The Mechanical Properties of Elastic Arteries in
Ehlers–Danlos Syndrome

B. Sonesson, F. Hansen and T. Länne

Departments of 1Vascular and Renal Diseases and 2Clinical Physiology, Malmö University Hospital, S-205 02 Malmö, Sweden

Objective: To study whether measurements of wall mechanics can be used as an indicator of disturbed vessel wall integrity and predictor of vessel fragility in Ehlers–Danlos Syndrome (EDS).

Methods: The wall mechanics of the abdominal aorta (AO) and common carotid artery (CCA) were estimated from the indices Ep (pressure strain elastic modulus) and stiffness (β) in twelve individuals with EDS of different subtypes and compared with the results of a healthy reference population. Ep and β were calculated from diameter and pulsatile diameter change determined non-invasively with the aid of an ultrasonic echo-tracking system and blood pressure obtained by the auscultatory method.

Results: Compared with normal individuals and their confidence intervals, subjects with EDS had unaltered diameter, Ep and β in the AO, as well as in the CCA. Analysis of covariance (ANCOVA) also showed unaltered results. AO: diameter (males p=0.66, females p=0.27), Ep (males p=0.81, females p=0.27) and β (males p=0.95, females p=0.12). CCA: diameter (males p=0.36, females p=0.46), Ep (males p=0.93, females p=0.48) and β (males p=0.86, females p=0.47).

Conclusions: This investigation could not demonstrate any alteration in wall mechanics as a sign of disturbed vessel wall integrity of elastic arteries in EDS. This might indicate that the structural defect in the arterial wall collagen, and thus the tendency to vessel fragility, cannot be revealed under normal physiological pressure conditions.

Key Words: Ehlers-Danlos syndrome; Arterial distensibility; Wall mechanics; Compliance; Echo-tracking; Ultrasonography.

Introduction

Ehlers–Danlos syndrome (EDS), in its most severe form, can present with spontaneous rupture of large arteries that may be fatal. EDS was first described by the dermatologist Ehlers in 1901, and then by Danlos in 1908. At that time, however, it was considered to be only a dermatological disease combined with hypermobile joints. The main clinical features of EDS are characterised by hyperextensible skin (cutis laxa), tissue fragility, extensive scarring, hypermobile joints and sometimes bruising. Not until 1960 was it recognised that some individuals with this syndrome could have spontaneous fatal rupture of large arteries. The basic defect in this heterogenous clinical syndrome, often with a family history, was later found to be various collagen abnormalities. The syndrome is now classified in eleven subtypes according to various genetic characteristics, biochemical abnormalities and clinical manifestations. Recently, Kontusaari found a phenotypic overlap between familial aortic aneurysms and EDS type IV.

In EDS type IV, the most severe form, the defect is collagen type III deficiency. This type, and also occasionally EDS type I, have spontaneous rupture of large arteries. Large and medium sized arteries are most at risk, and rupture of thoracic, abdominal and iliac arteries usually leads to catastrophe. Most cases of arterial rupture in EDS occur in non-aneurysmal vessels.

The wall mechanics of large arteries are mainly determined by the collagen-to-elastin ratio of the media. Changes in the amount or quality of these components alter wall mechanics, e.g. in Marfan’s syndrome with a defect fibrillin giving rise to abnormal elastic fibres. It is not known if collagen defects as in EDS will change wall mechanics and could be used as a predictor of vessel fragility.

The aim of the present study was to investigate whether the mechanical properties of the abdominal aorta and common carotid artery in individuals with Ehlers–Danlos syndrome differ from those found in a
healthy age- and sex-matched reference population,\textsuperscript{11-13} in order to assess if the results could be used as an indicator of disturbed vessel wall integrity and a predictor of vessel fragility.

