JACC Vol. 8, No. 5
November 1986:1182–8

Regional Blood Flow and Metabolite Levels in the Left Ventricular Free Wall and Septum During Aortic Insufficiency: Implications for the Development of Asymmetric Septal Hypertrophy

ROBERT B. DUNN, PHD

Chicago, Illinois

Asymmetric septal hypertrophy is considered by many to be pathologic but its presence in a number of states associated with left ventricular overload indicates that it may develop as an adaptive feature in the overloaded heart. This hypothesis implies that initially in these states a greater systolic stress and thus energy metabolism occurs in the ventricular septum than in the left ventricular free wall. It was previously demonstrated that in the early stages of ischemia regional differences in energy metabolism could be determined by comparisons of tissue high energy phosphate depletion and lactate accumulation. In the present study these measurements were made in an animal model of left ventricular overload. In open chest dogs aortic insufficiency was produced, which served to provide both volume overload to the left ventricle and regional myocardial ischemia. In addition to regional metabolite levels, measurements of regional blood flow were determined using radioactive microspheres. Tissue samples were taken from the left ventricle and interventricular septum, freeze clamped, divided transmurally into thirds and analyzed for creatine phosphate, adenosine triphosphate and lactate.

Animals with myocardial ischemia after aortic insufficiency were classified into two groups: those in which ischemia was limited to the inner left ventricle and left side of the septum and those with more extensive ischemia transmurally. In the latter group, creatine phosphate depletion and lactate accumulation were greater in the septum, but myocardial blood flow was also more depressed in the septum than in the left ventricle. In the former group, where ischemia was more restricted, metabolite changes were also more severe in the left septum than in the inner left ventricle. In this case blood flow was not different between the ischemic regions. It is concluded that these results indicate a greater energy metabolism in the left septum than in the inner left ventricular free wall and provide support for the hypothesis that asymmetric septal hypertrophy may develop as an adaptive process in response to a greater tension development by the septal fibers during left ventricular overload.

(J Am Coll Cardiol 1986;8:1182–8)

The presence of asymmetric septal hypertrophy is considered by many to be pathologic, but its high frequency in states such as hyperthyroidism (1), athletic conditioning (2,3), aortic stenosis (4) and hypertension (5) suggest the possibility of a physiologic origin. One hypothesis is that asymmetric septal hypertrophy may originate because of a greater stress on the interventricular septum than on the left ventricular free wall in the overloaded heart. Disproportionate septal thickening could then be considered in many cases as part of the adaptive compensatory phase of cardiac hypertrophy. This hypothesis is supported by the model recently developed by Heng et al. (6) to predict stress distribution between the free wall and septum of the left ventricle. Their calculations indicate that during systole a substantially greater stress should occur in the septum than in the left ventricular free wall of the overloaded heart.

The purpose of this study was to test the preceding hypothesis in an experimental animal model. Our approach was to compare indexes of myocardial energy utilization as a reflection of systolic stress distribution in the overloaded heart. Previously we demonstrated (7,8) that the rate of high energy phosphate depletion and tissue lactate accumulation in the initial stages of ischemia produced by abruptly stopping all coronary inflow was a function of myocardial tissue energy utilization. The procedure followed in this study was to induce aortic insufficiency in open chest dogs. Aortic insufficiency provided both a volume overload to the heart and regional myocardial ischemia. By comparing regional

From The Department of Physiology, The Chicago Medical School, North Chicago, Illinois. This study was supported by the Chicago Heart Association, Chicago, Illinois.

Manuscript received November 5, 1985; revised manuscript received May 9, 1986, accepted May 16, 1986.

Address for reprints: Robert B. Dunn, PhD, The Department of Physiology, The Chicago Medical School, North Chicago, Illinois 60064.

0735-1097/86/$3.50

blood flow measurements with ischemic metabolite changes, that is, high energy phosphate depletion and lactate accumulation, we were able to compare the rate of energy utilization in the left ventricular free wall and septum during the volume overload.

