**2nd Department of Medicine and Cardiology Center, Medical Faculty,
Albert Szent-Györgyi Clinical Center,
University of Szeged**

Aortic elasticity alterations in special disorders

Henriette Gavallér MD

PhD thesis

Tutor:

Attila Nemes MD, PhD

2012

Relevant publications

Full papers

I. Nemes A, Takács R, Gavallér H, Várkonyi TT, Wittmann T, Forster T, Lengyel C. Correlations between Arteriograph-derived pulse wave velocity and aortic elastic properties by echocardiography. *Clin Physiol Funct Imaging.* 2011; 31: 61-65. (Impact Factor: 1.213)

II. Gavallér H, Sepp R, Csanády M, Forster T, Nemes A. Hypertrophic cardiomyopathy is associated with abnormal echocardiographic aortic elastic properties and arteriograph-derived pulse-wave velocity. *Echocardiography.* 2011; 28: 848-852. (Impact Factor: 1.239)

III. Gavallér H, Sepp R, Csanády M, Forster T, Nemes A. Evaluation of aortic distensibility by echocardiography in patients with hypertrophic cardiomyopathy. *Cardiol Hung.* 2011; 41: 8-12.

IV. Szolnoky G, Nemes A, Gavallér H, Forster T, Kemény L. Lipedema is associated with increased aortic stiffness. *Lymphology* 2012; 45: 71-79. (Impact Factor: 1.023)

V. Nemes A, Gavallér H, Hőgye M, Pálinkás A, Forster T, Csanády M. Transthoracic echocardiographic evaluation of aortic distensibility in a Takayasu's arteritis patient. *J Card Surg*. 2006; 21: 593-595. (Impact Factor: 0.709)

Abstracts

I. Nemes A, Takács R, Gavallér H, Várkonyi T, Forster T, Lengyel C. Correlations between Arteriography-derived pulse wave velocity and aortic elastic properties by echocardiography. Eur J Echocardiography 2009; 10 (Suppl 2): ii86

II. Nemes A, Gavallér H, Csanády M, Forster T. Abnormal echocardiographic aortic elastic properties in patients with hypertrophic cardiomyopathy. Eur J Echocardiography 2010; 11 (Suppl 2): ii21

1. Introduction

There is an increased scientific interest on the evaluation of parameters characterizing aortic elasticity. The healthy human aorta is not a stiff tube and could be characterized by different elastic properties. During systole, the left ventricle (LV) ejects a stroke volume (SV) into the arterial system: half of this SV is directly forwarded to the peripheral circulation, but due to peripheral resistance and elastic extension of the aortic wall the other half of the SV is stored in the aorta . During diastole, the aorta recoils slowly and the stored volume is pressed into the peripheral circulation. This sort of buffering function is called as Windkessel function. Normally, LV ejection causes a pressure pulse with a relatively slow pulse wave velocity (PWV). When this wave is reflected by the peripheral circulation, it returns to the ascending aorta during early diastole inducing the dicrotic wave. The elastic properties of the aorta incorporate both the property of dilating by increasing pressure in systole and the property of recoiling slowly to its initial shape when blood pressure falls in diastole. Aortic stiffness describes the elastic resistance that the aorta sets against its distension. The inverse of stiffness is compliance, which describes the ease of systolic aortic expansion.

In different pathophysiologic conditions aortic stiffness increases due to fibrosis, medial smooth muscle cell necrosis, breaks in elastin fibers, calcifications or diffusion of macromolecules into the arterial wall, etc. Due to these alterations the aorta stiffens, the Windkessel function attenuates and the PWV increases.

There are now two different ways to evaluate aortic distensibility: measuring PWV and augmentation index (AIx) or calculating a modulus or index, in which changes in blood pressure and aortic size during a cardiac cycle are considered. Measurement of PWV and AIx by Arteriograph is a new emerging tool, it has just been validated against broadly accepted tonometric (SphygmoCor) and piezoelectronic (Complior) methods. Oscillometrically measured PWV and AIx showed strong correlation with the invasively obtained values, as well. On the other side, echocardiography can be used for noninvasive measurement of aortic diameters, and by using forearm blood pressure values, different aortic elastic properties could be assessed. This sort of characterization of aortic stiffness has been validated against invasive measurements, and became an accepted method for more than 20 years. There are several debate on the usefulness of Arteriograph in the clinical practice, especially due to the

limited number of validation studies. For instance, validation against echocardiography was missed.