**Materials and Methods**

The investigation was conducted on twelve individuals from six families with Ehlers-Danlos syndrome (EDS). They were recruited from southern Sweden (approximately 5 million inhabitants). The diagnosis of EDS was based on history and physical examination (joint mobility, tissue fragility, scarring, bleeding complications) and the different types of EDS were distinguished according to the Berlin classification.\textsuperscript{14}

**EDS type I**

*Family 1.* In this family there were affected members in four generations. Two affected members were studied, a 68-year-old woman and her 34-year-old daughter. They had easy bruisability, hyperextensible skin, prominent scarring and hypermobile joints. They were both smokers, and the 68-year-old female was treated for hypertension with a \( \beta \)-blocker and hydralazins.

*Family 2.* In this family there were affected members in two generations. One affected member, a 28-year-old woman, was studied. She had very mobile joints which often dislocated, and she had several operations due to this. She had frequent scarring, but the skin was only moderately extensible. She was smoking 20 cigarettes per day and had no history of cardiopulmonary disease.

**EDS type II**

*Family 3.* In this family there were affected members in three generations. One affected member, a 14-year-old girl, was studied. She had joint hypermobility, frequent spontaneous haematomas, scarring and very extensible skin. There was no history of cardiopulmonary disease, smoking or regular drug treatment.

*Family 4.* In this family there were affected members in two generations. One affected member, an 8-year-old boy, was studied. He had hypermobile joints, especially hands and feet, very extensible skin, multiple abnormal scars and frequent haematomas. He had no history of cardiopulmonary disease or any regular drug treatment.

**EDS type III**

*Family 5.* In this family there were affected members in three generations. Three affected members were studied, two 36-year-old monozygotic twin brothers and their 60-year-old mother. The twins were raised together and had the same occupation in the same company. They had very mobile joints and extensible skin. They had also spontaneous haematomas in their buttocks and fingers. Their mother seemed to be less affected. All three were non-smokers and had no history of cardiopulmonary disease or regular drug treatment.

**EDS type IV**

*Family 6.* In this family there were affected members in four generations. Four members of the family, three sisters aged 41, 39 and 29, and the 15-year-old son of the 41-year-old sister, were investigated. At 40 years of age their grandfather was operated on several times because of a spontaneously ruptured external iliac, but he died of uncontrolled bleeding. His grandson, and sibling of the 15-year-old boy investigated here, died at 14 years of age of a spontaneously ruptured thoracic aorta verified at autopsy. There were no data that indicated that a period of hypertension preceded rupture. The studied 41- and 39-year-old daughters had easy bruisability, joint hypermobility, mostly limited to fingers, but no skin hyperextensibility. The 29-year-old daughter had the same symptoms but seemed less affected. The 15-year-old boy, whose brother died, seemed to be unaffected. Judging from clinical features this family had EDS type IV. The 41-year-old daughter was treated for hypertension and was smoking seven cigarettes a day. The others had no history of cardiopulmonary disease, smoking or regular drug treatment.

Each subject and the parents of the 8-, 14- and 15-year-old patients gave informed consent to the studies. The investigations were approved by the Ethics Committee, Lund University, Sweden.
Echocardiography

Echocardiography was performed with a Hewlett-Packard Sonos 1000. Dimensions of the heart chambers and the aortic root were measured from parasternal M mode registrations, and normal values used according to Feigenbaum. Doppler registrations were made from the aortic-, mitral-, pulmonic-, and tricuspid valves to evaluate the presence and severity of valvular stenosis or incompetence.

The data on the healthy age- and sex-matched reference population have been published elsewhere. Briefly, we use an electronic echo-tracking instrument (Diamove, Teltec AB, Lund, Sweden) interfaced with a real-time ultrasound scanner (EUB-240, Hitachi, Tokyo, Japan) and fitted with a 3.5 or a 5 MHz linear array transducer. All examinations were performed with the subjects in the supine position and after at least 15 min of rest. The abdominal aorta was insonated from the epigastrium. Measurements were made in the young between the renal arteries and the aortic bifurcation, and in the adults approximately 3–4 cm proximal to the bifurcation. The common carotid artery was insonated from the neck behind the sternocleidomastoid muscle, and measurements were made 1–2 cm proximal to the bifurcation. The arteries were visualised in a longitudinal section on the real-time image. Two electronic markers, each representing one tracking gate, were aligned with and locked on the echoes from the posterior interface of the anterior wall and the anterior interface of the posterior wall, respectively. The echo-tracker measures the distance between the vessel walls perpendicular to the longitudinal axis of the vessel. A data acquisition system containing a personal computer type 386 (Express, Tokyo, Japan) and a 12-bit analogue to digital converter (Analogue Devices, Norwood, U.S.A.) was included for on-line monitoring of pulsatile vessel diameter. In the system used the smallest detectable movement is 7.8 μm. The repetition frequency of the echo-tracking loops is 870Hz, and the consequent time resolution approximately 12 ms. The inter- and intraobserver variability for pulsatile diameter change of the common carotid artery and abdominal aorta was between 10–15%.