Methods

Animal preparation. Fasted mongrel dogs were anesthetized with sodium pentobarbital (35 mg/kg body weight intravenously), with supplemental doses given as required during the experiment. The trachea was intubated and respiration was maintained with a Harvard respirator. End-tidal carbon dioxide was monitored continuously, and was maintained between 4.5 and 5% by adjusting ventilation. Supplemental oxygen was added to the inspired air (approximately 10% of the inspired air volume) to ensure a normal arterial oxygen tension. Blood gas samples were drawn anaerobically from an aortic catheter and read immediately on a Radiometer blood gas analyzer (model MK2) to ensure normal oxygen saturation and partial pressure of carbon dioxide. Rectal temperature was measured with a Yellow Springs telethermometer and maintained between 37 and 39°C by the use of a heating pad. Pressure in the aortic arch was monitored through a side hole polyethylene catheter passed retrograde from a femoral artery. A second arterial catheter was placed in the opposite femoral artery for reference sample withdrawal during microsphere injection. A catheter was inserted into a femoral vein for injections and infusions.

A right thoracotomy was performed and a catheter was inserted into the right atrium through a stab wound in its wall and advanced into the right ventricle for pressure recording. The pericardium in all animals remained intact and the small incisions necessary for the introduction of catheters were loosely sutured. A left thoractomy then was performed and a small catheter was placed into the left atrium for microsphere injection. A needle-tipped catheter (thin wall no. 17) was inserted through the left ventricular wall to measure intraventricular pressure. Heparin was administered (350 U/kg intravenously) and an arterial blood sample was drawn and precipitated with cold 6% perchloric acid for the subsequent determination of lactate (9). Dogs with an arterial lactate concentration greater than 1.75 m*M* were eliminated from the study; this occurred in two animals. The purpose of this procedure was to eliminate the possibility that abnormally high basal tissue lactate levels would influence the findings obtained after aortic insufficiency.

In experimental animals aortic insufficiency was produced by introducing a thick-walled glass tube into the aorta through the ligated subclavian artery and passing it retrograde toward the aortic valve. The cannula contained a small bend to permit easy negotiation around the aortic arch. To rupture an aortic leaflet the tube was positioned against a valve leaflet (established from observed pressure changes at the tube's tip) and sufficient pressure then applied to rupture the leaflet. The procedure was repeated so that in each animal two of the three aortic valve leaflets were ruptured. In control animals the glass cannula was advanced and positioned in the region of the aortic arch. After completion of each experiment the endocardial surface of the left ventricle was closely examined for any evidence of damage produced by the cannula during valve rupture. Damage to the myocardium was present in approximately 25% of the animals and when this occurred the experiment was rejected.

Experimental procedures. Data were obtained in control animals and in those with aortic valve rupture. In control animals left ventricular free wall and septal tissue samples were obtained after a single left atrial injection of microspheres. The microspheres (15 ± 3 μ in diameter; 3M), labeled with scandium-46, strontium-85 or chromium-51, were agitated before injection and complete dispersion of the spheres was verified by inspection under a light microscope. Arterial reference sample withdrawal (5.82 ml/min) was started 30 seconds before and continued for 90 seconds after completing the microsphere injection (injection time approximately 20 seconds). In experimental animals one microsphere injection was given before and a second containing a different isotope was given 2 to 5 minutes after completing aortic valve rupture. In these animals tissue sampling was performed immediately after completing the second arterial reference withdrawal.

Tissue sampling was performed in the anterior region at the base of the left ventricle, with a cylindrical cutting tool mounted on an electric drill, as previously described (7). Because the procedure was a destructive one, only one set of data was obtained in each animal. The sampling device consisted of a central shaft with an 18 gauge spinal needle to receive the tissue samples, and an outer shell with a sharpened rim. To obtain a free wall and septal tissue sample, we passed through the pericardium and penetrated the surface of the left ventricular wall with the sampling tool to a depth sufficient to impale both a transmural free wall and septal sample on the needle. After exposing the samples by withdrawing the outer shell, we quickly positioned the two tissue samples a small distance apart and toward the needle tip (pericardium remaining at the needle base) and compressed them between a pair of heavy metal tongs precooled in liquid nitrogen (sample thickness between 3.0 and 3.1 mm). The time required for cutting and compressing the samples was less than 5 seconds. The angle of penetration was such that the septal sample was, in most cases, from the ventricular base; if it was not, the experiment was rejected.