Over known diseases associated with vascular complications, there are several ones, in which vascular elasticity was not widely examined:

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease caused by a variety of mutations in genes encoding sarcomeric proteins and defined clinically by the presence of unexplained left ventricular (LV) hypertrophy with a varied clinical course and outcome. Vascular alterations are frequently associated with HCM including microvascular and / or peripherial endothelial dysfunction. Boosanyirant *et al.* were the first to demonstrate increased aortic stiffness characterized by magnetic resonance imaging (MRI)-derived PWV in patients with HCM. However, confirmation of their results by other methods was missed in the literature.

Lipedema was firstly described by Allen and Hines more than seven decades ago but its pathomechanism remained enigmatic. It is a disproportional obesity, that nearly always affects women and is characterized by bilateral, symmetrical, biker's hosiery-shaped fatty swelling of the legs with sparing of the feet. Arms are also comonly affected by adipous hypertrophy. However, under progression, the characteristic ''stove-pipe'' legs emerge and as a result of orthostatic prolongation a sharp demarcation between normal and abnormal tissue at the ankle with the filling of retromalleolar sulcus, giving the appearance of ''pantaloon''. The strongly reduced elasticity of the skin, the poor venoarterial reflex in conjunction with robust fatty enlargement substantially weaken venous calf pumps activity leading to impaired venous and lymphatic functions. Massively enlarged adipose tissue and accompanying oedema may enhance vascular resistance affecting arterial function. Some data suggest that body weight and fat distribution are related to higher arterial stiffness. These data give rise to the examination of aortic elasticity also in lipedema.

Takayasu's arteritis (TA) is a chronic, nonspecific, and rare inflammatory disease, which segmentally affects the aorta and its main branches. However, regionality of vascular function by a non-invasive method has not been assessed in TA.

2. Aims

To compare Arteriograph-derived pulse-wave velocity and augmentation index with aortic elastic properties by echocardiography

To evaluate echocardiographic ascending aortic elastic properties and Arteriograph-derived pulse-wave velocity and augmentation index in hypertrophic cardiomyopathy.

To measure aortic elasticity parameters in women with and without lipoedema.

To demonstrate the clinical usefulness of routine transthoracic echocardiography in the segmental evaluation of distensibility of ascending aorta in a patient with Takayasu's arteritis.

3. Methods

Patient population (general considerations). Hundreds of patients with different disorders and control subjects were selected to evaluate the aortic elasticity alterations by echocardiography and / or Arteriograph at the 2nd Department of Medicine and Cardiology Center, University of Szeged, Hungary. A complete standard transthoracic echo-Doppler study was performed in all patients extended with aortic stiffness measurements. Diabetes mellitus was defined in accordance with the American Diabetes Association and World Health Organization criteria. Hypertension was defined as either a systolic or a diastolic elevation of the blood pressure (>140/90 mmHg) or ongoing antihypertensive therapy. Hypercholesterolaemia was defined as a total cholesterol level >5.0 mmol/l or current treatment with lipid-lowering medications. The study complied with the Declaration of Helsinki. The local ethics committee of University of Szeged approved the study protocol and all patients gave informed consent.

Blood pressure measurement. Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in the supine position with an automatic mercury cuff sphygmomanometer from the left arm after 10 min of rest. None of the patients or control

subjects used coffee or tea within one hour before blood pressure measurements and by exclusion none of the patients or control subjects were smoker.

Transthoracic echocardiography. All subjects underwent a complete two-dimensional transthoracic echocardiography and Doppler study using Toshiba Powervision 8000 and Aplio echocardiography equipments (Toshiba, Tokyo, Japan) in the left lateral decubitus position from multiple windows. All echocardiographic studies were digitally stored and evaluated by a single expert (HG) who was blinded to the clinical data. All echocardiographic measurements were averaged from 3 beats. M-mode echocardiography was used to measure LV internal dimensions. LV mass was calculated according to the Penn convention: LV mass $(Penn) = [(EDD + IVS + PW)^3 – EDD^3] * 1.04 – 13.6$ g, where EDD is the LV end-diastolic diameter, IVS is the interventricular septum and PW is the LV posterior wall. Du Bois and Du Bois formula was used to calculate body surface area BSA (m²) $= 0.20247$ x height $(m)^{0.725}$ x weight $(kg)^{0.425}$. LV hypertrophy was defined as LVM/BSA (LVMI) >134 g/m^2 for men and >110 g/m^2 for women.