Ultrasound phase-locked echo-tracking

The method for non-invasive monitoring of pulsatile diameter changes in the distal abdominal aorta and the common carotid artery has been described previously. Briefly, we use an electronic echo-tracking instrument (Diamove, Teltec AB, Lund, Sweden) interfaced with a real-time ultrasound scanner (EUB-240, Hitachi, Tokyo, Japan) and fitted with a 3.5 or a 5 MHz linear array transducer. All examinations were performed with the subjects in the supine position and after at least 15 min of rest. The abdominal aorta was insonated from the epigastrium. Measurements were made in the young between the renal arteries and the aortic bifurcation, and in the adults approximately 3–4 cm proximal to the bifurcation. The common carotid artery was insonated from the neck behind the sternocleidomastoid muscle, and measurements were made 1–2 cm proximal to the bifurcation. The arteries were visualised in a longitudinal section on the real-time image. Two electronic markers, each representing one tracking gate, were aligned with and locked on the echoes from the posterior interface of the anterior wall and the anterior interface of the posterior wall, respectively. The echo-tracker measures the distance between the vessel walls perpendicular to the longitudinal axis of the vessel. A data acquisition system containing a personal computer type 386 (Express, Tokyo, Japan) and a 12-bit analogue to digital converter (Analogue Devices, Norwood, U.S.A.) was included for on-line monitoring of pulsatile vessel diameter. In the system used the smallest detectable movement is 7.8 μm. The repetition frequency of the echo-tracking loops is 870Hz, and the consequent time resolution approximately 12 ms. The inter- and intraobserver variability for pulsatile diameter change of the common carotid artery and abdominal aorta was between 10–15%.

The mechanical properties of arteries are described as the stiffness of the arterial wall expressed as pressure strain elastic modulus (Ep) or stiffness (β). Pressure strain modulus (Ep) was defined according to Peterson et al. (1960) as:

\[
E_p = K \times \frac{P_{\text{systolic}} - P_{\text{diastolic}}}{D_{\text{systolic}} - D_{\text{diastolic}}} / D_{\text{diastolic}}
\]

From the equation above it is obvious that E_p is pressure-dependent because of the non-linear pressure/diameter behaviour of the arterial wall. This somewhat limits its use. Hayashi et al. (1980) established a relation for calculation of distensibility in vitro that is less dependent on pressure and based on the observed linear relation between the logarithm of relative pressure and distension ratio. The slope of this exponential function was called β or stiffness. This characterises the entire deformation behaviour of the arterial wall without pressure dependence in the physiological range. This stiffness index was later modified and used in vivo by Kawasaki et al. (1987). The lesser pressure dependence of β compared with E_p has later been verified by Länne et al. (1992) and Sonesson et al. (1993). Stiffness (β) was defined as:

\[
\text{Stiffness} = \frac{\ln(P_{\text{systolic}}/P_{\text{diastolic}})}{(D_{\text{systolic}} - D_{\text{diastolic}}) / D_{\text{diastolic}}}
\]

In the equations for both E_p and β, P_{systolic} (mmHg) and P_{diastolic} (mmHg) are the maximum systolic and end-diastolic blood pressure levels, respectively. D_{systolic} (mm) and D_{diastolic} (mm) are the corresponding vessel diameters. E_p is measured in N/m². The factor for converting mmHg to N/m² in the equation for E_p is (K) = 133.3.

