Transverse Stiffness: A Method for Estimation of Myocardial Wall Stress

Henry R. Halperin, Paul H. Chew, Myron L. Weisfeldt, Kiichi Sagawa, Jay D. Humphrey, and Frank C.P. Yin

Determination of regional ventricular wall stress would allow quantification of both regional contractile state and its interplay with global function. Current methods for quantifying regional stress include mathematical modelling and measurements with strain gauges. Both methods are difficult to validate. We hypothesized that transverse stiffness (i.e., the ratio of indentation stress to strain as the ventricular wall is indented in the direction perpendicular to the wall) would be proportional to the stresses in the plane of the wall and could be used to estimate the latter. To test this hypothesis, 6 arterially perfused canine ventricular septa were mounted in an apparatus that could exert biaxial load in the plane of the wall. A servo system maintained the central third of the septa isometric during active contractions while the septa were paced at 30–60 pulses/min. In the center of the isometric region, a probe of 7 mm diameter indented the septa while the transverse indentation stress and strain were measured. For values of peak systolic in-plane stress from 0.56 to 2.6 g/mm², the transverse stiffness varied from 1.2 to 11.7 g/mm² and was linearly related to the in-plane wall stress in each septum (p<0.001, ANOVA). After cardioplegia, the transverse stiffness also correlated with passively applied wall stress for each dog (p<0.001). The slopes of the individual relations between transverse stiffness and wall stress from active contractions were similar to those from passively applied stress (mean±SEM; 1.82±0.36 versus 1.45±0.31, NS). The intercepts with the transverse stiffness axis from active contractions, however, were greater than those from passively applied stress (2.23±0.57 versus -0.16±0.12 g/mm², p<0.015). Moreover, at similar wall stresses, the transverse stiffness for active contractions was greater than that for passively applied stress (3.1±0.7 versus 1.1±0.2 g/mm², p<0.005). Thus, regional transverse stiffness appears to allow quantitative estimation of regional in-plane stresses and can distinguish between actively generated and passively applied stress. This approach may allow one to accurately quantify the regional contractile state and to determine whether regional dysfunction is due to abnormal muscle that is not generating stress or to muscle capable of generating stress but which is abnormally loaded. (Circulation Research 1987;61:695–703)

Multiple factors can influence regional function in diseased hearts, including regional variations in loading, contractility, vascular supply, external restraints, nervous supply, wall thickness, and wall curvature.1-4 With currently available methods, it is difficult to separate these factors.3,9-10 It is especially difficult to determine whether regional dysfunction is due to abnormal muscle that cannot generate stress or to normal muscle that is capable of generating stress but is abnormally loaded. To distinguish regional loading differences from regional contractile changes, one must be able to quantify the regional muscle contractile state, which includes measurements of wall stress and strain.

Regional wall strain has been measured reasonably accurately in vivo by optical techniques,11-12 by ultrasonic techniques,8,13,14 and by multiple markers visualized with radiographic techniques.13-19 Regional wall stress, however, is much more difficult to quantify accurately. Numerous investigators have attempted to directly measure ventricular wall stress using various strain gauge devices.20,21 These devices give uncertain results because of the unknown degree of coupling between the transducer and ventricular wall.21

Wall stresses, calculated using various thin-walled and thick-walled analytical models,22-25 obviously are not applicable to regional stress estimates. Stresses in nonaxisymmetric geometries can be estimated with finite element methods,26 but these stresses can differ markedly from those predicted by the analytical models.2 Regardless, since the various estimates of ventricular wall stress cannot be validated, current techniques do not allow reliable quantification of regional wall stress.2,22,24

Based on the observations that both the active and passive stiffness of uniaxially loaded papillary muscle and trabeculae carneae are directly related to active and passive stress,23,26 we assumed that biaxially loaded tissue should have similar behavior. Furthermore, we hypothesized that the stiffness transverse to the plane of the tissue, determined by an indentation test, should also be related to both the in-plane actively developed and passively applied stresses. Isolated, perfused ventricular septa were used to test this hypothesis by directly measuring simultaneous in-plane stress and strain as well as transverse stiffness.
Materials and Methods

Preparation

Six mongrel dogs weighing 18–23 kg were anesthetized with sodium pentobarbital (35 mg/kg i.v.). After systemic heparinization (3,000 U i.v.), the heart of each dog was arrested by cross clamping the ascending aorta and injecting iced, hyperkalemic Krebs solution (in g/l: NaCl 6.662, KH$_2$PO$_4$ 0.054, MgSO$_4$·7H$_2$O 0.246, NaHCO$_3$ 2.352, CaCl$_2$·2H$_2$O 0.220, dextrose 1.0, KCl 1.581) directly into the left ventricle via a large-bore needle placed through the ventricular free wall, thereby filling the coronary arteries. The fibrillating heart was excised and rinsed with iced, hyperkalemic Krebs solution. The heart was then placed in a dissecting dish, where the right and left ventricular free walls were removed (Figure 1), and the septal artery was cannulated with a double lumen catheter. One lumen was used for perfusion, and the other lumen was used for measuring the perfusion pressure. The time from excision to successful cannulation was usually 1–2 minutes. The septum was then mounted in the triaxial tissue testing apparatus while iced, hyperkalemic Krebs solution continued to perfuse it.

