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Rationale of Echocardiographic Assessment of Left Ventricular Wall Stress and Midwall Mechanics in Hypertensive Heart Disease

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Active reduction of left ventricular chamber size during systole is the final effect of complex interaction mechanisms involving layers of differently oriented myocardial fibres, the shortening of which is less than the one measured as shortening of the left ventricular diameter at the level of the endocardium. This biological phenomenon is particularly evident in conditions such as arterial hypertension in which left ventricular geometry is altered. Due to the double effect of contraction on both the longitudinal (shortening) and transverse (thickening) axes of the myocardial fibres, the shortening of single myocardial fibres is amplified at the level of the endocardium and this amplification is a function of wall thickness. Increased wall thickness can enhance at the endocardial level the effect of myocardial fibres with reduced shortening, allowing preservation of ejection fraction despite depressed midwall shortening, through a 'contractile gradient' proceeding from epicardium to endocardium. This is detectable using tagged MRI or even quantitative echocardiography. This discrepancy between chamber and wall mechanics, seen in arterial hypertension and in other clinical conditions characterized by alteration of left ventricular geometry, is at the basis of the better prediction of cardiovascular risk in hypertensive patients by measures of left ventricular wall mechanics than by measures of left ventricular chamber function.
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Key Words: cardiac function; afterload, echocardiography; contractility; myocardium.

Introduction

The left ventricular ejection fraction and its one-dimensional equivalent, minor-axis fractional shortening, are the result of complex mechanical processes involving myocardial structures of the ventricular wall that are regulated by the interaction among different myocardial muscle layers with different spatial orientations. In 1967, Ross *et al.*[1] reported a canine experiment in which left ventricular minor-axis shortening was disproportionally greater at the level of endocardium (26%) than at the level of midwall (16%) or at the epicardium (8·5%). When the left ventricular wall thickens, as occurs in arterial hypertension, those differences also increase. Echocardiography and new imaging techniques have contributed to elucidating those observations by investigating in vivo left ventricular wall mechanics in animals as well as in humans.

We will review the relationship between the ability of the left ventricle to pump blood into the arterial tree, as defined by ejection phase indexes, and intra-parietal left ventricular mechanics in arterial hypertension, to focus on whether the left ventricular wall–chamber relationship can be evaluated, based on simple echocardiographic parameters.

Left Ventricular Myocardial Architecture

In 1669, Richard Lower accurately described left ventricular myocardial architecture[2] as an assembly of

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muscular layers, similar to the layers of an onion. These muscular layers are differently oriented and, roughly, three types of orientations can be recognized: the two external muscular layers (subepicardial and subendocardial) are prevalently longitudinal and helically oriented, whereas the larger middle layer is principally oriented in the circumferential direction[3]. Although the transition among the different orientations is gradual, this simplification makes it possible to derive many physiological inferences applicable to the clinical setting.

Left ventricular chamber size reduction during systole is the consequence of the simultaneous contraction of myocardial layers in the different directions, yielding the three basic left ventricular geometric changes: reduction of minor axis, shortening of long axis and twisting of the apex[4–6]. The greatest proportion of ventricular myocardium (about 60%) is in the midwall, is oriented circumferentially[7] and accounts for circumferential left ventricular contraction, the basic mechanism of systolic reduction of minor axis diameter. The larger number of cardiac myocytes prevalently oriented in the circumferential direction explains the fundamental role of minor-axis shortening in squeezing of left ventricular cavity and sustaining ejection fraction[4,7], as compared to longitudinal shortening[8], and clarifies the practical interchangeability of ejection fraction and systolic fractional shortening of minor axis, as measures of left ventricular chamber function[9], when the left ventricle contracts symmetrically.

