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Review

Non-invasive ultrasound in arterial wall dynamics in humans: what have we learned and what remains to be solved

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In the past decades, non-invasive vascular ultrasound has substantially improved our insights into artery wall dynamics under normal circumstances and in disease. Although we have learned a lot, the methods in use are subject to improvement. In this review, we discuss the most important achievements in non-invasive assessment of dynamic artery wall properties in humans with emphasis on the clinical relevance of the observations. Special attention will be paid to the changes observed in aging, and in essential and borderline hypertension, because the loss of compliance (i.e. the ability to store volume thereby reducing pressure increases during ejection) of the elastic arteries in the elderly and in these patients possibly has consequences on their management. The changes in dynamic artery wall properties in diabetes and atherosclerosis are briefly discussed as well. A new approach to the determination of baroreceptor sensitivity, using artery stretch as input, is presented. The review starts with a description of the parameters most commonly used to describe dynamic artery wall properties and of the techniques employed to assess these parameters. The problems encountered in these assessments and the possible solutions to these problems are addressed as well.

Introduction

Since Strandness *et al.*[1] indicated that Doppler techniques could be used to non-invasively identify atherosclerotic lesions in arteries accessible to ultrasound, non-invasive vascular ultrasound, generally combining anatomic and flow information, has routinely been used to diagnose these lesions clinically.[2] Besides being used to diagnose atherosclerotic lesions, non-invasive vascular ultrasound is used to assess intima-media thickness (IMT), a parameter commonly employed in epidemiological[3,4] and intervention studies,[5] as an indicator of atherosclerotic disease,[6] although proof of a causal relation between IMT and atherosclerosis is lacking.

More recently, the focus of non-invasive vascular ultrasound has been on the assessment of artery wall properties, in terms of distension, circumferential strain, distensibility, compliance, and Young's modulus.[7–10] An insight into these mainly dynamic parameters is of utmost importance in patient management, because loss of elastic properties of elastic arteries, as in aging[11,12] and in borderline[13,14] and essential hypertension,[15,16] contributes substantially to the increase in systolic arterial and pulse pressure, known independent risk factors.[17,18] Ultrasonic techniques have been developed

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to non-invasively determine diameter, distension, circumferential strain, and IMT with great detail. Because these parameters and, hence, distensibility, compliance, and the Young's modulus can be determined with one and the same ultrasound system,[19] their interrelation at a particular site along the arterial tree can be investigated. The non-invasive assessment of distension and circumferential strain also makes it possible to distinguish in humans vascular-induced changes from central-induced changes in baroreceptor sensitivity.[20]

In this review, we will address the most important achievements in the non-invasive assessment of artery wall dynamics in humans. We have limited ourselves to the processes and diseases, known to be associated with vascular pathology. The focus will be on the changes observed in aging, and in essential and borderline hypertension, topics most extensively studied and essential hypertension being the most prevalent chronic disease in the world. The changes in artery wall properties in atherosclerosis and diabetes and the use of non-invasive vascular ultrasound in the assessment of baroreceptor sensitivity will be discussed as well. Most of the data presented are derived from clinical studies; observations made in epidemiological and pharmacological studies are included where relevant. The review starts with a description of the parameters in use to assess dynamic artery wall properties and of the methods employed to determine these parameters. The limitations of these methods and the problems to be solved are discussed as well.

Basic aspects and assessment of vascular dynamics

Parameters to characterize the elastic behaviour of arteries are distensibility and compliance, defined as the relative ($\Delta V/V$) and absolute (ΔV) change in arterial volume (V) for a change in pressure (Δp), respectively. Distensibility, reflecting the mechanical load of the artery wall, and compliance, reflecting the ability to store volume thereby reducing pressure increases during ejection, are generally expressed as changes in lumen cross-sectional area A during the cardiac cycle. This is allowed because artery length hardly changes during the cardiac cycle owing to longitudinally tethering of arteries at their *in vivo* length.[21,22] Local pulse pressure, the difference between systolic and diastolic pressure, is generally substituted for Δp. In elastic arteries, e.g. aorta and carotid artery, the relationship between A and Δp is linear[23] and the error arising from this approximation is small for the changes in pressure and A during the cardiac cycle. In muscular arteries, e.g. brachial and femoral artery, the error made in this approximation can be substantial.