After each specimen was mounted, septal artery flow was set by a roller pump (model WZ1R057, Cole-Parmer Instrument Co., Chicago) to a value between 40 and 60 ml/min that produced a perfusion pressure in the range of 100–150 mm Hg. Flow was then maintained constant. Perfusate dripped from the cut surfaces of the septum into a bath. From the bath, the perfusate was channeled through a filter, through a chamber where it was bubbled with oxygen, and then back into the septal artery cannula.

Triaxial Tissue Testing Apparatus

The triaxial tissue testing apparatus consists of two parts and is shown schematically in Figure 2. The first part is a biaxial servo-controlled system that allows independent control of force or length in two orthogonal directions in the plane of the septa. The septa are mounted in the triaxial tissue testing apparatus while iced, hyperkalemic Krebs solution continued to perfuse it.
attached in the manner of a trampoline to two sets of carriages by loops of 3-0 silk thread. An adjusting screw that is underneath the central portion of the septum is used to zero the angle between the septa and the plane of the threads. In-plane force is measured by transducers coupled to the carriages, and in-plane length is measured between pairs of centrally placed carbon markers by two video analyzers. The second part of the apparatus is the transverse indenter. The indenter consists of a stepper-motor (model 18566, Oriel Corp., Stratford, Conn.) controlled arm that was mounted so as to bisect the angle between two of the thread arrays, allowing visualization of all four carbon markers by the TV cameras. The position of the arm along the z axis is determined by counting the number of pulses to the stepper motor since each pulse generates a step of 0.002 mm. A round probe (7 mm diameter) was attached to the arm so that for each step of the stepper motor, the probe moved 0.002 mm along the z axis. The probe indented the septum, and the resultant force was measured by the transverse (z axis) force transducer.

Data output from the system included force and dimension in each of the 3 axes. In the plane of the septum (x and y directions), the forces were those imposed at the edges, and the dimensions were the distances between the markers. Transverse to the plane of the septum, the force was that of indentation. Selected analog signals were digitized and stored in a microcomputer-based data acquisition system. The distance (thickness) between the adjusting screw under the septum and the probe tip was determined before the septum was mounted from a measurement with a ruler and afterwards from the total number of stepper-motor pulses used to move the probe toward (negative) and away from (positive) the septum: thickness (mm) = initial thickness + (0.002 \times \text{total negative pulses}) - (0.002 \times \text{total positive pulses}).

Calculations

During indentation of a specimen by the probe, the indentation stress was calculated by dividing the force in the z direction by the cross-sectional area of the indenting probe (38.5 mm²). The indentation strain was calculated by taking the difference between the nonindented and indented thicknesses of the septum and dividing by the nonindented thickness. The transverse stiffness was defined as the slope of the relation between the peak indentation stress (i.e., the stress at the peak of an active contraction or at the peak of a passively applied waveform) and the strain for the range of indentation strains imposed (Figure 3).

Stresses in the plane of the septa were calculated by dividing the forces in the x and y directions by the appropriate cross-sectional areas. To quantify the in-plane stress state in terms of a single quantity, an in-plane stress index was defined as the square root of the sum of the squares of the magnitudes of the two in-plane stresses.

The stretch ratios in the plane of the septa were calculated by dividing the stressed lengths between the carbon markers in the x and y directions by the appropriate unstressed lengths. To quantify the in-plane strain state in terms of a single quantity, an in-plane strain index was defined as the square root of one half of the sum of the squares of the two stretch ratios.

Initial Studies

These studies (n = 3) were used to determine what kind of relation existed between the transverse stiffness and the in-plane stress index. They showed that there was a linear relation between the transverse stiffness and the in-plane stress index and that the linear relation was relatively insensitive to different ratios of the magnitudes of the individual in-plane stresses (Figure 4). The linearity of the relation between the transverse stiffness and the in-plane stress index implies that only a small number of transverse stiffness determinations are necessary to define the relation.