Evaluation of aortic elastic properties. Aortic elasticity parameters were calculated following a validated method. Systolic and diastolic ascending aortic diameters (DS and DD, respectively) were recorded in M-mode at a level of 3 cm above the aortic valve from a parasternal long-axis view (Figure 1). American Society of Echocardiography convention as the most accepted border definition criteria was used measuring the leading edge of each layers. The DS and DD were measured at the time out of maximum aortic anterior motion and at the peak of QRS complex, respectively. The following aortic elasticity parameters have been calculated:

- Aortic strain = (DS – DD) / DD
- Aortic elastic modulus E(p) = (SBP-DBP)/[(DS-DD)/DD]
- Young's circumferential static elastic modulus E(s) = E(p)*DD/2h, where „h" is the diastolic intima-media thickness
- Aortic stiffness index (β) = ln (SBP / DBP) / [(DS - DD) / DD], where 'ln' is the natural logarithm.
- Aortic distensibility = 2 x (DS – DD) / [(SBP – DBP) x DD].

Pulse wave measurement by Arteriograph. Arteriograph is a new tool to measure PWV and Aix and just validated against other non-invasive and invasive methods. The Arteriograph measures the blood pressure in the upper arm by oscillometric method, and then produces a cuff pressure over the brachial artery (sytolic blood pressure measured plus 35 mm Hg). Periodic pressure changes in the inflated cuff are produced by fluctuations in pulsatile pressure in the artery under the inflated cuff. Pressure oscillations in the brachial artery are detected by the cuff, which are recorded and analysed as pulse waves by the computer. The time difference between the beginning of the first and the reflected second waves is related to the distance from the jugulum to the symphysis, and it results in the PWV in m/s. The software of the Arteriograph separates the early, late systolic and diastolic waves and the onset and the peaks of the waves are also detected. The onsets of the waves are determined by using first and second derivatives for PWV analysis. In order to intensify the signal and differentiate the initial wave from the reflective wave the Arteriograph only evaluates the pulse waves when a suprasystolic pressure of 35 mm Hg has been attained. The augmentation index (AIx) corresponds to the pressure difference (amplitude difference; S1-S2) between the first and second wave in relation to the pulse pressure (PP). The Arteriograph calculates the AIx on the basis of the formula $AIx\% = [(S2-S1)/PP] \times 100$ and thus provides the brachial AIx without applying a transfer function.

Statistical analysis. Continuous data with normal distribution were presented as mean ± standard deviation, while dichotomous data were presented as number and percentage. Between-group comparisons were made with the unpaired Student's *t*-test. For the dichotomous variables, chi-square analysis and Fisher's exact test were performed. Mann-Whitney test was used when needed. Numerical correlations were established by a Pearson correlation. Values for R were interpreted in the following way: 0.9-1: excellent, 0.7-0.89: good, 0.5-0.69: moderate, 0.3-0.49: low. Interobserver reproducibility for measuring systolic and diastolic ascending aortic diameters is 84 and 88%, respectively. A value of $p < 0.05$ was considered to be statistically significant. Medcalc software (Medcalc, Mariakerke, Belgium) and SPSS 12.0 and 14.0 softwares (SPSS Inc., Chicago, Illinois, USA) were used for statistical calculations.

4. Results

4.1. Correlations between Arteriograph-derived pulse wave velocity and aortic elastic properties by echocardiography

Study population. The study comprised 21 healthy volunteers. Echocardiographic parameters were normal in all subjects, none having significant valvular heart disease, segmental wall motion abnormalities or myocardial hypertrophy.

Results. Arteriograph-derived AIx80 and PWV values correlated with aortic strain (R = -0.495, p = 0.023 and R = -0.527, p = 0.014, respectively). Aortic distensibility did not show linear correlation with AIx80 (R = -0.344, p = 0.127), only with PWV (R = -0.593, p = 0.005). Aortic stiffness index had correlation both with AIx80 (R = 0.454, p = 0.039) and PWV (R = 0.608, p = 0.003).