The frozen left ventricular free wall sample was divided into outer, middle and inner thirds, and the frozen septal sample was divided into left, middle and right septal portions. Each portion was weighed, pulverized and extracted

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with perchloric acid. The supernatant extract was analyzed for creatine phosphate (10), adenosine triphosphate (11) and lactate (9). All metabolite data are expressed as micromoles per gram wet weight.

The remainder of the heart was placed in a buffered formalin solution for 3 to 4 days. The free wall of the left ventricle and septum then was separated and divided into 20 to 30 and 12 to 16 transmural pieces, respectively. Each transmural piece was divided into thirds, weighed and counted in a Packard Auto-Gamma Counter. Blood flow to each tissue sample was determined by the reference sample method.

Animal groupings. The animals were categorized into four groups: one control (Group I) (n = 6) and three experimental groups (Groups II, III and IV) (n = 19). Inclusion within a particular experimental group was based on the presence as well as the extent of regional ischemia after aortic valve rupture. Specifically, the transmural tissue lactate values of the left ventricular free wall were compared with those obtained in control animals.

Criteria were as follows: Animals in Group II had no regional ischemia; tissue lactate values in all three transmural regions were within the range obtained in control animals. Animals in Group III had restricted regional ischemia; elevated tissue lactate levels were limited to the inner sample and middle and outer lactate values were within the control range. Animals in Group IV had extensive ischemia; ischemia extended beyond the inner region to include the middle and in some cases the outer free wall region as well.

Completion of the first 12 successful experimental protocols produced a disproportionately large number of Group II animals, that is, dogs with normal tissue lactate levels after aortic valve rupture (n = 7 in Group II, 3 in Group III and 1 in Group IV). To increase the likelihood of producing ischemic changes in the subsequent experiments, an additional procedure was employed before the initial microsphere injection. This consisted of equal volumes of venous blood withdrawals and 6% dextran injections (35 ml aliquots). Initially, five exchanges were performed, followed by a 10 to 15 minute equilibration period and hematocrit measurement. Additional exchanges were performed until hematocrit had decreased to approximately 5% less than initial values. This procedure produced no observable changes in either systemic arterial or left ventricular pressures. The experimental protocol was then completed as previously outlined.

Statistical methods. Within each group, the transmural free wall and the transmural septal metabolite and blood flow data were tested by an analysis of variance. If a statistically significant value was found ($p < 0.05$), individual values were compared by the Student-Neuman-Keuls test. Paired comparisons of the tissue data were also made by a *t* test, between what we considered anatomically analogous regions of the left ventricular free wall and septum. The regions adjacent to the left ventricular cavity, that is, the inner left ventricular free wall and left septum, were compared; the middle and outer left ventricular free walls were compared with the middle and right septum, respectively. An unpaired *t* test was used to compare a particular region in an experimental group with the Group I (control) value (for example, an outer experimental value versus a Group I outer value of the same variable).

Results

Hemodynamics (Table 1). Aortic insufficiency dramatically reduced aortic diastolic pressure to 39 ± 3.8, 31 ± 2.4 and 32 ± 3.2 mm Hg in Groups II, III and IV, respectively, but no significant change occurred in aortic systolic pressure. There was a modest increase in left ventricular end-diastolic pressure in Group II and Group III animals after aortic insufficiency, but in Group IV the increase was much greater, reaching a mean value of 19 ± 2.8 mm Hg. Right ventricular pressures remained un-

