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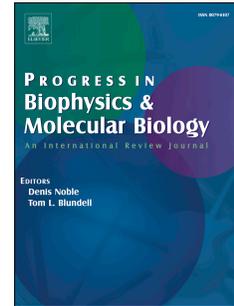
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## Biomechanical Property and Modelling of Venous Wall

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## Abstract

Human saphenous vein has long been used as coronary artery bypass grafts to survive a heart arrested by blocked coronary arteries. Biomechanical properties of the saphenous vein can be critical because mismatch in the biomechanical property between a coronary artery and a graft will reduce graft patency and speed up disease development in the graft. In this paper hence the active and passive biomechanical behaviours of the human saphenous vein and other venous walls were reviewed extensively and comprehensively. The existing *in vitro* uniaxial, bulge, planar and tubular biaxial tensile testing methods, *in vivo* testing cases, property variables, various tested results, constitutive models and their mathematical modelling methods, viscoelasticity, and residual strain/stress are highlighted and summarized. It is demonstrated that the biomechanical properties of the human saphenous vein and other venous walls are not well documented, and their modelling approaches are limited and subjected to be updated in a great deal. Additionally, a few important research issues are proposed. The paper has provided a piece of useful information to investigation into coronary artery bypass grafts.

Keywords: saphenous vein; uniaxial tensile test; tubular biaxial inflation test; coronary artery bypass graft; residual strain; constitutive law

## 49 1 Introduction

50 Coronary artery disease (CAD) is an important cause of mortality all over the world. Human  
51 great saphenous vein (GSV) frequently serves as coronary artery bypass graft (CABG) to treat CAD  
52 because it easily is harvested and handled and without allograft rejection. Even though this idea can  
53 be traced back to 1930's [1], the direct coronary artery surgery by using CABG technique began  
54 actually in 1968 in the USA [2]. Currently, nearly 20,000 CABGs are carried out every year by NHS  
55 mainly to treat old people with age of at least 60years in England [3].

56 The GSV is a large, subcutaneous, superficial vein of the human leg. The vein runs along the  
57 length of the lower limb, as shown in Fig. 1(a). A segment of GSV can be cut off and used to bridge  
58 the blocked coronary artery and the aorta and form a bypass duct, see Fig. (b), eventually the blood  
59 can flow into the coronary artery to make the heart working properly.

60 Unfortunately, saphenous vein CABG has to experience an arterialization process after the  
61 surgery. In the process saphenous vein CABG can be failure and subsequent remodelling as well as  
62 develop various diseases such as aneurysms, thrombosis, atherosclerosis and fibro-intimal hyperplasia  
63 [6-10] which are associated with smooth muscle cells and extracellular matrix. In the first post-  
64 surgery month, 13-14% of grafts occlude because of thrombosis. By the end of the first year of the  
65 surgery, intimal hyperplasia develops to reduce graft diameter by 25-30%. In the following years,  
66 grafts occlude at a rate of 2% per year as intimal hyperplasia develops. Beyond 5years, vein grafts are  
67 in atherosclerosis due to necrosis, haemorrhage, calcification and thrombosis [10].

68 The failure and disease are closely linked to CABG physiological hemodynamic conditions  
69 [11] and GSV itself mechanical property such as compliance [12]. Up to now, a significant amount of  
70 review papers have appeared to clarify the problems in pathology, surgery and hemodynamic factors  
71 associated with saphenous vein CABGs, such as [6-11], just to name a few.

72 Additionally, there are a few review papers on artificial vascular grafts. The textile structures  
73 used in the construction of artificial vascular grafts were reviewed in detail and the structural factors  
74 relating to the failure of vascular grafts were identified [13]. The material properties and methods for  
75 determining the attributes of these factors to the failure are emphasized for further research. The  
76 mechanical mismatch of the artificial small-diameter vascular graft to the host vessel was reviewed  
77 and discussed [14]. It was pointed out that detailed characteristics, like anastomic behaviour,  
78 longitudinal elasticity, and flow-related variables should be taken seriously. Mismatch in compliance  
79 and diameter at the end-to-end anastomosis of a compliant artery and rigid artificial graft was  
80 reviewed comprehensively because the mismatch could result in shear rate disturbances to induce  
81 intimal hyperplasia and ultimately graft failure [15]. How mechanical properties, for example  
82 compliance mismatch, diameter mismatch, Young's modulus and impedance phase angle influence  
83 graft failure owing to intimal hyperplasia was discussed. The principal strategy was proposed to  
84 prevent intimal hyperplasia based on the design and fabrication of compliant synthetic or innovative

85 tissue-engineered grafts with viscoelastic properties similar to those of the human artery. A broad  
86 overview of the current state of prosthetic bypass grafts was conducted [16] and it was shown that  
87 prosthetic materials were most commonly used in high pressure, large flow conditions, such as the  
88 aorta and femoral arteries, but had not been as successful in other regions like carotid and coronary  
89 artery bypass surgeries. A new generation of polymers like polyurethanes should be used promptly.

90 A literature survey made by us with PubMed showed that a little attention has been paid upon  
91 biomechanical properties of GSV since 1960's. In consequence, there has not been such a paper to  
92 review the biomechanical properties of venous walls with an emphasis on GSVs so far. In this  
93 contribution, an attempt is made to summarize and interpret existing experimental and analytical  
94 results of the biomechanical properties and modelling methods of native venous walls. At first, the  
95 histology of venous wall is described briefly; then biomechanical properties of venous wall, including  
96 active tension, passive biomechanical properties are demonstrated and discussed; thirdly the methods  
97 for modelling the passive biomechanical properties are highlighted and summarized; finally need for  
98 further research and conclusions are drawn. The paper can be meaningful for biomechanical property  
99 identification, design of CABG, and biomechanical property modelling of veins.

## 100 **2 Histology of venous wall**

101 In average, the human vein is with 5mm diameter and 0.5mm thickness compared with the  
102 artery in 4mm diameter and 1mm thickness [17]. A healthy human saphenous vein wall consisted of  
103 three layers, namely intima, media and adventitia from inner to outer surface of the wall [18-21].  
104 Generally, the intima was thin as  $60.07\mu\text{m}\pm 1.12$ , composed of endothelium and an internal elastic  
105 lamina next to the media. The media mean thickness was  $360.54\mu\text{m}\pm 4.56$ , in which there were  
106 longitudinally oriented and smooth muscle cells next to the intima and circular smooth muscle cells  
107 next to the adventitia, the two smooth muscle layers were separated by a collagen fibres. The  
108 adventitia was full of collagen fibres with some fibroblasts and capillaries as well as longitudinally  
109 oriented smooth muscle cells [21].

110 A detailed image of layer structure of blood vessel in the transverse section [17] is illustrated  
111 in Fig. 2. The intima is separated from the media by a thick elastic lamina. The intima is composed of  
112 single layer endothelial cells. The adventitia is separated from the media by another thick elastic  
113 lamina. The adventitia consists of dense collagen fibres, a few fibroblastic cells, occasional elastic  
114 fibres and vasa vasorum. The media has alternating layers of smooth muscle cell, elastin and collagen.  
115 Collagen appears to be blended with the elastin fibres. The smooth muscle cells connect with each  
116 other forming circumferential bundles. The smooth muscle cells link with the collagen and elastin  
117 fibres in parallel, which is consistent with the observation in [22]. Proteoglycans (PG) are the densest  
118 in the media than in intima and adventitia.

119 Presently, there is little information about collagen fibre orientation and dispersion in the  
120 human saphenous vein. A mean fibre orientation of  $37\pm 6^\circ$  against the circumferential direction in the

121 media [23] in comparison with  $40^\circ$  in porcine vascular tissues (including vena cava, abdominal aorta  
122 and iliac artery) was observed [17]. In the adventitia of the porcine vascular tissues, the fibre mean  
123 orientation was  $60^\circ$  from the circumferential direction [17], see Fig. 3.

124 Collagen fibres were wavy at zero-load, and then they became straight with increasing load  
125 [24]; this is so-called fibre recruitment mechanism for the engagement of tension. Waviness index  
126 (WI) and its probability density distribution are of vital importance for describing the recruitment  
127 mechanism of fibres. WI was defined as the ratio of the length of an elastin lamella to the straight line  
128 distance between two reference points [24]. In the rabbit aortic media, WI decreased to 1.05 at  
129 80mmHg transluminal pressure or more from 1.65 at zero pressure [24].

130 For the rabbit descending thoracic aorta, left common carotid artery (between its origin and  
131 carotid bifurcation), inferior vena cava (thoracic segment), and external jugular (on the same side and  
132 height as the carotid artery), the WIs of elastin in media and adventitia and the WI of collagen in  
133 media were measured optically at zero-load state [25]. It was found that WI of collagen was 1.2 in the  
134 aorta and carotid artery, but 1.57 in the inferior vena cava and jugular vein. WI of elastin in media and  
135 adventitia showed a little difference, it was 1.1 in the aorta and carotid artery, but increased to 1.42 in  
136 the inferior vena cava and jugular vein.

137 The orientation and WI of collagen fibres in media and adventitia of the human inferior vena  
138 cava were measured optically [26]. The collagen fibres were distributed circumferentially in the  
139 media but longitudinally in the adventitia. The mean WI of collagen fibres was 1.24 compared with  
140 1.57 in the rabbit jugular vein [25] and 1.25 in the rabbit carotid artery adventitia [27]. Further, the WI  
141 stochastic distribution in the media adventitia could be best fitted by using Weibull, Gama and Beta  
142 probability density distributions, respectively.

143 The dry weight contents of collagen, elastin and smooth muscle in walls of the man aorta and  
144 femoral vein, saphenous vein were measured chemically [28], and the femoral vein is subject to a  
145 double high collagen content and one third elastin content as well as 5% less smooth muscle content  
146 in comparison with the aortic wall, see Fig. 4(a). In the wall of the super segment of saphenous veins,  
147 the contents of collagen, elastin and smooth muscle are basically identical to the femoral vein for the  
148 subjects at different ages, as shown in Fig. 4(b).

149 Recently, volume fractions of collagen and elastin were measured in the porcine aorta, carotid,  
150 iliac and vena cava, are shown in Table 1 [17]. The total collagen volume fraction in the vena cava is  
151 higher than those in aorta, carotid and iliac artery, but the elastin in the vena cava seems to close to  
152 the aorta and less than carotid iliac artery. In media, the content of collagen is less than those in aorta,  
153 carotid and iliac artery. The content of collagen in the adventitia is higher than in the adventitia of  
154 aorta, carotid and iliac artery. Thus, the vein will be more compliant at a small strain, but stiffer at a  
155 large strain.

156 For the rabbit descending thoracic aorta, left common carotid artery, inferior vena cava, and  
157 external jugular vein, the area fractions of collagen, elastin and smooth muscle in them were measured

158 [25] and listed in Table 2. Clearly, the venous walls are subject to higher collagen content but lower  
159 elastin and smooth muscle contents compared with the arteries.

160 The contents of collagen I, III and IV and elastin in the human femoral vein (FV),  
161 incompetent saphenous vein (ISV) and competent saphenous vein (CSV) were measured by using  
162 computer-image-analysis system connected to a microscope based on immunohistochemically  
163 staining technique in terms of area fraction occupied by collagen or elastin in transverse sections [29].  
164 The area fractions of these vein samples are tabulated in Table 3. ISV is subject to the highest elastin  
165 content and the least compliance in comparison with CSV.

166 Note that collagen content in healthy venous walls is different from diseased venous walls.  
167 For example, the long saphenous vein was subject to a low level of collagen content than in varicose  
168 veins [30, 31].

### 169 **3 Biomechanical properties of venous wall**

170 Like the biomechanical properties of arterial tissue, the biomechanical properties of venous  
171 wall consist of active behaviour and passive characteristics. The active behaviour is associated with  
172 the contraction of smooth muscle cells in the wall under a stimulus. The contraction can induce the  
173 other tissue components such as elastin and collagen fibres are in tension to raise the  
174 transmural/transluminal pressure level. The passive characteristics of venous wall stand for the  
175 hyperelasticity and viscoelasticity of the wall under a transmural pressure and at an axial stretch when  
176 a stimulus is absent.

#### 177 **3.1 Active biomechanical property**

178 Because venous wall has smooth muscle, it naturally can generate contracting tension.  
179 Usually, the active contracting behaviour of venous wall is characterized *in vitro* by means of  
180 mechanical or electrical or chemical stimuli on a strip harvested from a venous wall under isometric  
181 or isotonic conditions. Until 1960's, observations on the active contracting are not quantitative  
182 basically. For example, a very early observation on active contraction of venous wall was made in  
183 1902 [32]. Arteries from 35 oxen and a considerable number of horses, cats and men were examined  
184 with various stimulators such as freezing, heating, bathing of olive oil and so on. Like arteries, jugular  
185 vein could respond to stimuli generated by these stimulators, exhibiting an active contraction.

186 Helically cut strips of the cat portal vein were stretched isotonicly with and without  
187 norepinephrine, epinephrine, isoproterenol, K ion and so on, it was confirmed that these chemicals  
188 could induce venous smooth muscle to contract [33]. The same experimental method was applied into  
189 helically cut strips of the cat portal vein as well [34], it was identified that the intracellular  
190 concentration level of calcium ion exhibited a key effect on determining resistance of smooth muscle  
191 to stretch. In [35], the contractile properties of spiral strips and isolated segments of the lateral  
192 saphenous vein of the dog were studied with electrical stimulation. Stimulation could make length-

193 load or pressure-volume curves stiffer, and the active tension first increased with progressive stretch,  
194 but it reduced when the specimens were overstretched. In [36], strips of the dog saphenous vein were  
195 examined and it was found that they could contract during warming (43°C) and relaxed a little during  
196 cooling (to 29°C). Spontaneous rhythmic contractions were observed in a few preparations of the  
197 human isolated saphenous veins from old subjects (>60 years) [37]. These experimental facts  
198 suggested that contraction of saphenous veins was related to intracellular  $\text{Ca}^{2+}$  signalling which was  
199 involved smooth muscle [38-40], and might be modelled by using methods proposed in [41-43].  
200 However, there has been no investigation into active contraction of saphenous vein so far.

