Quantification of the contractile response to injury: assessment of the work-length relationship in the intact heart

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ABSTRACT We used a sonomicrometric determination of ventricular dimension to examine the effect of ischemia and reperfusion on the work-length relationship in the intact heart to develop a useful and precise variable of ventricular contractile response to injury. Twenty anesthetized dogs were instrumented with epicardial ultrasonic dimension transducers to record right ventricular free wall chord length and left ventricular minor-axis length, micromanometers to record ventricular pressures, and an electromagnetic probe to record pulmonary arterial (n = 8) or aortic (n = 7, n = 7) flow. Dogs were subjected to either 20 min (n = 7) or 30 min (n = 13) of global cardiac ischemia supported by cardiopulmonary bypass. Data were acquired over a range of end-diastolic volumes produced by transient (5 to 10 sec) caval occlusion before and after ischemia. In both ventricles, systolic epicardial dimensional shortening correlated with flow probe--measured stroke volume (mean r = .969) and regional stroke work calculated as the integral of instantaneous ventricular pressure and epicardial dimension correlated with measured global stroke work (mean r = .960), confirming the validity of dimensional measurements. Regression analysis demonstrated a highly linear relationship between calculated regional stroke work and end-diastolic length in the right ventricle (mean r = .973) and left ventricle (mean r = .967), quantifiable by a slope (Mw) and x intercept (Lw). Change in afterload produced by pulmonary arterial or aortic constriction resulted in no significant changes in Mw or Lw in either ventricle. Ischemia and reperfusion decreased Mw and shifted Lw to the right in both ventricles. The decrease in Mw with 30 min ischemia exceeded the decrease with 20 min ischemia by 29% in the right ventricle and by 32% in the left (p < .04) with up to 1 hr of reperfusion. Changes in Lw were not related to severity of injury. After ischemia, infusion of calcium increased Mw by 177% in the right ventricle and by 67% in the left (p < .03) without significant changes in Lw. Independent of load conditions, the slope, Mw, of the linear stroke work vs end-diastolic length relationship is a valid and precise index of right and left ventricular contractile response to global ischemia in the intact circulation. This variable may be useful in evaluating therapies designed to limit myocardial injury and enhance ventricular functional performance.


AN IMPORTANT GOAL of both cardiovascular research and clinical practice is to minimize myocardial damage during periods of arrested coronary perfusion and to aid recovery of depressed myocardial performance after reperfusion. Biochemical variables may serve as precise indicators of acute myocardial cell injury, but the development of sensitive functional variables of injury and recovery is important, since ventricular contractile performance ultimately determines survival. The ability to quantify numerically intrinsic right and left ventricular performance after ischemic injury would permit more rigorous experimental evaluation of interventions designed to limit myocardial ischemic damage and lead to a better understanding of the pathophysiology of acute ventricular dysfunction.

One of the most widely used characterizations of ventricular contractile performance is that first proposed by Frank and Patterson and Starling relating the amount of mechanical energy generated by the ventricle during each cardiac cycle to initial muscle fiber length. Numerical quantification of ventricular performance via this relationship has been difficult because...
of the presumed curvilinear nature of the relation between ventricular performance and ventricular filling. Sarnoff and Berglund\(^3\) predicted, but were unable to demonstrate, a linear relationship between ventricular stroke work and end-diastolic volume. More recent work\(^4\)\(^-\)\(^7\) employing more sophisticated methods to examine the length-dependent properties of the intact ventricle has shown the relationship between left ventricular stroke work and end-diastolic volume (or dimension) to be linear. This linear relationship is insensitive to alterations in load conditions, and changes in the contractile state of the ventricle are reflected as changes in the slope of the relationship.\(^7\)

The relationship between ventricular stroke work and end-diastolic dimension has been characterized only in the normal left ventricle. The apparent complexity of right ventricular three-dimensional geometry has hindered assessment of the relationship in the right ventricle. In addition, the relationship has not yet been examined after global ischemia in either ventricle. Potentially, this variable offers a means to quantify ventricular contractile response to injury.

The purpose of this study was to examine the effect of a varying period of global myocardial ischemia followed by reperfusion on ventricular ability to generate stroke work as function of end-diastolic dimension in an attempt to develop a valid, precise, and useful variable of ventricular contractile response to ischemic injury in the intact circulation. Specifically, we tested three hypotheses: (1) that accurate determinations of dynamic ventricular volume and stroke work may be based on simplified epicardial dimensional analyses in the right and left ventricles both before and after global ischemia and reperfusion, (2) that the relationship between ventricular stroke work and end-diastolic dimension is linear and load insensitive in the right as well as the left ventricle, both before and after ischemia, and (3) that quantifiable alterations in the relationship between ventricular stroke work and end-diastolic dimension are related to the severity of acute ischemic injury and are insensitive to changes in load conditions, therefore providing quantification of ventricular contractile response to injury.

