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Continuous assessment of carotid intima-media thickness applied to estimate a volumetric compliance using B-mode ultrasound sequences

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Abstract

Recent reports have shown that the carotid artery wall had significant movements not only in the radial but also in the longitudinal direction during the cardiac cycle. Accordingly, the idea that longitudinal elongations could be systematically neglected for compliance estimations became controversial. Assuming a dynamic change in vessel length, the standard measurement of cross-sectional compliance can be revised. In this work, we propose to estimate a volumetric compliance based on continuous measurements of carotid diameter and intima-media thickness (IMT) from B-mode ultrasound sequences. Assuming the principle of conservation of the mass of wall volume (compressibility equals zero), a temporal longitudinal elongation can be calculated to estimate a volumetric compliance. Moreover, elongations can also be estimated allowing small compressibility factors to model some wall leakage. The cross-sectional and the volumetric compliance were estimated in 45 healthy volunteers and 19 asymptomatic patients. The standard measurement underestimated the volumetric compliance by 25% for young volunteers ($p < 0.01$) and 17% for patients ($p < 0.05$). When compressibility factors different from zero were allowed, volunteers and patients reached values of 9% and 4%, respectively. We conclude that a simultaneous assessment of carotid diameter and IMT can be employed to estimate a volumetric compliance incorporating a longitudinal elongation. The cross-sectional compliance, that neglects the change in vessel length, underestimates the volumetric compliance.

Keywords: cross-sectional compliance, carotid artery, compressibility, arterial stiffness, distensibility

(Some figures may appear in colour only in the online journal)

1. Introduction

For the carotid artery, local arterial stiffness and intima-media thickness (IMT) can be non-invasively determined using B-mode ultrasound measurements. These diagnostic tools contribute in the prediction of coronary heart disease and stroke, the two leading causes of cardiovascular mortality (Simon *et al* 2002, Laurent *et al* 2006). Arterial compliance is defined as a change in blood volume for a given change in pressure. To estimate carotid compliance from B-mode ultrasound images, several assumptions are traditionally adopted. The principle of conservation of mass of wall volume states that the artery wall is incompressible (Girerd *et al* 1992). This principle is generally accepted, although some reports introduced the idea of a leakage factor, allowing some degree of wall compressibility (Boutouyrie *et al* 2001). In a standard measurement, the vessel is considered a thin wall cylinder with constant length and the cross-sectional compliance is calculated from systolic and diastolic diameter measurements. In other words, changes in IMT and vessel length during the cardiac cycle are systematically neglected (Laurent *et al* 2006, Gonzalez *et al* 2008). This simplification is now under discussion, because the longitudinal wall movement was reported to have similar magnitudes of the radial expansion (Tozzi *et al* 2003, Cinthio *et al* 2006, Svedlund and Gan 2011).

Cinthio *et al* have reported an echo tracking method to measure carotid wall movements in radial and longitudinal directions (Cinthio *et al* 2005). This method was also implemented using B-Mode echographic images (Persson *et al* 2003). In the common carotid artery of 10 healthy volunteers they found that the magnitude of longitudinal movements was similar to pulse diameter values (≈0.65 mm). The coefficient of variation (CV) for these measurements remained below 16% (Cinthio and Ahlgren 2010). A clinical approach was reported by Svedlund and Gan, that evaluated longitudinal and radial movements as a potential risk marker using velocity vector imaging techniques (Svedlund and Gan 2011). Total longitudinal displacements were ≈0.5 mm, similar to radial movement amplitudes, with maximum intra-observer variations of 12%. Similar conclusions were found in pigs, measuring radial and longitudinal expansions *in-vivo* (Tozzi *et al* 2001). If the assumption that the vessel length does not change during the cardiac cycle is not further valid, standard values of cross-sectional compliance should be revised (Tozzi *et al* 2003). The challenge would be to propose a non-invasive method to assess vessel elongation using standard B-mode measurements.