Protocol

To test the relation between transverse stiffness and the in-plane stress index, as well as study this relation under cardioplegia and during active contractions, a two part protocol was used. First, during cardioplegia, the specimens were passively stretched by the in-plane actuators while they were transversely indented. Second, the specimens were resuscitated by washing out the cardioplegic agent and perfusing with oxygenated fluorocarbon while they were stretched in increments. At each increment in stretch, the center of each specimen was held isometric while indentation was performed.

During cardioplegia, the in-plane linear actuators were driven by a triangular waveform, thereby stretch-
ing the septa at a cycle rate of 30-60 pulses/min. Each septum was then simultaneously indented by the probe at incremental depths of 0.05-0.1 mm. Each increment was maintained for 3-6 seconds, and 7-14 increments were used. The resultant indentation stress at the peak of each cycle was measured. The in-plane stretch was then changed in 3 or 4 steps, and the indentation protocol was repeated at each step. These steps resulted in peak passive in-plane stresses ranging from 0.1 to 1.8 g/mm².

Perfusion was then changed to oxygenated fluorocarbon (Oxypherol E.T., Alpha Therapeutics Corp., City of Industry, Calif.) with 3% starch suspended in a modified Krebs-bicarbonate buffered solution ([wt/vol] Perfluorotributylamine (FC-43) 20, Pluronic (F-68) 2.56, NaCl 0.60, KCl 0.034, MgCl₂ 0.020, CaCl₂ 0.028, NaHCO₃ 0.21, glucose 0.18, hydroxyethyl starch 3.0). The temperature of the perfusate was 25°C. After 5-10 minutes, the specimen was stimulated electrically (model S88D stimulator, Grass Instruments Co., Quincy, Mass.) with suprathreshold voltage at a rate of 30-60 pulses/min. Baseline forces in both in-plane axes were adjusted to about 1g. The in-plane lengths in the center of the septum were held isometric by the servo system, and force was measured in both directions in the plane of the septum. The specimen was then indented in a similar fashion as described above. Both in-plane lengths were changed in 3 or 4 steps, thereby changing the peak developed in-plane stress, and the indentation protocol was repeated at each step. In all 6 specimens, the peak in-plane stresses (either actively developed or passively applied), as well as transverse stress and strain, were recorded. To study the relation between the transverse stiffness and the in-plane strain, the in-plane strain was also recorded in 4 of the specimens.

At the end of the study, each specimen was weighed after blotting and removal of the threads and markers (wet weight). The specimen was then desiccated and reweighed (dry weight). The percent water content was calculated by subtracting the dry weight from the wet weight, dividing by the wet weight, and multiplying by 100. The percent water content was determined in a similar fashion for the left ventricular free wall.

Statistical Analysis

Relations between paired data were tested with regression analysis or the paired t test. The correlation between transverse stiffness and the in-plane stress index was tested by analysis of variance. Differences between the transverse stiffness—inh-plane stress index relations for active contractions and those for passively applied stress were tested by analysis of variance with covariance. Differences between the transverse stiffness—in-plane strain index relations for active contractions and those for passively applied stress were also tested by analysis of variance with covariance. Differences between the transverse stiffness at comparable wall stresses for active contractions and passive stretching were tested by nonparametric analysis (Spearman rank correlation). Regression of either the slopes or intercepts of the transverse stiffness—in-plane stress relations on the slopes and intercepts of the transverse stiffness—in-plane strain relations was performed with multiple linear regression analysis. A probability less than 0.05 was considered statistically significant. Data are expressed as mean ± SEM.

Results

Viability of the Isolated, Perfused Interventricular Septa

Viability of the septa was shown by the following: the septa maintained their Starling effect as evidenced by the increase in developed stress with an increase in stretch (Figure 5), and the septa generated wall stresses that are comparable to those expected in an intact ventricle.

Transverse Stiffness of Ventricular Septa

Results from a contracting septum are shown in Figure 6. This tracing shows the stresses in the three orthogonal directions, as well as the indentation strain, during an indentation protocol at one level of in-plane stretch. The peak indentation stress increases as the
FIGURE 5. Demonstration of the Starling mechanism for the contracting ventricular septum. Servo system applies a baseline stress that is increased and decreased linearly. Developed stress, which is the difference between maximum and minimum stress for each beat, increases as septum is stretched.

septum is indented. The results are quite stable as evidenced by the stresses in the plane of the septum that remain constant during the transverse indentation.

In Figure 7, the peak indentation stress is plotted against the indentation strain for 1 indentation protocol during active contractions. The indentation stress is linearly related to the indentation strain over this small range of indentations. Therefore, the slope of the indentation stress-strain relation, i.e., the transverse stiffness, is independent of the depth of penetration for small indentation strains.