Arterial blood pressure was measured by the auscultatory method with a sphygmomanometer on the left upper arm immediately after measurement of the pulsatile aortic and carotid diameter. This was approximated as central blood pressure. It is well known that arterial pressure waves undergo transformation, with peaks more prominent as the waves travel further from the heart. This might induce some error. However, these differences in central and peripheral pressures are reduced and disappear at older ages. Earlier investigations by us found that pressure, measured by the auscultatory method in the brachial artery rather than direct in the abdominal aorta, leads to a systematic underestimation of E_p and β by 15–20%. No difference in relation to age and gender was observed, justifying the pressure approximation used.
Table 1. Data obtained from the ultrasonic echo-tracking examination of the individuals with Ehlers-Danlos syndrome

<table>
<thead>
<tr>
<th>Family</th>
<th>EDS subtype</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Aortic mean diameter (mm)</th>
<th>Carotid mean diameter (mm)</th>
<th>Aortic $E_p$ (10$^5$ Nm$^{-2}$)</th>
<th>Carotid $E_p$ (10$^5$ Nm$^{-2}$)</th>
<th>Aortic $\beta$</th>
<th>Carotid $\beta$</th>
<th>MAP (mmHg)</th>
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<td>34</td>
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<td>5.10</td>
<td>102</td>
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<tr>
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<tr>
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<td>0.64</td>
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</table>

Each individual was examined three times, with calculation of $E_p$ and $\beta$ from the corresponding diameter, pulsatile aortic diameter change and blood pressure.

**Statistics**

Two methods were used for the statistical analysis. The first method employs confidence intervals (CI). Analyses of non-linear regression with 95% confidence intervals for individual prediction were used to define the normal ranges for $E_p$, stiffness, diameter and blood pressure in the healthy reference population according to age and gender. The results from the male and female subjects with EDS were compared with these confidence intervals. The second method uses analysis of covariance (ANCOVA) between the subjects with EDS and the healthy reference population. $p<0.05$ was considered significant.

**Results**

The data on diameter, blood pressure, pressure strain elastic modulus ($E_p$) and stiffness ($\beta$) in the infrarenal aorta and common carotid artery, respectively, as well as the echocardiographic findings relating to the subjects with EDS, are compiled in Table 1.

**Echocardiography**

Echocardiography revealed a small aortic insufficiency without any clinical symptoms in three of the 12 subjects investigated. No sign of aortic root dilatation was found.

**Aortic and carotid diameter**

There was no difference in infrarenal aortic or common carotid artery diameter in subjects with EDS compared with the reference population (mean ± 95% CI). No significant difference in aortic diameter was shown in males ($p=0.66$) nor in females ($p=0.27$) as analysed by ANCOVA adjusted for age, sex and differences in body surface area compared with the controls. Neither was there any difference in diameter of the carotid artery in males ($p=0.36$) nor in females ($p=0.46$) as analysed by ANCOVA adjusted for age and sex.

**Aortic stiffness ($\beta$) and $E_p$**

Figure 1 shows that stiffness ($\beta$) was unchanged in the infrarenal aorta in both males and females with EDS compared with the reference population (mean ± 95% CI). No significant difference in $\beta$ or $E_p$ was shown in males ($p=0.95$ and $p=0.81$, respectively) nor in females ($p=0.12$ and $p=0.27$, respectively), with EDS as analysed by ANCOVA adjusted for age, sex and differences in blood pressure compared with the controls.

**Common carotid artery stiffness and $E_p$**

Figure 2 shows that stiffness ($\beta$) was unchanged in the common carotid artery in both males and females with Ehlers–Danlos syndrome compared with the reference population (mean ± 95% CI). No significant difference in $\beta$ or $E_p$ was shown in males ($p=0.86$ and $p=0.93$, respectively), nor in females ($p=0.47$ and $p=0.48$, respectively) with EDS as analysed by ANCOVA.
Fig. 1. Stiffness ($\beta$) of the abdominal aorta in individuals with EDS. The solid line represents mean and the dotted lines represent upper and lower 95% confidence interval for the reference population. (\(\triangle\)) EDS type I; (\(\square\)) EDS type II; (\(\bigcirc\)) EDS type III; (+) EDS type IV.