Carotid diameter and IMT can simultaneously be assessed with B-mode ultrasound using different techniques (Wendelhag *et al* 1991, Graf *et al* 1999, Selzer *et al* 2001, Potter *et al* 2007). Several considerations as reproducibility and ultrasound settings should be ensured for a proper measurement (Wikstrand 2007, Gonzalez *et al* 2008, Potter *et al* 2008). IMT is routinely assessed during diastole, where its value is maximum. However, a continuous estimation of IMT is also possible (Haller *et al* 2007, Menees *et al* 2010) and was reported to reduce the measurement variability (Haller *et al* 2007). In the present study we propose to calculate the longitudinal elongation of the carotid artery from continuous diameter and IMT automated measurements. Healthy volunteers (with small IMT values) and asymptomatic patients were measured. Assuming wall incompressibility, the temporal variation of cross-sectional wall area (CSWA) was employed to estimate a vessel length change. Values of wall compressibility

from 0 to 10% were also tested. The volumetric compliance was calculated and compared with standard measurements for volunteers and patients.

2. Materials and methods

2.1. Compliance and distensibility estimations

Arterial compliance is defined as the variation of blood volume due to the variation of blood pressure:

$$C_{\mathrm{v}} = \frac{V_{\mathrm{s}} - V_{\mathrm{d}}}{P_{\mathrm{s}} - P_{\mathrm{d}}} = \frac{\Delta V}{P_{\mathrm{p}}}, \tag{1}$$

where V_{s} and V_{d} stand for systolic and diastolic blood volume, and P_{s}, P_{d} and P_{p} are systolic, diastolic and pulsatile blood pressure, respectively. We will name C_{v} as the volumetric compliance. Assuming a cylindrical model of length $L(t)$ and an internal diameter $D(t)$, the blood inside the cylinder at a given time t is:

$$V(t) = \frac{\pi}{4} D(t)^2 L(t)\,. \tag{2}$$

Using (1) and (2), C_{v} can be redefined as:

$$C_{\mathrm{v}} = \frac{\pi}{4P_{\mathrm{p}}}\left(L_{\mathrm{s}} D_{\mathrm{s}}^2 - L_{\mathrm{d}} D_{\mathrm{d}}^2\right), \tag{3}$$

where the sub-indexes d and s represents diastolic and systolic values, respectively.

The CSWA can be calculated as:

$$\mathrm{CSWA}(t) = \pi \mathrm{IMT}(t)\,[\mathrm{IMT}(t) + D(t)\,]\,. \tag{4}$$

As we observed that this wall area was smaller in systole that in diastole, we thought to test two possibilities: (i) that some wall mass squeezed to lengthen the artery and (ii) there was some leakage from inside the wall to external regions.

The variation of the cylindrical vessel wall volume, $W(t)$, can be calculated as a function of IMT(t) using the expression:

$$W(t) = \pi L(t)\,\mathrm{IMT}(t)\,[D(t) + \mathrm{IMT}(t)\,]\,. \tag{5}$$

Assuming incompressibility, vessel wall volume in diastole (W_{d}) and systole (W_{s}) should be identical. If some degree of compressibility is allowed, then:

$$W_{\mathrm{s}} = (1 - \alpha)\, W_{\mathrm{d}}, \tag{6}$$

where α represents a compressibility factor that takes into consideration wall volume variations by the blood flow that enters or leaves the vessel wall in the cardiac cycle. If α equals zero, an incompressible vessel wall is assumed, i.e. the vessel wall volume is constant in every moment of the cardiac cycle.

Considering a vessel wall portion with diastolic length L_{d}, its corresponding length in systole L_{s} is defined as:

$$L_{\mathrm{s}} = L_{\mathrm{d}} + \Delta L\,. \tag{7}$$

If L_{s} is assumed to be different from L_{d} due to a longitudinal vessel stretching, the difference between both magnitudes can be calculated by combining (5), (6) and (7). This

Table 1. Clinical data of the subjects studied. All values are expressed as mean ± standard deviation or absolute value (percentage). Parameters of volunteers and patients were compared using a χ^2 statistic for dichotomous variables and Student's *t*-test for continuous variables.