Influence of Left Ventricular Geometry on Chamber Emptying

The concept that left ventricular ejection is also a function of the chamber's geometry, namely of the wall thickness/chamber radius ratio (relative wall thickness), has been addressed by a number of pilot studies[10–12]. In a non-theoretical context, Palmon *et al.*[13] demonstrated that the shortening of single myocardial segments, evaluated using tagging MRI, is reduced in hypertensive patients with left ventricular hypertrophy, who exhibited, however, normal ejection fractions. The apparent inconsistency of normal left ventricular chamber function despite depressed myocardial function could be explained by the presence of concentric left ventricular hypertrophy. Similarly, Aurigemma *et al.*[14] demonstrated normal echocardiographic ejection fraction in elderly patients with high relative wall thickness and depressed fractional shortening measured at the left ventricular midwall. When left ventricular wall thickness is increased, a given magnitude of systolic wall thickening and of the resultant endocardial shift toward the cavity's centre, can indeed be obtained with lesser myocardial fibre shortening[15]. Because of this reciprocal relation between wall thickness and the amount of myocardial fibre shortening needed to cause a given displacement of the endocardium, the magnitude of systolic shortening measured at the endocardium does not directly reflect the intramural shortening[16].

Under usual conditions, single sarcomeres shorten by about 15%[17], while systolic shortening measured at the level of endocardium is about twice as great, but can easily reach 40%! Geometric considerations suggest that with 15% shortening, a cylindrical myocardial fibre should thicken by about 8·5%[12]. The sum of these two forces (i.e. meridional and radial) in differently oriented myocardial layers produces the phenomenon of 'cross-fibre shortening', of the left ventricular radius, associated with a 'cross-fibre thickening' of the myocytes that is characteristic and particularly evident at the inner subendocardial longitudinal layer[18], because in that site the combined effect of all outer muscular layers converges.

Based on a cylindrical model for myocardial fibres (that is $V=\pi r^2 L$), and under the assumption that myocyte mass is incompressible and cannot change between contraction and relaxation, at a given fibre shortening the corresponding fibre thickening can be calculated. A simplified relation between shortening and thickening of a single circumferentially layered cylindrical model is shown in Fig. 1. For a true myocardial shortening of 15%, therefore, the effect in the radial orientation is:

$$\frac{1}{(1-0{\cdot}085)*(1-0{\cdot}15)}=1{\cdot}29 \qquad (1)$$

This calculation indicates that for a given 15% fibre shortening and 8·5 consequent thickening, a 29% endocardial displacement might be expected. In a three-layered myocardial shell, which approaches the true myocardial architecture, the effect on contraction in the radial orientation is more complex, being also a function of the thickening of the inner and outer longitudinally oriented myocardial fibres. Accordingly:

$$\frac{1}{(1-0{\cdot}085)*(1-0{\cdot}15)*(1-0{\cdot}085)*(1-0{\cdot}085)}=1{\cdot}54 \qquad (2)$$

Therefore, for a 15% fibre shortening the endocardial displacement caused by the three-layered left ventricular wall thickening is about 54%. Comparing the relation between midwall shortening and the per cent thickening of posterior wall in hypertensive patients studied by echocardiography (Fig. 2) with the theoretical calculations in Fig. 1, the latter theoretical approximation corresponds closely to the observed relation between left ventricular posterior wall thickening and midwall shortening (e.g. 52% thickening at 15% midwall shortening).

Studies using the tagging MRI technique have directly documented the phenomenon of cross-fibre shortening which is associated with a consequent 'cross-fibre thickening', as shown in formula (2), demonstrating that segmental intramural shortening can markedly increase its effect at the endocardial level. Rademakers *et al.*[18] confirmed that 'cross-fibre shortening' is more evident at the endocardial than at the epicardial level and is more pronounced than the shortening of either endocardial or epicardial fibres along their longitudinal axis. As a