The expression for distensibility coefficient (DC) in terms of end-diastolic diameter (d) and the change in diameter (Δd) from diastole to systole (distension), assuming a circular lumen cross-section is

$$\mathrm{DC} = \frac{\Delta A/A}{\Delta p} = \frac{((d+\Delta d)^2 - d^2)/d^2}{\Delta p}\ (\mathrm{Pa}^{-1}) \qquad (1)$$

Similarly, the compliance coefficient (CC) can be rewritten as

$$\mathrm{CC} = \frac{\Delta A}{\Delta p} = \frac{\pi((d+\Delta d)^2 - d^2)}{4\Delta p}\ (\mathrm{m}^2/\mathrm{Pa}) \qquad (2)$$

d and Δd (*Figure 1*) can be measured accurately and reliably with modern echo tracking systems,[24] using a two-dimensional B-mode imager attached to a vessel wall

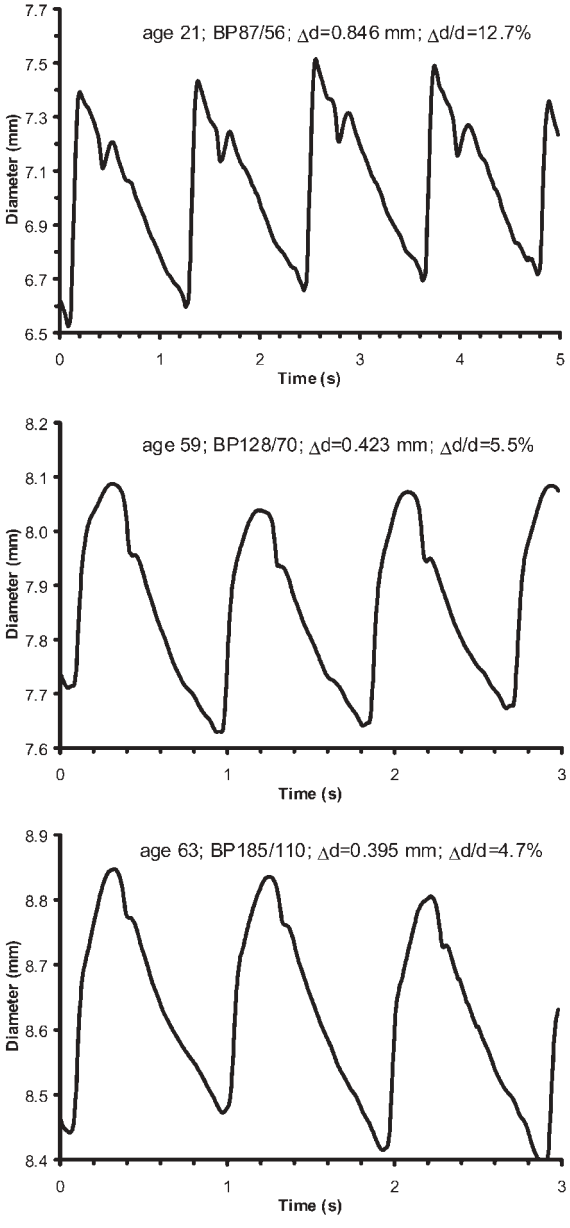

Figure 1 Distension waveforms as recorded in the common carotid artery of a young (top) and an older normotensive volunteer (middle), and an older hypertensive patient (bottom). During the recordings the volunteers and the patient were fully relaxed. Note the reduced distension (Δd) and circumferential strain ($\Delta d/d$; d, diameter) at even a higher blood pressure, in normotensive volunteer at older age, reflecting increased arterial stiffness. In hypertension, arterial stiffness is further increased as indicated by the slightly reduced distension and the substantially reduced circumferential strain at a significantly higher blood pressure.

moving detector system.[7] Artery wall displacements of a few micrometers can be resolved with these systems. In the most recent systems, the displacement detection algorithm is based on radiofrequency (RF) correlation tracking rather than Doppler processing.[25] Processing in the RF domain has the advantage of high depth resolution (echo-mode) and high accuracy, even when extremely short (few milliseconds) temporal estimation windows are used. In the most recent systems, artery wall–lumen transition at end-diastole can be identified automatically, allowing real-time presentation of d and Δd, opening up new potential avenues of research (discussed in a subsequent section; baroreceptor sensitivity). Accurate assessment of DC and CC requires the determination of Δp at the site of measurement of d and Δd or at a representative site elsewhere, which is still problematic (discussed in a subsequent section).