**Methods**

**Experimental preparation.** Twenty adult mongrel dogs were studied in the anesthetized open-chest state. Each dog received intravenous sodium pentobarbital (30 mg/kg) and succinylcholine (1 mg/kg) and was artificially ventilated. Through a median sternotomy, the pericardium was incised and the heart supported in a pericardial sling. Pulse transit ultrasonic dimension transducers connected to a sonomicrometer (Model 120, Triton Technology Inc., San Diego) were positioned to record instantaneous right and left ventricular dimensions. One pair of dimension transducers (cylinder length 0.16 cm, od 0.16 cm; Vemtriton, Bedford, OH) were placed approximately 1 cm apart subepicardially near the intersection of the long and short axes of the right ventricular free wall to record right ventricular chord dimension. The orientation of the transducers was perpendicular to the right ventricular long axis. A second pair of epicardial dimension transducers (hemisphere diameter 0.5 cm; Channel Industries, Santa Barbara) was placed to record left ventricular anterior-posterior minor-axis dimension. Instantaneous right and left ventricular pressures were recorded by micromanometers (Model PC-350, Millar Instruments, Houston) passed into the right ventricular chamber via a 0.5 cm incision in the outflow tract and into the left ventricular chamber via a 0.5 cm incision in the outflow tract and into the left ventricular chamber via a 0.5 cm incision in the apex. Central aortic pressure was monitored by a fluid-filled catheter passed through the carotid artery.

In eight dogs an electromagnetic flow probe (HQ series; Howell Instruments, Camarillo, CA) was placed around the main pulmonary artery to record instantaneous pulmonary arterial flow. In seven dogs a flow probe was placed around the ascending aorta to record aortic flow. The sinus node was crushed and the right atrium paced at a rate of 150 beats/min.

A bubble oxygenator (Optiflo; Cobe Laboratories, Lakewood, CO) was primed with 1.5 liters of heparinized homologous whole blood. Each dog received heparin (250 U/kg), and cardiopulmonary bypass was initiated at normothermia (37°C) with arterial inflow via the femoral artery and venous outflow from the superior and inferior vena cavae via the right atrium. The azygous vein was ligated. Mean arterial pressure was maintained at 65 to 75 mm Hg by adjusting bypass flow. Arterial P\(_{O_2}\), P\(_{CO_2}\), and pH were monitored and corrected as necessary. After a 15 min period of equilibration on cardiopulmonary bypass, each dog was subjected to 20 min (n = 7) or 30 min (n = 13) of normothermic global cardiac ischemia produced by aortic cross-clamping. During the ischemic period, the left ventricle was vented and right ventricular free wall, septal, and left ventricular free wall temperatures were monitored by thermistor probes (Shiley, Inc., Irvine, CA). Myocardial temperature was maintained at 37 ± 0.5°C during the ischemic period by continuously bathing the pericardial wall with warmed blood. After ischemia, the aortic cross-clamp was removed and the heart defibrillated. Cardiopulmonary bypass was continued and the heart reperfused for 30 min in the beating, nonworking state, after which the dog was weaned from bypass.

**Experimental design and data acquisition.** In each study, right and left ventricular functional performance was assessed off cardiopulmonary bypass at control before ischemia and after ischemia at 30 and 60 min of reperfusion. At each sampling time, pressure, dimension, and flow data were acquired over a range of end-diastolic volumes produced by transient venous caval occlusion. Data were sampled for 10 to 25 cardiac cycles over 5 to 10 sec during volume emptying. Venous caval occlusion was released, and before acquisition of the next set of data several minutes were allowed to elapse to permit hemodynamic equilibration.

In seven dogs, ventricular functional performance was also assessed after short-term elevation of right and left ventricular afterload. Right ventricular afterload was elevated by gradual constriction of the main pulmonary artery by an encircling snare over a period of 1 to 2 min to a degree sufficient to raise peak right ventricular pressure by 30% to 40%. Data were then obtained over a range of end-diastolic volumes produced by transient venous caval occlusion as described above. Left ventricular afterload was similarly increased by constriction of the descending aorta sufficient to raise mean proximal aortic pressure by 30% to 40% and data acquired during venous caval occlusion. Between each of these afterload interventions, performed
both at control and at 60 min of reperfusion after ischemia, hemodynamic conditions were returned to baseline.