201         Adaptation of active contraction of saphenous vein along with smooth muscle cell orientation  
202 in arterial circulation after CABG surgery is another key important issue. In [44], a segment of the  
203 canine saphenous vein was used as arterial graft, and its thickness and content of all measured  
204 proteins increased but the maximum contractile response decreased. Additionally, the response  
205 characteristics of saphenous vein grafts to various medicines in arterial flow condition have been  
206 clarified by a number of researchers [45-50]. However, these interesting outcomes are belong to  
207 biochemical subjects and out of the scope of this paper, thus have to be omitted here.

## 208 **3.2 Passive biomechanical property**

209         Passive biomechanical property of venous wall is composed of two properties, namely  
210 hyperelasticity and viscoelasticity. The hyperelasticity can be achieved by preconditioning *in vitro*  
211 only and is independent of stain rate, and eventually can be described by a constitutive law. Such a  
212 law can be presented by capacity or compliance, pressure-diameter/radius relationship, incremental  
213 Young's modulus, stress-stretch/strain relationship and strain energy function etc., depending on the  
214 level of our understanding of the subject and our interests. The viscoelasticity is a passive property of  
215 a venous wall *in vivo* or *in vitro* without preconditioning. This property cannot be represented by a  
216 constitutive law for hyperelasticity alone; instead both strain rate and time-history effects should be  
217 considered together.

### 218 **3.2.1 The hyperelasticity property**

219         Usually, the hyperelasticity property of venous wall is characterized experimentally *in vitro*.  
220 The experimental methods include tubular simple inflation test, biaxial inflation test, and uniaxial  
221 simple/tensile test as well biaxial tensile test. The tubular simple inflation test started in 1960's. In the  
222 experiment, a blood vessel segment was isolated from the organ, the one end of the segment was  
223 closed and the other end was connected to a tube. The segment was immersed in the saline in a basin  
224 and inflated with a positive pressured fluid through the tube, and only the diameter of the segment  
225 was recoded manually at each experimental transluminal pressure. A typical tubular simple inflation  
226 experimental apparatus can be found in [51]. Based this method, compliance, pressure-  
227 diameter/radius relationship, global and incremental Young's moduli of a venous wall can be obtained.

228 It was worthy of mentioning that an apparatus was designed to measure dynamic compliance  
229 of blood vessel by using a sensor, i.e. a miniature elastic cantilever beam *in vivo* [52].

230 As an updated version of tubular simple inflation experiment, in the latter of 1960's, a few  
231 biaxial inflation approaches, namely bulge method [53, 54] and vessel segment inflation method [55-  
232 58], were designed to identify the biaxial biomechanical properties of the vessel. In the bulge method,  
233 a flat piece of a vessel was fixed between two plates, which had a circular hole and were mounted on  
234 a rigid container. The container was inflated with a positive pressure and the flat piece forms a dome-  
235 shaped bulge. The dome was approximated by a part of a sphere and the tension or the Cauchy stress  
236 was calculated from the Young-Laplace's law for sphere. The radius of the sphere could be  
237 determined with optically measured displacements of the markers on the dome surface [53], or  
238 estimated with the instant liquid volume delivered by the infusion pump and the measured apex height  
239 as well as the radius of the hole [54].

240 In principle, if the sphere approximation is held, the bulge method is applicable for isotropic  
241 elastic materials *in vitro* only. Recently, the method has been utilized to identify anisotropic soft tissue  
242 by employing both a high resolution approach for measuring strain field and a complicated numerical  
243 method for dealing with mechanics model to extract biomechanical properties [59, 60].

244 During vessel segment inflation tests [55-58], both the diameter and the length of the segment  
245 were recoded simultaneously, the tests could capture the biaxial deformation feature in the vessel. In  
246 the vessel segment inflation method of [55], the segment was in dry air, however, in the segment  
247 inflation method of [56-58], the specimen was immersed horizontally in a liquid basin to make  
248 experimental temperature controllable.

249 Vessel segment inflation tests are subject to a few limitations, namely complex equipment,  
250 tedious testing procedure and being difficult to capture the break/fracture behaviour of soft tissue.  
251 Hence, since 1970's uniaxial simple/tensile testing method has emerged. In the method, one specimen  
252 is a ring cut from a vessel and is used to show the mechanical property in the circumferential direction,  
253 the other specimen is a segment [61] or a strip sample [62-64] harvested from the vessel  
254 longitudinally. Then two specimens are stretched on a material testing machine, respectively.

255 In uniaxial tensile tests, the soft tissue is stretched in the loading direction only, in the two  
256 transverse directions, however, the tissue is compressed, and in consequence the fibres in the tissue  
257 are compressed in these directions as well. In order to break the specimen, the tissue must undergo a  
258 significant large stretch to achieve the fibre ultimate strength or stretch. Usually, the stretch applied is  
259 much larger than the stretch in a soft tissue under physiological conditions.

260 To remove the limitation of uniaxial tensile test, planar biaxial testing method occurred in  
261 1970's. In the test, a soft tissue specimen is in squared-shape, and is stretched in two orthogonal  
262 directions with a certain transverse extension ratio, which is the ratio of the extension in the primary  
263 direction to the extension in the transverse direction when two loadings are applied during an  
264 experiment [65, 66]. Since the tissue is stretched in both directions, the fibres in the tissue are always

265 in tension and can reach their ultimate stretch or strength very quickly with increasing two stretches  
 266 applied. In fact, we don't exactly know what the extension ratio is when a soft tissue works under  
 267 physiological conditions. Therefore, the soft tissue has to be tested under various transverse extension  
 268 ratios. Obviously, how to specify the ratio in a biaxial tensile test for mechanical property constants  
 269 determination is an issue of test protocol [67, 68], because the mechanical property constants depend  
 270 on the transverse extension ratios [68].

271 Vessel segment inflation test mentioned above is tubular biaxial tensile test. An interesting  
 272 comparison of two typical biaxial testing methods was made [69] by using the porcine coronary  
 273 arteries. The mechanical property constants were determined based on planar biaxial tests firstly, then  
 274 applied them into the porcine coronary arteries at 0-120mmHg intraluminal pressures. It was turned  
 275 out there was a 12.3% error in pressure-diameter relation against the inflation test and the difference  
 276 in circumferential stress could be as high as 50.4% between the model and the measurements.

277 By making use of the experimental methods above, a few important characters of venous  
 278 walls, such as compliance, pressure-diameter/radius relationship, global and incremental Young's  
 279 moduli and stress-strain curve of a venous wall, have been measured and interpreted extensively in  
 280 literature. Here just a brief summary is delineated and highlighted.

### 281 1) Compliance

282 Compliance of a pressurized organ is defined as a volume change with respect to intraluminal  
 283 pressure change, i.e.

$$284 \quad C = \Delta V / V \Delta p \times 100\% \quad (1)$$

285 where  $V$  is the initial volume of the organ,  $\Delta p$  is the pressure change, and  $\Delta V$  is the change in  
 286 volume induced by  $\Delta p$  [52]. For a cylinder model of the organ, the compliance can be simplified to  
 287 the following expression

$$288 \quad C = \Delta D / D \Delta p \times 100\% \quad (1a)$$

289 where  $D$  is the initial diameter of a vessel segment and  $\Delta D$  is the change in diameter induced by  $\Delta p$ .  
 290 In [51], however, the compliance was called volume distensibility coefficient. The reciprocal of the  
 291 compliance was considered the Young's modulus of an organ segment [70]. The compliance  
 292 represents a global biomechanical behaviour of an organ simply and roughly, and has been applied in  
 293 clinical practice extensively. The compliance includes static value [51] and dynamic value that related  
 294 to the heart systolic and diastolic states [52] and can be measured *in vitro* [52, 71] and *in vivo* [72].

295 Compliance mismatch between saphenous vein graft and artery can degrade the graft  
 296 performance and result in a loss of patency, which is the degree of openness of a vessel, in term of  
 297 time after surgery [73]. The compliance of eight human femoral arteries, five types of arterial grafts  
 298 such as human GSV, Glutaraldehyde-treated human umbilical cord veins, modified bovine heterograft,  
 299 velour Dacron and expanded polytetrafluoroethylene were measured by inflating the segments of

300 these conduits on a device [74]. The compliances of the human GSV, Glutaraldehyde-treated human  
301 umbilical cord veins were  $3/4$  and  $2/3$  of the compliance of the human femoral artery, respectively.  
302 The compliance of the rest grafts was half below the compliance of the artery. Experiments were  
303 performed on a low flow canine femoral artery bypass models of femoral vein, double velour Dacron  
304 and expanded polytetrafluoroethylene (ePTFE) [75]. The compliances of dissected artery, femoral  
305 vein, double velour Dacron and PTFE were 0.074, 0.027, 0.019 and 0.016%/mmHg, respectively. It  
306 was identified that the larger the compliance was, the higher the patency was. Similarly, the  
307 compliances of poly (carbonate) polyurethane (CPU) vascular graft, artery, ePTFE, Dacron and  
308 human saphenous vein were measured under the pulsatile flow condition of a phantom *in vitro* [76], It  
309 was shown that CPU and artery were subject to 0.081 and 0.080%/mmHg mean compliances, but  
310 ePTFE and Dacron were with mean compliances as low as 0.018 and 0.012%/mmHg, respectively.  
311 The human saphenous vein had a similar mean compliance at a lower pressure than 30mmHg,  
312 however, its mean compliance dropped significantly at a pressure of 30-50mmHg, and beyond  
313 50mmHg, the compliance remained unchanged.

314 Like [15], the patency will present a linear relationship with the compliance, as shown in Fig.  
315 5 if the experimental patency and compliance are plotted together for the host artery and various kinds  
316 of grafts one year after graft surgery. A comprehensive review on compliance and its measurement  
317 methods for vascular grafts has been made in [15], and they are no longer repeated here.

318 Based on the work in [77, 78], the diameters of GSV with and without nitroglycerine were  
319 examined by using ultrasound method *in vivo* in 12 elderly and 5 young healthy men after 6min  
320 venous stasis (up to 60mmHg cuff pressure) and the compliances of GSV were calculated [79]. It was  
321 indicated that GSV compliance in the elder group was higher than the younger group. Nitroglycerine  
322 could make GSV more compliant in both groups.

## 323 2) Pressure-diameter relationship

324 The internal diameter/radius-pressure relationship is one important response of saphenous  
325 veins or arterial grafts to a series of pressures *in vitro* or *in vivo*, and it can reflect the change of  
326 passive biomechanical behaviour during arterialization. It can be used as an index of passive  
327 biomechanical property of arterial grafts in clinical application potentially.

328 The pressure-diameter relationship of GSVs harvested from the human lower leg and upper  
329 legs was tested *in vitro* in [73]. The GSV vein segments of the upper leg were softer than those of the  
330 lower leg if the pressure was lower than 50mmHg, beyond that pressure two groups share nearly the  
331 same pressure-diameter relationship.

332 The external jugular veins and femoral veins were obtained from adult cats and their volume-  
333 pressure relationship was measured *in vitro* [80]. Subsequently, the volume-pressure relations of  
334 healthy human GSVs and the GSVs from patients with varicose veins were tested *in vitro*, and it was

335 clarified that the GSVs from patients with primary varicose veins exhibited larger radii and were more  
336 distensible than the healthy GSVs [81].

337 Passive biomechanical and histological properties of dog femoral veins were investigated  
338 after their implantation as grafts to bypass the ligated femoral arteries [82]. The internal diameter of  
339 the grafts increased quickly in 4weeks after implantation. Intimal hyperplasia and medial thickening  
340 were observed in response to high blood velocity and pressure in the arterial physiological condition.

341 Before CABG surgery, GSV segments need to be distended manually with liquid solutions to  
342 increase their patency. It was demonstrated that a pressure between 150-300mmHg could result in  
343 medial damage [83].

344 The saphenous vein grafts can be implanted in situ or reversely. The effects of these two  
345 techniques were examined by measuring the elastic properties of newly implanted grafts with vessel  
346 wall Doppler tracking method [84]. The diameter and pulse pressure were recorded, and relative  
347 distension, distensibility coefficient and compliance were calculated. The elastic properties of newly  
348 implanted grafts were comparable with native artery. Compliance mismatch was found around the  
349 proximal anastomoses of the grafts reversely implanted in comparison with the graft implanted in situ.

350 The diameter-pressure relationship of GSVs harvested from the human lower leg and upper  
351 leg was tested *in vitro* [85]. The internal pressure in these samples was increased up to 150cm H<sub>2</sub>O  
352 stepwisely and the outer diameter was measured continuously with a video micrometre system in  
353 which a microscope was connected to a video camera and a monitor, the diameter was calculated by  
354 triggering dark-light transitions in the video signal. Eventually, compliance was calculated and plotted  
355 against the pressure. It was identified that the human lower leg and upper leg GSVs showed less  
356 difference either in diameter-pressure or compliance-pressure relationships, especially at a pressure  
357 more than 50cm H<sub>2</sub>O.

358 An experimental set up was built, and 25-40mm long human saphenous vein segments were  
359 inflated with a pressure up to 100kPa and an axial load ranging up to 100N. The surface deformation  
360 was tracked by tracing twelve markers in 3D space using 2 CCD cameras. Results showed that the  
361 deformation of the vein was not axis-symmetric. The loading and unloading paths were not different,  
362 and the vein was compressible [86].