Parameter	Volunteers	Patients	*p*
Number of subjects	45	19	—
Age, years	21.8 ± 1.6	54.4 ± 7.8	<0.01
Male, *n* (%)	25 (56%)	14 (74%)	ns
Body mass index, kg m^{-2}	23 ± 3	28 ± 6	<0.01
Systolic pressure, mmHg	121 ± 14	130 ± 12	<0.01
Diastolic pressure, mmHg	77 ± 8	74 ± 9	ns
Pulse pressure, mmHg	44 ± 12	56 ± 9	<0.01
Smokers, *n* (%)	0 (0%)	12 (63%)	<0.01
Hypertensive, *n* (%)	0 (0%)	11 (58%)	<0.01
Hypercholesterolemia, *n* (%)	0 (0%)	13 (68%)	<0.01
Diabetes, *n* (%)	0 (0%)	2 (11%)	<0.05
Heart rate, bpm	74 ± 11	68 ± 11	<0.05
Carotid plaques, *n* (%)	0 (0%)	9 (47%)	<0.01
Femoral plaques, *n* (%)	0 (0%)	11 (58%)	<0.01

results in a definition of the longitudinal strain $\Delta L/L_d$ within the cardiac cycle, given by the expression:

$$\frac{\Delta L}{L_d} = (1-\alpha)\,\frac{\mathrm{IMT_d}\,(D_d + \mathrm{IMT_d})}{\mathrm{IMT_s}\,(D_s + \mathrm{IMT_s})} - 1. \tag{8}$$

From (3) and (7) a complete definition for arterial volumetric compliance can be derived:

$$C_v = \frac{\pi}{4P_p} L_d \left(D_s^2 - D_d^2\right) + \frac{\pi}{4P_p} L_d D_s^2 \frac{\Delta L}{L_d}. \tag{9}$$

According to (9), C_v is the sum of two terms: The left-hand term stands for the standard cross-sectional compliance (C_{cs}) that neglects longitudinal strain, and the right-hand term corresponds to the additional compliance that appears when length changes are allowed. In this work, L_d was considered 1 cm in the calculation of volumetric and cross-sectional compliance.

Arterial distensibility refers compliance to initial artery size and is recommended as an arterial stiffness indicator in several clinical guidelines (O'Rourke *et al* 2002, Van Bortel *et al* 2002, Laurent *et al* 2006). Thus, arterial volumetric and cross-sectional distensibility were calculated normalizing compliance to diastolic volume and diastolic cross-sectional area, respectively.

2.2. Subjects description

For this study we included 45 young healthy volunteers (age 22 ± 2 years; 56% men) and 19 asymptomatic patients (age 54 ± 8 years; 74% men). The volunteers were recruited from the staff of the Favaloro University with the following inclusion criteria: younger than 30 years old, nonsmokers, non-diabetics, normotensives and with no diagnosed hypercholesterolemia. Patients were consecutively recruited by the Echocardiography and Vascular Doppler Unit of the Favaloro Foundation Hospital during a month. All measurements met the ethical requirements of the institution. Table 1 shows clinical data of all the participants.

2.3. Data acquisition

Each individual underwent an echographic examination performed by the same sonographer (RD). Carotid arteries were visualized longitudinally using a high resolution ultrasound apparatus (Philips HD11XE) in B-mode (10 MHz transducer). All subjects laid down 5–10 min before examination. Brachial blood pressure was recorded using an automatic oscillometric tensiometer before and after the acquisition. Sequences of 5 s during a single breath-hold were recorded in DICOM format and exported to a PC for digital processing with a custom program developed in our laboratory (Graf *et al* 1999). A double line pattern of intima-media complex was visible during the whole sequences (Wikstrand 2007).

2.4. Diameter, IMT and compliance assessment

In previous works of our group we continuously measured carotid diameter and estimated diastolic IMT using longitudinal images with an automated validated method (Graf *et al* 1999). In this work we extended the analysis to obtain a continuous estimation of IMT. Briefly, all longitudinal B-mode ultrasound images (25 images s^{-1}) were digitized in real-time into 640 × 480 pixels with 256 grey levels and stored for post-treatment. A strictly parallel longitudinal view of the carotid artery with both the lumen-to-intima and media-to-adventitia interfaces was required. Calibration of the images was made using the 1 cm built-in landmarks of the echograph. A 1 cm length region of interest (ROI) was selected containing both near and far artery walls during the whole sequence. For each column inside the ROI, a maximum rate of change in grey-level intensity was calculated to detect each interface. The rising of the grey-level intensity was systematically chosen because this point corresponds to the leading edge of the echo, which is on the same level as that of the interface that creates de echo and is not gain-dependent (Wendelhag *et al* 1991, Wikstrand 2007). Three lines were visualized: near wall intima-lumen, far wall lumen-intima and far wall media-adventitia interfaces. Diameter and IMT were computed as the mean distance between these interfaces on at least 20 consecutive points per cm of arterial length.

