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ORIGINAL ARTICLE

Angiography

The Clinical Significance of Aortic Compliance and Its Assessment with Magnetic Resonance Imaging

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ABSTRACT

The biophysical properties of the aortic wall seems to play a significant role in the pathogenesis of cardiovascular disease such as atherosclerosis, hypertension, aneurysm formation, Marfan's syndrome, and in normal aging. The presence and the proportion of smooth muscle, collagen, and elastin proteins contribute to the compliance of the vessel wall with the latter being the most extensible component. However, elastin fibers fracture at low stresses contributing to a decrease of the aortic compliance and consequently to an elevation of the pulse pressure, which is a risk factor of cardiovascular disease. Early detection of a decrease in the aortic compliance could help to identify early cardiovascular disease in asymptomatic patients and monitor the results of the therapeutic interventions. Therefore, estimation of the aortic compliance can be used for both screening as well as long-term follow-up.

Magnetic resonance imaging which is a noninvasive, accurate, and reproducible method can estimate the compliance of the aortic wall either by measuring the relative change in cross sectional area of a chosen segment using ECG-triggered spin echo or gradient echo sequences or by measuring the pulse wave velocity through the aorta using the phase contrast-magnetic resonance imaging (PC-MRI)

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technique. Both techniques have been validated and many studies suggest MRI as a valuable tool for evaluating aortic wall function. However, large prospective studies are mandatory for the method to be established as a screeing tool.

Key Words: *Magnetic resonance imaging; Aortic compliance; Hypertension; Atherosclerosis; Marfan's disease*

INTRODUCTION

There is increasing interest in the evaluation of biophysical properties of the aortic wall and their relation to cardiovascular disease.[1] The elastic properties of the aortic wall seem to play an important role in the pathogenesis of cardiovascular disease including atherosclerosis, hypertension, other aortic wall abnormalities, and probably in normal aging. In all the above states, the compliance of the aorta is decreased and all the data suggest that early detection of this dysfunction could provide a tool for early identification of cardiovascular disease.

However, to detect and monitor the aortic elastic properties in a routine basis, a noninvasive, accurate, reproducible, and safe method is required. In this review, the biophysical properties and the histochemical structure of the aortic wall are discussed and the clinical relevance of the aortic compliance evaluated by MRI is emphasized.

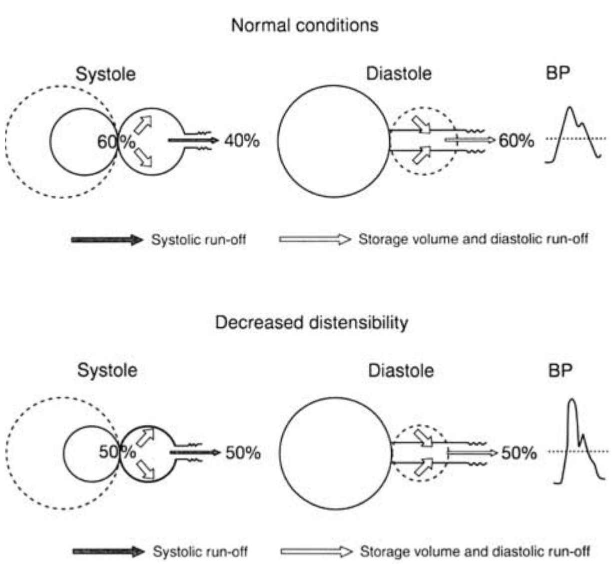


Figure 1. Diagrammatic representation of the "Windkessel function" of arteries in normal and with decreased arterial distensibility conditions. BP, blood pressure (Gerard M. London, et al. Am. Heart J. **1999**, *138*, S220–S224, with permission).

BIOPHYSICAL MECHANICAL PROPERTIES OF THE AORTIC WALL

The central aorta has two important functions. First, it acts as a conduit delivering blood from the left ventricle to the peripheral tissues and secondly, it transforms the pulsatile effect caused by ventricular ejection into a continuous blood flow in the periphery. Blood flow through the capillaries should be steady during the cardiac cycle in order to minimize the load on the left ventricle and keep the flow steady in the coronary circulation. During systole, the central aorta distends and accommodates briefly part of the stroke volume, storing part of the energy of the left ventricular contraction. Almost 60% of the stroke volume is accommodated by distension in the aorta and the major arteries. Furthermore, the stored energy recoils the arterial wall during diastole and forwards the accommodated blood to the periphery (Fig. 1). The mechanism responsible for the transformation of the pulsatile flow of the central arteries into the steady flow of the peripheral tissues is called "Windkessel function." The efficiency of this cushioning function is determined by the viscoelastic properties of the arterial wall described in terms of compliance (C) and defined by Spencer and Denison[2] as the change in arterial blood volume (ΔV) caused by a given change in arterial blood pressure (ΔP), i.e., $C = \Delta V/\Delta P$.