In six dogs, data were also acquired after intravenous infusion of calcium chloride (25 mg/kg) after 60 min of posts ischemia reperfusion.

**Data analysis.** Pressure, dimension, and flow data were sampled at 5 msec intervals, converted to digital form in real time by an analog-to-digital converter (Model 1023; DEC, Maynard MA) and stored on hard disk by microcomputer (PDP 11/23; DEC). Subsequent data processing and analysis were accomplished by interactive software developed in our laboratory. Right and left ventricular dP/dt and end-systolic dimension at peak systole were determined by two-way analysis of variance. For the left ventricle, end-diastolic length was determined as the dimension 5 msec before the point of peak positive left ventricular dp/dt. Review of analog tracings confirmed this to be a readily identifiable point marking the early portion of the near isometric phase before initiation of left ventricular ejection. Since a truly isometric phase of systole was not apparent in all dogs, this point was taken as a consistent approximation of end-diastole. Left ventricular end-systolic length was determined as the dimension 10 msec before peak negative left ventricular dp/dt as previously described. For the right ventricle, end-diastolic length (EDL) was determined as the dimension 5 msec before peak positive right ventricular dp/dt and end-systolic length (ESL) as the dimension at peak negative right ventricular dp/dt. These determinations were also confirmed by review of analog tracings and have been shown to mark accurately the initiation and end of right ventricular ejection, respectively.

For both the right and left ventricles, systolic dimensional shortening (ΔL) was determined for each cardiac cycle as:

\[
\Delta L = EDL - ESL
\]

(1)

Right and left ventricular regional stroke work (SW) values were calculated from instantaneous ventricular pressure (P) and dimension (L) data for each cardiac cycle as:

\[
SW = \int P \cdot dL
\]

(2)

In dogs instrumented with electromagnetic flow probes, right or left ventricular stroke volume (SV) was measured from instantaneous flow (Q) data for each cardiac cycle as:

\[
SV = \int Q \cdot dt
\]

(3)

Global right and left ventricular stroke work (SW_global) values were determined from ventricular mean ejection pressure (MEP) and end-diastolic pressure (EDP) for each cardiac cycle as:

\[
SW_{global} = SV \times (MEP - EDP)
\]

(4)

Data from each vena caval occlusion were subjected to linear regression analysis and were fitted to the following formulas:

\[
SV = M_{sv} (\Delta L - L_{sv})
\]

(5)

\[
SW = M_{regional} (SW_{global} - W_{regional})
\]

(6)

\[
SW = M_{w} (EDL - L_{w})
\]

(7)

relating stroke volume (SV) to systolic dimensional shortening (ΔL), calculated regional stroke work (SW) to measured global stroke work (SW_global), and calculated regional stroke work (SW) to end-diastolic length (EDL) for both the right and left ventricles. In each dog, the slope (M_{sv}, M_{regional}, M_{w}), x intercept (L_{sv}, W_{regional}, L_{w}), and correlation coefficient were determined for each of these relations for each vena caval occlusion.

Mean values for slope, x intercept, and correlation coefficient were calculated for each study condition by averaging values for two to five vena caval occlusions (average 2.7 occlusions per study condition). Statistical analysis of the effects of altered afterload, ischemia, and calcium infusions on slopes and intercepts was by one-way analysis of variance. Comparison between groups of dogs subjected to different periods of global ischemia was by two-way analysis of variance. Statistical significance was accepted at p < .05. All data are expressed as mean ± SEM.

**Results**

Representative simultaneous right and left ventricular pressure, dimension, and pulmonary flow analog data from a single dog are depicted in figure 1. In both ventricles, systolic dimensional shortening correlated with measured stroke volume (figure 2) and regional stroke work correlated with global stroke work (figure 3) before and after ischemia. The mean slope and x intercept of equation 5 relating stroke volume to dimensional shortening and of equation 6 relating regional to global stroke work did not change with ischemia and reperfusion (tables 1 and 2). Regional muscle performance assessed by simplified epicardial dimensional analyses remained a valid and accurate reflection of global chamber performance.