The linear correlation between the peak indentation stress and the indentation strain was always high. The average $r^2$ for active contractions was 0.98 ± 0.03 ($n = 22$) and for passive stretching was 0.95 ± 0.04 ($n = 19$). In addition, repeated determinations of transverse stiffness performed under identical loading conditions were always within 5% of each other.

The transverse stiffness correlated with the peak in-plane stress index for each dog ($p < 0.001$, ANOVA). In addition, the transverse stiffness—in-plane stress index relations for active contractions were different from those for passively applied stress ($p < 0.001$, ANOVA with covariance).

The transverse stiffness is plotted against the peak in-plane stress index for both actively developed and passively applied stress in Figure 8. The data from 6 dogs (A–F) are plotted separately. The slopes of the relations for actively generated stress were not significantly different from those for passively applied stress (Table 1). The intercepts, however, were significantly different (Table 1).

The transverse stiffness for actively generated and passively applied stress is shown in Figure 9. For each connected pair of points, the peak in-plane stress indexes were comparable. The transverse stiffness for active contractions was greater than those of passive stretching ($p < 0.005$).

Figure 10 shows the relation between the transverse stiffness and the in-plane strain index for 4 specimens. As with the stiffness-stress relation, there is a clear separation between the transverse stiffnesses from active contractions and those from passive stretching ($p < 0.001$, ANOVA with covariance). The slopes and
Figure 8. Relations between transverse stiffness and peak in-plane stress index for active contractions and passive stretching. Each panel shows relation for an individual dog (A–F). □, data from active contractions; ○, data from passive stretching. Lines are regressions on active (—) and passive (-----) data. In-plane stress index is square root of the sum of the squares of the magnitudes of the 2 in-plane stresses. During active contractions, the central third of specimens is held isometric. During passive stretching, specimens are strained by servo system. There is a difference overall between active and passive relations (p<0.001. ANOVA).

Intercepts from linear regressions performed on the individual dog data are listed in Table 2. For the regression, the strain index was transformed by subtracting 1 and then multiplying by 10.

The intercepts (Int) of the individual dog relations between transverse stiffness and the peak in-plane stress index could be predicted from the slopes (Slope) and intercepts (Int) of the transverse stiffness-strain relations: Int = 2.07 × Slope + 0.30 × Int − 0.29 (r = 0.94, p<0.002). This relation was valid for active contractions as well as for passively applied stress.

The percent water contents for the individual specimens are listed in Table 3. The left ventricular free walls were not perfused during the experiments. There was a small, but significant, increase in water content for the septa. Table 3 also lists the perfusion flows that were used for each septum as well as the perfusion pressures at the onset and at the end of the indentation protocols. Perfusion pressure increased an average of 10% (p<0.002).

Discussion

The importance of distinguishing active from passive wall stress becomes apparent when considering changes in wall motion brought about by myocardial ischemia. It is obvious that coronary occlusion causes myocardial dysfunction in regions of muscle where blood flow has ceased. It has been shown, however, that regions adjacent to infarcted tissue have abnormal wall motion despite normal blood flow. The dysfunction in the muscle in these adjacent regions could be due to damage to the muscle, or alternatively, could be due to abnormal loading by the infarcted muscle. If the transverse stiffness of the muscle in the adjacent regions was low compared with that of muscle in distant regions that functioned normally at comparable levels of the strain index, one would conclude that the muscle in the adjacent regions was damaged and was being passively stretched by the functioning muscle. In addition, with hypertrophic cardiomyopathy where there is asymmetric septal hypertrophy, the septum has been noted to contract little if at all. This lack of contraction could be due to abnormal loading of otherwise normal muscle because of geometric factors or could be due to abnormal muscle that is not capable of generating wall