When aortic compliance is decreased, less proportion of the stroke volume is stored in the aorta during systole and more is forwarded to the peripheral circulation. As a result, systolic blood pressure and the amplitude of the arterial pulse wave are increased. Moreover, during the diastole and the closure of the aortic valve, arterial pressure begins to fall since peripheral run-off from the aorta to the peripheral arterial system occurs. The rate of the diastolic pressure fall is determined by the peripheral resistance and the viscoelastic properties of the artery. Thus, for a given peripheral resistance the diastolic pressure is decreased and the systolic pressure is increased resulting in an increase of pulse pressure (PP). Since there are increasing evidence that an elevated PP, an indicator of aortic compliance, is a risk factor of coronary heart disease,[3] the concept of arterial wall stress has been introduced in the investigation of aortic structure and function.

HISTOCHEMICAL STRUCTURE OF THE AORTIC WALL

The aorta's mechanical properties depend largely on the presence, the proportion and the interaction of smooth muscles, collagen, and elastin proteins. Each of these components has its own characteristic properties and contributes to the compliance of the vessel wall. Smooth muscle changes the diameter of the lumen or the tension of the wall, by contraction, whereas elastin and collagen act essentially in a passive way. Elastin is a highly extensible protein with a remarkable longevity and no appreciable synthesis in the adult aorta (Fig. 2a). Elastin fibers can be stretched up to 300% of their length at rest without rupturing,[4] return to their original state when released and have a half-life of about 40 years.[5,6] However, they fracture at low stresses contributing to the decrease in aortic compliance (Fig. 2b).[9] On the other hand, collagen acts as a stiff reinforcing component, as it is relatively inextensible (Fig. 2c and d). Although the elastic modulus of collagen fibers has not been measured directly, it is estimated that it is 1000 times less extensible than elastin fibers and can resist stresses 100 times more than the fracture stress of elastin.

The proportion of the collagen and elastin contents varies among vessels with elastin accounting for 60% and collagen for 40% of total fibrous element in thoracic aorta. The mixture of components with different elastic properties results in a nonlinear behavior of the pressure–volume curve of the aortic wall when distended and is the key to elastic stability, protecting against aneurysm formation, and rupture[7,8] (Fig. 3). Considering the pressure–volume curve, Roach and Burton[9] demonstrated the individual mechanical role of collagen and elastin by selectively digesting each from samples of human artery. They found that the initial stiffness of the artery wall represented the elasticity of elastin, while the much higher stiffness at high strains represented the contribution of fully stretched collagen fibers.

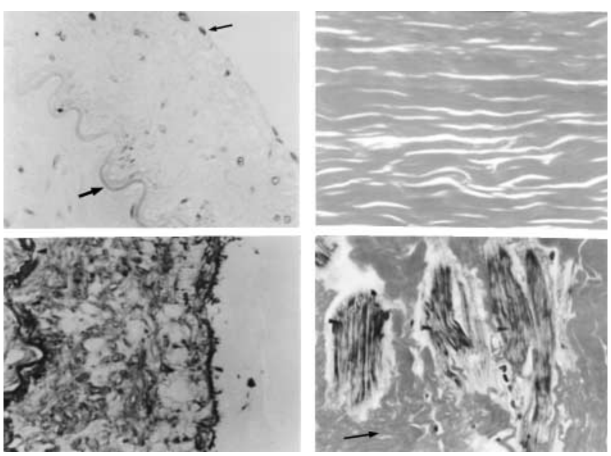


Figure 2. (a) Cross-section of a medium size artery from a 62-year-old male. The thin arrow shows a single layer of endothelial cells covering the intimal layer while the thick arrow shows a well-preserved internal elastic membrane (H + E ×430). (b) Cross-section of an aged medium size artery, showing thickening and edema of the intima, as well as slight fragmentation of the elastic lamellae (Elastic Orcein ×430). (c) Masson trichrome staining showing dense collagen fibers from normal tendon. (d) Section from the myocardium of the left ventricle with old myocardial infarct. The arrow shows a scar consisting of dense collagenous tissue, whereas the arrowheads point fragmented cardiac muscle fibers which demonstrate patchy loss of cross striations (Masson trichrome ×430).