4.2. Alterations in aortic distensibility in hypertrophic cardiomyopathy

Study population. A total of 38 patients with typical features of HCM were involved into the present study. The diagnosis HCM was confirmed in all patients according to the guidelines. In all cases, hypertrophy was asymmetrical and had septal localization. All patients had undergone complete Doppler transthoracic echocardiographic examination to evaluate aortic elastic properties and Arteriograph-derived measurement of PWV and AIx. Their results were compared to 20 hypertensive patients with LV hypertrophy and 23 controls.

Clinical and echocardiographic data. In HCM patients, 20 had systolic anterior motion (SAM) of the mitral valve, 8 had >30 mm Hg resting aortic gradient, 7 had ICD, 1 had prosthetic mitral valve and 4 patients were after percutaneous transluminal septal myocardial ablation (PTSMA). The mean aortic gradient in this HCM population was 29.2 ± 33.5 mm Hg. LV mass was significantly increased in HCM compared to controls.

Aortic stiffness parameters. Despite blood pressure values of HCM patients were significantly lower compared to hypertensive cases, aortic elastic properties showed similar

alterations compared to controls: aortic stiffness index, PWV and Aix were significantly increased, while pulsatile change in aortic diameter, aortic strain and aortic distensibility were significantly decreased in HCM patient.

4.3. Alterations in aortic distensibility in lipoedema

Study population. The study comprised 14 women with and 14 without lipoedema. All of them were referred to our outpatient clinic for a routine cardiological examination, whereas lipedema patients were first seen at the lymphedema outpatient care unit of the Department of Dermatology and Allergology (table 1 displays patient demographics). All patients underwent physical examination, 2DE and blood pressure measurement. Patients with coronary or valvular heart disease, atrial fibrillation or other arrhythmic problems, heart failure, unstable angina pectoris or acute myocardial infarction were excluded from this study. Body mass index (BMI) was calculated by dividing the participant's weight in kilograms by the square of his/her height in meters. The following classification was used: overweight (BMI 25–29.9 kg/m^2), grade 1 obesity (BMI 30–34.9 kg/m^2), grade 2 obesity (BMI 35–39.9 kg/m^2) and grade 3 obesity (BMI greater than 40 kg/m^2).

Results. There was no mismatch between patient and control groups from the aspect of age (40.3 ± 9.0 vs. 35.5 ± 8.1 years, P >0.05) and mean BMI values (27.6 ± 1.7 vs. 27.2 ± 3.3 kg/m^2, P >0.05). None of them had relevant risk factors including lipid metabolism disturbance, diabetes mellitus, anemia. Mean systolic and diastolic aortic diameters and aortic stiffness index were significantly higher, while aortic strain and distensibility were considerably lower in lipedematous patients compared to control persons.

4.4. Evaluation of aortic distensibility in a patient with Takayasu's arteritis

A 45-year-old treated hypertensive TA woman with diminished pulses was referred to the Echocardiographic Laboratory of University of Szeged. TA was diagnosed in 2003 according to the criteria established by the American College of Rheumatology, since she had been treated with methyl-prednisolon. At the time of her admission, digital subtractional angiography was performed showing 50% to 75% carotis communis stenoses at both sides

and >90% right subclavian arterial stenosis and total occlusion of the subclavian artery at the left side. The aortic arch and descending aorta were found to be normal. Following the steroid treatment, the symptoms (headache, arm torpidity and pain, dizziness and vomiting) regrediated. The routine 2-dimensional transthoracic echocardiographic examination showed normal left ventricular dimensions and ejection fraction. To determine aortic distensibility indices, elastic modulus [E(p)] and Young's circumferential static elastic modulus [E(s)] of the ascending aorta were evaluated. For this purpose, systolic and diastolic aortic diameter, intimomedial thickness, and blood pressure data were measured and corrected E(p) and E(s) were calculated (0.20 and 2.05, respectively). In the present case, the [E(p) in 10^3 mmHg] and [E(s) in 10^3 mmHg] were decreased (aortic distensibility was practically normal) suggesting that ascending aorta was not affected by TA.