In the case of the diameter and IMT time-variation computing, the sequence of images was analysed frame by frame. Values of systolic and diastolic IMT were calculated at maximum and minimum diameter instants for at least three consecutive heart beats and averaged for each sequence. All measurements were made by the same user (AFP). Carotid volumetric compliances (C_v) were calculated for each sequence using equation (9). Cross-sectional compliance (C_{cs}) were estimated setting $\Delta L = 0$ from the same equation.

2.5. Automated measurement variability

The reproducibility of diameter and IMT assessment using this methods was reported before (Graf *et al* 1999). CVs for two repeated examinations were 10% and 4.3% for diameter and IMT, respectively. The inter-observer error was 7%. To test the repeatability of the continuous IMT estimation algorithm and compliance calculation, the same observer processed twice all volunteers and patients. Diameter, IMT and compliance values were compared between the two measurements.

2.6. Wall compressibility analysis

The change in volumetric compliance values assuming different degrees of arterial wall compressibility was studied modifying α in (6). Values of α in the range 0% to 10% were

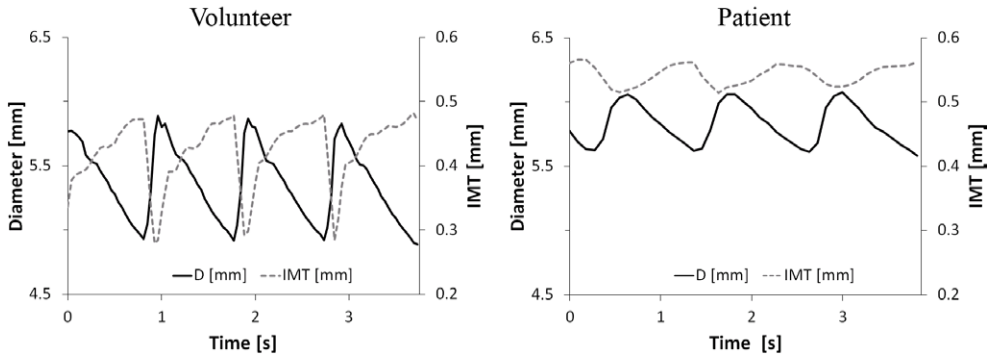

Figure 1. Diameter and IMT measurements in a representative volunteer and patient.

considered for each sequence. A linear regression was calculated for the group of volunteers and for the group of patients. The standard cross-sectional compliance, that do not depend on the compressibility factor α, was also calculated.

2.7. Statistical analysis

Baseline characteristics of volunteers and patients were compared using a Chi Square statistic for dichotomous variables and Student's *t*-test for continuous variables. Student's *t*-test was used to compare diastolic and systolic values, cross-sectional and volumetric compliance. A paired *t*-test was employed for the intra-observer analysis and CVs were also calculated. Statistical analyses were performed with JMP software (SAS, NC). Significance level was set at $p < 0.05$.

3. Results

3.1. Diameter and IMT measurements

Diameter and IMT measurements on a representative volunteer and patient can be observed in figure 1. Globally, patients had larger diameter, less pulsatility and thicker IMT values than volunteers.

Table 2 shows mean values of diameter, IMT, their relative systolic/diastolic changes $((D_s - D_d)/D_d$ and $(IMT_s - IMT_d)/IMT_d)$ and CSWA for all volunteers' and patients' carotid arteries.

Diameters, IMTs, their relative systolic/diastolic changes and CSWAs were higher in patients with respect to volunteers ($p < 0.01$), except for systolic diameter that remained similar (p = ns). Both in volunteers and patients, D_s was higher than D_d ($p < 0.01$) and IMT_s was lower than IMT_d ($p < 0.01$). CSWA was smaller in systole than in diastole for volunteers ($p < 0.01$) and patients ($p < 0.05$).

3.2. Compliance and distensibility

Figure 2 shows both cross-sectional and volumetric compliances classified in volunteers and patients.

Table 2. Measurements of diameter, IMT, their relative changes and CSWA, classified in volunteers and patients. Left and right carotid arteries were considered together. All values are expressed as mean ± standard deviation.