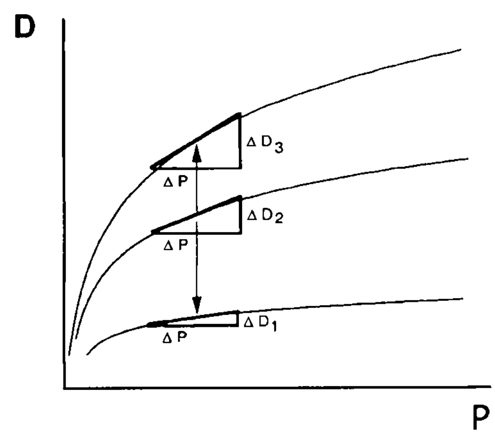


Figure 3. A diagram presenting the nonlinear pressure–diameter relationships for evaluating vascular compliance. Compliance is increasing when shifting to curve 3 (top) and decreasing when shifting to curve 1 (bottom) (Helmut F. Kuecherer, et al. Am. J. Physiol. Heart Circ. Physiol. **2000**, *278*, H1411–H1413, with permission).

CLINICAL IMPLICATIONS OF AORTIC COMPLIANCE ESTIMATED BY MAGNETIC RESONANCE IMAGING

Age

Compliance decreases more rapidly with age in the large arteries than in the peripheral ones,[10] and pulse wave velocity (PWV) that is directly related to the aortic compliance is more strongly related to biological age than graying of hair or skin elasticity, with correlation coefficient as high as 0.94.[11] Mohiaddin et al.[12] used phase contrast-magnetic resonance imaging (PC-MRI) to measure PWV in the thoracic aorta of 20 healthy volunteers and found a negative correlation between PWV and compliance in ascending aorta ($r = -0.75$). Furthermore, regular aerobic activity, favorably modifies the age-related reduction of central aorta compliance[13] contributing to the lower incidence of cardiovascular disease compared with sedentary lifestyle.[14] This is supported by studies of Kupari,[15] Resnick et al.,[16] and Mohiaddin et al.[17] indicating that aortic compliance assessment may predict the biological age, thus becoming a tool to evaluate age-related cardiovascular disorders and the results of life style associated modifications.

Atherosclerotic Disease

It is well known that atherosclerotic disease begins early in life, decades before clinical symptoms such as angina and myocardial infarction appears. In animal studies it has been shown that the presence of advanced atherosclerosis correlates with the degree of aortic stiffening, and regression of atherosclerotic lesions has been associated with a decrease in vessel wall stiffening.[18] Forbat et al.[19] measured aortic compliance by MRI and correlated these measurements with ultrasonography (carotid intima–media thickness) and electron beam CT (coronary calcifications score) in hypercholesterolemic patients with and without coronary artery disease during 1 year of fluvastatin induced reduction of cholesterol level. They demonstrated an improvement in aortic compliance following an increase of the high density lipoprotein and decrease of low density lipoprotein. In the same group of patients, the carotid intima–media thickness decreased from 1.09 to 0.87 mm ($p = 0.004$), supporting these results.

Moreover, there are studies indicating that estrogens administration in postmenopausal women, increases vascular compliance within 3 months[20] and reduces mortality from cardiovascular disease by 50%.[21] Furthermore, there are evidence that even a short-term increase of estrogens in premenopausal women, induced by menotropin treatment, is associated with increase in aortic compliance within 7 days.[22] MRI by assessing, noninvasively, aortic compliance changes in asymptomatic subjects could be an ideal tool in predicting the risk factors for cardiovascular disease, and the results of early therapeutic interventions.

Hypertension

In the Framingham Heart study, Franklin et al.[3] in a longitudinal follow-up of subjects over 50 years of age, found a strong correlation between PP and cardiovascular events (coronary artery accidents in particular) in both normotensive and hypertensive middle-aged adults. Since PP is an indicator of large artery compliance, the need for an accurate and noninvasive measurement of aortic compliance is emphasized. MRI could be a useful tool in both, identifying high risk hypertensive patients requiring more aggressive therapy and monitoring its results.