5. Discussion

5.1. Correlations between Arteriograph-derived pulse wave velocity and aortic elastic properties by echocardiography

To the best of the authors' knowledge this is the first time to evaluate correlations between Arteriograph-derived PWV and AIx and aortic elastic properties determined by echocardiography. Low to moderate correlations were found between these parameters in healthy volunteers. Arteriograph is a relatively new emerging tool for non-invasive calculation of PWV and Aix, but not really validated recently. Aortic elastic properties by echocardiography are widely used to describe vascular distensibility and they are based on blood pressure and aortic dimension changes during cardiac cycle. The scientific experience with echocardiographic aortic stiffness measurements is based on >1000 international publications since 1980-90s.

The normal human aorta is not a stiff tube, it acts as an elastic buffering chamber behind the heart. Due to its elastic properties the aorta can dilate by increasing blood pressure in systole and can recoil to its initial shape by decreasing pressure in diastole. Aortic stiffness characterizes the elastic resistance against the distension, whereas aortic compliance describes the readiness for systolic aortic expansion. Aortic stiffness is evaluated by the change in volume due to blood injection in the aorta as well as by the pressure change induced by this volume change. Aortic stiffness can be quantified by measurement of SBP and DBP, and

changes in aortic diameters (DS and DD). Transthoracic echocardiography is a routine non-invasive method for the measurement of DS and DD. Aortic elastic properties including aortic strain, distensibility and stiffness index can be calculated by using forearm SBP and DBP. The non-invasive echocardiographic method was compared to invasive angiographic stiffness measurement technique and its accuracy was proved in patients with coronary artery disease.

Another noninvasive opportunity to characterize aortic stiffness is by measuring PWV and AIx. Different tonometric (SphygmoCor) and piezo-electronic (Complior) methods are used for PWV measurement. One of the newly validated emerging methods is Arteriograph, its based on oscillometric measurements. In a recent study, Arteriograph was compared with SphygmoCor and Complior, and it was concluded that PWV by Arteriograph is easy-to-use and time-effective method for assessing arterial stiffness. Variability and reproducibility for PWV were best for the Arteriograph, followed by Complior and SphygmoCor. AIx (SphygmoCor versus Arteriograph) were very closely correlated. Rajzer *et al.* compared PWV measurements using Complior, SphygmoCor, and Arteriograph devices, and assessed the effect of pulse wave transit time and traveled distance on PWV values. They found that differences in PWV obtained by compared devices resulted primarily from using various methods for measuring traveled distance and suggested uniform principles for the measurement of it. Although Arteriograph values and the determinants of PWV and AIx are in close agreement with corresponding parameters obtained by Complior and SphygmoCor, respectively, the techniques are not interchangeable. In contrast, lack of correlation between PWV by validated PulsePen tonometer and PWV by Arteriograph and lack of prognostic significance of PWV by Arteriograph in patients on haemodyalisis were found suggesting limited validity of Arteriograph to determine PWV. Moreover, simulations by Trachet *et al.* question the working principle of the Arteriograph. They indicate that the method picks up wave reflection phenomena confined to the brachial artery, and derived values of PWV rather reflect the stiffness of the brachial arteries.

The present study could be considered as a validation study comparing two different approaches to evaluate aortic stiffness. Low to moderate correlations were found between aortic elastic properties by echocardiography and Arteriograph-derived PWV and Aix80. However, further studies are warranted to validate PWV by Arteriograph against invasive methodologies.

Limitation section. This was a single-centre experience and limited by a relatively small number of healthy volunteers. The study would have been statistically stronger, if larger number of subjects had been evaluated.

5.2. Aortic distensibility alterations in hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy, caused by mutation in one of the genes currently known to encode different components of the sarcomere, is characterized by LV hypertrophy in the absence of predisposing cardiovascular conditions. The clinical manifestations of HCM range from asymptomatic to progressive heart failure to sudden cardiac death and vary from individual to individual even within the same family. Recently, alterations in vascular function including increased MRI-derived PWV have been demonstrated in HCM. Elevated PWV was more pronounced in HCM patients with myocardial fibrosis. Further, aortic stiffening adversely affected LV performance. Aortic stiffness potentially has a role in evaluation of symptoms of patients with HCM. Moreover, age and PWV were found to be predictors of peak oxigen consumption [pVO(2)], independent of LV thickness, LV outflow tract gradient and diastolic indices. Our results are in agreement with these findings demonstrating abnormal echocardiographic aortic elastic properties and Arteriograph-derived PWV in HCM patients as compared to matched controls. Aortic elasticity parameters of hypertensive patients with LV hypertrophy were similar to HCM patients, despite HCM patients had lower blood pressure values.

