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Alexandre Franquet, Stéphane Avril, Rodolphe Le Riche, Pierre Badel, Fabien Schneider, et al.. Identification of the in vivo elastic properties of common carotid arteries from MRI: a study on subjects with and without atherosclerosis.. *Journal of the Mechanical Behavior of Biological Materials*, 2013, 27 (11), pp.184-203. 10.1016/j.jmbbm.2013.03.016 . hal-00805128

HAL Id: hal-00805128

<https://hal.science/hal-00805128v1>

Submitted on 27 Mar 2013

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1 Identification of the *in vivo* elastic properties of
2 common carotid arteries from MRI: a study on
3 subjects with and without atherosclerosis.

4
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15 **Abstract**

16 The stiffness of the arterial wall, which is modified by many cardiovascular
17 diseases such as atherosclerosis, is known to be an indicator of vulnerability.
18 This work focuses on the *in vivo* quantification of the stiffness of the common
19 carotid artery (CCA) by applying the Magnitude Based Finite Element Model
20 Updating (MB-FEMU) method to 13 healthy and diseased volunteers aged
21 from 24 to 76 years old. The MB-FEMU method is based on the minimisa-
22 tion of the deviation between the image of a deformed artery and a registered
23 image of this artery deformed by means of a finite elements analysis. Cross
24 sections of the neck of each subject at different times of the cardiac cycle are

25 recorded using a Phase Contrast cine-MRI. Applanation tonometry is then per-
26 formed to obtain the blood pressure variations in the CCA throughout a heart
27 beat. First, a time averaged elastic modulus of each CCA between diastole
28 and systole is identified and a stiffening of the artery with age and disease is
29 observed. Second, four elastic moduli are identified during a single heart beat
30 for each artery, highlighting the nonlinear mechanical behaviour of the artery.
31 A stiffening of the artery is observed and quantified at systole in comparison
32 to diastole.

33 **Keywords**

34 Identification, mechanical properties, elasticity, finite elements analysis, *in vivo* anal-
35 ysis, MRI, artery

36 **1 Introduction**

37 Arterial stiffness is known to be a crucial indicator for the diagnosis of arterial health
38 [14]. This indicator provides information on the ageing of the artery, or on the
39 progress of diseases such as atherosclerosis [19, 37] which mainly concerns the coro-
40 nary and the carotid arteries. Identifying the elastic properties of the Common
41 Carotid Artery (CCA) of a patient could then be a tool for improving diagnoses.

42 A variety of noninvasive techniques have been developed and used to try to iden-
43 tify the arterial stiffness *in vivo*. The Pulse Wave Velocity for instance is an indicator
44 of the mean arterial stiffness. It is estimated by measuring the travel time of a wave
45 between two measurement sites [33]. More advanced methods are used for the lo-
46 cal assessment of the arterial stiffness. Many studies track the change of arterial
47 diameter during heart beat by ultrasounds [30, 21, 4, 6, 3, 2]. The blood pressure
48 is generally measured in parallel on the brachial artery. The elastic modulus is then
49 deduced from these measurements by using assumptions such as the perfect circu-
50 larity of the artery with a free outer contour. For instance [30] have shown that the
51 elastic modulus of the CCA tends to increase with age. If this kind of approaches has
52 the advantage to be simple, and can be used for a rapid examination, the complex
53 nonlinear mechanical behaviour of arteries [11, 13, 28] cannot be assessed by a unique

54 modulus without requiring the linearisation of the stress-strain curve. To this aim,
55 other studies have considered nonlinearities and identified either nonlinear [25, 23] or
56 multi-linear [8, 15, 16] constitutive properties of the artery. Eventhough the artery is
57 still simplified as a tube, these recent studies have incorporated a surrounding tissue
58 around the artery. It has been shown that the surrounding tissue plays an important
59 role in the strain which effectively occurs in the artery (and as a consequence, on
60 the stresses) and then must be included in the models for the identification of the
61 mechanical properties [38, 24, 22, 27, 10]. Similarly the measurement of the blood
62 pressure is a sensitive step since it is directly involved in the estimation of the elastic
63 properties [17, 10]. A new methodology for identifying the mechanical properties of
64 tissues from MRI has recently been designed in our team [10]: the Magnitude Based
65 Finite Element Model Updating Method (MB-FEMU) works by registering a tem-
66 plate image using a Finite Element Analysis. The registered image, which depends
67 on the elastic properties input to the FE model, is compared to a target image. The
68 identification of the elastic properties of the FE model consists in minimising the
69 difference between the target and the registered image by iteratively updating the
70 elastic properties. The template and the target images are two experimental images
71 obtained using a cine Magnetic Resonance Imaging (MRI) sequence at different times
72 of the cardiac cycle.

73 In the current work, we investigate the identification of the elastic modulus of
74 the CCA *in vivo* using the MB-FEMU method. It has been applied in clinical con-
75 ditions to 9 healthy volunteers (24 to 63 years old) and 4 volunteer patients with
76 atherosclerosis (68 to 76 years old). A unique elastic modulus is first considered
77 before studying the evolution of the elastic modulus through the cardiac cycle. The
78 influence of the surrounding tissue and of the measurement of the blood pressure on
79 the identified mechanical properties is discussed in details.

80 2 Methods

81 2.1 Subjects and patients

82 The following research protocol was approved by the review board of Saint-Etienne
83 University Hospital and informed consent was obtained from all subjects. The sub-
84 jects studied were separated into three groups. The first group was named the “Young
85 healthy subjects” and was composed of 4 men without any declared disease aged from
86 24 to 26 years old. The second group of subjects (dubbed “Mid-age healthy subjects”)
87 was made of 5 healthy subjects (1 woman and 4 men) aged from 51 to 63 years old.
88 The third group, named “Old diseased patients” was composed of 3 men with se-
89 vere ($>80\%$ diameter reduction) unilateral carotid bifurcation occlusive disease and
90 1 woman with a bilateral post-radiation stenosis ($>80\%$) aged from 68 to 76 years
91 (report to the Table 1).

92 The mechanical properties of the CCA were estimated from Magnetic Resonance
93 2D images. A dedicated (1st and 2nd groups) or additional (3rd group) Phase Con-
94 trast (PC) sequence was used to obtain slices of the neck at different times of the
95 cardiac cycle (cine MRI). The acquisition of PC images lasts approximately 5 min-
96 utes depending on the heart rate of each individual. The subjects spent a total time
97 of approximately 30 minutes in the MRI (including 3 slices of the arterial tree in cine
98 MRI, positioning MR sequences -Time Of Flight-, Turbo Spin Echo sequences -T1
99 and T2 weighted images-). In this study only the PC cine MRI of one slice of the
100 CCA was used. The patients spent 45 minutes in the device including the additional
101 sequence and the routine pre-surgical cerebral sequence.

102 15 minutes after the MRI the subjects and patients had an applanation tonom-
103 etry examination in order to measure the variation of their blood pressure during a
104 cardiac cycle (a probe is applied on the carotid artery by a trained physician to de-
105 rive the physiological signal). Blood pressure was also measured before and after the
106 MRI (and during the MRI for 2 healthy subjects). For all the healthy subjects, an
107 additional echography was performed in order to measure the Intima-Media Thick-
108 ness of their common carotid. The experimental protocol is summarised in Figure
109 1.

Table 1: Description of the subjects. Three groups were defined: the “Young Healthy subjects” (YH) group, the “Mid Age Healthy subjects” (MAH) group and the “Old Diseased patients” (OD) group. IMT is the Intima Media Thickness which was measured by ultrasounds except for the OD group where values from the literature were used [7].

Subject Patient	Gender	Age (years)	Height (cm)	Weight (kg)	Diseased artery	IMT left/right (mm)
YH1	M	25	185	85	No	0.45/0.45
YH2	M	24	183	80	No	0.43/0.43
YH3	M	25	182	85	No	0.45/0.45
YH4	M	26	180	70	No	0.44/0.44
MAH1	M	59	163	72	No	0.83/0.72
MAH2	M	63	179	72	No	0.56/0.49
MAH3	M	51	175	74	No	0.62/0.51
MAH4	M	53	165	65	No	0.56/0.47
MAH5	F	57	155	62	No	0.58/0.48
OD1	F	70	158	57	Left/Right	0.70/0.70
OD2	M	68	182	87	Right	0.73/0.73
OD3	M	75	170	82	Right	0.73/0.73
OD4	M	76	178	78	Right	0.73/0.73

110 2.2 Imaging modalities

111 Magnetic Resonance Imaging was used with a Phase Contrast sequence to provide the
112 cross section of the carotid artery at different time steps (cine MRI). A 3T Siemens
113 Verio combined with a 4-Channel flex coil was used with a 2D spin echo FLASH
114 sequence to provide series of images during the cardiac cycle. The acquisition of
115 images was synchronised with the physiological signal which was captured by an
116 infrared spectroscopy device fixed on the subject’s finger. A single 4 mm thick slice
117 was used. The 2D in plane resolution was 0.586 mm \times 0.586 mm. The slice’s position
118 was 27 mm below the carotid bifurcation which was located on Time Of Flight images.
119 Its orientation was chosen to cut the two common carotid arteries perpendicularly.
120 The acquisition frequency was set automatically for each subject depending on his or
121 her heart rate, providing between 35 and 50 images per cardiac cycle. Note that these

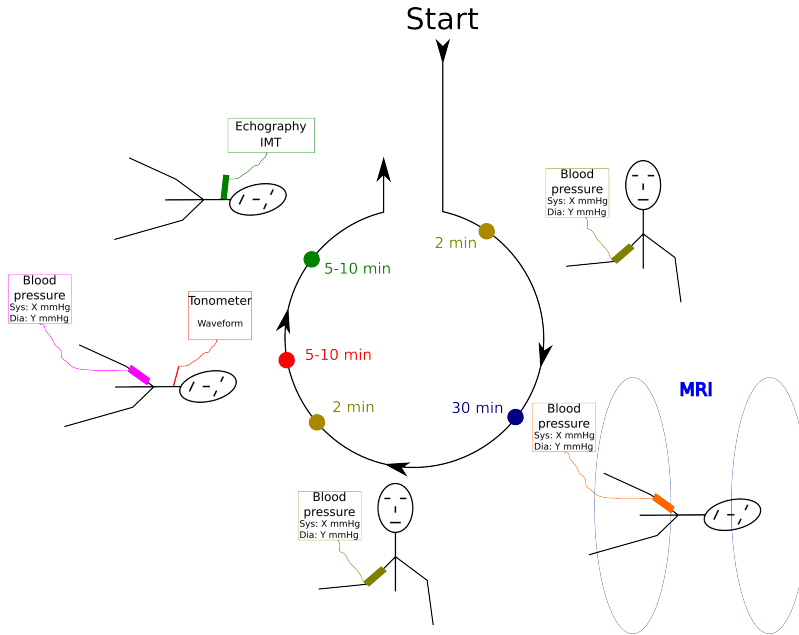


Figure 1: Description of the experimental protocol for a healthy subject. After admission at the radiological service, the blood pressure is measured by a trained physician using a digital sphygmomanometer. The MR exam lasts approximately 30 minutes depending in part on the heart rate of each subject. Note that the diseased patients spend 15 more minutes in the tube for their routine pre-surgical MR exam. The blood pressure is then measured in the radiological service one more time. The subjects reach the service of vascular medicine and after few minutes of rest, have an applanation tonometry examination with a trained physician where their blood pressure is recorded in order to scale their wave form obtained by tonometry. Finally, for the healthy subjects, it was possible to perform an echography in order to measure the Intima Media Thickness.