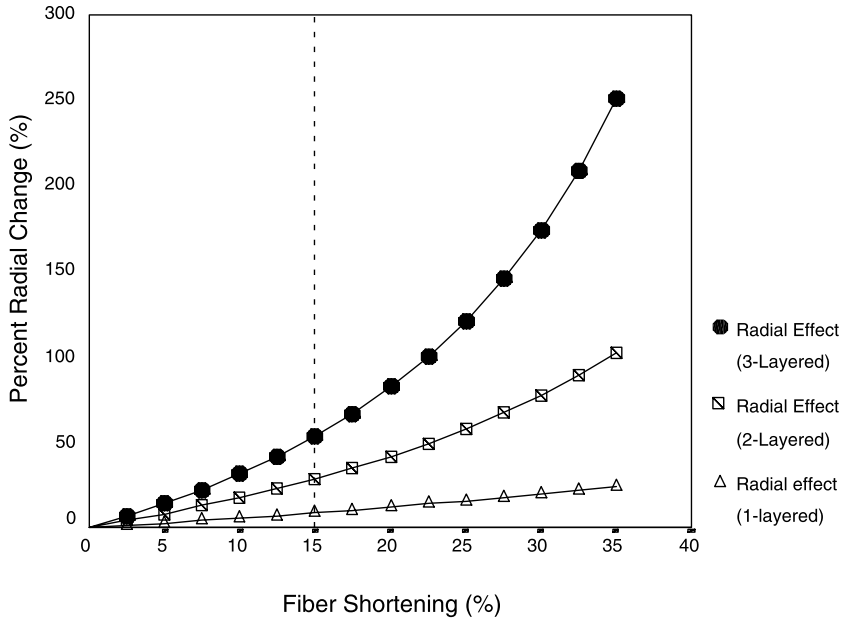

Figure 1. Per cent overall thickening in the radial direction (vertical axis) of an ideal wall formed by one layer (open triangles), two layers (open, dashed squares) or three layers (black circles) of cylindrical fibres shortening over a range between 5% and 35% (horizontal axis) and thickening accordingly in order to preserve their mass. For a three-layered shell, a single fibre shortening of 15% corresponds to wall thickening in the radial direction of 54%.

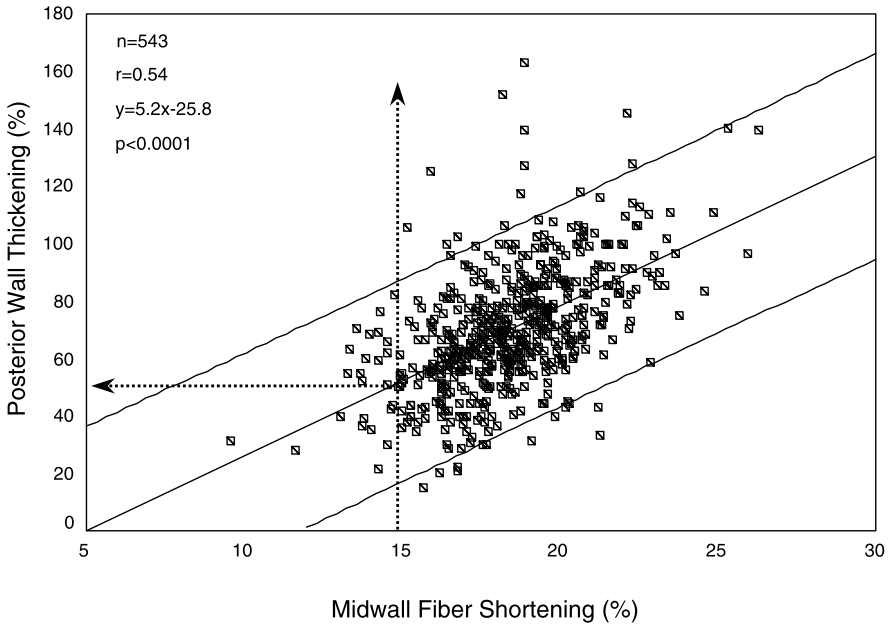

Figure 2. Posterior wall thickening (vertical axis) at each level of midwall shortening (horizontal axis) in a large population of normotensive and hypertensive subjects. Similar to the simulation in Fig. 1, an average midwall shortening of 15% corresponds to an average wall thickening of about 50%.

consequence, the direction of the maximal deformation parallels fibre direction at the epicardial level, whereas it is perpendicular to the fibre direction at the endocardial level[18]. Systolic shortening of longitudinally-oriented subepicardial and subendocardial fibres squeezes the circumferentially oriented fibres at the midwall level, thereby potentiating cross-fibre myocyte thickening and cross-fibre left ventricular radius shortening. Thus, the