LV Hypertrophy

In patients with essential hypertension, left ventricle hypertrophy (LVH) is a common finding and is considered as a consequence of the long-term increase in afterload.[23] The dominant factor contributing to the development of LVH is increased end-systolic stress[24] which is directly proportional to intra-ventricular pressure and inversely related to ventricular wall thickness. Therefore, LVH is a remodeling procedure representing the adaptation of the myocardium in order to normalize the increased wall stress.[25] However, there are evidence to suggest that the capacitive properties of the aorta are also involved in the cardiac function and that a decrease in arterial compliance appears to affect the degree of cardiac hypertrophy, independent of blood pressure. Moreover, there are clinical studies that have demonstrated that antihypertensive drugs show disparate effects on myocardial mass in LVH for the same degree of blood pressure reduction. Converting enzyme inhibitors and calcium antagonists have been shown to reduce LV mass mainly through an improvement of aortic compliance.[26–29] Savolaninen et al. assessed aortic elastic modulus by MRI in patients with essential hypertension before and after 3 weeks and 6 months of cilizapril or atenolol administration, respectively, and found that these drugs reduce the stiffness of the ascending aorta. Furthermore, Honda et al. evaluated the aortic distensibility of 33 hypertensive patients by MRI, before and after 12 weeks of trichlormethiazide, nicardipine, and alacepril treatment, respectively, and they showed that only the last two drugs had a beneficial effect on aortic distensibility.

The assumption that decreased aortic compliance seems to play an important role in the development of cardiac hypertrophy through increased systolic pressure and PP may have several clinical implications. For example, modifications in the therapeutic intervention that selectively improve the aortic compliance and potentially reverse cardiac hypertrophy in patients with higher PP could be a approach where functional MRI could provide useful information.

Marfan's Syndrome

The leading cause of death in patients with Marfan's syndrome is progressive aortic dilation with subsequent dissection and rupture due to structural abnormalities in elastin and collagen fibers. There are studies that demonstrated abnormal aortic compliance in these patients using MRI.[30] Groenink et al.[31] used MRI to assess the regional aortic compliance and measured the PWV in patients with Marfan's syndrome and healthy volunteers before and after beta-blockers therapy. They demonstrated that although the mean blood pressure decreased in both groups, aortic stiffness was reduced only in patients with Marfan's syndrome and they suggest MRI as a method with good reproducibility to evaluate aortic stiffness. Fattori et al.[32] studied 20 patients with Marfan's syndrome, 15 family members and 14 healthy volunteers using MRI to evaluate regional aortic compliance to conclude that abnormal compliance of ascending aorta measured by MRI may be used as an index of early aortic involvement, before dilation occurs.

Aortic Aneurysm

Preliminary results show that PWV measurements by MRI may be used in cases of aortic aneurysm and may predict the risk of sudden rupture.[33] In an ongoing study, MR PWV measurements is being applied to patients with infrarenal aortic aneurysms prior to surgery. The aim of the study is to correlate PWV with histopathological and intra-operative parameters and it seems promising (J. Boese et al., unpublished data).

MEASUREMENT OF AORTIC WALL COMPLIANCE

There are mainly two ways to measure aortic compliance. First, by the change in aortic diameter and blood pressure over the cycle measured by ultrasound,[34] x-ray imaging[35] and MRI,[36–38] and second by measurement of the PWV along the aorta. A number of methods have been proposed for PWV measurements based on Doppler ultrasound,[39] applanation tonometry, and MR phase contrast imaging.[12,40–42] Transthoracic echocardiography and MRI are both noninvasive techniques and there are several studies referring to their advantages and drawbacks. Compared to ultrasound, MR has certain advantages. MR is not limited by acoustic window and allows the measurements to be made at the same level of the aorta increasing reproducibility. Furthermore, it has the potential to obtain accurate volumetric data. However, there are drawbacks in using MR as a screening method for evaluation of aortic compliance such as the limited availability and the high cost of the procedure.

ESTIMATION OF AORTIC COMPLIANCE BY MRI

Magnetic Resonance Imaging and Regional Aortic Compliance

Magnetic resonance imaging can estimate regional compliance by measuring the relative change in cross sectional area of a chosen segment divided by the PP estimated at the brachial artery by a sphygmomanometer. Both ECG-gated spin echo (SE) and ECG-triggered cine gradient-echo (GRE) sequences have been proposed for this purpose. The images are acquired perpendicular to the ascending aorta at a predefined level such as the bifurcation of the pulmonary artery (Fig. 4a). After the images are reconstructed, the endothelial border of the aortic lumen is outlined manually in systole and diastole, on the computer screen (Fig. 4b) and the change in cross-sectional area is divided by the average PP measured by a sphygmomanometer at the brachial artery during or immediately before and after the acquisition. Finally, the regional compliance (C) is calculated according to the equation $C = \mathrm{d}A/\mathrm{d}P$, where A represents the cross-sectional area and P the blood pressure. In ECG-gated SE sequence, two images are acquired, one at the end of diastole (100 msec before the average RR interval) and the other at the end of systole (at the end of the T wave). Proper selection of the gating delay for the systolic and diastolic slices is the major drawback of these sequences.

