Journal of the Mechanical Behavior of Biomedical Materials 77 (2018) 1–11

Contents lists available at ScienceDirect

Journal of the Mechanical Behavior of Biomedical Materials

journal homepage: www.elsevier.com/locate/jmbbm

Effects of clinico-pathological risk factors on *in-vitro* mechanical properties of human dilated ascending aorta

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ARTICLE INFO

Keywords:
Aneurysms
Ascending aorta
Clinico-pathological risk factors
Tissue mechanical properties
Uniaxial tensile tests

ABSTRACT

Ascending aorta aneurysms (AsAA) are associated with a degeneration of the aortic wall tissue, which leads to changes in tissue mechanical properties. Risk factors for the development of the AsAA disease are recognized in patient age and gender, valve type, hypertension, diabetes mellitus, smoking history, and a prior diagnosis of Marfan syndrome. The present study aims to assess how such clinico-pathological factors can affect the mechanical properties of human dilated ascending aorta. Specimens of AsAA are excised from 68 patients who underwent elective AsAA surgical repair and stretched until rupture during the execution of uniaxial tensile tests. Experimental stress-stretch curves are used to determine tissue mechanical properties (stress and stretch at failure point and at transition point, low and high elastic modulus). Data are divided into groups according to region (anterior *vs* posterior), direction (circumferential *vs* longitudinal), and then according to age (young *vs* old), gender (male *vs* female), valve type (tricuspid aortic valve, TAV, *vs* bicuspid aortic valve, BAV), and presence of hypertension, diabetes mellitus, and/or Marfan syndrome (*yes*/*no*). Moreover, data are grouped according to the critical value of body mass index (BMI), maximum AsAA diameter, and aortic stiffness index (ASI), respectively. Finally, a non-parametric statistical analysis is performed to find possible significant differences and correlations between mechanical properties and clinico-pathological data. Our results confirm the anisotropy and heterogeneity of the AsAA tissue and highlight that ageing and hypertension make the AsAA tissue weaker and less extensible, whereas the valve type affects the tissue strength with higher values in BAV than in TAV patients. No effects of gender, critical BMI, critical maximum AsAA diameter, critical ASI, smoking status, and presence of diabetes mellitus, and Marfan syndrome are evidenced.

1. Introduction

Ascending aorta aneurysm (AsAA) is a progressive and localized dilatation of the first part of the aorta. Usually, such a dilatation takes many years to develop remaining silent until the appearance of catastrophic complications, e.g., aortic dissection and/or aneurysm rupture. The presence of genetic mutations (e.g., Marfan syndrome (Gott et al., 1999; Brooke et al., 2008; Lindeman et al., 2010)), connective tissue disorders (e.g., Ehler Danlos disorders (Coady et al., 1999; Chu et al., 2012; Hamaoui et al., 2012)), and/or congenital cardiovascular conditions (e.g., bicuspid aortic valve (Tadros et al., 2009; Siu and Silversides, 2010; Bilen et al., 2012; Plaisance et al., 2012; Verma and Siu, 2014)) seem to accelerate the genesis and growth of the aneurysm. Clinico-pathological risk factors for the development of the AsAA disease are recognized with a general consensus in patient age, gender, smoking status, presence of hypertension, diabetes mellitus, severe atherosclerosis, and a positive family history (Virmani et al., 1991; Sawabe et al., 2011; Çetin et al., 2012; Howard et al., 2013).

The standard treatment for the AsAA disease is the replacement of the dilated part of the aorta by surgical repair. The optimal timing of surgical intervention is established by experienced clinicians and surgeons after a balance between the risk of complications involved in the surgery and the risk of the AsAA rupture (Dapunt et al., 1994; Ergin et al., 1994; Kouchoukos and Dougenis, 1997; Elefteriades, 2002). Most of the international guidelines recommend elective surgery when the aorta reaches a diameter of 5.5 cm (Davies et al., 2002; Elefteriades and Farkas, 2010) or a lower value in presence of co-morbidities, e.g., 4.5 cm in patients with Marfan syndrome (Roman et al., 1993) and 4.0 cm in patients with Loeys-Dietz disease (Loeys et al., 2006). Alternatively, Davies et al. (2006) recommend elective surgery when the aortic size index, which takes into account both maximum aortic diameter and body surface area, is greater than 2.75 cm/m^2.

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http://dx.doi.org/10.1016/j.jmbbm.2017.08.032
Received 22 May 2017; Received in revised form 24 August 2017; Accepted 28 August 2017
Available online 31 August 2017
1751-6161/

However, the previous mentioned criterion disregard the knowledge of tissue mechanical properties which, on the contrary, could be helpful in the prediction of the AsAA rupture and in the selection of the more appropriate time for elective surgery (Dobrin, 1989; Fillinger et al., 2003; Fillinger, 2007).

In this regard, it is known that the AsAA formation is characterized by a structural degeneration of the tissue resulting from alterations in the content and in the concentration of both elastin and collagen fibers (Tang et al., 2005; Tsamis et al., 2013). Such a tissue degeneration leads to changes in the related mechanical properties inducing decreased local strength and increased wall stresses favouring dissection and/or rupture phenomena.

As previously mentioned, it is also known that genetic and cardiovascular risk factors are also implicated in the development and in the progression of AsAA. For example, it is shown that patients with a bicuspid aortic valve, BAV, (i.e., a congenital cardiovascular anomaly occurring when two of the three valve leaflets fuse into one) are more likely to develop AsAA than patients with a tricuspid aortic valve, TAV, (i.e., patients without such a valve anomaly) (Losenno et al., 2012; Abdulkareem et al., 2013). Moreover, the high prevalence of hypertension in patients with AsAA induces to consider the hypertension as an additional factor for the development of AsAA (Howard et al., 2013). However, the precise role of clinico-pathological risk factors in altering AsAA mechanical properties is not well understood.

