Wall stress misrepresents afterload in children and young adults with abnormal left ventricular geometry

THOMAS L. GENTLES1 AND STEVEN D. COLAN2,3

1Department of Paediatric Cardiology, Green Lane Hospital, Auckland 1003, New Zealand; and 2Department of Cardiology, Children’s Hospital, and 3Department of Pediatrics, Harvard Medical School, Boston, Massachusetts 02115

Received 18 July 2001; accepted in final form 6 November 2001

Gentles, Thomas L. and Steven D. Colan Wall stress misrepresents afterload in children and young adults with abnormal left ventricular geometry. J Appl Physiol 92: 1053–1057, 2002; 10.1152/japplphysiol.00750.2001.—Wall stress, although commonly used as an index of afterload, fails to take into account forces generated within the wall of the left ventricle (LV) that oppose systolic fiber shortening. Wall stress may, therefore, misrepresent fiber stress, the force resisting fiber shortening, particularly in the presence of an abnormal LV thickness-to-dimension ratio (h/D). M-mode LV echocardiograms were obtained from 207 patients with a wide range of values for LV mass and/or h/D. Diagnoses were valvar aortic stenosis, coarctation repair, anthracycline treated, and severe aortic and/or mitral regurgitation. End-systolic wall stress (WSes) and fiber stress (FSes) were expressed as age-corrected Z scores relative to a normal population. The difference between WSes and FSes was extreme when h/D was elevated or reduced [WSes Z score – FSes Z score = 0.14 × (h/D)−1.47 – 2.13; r = 0.78, P < 0.001], with WSes underestimating FSes when h/D was increased and overestimating FSes when h/D was decreased. Analyses of myocardial mechanics based on wall stress have limited validity in patients with abnormal ventricular geometry. hypertrophy; contractility; echocardiography; left ventricle

LEFT VENTRICULAR (LV) afterload has generally been assessed by using wall stress calculated in the meridional (WSM) or circumferential direction, neglecting the effect of radial forces. Fiber stress, as discussed by Arts et al. (3), Mirsky (19), and Regen (23, 24), takes into consideration the radially directed forces or forces generated within the wall that oppose fiber shortening. Fiber stress is, therefore, a more accurate measure of the force generated by, and acting on, the contracting myofiber. The degree to which wall stress misrepresents the forces acting on the myofiber is related to the wall thickness-to-chamber dimension (h/D) or mass-to-volume ratio (mass/volume). Hence, LV afterload is most likely understated by conventional wall stress measurements in thick-walled ventricles and overstated in dilated, thin-walled ventricles. The magnitude of this misrepresentation is unknown, but it may have important implications in the assessment of afterload in patients with congenital or acquired heart disease known to have abnormal LV mass or abnormal mass/volume. When this is the case, it is likely that analyses of myocardial mechanics that rely on wall stress as an index of afterload are misleading. Failure of wall stress to take into account radial forces opposing fiber shortening might also contribute to the observed but incompletely explained relationship between afterload and age previously reported in normal children (8), particularly in view of the colinearity of age, wall thickness, chamber dimension, and blood pressure.

To further investigate these hypotheses, we evaluated end-systolic wall stress (WSes) and fiber stress (FSes) in normal subjects and in four groups of patients with varying h/D and LV mass.

METHODS

Normal population. Analysis of myocardial mechanics was performed in 305 normal subjects, varying in age from 10 days to 35 yr. This population has been described previously (8, 14), including the criteria for the definition of normal and a detailed description of the population. Each of the normal controls was free of evidence of heart disease, was taking no cardioactive medications, and had no history of hypertension or other systemic disorder. Data derived in these normal subjects were used to determine the normal range for each of the echocardiographic parameters and to describe age- and body surface area-related trends. Patient population. The 52 patients with congenital aortic stenosis were aged 6–39 yr (median 12 yr) and had a Doppler-derived maximum instantaneous gradient ranging from 50 to 140 mmHg (median 76 mmHg). The 57 patients in the coarctation group were aged 1.2–32 yr (median 12 yr) and were examined 1.2–22 yr after their coarctation repair. The upper-to-lower extremity systolic blood pressure gradient ranged from −19 to 60 mmHg and was >15 mmHg in 24 patients (43%). The 51 patients in the anthracycline group were aged 3–21 yr (median 8 yr) and had received anthracycline for treatment of childhood acute lymphocytic leukemia. The 51 with severe valvar regurgitation were aged 9–24 yr (median 15 yr). Twenty-six (51%) had lesions of the aortic valve, 17 (33%) the mitral valve, and 8 (16%) both. The

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
etiology was rheumatic in 44 (86%), aortic valve prolapse in 4 (8%), and mitral valve prolapse in 3 (6%).