### 363 3) Global and incremental Young's moduli

364 Global Young's modulus or volume stiffness is the reciprocal of the compliance,  $C$ ,  
365 mathematically [70], i.e.

$$366 E_p = V\Delta p / \Delta V \quad (2)$$

367 or the pressure strain elastic modulus or elastance [52]

$$368 E_p = D\Delta p / \Delta D \quad (2a)$$

369 Like compliance, the global Young's modulus stands for the stiffness of an organ as a whole  
370 only. The elastance of normal artery, autogenous vein graft of the dog, Dacron graft and synthetic  
371 graft material-modified human umbilical cord vein with a polyester mesh covering (DBM) were  
372 measured dynamically with a mean pressure 133mmHg *in vitro* initially, then the elastances at  
373 implantation and after the implantation for 2weeks were measured [52] and illustrated in Fig. 6.  
374 These graft materials seem stiffer than the host arterial wall and become softer after implantation.

375 The elasticity of the human vein segments harvested from autopsy material was measured in  
376 terms of global Young's modulus in five age groups such as 10-14, 20-30, 30-40, 40-50 and 50-  
377 70years by using *in vitro* vessel segment inflation experiment when the transmural pressure was in a  
378 range of 20-60mmHg, and a few *in vivo* experiments were conducted, too [70]. The global Young's  
379 modulus varied significantly in terms of subject age and decreased consistently with increasing age.

380 The incremental Young's modulus is defined as the ratio of an incremental stress to the  
381 incremental strain caused from the incremental stress at a strain

$$382 \quad E = \Delta\sigma / \Delta\varepsilon \quad (3)$$

383 where  $\Delta\sigma$  is the incremental stress, and  $\Delta\varepsilon$  is the incremental strain due to  $\Delta\sigma$ . This is a quasi-  
384 linear method to characterize a nonlinear stress-strain curve. Naturally, the incremental Young's  
385 modulus is dependent on strain itself.

386 Dog pericardium and cat mesentery were measured using the bulge method and the Cauchy  
387 stress-stretch curves were fitted by using the stress-stretch relation for rubbers [53]. The incremental  
388 Young's moduli and compliances of canine femoral and jugular vein segments were studied with the  
389 bulge method as well [54]. The compliances of the femoral and jugular veins were lower than those of  
390 the carotid artery by nearly half at an intraluminal pressure higher than 40mmHg; accordingly, their  
391 incremental Young's moduli were larger than the artery.

392 A bulge inflation device was designed and used to measure the samples of 11 patients' human  
393 saphenous vein. The bulged surface was monitored with a microscopic camera; the deformed shape  
394 was best fitted in finite element analysis (FEA) simulations of ADINA 8.8 software by assuming the  
395 Young's modulus on a trial-and-error basis by employing on the linear homogenous elastic model at a  
396 pressure such as 22, 25, 31, 37, 43, 49, 60, 72 and 84kPa [87]. The Young's moduli determined  
397 showed a rising trend with increasing internal pressure.

398 The vessel segment inflation method was used to study incremental Young's moduli of dog  
399 and man venous walls [55]. A 5-10cm segment of vein was isolated and its length and diameter were  
400 measured *in vivo*, finally dissected from a subject. Special supporting plugs were inserted into the  
401 lumen. The superior plug was with a needle to allow a pressured normal saline with 5% dextrose to be  
402 pumped into the lumen. The segment was suspended vertically from its superior plug and the *in vivo*  
403 length was restored by using a small weigh of 5g hung on the other plug. The length and diameter of  
404 the segment were monitored with a 35mm camera and in experiments when the pressure was in a

405 range of 0-200cm H<sub>2</sub>O with longitudinal forces ranging 0-20g. Based on the homogeneous, thin-  
 406 walled, cylindrical vessel segment membrane model, i.e. stresses are uniform across the wall  
 407 thickness [88], three Cauchy stress components at an intraluminal pressure,  $p$ , and a longitudinal  
 408 force,  $F$ , are estimated by using the following equations

$$409 \quad \begin{cases} \sigma_{\theta} = p(r/h - 1/2) = p(\lambda_{\theta}r_0/\lambda_r h_0 - 1/2) \\ \sigma_z = \frac{p}{2}(r/h - 1/2) + F/2\pi r h = \frac{p}{2}(\lambda_{\theta}r_0/\lambda_r h_0 - 1/2) + F/2\pi\lambda_{\theta}r_0\lambda_r h_0 \\ \sigma_r = -\frac{p}{2} \end{cases} \quad (4)$$

410 where  $\sigma_{\theta}$ ,  $\sigma_z$  and  $\sigma_r$  stand for the stresses in the circumferential, longitudinal and radial directions,  
 411 respectively, and  $r$  is the mid-wall radius,  $r = \lambda_{\theta}r_0$ ,  $r_0$  is the un-deformed mid-wall radius and  $\lambda_{\theta}$  is  
 412 the circumferential stretch, the longitudinal stretch,  $\lambda_z = l/l_0$ ,  $l$  is the segment length at a  $p$  and  $F$ ,  
 413  $l_0$  is the un-deformed length, based on the assumption of incompressibility of tissue,  $\lambda_{\theta}\lambda_z\lambda_r = 1$ , the  
 414 radial stretch is calculated by  $\lambda_r = 1/\lambda_{\theta}\lambda_z$ ,  $h_0$  is the un-deformed wall thickness.

415 Once having the stress values, two incremental Young's moduli can be calculated by the  
 416 following expressions [55]

$$417 \quad \begin{cases} E_{\theta} = (1-\nu^2) \frac{\Delta\sigma_{\theta}}{\Delta\lambda_{\theta}/\lambda_{\theta}} \\ E_z = (1-\nu^2) \frac{\Delta\sigma_z}{\Delta\lambda_z/\lambda_z} \end{cases} \quad (5)$$

418 where  $\nu$  is the Poisson ratio, and  $\nu=0.5$  for incompressible tissues. Two Young's moduli in Eq. (5)  
 419 are determined under  $\lambda_z = \text{constant}$  and  $\lambda_{\theta} = \text{constant}$  conditions, respectively. Note that a general  
 420 method for calculating incremental Young's moduli in variable  $\lambda_z$  and  $\lambda_{\theta}$  circumferences was  
 421 developed in [58], because of its linear infinite strain assumption, unfortunately, the method is no  
 422 longer popular presently.

423 According to the vessel segment inflation method above, the relationships between radius and  
 424 intraluminal pressure, incremental/tangential Young's modulus and intraluminal pressure of dog vena  
 425 cava, jugular vein were presented and compared with those of pulmonary artery, descending aorta and  
 426 carotid artery [55]. It was identified that the veins were much less flexible than the arteries, i.e. at the  
 427 same intraluminal pressure level the radius of veins was smaller than the arteries. Accordingly, the  
 428 circumferential incremental/tangential Young's modulus of the veins was much higher than the  
 429 arteries, for instance, at 50cm H<sub>2</sub>O (36.8mmHg) column height, the former was 4000kPa, but the latter  
 430 was 100kPa only.

431 The author of [89] illustrated and interpreted his *in vitro* vessel segment inflation  
 432 experimental results simply, especially the incremental circumferential Young's modulus, on the dog  
 433 vena cava, jugular vein, pulmonary artery, descending aorta and carotid artery. In the range of 0-  
 434 100cm H<sub>2</sub>O pressure, the Young's moduli of two veins were higher than the arteries.

#### 435 4) Stress-stretch curves

436 The vena cava superior, and the intrathoracic and abdominal portions of vena cava inferior  
437 excised from dogs and their stress-strain curves were measured [90]. The circumferential and  
438 longitudinal stresses,  $\sigma_c$  and  $\sigma_l$ , were fitted by the exponential functions of the circumferential and  
439 longitudinal strains,  $\varepsilon_c$  and  $\varepsilon_l$ , independently.

440 About fifty 3mm samples were cut circumferentially from segments of the human long  
441 saphenous vein at the thigh, near knee and near the ankle for normal and varicose veins and stretched  
442 on a material testing machine under moist conditions [30]. The breaking strength was obtained, and  
443 the normal veins were with 970kPa mean breaking strength compared with 490kPa breaking strength  
444 for varicose veins. At the thigh, knee and ankle, the mean breaking strengths were 1100(710), 740(48)  
445 and 50(30)kPa for the normal (varicose) veins.

446 Human saphenous and umbilical veins were obtained from patients after their CABG surgery.  
447 The longitudinal specimens and circumferential rings from the veins were measured by simple tension  
448 test, respectively [64]. The circumferential and longitudinal stress-stretch curves were fitted with a 4<sup>th</sup>-  
449 order polynomial and the maximum stress and stretch were analysed. Typical stress-stretch curves of  
450 four pairs of the human saphenous vein specimens and three pairs of the human umbilical vein  
451 samples are illustrated in Fig. 7. Both the veins are stiffer in the longitudinal direction than in the  
452 circumferential direction.

453 Saphenous vein segments (45 samples circumferentially, and 38 longitudinally) were  
454 harvested from 22 patients in whom there was excess vein after CABG surgery [91]. The longitudinal  
455 samples were in 40mm length, and the circumferential samples were 5mm wide rings. Both were  
456 stretched in the uniaxial direction in a servo-hydraulic material test system along with videocassette  
457 camera. A series of parameters, for example failure force, ultimate force, stiffness, failure stress,  
458 failure strain and modulus were decided. It was shown that the saphenous vein was stiffer in the  
459 longitudinal direction than in the circumferential direction.

460 Specimens of bovine jugular and lumbar veins harvested circumferentially and longitudinally  
461 and stretched using a custom-built saline bath in a MTS Tytron 250 material testing system [92], and  
462 results demonstrated the bovine veins were generally stiffer in the circumferential direction than in the  
463 longitudinal, as shown in Fig. 8, and the strain rate seemed to have little effect on the mechanical and  
464 failure property parameters of bovine veins, as has been observed in testing of other soft tissues.

465 Forty human saphenous vein samples were harvested after CABG surgery [93]. The planar  
466 biaxial tensile tests were conducted on the specimens from these samples. The stress-strain curves  
467 showed some degrees of anisotropy. The obtained stress-strain data were fitted with the anisotropic  
468 four-parameter Fung-type model and the five-parameter Mooney–Rivlin model. The tested data  
469 exhibited stiffer behaviour in the longitudinal direction in comparison with the circumferential

470 direction. The stretch in the circumferential direction was much higher than in the longitudinal  
471 orientation.

472 Excess segments of saphenous vein from the knee region were harvested from 15 patients that  
473 were subject to CABG surgery and measured by vessel segment inflation test in an organ bath [94],  
474 and the pressure-diameter relationship and stress-strain curves in both the circumferential and  
475 longitudinal directions were obtained. The stress-strain curve of the sample distended manually was  
476 stiffer than that without distension. Also, the longitudinal stress-strain curve was stiffer than the  
477 circumferential curve.

478 Saphenous vein segments were collected from 36 patients undergoing CABG surgery, and  
479 distended with a pressure in ranged 50-60, 75-100 and 130-150mmHg, and the ring-shaped samples  
480 were tested on a uniaxial material testing machine to get the circumferential stress-strain curves [95].  
481 It was indicated that the curves was stiffer with increasing distending pressure and micro-fibrillary  
482 damage was observed at an even low distending pressure, namely in a range of 50-60mmHg.

483 The inferior vena cava from two models used in tissue engineering: wild-type C57BL/6 and  
484 immuno-deficient CB-17SCID/bg mice was measured by using vessel segment inflation method [96].  
485 The circumferential and longitudinal stresses were fitted with the constitutive law of two-families of  
486 fibres in [97] and the law of four families of fibres in [98], respectively. Results demonstrated that  
487 inferior vena cava from the latter was considerably stiffer in the circumferential direction, both  
488 materially and structurally, even though there were a lower intramural content of collagen and similar  
489 wall thickness.

490 Three human GSV segments were inflated with an intraluminal pressure at 0.04, 0.5 and 1Hz  
491 loading rates, respectively [99], then the Cauchy stress-stretch curves were fitted with the constitutive  
492 law proposed by [97].

493 Human GSV segments were collected from patients after CABG surgery or autopsies with  
494 24h after death, then a series vessel segment inflation tests were conducted to obtain the  
495 circumferential and longitudinal stretch curves in terms of intraluminal pressure [100]. The curves  
496 were fitted by using strain energy function of [97] with residual circumferential stretch. Since the  
497 fibre orientation dispersion was not taken into account, fitted curves were slightly poor against  
498 experimental data.

### 499 **3.2.3 The viscoelastic properties of venous wall**

500 Blood vessels with collagen fibres can exhibit viscoelastic behaviour under physiological  
501 conditions. The behaviour is apparently a time lag in response to a loading applied because of the  
502 friction between molecules in the material [101]. This behaviour manifests itself in three appearances,  
503 depending on loadings and strain conditions, such as hypothesis loop for cyclic loading, relaxation at  
504 a constant strain and creep at a constant loading. The viscoelasticity can be characterized by using *in*  
505 *vivo* vessel diameter dynamic observation [101-103] and *in vitro* uniaxial tensile tests, namely

506 incremental stress-strain test [62, 63], normal stress-strain test with cyclic loading [92, 105, 105], and  
507 ramp stress-relaxation experiment [106, 107].

508         The ramp stress-relaxation experiment is actually a uniaxial tensile test with a ramp strain  
509 initially and a subsequently constant strain held for an hour for specimen relaxation. The quasi-linear  
510 viscoelastic (QLV) or Fung's theory is often used to build the viscoelastic constitutive model of the  
511 specimen. In the QLV theory, the history of the stress response is separated into the nonlinear elastic  
512 response and a time-dependent reduced relaxation. The nonlinear elastic response obeys ordinary  
513 constitutive laws for soft tissue. The reduced relaxation function with three material parameters  
514 represents the time lag in a response. If the exponential function with two material parameters is  
515 chosen as the stress-strain relation of nonlinear elastic response, the QLV viscoelastic constitutive law  
516 is subject to five parameters, which can be optimized with Levenberg-Marquardt algorithm or genetic  
517 algorithm [108] by minimizing the error in the stress between model predictions and experimental  
518 values at a series of strains.