As demonstrated in figure 4, plotting ventricular stroke work calculated as the integral of instantaneous pressure and dimension for each cardiac cycle as a function of end-diastolic length, expressed as SW = M_{w} (EDL - L_{w}), yielded a highly linear relationship. This was true for both the right and left ventricles and was observed in all 20 dogs under all experimental conditions.
conditions. For the right ventricle at control, the mean slope, $M_w$, of the SW vs EDL relation was $26 \pm 1.7$ dyne/cm$^2 \times 10^3$ (range 15.2 to 37.2), the mean $x$ intercept, $L_w$, was $0.96 \pm 0.05$ cm (range 0.58 to 1.08), and the mean correlation coefficient was $0.968 \pm 0.003$ (range 0.957 to 0.996). For the left ventricle, the mean $M_w$ was $90.3 \pm 3.4$ dyne/cm$^2 \times 10^3$ (range 57.1 to 123.9), the mean $L_w$ was $4.61 \pm 0.09$ cm (range 3.57 to 5.32), and the mean correlation coefficient was $0.982 \pm 0.002$ (range 0.976 to 0.994).

Figure 5 demonstrates the observed effect of pulmonary arterial constriction on right ventricular performance in a representative dog. At a given end-diastolic length, ventricular developed pressure increased and systolic dimensional shortening decreased compared with control values (figure 5, A). Over a wide range of preload, there was a decrease in systolic shortening as a function of end-diastolic length (figure 5, B). However, stroke work as a function of end-diastolic length remained unchanged (figure 5, C).

For the entire group of dogs, short-term elevation of right ventricular afterload produced by pulmonary arte-
TABLE 1
Effect of ischemia and reperfusion on the relation between measured stroke volume$^A$ and systolic dimensional shortening in the right and left ventricles

<table>
<thead>
<tr>
<th></th>
<th>RV</th>
<th></th>
<th>LV</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>$M_{SV}$ (ml/cm)</td>
<td>$L_{SV}$ (cm)</td>
<td>$r$</td>
<td>$M_{SV}$ (ml/cm)</td>
</tr>
<tr>
<td>Control</td>
<td>0.39 ± 0.04</td>
<td>-0.02 ± 0.02</td>
<td>.973 ± .009</td>
<td>0.19 ± 0.04</td>
</tr>
<tr>
<td>Post ischemia</td>
<td>0.38 ± 0.04</td>
<td>0.01 ± 0.01</td>
<td>.967 ± .006</td>
<td>0.18 ± 0.03</td>
</tr>
<tr>
<td>$p$ = NS</td>
<td>$p$ = NS</td>
<td>$p$ = NS</td>
<td>$p$ = NS</td>
<td>$p$ = NS</td>
</tr>
</tbody>
</table>

Values are mean ± SEM for $n$ = 8 dogs (RV) and $n$ = 7 dogs (LV).

$M_{SV}$ = slope; $L_{SV}$ = x-intercept.

$^A$SW = $M_{SV}$ (AL-$L_{SV}$), where SV is stroke volume and AL is systolic dimensional shortening.

...rial constriction resulted in no significant change in either $M_w$ or $L_w$ of the linear SW vs EDL relationship either before or after ischemia and reperfusion (table 3).

The effect of aortic constriction on left ventricular performance is depicted in figure 6. Left ventricular developed pressure increased and systolic dimensional shortening decreased at a given end-diastolic length compared with control (figure 6, A). Systolic shortening decreased (figure 6, B) with no change in left ventricular stroke work as a function of end-diastolic length (figure 6, C). For the entire group of dogs, short-term elevation of left ventricular afterload produced by aortic constriction had no effect on $M_w$ or $L_w$ either before or after ischemia (table 3).

After ischemia and reperfusion, both the right and left ventricular SW vs EDL relationships remained linear. For the right ventricle, after ischemia the mean correlation coefficient was .965 ± .009; for the left ventricle the mean correlation coefficient was .961 ± .008.

Ischemia resulted in consistent and characteristic alterations in the SW vs EDL relationship that were similar in both the right and left ventricles. After ischemia and reperfusion, there was a reduction in $M_w$ and a rightward shift of $L_w$ (table 4). For both the right and left ventricles, the decrease in $M_w$ that occurred after 30 min of ischemia and up to 60 min of reperfusion exceeded the decrease in $M_w$ that occurred after 20 min of ischemia and up to 60 min of reperfusion (figure 7). In the right ventricle, the decrease in $M_w$ with 30 min ischemia exceeded the decrease in $M_w$ with 20 min ischemia by 28% at 30 min reperfusion and by 22% at 60 min reperfusion ($p < .02$). In the left ventricle, the decrease in $M_w$ with 30 min ischemia exceeded the decrease with 20 min ischemia by 29% at 30 min reperfusion and by 32% at 60 min reperfusion ($p < .04$). There was no significant difference between the observed increase in $L_w$ that occurred with 20 and 30 min of ischemia in either the right or left ventricle (table 4).