122 images were reconstructed from several cardiac cycles although an image sample at
 123 each time step was recorded at each cardiac cycle. The magnitude of images was
 124 digitised with a 12 bits resolution so that each voxel has an integer value between 0
 125 and 4,095.

126 For each subject and each artery, a region of interest of 21×21 pixels centred
 127 on the carotid was delineated on the magnitude PC images which yields the raw
 128 2D experimental images recorded at different time steps. The images were filtered

129 along the time axis using a temporal Gaussian filter with a kernel size $\sigma = 1.5$.
 130 Each carotid was considered as independent so that the total number of experiments
 131 reached $2 \times 13 = 26$ specimens.

132 2.3 Identification method

133 The Magnitude-Based Finite Element Model Updating method (MB-FEMU), which
 134 has some common features with the Modality Independent Elastography method
 135 [36], was developed in a previous work [10]. The principle is to build up a registered
 136 image from an initial, measured, template image using a displacement field computed
 137 by a Finite Element Analysis. The elastic properties of the finite elements model are
 138 updated until the registered image matches a target measured image. The template
 139 and the target images correspond to the initial undeformed and deformed (i.e. after
 140 the application of external forces) states, respectively. In our case, the imaged object
 141 was a cross section of the CCA, and the force applied between the template and the
 142 target was the differential blood pressure. This technique requires the acquisition
 143 of both the images of the artery at two different times of the cardiac cycle, and the
 144 differential blood pressure between these two times. Note also that a correction of
 145 rigid motions between the template and the target images was applied before the use
 146 of the MB-FEMU (see Section 2.5.2). The flow-chart of the method is summarised
 147 in Figure 2.

148 The identification of the mechanical properties was achieved by minimising a
 149 cost function defined as the difference in intensity between the target image and the
 150 registered image:

$$J_2(E) = \frac{1}{2 \cdot N_{pix}} \sum_{i=1}^{N_{pix}} (I_{target}^i - I_{registered}^i(E))^2 \quad (1)$$

151 This cost function was calculated only at the pixels where the partial volume
 152 effect occurs: the pixels are filled with different materials so their intensity values
 153 depend on the proportion of the different materials. A binary mask was defined to
 154 this aim, as the dilation of a first binary mask which contains the pixels where the
 155 inner contour of the artery was found (see Section 2.4.1). The first binary mask

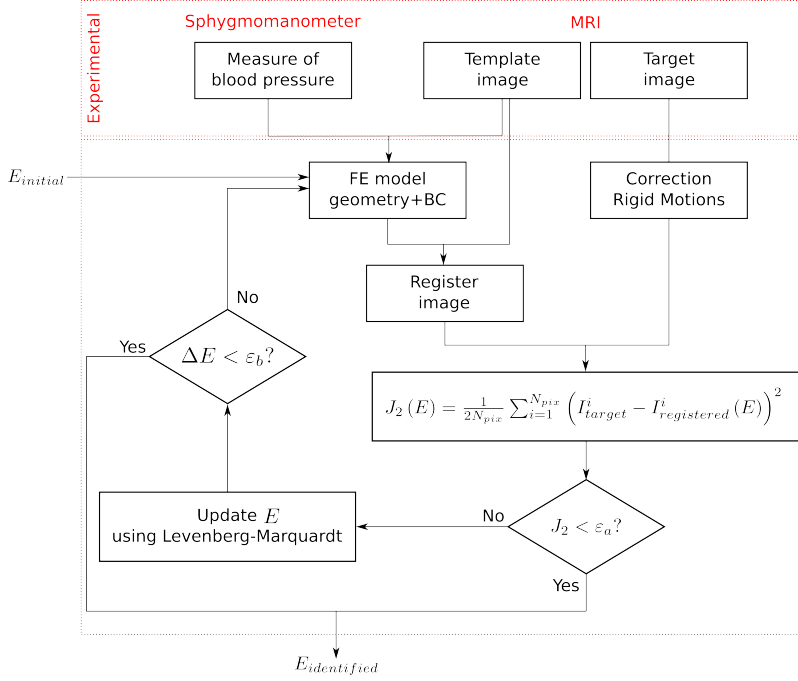


Figure 2: Flow-chart of the MB-FEMU method applied to the identification of the mechanical properties of the artery using MR images. A template and a target images are acquired using a MRI device. Blood pressure is measured at the same time. A finite element model is defined from the template image, mechanical assumptions, and blood pressure. The computed displacement field is a function of the elastic properties of the materials and is used to register the template image. Note that a procedure of correction of the rigid motions between the template and the target image is applied (see Section 2.5.2). A distance, J_2 , between the registered image and the target image is minimised with regards to the elastic properties of the artery, E .

156 was dilated using a square structuring element S of size 3×3 with $S_{ij} = 1$ (see
 157 Figure 3). In our study we used a bounded Levenberg-Marquardt algorithm [12] to
 158 minimise the cost function. The gradients of the computed intensity with regards
 159 to the mechanical properties were calculated by backward finite differences. The
 160 identification algorithm stops when one of the following criteria was reached: either
 161 the target and the registered images matched well, $J_2 < \varepsilon_a = 1$, or the identification
 162 algorithm was making too small steps, $\Delta E < \varepsilon_b = 10^{-3}$.

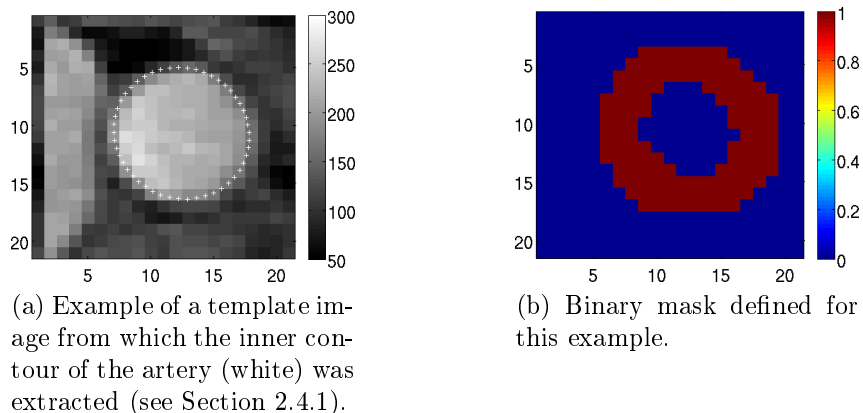


Figure 3: Example of the definition of a binary mask on a template image. The cost function was only calculated where the binary mask is not null. The details of how the contour was obtained are described in Section 2.4.1.

163 2.4 Finite elements models and mechanical assumptions

164 2.4.1 FE model: geometry, boundary conditions and mesh definition

165 The geometry of the 2D FE models was derived from the initial (diastole) PC MR
 166 images of each subject. Each carotid was considered as independent so that two
 167 FE models were defined by subject, each representing a semi-neck. Three materials
 168 were segmented: (i) the inner contour of the carotid was determined by an automatic
 169 algorithm based on a Fourier polynomial description (see [10] for details). The artery
 170 was then defined as an homogeneous media and derived from this contour outwards
 171 with a thickness measured on an ultrasonic device (Intima Media Thickness (IMT) on
 172 the distal wall of each carotid artery). For the third experimental group (“old diseased
 173 group”), the IMT was not measured for non-medical reasons so thicknesses found in
 174 the literature [7] were used (0.70 mm for the woman and 0.73 mm for the men).
 175 (ii) An homogeneous material which surrounds the artery was segmented manually
 176 on the same initial image. The contours defined followed firstly, the jugular vein,
 177 secondly the external contour of the neck, and finally the spine. (iii) An artificial third
 178 material was created around the surrounding tissue. It had no mechanical influence
 179 and was only used for an easy implementation of our registration algorithm. Note
 180 that the radiological convention was applied throughout the manuscript. It means

181 that the left artery is located at the right of the spine and *vice versa*. The differences
182 between the left and right geometries will be discussed in the Discussion section.

183 For the boundary conditions, the spine was fixed and a vertical symmetry was
184 assumed since the semi-neck only was modelled for each experiment. A uniform
185 pressure was applied on the inner arterial wall. It corresponds to the differential
186 blood pressure measured on each subject between the deformed and the undeformed
187 states.

188 The mesh consisted in approximately 8,000 quadratic triangles (6 nodes) for each
189 FE model. This type of element can provide accurate displacement fields for those
190 types of problems [9]. The element size was refined on the artery's contour and
191 close to it. Finally the artery had approximately 1,000 elements and the surround-
192 ing tissue approximately 7,000. The third "artificial" material had a coarse mesh
193 (approximately 100 elements).

194 The FE computation ran on the 6.8 version of Abaqus© standard and took
195 approximately 5 seconds on a desktop PC (Core Quad 2.5 GHz, 4 GB RAM).

196 **2.4.2 Mechanical assumptions**

197 As a first approximation the three materials were considered as linear elastic since
198 we work on the differential state between diastole and systole so only the tangent
199 behaviour of the stress-strain relationship was taken into account. We assumed a
200 2D plane strain problem in the finite deformation framework. Quasi static conditions
201 were postulated because heart beat frequency was approximately 1 Hz.

202 The elastic properties of the surrounding tissue were set in the FE model to
203 $E = 30$ kPa with a Poisson's ratio $\nu = 0.49$ [29]. The elastic properties of the
204 "artificial" tissue were set to have no mechanical influence: $E = 10^{-6}$ kPa and $\nu = 0$.
205 We checked that the presence of this artificial tissue in the FE model had no influence
206 on the displacement fields. The Poisson's ratio of the CCA was set to $\nu = 0.49$. The
207 elastic modulus of the artery was unknown and had to be recovered.

208 2.5 Identified variables

209 2.5.1 Elastic properties of the common carotid arteries

210 The aim of this study is first to study the elastic properties of the CCA. The other
211 variables such as the mechanical properties of the surrounding material, the blood
212 pressure, or the geometry of the FE model was supposed to be known. We further
213 investigate the effects of these properties on the identified elastic properties of the
214 artery. For one subject and one side, we performed a total of 5 different identifi-
215 cations of the elastic properties of the CCA, which comprise one identification for
216 the diastole-systole average behaviour and 4 identifications at successive parts of the
217 cardiac cycle in which the template and target images are chosen.