The advantage of SE sequence is the high contrast between the endothelium and the lumen, although slow flowing blood during diastole may produce high signal and obscure the definition of the inner arterial wall.[12,48]

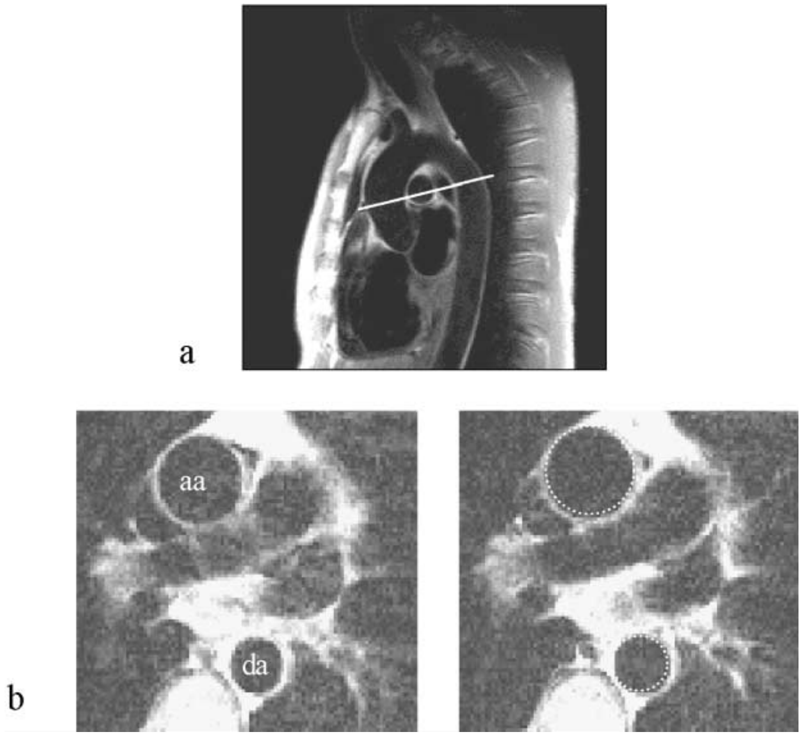
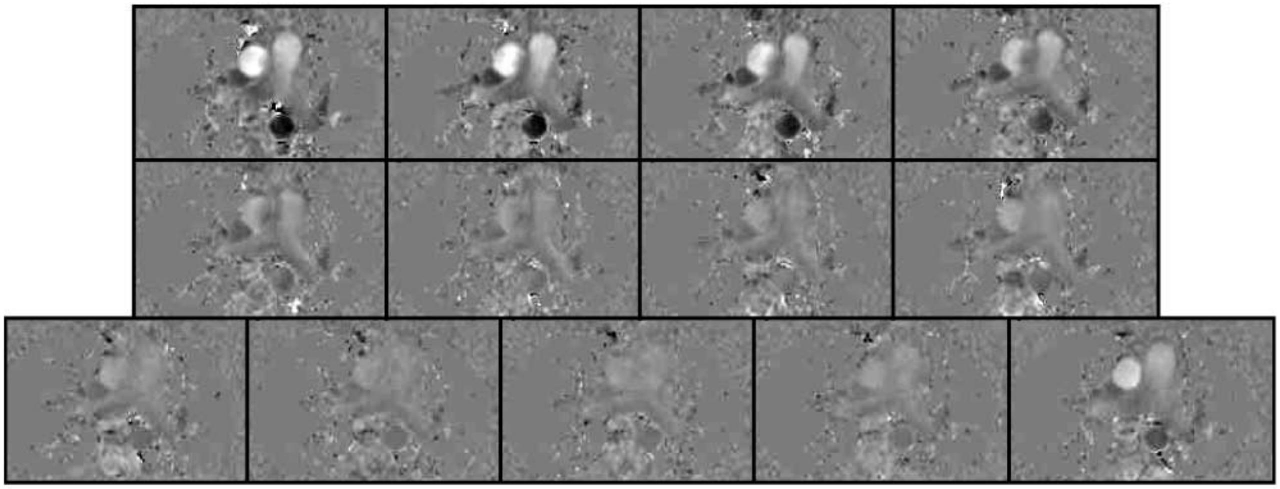


Figure 4. (a) Oblique image of the ascending aorta, aortic arch, and descending aorta shows the sites at which compliance is measured. (b) Diastolic and systolic images of the ascending and descending aorta showing the change in aortic area of a normal volunteer (Raad H. Mohiaddin, et al. J. Appl. Physiol. **1993**, *74* (1), 492–497, with permission).