Parameter	Volunteers	Patients	p
Number of carotids	90	27	—
D_d (mm)	5.16 ± 0.48	5.73 ± 0.88	<0.01
D_s (mm)	6.00 ± 0.56	6.25 ± 0.93	ns
$(D_s - D_d)/D_d$ (%)	16.21 ± 4.03	9.13 ± 2.93	<0.01
IMT_d (mm)	0.45 ± 0.09	0.58 ± 0.11	<0.01
IMT_s (mm)	0.37 ± 0.09	0.53 ± 0.12	<0.01
$(IMT_s - IMT_d)/IMT_d$ (%)	−18.23 ± 10.27	−9.60 ± 7.49	<0.01
$CSWA_d$ (mm^2)	8.02 ± 1.66	11.63 ± 3.03	<0.01
$CSWA_s$ (mm^2)	7.44 ± 1.88	11.35 ± 3.26	<0.01

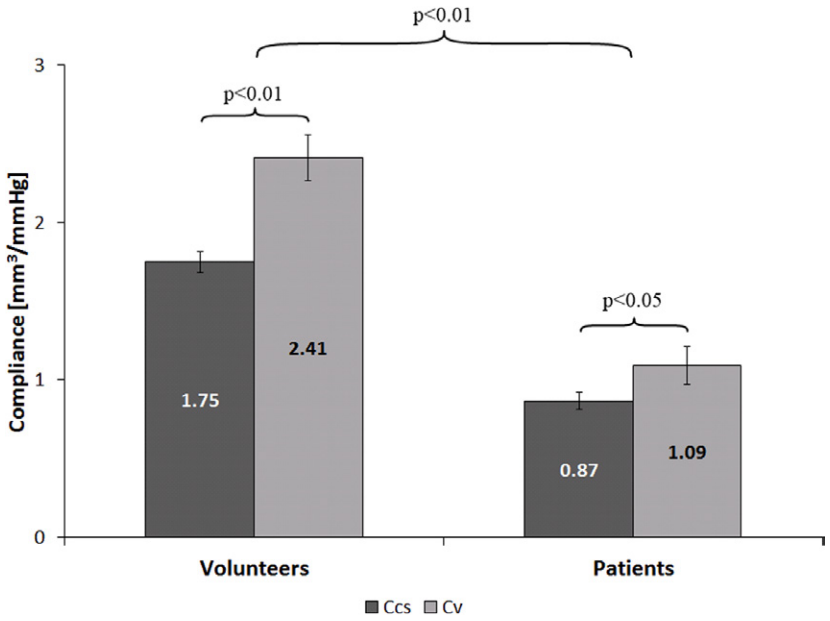

Figure 2. Comparison between cross-sectional and volumetric compliances separated in volunteers and patients. Values and bars indicate mean values and standard errors, respectively.

Both in volunteers and patients, C_v resulted higher than C_{cs}: 34% ($p < 0.01$) and 21% ($p < 0.05$), respectively. Both estimations of compliance were lower in patients than in volunteers ($p < 0.01$). Volumetric and cross-sectional distensibility in volunteers was $11.65 \pm 6.69 \times 10^{-3}\,mm\,Hg^{-1}$ and $8.52 \pm 3.27 \times 10^{-3}\,mm\,Hg^{-1}$ ($p < 0.01$), respectively. Volumetric and cross-sectional distensibility in patients was $4.19 \pm 2.28 \times 10^{-3}\,mm\,Hg^{-1}$ and $3.42 \pm 1.15 \times 10^{-3}\,mm\,Hg^{-1}$ ($p < 0.05$), respectively. Both estimations of distensibility were lower in patients than in volunteers ($p < 0.01$). The proportions of volumetric to cross-sectional distensibility did not change with respect to compliance and resulted 34% and 21%, respectively.

Table 3. Comparison of the obtained values (diastolic and systolic diameter and IMT) in both instances of measurement. Values are expressed as mean ± standard deviation or percentage.

Parameter	Measurement #1	Measurement #2	CV (%)
Number of carotids	117	117	—
D_d (mm)	5.27 ± 0.64	5.31 ± 0.65	1.0
D_s (mm)	6.03 ± 0.67	6.08 ± 0.68	0.9
IMT_d (mm)	0.48 ± 0.11	0.48 ± 0.11	2.7
IMT_s (mm)	0.41 ± 0.12	0.41 ± 0.12	3.6

3.3. Intra-observer variability

Values of diastolic and systolic diameter and IMT for both measurements, with the corresponding CVs are shown in table 3.