Table 2: Description of the 5 different couples of template/target images used for each hand side on each subject/patient.

Identification procedure	Template image	Target image
(a)	End-diastole	Mid-systole
(b)	Mid-systole	End-systole
(c)	Mid-diastole	End-systole
(d)	End-diastole	Mid-diastole
(e)	End-diastole	End-systole

218 The reader can refer to the Figure 4 for an illustration of the different identifica-
219 tion times. The mid-systole time was defined as the time from the end-diastole to
220 recover 50% of the systolic pressure. The same calculation was applied to recover
221 the mid-diastole time. The procedures (a) to (d) in Table 2 describe the variation of
222 the elastic properties through the cardiac cycle. The procedures (b) and (c) use the
223 deformed FE model obtained at the end of the identification procedures (a) and (d),
224 respectively. Note that only the geometry was imported and not the stress field. The
225 imposed boundary conditions in pressure are described in Section 2.6. The procedure
226 (e) uses the most deformed images that are, on the one hand the diastolic or initial
227 image as the template, and on the other hand the systolic image as the target. In
228 this case, the measured pulse pressure was applied.

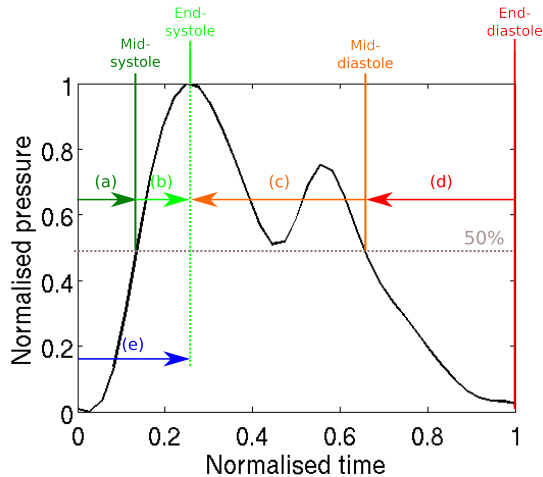


Figure 4: Illustration of the subsections of the cardiac cycle defined to identify 4+1 different elastic moduli throughout a cardiac cycle (identification procedures (a) to (d), the target and template images are chosen according to this scheme and the pressure applied as a boundary condition is the corresponding differential pressure). The identification procedures (b) and (c) use the deformed geometries obtained at the end of the identifications (a) and (d) respectively. For the procedures (c) and (d) the template image is taken later in time than the target image in order to keep a positive pressure inflation. The identification procedure (e) uses the measured pulse pressure as a boundary condition and the images at diastole and systole .

229 2.5.2 Correction of the in-plane translation

230 As described previously, the FE models were determined from the initial image.
 231 During the increase of pressure in the arterial tree, in-plane movements of the artery
 232 can potentially occur due the real complex 3D geometry. These movements are a
 233 translation of the artery in the cutting plane, that cannot be taken into account
 234 directly with our 2D FE model. Then, before each identification procedure, we
 235 estimated the in-plane translation of the artery by (i) first, defining a region of interest
 236 (ROI) on a "correction image" (template image registered with a displacement field
 237 of the FE model with $E_{artery} = 600$ kPa. This region of interest was a square that
 238 contains the artery. The square's limits were deduced from the binary mask used.
 239 (ii) Second, we performed a normalised cross-correlation between this ROI and the
 240 correction image, and this ROI and the target image. The difference between the

241 locations of the maximum of these normalised cross-correlations gives the estimated
 242 correction vector that is used throughout the identification procedure (see Figure
 243 5). In summary, a complete identification procedure consists in the estimation of
 244 the in-plane translation of the artery, and then of the identification of the elastic
 245 properties of the CCA using the MB-FEMU method. The effect of this correction
 246 vector is discussed later in the article.

247 2.6 Determination of the blood pressure

248 The diastolic and systolic blood pressure were measured several times during the
 249 protocol. Different digital or manual sphygmomanometers were used. It was assumed
 250 that the pressure in the CCA is the same as the pressure measured in the brachial
 251 artery. For several subjects, the blood pressure was measured before, during and after
 252 the MR exam on the left arm. In addition to these measurements of the diastolic and
 253 systolic pressures, an applanation tonometry examination was performed. It consists
 254 in applying a probe on the neck of the subject/patient for obtaining the profile of
 255 pressure variations throughout a cardiac cycle. A second approach was designed here
 256 for obtaining this data. The approach consists in estimating an index, called the "P-
 257 index" for "Pressure index", based on the mean deformation of the artery throughout
 258 the cardiac cycle. The idea behind the P-index is that the instantaneous artery size,
 259 as measured by MRI, is representative of its internal pressure.

260 The P-index is determined for each subject and for each neck-side. Considering
 261 the 2D+t set of images, the first image (diastole state) is subtracted from every
 262 image frame for which the P-index has to be computed (see Figure 6). Then the
 263 P-index is defined as:

$$\begin{aligned}
 \text{P-index}_{raw}(t) &= \frac{1}{N_{pix}} \sum_{i=1}^{N_{pix}} I^i(t) - I^i(t_0) \\
 \text{P-index}(t) &= \frac{\text{P-index}_{raw}(t) - \min(\text{P-index}_{raw}(t))}{\max(\text{P-index}_{raw}(t)) - \min(\text{P-index}_{raw}(t))}
 \end{aligned} \tag{2}$$

264 where N_{pix} is the number of pixels of the binary mask (Figure 3); i is the i^{th} pixel in
 265 this set of pixels; t_0 is the initial time (diastole).

266 Once the P-index is calculated, it is used to determine which image frame is
 267 respectively at the mid-systole time, end-systole time, mid-diastole time and end-

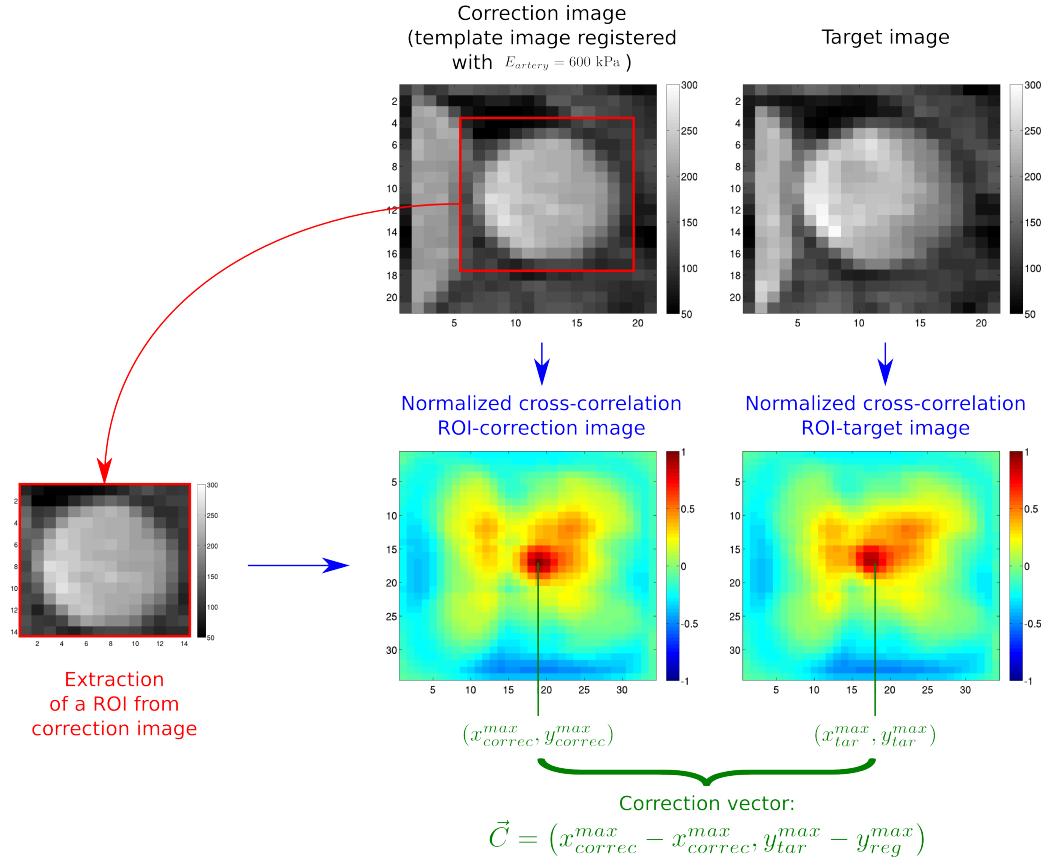
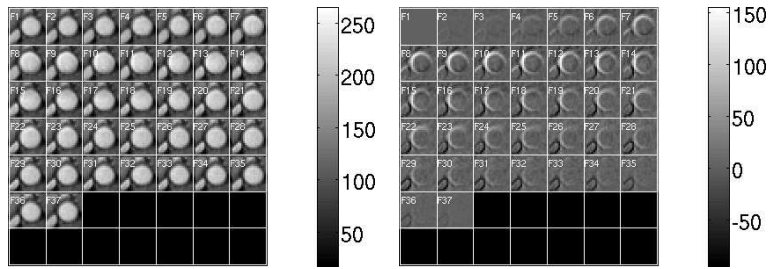


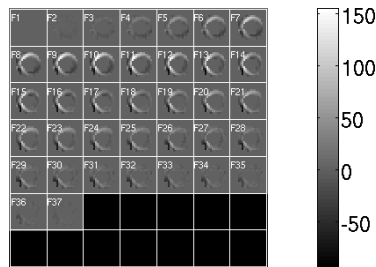
Figure 5: Principle of the correction of the translation between the template and the target image. The template image is first registered using an elastic modulus of the artery of 600 kPa. The ROI is chosen as the circumscribed square of the binary mask. A normalised cross-correlation between the ROI and the registered image gives a map where the maximum can be located. This corresponds to the location of the ROI in the registered image. The same operation is computed between the ROI and the target image to find the best location of the ROI in the target image. The difference between these two sets of coordinates gives the correction vector.

268 diastole time (see Figure 4). The end-diastole and end-systole images can be deter-
 269 mined directly: the end-diastole image is the first image and the end-systole image
 270 is the image where the P-index reaches its maximum. The mid-states (mid-diastole
 271 and mid-systole) images were chosen when the P-index reaches 50 % of its maximal
 272 value.

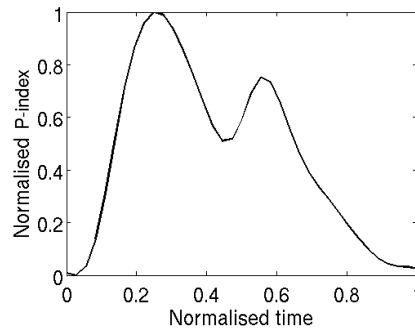


(a) Set of images throughout the cardiac cycle. This example is made up with 37 frames equally distributed throughout the cardiac cycle.

