Relation of left ventricular chamber and midwall function to age in normal children, adolescents and adults

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Key words:
Cardiac function; Afterload; Contractility; Aging.

Background. **The goal of this study was to identify the effect of body growth and aging, and normal limits of the relation of left ventricular endocardial and midwall shortening to wall stress.**

Methods. **Endocardial and midwall shortening and circumferential end-systolic stress were assessed in 388 normotensive, normal-weight adults (226 men, 162 women, age 18 to 85 years) and 332 children and adolescents (180 males, 152 females, age 4 to 17 years) by two-dimensional targeted M-mode echocardiography and cuff blood pressure measurements.**

Results. **End-systolic stress decreased with age in children and adolescents ($p < 0.001$), but not during adulthood and maturity. The negative relation of endocardial shortening to end-systolic stress was stronger in adults than in children and adolescents (slope difference $p < 0.005$). The negative relation of midwall shortening to end-systolic stress was negligible in children and adolescents ($r = -0.07$, $p = 0.18$), whereas it was more evident, although weak, in adults ($r = -0.14$, $p < 0.007$). For a given level of end-systolic stress, endocardial shortening decreased by 0.32%/year in children and adolescents (multiple $r = 0.51$, $p < 0.0001$) and by 0.05%/year in adults, whereas midwall shortening decreased by 0.26%/year during body growth and by 0.02%/year in adults.**

Conclusions. **In the presence of normal blood pressure and normal weight, the relations between left ventricular wall stress and both chamber and myocardial function are weakly but significantly influenced by age. Left ventricular chamber function is markedly influenced by wall stress, while this influence is reduced for left ventricular wall mechanics.**

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The assessment of left ventricular (LV) function is important in many circumstances in which information on myocardial status may influence decisions in patient management. Quantitative echocardiography is the most convenient way to study LV function, because of both the procedure s relatively low cost and the possibility to gain information on sing le-beat intrinsic myocardial contractility, by assessing the ability of LV minor axis to shorten during systole at the level of midwall[1-3]. Measurement of LV function by midwall shortening has indeed been shown to be more physiologically accurate in representing myocardial performance than is endocardial shortening[1-3], a measure of LV chamber performance, especially in the presence of LV geometry abnormalities, such as those occurring in arterial hypertension[4]. In contrast to LV minor-axis shortening measured at the endocardium, reduced midwall shortening in relation to wall stress is able to identify a subgroup of asymptomatic hypertensive patients with clinical and hemodynamic characteristics associated with high cardiovascular risk[3,5] and a high rate of subsequent morbid events[6]. In view of the importance of measurements of LV midwall function suggested by both cross-sectional and longitudinal studies, definition of midwall shortening-end-systolic stress relations in apparently normal individuals over a wide range of age appears to be important for the correct detection of clinical abnormalities that might encompass the extremes of the range. At the present time, the only available reference values come from relatively small study populations of healthy adults[1,3-7]. According ly, the present study was undertaken 1) to de-

fine the normal relation of endocardial and midwall shortening to end-systolic stress in a reference population encompassing a broad age range including children and adolescents, and 2) to assess the relation between age and midwall performance across the entire lifespan.

Methods

Participants. Seven hundred twenty normotensive, normal-weight individuals, aged 4 to 85 years, were studied in three University Hospitals: 343 adults from New York, NY, USA (207 men, 136 women, age 18 to 85 years); 39 adults (16 men, 23 women, age 18 to 69 years) and 105 children (65 boys, 40 girls, age 6 to 11 years) from Naples, Italy; and 227 children and adolescents (115 males, 112 females, age 4 to 17 years) and 6 young adults (3 males, 3 females, 18 to 23 years) from Cincinnati, OH, USA. The 343 adults from New York were part of employed populations studied in work-site programs; the adults from Naples were part of a screening program of the staff of the Department of Clinical and Experimental Medicine at the Federico II University Hospital School of Medicine of Naples, Italy, whereas children were studied in a school, as part of an epidemiological program among elementary school children (unselected participants, 98% participation rate), previously described in detail[8]. Children, adolescents and young adults from Cincinnati were recruited from schools in the Cincinnati area. Children in Cincinnati and in Naples were included in the study after informed consent by the subjects parents or guardians and, in Naples, also after permission of school authorities, since the study was performed in a school.

All participants underwent a complete clinical examination, including measurements of blood pressure, body weight, height, and 12-lead ECG, and were classified as normal individuals. In particular, blood pressure was consistently normal, according to established clinical criteria for adults (< 140/90 mmHg), and according to the definition of hypertension in children based on age, sex and height presented by Rosner et al.[9] for American children and by the Italian Blood Pressure Tables of the Italian Society of Pediatrics for Italian children[8,10]. All participants were also normal-weight according to the 1985 NIH Consensus Conference[11] or the Himes and Dietz simplified criteria for children[8,12]. M-mode echocardiographic endocardial fractional shortening was normal (range 26 to 49%).