After ischemia and reperfusion, infusion of calcium chloride increased ventricular developed pressure, systolic dimensional shortening, and stroke work as a function of end-diastolic length in both ventricles. Calcium chloride increased $M_w$ by an average of 177% in the right ventricle (13.1 ± 1.2 to 36.3 ± 7.7 dyne/cm$^2$ × 10$^3$; $p < .03$) and by an average of 67% in the left ventricle (60.5 ± 7.4 to 109.9 ± 9.5 dyne/cm$^2$ × 10$^3$; $p < .03$).

TABLE 2
Effect of ischemia and reperfusion on the relation between regional calculated stroke work$^A$ and measured global stroke work in the right and left ventricles

<table>
<thead>
<tr>
<th></th>
<th>RV</th>
<th></th>
<th>LV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M_{regional}$ (cm$^{-2}$)</td>
<td>$W_{regional}$ (dyne-cm × 10$^3$)</td>
<td>$r$</td>
<td>$M_{regional}$ (cm$^{-2}$)</td>
</tr>
<tr>
<td>Control</td>
<td>34.6 ± 3.5</td>
<td>10.9 ± 13.9</td>
<td>.973 ± .006</td>
<td>68.5 ± 11.3</td>
</tr>
<tr>
<td>Post ischemia</td>
<td>35.2 ± 3.8</td>
<td>-4.2 ± 6.5</td>
<td>.970 ± .007</td>
<td>66.8 ± 10.5</td>
</tr>
<tr>
<td>$p$ = NS</td>
<td>$p$ = NS</td>
<td>$p$ = NS</td>
<td>$p$ = NS</td>
<td>$p$ = NS</td>
</tr>
</tbody>
</table>

Values are mean ± SEM for $n$ = 8 dogs (RV) and $n$ = 7 dogs (LV).

$M_{regional}$ = slope; $W_{regional}$ = x-intercept.

$^A$SW = $M_{regional}$ (SW$^{global}$ - $W_{regional}$), where SW is calculated stroke work and SW$^{global}$ is measured global stroke work.
p < .002), with no change in $L_w$ in either the right (0.90 ± 0.09 to 0.91 ± 0.09 cm; p = NS) or left ventricle (4.66 ± 0.22 to 4.50 ± 0.24 cm; p = NS).

**Discussion**

Dimensional assessments of ventricular performance in the intact heart have been widely employed\(^4\)–\(^7\), \(^10\)–\(^16\) but largely limited to the normal, uninjured left ventricle. The relative simplicity of the left ventricular three-dimensional geometry and contraction pattern permit accurate determination of left ventricular volume based on a single left ventricular dimension in the beating heart.\(^17\)–\(^20\) A similar dimensional assessment of right ventricular performance has proved more difficult, hindered by the apparent greater complexity of right ventricular geometry and contraction pattern. Recently, however, it has been shown\(^9\) that accurate determinations of right ventricular volume may also be based on a single ventricular dimension in the normal heart.

**FIGURE 4.** Left panels depict simultaneous right and left ventricular pressure-dimension data from a single dog obtained during vena caval occlusion. Right panels depict plot of regional ventricular stroke work calculated as the integral of instantaneous ventricular pressure and dimension for each cardiac cycle as a function of end-diastolic length, demonstrating the linear SW vs EDL relationship in both the right and left ventricles.

**FIGURE 5.** Representative data from a single dog, demonstrating the effect of short-term elevation of afterload on right ventricular performance for cardiac cycles selected at matched end-diastolic lengths (A), on systolic dimensional shortening ($\Delta L$) as a function of end-diastolic length during vena caval occlusion (B), and on stroke work as a function of end-diastolic length during vena caval occlusion C).
TABLE 3
Effect of increased afterload on the SW vs EDL relationship\(^a\) before and after global ischemia in the right and left ventricles