Table 1. Relations Between Transverse Stiffness and Peak In-Plane Stress Index

<table>
<thead>
<tr>
<th>Dog</th>
<th>Slope Active</th>
<th>Passive</th>
<th>Intercept (g/mm²) Active</th>
<th>Passive</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.79</td>
<td>0.57</td>
<td>0.25</td>
<td>−0.15</td>
</tr>
<tr>
<td>B</td>
<td>0.58</td>
<td>1.02</td>
<td>1.37</td>
<td>0.40</td>
</tr>
<tr>
<td>C</td>
<td>1.17</td>
<td>1.75</td>
<td>2.34</td>
<td>−0.33</td>
</tr>
<tr>
<td>D</td>
<td>2.81</td>
<td>1.64</td>
<td>1.92</td>
<td>−0.18</td>
</tr>
<tr>
<td>E</td>
<td>2.79</td>
<td>2.73</td>
<td>4.24</td>
<td>−0.49</td>
</tr>
<tr>
<td>F</td>
<td>1.79</td>
<td>0.98</td>
<td>3.27</td>
<td>−0.18</td>
</tr>
<tr>
<td>Mean</td>
<td>1.82</td>
<td>1.45</td>
<td>2.23</td>
<td>−1.16*</td>
</tr>
<tr>
<td>SEM</td>
<td>0.36</td>
<td>0.31</td>
<td>0.57</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*p<0.015 vs. Active, paired t test.
stress. If the transverse stiffness of the septum was comparable to that of parts of the heart that were contracting normally, one could conclude that the septal muscle was generating stress but did not shorten or thicken because of abnormal loading conditions.

Both the in-plane stress index and the in-plane strain index were found to correlate strongly with the transverse stiffness. Furthermore, this correlation differed for two markedly different myocardial states: passive stretching during potassium cardioplegia and active contractions. These data suggest that there should be a direct relation between both the myocardial stress (e.g., circumferential and meridional) and strain indexes and regional transverse (radial) stiffness. In the intact heart, it is not possible to measure either the circumferential or meridional stress. Both the transverse stiffness and the in-plane strain index can, however, be measured explicitly. The fact that the transverse stiffness—in-plane strain index data can predict the transverse stiffness—in-plane stress index intercept strongly suggests that one can distinguish muscle properties due to active contractions from passive stretching. Moreover, once further studies establish that there is a one-to-one correspondence between the in-plane stress and strain indexes for a particular condition of the muscle, one will also be able to estimate the in-plane stress index by using the appropriate transverse stiffness—in-plane stress index relation.

It is important to note that while this approach may enable one to distinguish active from passive wall stress, one will not be able to determine the individual stress components since wall stress is a tensor quantity. In the intact heart, there are three major stress components, \( \sigma_r \), \( \sigma_\theta \), and \( \sigma_z \), and three corresponding strain components. A change in magnitude of any component may cause the other components to change. The transverse stiffness likely reflects a local radial stress-strain relation that, in turn, is affected by the two other stresses and strains. Our current method obviously cannot distinguish the individual in-plane stress components.

The potassium chloride-arrested state was used to study the transverse stiffness of noncontracting muscle. It is likely that the properties of potassium-arrested muscle. If the transverse stiffness of the septum was comparable to that of parts of the heart that were contracting normally, one could conclude that the septal muscle was generating stress but did not shorten or thicken because of abnormal loading conditions.

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Table 3. Water Content, Septal Artery Flow, and Septal Artery Pressure

<table>
<thead>
<tr>
<th>Dog</th>
<th>Water content (%)</th>
<th>Mean flow (ml/min)</th>
<th>Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>LV free wall 78.2</td>
<td>Septum 82.0</td>
<td>Onset 142</td>
</tr>
<tr>
<td>B</td>
<td>79.0</td>
<td>82.6</td>
<td>130</td>
</tr>
<tr>
<td>C</td>
<td>78.3</td>
<td>82.4</td>
<td>128</td>
</tr>
<tr>
<td>D</td>
<td>78.1</td>
<td>81.0</td>
<td>140</td>
</tr>
<tr>
<td>E</td>
<td>79.9</td>
<td>79.2</td>
<td>130</td>
</tr>
<tr>
<td>F</td>
<td>78.9</td>
<td>80.6</td>
<td>100</td>
</tr>
</tbody>
</table>

Mean: 78.7 81.3* 49 128 141†

SEM: 0.3 0.5 2.4 6.1 7.5

*p<0.02 vs. LV free wall; †p<0.002 vs. Onset; paired t test.

Water content of the left ventricular (LV) free wall was measured at onset of experiments and of the septum at end of experiments. Pressure was measured at onset and at end of measuring period.

The "hardness" of contracting myocardium has been measured previously by an indentation test. A probe was used to indent canine hearts a given amount, and the hardness was expressed as the displacement of a calibrated spring by the probe from the probe's fully extended position. The hearts were noted to be harder in systole than in diastole; and the hardness correlated with the left ventricular pressure. These studies did not show, however, whether the hardness was a property of the muscle per se or simply a direct result of changes in the intracavitary pressure. The results of the hardness measurements cannot, therefore, be used for direct comparison with transverse stiffness measurements.

In summary, no validated methods have thus far been available that can reliably quantify regional myocardial wall stress. Our data show that there is a predictable relation between the transverse stiffness and the in-plane stress index. Determination of transverse stiffness promises, therefore, to provide a method for quantitative estimation of regional myocardial wall stress.

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