Procedures. Two-dimensional targeted M-mode echocardiograms were performed as previously described[3,8,13] with the subjects in a partial left decubitus position using commercially available echocardiographs. Tracings were recorded on strip-chart paper at 50 mm/s. All echocardiograms were coded and interpreted by two investigators in each center, but the measurements were standardized thereafter as previously reported in detail[13]. Measurements of end-diastolic and end-systolic interventricular septal thickness, posterior wall thickness and LV internal dimension were taken at or just below the mitral valve tips, according to the American Society of Echocardiography recommendations[14]. If optimal M-mode beam orientation could not be obtained (as happens in the presence of low parasternal windows), linear LV measurements were made from two-dimensional recordings by the American Society of Echocardiography two-dimensional measurement convention[15,16], using a two-dimensional parasternal long-axis view with optimal aortic imaging. Reliability of echocardiographic measurements taken using either M-mode or two-dimensional views has recently been reported[17,18]. Segmental wall motion abnormalities were excluded by two-dimensional echocardiographic recordings in multiple standard projections. LV mass was calculated using the American Society of Echocardiography M-mode measurements[19,20]. Relative wall thickness was calculated by dividing posterior wall thickness by the LV internal radius.

Minor-axis shortening. Endocardial fractional shortening (eFS) was calculated as:

$$eFS = \frac{D_d - D_S}{D_d} * 100$$

where *D* was LV chamber diameter, subscript *d* was end-diastole and subscript *s* was end-systole.

Systolic shortening of LV minor axis at the midwall was calculated taking into account the epicardial migration of midwall during systole[1,3]. Midwall shortening (mFS) was computed as:

$$mFS = \frac{(1/2\, D_d + H_d) - (1/2 D_S + H_S)}{(1/2 D_d + H_d)} * 100$$

where *H* was $1/2$ (posterior wall + septum). The value of H_S takes into account the epicardial shift of midwall during systole, and was calculated assuming a constant wall volume during the cardiac cycle, based on a geometric model identical to that used to calculate LV mass[3]. According ly:

$$(1/2 D_d + H_d)^3 - D_d^3 = (1/2 D_s + H_s)^3 - D_s^3$$

and therefore:

$$Hs = [(1/2 D_d + H_d)^3 - D_d^3 + D_s^3]^{1/3} - 1/2 D_s$$

End-systolic stress. Myocardial afterload was represented as circumferential end-systolic wall stress (σ_c), calculated at the mid-ventricular level using a cylindrical model, which does not require measurement of long-axis dimension[1,3,6,21]:

$$s_c = \frac{BP_s * 1/2 D_s^2 \{1 + [(1/2 D_s + P_s)^2/(1/2 D_s + 1/2 P_S)^2]\}}{(1/2 D_s + P_s)^2 - 1/2 D_s^2}$$

where BP_s is brachial systolic blood pressure measured by mercury manometers using an arm-cuff of appropriate size at the end of echocardiogram, and *P* is posterior wall thickness. Brachial cuff systolic blood pressure has previously been shown to be closely related to central arterial end-systolic pressure in 85 normotensive (58 men, 27 women) and 197 hypertensive subjects (122 men, 75 women, 142 to 195 mmHg brachial systolic blood pressure)[22]. In that analysis, the value of end-systolic stress calculated with predicted central pressure gave a nearly identical rank-order of subjects and identified the same intergroup differences as stress calculated from brachial blood pressure.

Statistical analysis. Considering the demographic differences between Italian and American age-matched participants, echocardiographic variables were adjusted for a center effect using least squares linear regression with a dichotomous independent variable representing the center in age-matched groups of subjects, as previously reported in detail[13,23].

Data are expressed as mean – 1 SD. Descriptive statistics are presented using χ^2 and exact tests performed using the Monte-Carlo method. Least squares linear regression analysis was used to describe relations between age and study variables. Relation of LV minor-axis shortening to circumferential end-systolic wall stress was studied using linear and semi-logarithmic models of regression analysis[24]. Differences between regression lines were tested by computing F-statistics of the between-slopes sum of squares.

An age stratification was used, based on a rough partition between children and adolescents (4 to 17 years), and adults (> 17 years), which takes into account the estimated period of body growth.

Multiple regression analysis was used to study the independent effects of age and wall stress on LV shortening, by using stepwise procedures and including sex among the independent variables.

The null hypothesis was rejected at two-tailed α 0.05.

Results

In the entire study population, systolic blood pressure, measured shortly after the echocardiogram, was 72 to 138 mmHg, diastolic blood pressure was 34 to 88 mmHg, and heart rate was 42 to 141 b/min. Body mass index was comprised between 12.1 and 27.8 kg/m^2.