Vascular alterations are often seen in HCM. It is well known, that coronary microvascular dysfunction is frequently associated with HCM, which is an independent predictor of adverse LV remodeling, systolic dysfunction, and mortality in these patients. Dimitrow *et al.* found preserved endothelial function of peripheral conductance arteries in HCM. They concluded that a defect in the forearm arterial bed in HCM seems to be limited to mechanisms maintaining the dilation of resistance vessels during decreasing reactive hyperaemia flow. In contrast, Hefferanan *et al.* demonstrated impaired peripheral conduit vessel endothelial function in subjects with HCM, and the magnitude of impairment was similar to that seen in older patients with advanced coronary artery disease.

The precise etiology of increased aortic stiffness in HCM is uncertain. A number of factors can play a role reducing aortic distensibility in HCM including neurohormonal disturbances (increased LV pressure, activated renin-angiotensine-aldosterone system),

endothelial dysfunction, abnormal LV baroreceptor stimulation, intrinsic aortic wall fibrosis etc. Genetic factors and the effects of atherosclerosis and co-existing traditional cardiovascular risk factors should also be considered. Moreover, stiffening of the aorta may impose burden on an already stiff ventricle in HCM adversely affecting cardiac performance.

Study limitations

1) The blood pressure measured in the brachial artery may be different from the pressures in the ascending aorta, due to pulse pressure amplification towards the periphery. However, the results obtained by the methods used correlate well with those from invasive methods.

2) Some HCM patients had increased resting aortic gradient or were after PTSMA. There are no clinical data on the effect of obstruction on aortic stiffness in HCM. Therefore, further studies are warranted to examine whether differences exist in aortic elasticity parameters between HCM patients with vs. without aortic gradient. Moreover, the short and long-term effects of PTSMA on aortic elasticity should also be examined in obstructive HCM.

3) The medication used could theoretically also affect our results.

4) The available literature regarding validity of Arteriograph is limited, further validation studies are warranted.

5.3. Aortic distensibility alterations in lipoedema

The present study has clearly shown that aortic stiffness is increased in lipoedematous patients compared to healthy individuals within similar age group suggesting early vascular remodelling. Lipoedema is a peculiar form of adipose tissue deposition in a dysproportional fat accumulation in a biker's hosiery shape and is complicated by venous- and lymphatic insufficiency and also microangiopathy. The skin is usually normal in texture and appearance, without the dermal thickening or induration common in lymphoedema. At most, one in ten women or postpubertal girls may exhibit involvement to some degree. Lipoedema is presumably associated with genetic background, but, to date, none of the examined genes have proved to be responsible for the phenotypic appearance. It is easily distinguishable from lymphoedema and phleboedema by clinical features, and hormonal abnormality can

commonly be detected. Lipoedema is often combined with morbid obesity, although lipoedematous tissue hardly or never responds to diet and forced weight-loss.

Generalized obesity is known to be associated with structural (altered aortic size) and functional (decreased aortic elasticity) vascular abnormalities, where aortic enlargement may represent an adaptation process to accommodate for the increased blood volume. Wildman *et al* found that excess weight begins to affect the vascular system at a very early stage of vascular aging. We have recently shown that obesity is associated with aortic enlargement and increased stiffness regardless the age of patients.

Various mechanisms can be attributed to obesity-linked aortic stiffening including visceral adipose tissue throughout insulin resistance development. Hyperinsulinaemia can be associated with increased sodium reabsorption, a stimulated sympathetic nervous system and atherosclerosis. In obesity-related insulin resistant state the endothelium dependent vasodilator effects of insulin is weakened. Higher levels of nonesterified fatty acids have been found to be associated with central obesity by increasing α-adrenergic reactivity, vascular tone and blood pressure. Increased BMI has been associated with permanent low-grade inflammation and concomitantly increased expression of proinflammatory cytokines resulting in wall stiffening.