For arteries, circumferential strain provides a measure of the relative deformations to which arteries are exposed. It can be calculated as $\Delta d/d$. This strain is not a material property because it depends on stress. Stress per unit length is pulse pressure divided by wall thickness h. Wall material can be characterized by the Young's modulus, E, which is the ratio of stress and circumferential strain in the vessel wall.[9,26] Assuming pressure independence, E is related to DC as:

$$E = \frac{d/h}{\mathrm{DC}}\ (\mathrm{Pa}) \tag{3}$$

Non-invasive assessment of h by means of ultrasound is limited to IMT, because the adventitia cannot be distinguished reliably from surrounding structures. IMT can more reliably be assessed at the posterior than at the anterior artery wall, because in the latter large trailing echoes from the adventitia extend into the media. The use of IMT rather than whole wall thickness in assessing artery wall dynamics is acceptable, because the media is the most important determinant of these dynamics, at least under normal circumstances and in hypertension. In atherosclerosis, however, the intima is the layer most affected. Since the first IMT measurements by Pignoli *et al.*,[27] a variety of automated techniques have been developed.[28,29] All these techniques provide a mean IMT extracted from B-mode video-images over a length of 10–20 mm. Because video-processing is susceptible to the settings of gain and compression, we extended the RF system for the assessment of d and $\Delta d/d$ with an automated method to determine IMT locally.[30]

The definitions of the parameters to describe artery wall dynamics as used in this review and their units are presented in *Table 1*.

Table 1 Basic vascular parameters, as used in the present review, and their units

Vascular parameter	Basic relationship (unit)
Circumferential strain	$100 \times \Delta d/d$ (%)
Distensibility coefficient (DC)	$\frac{\Delta V/V}{\Delta p} = \frac{\Delta A/A}{\Delta p} \approx \frac{2\Delta d/d}{\Delta p}$ (MPa^{-1})
Compliance coefficient (CC)	$\frac{\Delta V}{\Delta p} = \frac{\Delta A}{\Delta p} \approx \frac{\pi \Delta d d}{2\Delta p}$ ($\mathrm{mm}^2/\mathrm{MPa}$)
Young's modulus (elasticity)	$E = \frac{d/h}{DC}$ (MPa)

ΔV is change in volume V, ΔA is change in lumen cross-sectional area A, and Δd is change in diameter d of an arterial segment due to the pressure change Δp during the cardiac cycle. End-diastolic values are used as reference.

What have we learned?

One of the most important lessons learned is that generalization and extrapolation must be avoided. It is not surprising that dynamic wall behaviour of elastic arteries differs from that of muscular arteries, but the fact that their properties adapt differently to, e.g. aging and hypertension was unknown until the introduction of dynamic vascular ultrasound. IMT also varies substantially, even within a relatively short arterial segment.[31]

Aging

Under normal circumstances, distensibility and compliance of the elastic carotid artery decrease linearly with age from the third age decade onwards, the reduction of compliance being less steep than the reduction of distensibility.[12] The latter can be explained by the increase in diameter with increasing age[9,11,12] (*Table 2*). In this way, elastic arteries counteract the reduction of their ability to store volume and, hence, the increase in systolic arterial and pulse pressure, with increase in age. In our analysis, end-diastolic diameter is considered. When mean diameter was considered the difference in reduction between distensibility and compliance would have been quantitatively different, but qualitatively similar. Distension and circumferential strain also decrease with age (*Figure 1*; *Table 2*). The loss of dynamic properties along the arterial tree is inhomogeneous. At older age, distensibility of the muscular common femoral artery is reduced, but the distensibility of the deep and superficial muscular femoral arteries[32] and the compliance of the muscular brachial artery are not.[33,34] Similarly in the elastic carotid artery bifurcation, distensibility of the bulb, where predominantly the baroreceptors are located, is more severely affected by age than the distensibility of the common carotid artery.[11,14]