There were no differences between measurements (p = ns). The CVs between measurements were below 1% for diameter and below 4% for IMT. CVs of the compliances were 4.5% for the cross-sectional and 13.7% for the volumetric.

3.4. Wall compressibility analysis

Preceding results are based on the assumption of an incompressible arterial wall ($\alpha = 0$). Figure 3 shows the averaged values of volumetric compliance as a function of the wall compressibility for volunteers and patients. This figure also shows the averaged cross-sectional compliance values for each group. Black arrows indicate compressibility values where both estimations of compliance are equal. These values can be interpreted as the compressibility for which the negligible axial strain hypothesis is accurate.

4. Discussion

In this work we estimated carotid volumetric compliance from continuous diameter and IMT measurements using B-mode ultrasound images. Assuming the artery wall incompressible, the vessel length change during the cardiac cycle was calculated, exhibiting an enhanced blood storage capacity than expected. Accordingly, values of volumetric compliance were 34% and 21% higher than standard cross-sectional estimations in young volunteers and patients, respectively. Distensibility is usually recommended over compliance because it is not dependent on initial size of the vessel (O'Rourke *et al* 2002, Van Bortel *et al* 2002, Laurent *et al* 2006). In our study, volumetric and cross-sectional distensibility showed the same proportions as compliances because all measurements were referred to diastolic values (including initial length) and then analogous conclusions could be inferred from both arterial stiffness indicators. Our findings indicate that reported movements of the carotid artery wall could be associated to biaxial elongations that might affect the vessel compliance estimation. The fact that longitudinal movements of the carotid artery wall are not negligible and even have similar magnitudes of radial displacements is not new (Cinthio *et al* 2005, 2006). Now, whether these movements are directly associated to artery elongations need further discussion. Longitudinal displacements of the artery wall were mathematically confirmed but vessel lengthening was not actually calculated (Warriner *et al* 2008). Aortic root motion during heart ejection could be at the origin of those wall movements and tethering conditions could also play an important role (Hodis and Zamir 2009, 2011). A few studies *in-vivo* analysed changes in vessel length. Lichtenstein *et al* (1995) reported systolic

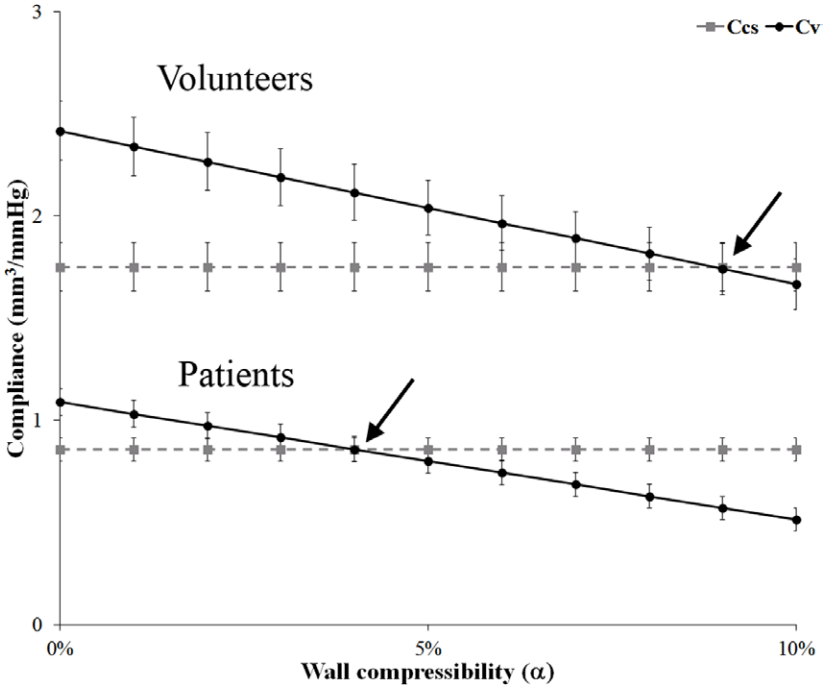

Figure 3. Dependence of compliance (volumetric and cross-sectional) with respect to arterial wall compressibility. Bars and arrows indicate standard error and wall compressibility values so that there is no longitudinal elongation, respectively.