Table 1. Hemodynamics in 25 Dogs

	Control Group I (n = 6)	Experimental Groups					
		Group II (n = 10)		Group III (n = 5)		Group IV (n = 4)	
		Control	AI	Control	AI	Control	AI
Pressures (mm Hg ± SEM)							
Aortic							
Systolic	134 ± 3.8	122 ± 4.8	123 ± 6.6	132 ± 5.2	121 ± 2.6	127 ± 8.0	106 ± 4.3
Diastolic	110 ± 5.3	99 ± 4.0	39 ± 3.8*	111 ± 5.2	31 ± 2.4*	109 ± 11	32 ± 3.2*
Left ventricular							
Systolic	132 ± 3.6	120 ± 5.1	121 ± 7.0	132 ± 6.3	123 ± 3.0	128 ± 8.3	105 ± 8.7
End-diastolic	6.0 ± 0.6	6.4 ± 0.4	10.4 ± 1.0*	5.2 ± 0.7	9.7 ± 0.4*	5.3 ± 0.6	19 ± 2.8*†
Right ventricular							
Systolic	29 ± 1.7	26 ± 0.7	27 ± 0.9	24 ± 1.0	26 ± 1.2	25 ± 1.0	35 ± 1.9*†
End-diastolic	2.9 ± 0.5	3.1 ± 0.3	3.3 ± 0.4	3.3 ± 0.4	3.7 ± 0.3	2.6 ± 0.1	5.6 ± 0.9*†
Heart rate (beats/min)	151 ± 10	152 ± 8.3	154 ± 7.6	143 ± 4.2	146 ± 6.0	146 ± 9.6	158 ± 7.5*

*$p < 0.05$ compared with control values of same group; †$p < 0.05$ compared with Group II and Group III values. AI = aortic insufficiency.

Table 2. Regional Blood Flow (ml/min per g) in 25 Dogs

	Free Wall					Septum					
	Outer	Middle	Inner	I/O	p Value*	Right	Middle	Left	L/R	p Value†	p Value‡
Group I (n = 6)											
Control	0.76 ± 0.05	0.86 ± 0.05	0.89 ± 0.04	1.18 ± 0.04	NS	0.72 ± 0.03	0.84 ± 0.04	0.91 ± 0.04	1.29 ± 0.04	L > R	NS
Group II (n = 10)											
Control	0.85 ± 0.07	0.87 ± 0.06	0.88 ± 0.05	1.12 ± 0.05	NS	0.79 ± 0.05	0.92 ± 0.06	0.96 ± 0.06	1.26 ± 0.03	NS	NS
AI	1.23 ± 0.07	1.34 ± 0.08	1.27 ± 0.05	1.07 ± 0.04	NS	1.16 ± 0.05	1.38 ± 0.06	1.38 ± 0.05	1.32 ± 0.05	R < MS,L	L > I
p Value§	<0.001	<0.001	<0.001			<0.01	<0.001	<0.001	<0.001		
Group III (n = 5)											
Control	0.93 ± 0.05	1.04 ± 0.07	1.04 ± 0.08	1.13 ± 0.07	NS	0.89 ± 0.03	1.12 ± 0.07	1.09 ± 0.08	1.25 ± 0.07	NS	NS
AI	1.31 ± 0.10	1.42 ± 0.11	0.97 ± 0.07	0.75 ± 0.02	O,M > I	1.23 ± 0.08	1.44 ± 0.13	1.02 ± 0.08	0.95 ± 0.03	MS > L,R	NS
p Value§	<0.01	<0.01	NS			<0.05	<0.01	NS			
Group IV (n = 4)											
Control	0.88 ± 0.07	0.97 ± 0.11	0.93 ± 0.10	1.06 ± 0.07	NS	0.89 ± 0.09	1.17 ± 0.10	1.04 ± 0.06	1.22 ± 0.07	NS	NS
AI	1.52 ± 0.14	1.03 ± 0.18	0.31 ± 0.06	0.20 ± 0.03	I < M,O	1.30 ± 0.16	0.87 ± 0.12	0.25 ± 0.05	0.18 ± 0.03	L < MS,R	I > L
p Value§	<0.05	NS	<0.025			NS	NS	<0.01			O > R

*Outer (O), middle (M) and inner (I) regions of the free wall compared with each other; †left (L), middle (MS) and right (R) regions of the septum compared with each other; ‡analogous regions of the free wall and septum compared (see Methods); §compared with control value of same group. AI = aortic insufficiency; I/O = inner flow ÷ outer flow; L/R = left flow ÷ right flow; NS = not significant. All values are mean ± SEM.

changed except in Group IV animals, where increases in both systolic and diastolic pressures occurred. Aortic insufficiency also tended to produce a slight increase in heart rate; however, only in Group IV was the increase statistically significant.