Buonocore and Bogren[43] reported a modification of the technique by the application of spatial presaturation pulses and optimization of the image quality. The unwanted signal from the slow blood flow was reduced by 77% and thus, both reproducibility and intra-observer variability was improved. In 1995, Forbat et al. tested the reproducibility of a modified SE sequence for the measurement of aortic compliance in 47 healthy volunteers. They showed that after modifying the technique, increasing the signal to noise ratio and the spatial resolution to 1 mm, both reproducibility and intra-observer variability were improved.[44] They concluded that aortic compliance could be measured with good reproducibility by using spin echo MR imaging provided good quality images with high resolution could be obtained.

In ECG-triggered cine GRE acquisition (Fig. 5), the images are acquired throughout the cardiac cycle which results in a multiphase image. Temporal resolution of approximately 25 msec can be obtained, thus allowing the accurate selection of the diastolic and systolic phase. The high temporal resolution that GRE offers is the main advantage of the sequence and allows studying the dynamic changes of the lumen cross-sectional area. The disadvantage of GRE sequence is that the inner border of the vessel wall is not clearly identified. The endothelial border is outlined manually by tracking around the bright signal produced by the flowing blood. As the intensity of the blood signal varies during the cardiac cycle, becoming higher in systole, this phenomenon results in an overestimation of the lumen and consequently introducing subjective error. To overcome this limitation, high spatial resolution of <1 mm is extremely important especially when studying stiff vessels where the change in cross section is so small approaching the limits of the resolution of the technique.[45] Another factor that effects the flow signal intensity is the RF flip angle. To reduce spin saturation effects during diastole, a small flip angle (20–30°) must be carefully selected. In the study of Chien et al., the authors concluded that high spatial and temporal resolution and a small flip angle improves significantly the quality of the image and the reproducibility of the method.

Both of these techniques are limited by the fact that PP that represents ΔP is measured indirectly at a peripheral artery and the measurement is used for



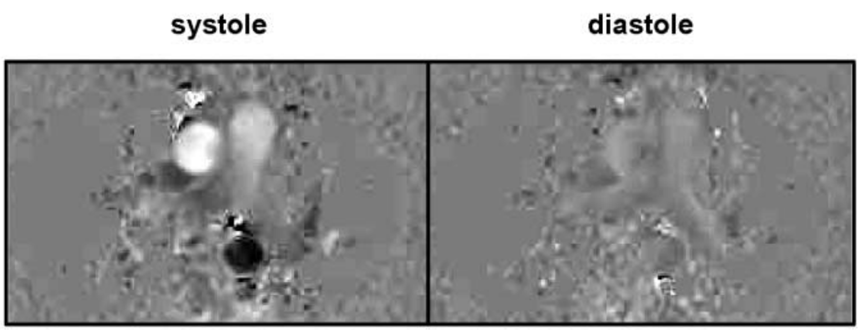


Figure 5. Diastolic and systolic phases of the ascending and descending aorta resulting from a cine multiphase GRE acquisition. Dpt. of MR Study, University Hospital of Ioannina, Greece.

estimation of the compliance of the central aorta. Since in young subjects the PP is much higher in the periphery than in central arteries, brachial blood pressure can induce large errors. With increasing age, as the aorta becomes stiffer, the PP gradient along the arteries tends to disappear and the errors due to brachial blood pressure measurements are decreased.