axial length increase in left common carotid arteries of rats resulting in enhanced volumetric compliance. This group found longitudinal distensibility to represent around one-third of radial distensibility for normotensive rats and one-sixth for hypertensive animals, indicating that differences are more important in healthy arteries. In our work, healthy volunteers were also those with more benefits from the extra-compliance due to lengthening. In another *in-vivo* report, common carotid arteries were surgically exposed in anesthetized pigs and arterial lengthening was measured using piezoelectric crystals, finding a systolic shortening of 3% for a diameter dilation of 5% (Tozzi *et al* 2001, 2003). As the vessel shortened in systole, cross-sectional compliance was said to overestimate arterial compliance. It is difficult to compare these results with non-invasive measurements in patients. However, the fact that the artery wall changes its length during the cardiac cycle seems reasonable. Two questions remain to be answered: What is the magnitude of those changes? Does the artery lengthens or shortens in systole?

The arterial wall of human medium sized arteries is usually considered incompressible, based on the principle of conservation of mass of wall volume (Girerd *et al* 1992). From this assumption, we used simultaneous measurements of diameter and IMT to calculate the cross-sectional artery wall area. This wall area was smaller in systole than in diastole, indicating that during expansion the vessel lengthened. We built our hypothesis based on the idea that this missing wall area during systole was distributed along the vessel length. Accordingly, this additional capacity of blood storage was translated into an enhanced volumetric compliance. An alternative hypothesis to explain differences in wall area could be the existence of leakage from the internal part of the wall to external regions (Boutouyrie *et al* 2001). In that case, the wall is considered compressible and all volumetric changes are associated to blood leakage into and from the arterial wall. We tested this possibility and allowed some degree of

compressibility in (6) to compensate for the wall area differences in diastole and systole. As shown in figure 3, if the leakage effect is supposed to completely explain these wall area differences, patients would have less compressible arteries than young volunteers with values of 4% and 9%, respectively. Probably, a combination of both longitudinal elongation and leakage take place. Further studies are needed to elucidate the exact proportion of these effects.

The calculation of a volumetric compliance in (9) was based on accurate estimations of diameter and IMT. Alternative methods were reported to non-invasively assess IMT in systole and diastole from echographic images (Selzer *et al* 2001, Haller *et al* 2007, Zahnd *et al* 2013). Probably, measurements in young patients was more challenging due to narrower walls, but entirely possible with new equipment (Jourdan *et al* 2005). Our automated method had intra-observer CVs below 1% and 4% for diameter and IMT, respectively. When these values were employed to calculate artery stiffness, the error was propagated and reached 5% for cross-sectional compliance and 14% for volumetric estimations. Recently, CV values below 16% were reported for wall movement estimations (Cinthio and Ahlgren 2010). In spite of this dispersion, significant differences were observed in our study between young volunteers and patients as seen in figure 2. Age and arterial pressure could reasonably explain these differences, whereas cross-sectional and volumetric compliances were significantly different inside each group. Further efforts should be made to optimize the algorithm and to reduce variability, while new studies are required to analyse the clinical impact of the volumetric compliance calculation.

This work had some limitations to be addressed. Manual interactions in the ROI and cardiac beats selection can be further automated to improve repeatability. Compliance was calculated using a brachial pressure, although central pressures could be more accurate, particularly in young subjects where amplification is more pronounced (Nichols and O'Rourke 1998). Given the inverse relationship between pressure and compliance, the amplification effect would result in even larger compliance values for the young group with respect to patients. Finally, the small number of patients in this study did not allow for a proper clinical evaluation of patients with different risk factors. New protocols should be designed, including more individuals and comparisons with alternative arterial stiffness measurements.

In conclusion, we developed a non-invasive method to estimate the arterial volumetric compliance, based on continuous diameter and IMT measurements on B-mode ultrasound sequences. With the hypothesis of an incompressible artery wall, longitudinal deformations were calculated, showing a vessel lengthening during expansion that was more pronounced in young volunteers than in asymptomatic patients. Accordingly, the volumetric compliance was higher than the standard cross-sectional compliance measurement, indicating that longitudinal elongations can play an important role in carotid wall biomechanics and should be taken into account in young individuals.

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