Regional Blood Flow and Tissue Metabolites

Group I animals. In the control group of animals, regional blood flow measurements showed no significant difference between the free wall and septum (Table 2). Creatine phosphate (Table 3) was lower in the inner than in the middle or outer regions of the left ventricular free wall; in the septum, creatine phosphate was lower in the left than in the middle or the right side of the septum. However, paired comparisons between analogous regions of the left ventricular free wall and septum, that is, outer versus right septum, middle versus middle septum and inner versus left septum, demonstrated no differences in creatine phosphate. Also, no differences were found either transmurally or between the free wall and septum for adenosine triphosphate (ATP) (Table 4) or lactate (Table 5).

Group II. Aortic insufficiency produced increases in regional myocardial blood flow to all transmural regions in both the free wall and the septum (Table 2). The animals in this group, having been selected for free wall lactate levels within the control range, also demonstrated control levels for the remaining metabolites in all regions (Tables 3 to 5).

Group III. After aortic insufficiency, blood flow to the outer and middle regions of the free wall and right and middle septal regions were elevated above control values (Table 2). However, blood flows to the inner free wall and left septal regions were not different from control values and they were not different from each other. Tissue ATP values were not different from those of control animals (Table 4). Creatine phosphate values were lower in all regions except in the outer free wall (Table 3). Paired comparisons between analogous regions of the left ventricular free wall and septum demonstrated lower values for creatine phosphate in all three septal regions. Tissue lactate levels were elevated only in the inner free wall and left septum and the increase in the left septum was greater than that in the inner free wall (Table 5). Thus, tissue creatine phosphate was lower and lactate was higher in the left septum compared with the inner free wall, although the blood flows to the inner free wall and left septum were essentially identical during aortic insufficiency.

Group IV. After aortic insufficiency, blood flow was maintained above control levels only in the outer free wall, whereas blood flows to the inner free wall and left septum were markedly lower than under control conditions (Table 2). Also, paired comparisons demonstrated blood flow to be lower within the right and left septal regions than within the outer and inner free wall regions. Tissue metabolites were markedly different within all regions when compared

Table 3. Tissue Creatine Phosphate in 25 Dogs (μmol/g wet weight)

	Free Wall				Septum				
	Outer	Middle	Inner	p Value*	Right	Middle	Left	p Value†	p Value‡
Group I (n = 6)	9.68 ±0.19	9.46 ±0.28	8.49 ±0.13	I < M,O	9.59 ±0.16	8.94 ±0.26	8.28 ±0.13	L < MS,R	NS
Group II (n = 10)	9.58 ±0.24	9.22 ±0.18	8.33 ±0.17	I < M,O	9.37 ±0.20	8.94 ±0.27	8.24 ±0.21	L < R	NS
p Value§	NS	NS	NS		NS	NS	NS		
Group III (n = 5)	8.89 ±0.52	8.32 ±0.46	6.71 ±0.48	I < O	7.87 ±0.50	6.87 ±0.49	5.24 ±0.23	L < MS,R	R < O MS < M L < I
p Value§	NS	<0.05	<0.01		<0.01	<0.01	<0.001		
Group IV (n = 4)	7.42 ±0.83	6.02 ±0.87	2.91 ±0.39	I < M < O	6.77 ±0.93	4.50 ±0.45	1.83 ±0.26	L < MS < R	R < O MS < M L < I
p Value§	<0.05	<0.01	<0.001		<0.01	<0.01	<0.001		

Symbols and abbreviations as in Table 2.

with values in control animals except for the outer and middle free wall ATP levels (Table 4). The remaining regions all demonstrated a lower ATP level than that found in control animals. Tissue creatine phosphate was reduced and tissue lactate was elevated in all regions (Tables 3 and 5). Comparisons of analogous regions showed creatine phosphate to be lower in all three septal regions compared with free wall values, but although all mean tissue lactates were higher in the septum than in the free wall only the inner free wall versus left septal values were significantly different. Also the middle and left septal ATP levels were lower than ATP levels in the middle and outer free walls.