519         The stress-relaxation tests in specimens harvested from the human saphenous veins in the  
520 circumferential and longitudinal directions were done with 20% and 50% strains [109]. It was  
521 demonstrated that the saphenous vein had non-linear viscoelastic behaviour. The QLV constitutive  
522 model was fitted with stress relaxation curves and the five model parameters were determined.  
523 However, the stress relaxation equation in [109] seemed incorrect because there was no integral with  
524 respect to time history in the equation.

### 525 **3.2.4 Residual strain in venous walls**

526         There is residual strain in the wall of tubular structures such as blood vessel, left ventricle,  
527 trachea, ureter, oesophagus and gastrointestinal tract and so forth when the loading on the structure is  
528 zero [110]. The residual strain in a structure must result in a residual stress in the structure under zero  
529 loading condition.

530         To decide the residual strain, we need know the zero stress state of the structure by releasing  
531 the residual stress. For a blood vessel, a simply approach for showing the zero stress state is to cut the  
532 vessel into a number of ring segments transversely, subsequently, each ring is cut radially once,  
533 resulting in it to open. These opening structures, which are in the first order of infinitesimals in zero  
534 stress, are considered the zero stress state of each vessel segment [111].

535         After the lengths of a vessel segment inner and outer walls in the zero load and zero stress  
536 states are measured, respectively, the residual strain in the zero load state can be calculated  
537 straightaway. Note that the vessel zero state structure likes a sector, thus an opening angle of the sector  
538 is used to characterize the structure feature. The opening angle is defined as the angle subtended  
539 between two radii with origin positioned at the midpoint of the inner wall and through the tips of the  
540 inner wall, see Fig. 9.

541 Usually, the opening angle of a blood vessel is larger than zero, suggesting its inner wall is  
542 compressed whilst its outer wall is in tension. As a result, the residual strain makes the circumferential  
543 stress distribution across the blood vessel wall more uniform than the case without residual strain, as  
544 shown in Fig. 10.

545 It is difficult to estimate the residual stress in a blood vessel based on a known residual strain.  
546 One method is bending vessel zero stress structure with a force step by step in an experiment until it is  
547 closed, then a beam mechanical model is established based on a homogenous linear stress-strain  
548 relationship or the well-known Fung's stress-strain exponential law, finally the mechanical property  
549 constants are determined inversely by minimizing the error in the displacements between  
550 measurement and model prediction with the modified Powell's hybrid algorithm [112]. Even though  
551 this method is applicable for a zero stress configuration in any shape, it requires extra experiments  
552 except the zero stress observations, and it is less in use at the moment.

553 The other method is thick-walled cylinder method which was proposed initially in [113]. In  
554 the method, the zero stress structure of a blood vessel is assumed to be a circular sector, the zero load  
555 configuration and loaded vessel all are cylindrical. Based on the incompressible condition, the  
556 geometrical relationship between the zero stress configuration and a deformed configuration can be  
557 established simply. If the zero load configuration and a series of stretch-pressure experimental data  
558 points have been available, then an inverse problem can be solved to obtain the biomechanical  
559 property constants in a constitutive law such as six-parameter Fung's model in [113] and three-  
560 parameter Guccione's model in [114]. Once these constants in the law are obtained, the residual stress  
561 can be calculated accordingly.

562 Like arteries, veins can be subject to residual strain, as shown see Fig. 11 for various veins of  
563 rat observed [115], in particular, the opening angle of the rat saphenous vein was as low as  $25^\circ$  in  
564 average. For porcine,  $115^\circ$  and  $120^\circ$  mean opening angles were found in the outflow cuff segment and  
565 the cerebral bridging vein [116]. Similarly, for the human, the mean opening angle of pulmonary  
566 veins was between  $89^\circ$  and  $128^\circ$  in comparison with  $92^\circ$  and  $163^\circ$  of the arteries [117].

567 For the human saphenous vein, the mean opening angle could be large as  $120^\circ$  [99]. However,  
568 more recent observations illustrated that the opening angle was in a range of  $34^\circ$ - $57^\circ$  with a mean of  
569  $45^\circ$  for four patients aged 55(F), 60(F), 67(M) and 65(M) [118].

570 Opening angles of 30 canine autogenous vein grafts after surgery at 1day, 1week, 4 and  
571 12weeks were measured and compared with the opening angle of canine femoral vein [119]. Results  
572 demonstrated that the mean opening angles of vein grafts were  $-0.4^\circ$ ,  $6.1^\circ$ ,  $25.4^\circ$  and  $47.8^\circ$ , respectively,  
573 at 1day, 1week, 4 and 12weeks in comparison with  $63^\circ$  of the normal formal veins of the subject. The  
574 increasing opening angle after surgery was related to non-uniform transmural tissue remodelling  
575 process, especially the intimal hyperplasia or thickening effect.

#### 576 **4 The hyperelastic property modelling**

577 As shown above, venous walls are an anisotropic, nonlinear elastic material. Even though  
 578 incremental circumferential and longitudinal Young's moduli can be obtained separately and in  
 579 uncoupled state, they are in coupling state in reality. Additionally, venous walls are with more content  
 580 of collagen but less mass of elastin in comparison with arterial walls as presented in Tables 1 and 2 as  
 581 well as Fig.4. As a result, the stress-strain curve of venous walls is more compliant than the curve of  
 582 arterial walls at a low strain, but stiffer than that of arterial walls at a high strain. In order to model the  
 583 hyperelastic biomechanical property of venous walls precisely, these two issues should be reflected in  
 584 modelling methods. This is the difficulty in constitutive law modelling for venous walls.

585 There are three types of method for modelling the hyperelastic biomechanical property of  
 586 venous walls, and summarized in Table 4. The first type is phenomenological method, in which one  
 587 stress component is correlated to its corresponding strain component empirically and separately, or  
 588 the coupling in the stress between the circumferential and longitudinal directions is handled with an  
 589 empirical correlation. In the second type, however, the coupling is accomplished mathematically by a  
 590 strain energy function based on a few strain/stretch invariants without the collagen fibre recruitment  
 591 mechanism explicitly but with an exponential function implicitly. In the third type, the coupling is  
 592 treated with a strain energy function with stochastic fibre recruitment mechanism.

#### 593 4.1 Phenomenological methods

594 Two exponential functions of circumferential and longitudinal strains,  $\varepsilon_c$  and  $\varepsilon_l$  were  
 595 proposed and applied to fit the circumferential and longitudinal stresses  $\sigma_c$  and  $\sigma_l$ , of the dog vena  
 596 cava, separately [90]. These exponential functions are presented by the following expressions

$$597 \begin{cases} \sigma_c = c_1 (e^{c_2 \varepsilon_c} - 1) + c_3 (e^{c_4 \varepsilon_c} - 1) \\ \sigma_l = c_5 (e^{c_6 \varepsilon_l} - 1) \end{cases} \quad (6)$$

598 where  $c_1$  to  $c_6$  are constants determined by a nonlinear least squares method. Since one stress  
 599 component is related to the strain along this stress component direction only, the two stress  
 600 expressions are uncoupled and independent of each other.

601 A piecewise expression was put forward to best fit experimental longitudinal stress-strain  
 602 curves of the rabbit inferior vena cava and external jugular vein and to precisely take into account of  
 603 the responses of elastin and collagen fibres in the venous walls [25]. The expression consists of a  
 604 power function and an exponential function of longitudinal strain

$$605 \sigma_l = c_1 \varepsilon_l^{c_2} + c_3 (e^{c_4 \varepsilon_l} - 1) \quad (7)$$

606 where  $c_1$  to  $c_4$  are constants determined by a nonlinear least squares method against the experimental  
 607 stress-strain data points.

608 In [120], 2D phenomenological constitutive law, called bedspring model, was put forward to  
 609 model the experimental data of thin-walled cylindrical rat vena cava. It was found that the

610 experimental circumferential-to-longitudinal first Piola-Kirchoff stress ratio could be best fitted with  
 611 an empirical hyperbolic correlation in terms of circumferential stretch with two constants as follows

$$612 \quad f(\lambda_\theta) \equiv \frac{s_\theta}{s_z} = \frac{c_1}{(c_2 - \lambda_\theta)^2} \quad (8)$$

613 where  $s_\theta$ ,  $s_z$  are the first Piola-Kirchoff stresses in the circumferential and longitudinal directions,  
 614 respectively,  $c_1$  and  $c_2$  are property constants. This correlation represents the coupling of two stress  
 615 components at a defined stretch components,  $\lambda_\theta$  and  $\lambda_z$ . Additionally,  $\lambda_\theta$  can induce a change in  $\lambda_z$ ,  
 616 and this change is related to  $\lambda_\theta$  by the following expression

$$617 \quad \lambda_{z,\theta} = -\frac{c_1}{c_2 - \lambda_\theta} \quad (9)$$

618 The longitudinal stress shares the same form of Eq. (8) but with different constants  $c_3$ ,  $c_4$   
 619 and in terms of combined longitudinal stretch,  $\lambda_z - \lambda_{z,\theta}$ , namely

$$620 \quad s_z = \frac{c_3}{(c_4 - \lambda_z - \lambda_{z,\theta})^2} \quad (10)$$

621 Based on a series of experimental  $s_\theta - \lambda_\theta$ ,  $s_z - \lambda_z$  data, one can obtain model constants  $c_1$  to  
 622  $c_4$ , then predict two stresses at a pair of  $\lambda_\theta$  and  $\lambda_z$  by using the model above in a sequence of Eq. (7)  
 623 to (10) and the expression  $s_\theta = s_z f(\lambda_\theta)$ . In the model, the hyperbola with power 2 exhibits a more  
 624 compliant behaviour at low strains and a stiffer feature at high strains in venous walls.

## 625 4.2 Strain energy function methods

626 Strain energy function is a mathematical representation of strain energy stored in a deformed  
 627 elastic body under the action of external forces in unit volume in terms of strains or their invariants.  
 628 Usually, vascular soft tissues are viscoelastic and their stress-strain curve exhibits a hysteresis loop  
 629 under a cyclic loading. To make the curve repeatable, a specimen of vascular soft tissue must  
 630 experience a cyclic loading for a number of times before conducting uniaxial/biaxial tensile tests. This  
 631 process is called preconditioning. The stress-strain curve of a preconditioned specimen is different  
 632 from that of the un-preconditioned specimen, but is simpler in some degree than the latter. Thus this  
 633 curve is pseudo elastic and the strain energy function for this curve is pseudo strain energy function  
 634 [121]. Unless specially stated, the strain energy functions in following sections are pseudo elastic.

635 Six individual strain energy functions have been proposed and applied in biomechanical  
 636 property modelling of venous walls, for example, two families of collagen fibres without orientation  
 637 dispersion in [97], two families of fibres with different property constants in [122], two families of  
 638 fibres with orientation dispersion [123] and four-family fibre without orientation dispersion [98], two  
 639 families of fibres with anisotropic elastin and fibre recruitment [124], and its update version with fibre  
 640 orientation [125]. The first four strain energy functions are deterministic, the last two are stochastic.

#### 641 4.2.1 Two families of fibres without orientation dispersion

642 In [97], a strain energy function was proposed based on transversely isotropic, homogenous  
643 matrix material and two families of collagen fibres arranged axis-symmetrically about the arterial  
644 longitudinal axis. Two families of fibres share the same biomechanical property constants. The  
645 mathematical expression of the function is written as [97]

$$646 \quad \psi = c(I_1 - 3) + \frac{k_1}{2k_2} \sum_{i=4,6} \left[ e^{k_2(I_i - 1)^2} - 1 \right] \quad (11)$$

647 where the first invariant  $I_1 = \lambda_r^2 + \lambda_\theta^2 + \lambda_z^2$ ,  $\lambda_r$  is the radial stretch, it yields the incompressible  
648 condition with the other stretch components,  $\lambda_\theta$  and  $\lambda_z$ , namely  $\lambda_r \lambda_\theta \lambda_z = 1$ , the second invariants  
649  $I_4 = \lambda_\theta^2 \cos^2 \beta + \lambda_z^2 \sin^2 \beta$ ,  $I_6 = \lambda_\theta^2 \cos^2(-\beta) + \lambda_z^2 \sin^2(-\beta)$ , the angles,  $\beta$  and  $-\beta$ , are the mean  
650 fibre angle measured from the circumferential direction for two families of fibres.

651 The model expressed with Eq. (11) was used to determine matrix stiffness constant  $c$ ,  
652 collagen fibre initial stiffness  $k_1$ , stiffness increasing rate  $k_2$  and mean fibre orientation angle  $\beta$   
653 from the Cauchy stress-stretch curves obtained in tubular biaxial inflation tests in [99, 100, 126].  
654 Since the fibre orientation dispersion is not taken into account, the error in the stress between  
655 measurement and model prediction needs to be improved.

#### 656 4.2.2 Two families of fibres with different property constants

657 Longitudinal and circumferential specimens cut from infrarenal vena cava of 15 lambs were  
658 measured by simple tensile test [122]. The Cauchy stress-stretch curves were fitted with three types of  
659 strain energy function without considering the collagen fibre orientation dispersion. The first strain  
660 energy function is Eq. (11). The second strain energy function is taken from [127], which is for rabbit  
661 left ventricular passive myocardium with one family of fibres, and then it is updated by adding  
662 another family of fibre. The updated strain energy function is read as follows [122]

$$663 \quad \psi = c_1 (e^Q + e^P - 1) \quad (12)$$

664 with

$$665 \quad Q = c_2 (I_1 - 3)^2 + c_3 (I_1 - 3)(I_4 - 1) + c_4 (I_4 - 1)^2 \quad (12a)$$

666 and

$$667 \quad P = c_5 (I_1 - 3)^2 + c_6 (I_1 - 3)(I_6 - 1) + c_7 (I_6 - 1)^2 \quad (12b)$$

668 where  $c_2 > 0$ ,  $c_4 > 0$ ,  $c_5 > 0$ ,  $c_7 > 0$ ,  $c_3$  and  $c_6$  are dimensionless, but  $c_1$  is in stress unit. Note that  
669 expression  $P$  was added by the authors of [122]. The third type of stain energy function that was put  
670 forward in [122] is written as the following

$$671 \quad \psi = c_1 (I_1 - 3) + c_2 (\sqrt{I_4} - 1)^2 + c_3 (\sqrt{I_6} - 1)^2 \quad (13)$$

672 where  $c_1$ ,  $c_2$  and  $c_3$  are positive property constant with stress unit.