(b) The first image (diastole) is subtracted to every image frame.



(c) The binary mask (Figure 3) is applied.



(d) Example of P-index profile throughout a cardiac cycle.

Figure 6: Principle of calculation of the P-index.

273 3 Results

274 3.1 Geometries of the subjects arteries

275 All the geometries were segmented independently. The diameter of the arteries was
 276 estimated from the cross-sectional area A of the 2D in-plane shape of the artery

277 ($D = 2\sqrt{(A/\pi)}$, see Figure 3). The mean diameter of the healthy arteries is
 278 6.45 ± 0.70 mm while the 5 diseased arteries have a mean diameter of 6.66 ± 1.54 mm.

Table 3: Equivalent diameters of the arteries of the subjects taking part to the experiment.

Subject/ Patient	Diameters (mm)	
	Left	Right
YH1	6.81	6.46
YH2	5.70	6.22
YH3	6.32	6.71
YH4	6.33	6.33
MAH1	6.05	6.60
MAH2	7.17	6.65
MAH3	7.40	6.25
MAH4	6.62	6.78
MAH5	5.45	5.39
OD1	5.57	5.06
OD2	6.00	6.64
OD3	8.48	9.04
OD4	5.68	7.01

279 The FE geometries were derived from the initial (diastole) image of each subject
 280 (see A). The variability of neck morphologies is evident. Oblong shapes (YH1, YH2,
 281 YH3, YH4, MAH1, MAH3, MAH5, OD1, OD4) and round shapes (OD2) can be
 282 observed as well as more angular shapes (MAH2, MAH4, OD3). Jugular veins (the
 283 internal jugular here) on a unique subject also present some variability. Two subjects
 284 exhibit a split vein close to the artery on one side only (MAH4 and MAH5). The
 285 vein is crushed for subjects YH4, MAH2 and MAH3 (one side), and for patient OD4.

286 The locations of the artery with regards to the spine also varies significantly (see
 287 Table 4). On the average, this distance is 7 mm but it varies from 2 mm to 12 mm
 288 between different individuals.

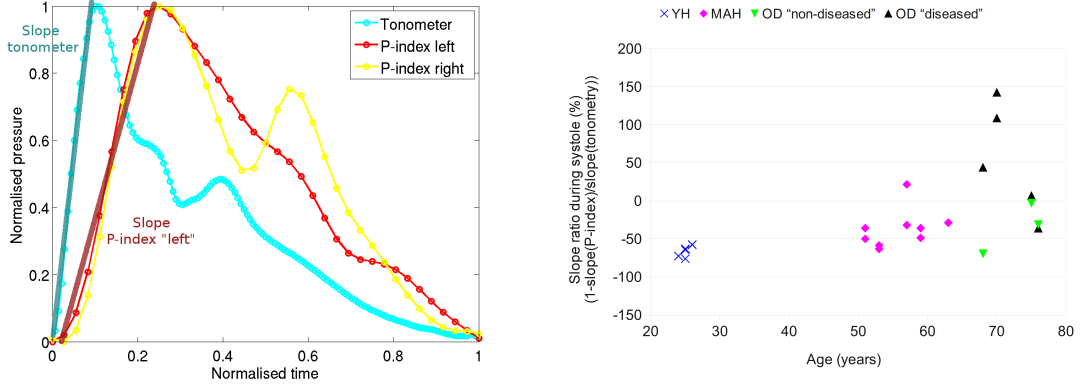
Table 4: Approximate distance between the spine and the inner contour of the CCA.

Subject/ Patient	Distance (mm)	
	Vertebral column - artery Left	Right
YH1	11	12
YH2	7	9
YH3	7	9
YH4	4	6
MAH1	2	6
MAH2	9	4
MAH3	7	5
MAH4	4	5
MAH5	10	10
OD1	7	6
OD2	4	7
OD3	5	9
OD4	12	12

289 3.2 Blood pressure

290 The results of the determination of the blood pressure in the CCA are shown in B.
 291 The P-index shows a profile that consists in a first rapid increase and then a decrease
 292 until reaching almost zero at the end-diastole state.

293 Differences between the P-index profiles and the pressure profiles obtained by
 294 applanation tonometry are significant. Figure 7 shows the difference in the initial
 295 slope defined as $(1 - Slope\ P\text{-index}/Slope\ \text{Tonometer}) \times 100$. On the average, there
 296 is a ratio between both initial slopes of -28.24% . This ratio is of $-67.41 \pm 0.07\%$
 297 for the YH group, $-35.91 \pm 14.08\%$ for the MAH group and $-34.49 \pm 33.37\%$
 298 and $50.50 \pm 72.99\%$ for the healthy and the diseased arteries of the OD group,
 299 respectively. These differences between initial slopes induce a time offset between
 300 the systole of the P-index and the systole from the pressure profile.



(a) Initial slopes of the pressure profile and of the P-index profile. (b) Slope ratios for the young subjects (YH), the mid-age subjects (MAH) and the old patients (OD).

Figure 7: Comparison between the initial slopes of the P-index and of the tonometer pressure.

3.3 Identified elastic moduli

The values of the identified elastic moduli are reported in Table 5. An indicator of the quality of image registration is also reported, defined as:

$$DI = 100 \times \frac{J_2 \left(E_{artery}^{identified} \right)}{J_2^\infty} \quad (3)$$

where J_2^∞ corresponds to the distance between the target image and the template image (only across the binary mask). J_2^∞ is the value of the objective function when neither deformation nor correction of displacement is allowed (see Figure 8). The DI index characterises the reduction of the cost function with the identification procedure.

Table 5: Identification results

Subject	Identification Procedure	Elastic modulus (kPa)		DI (%)	
		Left	Right	Left	Right
YH1	(a)	221	192	25.79	13.27
	(b)	349	303	50.48	56.06
	(c)	455	193	38.86	23.94
	(d)	185	456	13.19	20.79
	(e)	289	325	8.08	11.61
YH2	(a)	147	395	38.45	63.74
	(b)	662	213	88.69	56.39
	(c)	236	234	51.84	63.93
	(d)	208	347	43.36	55.38
	(e)	228	288	25.95	38.89
YH3	(a)	177	204	30.72	33.19
	(b)	793	1890	75.33	86.36
	(c)	250	308	34.03	31.24
	(d)	322	374	19.21	27.26
	(e)	318	363	10.15	14.85
YH4	(a)	132	119	23.82	40.93
	(b)	228	187	53.66	53.00
	(c)	230	128	50.43	38.20
	(d)	129	134	15.75	27.33
	(e)	224	490	36.21	21.83
MAH1	(a)	211	934	58.18	33.25
	(b)	499	848	86.33	28.99
	(c)	246	317	76.99	73.64
	(d)	292	167	55.06	17.83
	(e)	265	921	53.47	35.47
MAH2	(a)	374	338	51.17	47.84
	(b)	640	801	71.91	81.89

Continued on next page

Table 5 – *Continued from previous page*

Subject	Identification Procedure	Elastic modulus (kPa)		DI (%)	
		Left	Right	Left	Right
	(c)	423	580	69.01	71.07
	(d)	401	364	42.40	47.71
	(e)	446	464	40.61	42.84
MAH3	(a)	368	264	64.76	80.53
	(b)	503	574	83.25	88.03
	(c)	367	258	76.15	82.68
	(d)	448	604	72.20	86.64
	(e)	483	520	54.71	73.13
MAH4	(a)	200	386	49.69	66.78
	(b)	10843	1057	99.06	84.96
	(c)	454	545	64.76	62.84
	(d)	598	625	67.18	61.08
	(e)	503	563	35.85	47.30
MAH5	(a)	445	1281	47.55	13.95
	(b)	357	290	90.54	62.87
	(c)	642	1013	81.72	54.61
	(d)	285	245	56.89	59.61
	(e)	420	502	55.03	15.64
OD1	(a)	8781	5418	98.12	94.40
	(b)	600	7727	124.07	98.01
	(c)	50000	600	100.36	100.00
	(d)	812	655	68.39	74.65
	(e)	2239	6423	96.14	94.66
OD2	(a)	229	449	68.16	53.92
	(b)	213	724	55.81	89.48
	(c)	325	437	55.13	83.50
	(d)	406	491	67.54	69.42

Continued on next page

Table 5 – *Continued from previous page*

Subject	Identification Procedure	Elastic modulus (kPa)		DI (%)	
		Left	Right	Left	Right
OD3	(e)	392	487	41.57	58.14
	(a)	953	1165	53.01	70.07
	(b)	1117	2532	89.51	83.41
	(c)	1311	2065	79.96	81.01
	(d)	727	2098	64.92	71.35
	(e)	906	1308	61.56	62.04
OD4	(a)	235	528	64.02	78.11
	(b)	1499	424	97.51	68.14
	(c)	591	540	88.56	80.16
	(d)	376	577	70.94	69.53
	(e)	456	549	75.05	53.07

309

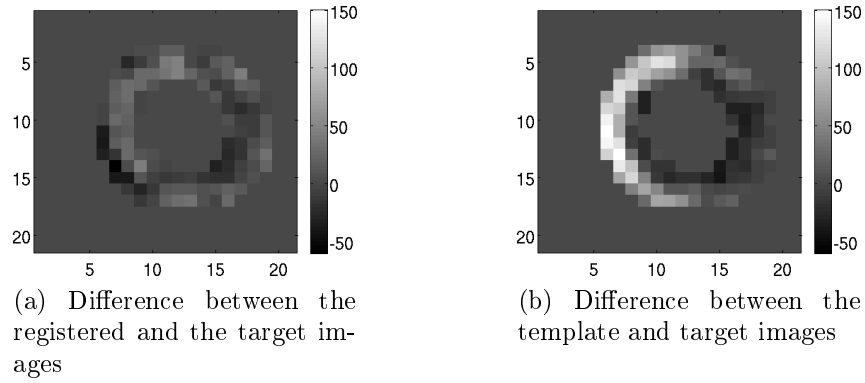


Figure 8: Difference between the target image and (a) the registered image after the identification or (b) the template image.

310 **3.3.1 Elastic modulus**

311 Using the MB-FEMU method, the elastic moduli of the CCA (left and right) of each
 312 subject is identified. First, we calculated the global modulus throughout the whole
 313 cardiac cycle. The global modulus is estimated with the diastole image as template
 314 image and the systole image as target image. The pressure which is applied as
 315 a boundary condition in the model is the difference between diastolic and systolic
 316 pressures measured on each subject.