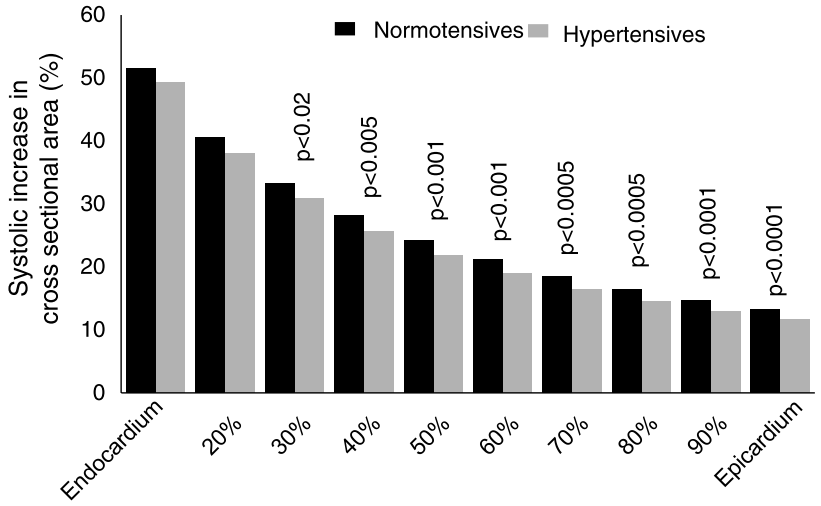

Figure 3. Systolic increase in cross-sectional area from endocardium to epicardium in normotensive (black bars) and hypertensive subjects (grey bars). Beginning at 30% of inner diastolic wall thickness, systolic increase in cross-sectional area progressively and proportionally decreased more in hypertensive subjects than in normotensive controls (with P value going from <0·02 to <0·0001). From Ref.[19], with permission.

characteristic marked ventricular radius shortening at the endocardium is the consequence of the interaction of contraction and thickening of differently aligned myocardial muscular layers located at a distance.

The close relation between regional thickening and left ventricular radius shortening[10–14]indicates that this mechanism of amplification can be used to enhance the effect of a reduced myocardial fibre shortening, to yield better parietal thickening and endocardial excursion and suggests that a depressed fibre shortening can be a biological signal for left ventricular remodelling in order to preserve left ventricular chamber function. The magnitude of amplification produced by 'cross-fibre shortening' increases progressively from epicardium to endocardium, using the gradual increase of the interaction among differently aligned muscular layers to yield a 'contractile gradient' that proceeds from the most external epicardial layers toward the inner subendocardial layer. Recently, this epicardium→endocardium 'contractile gradient' was also demonstrated using computerized calculations done by M-mode echocardiographic measurements in 50 normotensive and 50 hypertensive subjects[19]. Systolic increase of short-axis cross-sectional area in the outer 10% of the diastolic wall thickness (subepicardial) was 13% lower in hypertensive patients than in normal subjects (P<0·001, Fig. 3). The % systolic increase in cross-sectional area increased progressively towards the endocardium in both groups. At the inner 20% of diastolic wall thickness, the systolic increase in cross-sectional area was no longer statistically different in normotensive and hypertensive subjects and at the subendocardial layer became virtually identical (51·5% and 49·2%, respectively). This 'compensation' was substantially due to the high relative wall thickness in hypertensive patients. A marked dependence of ejection-phase indexes of left ventricular chamber function on left ventricular geometry is therefore evident.

Differences Between Chamber and Wall Mechanics

The force limiting left ventricular ejection (i.e. chamber function) is myocardial afterload, which can be measured as wall stress at end-systole, according to the principles of Laplace's law[20]. Under the simplifying assumption that myocardium is formed by isotropic material, there are two major types of end-systolic wall stress which can be measured, acting as counter-forces to fibre shortening in different directions. Accordingly, circumferential fibre shortening is limited by circumferential end-systolic wall stress, whereas, longitudinal shortening is (at least theoretically) limited by longitudinal (meridional) end-systolic wall stress[21]. Although useful in clinical applications, Laplace-based estimation of myocardial afterload is a simplification which holds a number of errors[22]. Among them, one important but often unconsidered limitation of measurements of myocardial afterload based on Laplace's law is their unidirectionality, which does not take into account the phenomenon of cross-fibre shortening, that amplifies at the endocardial level the real extent of shortening of single myocardial layers. Thus, at a given inotropic state, a greater wall thickness will reduce end-systolic wall stress, and, simultaneously, will enhance effects of cross-fibre shortening at the endocardial level: as a consequence, for a given myocardial afterload and inotropic state, left ventricular chamber size shrinkage during systole will be greater as the left ventricular wall

Table 1. Equations relating left ventricular endocardial (*eS*) and midwall shortening (*mS*) with circumferential end-systolic stress (σ_c), adjusting or not for age, in children–adolescents (4–17 years) and adults ($\geq$18 years).