673 It was shown that three models could fit the experimental data well [122], but the  
674 performance of the model in Eq. (12) was the best one; the rest models performed just satisfactorily  
675 with nearly equally large errors.

#### 676 4.2.3 Two families of fibres with orientation dispersion

677 In reality, collagen fibre orientation does not direct a unique direction exactly; instead, the  
678 orientation is subject to dispersion. To consider this effect, the constitutive model, Eq. (11), was  
679 extended with fibre orientation dispersion [123], and the updated version of the strain energy function  
680 is written as,

$$681 \quad \psi = c(I_1 - 3) + \frac{k_1}{2k_2} \sum_{i=4,6} \left[ e^{k_2[\kappa(I_1-3)+(1-3\kappa)(I_i-1)]^2} - 1 \right] \quad (14)$$

682 where  $\kappa$  is the fibre orientation dispersion coefficient,  $\kappa = 0-0.33$ , it can be obtained by microscope  
683 observation or inversely determined along with the other constants  $c$ ,  $k_1$ ,  $k_2$  and  $\beta$  based on known  
684 stress-stretch curves in the circumferential and longitudinal directions.

685 A series of specimens of murine inferior vena cava under normal and post-phlebotic  
686 conditions were tested on a custom-built biaxial mechanical testing device [128]. The strain energy  
687 function, Eq. (14), was applied to fit the experimental stress-stretch curves, and five model constants  
688 were extracted/optimized and compared between the healthy and diseased groups and the results were  
689 encouraging.

#### 690 4.2.4 Four families of fibres model without orientation dispersion

691 Based on the constitutive law in Eq. (11), the two families of collagen fibres were taken by  
692 four families of fibres (two diagonally, one circumferentially, and one longitudinally) to reduce the  
693 errors in fitting pressure-radius and axial force-radius curves of porcine jugular veins [98]. The first  
694 term in Eq.(11) remains unchanged. Then the strain energy function takes the following form

$$695 \quad \psi = c(I_1 - 3) + \frac{k_1}{2k_2} \sum_{i=4,6} \left[ e^{k_2(I_i-1)^2} - 1 \right] + \frac{k_{1i}}{2k_{2i}} \sum_{i=\theta,z} \left[ e^{k_{2i}(\lambda_i^2-1)^2} - 1 \right] \quad (15)$$

696 where  $k_{1i}$  and  $k_{2i}$  are the property constants for the circumferential and longitudinal fibres,  
697 respectively, i.e.  $i = \theta, z$ . It was stated that the arrangement of four families of collagen fibres was  
698 consistent with vein angioarchitecture observed histologically [98].

699 Similarly, the noe-Hookean term in Eq. (15) could be replaced with a quadratic function of  
700 two strain components to handle the response of elastin and are written as follows [98]

$$701 \quad \psi = b_1 E_\theta^2 + b_2 E_z^2 + b_3 E_\theta E_z + \frac{k_1}{2k_2} \sum_{i=4,6} \left[ e^{k_2(I_i-1)^2} - 1 \right] + \frac{k_{1i}}{2k_{2i}} \sum_{i=\theta,z} \left[ e^{k_{2i}(\lambda_i^2-1)^2} - 1 \right] \quad (16)$$

702 where  $E_\theta$  and  $E_z$  are the circumferential and longitudinal strain components, and related to the  
 703 circumferential and longitudinal stretch components,  $\lambda_\theta$  and  $\lambda_z$ , with  $E_\theta = 0.5(\lambda_\theta^2 - 1)$  and  
 704  $E_z = 0.5(\lambda_z^2 - 1)$ ;  $b_1$  to  $b_3$  are model constants inversely determined based on experimental data.

705 It was demonstrated that the models in Eqs. (15) and (16) performed equally better than the  
 706 Fung's model proposed in [121].

#### 707 4.2.5 Two families of fibres with anisotropic elastin and fibre recruitment

708 For rat carotid artery in passive state, a constitutive model was developed [129]. In the model,  
 709 it was considered that the arterial wall was composed of isotropic and homogenous matrix of elastin  
 710 and two families of collagen fibres with mean orientation angles,  $\beta$  and  $-\beta$ , with respect to the  
 711 circumferential direction. The fibres engage in tension based on a recruitment process. The strain  
 712 energy function is written as [129]

$$713 \quad \psi = f_{elast}c(I_1 - 3)^{3/2} + f_{coll} \sum_{i=4,6} \left[ \frac{1}{2} \int_{-\infty}^{+\infty} \psi_{fibre}(x) \rho_{fibre}(\varepsilon_i - x) dx \right] \quad (17)$$

714 where  $f_{elast}$  and  $f_{coll}$  are the area fractions of elastin and collagen fibre in the tissue, respectively,  
 715  $f_{elast} = 0.306$  and  $f_{coll} = 0.203$  for rat carotid arterial wall,  $c$  is property constant of the elastin,  $\varepsilon_i$  is the  
 716 strain of fibres in two families,  $\varepsilon_i = \sqrt{I_i} - 1$ ,  $i = 4, 6$ ,  $\psi_{fibre}$  is the strain energy function of an  
 717 individual collagen fibre and takes the following form [129]

$$718 \quad \psi_{fibre}(\varepsilon_i) = \begin{cases} 0 & \text{for } \varepsilon_i \leq \varepsilon_0 \\ c_{coll} [\varepsilon_i - \log(\varepsilon_i + 1)] & \text{for } \varepsilon_i > \varepsilon_0 \end{cases} \quad (18)$$

719 where  $c_{coll}$  is the Young's modulus of the collagen fibre,  $c_{coll} = 200\text{MPa}$ ,  $\varepsilon_0$  is the fibre straightening  
 720 strain at which a collagen fibre gets into tension,  $\varepsilon_0 = 0$  (WI=1) [129].  $\rho_{fibre}$  is a log-logistic  
 721 probability distribution function of fibre strain to regulate the fibre recruitment process and expressed  
 722 by

$$723 \quad \rho_{fibre}(\varepsilon_i) = \begin{cases} 0 & \text{for } \varepsilon_i \leq \varepsilon_0 \\ \left(\frac{k}{b}\right) \frac{(\varepsilon_i - \varepsilon_0/b)^{k-1}}{[1 + (\varepsilon_i - \varepsilon_0/b)^k]^2} & \text{for } \varepsilon_i > \varepsilon_0 \end{cases} \quad (19)$$

724 where  $b$  ( $>0$ ) is a scaling parameter and  $k$  ( $>0$ ) defines the shape of  $\rho_{fibre}$ . The four constants  $c$ ,  $\beta$ ,  
 725  $k$  and  $b$  are determined inversely with experimental data in tubular biaxial vessel segment inflation  
 726 tests.

727 It was observed that the longitudinal stress-strain curve of elastin was stiffer than the  
 728 circumferential curve, showing an anisotropic property in the longitudinal direction [124]. To involve

729 this effect, the first term in Eq. (17) is replaced with additional term and the last term remains  
 730 unchanged, then the following strain energy function is resulted

$$731 \quad \psi = f_{elast} c (I_1 - 3)^{3/2} + f_{elast} c_1 \left( \lambda_z^2 + \frac{2}{\lambda_z} - 3 \right) + f_{coll} \sum_{i=4,6} \left[ \frac{1}{2} \int_{-\infty}^{+\infty} \psi_{fibre}(x) \rho_{fibre}(\varepsilon_i - x) dx \right] \quad (20)$$

732 where five constants  $c$ ,  $c_1$ ,  $\beta$ ,  $k$  and  $b$  are decided inversely with experimental data in tubular  
 733 biaxial inflation tests of facial vein segments of rabbits and a better result has been achieved [124].

#### 734 4.2.6 Two families of fibres with anisotropic elastin, fibre recruitment and orientation 735 dispersion

736 In Eq. (20), the collagen fibre orientation dispersion is excluded. In reality, collagen fibres do  
 737 not orientate one direction exactly; instead they orientate various directions by deviating from the  
 738 mean orientation. To take this effect into account, the constitutive law presented by Eq. (20) was  
 739 updated with fibre orientation dispersion, while the two terms for the elastin response remained  
 740 unchanged [125]. Here just the modified stain energy function of collagen fibres is illustrated [125].

741 For two given Green strain components in a cylinder wall, such as  $E_\theta$  and  $E_z$ , the strain  
 742 along a fibre, which is subject to a fibre angle  $\beta$  measured from the circumferential direction, is  
 743 written as

$$744 \quad E_f = E_\theta \cos^2 \beta + E_z \sin^2 \beta \quad (21)$$

745 The true strain along the fibre with respect to the fibre straightening strain  $\varepsilon_0$  is calculated by

$$746 \quad \varepsilon_f = \frac{E_f - \varepsilon_0}{E_f + 2\varepsilon_0} \quad (22)$$

747 where  $\varepsilon_0 = 0.5(\lambda_0^2 - 1)$ ,  $\lambda_0$  is the fibre straightening stretch,  $\lambda_0 = WI$ , is a stochastic variable in a soft  
 748 tissue, can be measured by microscope and yields the same probability density distribution as Eq. (19),  
 749 then the fibre recruitment process is specified by

$$750 \quad \rho_{fibre}(\varepsilon_f) = \begin{cases} 0 & \text{for } \varepsilon_f \leq \varepsilon_0 \\ \left(\frac{k}{b}\right) \frac{(\varepsilon_f - \varepsilon_0/b)^{k-1}}{\left[1 + (\varepsilon_f - \varepsilon_0/b)^k\right]^2} & \text{for } \varepsilon_f > \varepsilon_0 \end{cases} \quad (23)$$

751 The fibre is a linear material with a modulus  $c_{coll}$  and its strain energy function is in the  
 752 following form

$$753 \quad \psi_{fibre}(\varepsilon_f) = \begin{cases} 0 & \text{for } \varepsilon_f \leq \varepsilon_0 \\ \frac{1}{2} c_{coll} \varepsilon_f^2 & \text{for } \varepsilon_f > \varepsilon_0 \end{cases} \quad (24)$$

754 Then the strain energy function of the fibre with the fibre angle  $\beta$  is calculated by the  
 755 flowing equation when the recruitment is considered

$$\psi_{fibre}^{\beta}(\varepsilon_f) = \int_0^{\varepsilon_f} \rho_{fibre}(\varepsilon_0) \psi_{fibre}(\varepsilon_f) d\varepsilon_0 \quad (25)$$

757 Finally, the strain energy function of one family of fibres will be estimated by integrating Eq.  
 758 (25) with respect to  $\psi_{fibre}^{\beta}(\varepsilon_f)$  and fibre orientation distribution function  $R(\beta)$  in the following  
 759 expression

$$\psi_{fibre}^{\bar{\beta}}(\varepsilon_f, \bar{\beta}) = \int_0^{\varepsilon_f} \int_0^{\pi} \rho_{fibre}(\varepsilon_0) \psi_{fibre}(\varepsilon_f) R(\beta) d\varepsilon_0 d\beta = \frac{1}{2} c_{coeff} \int_0^{\varepsilon_f} \int_0^{\pi} \rho_{fibre}(\varepsilon_0) \varepsilon_f^2 R(\beta) d\varepsilon_0 d\beta \quad (26)$$

761 where  $\bar{\beta}$  is the mean fibre angle,  $R(\beta)$  is the planar  $\pi$ -periodic von-Mises distribution for fibre  
 762 orientation profile, i.e.

$$R(\beta, \bar{\beta}, a) = \frac{1}{\pi I_0(a)} e^{a \cos[2(\beta - \bar{\beta})]}, \quad I_0(a) = \frac{1}{2\pi} \int_0^{2\pi} e^{a \cos \beta} d\beta, \quad \beta \in [0, \pi] \quad (27)$$

764 where  $\bar{\beta}$  and  $a$  are fibre structure parameters and can be determined by fitting histologically  
 765 experimental  $\beta$  profiles.

766 The strain energy function of the other one family of fibres with a  $-\bar{\beta}$  mean fibre angle and  
 767 the same parameter  $a$  is identical to Eq. (26). As such the updated stain energy function is written

$$\psi = f_{elast} c (I_1 - 3)^{3/2} + f_{elast} c_1 \left( \lambda_z^2 + \frac{2}{\lambda_z} - 3 \right) + f_{coll} c_{coeff} \int_0^{\varepsilon_f} \int_0^{\pi} \rho_{fibre}(\varepsilon_0) \varepsilon_f^2 R(\beta) d\varepsilon_0 d\beta \quad (28)$$

769 This strain energy function has been used to fit the pressure-radius, pressure-axial force  
 770 experimental data of rabbit facial vein segment and a good result was achieved [125].

771 Note that the strain energy functions in Eqs.(20) and (28) are quite time-consuming due to the  
 772 integrals involved in comparison with those in Eqs.(11) to (16). Thus two functions Eqs.(20) and (28)  
 773 might not be applicable in FEA simulations.

## 774 4.3 Applications of constitutive law

### 775 4.3.1 Image-based *in vivo* property constants determination

776 Ultrasound images of femoral vein of healthy 40year-old volunteer were captured in real time,  
 777 and registered by using a time sequence of 10s. The intraluminal pressure of the vein was recorded as  
 778 well. The circumferential and longitudinal Cauchy stresses were estimated by using thin-walled model  
 779 without residual strain [130].