Despite these limitations many investigators have reported accurate and reproducible results by using this technique in the study of cardiovascular diseases.[31,32,46–49]

Magnetic Resonance Imaging and Pulse Wave Velocity

> "The pulse wave in man travels in the arteries at a speed of 4–10 m/sec. Its velocity depends … chiefly upon the elastic conditions of the arterial wall, which is affected by a variety of factors in health and disease."—Bramwell and Hill—1922

For many years, invasive methods have been the "gold standard" for measuring the PWV but recently noninvasive methods have been used including Doppler and MRI.[12,38,40–42] Both methods rely on the estimation of the PWV which represents the velocity of the waveform of the flow in the artery. PWV is defined as the distance (D) between two points (A and B) divided by the time ($\mathrm{d}t$) needed for the pulse wave to propagate from point A to point B. PWV is directly related to the elastic properties of the vessel wall[49] according to the equation $C = 1/c^2p$ (C = compliance, c = wave velocity, and p = blood mass density). Thus, the increase in PWV with age in the aorta reflects a decrease in the compliance.[50]

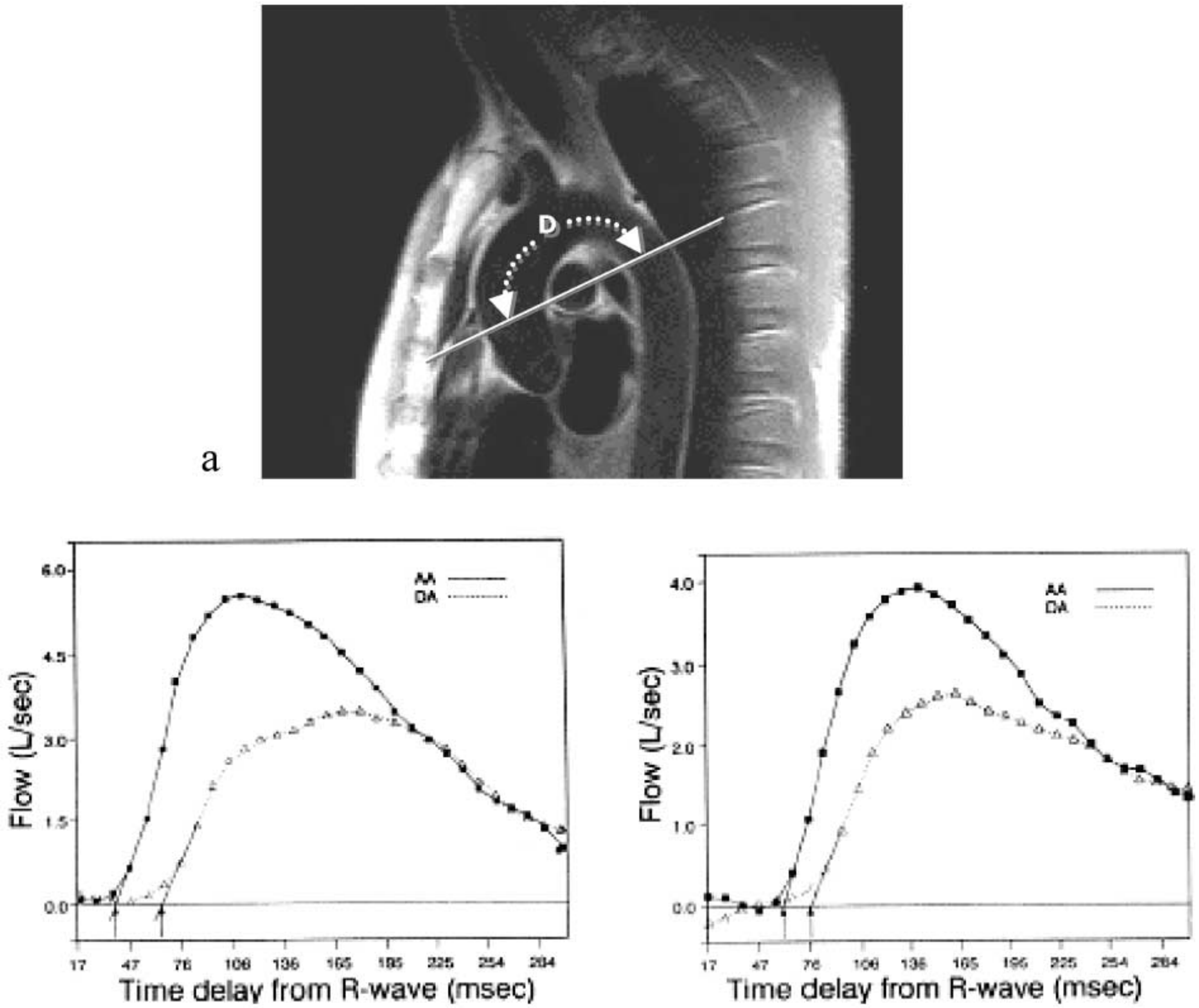


Figure 6. (a) Spin echo oblique image of the thoracic aorta that shows the sites where phase contrast images are acquired. *D*, distance between two points where PWV was measured. (b) Foot of flow is defined by extrapolation of rapid upstroke of flow wave to baseline. Transit time needed for flow wave to propagate from a point on midascending aorta and a point on middle-ascending thoracic aorta can then be calculated. Data obtained from an elderly normal subject with poor compliance, for whom transit time is shorter (*left*) and from a young normal subject with good regional compliance (*right*). (R.H. Mohiaddin et al., 1993, with permission).