<table>
<thead>
<tr>
<th></th>
<th>Before ischemia</th>
<th>After ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(M_w) (dyne/cm(^2) \times 10(^3))</td>
<td>(L_w) (cm)</td>
</tr>
<tr>
<td>RV Control</td>
<td>24.4 (\pm) 1.6</td>
<td>0.94 (\pm) 0.05</td>
</tr>
<tr>
<td>Increased afterload</td>
<td>25.5 (\pm) 2.6</td>
<td>0.94 (\pm) 0.04</td>
</tr>
<tr>
<td>LV Control</td>
<td>86.9 (\pm) 4.0</td>
<td>4.55 (\pm) 0.12</td>
</tr>
<tr>
<td>Increased afterload</td>
<td>89.3 (\pm) 4.0</td>
<td>4.63 (\pm) 0.13</td>
</tr>
</tbody>
</table>

Values are mean \(\pm\) SEM for \(n = 7\) dogs.
\(M_w\) = slope; \(L_w\) = x-intercept.
\(^a\)SW = \(M_w\) (EDL - \(L_w\)).

The validity of epicardial dimensional analyses to assess chamber volume in either ventricle injured by global ischemia has been questioned\(^{21, 22}\) because of supposed alterations in ventricular wall thickness and myocardial mass attributable to postischemic myocardial edema. Our data demonstrate that change in epicardial dimension remains an accurate indicator of change in chamber volume after global ischemia and reperfusion. There were no significant changes in the correlation between systolic dimensional shortening and measured stroke volume or in the correlation between calculated regional stroke work and measured global stroke work in either ventricle. We conclude that a valid and simplified assessment of both right and left ventricular dynamic chamber volume and SW before and after global ischemia may be based on analysis of a single epicardial ventricular dimension.

Using this method to assess the work-length relationship in the intact heart, we were able to demonstrate that regional stroke work was a linear function of end-diastolic length in the right and left ventricles in the normal heart, in the heart injured by global ischemia, and in the injured heart after infusion of calcium chloride to enhance contractile state. These observations are consistent with the Frank-Starling concept of the length-dependent property of cardiac performance, whereby the greater the end-diastolic volume, the larger the ventricular force generated during systole. The work-length properties of right and left ventricular myocardium and of normal and ischemically injured hearts.

FIGURE 6. Representative data from a single dog, demonstrating the effect of short-term evaluation of afterload on left ventricular performance for cardiac cycles selected at matched end-diastolic lengths (A), on systolic dimensional shortening (\(\Delta L\)) as a function of end-diastolic length during vena caval occlusion (B), and on stroke work as a function of end-diastolic length during vena caval occlusion (C).
myocardium are shown to be fundamentally similar. In each case, myocardial work is a linear function of initial muscle fiber length. Contractile performance may be quantified by a slope and \( x \) intercept.

With short-term elevation of ventricular afterload produced by partial outflow obstruction, the ability of the ventricle to generate stroke work as a function of end-diastolic dimension was shown to remain unchanged. Consistent with the findings of others for both the right\(^23\) and left ventricles,\(^7, 13, 24\) there was a decrease in \( \Delta L \) and stroke volume at a given end-diastolic dimension with increased afterload. Increased outflow resistance also resulted in increased ventricular developed pressure at a given end diastolic dimension as previously described.\(^7, 23, 25-32\) However, stroke work (determined as the integral of instantaneous pressure and dimension) as a function of end-diastolic length for each cardiac cycle remained unchanged. Pressure-work was substituted for volume-work with no change in total work in response to increased after-

### TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>RV(^c)</th>
<th>LV(^c)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>20 min ischemia</td>
<td>30 min ischemia</td>
</tr>
<tr>
<td></td>
<td>( M_w ) (dyne/cm(^2) \times 10^3)</td>
<td>( L_w ) (cm)</td>
</tr>
<tr>
<td>RV(^c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>22.8 ± 3.1</td>
<td>0.82 ± 0.06</td>
</tr>
<tr>
<td>30 min reperfusion</td>
<td>15.4 ± 2.6</td>
<td>0.95 ± 0.08(^b)</td>
</tr>
<tr>
<td>60 min reperfusion</td>
<td>17.5 ± 2.1</td>
<td>0.91 ± 0.07(^b)</td>
</tr>
<tr>
<td>LV(^c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>91.8 ± 8.2</td>
<td>4.46 ± 0.20</td>
</tr>
<tr>
<td>30 min reperfusion</td>
<td>57.6 ± 8.9(^b)</td>
<td>4.66 ± 0.18(^b)</td>
</tr>
<tr>
<td>60 min reperfusion</td>
<td>86.5 ± 8.9</td>
<td>4.59 ± 0.17</td>
</tr>
</tbody>
</table>

Values are mean ± SEM for \( n = 7 \) dogs (20 min ischemia) and \( n = 13 \) dogs (30 min ischemia).