780 The constitutive law Eq. (11) was simplified by assuming that there was one family of fibres  
 781 only in the femoral vein wall, then a method was designed to estimate remaining four model  
 782 parameters based on clinically observed instant pressure and inner diameter of femoral vein and a  
 783 constant longitudinal stretch 1.08. The predicted inner diameter of formal vein is compared with the  
 784 diameters from the images in Fig. 12. Since the viscoelastic property of the vein wall was not taken  
 785 into account, the model prediction was a single-line curve only.

#### 786 4.3.2 FEA of junction of vein graft with artery

787 A computational method for simulating CABG surgery was proposed, and effects of two  
788 clinically parameters, such as incision length and insertion angle on artery and graft responses, were  
789 analysed at a fixed graft diameter, based on actual 3D vessel dimensions of a human coronary artery  
790 and a saphenous vein [131]. The end-to-side anastomosis structure, residual stresses, anisotropic and  
791 nonlinear feature of blood vessels were considered. The coronary artery was a three-layer thick-  
792 walled cylinder.

793 A series of FEA simulations were performed to predict deformation and stress distribution in  
794 the end-to-side anastomosis at various stages of CABG surgery. It was shown that the arterial incision  
795 had a significant effect on the size of the arterial opening, depending on the residual stress only. The  
796 incision length influenced critically the graft shape and the stress level in the graft wall. Stress level in  
797 the heel region was higher than in the toe region, see Fig. 13 and 14. A stress concentration could be  
798 found at the incision ends.

799 The proposed computational methodology may be useful in designing a coronary anastomotic  
800 device to reduce surgical trauma. It may improve the quantitative knowledge of vessel diseases and  
801 serve as a tool for virtual planning of vascular surgery.

### 802 5 Discussions

#### 803 5.1 Difference in stress-stretch curves

804 The biomechanical property of saphenous vein wall can be characterized *in vitro* by uniaxial  
805 and tubular biaxial tensile tests as shown in the previous sections. What is the difference in Cauchy  
806 stress-stretch curves in both tests for the human saphenous vein? In Fig. 15, a comparison of Cauchy-  
807 stretch curves is made for the human saphenous vein measured by two tensile tests. The tensile data of  
808 sample saphenous vein 2 (SV2) are taken from [64], while the first tubular biaxial inflation test data  
809 were measured in [99] at 4Hz loading rate on the human saphenous vein segments.

810 In comparison with the uniaxial tensile test results, the stress-stretch curves measured by the  
811 tubular biaxial inflation tests show more wide stretch range at a very low stress level, see Fig. 15.  
812 Which data group is mostly suitable for saphenous vein CABG under arterial physiological conditions?  
813 Obviously, this problem needs further research in the future.

#### 814 5.2 Biomechanical property identification *in vivo*

815 It may be very significant for the diagnosis of disease in saphenous vein CABGs by  
816 characterizing the passive biomechanical property *in vivo*. Further, this characterization can involve  
817 the viscoelasticity of saphenous veins. Currently, this issue is little tackled in literature [101, 130].  
818 More advanced devices and modelling methods are on demand presently.

#### 819 5.3 Tissue damage effects

820 It was observed that the saphenous vein wall could be damaged when transmural pressure was  
821 in a range of 50-60mmHg [95]. Under coronary artery physiological conditions, the intraluminal  
822 pressure is higher than this pressure level, as such the tissue of human saphenous vein CABGs may be  
823 subject to damage or sub-failure. For the rat ligament, damage or sub-failure threshold in fibre stretch  
824 was 1.0514 [132]. What is the damage or sub-failure threshold for the human saphenous vein CABGs ?  
825 How to model the damage or sub-failure effect in the human saphenous vein CABGs by using  
826 constitutive laws ?

#### 827 **5.4 Residual strain/stress**

828 In section 3.2.4, it is shown that the residual strain/stress does exist in the human saphenous  
829 vein. Currently, the mean opening angle is as high as 120° for 15 patients [94] in comparison with an  
830 angle as low as 45° of four patients [118]. Such a huge difference needs to be clarified with significant  
831 further observations in the future.

#### 832 **5.5 CABG Remodelling**

833 After surgery, CABGs are subject to thickening and remodelling processes in coronary artery  
834 environment. These two processes are induced and regulated by blood shear stress applied on the graft  
835 wall and the stress in the wall under an increased intraluminal pressure load [133, 134]. The vein graft  
836 remodelling initiated by blood shear stress has been studied extensively, such as those in [135, 136].

837 Blood pressure in the left femoral vein of the rabbit was chronically elevated by the  
838 constriction in the left external iliac vein to clarify the changes in biomechanical properties caused by  
839 such a hypertension [137]. Wall thickness and active passive biomechanical properties of the vein  
840 were measured *in vitro* at 1, 2 and 4weeks after surgery. Wall thickness was increased even at 1week  
841 to restore circumferential wall stress to a control level. Vascular tone and contractility were intensified  
842 by the hypertension; however, wall incremental Young's modulus and compliance remained at a  
843 normal level. These results suggested that veins could remodel themselves against a raised blood  
844 pressure like arteries.

845 Interestingly, arteriovenous fistulas were generated by implanting e-PTFE grafts between  
846 carotid artery and jugular vein in healthy pigs under over-loaded flow and pressure conditions [138].  
847 The wall thickening was exhibited in grafted vessels in 2weeks; the intramural stresses was restored to  
848 homeostatic levels, and the internal diameter enlargement got less, the intimal shear stress became  
849 normal gradually after 4weeks. The residual strains and opening angle increased at 12weeks. There  
850 was a correlation between intimal hyperplasia and opening angle increase. Elastin contents reduced  
851 but collagen contents increased within the first 4weeks. In vessel segment inflation tests, the vein  
852 walls showed a stiffer behaviour in comparison with the baseline levels. The experimental pressure-  
853 radius, axial force-radius data points of the post-fistula measured at 2, 4 and 12weeks were fitted

854 with Eq. (16), and the extracted material constants were correlated to elastin and collagen contents  
855 observed [139]. This research methodology has provided a good idea for CABG remodelling problem.

856 At the moment, the wall stress factor is not involved in experiments and mathematical models  
857 in human venous graft remodelling. The saphenous vein CABG remodelling needs to be tackled  
858 experimentally and mathematically by involving shear stress on venous wall and stresses in the wall.

## 859 **5.6 Regional Deformation and Material Properties**

860 The biomechanical properties of human vein were not homogenous circumferentially and  
861 longitudinally, showing variable material properties and deformation from one region to another [140].  
862 This heterogeneity has not been considered in saphenous vein CABG modelling and experiments so  
863 far. If this issue can be addressed in the near future, it will be beneficial to CABG design and surgery.

## 864 **5.7 Applications of FEA in CABGs**

865 FEA is an important method in biomechanical engineering, especially in biomechanics and its  
866 clinical application for soft tissue. In Section 4.3.2, it is seen that the cases of FEA for prediction of  
867 deformation and stress in CABGs are very lack. This may be caused from a little known about the  
868 constitutive law of layered human saphenous vein walls or complicated interaction between the  
869 coronary artery and a vein graft. Furthermore, the fluid-structure interaction in saphenous vein  
870 CABGs is little tackled at the moment as well.

## 871 **6 Conclusions**

872 Biomechanical properties of the human saphenous vein, which has been applied in blocked  
873 coronary artery to serve as a bypass graft and survive the diseased heart, were reviewed  
874 comprehensively in terms of active and passive mechanical behaviours. Particularly, the passive  
875 biomechanical properties have been extensively discussed by summarizing and interpreting existing *in*  
876 *vitro* uniaxial, bulge, planar and tubular biaxial tensile testing methods, *in vivo* test methods, property  
877 variables, various test results, constitutive laws and their mathematical modelling approaches,  
878 viscoelasticity, and residual strain/stress. It is shown that very limited attention has been paid to the  
879 biomechanical properties of the human saphenous vein and their modelling approaches need to be  
880 updated by considering the fibre orientation dispersion and sub-failure/damage effects in the tissue.  
881 The *in vivo* study on the biomechanical properties of the human saphenous vein is very rare. In the  
882 future, important research issues, such as the feasibility of constitutive laws under coronary artery  
883 physiological conditions based on uniaxial, tubular biaxial inflation test results of the human  
884 saphenous vein, biomechanical property identification *in vivo*, tissue damage effects, residual  
885 strain/stress identification, coronary artery bypass graft remodelling, regional deformation and  
886 material properties of coronary artery bypass graft, finite element analysis application in coronary  
887 artery bypass grafts have to be addressed.

888 **Declaration of interest**

889 There are no conflicts of interest.

890

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Table 1 Volume fractions of collagen and elastin in various vascular veins

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Vessel	Collagen		Elastin	
	Total	Media	Total	Media
Aorta *	71.4±3.6 \$#	52.7±14.7	7.8±3.5 \$	8.6±3.5 \$
Carotid \$	44.7±19.5 *#	39.7±22.4	17.3±5.4 *%#	17.1±6.6 *%
Iliac %	61.6±11.9 #	49.3±16.0	9.6±2.8 \$	8.8±3.1 \$
Vena cava #	79.7±6.2 *\$	32.9±15.4	8.0±2.9 \$	8.4±6.4

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Table 2 Area fractions of collagen, elastin and smooth muscle in various blood vessels of the rabbit

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Vessel	Collagen (%)	Elastin (%)	Smooth muscle (%)
Thoracic aorta	28.66	23.58	41.87
Carotid artery	44.11	12.80	34.76
Inferior vena cava	61.99	18.50	8.13
Jugular vein	69.11	5.08	15.45

Area fractions are taken from Fig. 6(c) in [25].

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Table 3 Area fractions of collagen and elastin in various vascular veins

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Vessel	Collagen		Elastin (%)	Elastin/Collagen index (%)
	Collage I (%)	Collagen IV (%)		
FV	18.0	37.5	9.5	15.0
CSV	35.0	17.5	17.5	24.0
ISV	55.0	15.0	42.5	40.0

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Area fractions of transverse section of collagen and elastin in human veins are presented as percent area, FV-femoral vein, CSV-competent saphenous vein, ISV-incompetent saphenous vein. The table drafted is based on Figs 2, 3 to 5 in [29].

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Table 4 Existing methods for biomechanical property modelling of venous walls

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Type	Method/model	Contributor	Feature
Phenomenological	Uncoupled model	Akio, Masamitsu & Toshiaki (1988) [90]	<ol style="list-style-type: none"> <li>1) One stress component is fitted by an exponential function of the strain along the stress component direction only;</li> <li>2) Two stress components are uncoupled.</li> </ol>
	Piecewise model	Sokolis (2008) [25]	<ol style="list-style-type: none"> <li>1) Stress component is fitted by a piecewise expression of power and exponential functions of the strain in the stress component direction.</li> </ol>
	Bedspring model	Desch & Weizsacker (2007) [120]	<ol style="list-style-type: none"> <li>1) Empirical correlation of circumferential-to-longitudinal first Piola-Kirchoff stress ratio in terms of circumferential stretch by hyperbola based on experiment;</li> <li>2) Longitudinal stretch consists of two parts, one part is related to circumferential stretch only, one part corresponds to longitudinal stress;</li> <li>3) Longitudinal stress is as a hyperbolic function of the modified longitudinal stretch in which the stretch relating to the circumferential stretch has been excluded.</li> </ol>
Strain energy function (deterministic)	Two families of fibres model	Holzappel, Gasser and Ogden (2000) [97]	<ol style="list-style-type: none"> <li>1) Axis-symmetrical or diagonal two families of collagen fibres with equal property constants;</li> <li>2) Fibre orientation without dispersion;</li> <li>3) Fibre mechanical response as exponential function of squared fibre stretch;</li> <li>4) Elastin, smooth muscle and the rest material form homogenous matrix, which obeys neo-Hookean model.</li> </ol>
	Two families of fibres with different property	Alastrue, Pena, Martinez & Doblare (2008) [122]	<ol style="list-style-type: none"> <li>1) Axis-symmetrical two families of fibres with different property constants;</li> <li>2) Fibre orientation without dispersion;</li> <li>3) Fibre mechanical response as parabolic function of squared fibre stretch;</li> <li>4) Elastin, smooth muscle and the rest material form homogenous matrix, which obey neo-Hookean model.</li> </ol>
	Two families of fibres with orientation dispersion	Gasser, Ogden and Holzappel (2006) [123]	<ol style="list-style-type: none"> <li>1) Axis-symmetrical two families of fibres with equal property constants;</li> <li>2) Fibre orientation with dispersion;</li> <li>3) Fibre mechanical response as exponential function of squared fibre stretch;</li> <li>4) Elastin, smooth muscle and the rest material form homogenous matrix, which obeys neo-Hookean model.</li> </ol>
	Four families of fibres model	Sokolis (2013) [98]	<ol style="list-style-type: none"> <li>1) Four families of fibres (two diagonal with equal property constants, one circumferential and one longitudinal with their own constant);</li> <li>2) Fibre orientation without dispersion;</li> <li>3) Fibre mechanical response as exponential function of squared fibre stretch;</li> <li>4) Elastin, smooth muscle and the rest material form homogenous matrix, which yields neo-Hookean or quadratic model.</li> </ol>

Table 4 Existing methods for biomechanical property modelling of venous walls (continued)