LV chamber dimension ranged from 2.82 to 6.34 cm (2.25 to 3.61 cm/m body height). Endocardial fractional shortening ranged from 26 to 49%, midwall shortening from 13 to 28%, and circumferential end-systolic stress from 48 to 282 kdynes/cm^2.

Effect of age on left ventricular minor-axis shortening-wall stress relations. In the whole study population, endocardial shortening was strong ly influenced by wall stress (Fig. 1), whereas this influence was much less pronounced for midwall shortening (Fig. 2). For either measure of shortening, both r^2 and F-statistics increased with the semi-logarithmic model as compared to the linear one. Consistent with previous studies[3,25], the logarithmic models were therefore examined in detail.

Reduction of endocardial shortening with increasing circumferential end-systolic wall stress was more pronounced in adults than in children and adolescents (both $p < 0.0001$, Table I, slope difference $p < 0.005$).

The negative relation of midwall shortening to end-systolic stress was neg ligible in children and adoles-

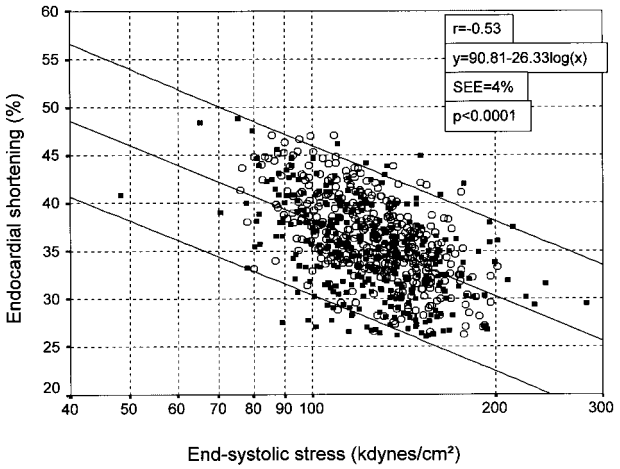

Figure 1. *Relation between endocardial fractional shortening* (vertical axis), *and circumferential end-systolic stress plotted in a logarithmic scale* (horizontal axis) *in the whole study population (n = 720, r = -0.53, SEE = 4%, p < 0.0001). The regression lines and 95% confidence limits are shown.* Closed small squares *represent children and adolescents and* open squares *are adults.*

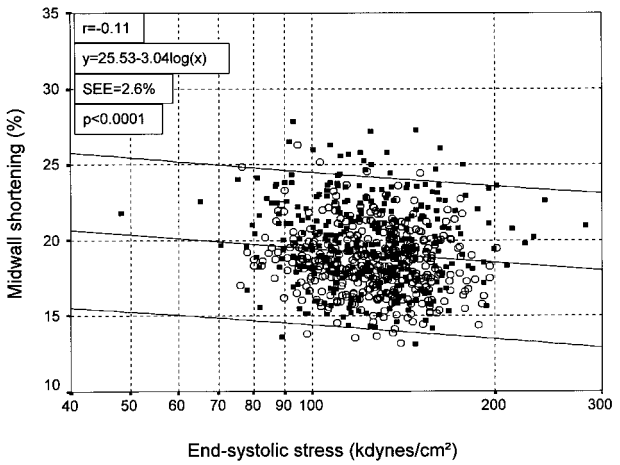

Figure 2. *Relation between midwall fractional shortening* (vertical axis) *and circumferential end-systolic stress plotted on a logarithmic scale* (horizontal axis) *in the whole study population (n = 720, r = -0.11, SEE = 2.6%, p < 0.0001). The regression lines and 95% confidence limits are shown.* Closed small squares *represent children and adolescents and* open squares *are adults.*

Table I. Stress-shortening relations in the two age strata, with or without inclusion of age into the regression model.

Children and adolescents (n=332)		Adults (n=388)	
Equation of regression – SEE	r	Equation of regression – SEE	r
eS = 82.20-22.60*log [σ_c] – 4.26%	-0.47	eS = 103.03-31.81*log [σ_c] – 3.53%	-0.60
mS = 24.20-2.08*log [σ_c] – 2.85%	-0.07	mS = 25.99-3.54*log [σ_c] – 2.13%	-0.14
eS = 90.13-24.89*log [σ_c] -0.32 [years] – 4.16%	Multiple 0.51	eS = 99.33-31.11*log [σ_c] +0.05 [years] – 3.50%	Multiple 0.62
mS = 30.78-3.98*log [σ_c] -0.26 [years] – 2.75%	Multiple 0.29	mS = 27.72-3.87*log [σ_c] -0.02 [years] – 2.11%	Multiple 0.19

cents, whereas it was more evident in adults ($p < 0.007$, Table I). While no gender difference was detected for the stress/endocardial shortening in both age strata, females showed marginally closer relations than males between wall stress and midwall shortening in both age strata (not shown).