Moving from such considerations, the present study aims to fill such a gap by determining the possible effects of clinico-pathological risk-factor on the *in vitro* mechanical properties of dilated human ascending aorta. In particular, we consider the following clinical data: patient age, gender, body mass index, maximum AsAA diameter, aortic size index, valve type and the presence of hypertension, diabetes mellitus, smoking history, and a prior diagnosis of Marfan syndrome. The testing procedure, suited to mechanical characterization, is carried out by using the same protocol adopted in a previous work of our group (Ferrara et al., 2016), which mainly focused on the detection of regional/directional differences in the mechanical response of the AsAA tissue. Herein, in addition to peak strain, peak stress and maximum elastic modulus (related to the stiff region of the tensile curve), we also compute the low elastic modulus (related to the initial compliant region of the tensile curve) and the so-called *transition point* between the compliant and the stiff regions (Guinea et al., 2010; García-Herrera et al., 2012; Babu et al., 2015). The previous mentioned local mechanical properties are easily understood by clinicians for their direct mechanical significance and even more useful for analysis on AsAA groups. Then, we perform comparisons/correlations between clinical data and mechanical properties by a non-parametric statistical analysis. The reliability of the present results is also improved by the consistent enlargement (of about 42%) of patient database than our previous work.

To the author's knowledge, this is the first study documenting at the same time the size effects of a large number of clinico-pathological on different *in-vitro* mechanical properties of AsAA tissue. It is hoped that the present work may provide a valid contribution to a better understanding of the role of clinico-pathological factors in altering aortic mechanical properties of the AsAA tissue, and an improved clarification of the causes of aortic dissection and/or rupture.

2. Materials and method

2.1. Clinical data

The present study includes 68 patients (where the first 46 were considered in our previous study (Ferrara et al., 2016)) who underwent elective AsAA surgical repair at IRCCS Policlinico San Matteo of Pavia, Italy, between May 2013 and December 2016.

Clinical data of considered patients, as age, gender, maximum preoperative AsAA diameter, body weight and height are collected from clinical charts. In particular, the maximum AsAA diameter is measured at the systolic condition during the echocardiography or computed tomography exams. Given patient's body weight and height, the body surface area (BSA) is computed with the formula of Du Bois and Du Bois (1989): BSA $[m^2] = 0.20247 \times height\ [m]^{0.725} \times weight\ [kg]^{0.425}$, whereas the body mass index (BMI) is calculated as: BMI $[kg/m^2] = weight$ [kg] divided by *height* [m] $\times$ *height* [m], and the aortic size index (ASI) as Davies et al. (2006): ASI $[cm/m^2] = maximum\ AsAA\ diameter$ [cm] divided by *BSA* $[m^2]$. Clinical data include also positive smoking status, presence of tricuspid or bicuspid aortic valve (TAV *vs* BAV), presence or not of hypertension, diabetes mellitus, or a prior diagnosis of Marfan syndrome.

2.2. Mechanical characterization

The experimental procedure, for mechanical characterization, is conducted at the Department of Civil Engineering and Architecture of the University of Pavia within 12–24 h from surgery. The use of human tissues is approved by the Ethical Committee of IRCCS and informed consent is obtained from patients.

2.2.1. Testing procedure

Preparation and testing procedure is carried out by the same operator according to a standard protocol useful for biological materials. More details on the adopted procedure can be found in our previous study (Ferrara et al., 2016). In the following, we outline the main aspects.

A tubular portion of ascending aorta is harvested above the sino-tubular junction from each patient during surgical repair, stored in isotonic physiological solution, and kept in a refrigerator at 4 °C until specimen preparation and mechanical testing. After equilibration at

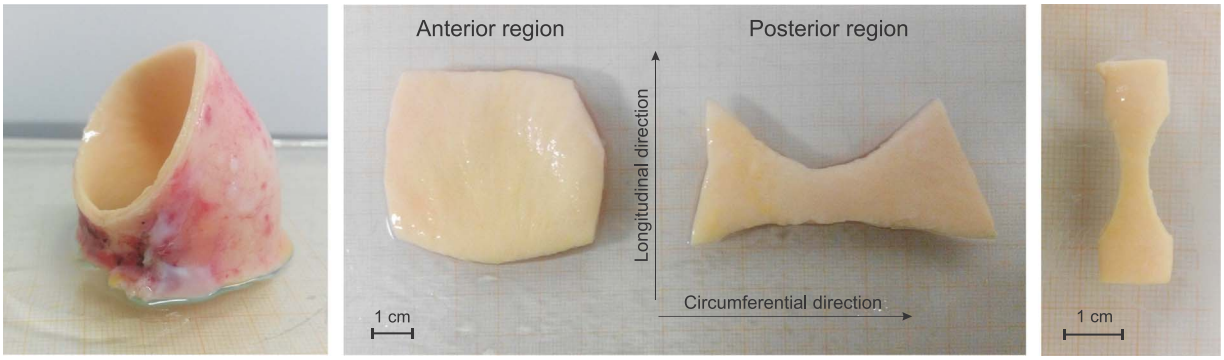

Fig. 1. Representative pictures of (a) fresh tubular sample of dilated ascending aorta (AsAA), (b) anterior (A) and posterior (P) regions excised from the tubular sample, (c) dog-bone-shaped specimen excised in the circumferential (C) and longitudinal (L) directions from the two regions.