\( M_w = \) slope; \( L_w = \) \( x \) intercept.

\(^a\)SW = \( M_w (EDL - L_w) \).

\(^p < .05\) vs control; \(^p < .02\) for \( M_w \); \( p = \) NS for \( L_w \) 20 vs 30 min ischemia; \(^b\)\( p < .04\) for \( M_w \); \( p = \) NS for \( L_w \) 20 vs 30 min ischemia.

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**FIGURE 7.** Effect of the duration of global ischemia on the mean slope, \( M_w \), of the SW vs EDL relationship in the right and left ventricles for the entire group of dogs. Mean values ± SEM.
load. Earlier investigations examining the effect of altered afterload conditions on systolic performance of the ventricle reported stroke work to be increased, decreased, and unchanged afterload-induced changes in preload, which likely account for most of the changes in stroke work observed with short-term alterations in afterload. We examined ventricular performance as a function of end-diastolic dimension in the presence and absence of a physiologic increase in outflow resistance. Doing so, we demonstrated that stroke work remained a linear function of end-diastolic length. Furthermore, we were unable to detect a significant change in either the slope or x intercept of the SW vs EDL relationship. The insensitivity of the SW vs EDL relationship to alterations in load, previously described in the normal left ventricle, is demonstrated in the normal right ventricle and in the right and left ventricles injured by global ischemia.

Despite the complexity of numerous interacting factors that could be expected to affect ventricular performance after global ischemic injury, the slope, M_w, of the SW vs EDL relationship was sufficiently sensitive to detect a significant, quantifiable difference in ventricular contractile response to 20 and 30 min of global cardiac ischemia. The longer period of ischemia resulted in a greater reduction of ventricular ability to augment stroke work as a function of augmenting end-diastolic volume. We chose to use a global rather than regional ischemic injury to maintain validity of ventricular dimensional analyses and to minimize heterogeneity in the degree of injury attributable to variation among dogs in coronary vascular anatomy. The 20 and 30 min durations of ischemia were chosen empirically based on several factors. In our experience, after 30 min of normothermic ischemia and reperfusion, dogs are weaned routinely from cardiopulmonary bypass. Longer durations of ischemia result in a significant number of dogs that cannot be weaned from bypass. Thirty minutes of global ischemia has been reported to result in a 60% to 65% depletion of myocardial adenine nucleotide content in the dog, whereas 20 min of ischemia results in a 48% depletion. We reasoned that 30 min of ischemia represented a severe but nonfatal degree of ischemic injury, whereas 20 min of ischemia represented a more moderate degree of injury. In both ventricles, 30 min of ischemia resulted in an average of 20% to 30% greater reduction in M_w than did 20 min of ischemia.

The increase in M_w in response to calcium chloride infusion after ischemia in the right and left ventricle indicates the SW vs EDL relationship reflects alterations in contractile state in the injured heart and suggests that M_w is a useful variable to evaluate interventions designed to enhance recovery of ventricular contractile performance after ischemic injury.

The use of the linear SW vs EDL relationship as a variable of ventricular contractile performance offers several advantages. First, the relationship is a cogent variable for the clinician. Unlike the end-systolic pressure-volume relationship, the SW vs EDL relationship is a descriptor more similar to the Frank-Starling concept of ventricular performance, assessing work performed by the ventricle during each cardiac cycle as a function of diastolic filling. Second, the linearity of the SW vs EDL relationship permits precise quantification of ventricular performance over a range of load conditions. Third, the expression of stroke work as a function of end-diastolic volume or length rather than end-diastolic pressure avoids the influence of factors that alter diastolic compliance. Ischemia, constraining effects of the pericardium, and contralateral ventricular load conditions significantly alter the ventricular end-diastolic pressure-volume curve. Changes in ventricular compliance may result in changes in end-diastolic pressure not reflective of ventricular end-diastolic volume. Expression of ventricular diastolic filling by pressure rather than volume would result in apparent alterations in systolic performance attributable solely to alterations in diastolic compliance. The slope, M_w, of the SW vs EDL relationship predictably would be insensitive to changes in diastolic compliance.