In multiple regression models including log of end-systolic stress, age, and sex, among children and adolescents, for a given level of end-systolic stress ($\beta = -0.52$, $p < 0.0001$), endocardial shortening decreased with age ($\beta = -0.20$, $p < 0.0001$) during body growth (Table I, $p < 0.0001$), whereas sex did not enter the model. In contrast, during adulthood, for a given end-systolic stress ($\beta = -0.59$, $p < 0.0001$), endocardial shortening increased with age ($\beta = 0.14$, $p < 0.001$, Table I), but again sex was excluded from the final model.

For comparable levels of end-systolic stress ($\beta = -0.14$, $p < 0.01$), midwall shortening decreased with age ($\beta = -0.28$, $p < 0.0001$) in children and adolescents (Table I, $p < 0.0001$). Similarly, at a given end-systolic stress ($\beta = -0.15$, $p < 0.003$) midwall shortening decreased with age ($\beta = -0.14$, $p < 0.008$) also in adults (Table I, $p < 0.0001$).

Discussion

Technical limitations affect the reliability of noninvasive evaluation of myocardial afterload, substantially due to both the method of approximating central end-systolic pressure using brachial peak systolic pressure (already highlighted and discussed in previous reports[22,23]) and the use of a modeling of stress based on the assumption that the myocardium is formed by isotropic material. In spite of such limitations, the stress/shortening relations assessed by quantitative echocardiography are widely used as load independent indices of steady-state contractility in a variety of diseases in humans and have been proven to be useful both for physiological inference and for clinical insights, being able to improve our ability to stratify cardiovascular risk[1-7,26-31].

In a large data set of normal individuals over a wide range of age, results from the present study demonstrate that systolic shortening of LV minor axis measured at the endocardium (LV chamber function) and at midwall (LV myocardial function) exhibits different sensitivities to myocardial afterload[3]. The difference in correlation coefficients has previously been attributed to the smaller range of variation of midwall shortening as compared to endocardial shortening[3]. Also in the present study, over a wide range of values of end-systolic stress, the standard error of the estimate of midwall shortening in relation to wall stress was confirmed to be lower (2.57%) than the one of endocardial shortening in relation to wall stress (3.97%). However, the difference between the two relations could also reflect the close interaction between LV wall thickness and systolic reduction of chamber volume, which is not entirely mediated by wall stress, but is also due to the interaction of differently aligned myocardial fibers (cross-fiber shortening)[32]. Studies using tagging magnetic resonance techniques[32,33] and computer-resolved analysis of M-mode echocardiograms[34] indicated that shortening measured at the endocardium is a function of wall thickness[7,35] which in turn negatively influences the magnitude of wall stress, yielding an amplification of stress-shortening relation at the chamber level.

In children and adolescents, the decrement in endocardial shortening with age, as well as the decrement in shortening for any given wall stress with advancing age are similar to those reported by Colan et al.[36]. During adulthood, at the end of the growth process, LV chamber performance tends to slightly increase with age, and this trend might be due to the progressive LV concentric remodeling overbalancing the slightly progressive decline in myocardial contractility[37,38]. The relative concentric remodeling occurring late in life[38] (and also present in this study population $r = 0.37$ between age and relative wall thickness, $p < 0.0001$) may allow elderly individuals to maintain their LV chamber function by using cross-fiber LV radius shortening amplification in the thickened wall, despite a modestly reduced myocardial contractility[39]. Introduction of age in the equation is the main difference from the equations proposed in our previous study[3]. This difference is particularly relevant also in adults because the interrelations among myocardial afterload, LV endocardial and midwall shortening can be influenced by the age-dependent increase in relative wall thickness[38,39]. Another important distinction from the previous equation was in the different characteristics of normal subjects participating in the present study, who encompassed a wider age-span and were conserv-

atively normal-weight (i.e. 1985 NIH Consensus). These characteristics make this normal population a real normal reference .

The use of stress/shortening relations is quite common in studies on arterial hypertension[1-8]. Since the information on intrinsic wall mechanics is associated with prognosis[6], the relation between midwall shortening and circumferential wall stress might be especially important to identify patients with poor LV contractility, who might have good LV chamber function, due to coexistent concentric LV geometry[39], in every condition in which some degree of afterload-mismatch occurs, including valve diseases, as suggested by former studies[40] and new preliminary findings[41].

In conclusion, the relations between LV wall stress and both chamber and myocardial function are weakly but significantly influenced by age. Normal regression equations have been generated including both end-systolic stress and age, which should be considered as an independent determinant of chamber and myocardial function especially during infancy and adolescence.

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