Data collection. The method of echocardiographic data collection has been described in detail elsewhere (6–8). Patients <3 yr of age were sedated with 50–100 mg/kg chloral hydrate as needed. Commercially available echocardiographic equipment (Hewlett-Packard 77020, Sonos 1000 or Sonos 1500 Cardiac Imager, or Acuson 128) and transducers appropriate for body size and habitus were used for imaging. Complete two-dimensional and Doppler examinations were performed to identify additional abnormalities and to assess LV regional wall motion. High-speed (100 mm/s), hard-copy, two-dimensional echocardiographic directed M-mode recordings of the LV short axis were obtained simultaneously with an electrocardiogram, phonocardiogram, and indirect carotid artery pulse tracing (or auxiliary artery pulse tracing in patients <4 yr of age). Systolic and diastolic blood pressures were obtained as the average of three automated cuff recordings using a Dinamap 845 Vital Signs monitor (Criticon).

Data analysis. The indirect arterial pulse trace, the left and right ventricular endocardial borders of the septum, and the endocardial and epicardial borders of the LV posterior wall were hand digitized from the M-mode echocardiogram with the use of a microcomputer-based digitizing system and custom software (8). The pulse transmission delay was corrected by electronically aligning the dicrotic notch of the pulse tracing with the use of a microcomputer-based digitizing system and transducers appropriate for body size and habitus were used for imaging. Complete two-dimensional and Doppler examinations were performed to identify additional abnormalities and to assess LV regional wall motion. High-speed (100 mm/s), hard-copy, two-dimensional echocardiographic directed M-mode recordings of the LV short axis were obtained simultaneously with an electrocardiogram, phonocardiogram, and indirect carotid artery pulse tracing (or auxiliary artery pulse tracing in patients <4 yr of age). Systolic and diastolic blood pressures were obtained as the average of three automated cuff recordings using a Dinamap 845 Vital Signs monitor (Criticon).

Data analysis. The indirect arterial pulse trace, the left and right ventricular endocardial borders of the septum, and the endocardial and epicardial borders of the LV posterior wall were hand digitized from the M-mode echocardiogram with the use of a microcomputer-based digitizing system and custom software (8). The pulse transmission delay was corrected by electronically aligning the dicrotic notch of the pulse tracing with the first high-frequency component of aortic valve closure on the phonocardiogram. Continuous LV internal diameter and posterior wall thickness averaged over three to six cycles were obtained from these data. Pressure during ejection was calculated by interpolation of the indirect pulse trace using the formula of Grossman et al. (15)

\[
WS_{es} = \frac{(1.35)(P)(D)}{(h)(1 + h/D)(4)}
\]

where \( P \) is pressure (in mmHg), \( D \) is the LV internal chamber dimension (in cm), and \( h \) is the posterior wall thickness (in cm). Meridional fiber stress (FS \( _{M} \)) was calculated according to the formula of Regen (24)

\[
FS_{M} = (1.35)(P)(b_{m})/(2h)
\]

where \( b_{m} \) is the midwall minor semiaxis expressed as

\[
h = \ln(0.5D + h) - \ln(0.5D)
\]

End systole was defined as the time of aortic valve closure, and end diastole as the time of the maximal LV dimension. LV mass was calculated using the formula of Devereux and Reichek (12)

\[
LV\ mass\ (g) = 0.83[(D_{ad} + h_{ad} + S_{ad})^{3} - (D_{ad})^{3}] + 0.6
\]

where \( D_{ad} \) is end-diastolic \( D, h_{ad} \) is end-diastolic \( h, \) and \( S_{ad} \) is the end-diastolic septal thickness. If \( S_{ad} \) could not be accurately measured, LV mass was calculated by assuming septal and posterior wall thickness to be equal. \( h/D \) was calculated as the LV end-diastolic posterior wall thickness divided by the LV end-diastolic dimension.