Hypertension

In patients with essential hypertension, arterial stiffening[35,36] (*Figure 1*) is not a generalized phenomenon along the arterial tree. In untreated hypertensive patients, at ambient mean arterial pressure, distensibility and compliance of the elastic carotid artery (*Table 3*), but not of the radial artery,[37] are significantly reduced.[16] In the latter, the Young's modulus was found

Table 2 Diameter (d) and percentage systolic circumferential strain ($\Delta d/d \times 100\%$) as function of age per decade in the right common carotid artery in females ($n = 55$) and in males ($n = 56$)

Age (years)	Females			Males		
	n	d (mm)	$\Delta d/d$ (%)	n	d (mm)	$\Delta d/d$ (%)
10–19	10	5.9 ± 0.3	13 ± 2	8	6.0 ± 0.3	14 ± 3
20–29	12	6.0 ± 0.3	10 ± 1	12	6.5 ± 0.6	10 ± 2
30–39	15	6.2 ± 0.5	8 ± 2	18	6.5 ± 0.5	9 ± 2
40–49	10	6.4 ± 0.6	7 ± 2	10	6.5 ± 0.4	6 ± 2
50–59	8	6.3 ± 0.3[a]	6 ± 2[a]	7	6.4 ± 0.5[a]	5 ± 2[a]

Data are presented as mean ± SD.
[a]Significantly different from second age decade. After Samijo *et al.*[73]

Table 3 Carotid artery diameter, distensibility, and compliance in patients with essential hypertension (HT; 54 ± 15 years) and in age-matched normotensives (NT; 48 ± 15 years)

	HT ($n = 15$)	NT ($n = 14$)
At mean arterial pressure		
Diameter (mm)	7.3 ± 0.3	6.9 ± 0.2
Distensibility (MPa^{-1})	7.8 ± 0.7[a]	11.7 ± 1.7
Compliance (mm^2/MPa)	0.6 ± 0.1[a]	0.9 ± 0.1
At 100 mmHg		
Diameter (mm)	7.5 ± 0.3	7.3 ± 0.2
Distensibility (MPa^{-1})	10.0 ± 1.0	9.0 ± 1.1
Compliance (mm^2/MPa)	0.8 ± 0.1	0.7 ± 0.1

Data are presented as mean ± SEM.
[a]Significantly different from NT. After Laurent *et al.*[39]

Table 4 Percentage peak systolic circumferential strain ($\Delta d/d \times 100\%$; Mean ± SD) in the common carotid artery (CCA), in the proximal (B_p) and distal (B_d) parts of the carotid artery bulb as well as at the level of its maximum diameter (B_{max}) in normotensive young (NTY; 24 ± 3 yr) and older (NTO; 38 ± 5 yr) volunteers, and in borderline hypertensives (BHT; 38 ± 3 yr).

	n	CCA	B_p	B_{max}	B_d
BHT	16	6.3 ± 1.3	3.8 ± 1.4[a]	5.1 ± 1.4[a,b]	5.4 ± 1.6[a,b]
NTO	15	7.5 ± 1.9	5.7 ± 2.3[a]	7.0 ± 1.9	5.4 ± 2.3[a]
NTY	18	9.5 ± 2.2	9.2 ± 2.4	9.9 ± 2.3	8.7 ± 2.6

Data are presented as mean ± SD.
[a]Significantly different from CCA.
[b]Significantly different from B_p. After Van Merode *et al.*[14]

to be similar in essential hypertensive patients and in age-matched control subjects.[26]

Also in borderline hypertensives, distensibility and compliance are significantly reduced.[13,38] In the carotid arteries, the substantial decrease in distensibility and compliance is already apparent at relatively young age.[13] There are indications that these arteries age more quickly in borderline hypertensives than in normotensives: circumferential strain in the carotid artery bulb, especially in the most proximal part, is more reduced in borderline hypertensives than in normotensives of comparable young age (*Table 4*).[14]