Discussion

Blood flow and energy metabolism in septum versus left ventricular free wall. The major aim of this study was to determine whether a greater rate of energy metabolism occurred in the septum than in the left ventricular free wall in the overloaded heart. Previously we reported that this occurred in open chest dogs under normal left ventricular loading conditions. Our conclusions were based on the observation that when all coronary inflow was stopped by occluding the main left and right coronary arteries, creatine phosphate decline and lactate accumulation were more rapid within the septum than in the left ventricular free wall (8). With aortic insufficiency, flow remained as a variable and thus was a major factor influencing ischemic metabolic changes. We grouped the experimental animals according to ischemic severity because doing so also grouped them in relation to regional blood flow patterns. In Group IV animals, severe global ischemia resulted in more severely depressed creatine phosphate and greater lactate accumulation in the septum than in the left ventricular free wall but blood flow was also more severly depressed in the septum. Thus, the metabolite differences between the free wall and septum were, at least in part, flow mediated.

The reason why blood flow was lower in the septum than in the free wall of Group IV animals is not clear. In the normally functioning well perfused heart, pharmacologically induced maximal vasodilation produces equally high blood flows to the septum and free wall (12). It is known

Table 4. Tissue Adenosine Triphosphate in 25 Dogs (μmol/g wet weight)

	Free Wall				Septum				
	Outer	Middle	Inner	p Value*	Right	Middle	Left	p Value†	p Value‡
Group I (n = 6)	5.14 ±0.22	5.10 ±0.14	5.12 ±0.17	NS	5.15 ±0.15	5.26 ±0.10	5.16 ±0.08	NS	NS
Group II (n = 10)	5.03 ±0.11	5.55 ±0.14	5.42 ±0.13	NS	5.58 ±0.11	5.55 ±0.15	5.30 ±0.12	NS	NS
p Values§	NS	NS	NS		NS	NS	NS		
Group III (n = 5)	5.14 ±0.10	5.37 ±0.13	4.99 ±0.08	NS	5.15 ±0.04	5.33 ±0.06	5.29 ±0.19	NS	NS
p Value§	NS	NS	NS		NS	NS	NS		
Group IV (n = 4)	5.18 ±0.21	5.26 ±0.14	4.36 ±0.14	I < M,O	4.69 ±0.08	4.55 ±0.23	3.41 ±0.28	L < MS,R	MS < M L < I
p Value§	NS	NS	<0.025		<0.05	<0.01	<0.001		

Symbols and abbreviations as in Table 2.

Table 5. Tissue Lactate in 25 Dogs (μmol/g wet weight)

	Free Wall				Septum				
	Outer	Middle	Inner	p Value*	Right	Middle	Left	p Value†	p Value‡
Group I (n = 6)	0.242 ±0.024	0.249 ±0.021	0.242 ±0.017	NS	0.279 ±0.018	0.322 ±0.043	0.270 ±0.021	NS	NS
Group II (n = 10)	0.307 ±0.026	0.297 ±0.024	0.287 ±0.027	NS	0.309 ±0.030	0.320 ±0.030	0.337 ±0.033	NS	NS
p Value§	NS	NS	NS		NS	NS	NS		
Group III (n = 5)	0.324 ±0.055	0.298 ±0.026	0.826 ±0.086	I > M,O	0.410 ±0.031	0.416 ±0.055	1.35 ±0.168	L > MS,R	L > I
p Value§	NS	NS	<0.001		NS	NS	<0.001		
Group IV (n = 4)	0.642 ±0.237	2.11 ±0.727	6.14 0.901	I > M,O	1.44 ±0.818	2.83 ±0.949	8.18 ±1.38	L > MS,R	L > I
p Value§	NS	<0.05	<0.001		<0.05	<0.01	<0.001		

Symbols and abbreviations as in Table 2.

(13) that in global ischemia a rising ventricular diastolic pressure reduces coronary blood flow further, particularly in the subendocardial region. In Group IV animals diastolic pressure was rising in both ventricles and, because the septum has two endocardial surfaces, a greater effect of ventricular diastolic pressure on coronary blood may occur in the septum than in the free wall.