Calculation of Z scores relative to normal population. LV dimensions, wall thickness, and mass are known to vary with body surface area. As previously reported, WS_{es} varies in an age-related fashion (8). To permit comparison of patients of different ages and body size, each of these variables was expressed as a Z score relative to its nonlinear distribution with respect to age or body surface area in the normal population. The Z score, or normal deviate, represents the number of SDs from the normal population mean value. Thus Z scores of –1, 0, and +1 indicate values 1 SD below normal population mean, the population mean, and 1 SD above the population mean, respectively.

Statistical analysis. t-Tests were used to compare dichotomous variables. Differences between WS_{es} and FS_{es} Z scores were further investigated by two-way repeated measures analysis of variance, comparing each patient group with the normal population and treating the afterload index (WS_{es} and FS_{es}) as the repeated variable. Linear and nonlinear regression were used to examine the interrelations between continuous variables. Results are presented as means ± 1 SD, unless otherwise specified. A P value <0.05 was considered statistically significant.

RESULTS

Normal population. FS_{es} was found to increase non-linearly with age (Fig. 1) in a fashion similar to the relationship of WS_{es} to age that our laboratory has previously reported (8). Although there was a close correlation between WS_{es} and FS_{es} (r = 0.96, P < 0.001, Fig. 2A), the residuals of this regression correlated inversely with h/D (r = 0.51, P < 0.001, Fig. 2B), indicating that LV geometry contributed to the disparity between these two indexes of afterload.

Patient population. The four patient groups had widely varying values of LV mass and h/D (Table 1). Those with congenital aortic stenosis demonstrated marked concentric hypertrophy, whereas patients who had undergone coarctation repair demonstrated an increase in posterior wall thickness with increased LV mass. Although h/D in the coarctation group was normal overall, the Z score was >1 in 15 (26%) and >2 in 9 patients (16%). In the anthracycline-treated group, LV geometry was characterized by decreased wall thickness, decreased h/D, and decreased mass. Abnormalities in those with valvar regurgitation were more extreme; despite a marked decrease in h/D, LV mass

![Fig. 1. Normal population. End-systolic wall stress (WS_{es}; A) and end-systolic fiber stress (FS_{es}; B) vs. age. SEE, standard error of estimate. Lines are population means ± 2 SDs.](http://www.jap.org/1054/1054-00110.png)
was increased to a greater degree than in those with congenital aortic stenosis.

WSes and FSes Z scores were significantly different compared with normal in all groups, except for the anthracycline group in which both WSes and FSes were similar to that of the normal population (Fig. 3). In the group with congenital aortic stenosis, both indexes of afterload were reduced compared with normal, but WSes was reduced significantly more so than FSes (−4.0 ± 1.3 vs. −2.8 ± 1.2, P < 0.001). Within the coarctation group, WSes was reduced (−0.7 ± 2.2, P = 0.02) whereas FSes was no different from that in the normal population (−0.1 ± 1.8, P = not significant). Furthermore, the difference between WSes and FSes Z scores was significantly greater in those with a h/D Z score >1 compared with those with a Z score <1 [difference (WSes − FSes): −1.2 ± 0.5 vs. −0.4 ± 0.6; P < 0.001]. In contrast, both WSes and FSes were elevated in the valvar regurgitation group, but WSes was elevated significantly more so than FSes (3.1 ± 3.5 vs. 2.1 ± 2.4, P < 0.001). Two-way repeated measures analysis of variance demonstrated a significant interaction term (P < 0.001) for all groups, except for the anthracycline group. This indicates that the difference between WSes and FSes Z scores is significantly greater in each of the three patient groups (coarctation repair, congenital aortic stenosis, and aortic and/or mitral regurgitation) compared with the normal subjects.

When all patient groups were combined, there was a significant nonlinear relationship between the difference of the two indexes of afterload and h/D (Fig. 4). As h/D deviated from normal, the absolute difference between WSes and FSes Z scores increased, with WSes exceeding FSes when h/D was reduced and FSes exceeding WSes when h/D was elevated.

These findings indicate that the relationship between WSes and FSes is dependent on both the h/D and the absolute value of WSes. When WSes is normal (as in the normal population and the anthracycline group), there is little difference between this index of afterload and FSes, regardless of the h/D (Figs. 2 and 3). However, when WSes is elevated and h/D is reduced, WSes overestimates FSes, and when WSes is reduced and h/D increased, WSes underestimates FSes.