Children and adolescents (n=332) Equation of regression ± SEE	Adults (n=388) Equation of regression ± SEE
$eS = 82{\cdot}20 - 22{\cdot}60*\log[\sigma_c] \pm 4{\cdot}26\%$	$eS = 103{\cdot}03 - 31{\cdot}81*\log[\sigma_c] \pm 3{\cdot}53\%$
$mS = 24{\cdot}20 - 22{\cdot}08*\log[\sigma_c] \pm 2{\cdot}85\%$	$mS = 25{\cdot}99 - 3{\cdot}54*\log[\sigma_c] \pm 2{\cdot}13\%$
$eS = 90{\cdot}13 - 24{\cdot}89*\log[\sigma_c] - 0{\cdot}32[\text{years}] \pm 4{\cdot}16\%$	$eS = 99{\cdot}33 - 31{\cdot}11*\log[\sigma_c] + 0{\cdot}05[\text{years}] \pm 3{\cdot}50\%$
$mS = 30{\cdot}78 - 3{\cdot}98*\log[\sigma_c] - 0{\cdot}26[\text{years}] \pm 2{\cdot}75\%$	$mS = 27{\cdot}72 - 3{\cdot}87*\log[\sigma_c] - 0{\cdot}02[\text{years}] \pm 2{\cdot}11\%$

In the first two lines the usual stress/shortening equations are shown. In the last two lines, stress/shortening equations also include age. Age is positively and independently related to *eS* during childhood. From Ref.[28], with permission.

is thicker[23]. This biological phenomenon is at the basis of the evidence of the apparently supranormal left ventricular systolic function in hypertensive patients reported in the 1980s, leading to the suggestion that contractility could be increased in those patients[24–26]. As part of a compensatory mechanism, in many hypertensive patients left ventricular chamber contractility is indeed supranormal as compared with the mean level of wall stress measured across the left ventricular wall. This occurs because, at a given myocardial afterload, the result of the interaction among the differently aligned myocardial fibres causes the magnitude of endocardial displacement to depend negatively on the magnitude of wall stress but positively on the absolute (and especially on the relative) left ventricular wall thickness[12,14].

Measurement of circumferential left ventricular shortening in the middle of the diastolic wall thickness presents, therefore, a number of advantages from both anatomic and physiologic points of view. First, the midwall is the anatomic site where the circumferential orientation of myocardial fibres is maximal. Because the systolic reduction of the minor axis principally occurs due to the shortening of circumferentially-oriented left ventricular myocardial fibres, the most important biological change of left ventricular systole can be directly measured, without the interference of the inner myocardial layers. Secondly, circumferential shortening occurs in a myocardial plane where the counter-force directly opposing that shortening can be measured from single echocardiographic measurements, i.e. midwall circumferential end-systolic stress[8]. Although meridional wall stress has been widely used as a surrogate measure of myocardial afterload and recently has been proposed as the counter-force of longitudinal shortening[8,14], the actual wall stress opposing the reduction of left ventricular long-axis is more difficult to calculate because part of the force that shortens the left ventricular long axis during systole is supplied by papillary muscles, pulling the mitral annulus towards the left ventricular apex, which remains almost immobile[27].

Another interesting difference between shortening measured at the level of endocardium or midwall is related to the effect of age. For a given level of end-systolic stress, both endocardial and midwall shortening decreased by 0·32%/year and 0·26%/year, respectively, in children and adolescents (during body growth). When body growth is completed, during adulthood and maturity, midwall shortening continues to decrease by 0·02%/year in adults, whereas endocardial shortening increases with ageing by 0·05%/year[28] (Table 1). This difference is related to the increase in wall thickness accompanying maturity[29].