It is still incompletely understood whether, the reduction of artery wall distensibility and compliance of the elastic arteries in essential hypertension, is caused by the increase in blood pressure or whether intrinsic changes in the wall contribute to this process. The observation of Laurent *et al.*[39] (*Table 2*) is in favour of a dominant role of increased arterial pressure, but our observations in borderline hypertensives[14,40] indicate that the reduction of dynamic artery wall properties cannot be explained by increased blood pressure alone and is even independent of elevated blood pressure in young spontaneously hypertensive rats.[41] The latter observation is in agreement with the more recent finding that in younger essential hypertensives, intrinsic changes in the artery wall contribute to increased stiffness of the arteries.[42] Therefore, in the treatment of patients with essential and borderline hypertension not only the reduction of blood pressure, but also the enhancement of compliance of elastic arteries has to be considered, especially because the loss of compliance and distensibility strongly correlates with left ventricular hypertrophy.[43] Compliance and distensibility of elastic arteries can be increased substantially by pharmacological intervention (increases up to 16%), but one should bear in mind that not all anti-hypertensive drugs improve artery wall compliance, despite their blood pressure lowering effect.[44]

Baroreceptor sensitivity

Baroreceptor sensitivity is reduced in older subjects and in patients with essential hypertension.[36,45] Using pressure derived measures to assess baroreceptor sensitivity,[46,47] it is impossible to determine whether this reduction is caused by reduced arterial distensibility or disturbances in the neural transduction part of the baroreflex arc. Distinction between both components can be achieved by assessing the transfer function between spontaneously occurring changes in arterial diameter, and its derivatives, during the cardiac cycle and cardiac R–R interval.[20] In this way, we were able to demonstrate that neural control of the baroreceptor is impaired with increasing age, in both normotensive[48] and hypertensive subjects.[48] When compared with normal subjects, in hypertensives the neural control of the baroreceptor was reduced only below the age of 50 years; beyond this age, the effect of aging obscured the difference.[48] Because dysfunction of autonomic cardiovascular control, which is characterized by baroreflex (patho)physiology,[47] is associated with increased morbidity,[49] our approach may be used to early diagnose this disorder.

Diabetes

The changes in arterial dynamic properties have less extensively been investigated by means of non-invasive vascular ultrasound in diabetic than in hypertensive patients. In cross-sectional studies, elastic and muscular arteries are generally found to be stiffer in diabetic patients than in age-matched control subjects,[50] although the findings in insulin-dependent diabetes mellitus (IDDM; type I diabetes) are inconsistent. For example, in patients with uncomplicated IDDM, Kool *et al.*[51] did not find an obvious reduction of wall properties of elastic and muscular arteries in young patients, whereas Hu *et al.*[52] observed increased stiffness of the descending aorta in children and adolescents. The observations in non-IDDM (NIDDM; type II diabetes) are far more consistent in the studies published so far. In cross-sectional[53] and population-based studies,[54] NIDDM was shown to be associated with loss of distensibility and compliance of both elastic and muscular arteries. Distensibility of the carotid artery is even reduced in healthy, non-diabetic subjects with an insulin resistance syndrome,[55] indicating that artery stiffening is an early marker of pathology in this disorder.

Atherosclerosis

Relatively little is known about arterial dynamic properties in atherosclerosis. In a population-based study, we could demonstrate that both aortic and common carotid artery stiffness have a strong positive association with carotid IMT and severity of plaque in these vessels.[56] Also in hypertensive patients arterial stiffness was found to be associated with the presence and extent of atherosclerosis.[57] These findings, however, do not imply a causal relation between artery stiffening on one hand and plaque formation on the other, especially because the dominating foam cells in atherosclerotic processes are supposed to be not stiff. At the site of the plaque, artery wall distension is substantially reduced,[58,59] a criterion successfully used in improving non-invasive diagnosis of minor carotid artery lesions in patients with focal neurological symptoms.[58]

What remains to be solved?