Table 1. Z scores for measured and derived variables

<table>
<thead>
<tr>
<th>Aortic Stenosis Mean ± SD</th>
<th>P value</th>
<th>Coarctation Repair Mean ± SD</th>
<th>P value</th>
<th>Anthracycline Treated Mean ± SD</th>
<th>P value</th>
<th>Valvar Regurgitation Mean ± SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dtd</td>
<td>−0.9 ± 1.7</td>
<td>&lt;0.001</td>
<td>0.5 ± 1.3</td>
<td>0.003</td>
<td>−0.1 ± 1.1</td>
<td>NS</td>
<td>5.6 ± 2.5</td>
</tr>
<tr>
<td>htd</td>
<td>3.3 ± 2.6</td>
<td>&lt;0.001</td>
<td>0.6 ± 1.8</td>
<td>0.01</td>
<td>−0.6 ± 0.9</td>
<td>&lt;0.001</td>
<td>0.6 ± 1.7</td>
</tr>
<tr>
<td>h/D</td>
<td>3.2 ± 2.9</td>
<td>&lt;0.001</td>
<td>0.2 ± 1.6</td>
<td>NS</td>
<td>−0.6 ± 0.9</td>
<td>&lt;0.001</td>
<td>−1.6 ± 1.1</td>
</tr>
<tr>
<td>LV mass</td>
<td>2.0 ± 1.8</td>
<td>&lt;0.001</td>
<td>1.0 ± 1.4</td>
<td>&lt;0.001</td>
<td>−0.3 ± 0.9</td>
<td>0.03</td>
<td>4.8 ± 3.0</td>
</tr>
</tbody>
</table>

Dtd, left-ventricular (LV) end-diastolic internal chamber dimension; htd, LV end-diastolic wall thickness; h/D, end-diastolic posterior wall thickness-to-chamber dimension ratio. The listed P values are derived from t-test comparing the Z scores for each variable to the normal population. Mean ± SD, mean Z score ± 1 SD. NS, not significant (P > 0.05).
and outer semiaxes (24). Mirsky and colleagues (1, 20) 

dia
tic wall thickness-to-chamber dimension ratio. These derivations are similar 

by necessity accompanies 

by intramural pressure. These derivations are similar 

in concept to the 

im
t ossure is included as a negative component in the 

of fiber stress derived by Arts 

–

28). This report indicates that 

es of persistently reduced afterload implies an excessive 

hypertrophic response. Although we also found WSes to 

be persistently below normal late after coarctation repair (17, 21). The magnitude of this reduction in afterload is more readily explained in the context of aortic stenosis in which there is a marked discrepancy between peak pressure and end-systolic pressure; hypertrophy is driven by peak fiber stress so that end-systolic stress is low (5). Nevertheless, WSes significantly overestimated the magnitude of this reduction in afterload.

In contrast, WSes overestimated afterload in patients with severe valvar regurgitation who had a reduced 

h/D. Artificial elevation of WSes is of particular importance when evaluation of contractility is based on stress-adjusted indexes, such as the stress-velocity and stress-shortening relationships. Under these circumstances, impaired contractile function may be incorrectly classified as normal. This is of concern in a patient group in which contractile function is an important determinant of outcome (13, 29, 30).

Finally, when afterload is normal, wall stress and fiber stress are similar, as was seen in the group of patients treated with anthracycline. In addition, FSes manifests the same pattern of age modulation in the normal population that has been previously defined for WSes (8).

Limitations. The present study uses one-dimen-

sional measurement of LV wall thickness and chamber 

dimension and assumes homogenous regional midwall 

fiber stress. The relationship between circumferential 

wall stress and fiber stress may be different from that 

between the respective meridional components, particu-

larly when the long axis-to-short axis ratio is abnor-

Fig. 4. Difference between WSes and FSes Z scores vs. the end-

diastolic wall thickness-to-chamber dimension ratio.

**DISCUSSION**

Recent reports have highlighted the superiority of 

midwall fiber shortening as a descriptor of myocardial 

performance in ventricles with elevated mass/volume, 

where endocardial indexes of shortening may be elev-

ated (10, 11, 14, 22, 26–28). This report indicates that 

similar sources of bias are problematic when afterload 

is assessed. Wall stress, the total force in a given 

direction per unit area of myocardium normal to that 

direction, is the most commonly used index of afterload 

applied to the analysis of ventricular mechanics. Nev-

ertheless, as has been pointed out by numerous au-

thors, wall stress does not fully account for forces 

acting at the fiber level, because pressure in the wall 

transmitted from the cavity or exerted by more exter-

nal fibers is included as a negative component in the 

calculation. Neither does it express the recoil response to stretch (3, 4, 9, 23, 24). Because of this, wall stress misrepresents afterload at the average or midwall fiber in absolute terms, and the magnitude of misrepresentation is amplified in ventricles with abnormal mass/volume characteristics. Fiber stress, which is the fiber-

pulling force per unit area, accounts for the effects of ambient pressure and is, therefore, a more accurate measure of the force generated by the individual myo-

fibrils.