Type	Method/model	Contributor	Feature
Strain energy function (stochastic)	Two families of fibres with anisotropic elastin and fibre recruitment	Rezakhaniha and Stergiopoulos (2008) [124]	<ol style="list-style-type: none"> <li>1) Axis-symmetrical two families of fibres with the same property constants;</li> <li>2) Fibre orientation without dispersion;</li> <li>3) Individual fibre mechanical response obeys a recruitment law, the total fibre response is the integral of all individual fibre contributions.</li> <li>4) Elastin is homogenous but with isotropic and anisotropic parts, the isotropic part yields modified neo-Hookean model, while the anisotropic part obeys a new strain energy function.</li> </ol>
	Two families of fibres with anisotropic elastin, fibre orientation dispersion and fibre recruitment	Agianniotis, Rezakhaniha & Stergiopoulos (2011) [125]	<ol style="list-style-type: none"> <li>1) Axis-symmetrical two families of fibres with the same property constants;</li> <li>2) Fibre orientation with dispersion;</li> <li>3) Individual fibre mechanical response obeys a recruitment law, the total fibre response is the integral of all individual fibre contributions.</li> <li>4) Elastin is homogenous but with isotropic and anisotropic parts, the isotropic part yields modified neo-Hookean model, while the anisotropic part obeys a new strain energy function.</li> </ol>

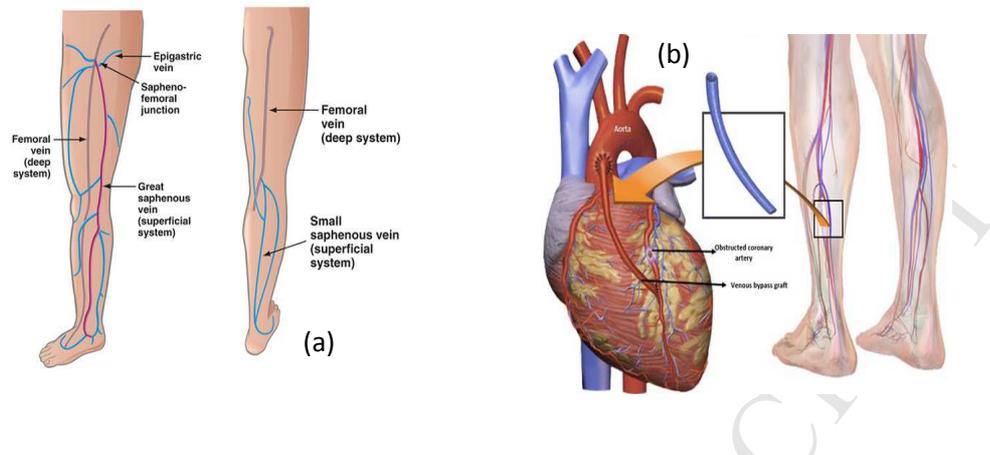


Fig. 1 Greater saphenous vein in human leg (a) and its bypass graft (b), the picture (a) was from [4], the picture (b) was on [5]

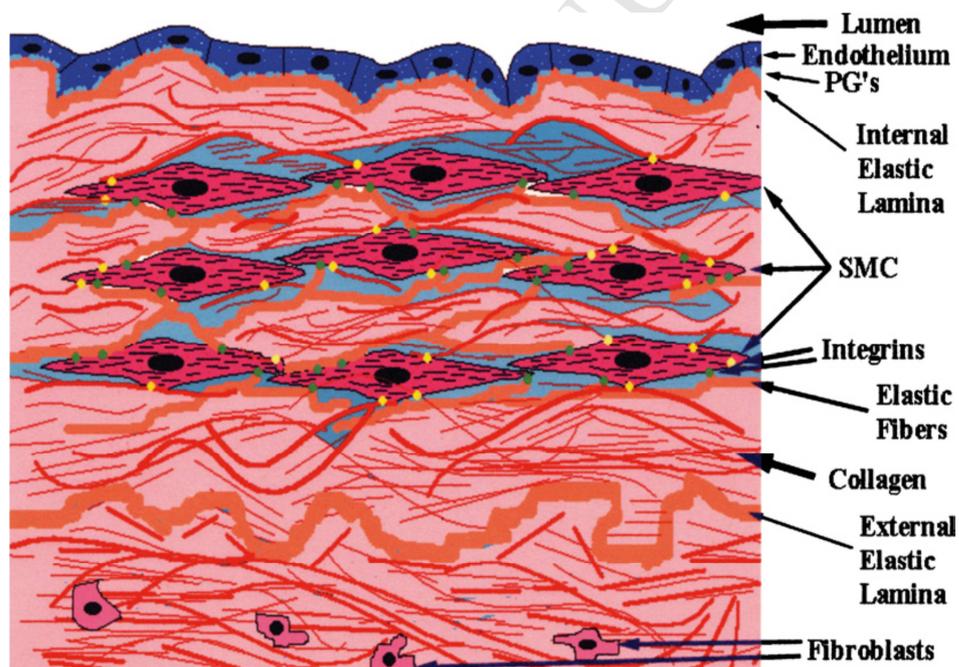


Fig. 2 Image of the transverse section in a vascular wall. In the picture, large fusiform cells are smooth muscle cell (SMC), elastic tissue (thick fibres) and collagen (thin wavy fibres) are connected to integrins on the SMC surface (dots on cell perimeter) and the fibres are oriented in the circumferential direction. Proteoglycans (PG, lightly shaded) surround the SMC. There are links between collagen and elastin fibres. Endothelial cells (cuboidal) also have some PGs connected with them. Fibroblasts (small irregular cells) occur in the adventitia, which is composed mostly of collagenous tissue. This picture is from [17].

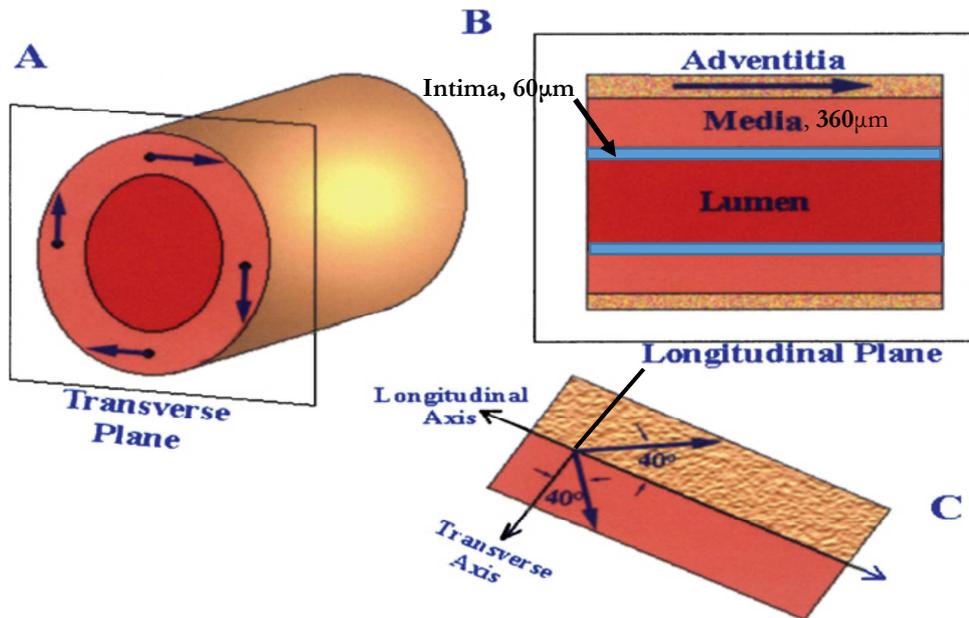


Fig. 3 Histology and mean fibre orientation of porcine vascular tissues the picture was from [17]

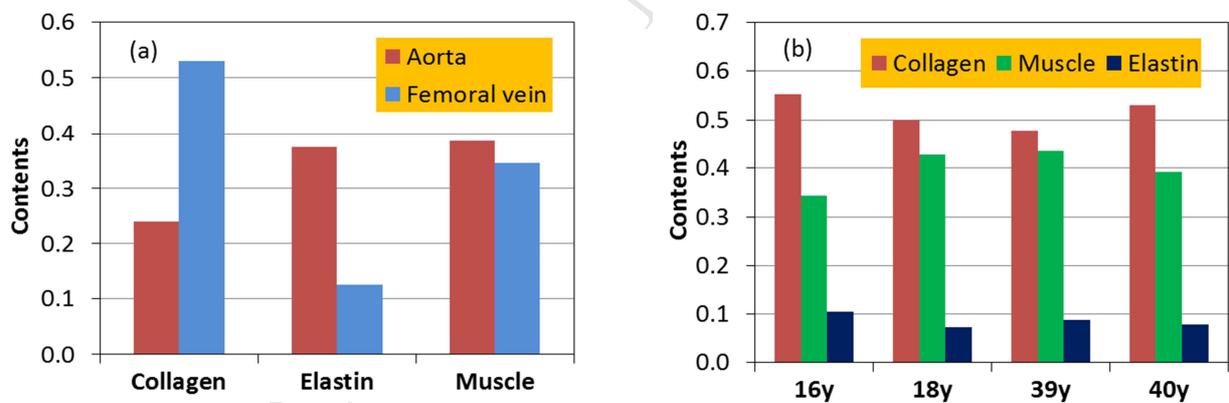


Fig. 4 Dry weigh contents of collagen, elastin and smooth muscle in walls of man aorta, femoral vein and super segments of saphenous vein, (a) aorta and femoral vein(mean of six observation [28]), (b) saphenous vein of subjects in various ages (mean for the veins in the left and right legs [28])

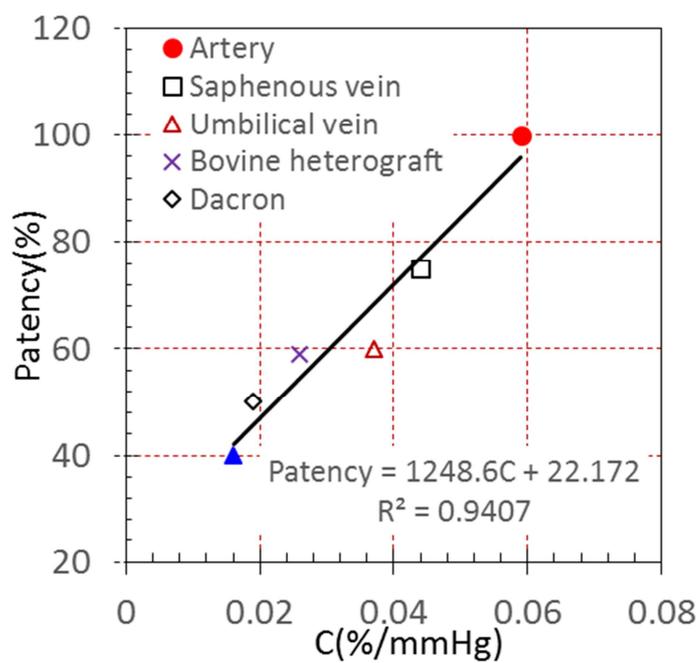


Fig. 5 Relationship between patency and compliance one year after graft surgery

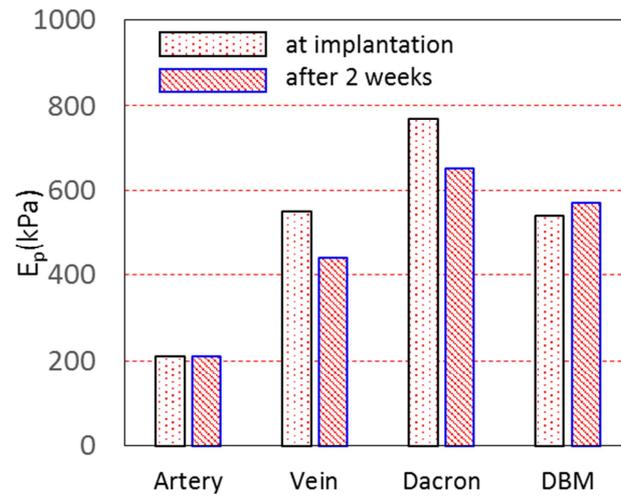


Fig. 6 Changes in global Young's moduli at graft implantation and after 2 weeks

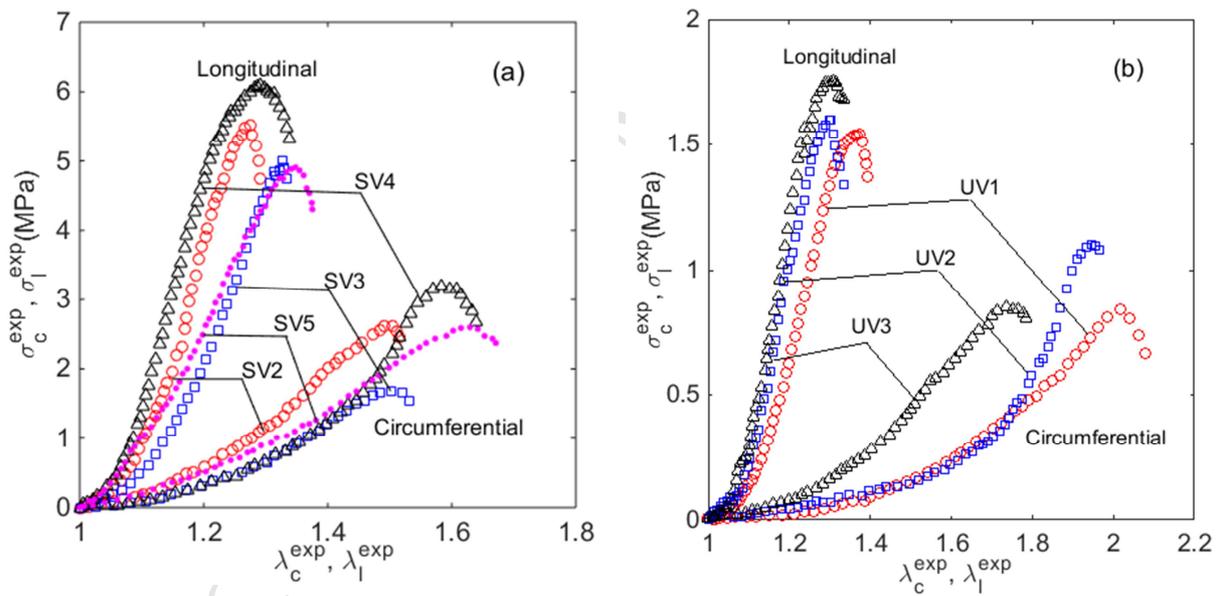


Fig. 7 Experimental stress-stretch data of human saphenous and umbilical veins in [64], (a) saphenous veins (SV), SV2-SV5, (b) umbilical veins(UV), UV1-UV3