Fig. 2. Stiffness ($\beta$) of the common carotid artery in individuals with EDS. The solid line represents mean and the dotted lines represent upper and lower 95% confidence interval for the reference population. (\(\triangle\)) EDS type I; (\(\square\)) EDS type II; (\(\bigcirc\)) EDS type III; (+) EDS type IV.

Blood pressure

In males with EDS no significant difference in mean arterial ($p=0.28$), systolic ($p=0.70$) or diastolic ($p=0.22$) pressure was observed as analysed by ANCOVA adjusted for age.

In females with EDS, mean arterial pressure was increased to 108% of predicted normal values ($p=0.025$). Systolic and diastolic pressure showed no significant difference ($p=0.06$ and $p=0.06$, respectively) as analysed by ANCOVA adjusted for age.
Ehlers-Danlos Syndrome

Discussion

Ehlers-Danlos syndrome is a rare condition with an overall incidence of 1/150 000. In the potentially life-threatening types, EDS type I with occasionally arterial ruptures and EDS type IV with frequent ruptures, it is even more rare, with an incidence of 1/650 000 and 1/5 million, respectively.

The mechanical properties and integrity of the wall of large elastic arteries are mainly determined by the matrix components of the wall. These are predominantly elastin, collagen and smooth muscle cells. Elastin and collagen determine the passive mechanical properties, whereas smooth muscle cells have the potential to contract and relax with modulation of wall mechanics. The latter is probably of no practical importance in large elastic arteries. The distensible elastin is load-bearing at low pressures and the much stiffer collagen at high pressure, giving rise to the non-linear pressure diameter curve. Thus, it is clear that the collagen-to-elastin ratio is the principal determinant of wall mechanics. However, as only a minor part of the collagen is load-bearing in the physiological pressure range, the amount and function of elastin compared with collagen will probably have the largest impact on the outcome of the measurements. Earlier investigations of wall mechanisms have shown a relation between elastin content and arterial stiffness.

The basic defect in EDS is different collagen abnormalities, which may arise either from a gene mutation or enzymatic defects during synthesis. In EDS type IV the amount of collagen III is decreased. This type of collagen compromises only one-third of the media collagen, but it is the more extensible collagen and therefore important in resisting pulse pressure. Dobrin (1989) treated arteries with elastase and/or collagenase and showed that elastin failure leads to dilatation, while collagen failure leads to rupture. This shows that collagen provides the tensile strength and prevents excessive distension and rupture of the vessel.

No significant signs of defect wall mechanics were detected in the EDS population. This might be due to the fairly low number of patients investigated. However, not even a tendency was noted (Figs 1 and 2). The same was true in the investigated EDS types I and IV, which have the highest risk of arterial ruptures. Previous reports on the mechanical properties of large arteries in EDS for comparison in the literature are sparse. Both Child (1981) and Francois (1986) used pulse wave velocity (PWV) as an indicator of wall mechanics. Their results indicated a more distensible arterial wall in EDS. However, an indirect method was used, measuring the overall distensibility of the arterial tree, and cannot directly be equated with our measurements.

A tentative explanation of our data might be that collagen abnormalities in the arterial wall are more difficult to detect in regard to changed vessel wall movements, at least in the physiological pressure range. However, it is possible that if the study had been conducted during a hypertensive state, that is with recruitment of more collagen fibres, the defects might have been detected. Powell et al (1991) demonstrated an increased stiffness of AAA with a defect in the collagen III gene compared with AAA, where no gene mutation could be proved. However, they did not report if there were any differences in elastin content between the two groups of AAA. A difference in elastin content might be an alternative explanation of their findings.

In conclusion, this investigation could not demonstrate any change in wall mechanisms as a sign of disturbed vessel wall integrity of elastic arteries in individuals with EDS in the physiological pressure range. This might indicate that the structural defect in their arterial walls, and thus the tendency to vessel fragility, can only be revealed at supraphysiological pressures.

Acknowledgements

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