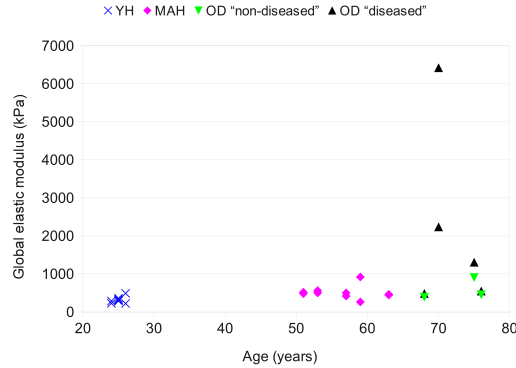
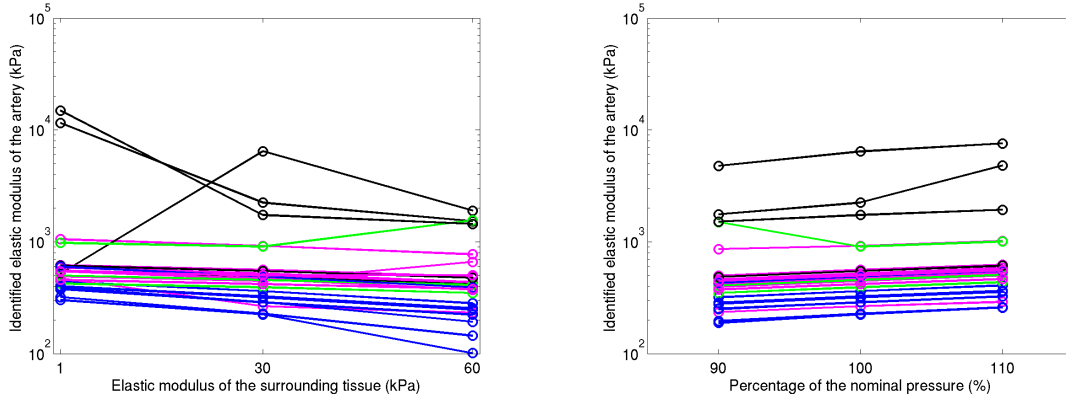


Figure 9: Global elastic modulus identified throughout a whole cardiac cycle.

317 **Effect of age and disease** The results show an increase in the elastic modulus of
 318 the CCA with age and disease (see Figure 9). The YH group exhibits a mean elastic
 319 modulus of 315 ± 29 kPa. It is 38 % inferior to the mean modulus of the MAH group
 320 (509 ± 65 kPa). The means of the OD group has not been calculated due to a lack
 321 of data.

322 **Effect of the surrounding tissue** It has been shown previously that, through a
 323 stiffness compensation effect, the identified elastic modulus of the CCA E_{artery} using
 324 the MB-FEMU is influenced by the estimation of the elastic properties of the sur-
 325 rounding tissue $E_{surrounding}$ [10]. Figure 10a shows how the estimation of these elastic
 326 properties can affect the identified elastic properties of the artery, E_{artery} . If E_{artery}
 327 when $E_{surrounding} = 30$ kPa is taken as a reference, E_{artery} is overestimated by 19 %

328 when $E_{surrounding} = 1$ kPa and underestimated by -18% when $E_{surrounding} = 60$ kPa
 329 on the average (excluding OD1 and OD3). The relationship between $E_{surrounding}$ and
 330 E_{artery} is linear in most of cases (25/26 arteries show a Pearson's correlation coef-
 331 ficient (PCC) $r < -0.9$). It is particularly the case for the YH group who have a
 332 mean PCC $r < -0.99$. The non-diseased arteries of the OD group present the worst
 333 coefficient $r = -0.39$ but there are only 3 specimens and the values are scattered
 334 (from $r = -1$ to $r = 0.82$).



(a) Influence of the elastic modulus of the sur-
 rounding tissue. The elastic modulus of the
 surrounding tissue has been changed in the FE
 model from 1 kPa to 60 kPa.

(b) Influence the estimated blood pressure. The
 applied blood pressure has been under or over
 estimated by 10%.

Figure 10: Influence on the global identified elastic modulus of the estimation of (a)
 the elastic modulus of the surrounding tissue and (b) the estimated blood pressure
 (YH: blue; MAH: magenta; OD non-diseased/diseased: green/black).

335 **Effect of the pressure** The pressure has a similar effect on the identified elastic
 336 modulus since it participates to the boundary conditions of the FE model. E_{artery}
 337 is underestimated by -10% with a pressure underestimation of -10% . When the
 338 pressure is overestimated by $+10\%$, E_{artery} is overestimated by $+12\%$ (excluding
 339 OD1). The PCC with regards to the evolution of the pressure applied is $r = 0.99$
 340 excluding the left hand side of OD3 (negative coefficient).

341 3.3.2 Evolution of the elastic modulus during a cardiac cycle

342 We have then identified elastic moduli at different times of the cardiac cycle:

343 a Between the diastole and the mid-systole

344 b Between the mid-systole and the systole

345 c Between the systole and the mid-diastole

346 d Between the mid-diastole and the diastole

347 Each modulus is estimated with the appropriate template and target images
348 determined from the considered fraction of the cardiac cycle. The pressures which are
349 applied as boundary conditions in the model are calculated using the P-index profiles.
350 Results are shown in Figure 11 for the YH, MAH and OD group. The identification in
351 the OD1 case has been excluded because it has failed, which numerically means that
352 the Levenberg-Marquardt algorithm stops due to a null gradient and $DI > 100\%$.

353 The YH group has an average elastic modulus of 325 kPa over the whole cardiac
354 cycle whereas the MAH group has an average elastic modulus of 752 kPa. The value
355 of the elastic modulus for the YH group starts from 198 kPa during the first fraction
356 of the cardiac cycle (see Figure 4), then it increases to 578 kPa in the second fraction
357 of the cardiac cycle, and is finally stable in the two last fractions until the return to
358 the diastole state (254 kPa and 269 kPa). The evolution of the elastic modulus of the
359 artery through the cardiac cycle is similar for the MAH group, with a higher elastic
360 modulus in the (b) fraction of the cardiac cycle than in the (a) fraction (619 kPa
361 on the average versus 511 kPa, excluding MAH4), and a stable modulus during
362 the diastolic phase ((c): 488 kPa on the average, (d): 381 kPa) (see Figure 11e).
363 The number of data for the OD group is very limited so that the means are not
364 meaningful.

365 4 Discussion

366 4.1 Effect of the age and of disease on the stiffness

367 The results show that there is an increase of +38% of the global elastic modulus
368 of the artery between the YH group and the MAH group. A Student's t-test on
369 the identified modulus of Table 5 (identification procedure (e)) reveals a significant
370 difference between the means of these two groups with a p -value¹ $p = 0.9968$ ².
371 These findings are in agreement with the literature. The large study of [30] shows
372 that there was a significant increase of the stiffness of the carotid arteries for males
373 and females from 40 years old to 64 years old. This increase has also been pointed
374 out in the review of [26]. The low number of data points for old and diseased patients
375 renders difficult the interpretation of the mean values, and other experiments should
376 be conducted. We can note that the diseased artery is always stiffer than the non-
377 diseased artery for patients OD2, OD3 and OD4 who have a unilateral lesion (392 kPa
378 vs 487 kPa, 906 kPa vs 1732 kPa, 456 kPa vs 549 kPa, respectively).

379 4.2 Comparision between the P-index profile and pressure 380 profiles obtained by the applanation tonometry technique

381 It is interesting to see the differences between the blood pressure measured by appla-
382 nation tonometry and the P-index profiles. For all cases excepted the old diseased
383 patients, the pressure increase as seen through the P-index is slower than that seen
384 by tonometry. These differences could be explained by the possible inertia of the
385 artery to be deformed or by the MRI artefacts. Figure 7 reveals that the difference
386 of slope between the P-index and the tonometry during the systole evolves with age
387 and disease in the same way as the stiffness of the artery: $YH < MAH$ ($p = 0.9989$),

¹the p -value is the probability of having an observation at least as extreme as the observation if the hypothesis H_0 is true. Low p -values (lower than a chosen significance level) may induce a rejection of H_0 .

²data fit a standard distribution, the variances are assumed to be unequal (Behrens-Fisher problem [18]), unilateral test with the null hypothesis H_0 : "mean from data set 1 is lower than mean from data set 2"

388 MAH < non-diseased OD ($p = 0.5248$), non-diseased OD < diseased OD ($p = 0.9698$)³.

389 **4.3 Evolution of elastic properties throughout the cardiac cy-** 390 **cle**

391 Arteries are known to be nonlinear [11, 13]. Since we have considered a linear me-
392 chanical behaviour, we have identified different elastic properties at different fractions
393 of the cardiac cycle. Note that there is a clear increase of the elastic modulus just
394 before the end-systole (identification at the (b) part of the cardiac cycle) for both
395 the YH group ($p = 0.95$) and the MAH group ($p = 0.74$)⁴. There is also a significant
396 decrease of the elastic modulus during the return to diastole (identification at the (c)
397 part of the cardiac cycle) for both groups ($p = 0.93$ and $p = 0.82$, respectively⁵). The
398 decrease of the elastic modulus between the cardiac cycle parts (c) and (d) is not
399 clear ($p = 0.40$ and $p = 0.83$ for the YH group and the MAH group, respectively).
400 We have also seen that the moduli from the identification procedures (a), (c) and
401 (d) are relatively close for both groups ($198 \rightarrow 269$ kPa and $381 \rightarrow 488$ kPa, respec-
402 tively). In both groups the elastic modulus is minimum during the first part of the
403 cardiac cycle, then increases during systole, and finally decreases during the return
404 to diastole and goes back to its initial value for the identification procedure (d). The
405 lack of data on the OD group has prevented to perform the t-tests. Other authors
406 were able to observe the differences between the elastic modulus of the artery at di-
407 astole and systole: [8] have studied the propagation of shear waves in arteries using
408 ultrasounds. They found on a unique subject that the elastic modulus steps up from
409 258 kPa during diastole to 402 kPa during systole. It is an increase of +56 % which
410 is less than what we found on the YH group (+191 %) and higher than what we
411 found on the MAH group (+21 %). Interestingly, the tested subject was 30 years
412 old while the mean age of the YH group was 25 years old and the mean age of the

³unpaired Student's t-test, data fit a standard distribution, the variances are assumed to be unequal, unilateral test with the null hypothesis H_0 : "mean from data set 1 is lower than mean from data set 2"

⁴paired Student's t-test, the difference between the paired data fit a standard distribution, unilateral test with the null hypothesis H_0 : "mean from data set 1 is lower than mean from data set 2"

⁵null hypothesis H_0 : "mean from data set 1 is higher than mean from data set 2"

413 MAH group was 57 years old.

414 **4.4 On the importance of an accurate measurement of the** 415 **blood pressure**