A further advantage of the SW vs EDL relationship is that it provides a useful means to quantify right ventricular contractile performance. Earlier attempts to quantify right ventricular functional response to injury demonstrated no detectable hemodynamic impairment after even severe right ventricular injury. These observations led to the presumption that right ventricular myocardial contraction does not contribute significantly to cardiac pump performance or that the right ventricle is relatively resistant to ischemic injury. More recently, the clinical significance of right ventricular injury and dysfunction has been better appreciated. The inability to detect impairment of right ventricular performance after injury is due to the apparent insensitivity of various hemodynamic variables and the extent to which impairment of right ventricular contractility may...
be masked by favorable load conditions resulting in normal ventricular pump function. The SW vs EDL relationship was sufficiently sensitive to detect a significant impairment of right ventricular contractile performance after 30 min of ischemia. A trend toward impairment of contractile performance was noted after 20 min of ischemia. These changes were apparent in the absence of pharmacologic blockade of the autonomic nervous system. Attenuation of sympathetic-mediated stimulation of contractility in response to ischemia may have resulted in a statistically significant decrease in right ventricular $M_w$ with the lesser degree of injury.

Several potential limitations in the methods of this study should be considered. First, in measuring dynamic ventricular dimension rather than volume, we assumed that regional ventricular hydrodynamic performance accurately reflected global ventricular hydrodynamic performance. As evidenced by the consistent correlation between systolic dimensional shortening and stroke volume and between regional and global stroke work, this would appear to be a valid assumption. Regional ischemic injury or regional heterogeneities in global ischemic injury would make such an assumption less valid. In the absence of a heterogeneous pattern of injury, however, regional events remain an accurate reflection of global events. A second limitation of this study is that the cause and significance of the rightward shift of the SW vs EDL relationship with ischemia and reperfusion is not fully explained. Previous investigators have described an increase in the unstressed volume of the left ventricle at zero transmural pressure after global ischemia followed by reperfusion. This was attributed to myocardial "creep" or stress relaxation. This same phenomenon could account for the observed increase in $L_w$ and rightward shift of the SW vs EDL relationship. Whether the rightward shift of $L_w$ after ischemia is caused by myocardial creep or other factors, several points should be noted. First, change in epicardial dimension consistently correlated with change in ventricular chamber volume. Factors responsible for the rightward shift of the SW vs EDL relationship would not affect the accuracy of epicardial dimension analyses in assessing changes in ventricular chamber volume. The slope, $M_w$, of the SW vs EDL relationship still accurately quantifies change in ventricular stroke work as a function of change in end-diastolic volume. Second, the increase in $L_w$ observed with ischemia was not related to the duration of the ischemic period, nor was there any significant change in $L_w$ with calcium infusion in either the injured right or left ventricle. Degrees of injury or inotropic interventions other than those examined in this study may have resulted in a demonstrable correlation between severity of injury or inotropic state and changes in $L_w$. However, under all studied conditions, changes in $M_w$, not $L_w$, were consistently reflective of severity of injury and inotropic state. Further work is needed to determine the cause and significance of the observed rightward shift of $L_w$ after ischemia and reperfusion.

A final limitation of the study to be considered is that the effect of contralateral ventricular performance on the SW vs EDL relationship was not examined. In this study, interventions to impair or enhance ventricular performance were directed to an equal extent at both ventricles. This did not allow us to confirm that, in the presence of disparate levels of ventricular performance, the SW vs EDL relationship quantifies ventricular contractile performance independent of performance of the contralateral ventricle. Work by others suggests the predominant interactive effects between right and left ventricular performance are limited to alterations in load conditions and diastolic compliance. If so, the SW vs EDL relationship expectedly would not be influenced by ventricular interaction. However, other direct mechanical interactions between right and left ventricular contractions have been hypothesized to occur. Such mechanical interactions may be more apparent with disparate levels of ventricular performance and in the closed-chest preparation. Additional work is needed to characterize more completely the effect of contralateral ventricular performance on systolic function assessed by this variable.

Despite these potential criticisms, several conclusions may be drawn. This study demonstrates that a simplified epicardial dimensional analysis is a valid technique of assessing dynamic ventricular volume and stroke work after global injury in both the right and left ventricles. Changes in ventricular epicardial dimension accurately reflect global chamber performance in the absence of heterogenous injury. With this technique to assess the work-length relationship in the right and left ventricles, regional stroke work is shown to be a linear function of end-diastolic length. The slope, $M_w$, of the linear SW vs EDL relationship is insensitive to alterations in load and provides a means to quantify precisely ventricular contractile response to injury in the intact circulation of the open-chest dog. This variable offers the potential to aid in better understanding ventricular dysfunction and in evaluating various interventions designed to affect ventricular functional performance after ischemia and reperfusion.
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