanisms contribute to the preservation of plasma oncotic pressure, and are considerable predictive factors of intravascular volume. PV is determined essentially by macromolecular components and the water content of blood. In our study, there was a positive correlation between PV and age. It has been established that the total volume of body water decreases with age. This correlation may be due to by changes in the ratio and/or distribution of body water. This age-related decrease in body water content can cause an increase in PV. An increase in PV may lead to greater permeability and glomerular capillary pressure. The changing PV is regulated and balanced by the effect of colloid osmotic (oncotic) pressure [23-25]. It is important to remember that fibrinogen is also a major determinant of PV. Among other factors, PV is affected by plasma proteins, and particularly by fibrinogen, due to its asymmetric molecular configuration [21, 22]. However, the observed significant association between PV and AsAA cannot be accounted for by decreased levels of fibrinogen. Vasodilation leads to alterations in blood flow, intravascular coagulation, and the formation of fibrin. Fibrin deposition causes a depletion of coagulation factors, particularly fibrinogen [26, 27]. The fibrinogen level may have been reduced in the AsAA group as a result of impaired production or increased consumption due to intravascular coagulation in the preoperative AsAA cases. Fibrinogen may have been elevated postoperatively due to an acute phase response to surgery.

NOS enzymes are responsible for the synthesis of NOx and serve as a signaling molecule in the cardiovascular system [28]. NO maintains the integrity of the vascular endothelium by inhibiting platelet aggregation, vascular smooth muscle proliferation, and leukocyte-endothelium adhesion [13, 14]. Endothelial NOS (eNOS) is a major source of vasoprotective NO, and inducible NOS (iNOS) is produced by vascular smooth muscle cells and inflammatory cells. Although an association between the development of aortic aneurysm and iNOS has been reported, the exact role of eNOS in the pathophysiology of aneurysmal disease remains to be elucidated [15, 29]. Although the difference was not significant, AsAA patients in our study demonstrated increased NOx preoperatively. The reason for the elevated NOx may be due to the increase in hemodynamic shear stress, which is the strongest physiological regulator of eNOS. Increased preoperative NOx may represent an attempt to reduce the elevated pressure in the aorta. In addition, it is well known that shear stress induces vessel dilation in an acute stage. Conversion from laminar to turbulent flow characteristics in expanded segments of the aorta may be partly responsible for the increased preoperative level of NOx. AsAA patients may be synthesizing higher quantities of NOx as a regulatory mechanism for disrupted blood flow, with the aim of preventing clot formation in those segments.

Of interest, there was a moderate decrease in ADMA observed in the AsAA patients. While a preoperatively low level of ADMA probably represents an inhibitory mechanism against elevated NOx levels, no significant difference was noted postoperatively. These results may suggest that less ADMA was consumed postoperatively as a consequence of the repair process involving the damaged endothelium. It therefore seems plausible to assume that angiotensin-converting enzyme inhibitors may confer vasoprotective effects through increased NOx availability and decreased ADMA concentrations in this setting.

Correction of an aortic aneurysm results in the re-establishment of laminar flow and ameliorates endothelial damage, potentially explaining the absence of a significant difference between the control subjects and the postoperative AsAA patient values in terms of PV and NOx. Fibrinogen and ADMA levels rose after surgery, approaching values routinely observed in healthy individuals.

Conclusion

Literature data on the cardiovascular effects of PV and oxidative stress parameters are scarce. The unique perspective of our study involves a direct assessment of these parameters and their interactions in AsAA patients. The aim of surgery in AsAA is to prevent the rupture of an aneurysm and sudden death. In this regard, there are 2 major conclusions from our findings. First, postoperative normalization of the measured parameters may be associated with an alleviation of risk factors for atherosclerosis, providing protection against this condition in the long term. Second, it was concluded that changes in the lipid profile would reflect viscosity in the follow-up of patients. Thus, based on our observations, PV, fibrinogen, NOx, and ADMA represent independent risk factors for AsAA. In particular, PV is a parameter that can be used to follow personal changes. PV measurement appears to bear clinical significance, as it is provides a cost-effective, rapid, and reproducible assessment with only minimal blood flow variability. Since changes in the lipid profile, and especially in the fibrinogen, can be seen in the blood flow in a very short period of time using the PV measure, analysis of these parameters may make the follow-up of patients or illnesses easier. Age, TG, TC, HDL-C, LDL-C, and ADMA may contribute significantly to clinical follow-up and patient treatment. Further studies are required to investigate flow changes in cardiovascular pathologies, and especially in AsAA. In our next study, we aim to examine tissue

changes using imaging and to analyze these changes in association with molecular bonds and trace elements.

Conflict of interest: None declared.

Ethics Committee Approval: Republic of Turkey Ministry of Health, Public Hospitals Administration of Turkey, Kartal Koşuyolu High Specialization Training and Research Hospital, Date: 27.03.2013 Number of Approval: 2013.1/21.

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Authorship contributions: Concept – C.K., S.G., A.M.E., B.O.K.; Design – C.K., S.G., A.M.E., B.O.K.; Supervision – C.K., S.G., A.M.E., B.O.K.; Funding – None; Materials – C.K., S.G.; Data collection &/or processing – C.K., S.G., A.M.E., B.O.K.; Analysis and/or interpretation – A.M.E., B.O.K.; Literature search – A.M.E., B.O.K.; Writing – C.K., A.M.E., B.O.K.; Critical review – C.K., S.G., A.M.E., B.O.K.

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