416 Results from Section 3.3.1 and previous tests on the MB-FEMU method [10] have
417 pointed out the major role of the blood pressure for the estimation of the artery's
418 stiffness *in vivo*. We have found that the identified elastic modulus of the artery is
419 directly influenced by how the blood pressure is measured. In the literature, many
420 authors used a direct formula that links the elastic modulus to the variation of
421 diameter of the artery [30, 21]. The effect of the measurement of pressure is then
422 also crucial. In a previous article [10] we noticed the substantial variation of the
423 pulse pressure of a subject just before the MRI and 15 minutes after the exam (pulse
424 pressure $P_{MRI} = 85$ mmHg vs $P_{MRI+15 \text{ min}} = 62$ mmHg) while the normal value is
425 $P = 40$ mmHg. In the present study, the blood pressure of three healthy subjects
426 was measured every 2 minutes using a programmable digital sphygmomanometer
427 throughout the whole MR exam. An inflation armband was fixed on the arm of the
428 subject before the exam. The results are shown in Figure 12. They reveal significant
429 changes of the blood pressure during the MR exam. These changes may be explained
430 in part by the stress provoked by the exam. We can see on the curves that MAH2 has
431 apparently increased his systolic and diastolic pressures after 18 minutes in the MRI.
432 This increase is correlated to the start of the PC sequence which is very noisy due
433 to the flip of the magnetic field. On the contrary, the diastolic and systolic pressures
434 of MAH3 and MAH4 are relatively stable, with a tendency to decrease. If we look
435 at the pulse pressure, and if we consider the mean pulse pressure of each subject as
436 the reference, the variation is very important during the exam (-17% / $+14\%$ for
437 MAH2, -21% / $+18\%$ for MAH3 excluding the first data, -15% / $+12\%$ for
438 MAH4). This variation of blood pressure has also consequences on images because
439 it introduces blur on the contour of the artery: indeed each frame image is the
440 reconstruction of a k-space which has been filled during several cardiac cycles [5]. If
441 the blood pressure was different between the cardiac cycles, the displacement of the
442 artery would also be different. This could explain the special shapes of the P-index

443 for certain subjects and patients (YH4, MAH3, MAH4, MAH5, OD2).

444 Moreover in this study we considered that the pulse pressure in the CCA was
445 identical to the pulse pressure in the brachial artery. In reality, it has been reported
446 that the pulse pressure in the brachial is typically larger to that in the CCA by
447 about 10 – 14 mmHg [32, 31]. In our case it means that the identified moduli are
448 slightly overestimated. The applanation tonometry exam could estimate the pulse
449 pressure in the carotid after a proper calibration [34, 20], but it has not been used
450 here because the procedures are time consuming and not compatible with our clinical
451 conditions.

452 **4.5 Assumptions made within the Finite Element Model**

453 In this study, as well as in our previous work [10], we have underlined the influence
454 of the mechanical properties of the surrounding tissue. The elastic properties of
455 the surrounding tissue can be potentially identified simultaneously with the elastic
456 properties of the artery as in [22]. But this induces several difficulties: (i) The total
457 identification time is multiplied by three. (ii) The solution is potentially not unique,
458 whereas it is the case when only one modulus is identified. (iii) The obtained solutions
459 can be meaningless with regard to the physics. Here the choice of a homogeneous
460 model of the surrounding tissue is not realistic. The surrounding medium is much
461 more complex and heterogeneous (muscle, tendons, fascias, etc.) but since we focused
462 only on the mechanical properties of the artery we have chosen not to refine the
463 FE model. In addition, the correction of images that occurs at the beginning of
464 each identification procedure has been designed to incorporate rigid displacements
465 that are due to the real 3D geometry of the neck. Our implementation was fast
466 and simple. It is then possible to recover the coordinates of the correction vector
467 simultaneously with the elastic properties of the artery with a limited impact on
468 the total identification time since no additional FE computation is necessary. The
469 geometry of the FE models is important because it imposes strong constraints on
470 the registration framework. We have seen that the diameters of the arteries and
471 more generally the morphologies of the subjects and patients differ significantly from
472 one subject to another and even among the subjects and patients themselves. But

473 no correlation appears between the diameter of the artery and the identified elastic
474 modulus, or between the distance between the artery and the spine and the elastic
475 modulus. This means that the geometry of the FE model is crucial for an accurate
476 identification, but its influence on the mean identified elastic modulus is limited.
477 Other approaches such as the "hyperelastic warping" [35] exist which, by releasing
478 some of the assumptions on the geometry, could improve the results.

479 4.6 Limitation

480 Two words of caution are needed for clinical use of the proposed identification
481 method. First, if the patient is taking medications that affect the mechanical proper-
482 ties of the arteries such as beta-blockers, the identified mechanical properties of the
483 arteries will include the effect of the medication. If the patient is taking medications
484 that affect the blood pressure without changing the mechanical properties of the
485 arteries, the method will correctly identify the mechanical properties of the arteries
486 because the actual blood pressure is estimated and used as a boundary condition.
487 Second, if the patient suffers severe cardiac rhythm disorders, the MRI images can
488 be blurred because a single image is reconstructed from images taken during several
489 cardiac cycles [5, 1]. In this case, a finer analysis of the MRI reconstruction method
490 coupled with accurate *in situ* blood pressure measurements could be appropriate but
491 such research topic is out of the scope of this work.

492 5 Conclusion

493 In this study we successfully applied the MB-FEMU method [10] for identifying the
494 *in vivo* elastic moduli of the common carotid arteries of 13 healthy subjects and
495 sclerosed patients from 24 to 76 years old based on data provided by cine MRI.
496 These data have been obtained in clinical conditions from existing Phase Contrast
497 MR sequence. This approach requires to record at the same time the blood pressure.
498 An increase of the artery's stiffness with age and atherosclerosis has been observed.
499 More experiments are however needed to determine if the diseased arteries can be
500 distinguished from non-diseased arteries based on the analysis of stiffness. The vari-

501 ation of the elastic modulus of the artery during a single cardiac cycle has also been
502 observed and a stiffening of the artery during systole has been underlined. This
503 opens the door to the identification of the nonlinear mechanical properties of the
504 artery *in vivo*. Additional steps are nevertheless required, such as the necessity of a
505 very accurate measurement of the blood pressure, and the use of an appropriate FE
506 model with a refined surrounding media. The MB-FEMU method is promising for
507 the identification of heterogeneous and complex *in vivo* mechanical properties of any
508 artery, and the application of this method on atherosclerosed sites could improve our
509 knowledge about the biomechanical properties of plaques.

510 Acknowledgements

511 This work is part of the Imandef Project (*in vivo* mechanical identification of tissues
512 using medical imaging, grant ANR-08-JCJC-0071) funded by the ANR (French Na-
513 tional Research Agency). We would like to thank the volunteers for their time and
514 implication.

515 We would like to thank the Journal of the Mechanical Behaviour of Biomedical
516 Materials (please visit [http://www.journals.elsevier.com/journal-of-the-mechanical-
517 behavior-of-biomedical-materials/](http://www.journals.elsevier.com/journal-of-the-mechanical-behavior-of-biomedical-materials/)).

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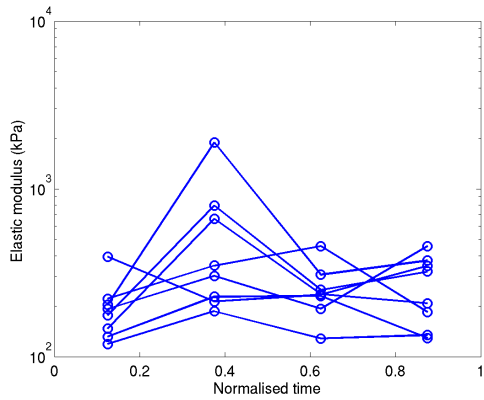
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638 **A Finite element models for subjects and patients**

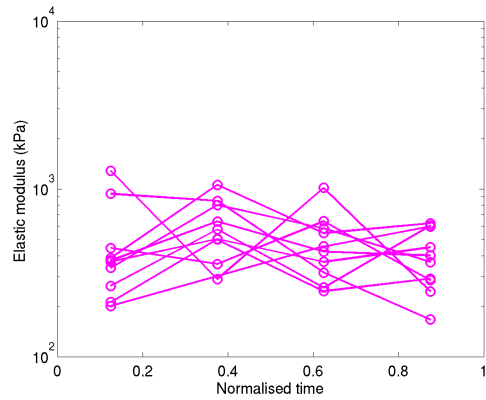
639 See Figures 13, 14 and 15.

640 **B Evolution of the blood pressure by applanation** 641 **tonometry and P-index**

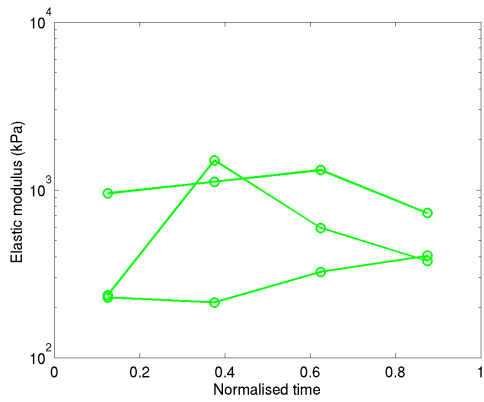
642 See Figures 16, 17 and 18.



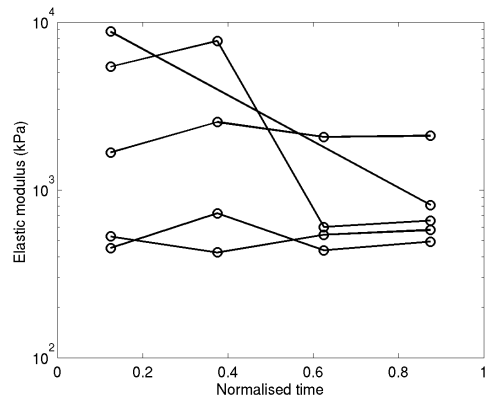
(a) Young healthy subjects



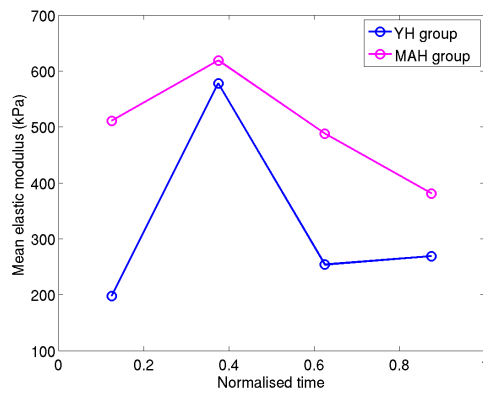
(b) Mid-age healthy subjects



(c) Old diseased patients with non-diseased arteries



(d) Old diseased patients with diseased arteries



(e) Mean elastic moduli identified for the YH and the MAH groups at each time of the cardiac cycle.

Figure 11: Evolution of the elastic modulus during the cardiac cycle. The different points correspond to different fractions of the cardiac cycle.