A number of formulas have been used to calculate 

fiber stress. The method used in the present report 

derives average or midwall fiber stress; the minor axis 

(b_m) is defined as the logarithmic means of the cavity 

and outer semiaxes (24). Mirsky and colleagues (1, 20) 

have utilized a similar measure of fiber stress, which 

they referred to as incremental stress or stress differ-

ence, obtained by subtracting radial stress from cir-

cumferential wall stress or WSM. Both of these meth-

ods illustrate the dependence of fiber stress on intramural pressure, wherein the fiber thickening that 

by necessity accompanies fiber shortening is opposed by intramural pressure. These derivations are similar 

in concept to the fiber stress formulas derived by Arts 

et al. (2, 3) and are based on a cylindrical model with 

varying nonradial fiber orientations similar to those of the free wall and septum of the LV. Subsequent mod-

ification by Regen and colleague (24, 25) to account for 

midwall volume results in a formula similar to that 

used in the present analysis.

In accordance with theory, we found significant dif-

ferences between FSes and WSes. These differences 

were related to h/D and support the theoretical predic-

tion that the magnitude of underestimation of after-

load by wall stress is greater when wall thickness is 

disproportionate to chamber size (24). The magnitude of the difference between WSes and FSes represents a clinically important source of error in analyses of the 

mechanical behavior of ventricles with abnormal mass/

volume characteristics. For example, previous investig-

ators have reported WSes to be significantly below 

normal in patients late after coarctation repair (17, 21). 

This finding is difficult to explain in that afterload is a 

major determinant of hypertrophy, acting as a feed-

back variable in a servo-controlled mechanism that can 

be described as “stress normalization” (18). The finding of persistently reduced afterload implies an excessive 

hypertrophic response. Although we also found WSes to 

be persistently below normal late after coarctation repair, myocardial afterload was normal when as-

sessed as FSes, a measure of stress that fully accounts 

for the fiber shortening force per unit area. These 

findings suggest that previous reports of low afterload 

may well reflect the failure of WSes to accurately reflect 

intrinsic pulling forces, particularly in patients with 

concentric hypertrophy. Both WSes and FSes were re-

duced in the aortic stenosis group. Reduced afterload is 

more readily explained in the context of aortic stenosis 

in which there is a marked discrepancy between peak 

pressure and end-systolic pressure; hypertrophy is 

driven by peak fiber stress so that end-systolic stress is 

low (5). Nevertheless, WSes significantly overestimated the magnitude of this reduction in afterload.

In contrast, WSes overestimated afterload in patients 

with severe valvar regurgitation who had a reduced 

h/D. Artificial elevation of WSes is of particular impor-

tance when evaluation of contractility is based on 

stress-adjusted indexes, such as the stress-velocity and 

stress-shortening relationships. Under these circum-

stances, impaired contractile function may be incor-

rectly classified as normal. This is of concern in a 

patient group in which contractile function is an 

important determinant of outcome (13, 29, 30).

Finally, when afterload is normal, wall stress and 

fiber stress are similar, as was seen in the group of 

patients treated with anthracycline. In addition, FSes 

manifests the same pattern of age modulation in the 

normal population that has been previously defined for 

WSes (8).

**J Appl Physiol • VOL 92 • MARCH 2002 • www.jap.org**
mal. Furthermore, there may be significant regional heterogeneity in fiber stress within the ventricle, as has been demonstrated with three-dimensional models using magnetic resonance imaging (16).

Conclusions. Wall stress significantly misrepresents fiber stress in ventricles with abnormal mass/volume characteristics. This misrepresentation is particularly important when wall stress forms the basis of an evaluation of cardiac contractility, such as stress-shortening and stress-velocity relationships.

This work was supported in part by the National Heart Foundation of New Zealand [Project Grant 792 and Senior Fellowship Grant (to T. L. Gentles)].

REFERENCES