Different Clinical Impact of Measurements of Chamber or Midwall Circumferential Shortening

In the presence of altered left ventricular geometry, as in arterial hypertension, systolic shortening measured at the level of endocardium is often higher than predicted from the measured level of end-systolic stress[19,30,31]. In contrast, when measured at the midwall level, where there is the highest circumferential fibre orientation and where the phenomenon of cross-fibre shortening is less than at the endocardium, because it is limited to the effect of external myocardial layers and long-axis shortening, systolic shortening is often depressed[30,31]. About one-sixth of asymptomatic hypertensive patients exhibit systolic dysfunction at the midwall level, though their endocardial shortening was not lower than in normotensive subjects[31].

The discrepancy between chamber and wall mechanics is even more evident when left ventricular geometry is altered due to enhanced relative wall thickness (Fig. 4). In normal conditions, and in diseases in which relative wall thickness is normal or reduced, left ventricular chamber and midwall function are superimposable[32–34].

The difference between left ventricular chamber and wall mechanics has potentially important clinical implications. Left ventricular minor-axis shortening at the endocardium and at the midwall were evaluated in 294 hypertensive patients in a 10-year follow-up[35]. During follow-up, 50 patients experienced at least one adverse cardiovascular morbid event and 14 died of cardiac causes. Reduced midwall shortening, but not endocardial shortening, predicted fatal and non-fatal

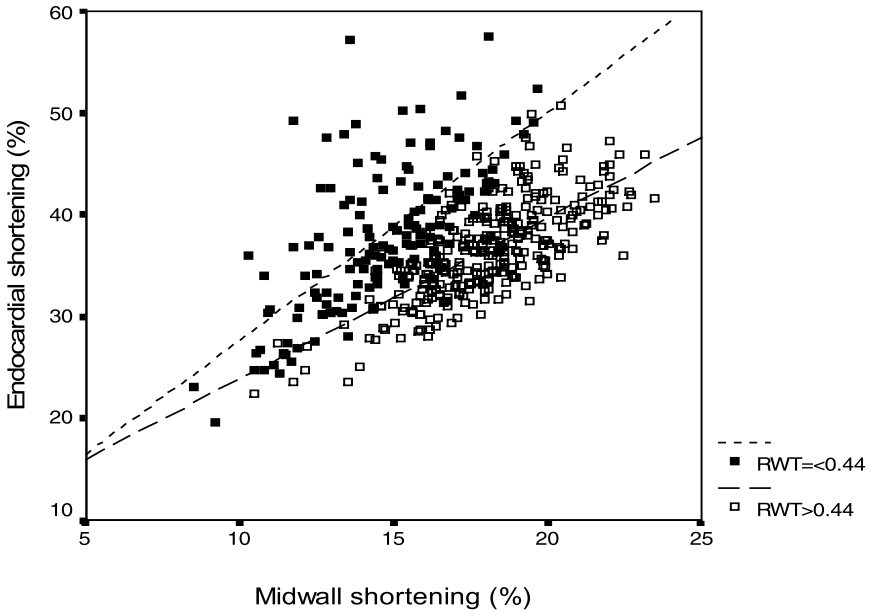

Figure 4. Relation between endocardial shortening (vertical axis) and midwall shortening (horizontal axis) in normotensive and hypertensive individuals with concentric (black symbols) or eccentric (open, dashed squares) left ventricular geometry. At every level of myocardial shortening the average endocardial shortening is markedly higher in the presence of concentric left ventricular geometry.

cardiovascular events and this adverse association was especially evident at the highest value of left ventricular mass[35].

Conclusions

Left ventricular chamber contraction is the consequence of the amplification at the endocardial level of the interaction among differently aligned myocardial fibres. This amplification is a function of wall thickness. Increased wall thickness can enhance at the endocardial level the effect of reduced myocardial fibre shortening, allowing preservation of ejection fraction despite depressed midwall shortening, through a 'contractile gradient' proceeding from epicardium to endocardium. This phenomenon has been documented in arterial hypertension and is at the basis of the better prediction of cardiovascular risk in hypertensive patients by measures of left ventricular wall mechanics than measures of left ventricular chamber function.

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