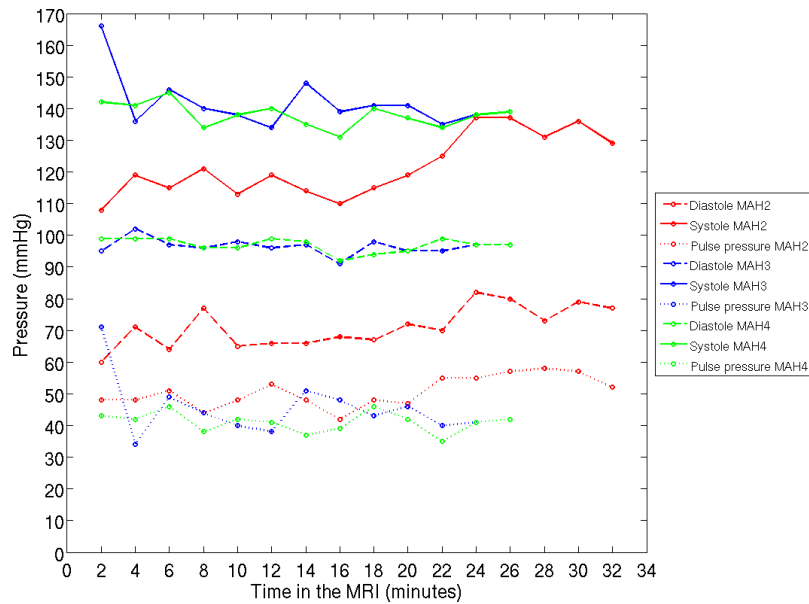


Figure 12: Evolution of the blood pressure during the MR exam for three healthy subjects. The blood pressure has been recorded every two minutes using a programmable digital sphygmomanometer.

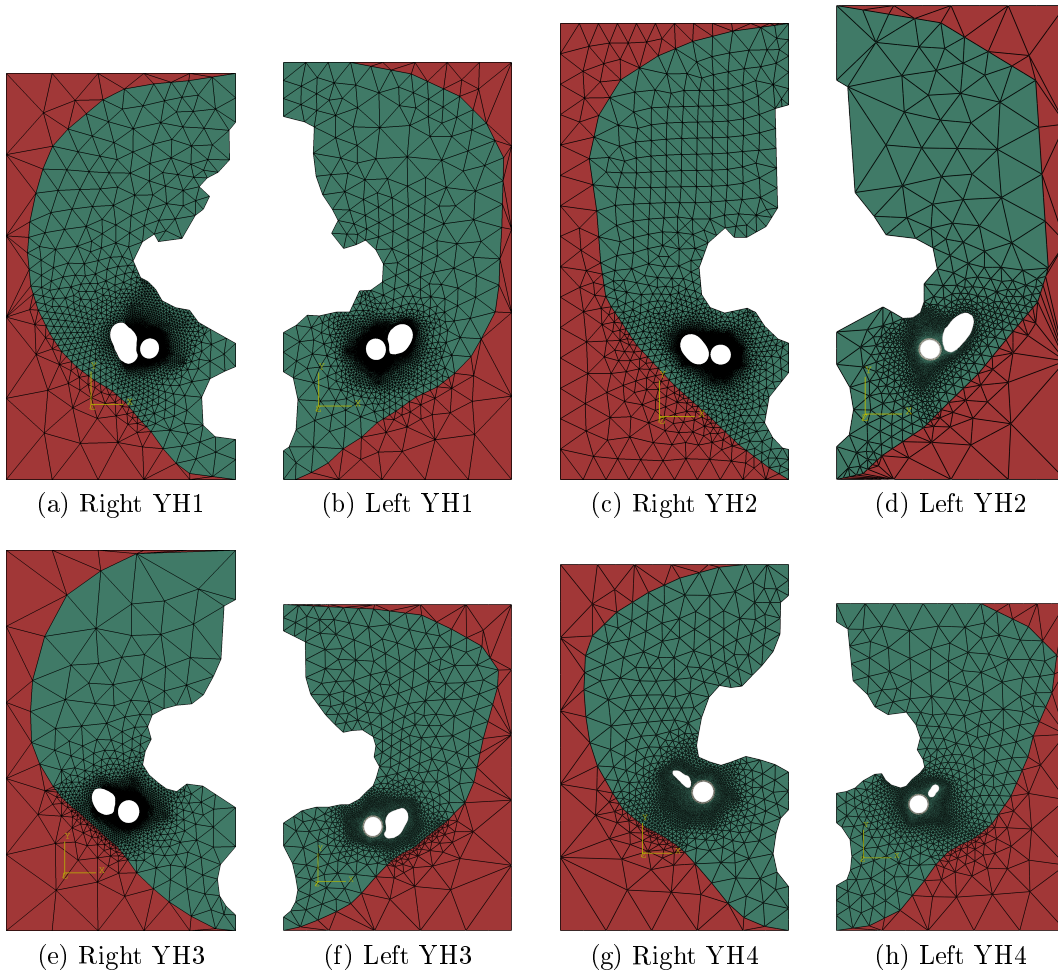


Figure 13: FE models of the “Young Healthy subjects“ (YH) group. Note that the radiological convention has been used so left and right hand sides are reversed from the common usage.

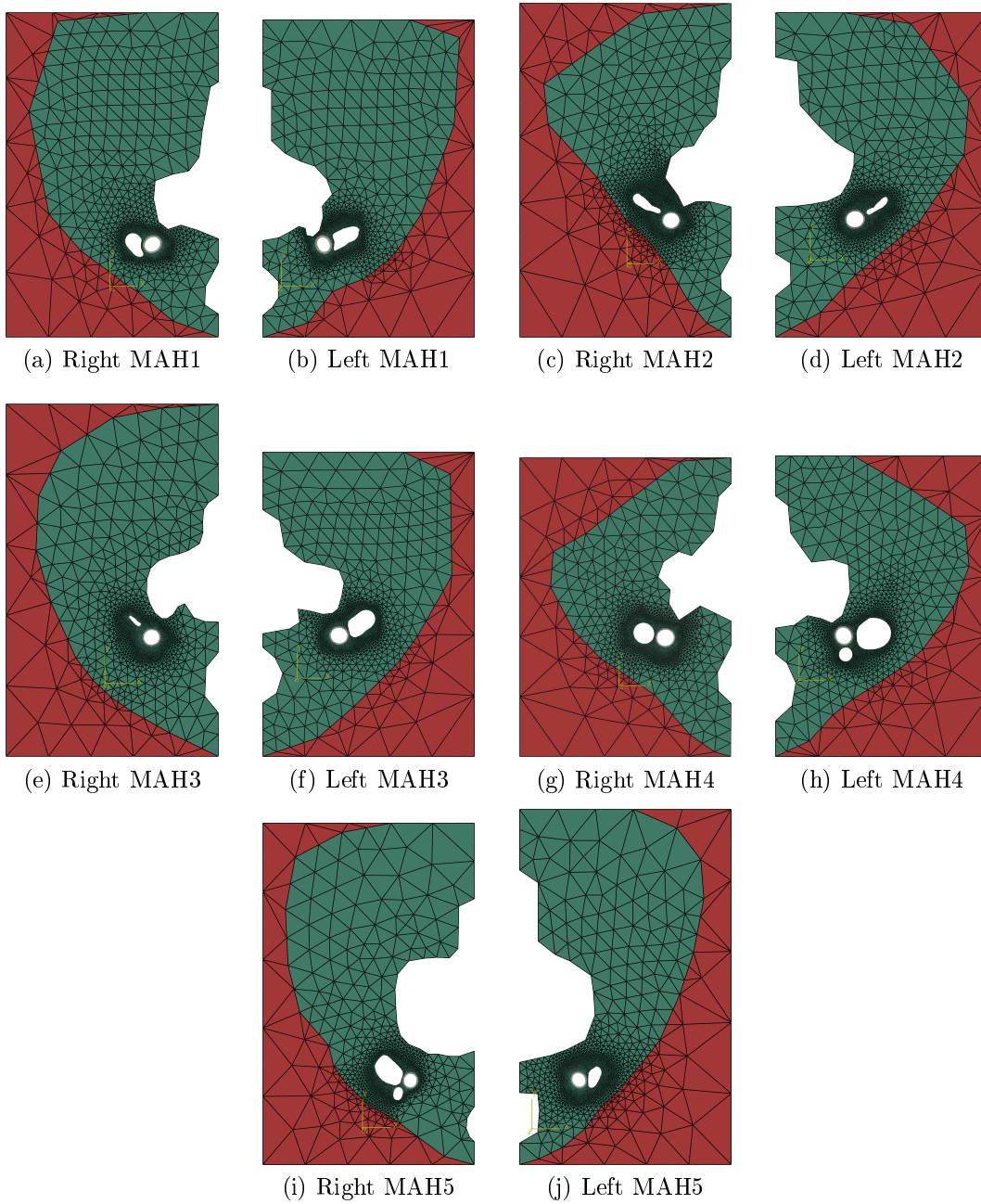


Figure 14: FE models of the “Mid-Age Healthy subjects“ (MAH) group. Note that the radiological convention has been used so left and right hand sides are reversed from the common usage.