The main drawback of transthoracic Doppler in assessing the PWV is the limited acoustic window along the aorta and the inability to register volumetric data. Furthermore, reproducibility studies have shown that the technique is affected by technical factors, such as transducer placement and beam angle, suggesting PWV measurement variations in the order of 10–20%.

Magnetic resonance imaging, by using the PC-MRI or velocity-encoding technique (VENC-MRI) provides a phase velocity map, which can be used for quantifying the blood volume flowing through the imaging plane. The PC sequence is acquired in a plane perpendicular to the lumen of the vessel at two different levels by encoding the velocities perpendicular to the aortic cross section (Fig. 6a). Slice separation of about 8–10 cm is used, in order to obtain more accurate measurements of the compliance, with an estimated error of 6.4%.[51] Two factors have a great impact in the assessment of flow measurements and these are the temporal and spatial resolution. Since high temporal resolution, of at least 25 msec, is extremely important for accurate quantification—particularly in the case of a highly pulsatile flow—a compromise at the expense of spatial resolution is mandatory. Tang et al.[52] demonstrated that at least 16 voxels, corresponding to in-plane resolution of 2 mm, must cover the cross-section of the aortic lumen in order to obtain an accuracy to within 10%.

A phase velocity map is generated and the mean flow velocity across a vessel cross-section area can be calculated and plotted as a function of time across the two levels. PWV is calculated by dividing the distance between the two levels by the transit time (d*t*) of the foot of the flow wave. The "foot" represents the steep ascent of the flow wave at the beginning of systole and is therefore largely independent of reflected waves that die out by the end of the cardiac cycle and can induce errors in the estimation of PWV (Fig. 6b). Finally, the distance is measured by tracing with a cursor along the centerline of the vessel, in an oblique saggital SE image. Artifacts from cardiac, respiratory, and patient motion can introduce errors in the assessment of PWV. Moreover, large errors can occur if the slices are positioned near large branches due to wave reflections or if there is cardiac arrhythmia. Other limitations of the technique include the subjectivity of the ROI definition that depends on variety of factors, such as flow velocity, signal from the surrounding tissues, imaging parameters, and the inaccuracy of the vessel length measurement, especially in tortuous vessel. Finally, it must be emphasized that the MR image is not a real-time image but is built up over many cardiac cycles. Therefore, the resultant image and quantitative data represent an average over these cardiac cycles.

Despite these limitations, both cine-GRE-PC and EPI-PC have been validated[53–56] and have been suggested that PC-MRI can provide accurate flow measurements in pulsatile vessels.

SUMMARY

One of the main functions of the aorta is to maintain a steady blood flow through the capillary bed by transforming the pulsatile flow generated by ventricle contraction into a continuous flow. This is particularly important for minimizing the load imposed on the left ventricle during cardiac systole. In order to maintain this pulse reducing effect on the flow, the aortic wall has to be compliant. Hypertension, atherosclerosis, and normal aging are the most common situations associated with a decrease in aortic compliance. Other aortic diseases like Marfan's syndrome, coarctation, and aneurysm formation seems to be related to the changes of the vessel wall elastic properties as well.

There is strong evidence that the decrease in aortic compliance is associated with an increase of the risk of cardiovascular disease. Therefore, aortic compliance measurements in combination with other risk factors may be able to identify early cardiovascular disease in asymptomatic patients and monitor subtle changes of the arterial wall elasticity, in response to various dietary and pharmacological manipulations. Furthermore, it could help researchers in better understanding the natural history of diseases that involve aorta. A method to be suited for screening large populations of symptom—free individuals and long-term follow-up of patients, should be noninvasive, reproducible, and accurate.

Magnetic resonance imaging can assess the aortic elastic properties either by measuring the regional compliance or the PWV. Both techniques have been validated and there are many studies that suggest MRI as a useful and accurate tool for the assessment of aortic wall function. However, to establish the technique as a screening tool, large prospective studies are required in order to correlate compliance measurements with clinical events in the long term. Furthermore, the limited availability and the cost effectiveness of the method should be taken into consideration.

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