In the Group III animals, ischemia was restricted to the regions most susceptible to ischemia, that is, to the inner left ventricular region and the left side of the septum. Within these two regions blood flow was equal, but creatine phosphate depletion and lactate accumulation were greater in the septum. Equal blood flow but more pronounced ischemic metabolite changes indicate a greater rate of energy utilization. Thus, comparing the inner left ventricular region with the left septum, we conclude that energy utilization and fiber tension development in the septum were greater than in the free wall. Whether this applies to a comparison of the entire free wall and septum is not clear, but some evidence does point to this possibility. In the Group III animals, even though tissue lactate levels were not different from control values in the middle and right septal regions, creatine phosphate levels were depressed and lower than in the middle and outer free wall regions. If creatine phosphate depression can be considered an imminent prelude to ischemia, the overall energy utilization in the septum may indeed exceed that in the left ventricular free wall under these experimental conditions.

Validation of procedures. The preceding conclusion is based on the assumption that these specific metabolite changes are proportionately related to the oxygen debt and that the metabolic responses of the left ventricular free wall and septum are the same. If the levels or storage sites of substrates are factors influencing the reaction rates or if overall flux rates differ in the fibers of the septum and free wall, our conclusions are inappropriate. For the free wall Griggs (14) demonstrated that the metabolite changes indicative of ischemia were related to the blood flow debt. We have previously shown (7,8), in both the free wall and the septum, that in the early stages of ischemia the rate of change of creatine phosphate and lactate is a function of fiber activity. This indicates that nonspecific factors are not responsible for the septal-free wall metabolite differences found in this study.

Clinical relevance. The important feature of this study is that it provides additional data consistent with the hypothesis that disproportionate septal thickening may occur as a physiologic adaptive process as well as a pathologic state. Increased stress and the stimulus for hypertrophy should include and be proportional to the increased metabolic demands of the myocardium. For disproportionate septal hypertrophy to develop one would expect a greater rate of energy metabolism in the septum. We have demonstrated that this appears to be true under the present experimental conditions but in a qualitative not a quantitative manner.

The presence of asymmetric septal hypertrophy appears to be more prominent in individuals with a pressure rather than a volume overload as utilized in this study. This is perhaps because for asymmetric septal hypertrophy to be present the septum must be 30% thicker than the left ventricular free wall. In addition, it is under a pressure overload that wall thickening is most prominent and easily measured. In most instances clinical situations that reveal significant left ventricular wall thickening also include some individuals with asymmetric septal hypertrophy. Examination of persons in the Framingham study (15) with left ventricular hypertrophy demonstrated a frequency of 10% for asymmetric septal hypertrophy. More recently, Abi-Samra et al. (16) reviewed the echocardiograms of a group of hypertensive patients at the Cleveland Clinic who had no evidence of other hemodynamically significant diseases and found the incidence of asymmetric septal hypertrophy to approximately equal that of concentric left ventricular hypertrophy. Previous studies of hypertensive individuals report both a

greater (5) and a less frequent (17) occurrence of asymmetric septal hypertrophy.

Regression of asymmetric septal hypertrophy has also been found in a few isolated cases. Hess et al. (4) demonstrated that with combined aortic stenosis and asymmetric septal hypertrophy, surgical correction of the stenosis produced a return of the septal-free wall ratio to normal when regression of the hypertrophy was observed. Oakley and Oakley (18) reported a similar result in an Olympic athlete after total cessation of training. More subtle septal-free wall differences with less dramatic hypertrophy have been reported in athletes from various sports (3), but in other studies (19) no septal-free wall differences were found. It is also of interest that as part of the aging process left ventricular wall thickness increases (20,21). In the one aging study (22) that compared the thickness increases of the free wall with that of the septum, the investigators reported a greater increase in the thickness of the septum.

Mechanism responsible for asymmetric septal hypertrophy. Although our data indicate a greater systolic tension development by the septal fibers, the basis of this phenomenon remains obscure. One hypothesis (23), considers it tied to a difference in the radius of curvature of the free wall and septum. This is the basis of the model of Heng et al. (6), which predicts only a slightly greater stress in the septum when ventricular load is normal but an accentuated difference when left ventricular load is increased above normal. This approach is very appealing but may be incomplete. Not considered is that septal stress may be influenced through its attachments to the left ventricular and right ventricular free walls (24) as well as its geometric shape. Unfortunately, such complex relations currently cannot be analyzed mathematically.

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