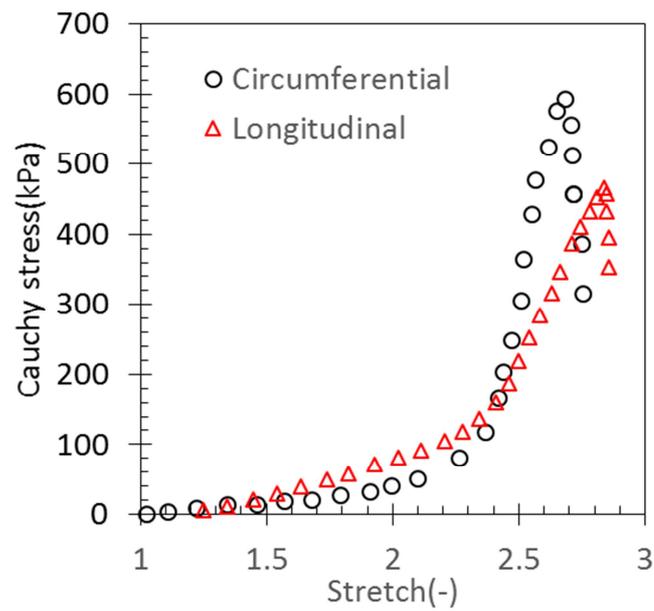


Fig. 8 Cauchy stress-stretch data of bovine vein tested in [92], strain rate is 100%/s

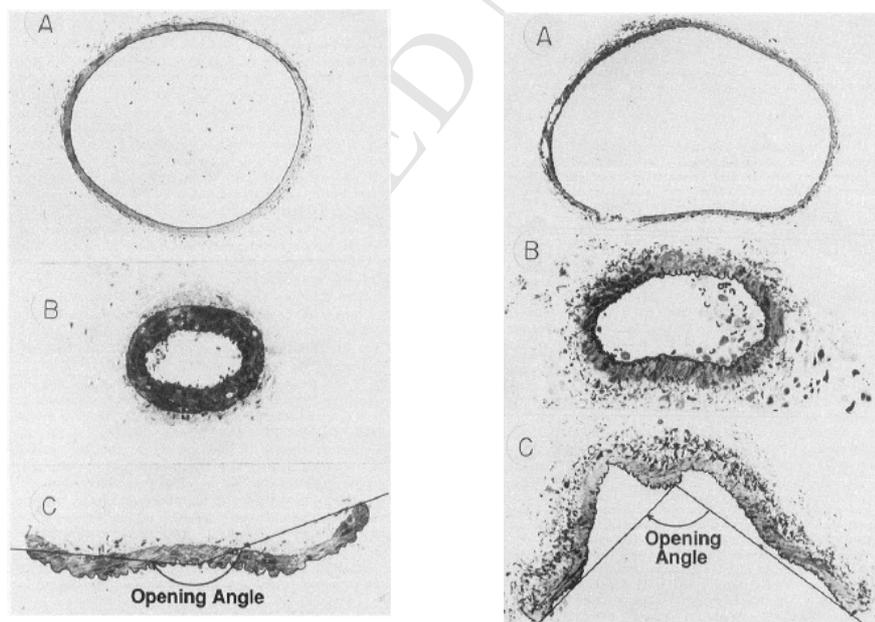


Fig. 9 Opening angle definition, the left: ileal artery fixed at three states: 120mmHg blood pressure (A), zero load (B) and zero stress (C), the right: ileal vein fixed at three states: 3mmHg blood pressure (A), zero load (B) and zero stress (C), the pictures are from [111]

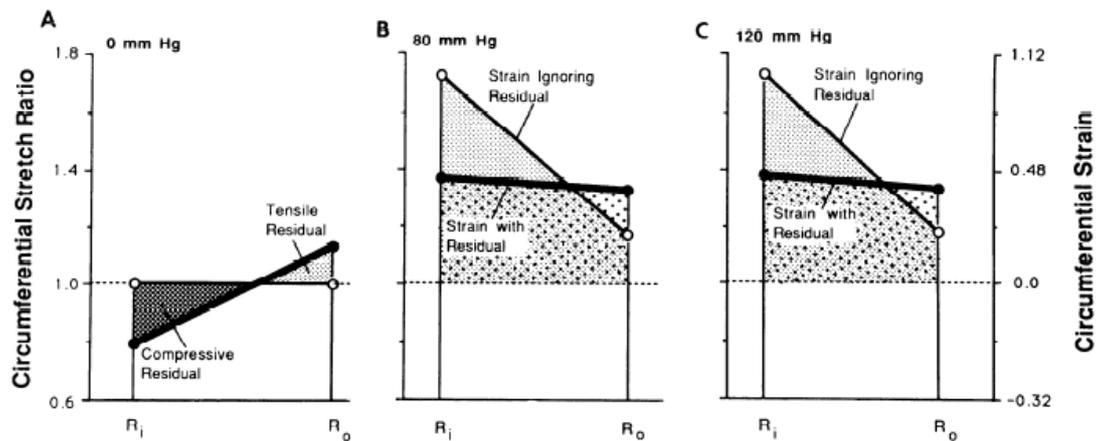


Fig. 10 Circumferential stress distribution across the ileal arterial wall. Zero load (A), 80 mmHg blood pressure (B) and 120mmHg blood pressure (C), the pictures are from [111]

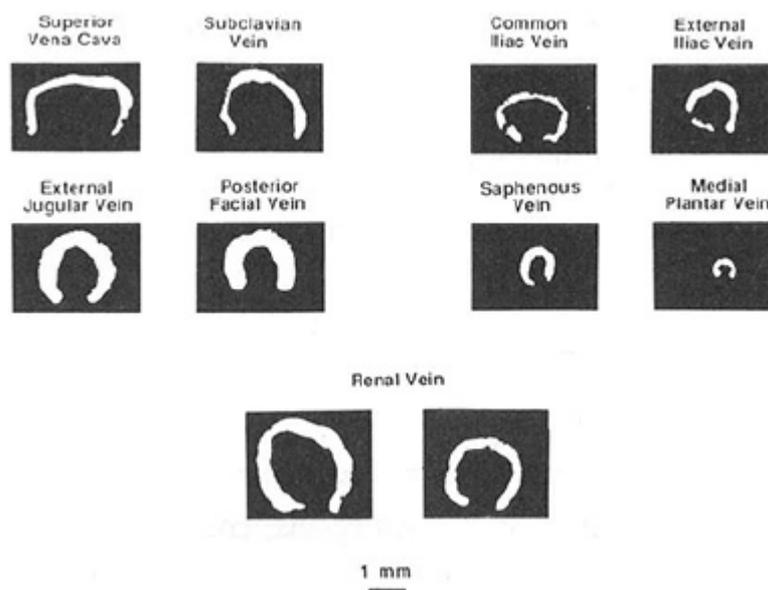


Fig. 11 Typical zero stress states of rat veins, the pictures are after [115]

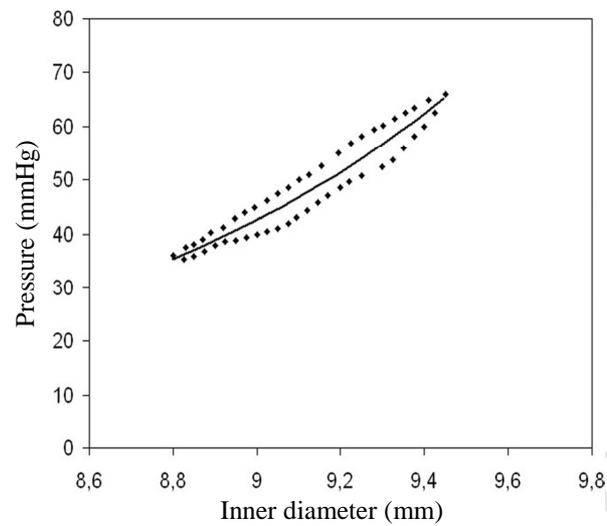


Fig. 12 Comparison of inner diameter of vein between observation and prediction, the picture is after [130]

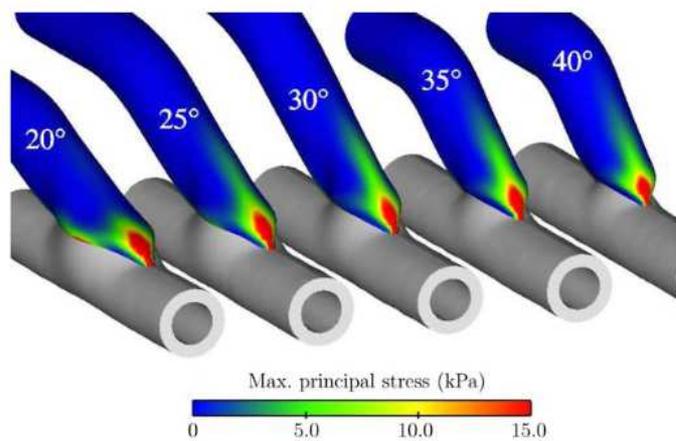


Fig. 13 The first principal stress contour in the implanted Saphenous vein grafts at various insertion angles, the picture is after [131]

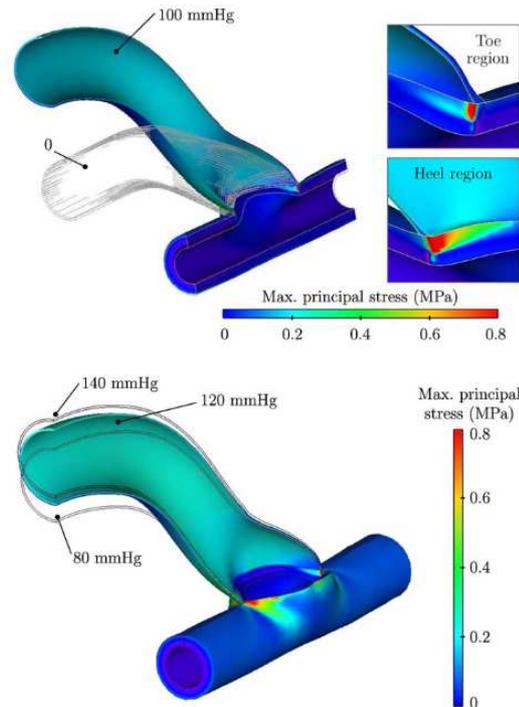


Fig. 14 The first principal stress contour and saphenous vein deformation at 0, 80, 100, 120 and 140mmHg arterial mean pressure, the insertion angle is  $25^\circ$ , the picture is after [131]

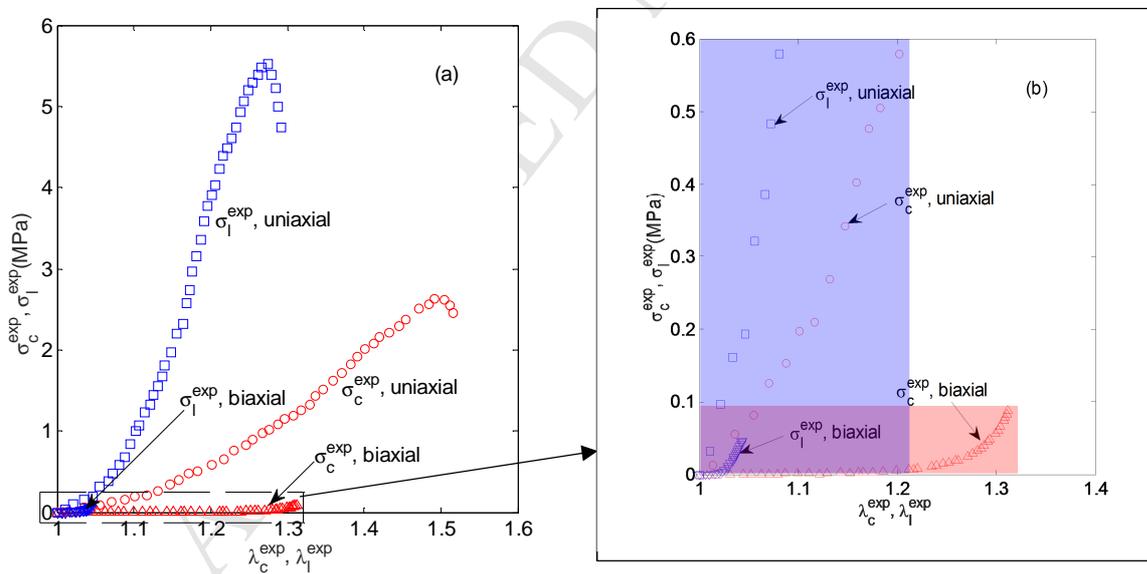


Fig. 15 A comparison of Cauchy-stretch curves measured by uniaxial and tubular biaxial tensile tests, the tensile test data of sample saphenous vein 2 (SV2) are from [64], the first tubular biaxial inflation test data are from [99] at 4Hz loading rate on the human saphenous vein segment

## Highlights:

- Biomechanical properties and modelling methods of the human venous wall are critical for coronary artery bypass graft.
- Active and passive biomechanical behaviours of the human venous wall were reviewed extensively and comprehensively.
- Biomechanical properties of the human venous wall are not well documented.
- Modelling approaches are subjected to be updated significantly.
- Important issues, namely suitability of constitutive law, biomechanical property identification in vivo, tissue damage effect etc. should be addressed in the future.