An important shortcoming in the non-invasive assessment of dynamic vascular properties is the lack of a method to reliably determine pulse pressure non-invasively at the site of measurement. Although pulse pressure in the brachial artery may be used as an approximation of pulse pressure in the common carotid artery,[60] this is not ideal because disease processes affect brachial and carotid artery wall properties, and hence pulse pressure, differently.[61] There is no pulse pressure substitute for the femoral artery. Reliable non-invasive assessment of pulse pressure is also necessary to adequately compare normotensives and hypertensives, requiring the construction and comparison of full pressure–diameter relations, which has only been achieved reliably in the radial artery.[26]

Local pulse pressure has been assessed by means of applanation tonometry.[62] In this approach, the distension waveform is recorded by means of a high fidelity strain gauge. Calibration[62] is achieved by assuming that diastolic pressure is constant and mean pressure does not change substantially along large arteries. Tonometry needs a lot of skill and requires stiff or bony background structures to flatten the artery and lean skin to avoid cushioning of the pressure pulse. Therefore, this approach is subject to error. Despite these limitations, tonometry has been used successfully in the carotid artery.[5,61] Carotid artery pulse pressure as determined in this way is a good predictor of carotid IMT and diameter enlargement.[63] Alternatively, the pressure waveform can be derived from the distension waveform, as recorded with a wall-track device.[64] This approach has the advantage that it can be used at more arterial sites and in the majority of obese subjects.[64]

Arterial transfer functions are used to transfer peripheral blood pressure waveforms back to their assumed aortic shape by correcting for the linear filter properties of the intermediate artery segment.[65,66] Tentative prospective studies indicate that this approach provides accurate estimates of systolic arterial and pulse pressure from peripherally recorded pressure waveforms.[67] It is still unclear, however, whether this method works out for comparison of non-matching groups, e.g. hypertensives and normotensives.

An alternative approach to assess artery wall stiffness is the use of pulse wave velocity (PWV): the stiffer the artery is, the higher the velocity will be.[68] A major advantage of this approach is that distensibility and, hence, compliance, can be assessed without measuring pulse pressure. PWV as determined with conventional techniques, however, provides information about arterial stiffness averaged over a relatively long artery segment with varying wall properties and does not allow the study of short-term variations. When interested in global rather than local artery wall stiffness, PWV has been shown to be a reliable parameter.[69] Moreover, PWV, as assessed in this way, is an independent predictor of all-cause and cardiovascular mortality in both hypertensive[57] and NIDDM patients.[70]

In a recent development, on the basis of a modelled approach for the exponential pressure–area relationship,[71] the rigidity coefficient is used as a single parameter, which can iteratively be estimated from the measured distension waveform.[23] The rigidity coefficient in combination with (brachial) diastolic pressure provides the pressure–diameter relationship, from which the elastic characteristics can be derived at any pressure.

In the assessment of the Young's modulus, it is essential that IMT can be determined accurately at a predetermined transmural pressure, i.e. at a selected distension. Methods based on a single RF line are inadequate, because it involves repeated measurements (temporal averaging) to reduce ultrasound speckle artifacts. Accuracy can be substantially improved by acquiring RF signals of two-dimensional images with

frame rates exceeding 200 Hz, facilitating spatial rather than temporal averaging with a minimal user interaction.[72]

Conclusions

Non-invasive assessment of artery wall dynamics is not perfect yet, but the approaches presently in use have improved our insights into the alterations in artery wall properties as in aging and hypertension. The lesson to be learned is that under these circumstances loss of compliance of the elastic arteries, which contributes substantially to the increase in systolic arterial and pulse pressure, known independent risk factors, already occurs at relatively young age. Therefore, in the management of hypertensive patients and of the elderly, treatment aiming at increasing arterial compliance should be considered, especially because in hypertensive patients, loss of compliance and distensibility strongly correlates with left ventricular hypertrophy. Another lesson is that aging and hypertension affect different arteries differently so that measurements have to be made on the artery of interest. The most serious limitation in assessing artery wall dynamics is the lack of a reliable method to determine blood pressure, and hence pulse pressure, locally at the site of measurement of distension and IMT. Promising approaches such as a modelled approach to assess the pressure–area relationship are under investigation. The determination of artery wall distension also allows us to better describe alterations in baroreceptor sensitivity.

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