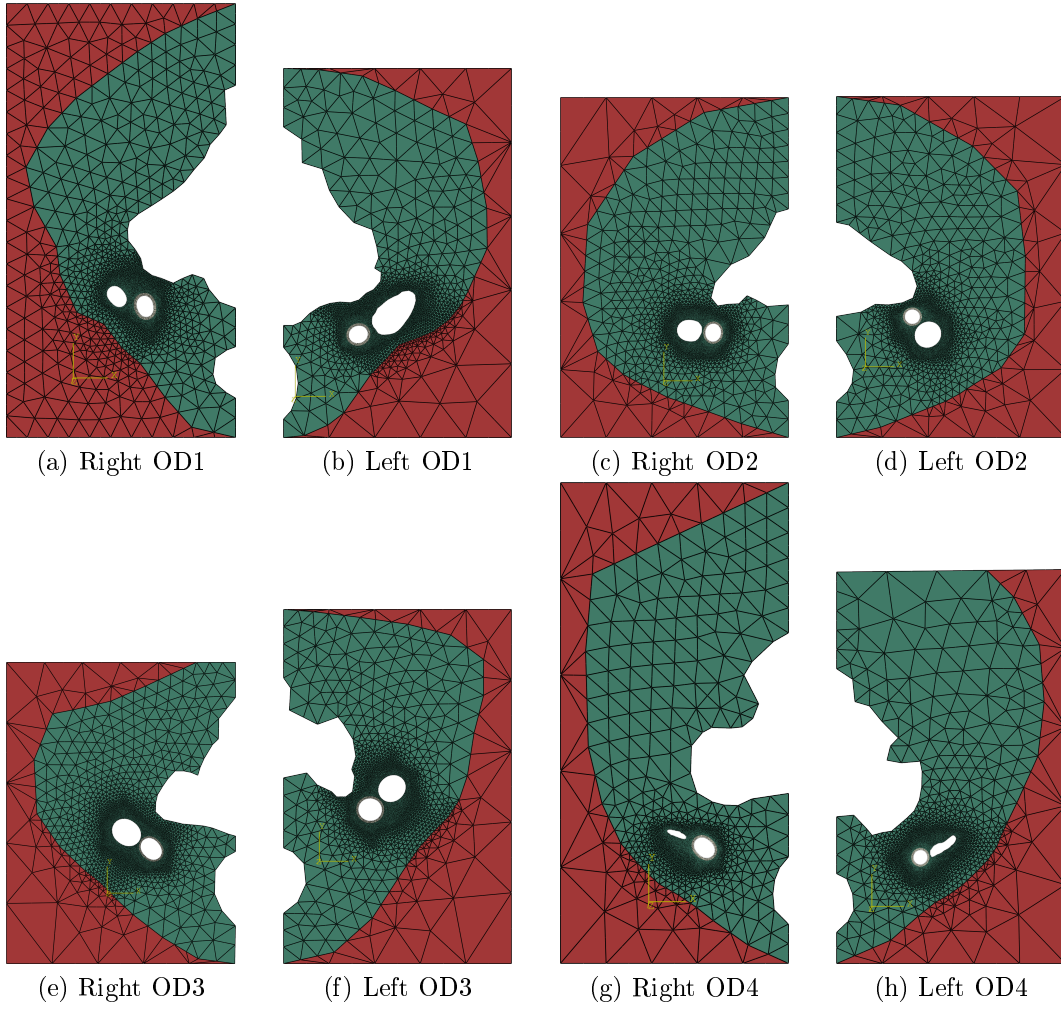
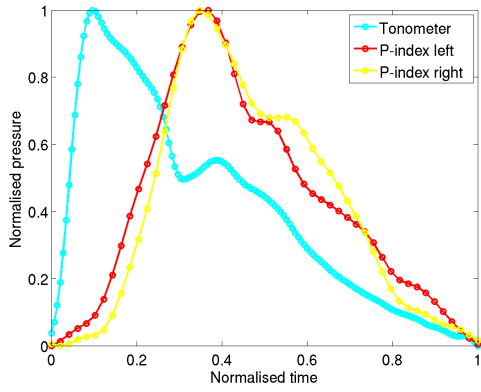
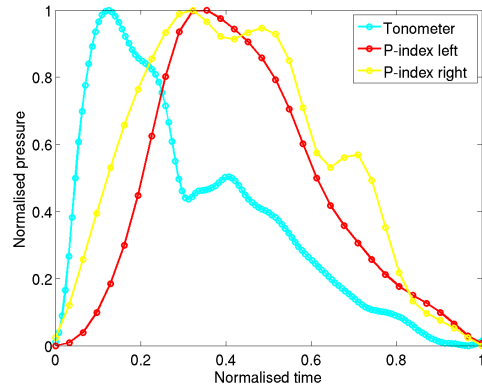


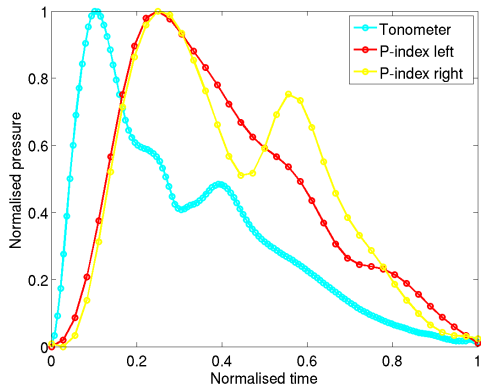
Figure 15: FE models of the “Old Diseased patients“ (OD) group. Note that the radiological convention has been used so left and right hand sides are reversed from the common usage.



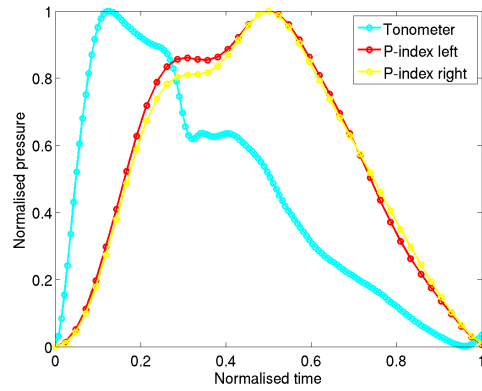
(a) YH1



(b) YH2

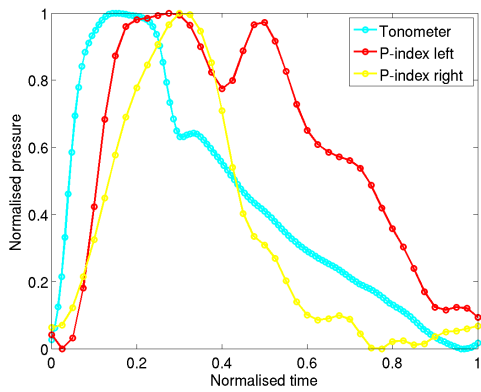


(c) YH3

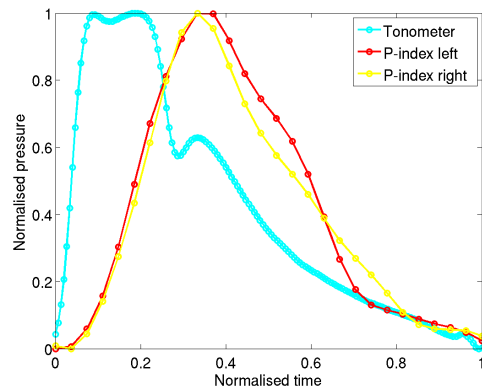


(d) YH4

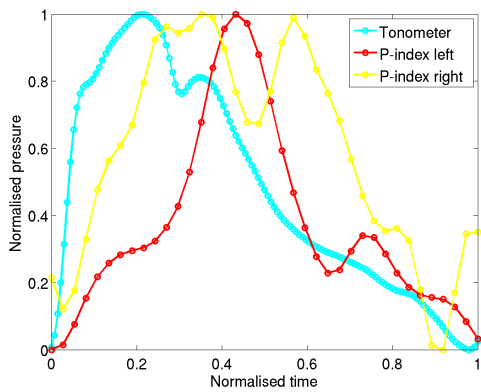
Figure 16: Young healthy subjects: curves of the blood pressure measured by tonometry or deduced from the images based on the P-index (left and right hand sides). Note that the time and the pressure are normalised.



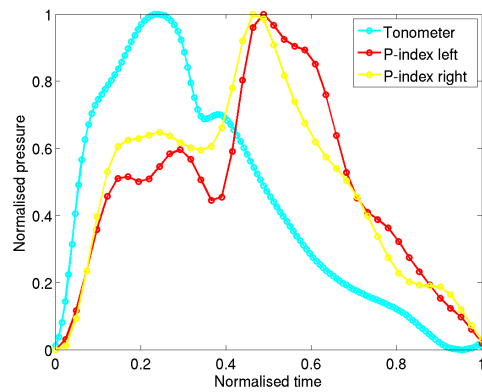
(a) MAH1



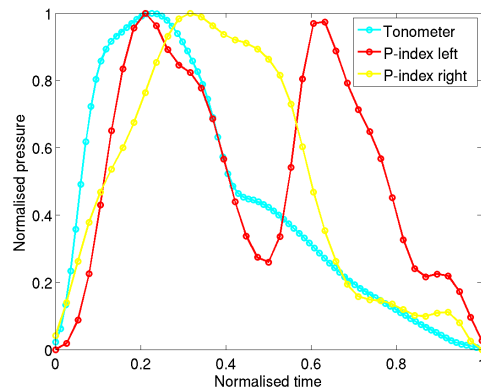
(b) MAH2



(c) MAH3

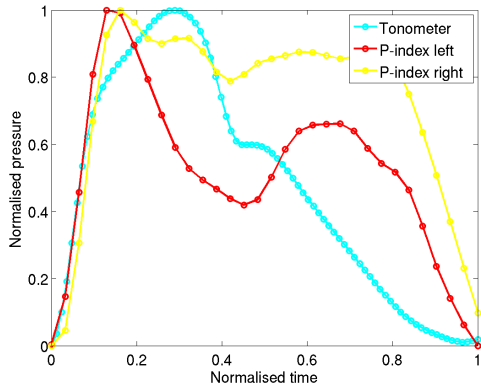


(d) MAH4

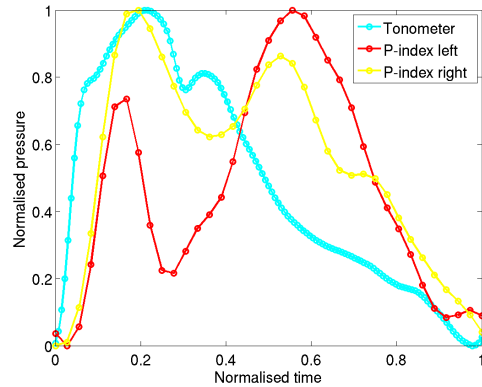


(e) MAH5

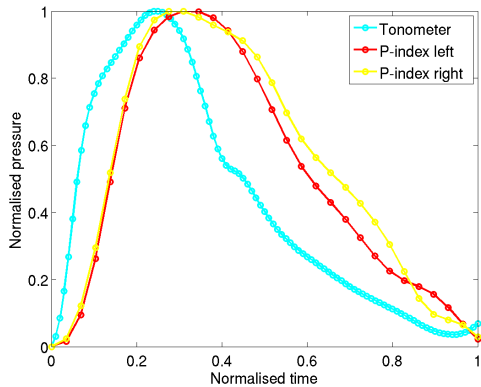
Figure 17: Mid-age healthy subjects: curves of the blood pressure measured by tonometry or deduced from the images based on the P-index (left and right hand sides). Note that the time and the pressure are normalised.



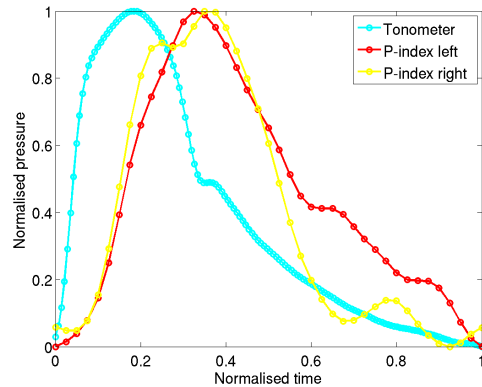
(a) OD1



(b) OD2



(c) OD3



(d) OD4

Figure 18: Old patients: curves of the blood pressure measured by tonometry or deduced from the images based on the P-index (left and right hand sides). Note that the time and the pressure are normalised.