Lipoedema patients nearly always complain of spontaneous or mild injury evoked pain upon palpation that worsens with aging. Another hallmarks are frequent hematoma formation due to even minor traumatic injuries and excessive bruising. Haematoma formation is presumably triggered by increased capillary fragility (CF) and possibly by impaired venoarterial reflex (VAR). CF measurement with a vacuum suction chamber, the Parrot's angiosterometer has clarified remarkable CF in the background of frequent haematoma formation. Decongestive lymphatic therapy (DLT) in combination with intermittent pneumatic compression (IPC) significantly decreased CF. Lipoedema is accompanied by local lymphatic and venous abnormalities (eg. irregularly dilated lymphatics, lymphatic microaneurysms and varicosity), major venous dysfunction is rarely found.

Several theories have been postulated regarding the etiology of lipoedema. Földi and Földi have proposed that microangiopathy in the area of the affected adipose tissue sets off the condition leading to increased permeability to proteins. Hypoxia is known to be a major induction factor for angiogenesis and, in the eye, pathological angiogenesis in the retina leads to catastrophic loss of vision in retinopathy of maturity, diabetic retinopathy. The principal feature of these newly formed capillary vessels in these disorders is also fragility. Angiogenesis is controlled by several factors, including vascular endothelial growth factor

(VEGF), and accordingly, abnormally high serum VEGF levels might be predicted in the presence of intensive angiogenesis and concomitant CF. A study examining effects of shock-wave therapy in patients with lipoedema or cellulite found nearly 4-fold higher plasma mean VEGF level at baseline compared to non-lipoedematous individuals. Other observations relate to immunohistochemical findings. In lipoedema, adipocytes undergo necrosis and are scavenged by macrophages. Hypoxia induced by excessive adipose hypertrophy has been proposed to cause adipose metabolic dysfunction and the production of adipose tissue cytokines related to inflammatory reaction might also be operative in lipoedema. Furthermore, adipocyte enlargement and Ki67 and CD34 positivity were also observed, which are associated with cell proliferation, and adipose stem/progenitor cells, respectively.

Observed and suspected pathological features of lipoedema suggest a possible explanation for the increased aortic stiffness. Lipoedematous adipous tissue as in generalized obesity may enhance peripheral vascular resistance causing increasing aortic stiffness. Additionally, at the microvascular level, localized hypertension accompanying arteriolar remodeling and capillary hyperpermeability can lead to microangiopathy interacting with macrovascular function. Expansion of the lipoedematous microvascular network and its fragility might be explained as a compensatory response to constant stimuli from local tissue pressure and vascular resistance. Thus, the known interaction of macro- and microcirculations observed in other disorders could account for the coexistence of raised CF and aortic stiffness in lipoedema.

5.4. Evaluation of aortic distensibility in a patient with Takayasu's arteritis

Takayasu's arteritis is a large vessel vasculitis that affects primarily women. The clinical presentation depends on the location of the affected vessels and the severity of the vascular inflammation. Involvement of large vessels revealed variations; the most common angiographic finding is the involvement of the ascending aorta, the aortic arch and its main branches, and the abdominal aorta.. Stefanadis *et al.* described an invasive evaluation of aortic elastic properties in TA patients. In the present case, for preoperative assessment, a noninvasive simple transthoracic echocardiographic method was used for the evaluation of ascending aorta distensibility. Neither angiography nor transthoracic echocardiography-derived aortic distensibility parameters confirmed that ascending aorta of the present case was affected by TA.

Takayasu's arteritis is an inflammatory disease affecting segmentally the large vessels. The present case suggests that for preoperative assessment, a routine transthoracic echocardiographic aortic stiffness assessment could be a valuable method for the noninvasive functional evaluation of the ascending aorta in TA.

6. Conclusions (new observations)

1. Significant correlations could be demonstrated between echocardiographic aortic elastic properties and Arteriograph-derived pulse-wave velocity and augmentation index.
2. Hypertrophic cardiomyopathy is associated with abnormal echocardiographic aortic elastic properties and Arteriograph-derived pulse-wave velocity
3. Remarkable alterations in aortic elastic properties could be demonstrated in female patients with lipoedema
4. Routine transthoracic echocardiography could be a valuable method for the noninvasive functional evaluation of the ascending aorta in Takayasu's arteritis

8. Acknowledgments