The Response of Left Ventricular Function and Size to Atrial Pacing, Volume Loading and Afterload Stress in Patients with Coronary Artery Disease

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SUMMARY To assess the response of left ventricular function and size to volume loading, atrial pacing and afterload stress, we studied 35 patients using equilibrium radionuclide angiography. All subjects had coronary heart disease, as evidenced by contrast angiography or previous myocardial infarction.

Fifteen patients received 500 ml of normal saline given as two rapid 250-ml infusions. Ejection fraction increased after the second infusion (0.49 to 0.55, p < 0.05), as did end-diastolic volume (p < 0.05), but there was little change in end-systolic volume or the ratio of systolic blood pressure to end-systolic volume. Eight patients were subjected to phenylephrine afterload stress, with a mean elevation of systolic blood pressure of 44.6 ± 12 mm Hg (p < 0.01 vs rest). Ejection fraction declined (0.52 ± 0.1 to 0.41 ± 0.13, p < 0.01), end-diastolic and end-systolic volumes increased (p at least < 0.01), and the ratio of systolic pressure to end-systolic volume decreased (2.31 ± 1.64 to 1.46 ± 0.67 mm Hg/ml, p < 0.05). Twelve patients underwent atrial pacing (from 80–130 beats/min), resulting in a decrease in ejection fraction, a decrease in end-diastolic and end-systolic volumes (p < 0.05) and an increase in the pressure-volume ratio (2.00 ± 0.30 to 2.45 ± 1.02 mm Hg/ml, p < 0.05).

We conclude that alterations in loading conditions affect indexes of left ventricular performance. The ejection fraction is reduced by elevations in blood pressure and increased by volume infusion, but appeared reduced by atrial pacing, probably due to the offsetting changes in heart rate and preload. The pressure-volume ratio did not change with volume loading, decreased with afterload stress and increased with atrial pacing. Thus, equilibrium radionuclide angiography can be used to assess noninvasively the effects of physiologic and pharmacologic interventions on left ventricular performance in patients with coronary heart disease.

MANIPULATIONS of heart rate, \(^4-^6\) ventricular volume\(^7-^9\) and systemic arterial pressure\(^2-^10-^12\) have a direct effect on measurements of a variety of indexes of left ventricular performance. Recent interest in the proposed load-independent relationship of end-systolic pressure and end-systolic volume\(^13-^14\) has led to use of the simple ratio of peak systolic blood pressure or left ventricular pressure to end-systolic volume as a measure of left ventricular function. To characterize the ventricular response to several well-defined physiologic and pharmacologic interventions, including saline loading, elevations in systemic blood pressure produced by phenylephrine and alterations in cardiac performance during atrial pacing, we used radionuclide angiography to study 35 patients with coronary heart disease. In all subjects left ventricular ejection fraction, volume and the ratio of systolic blood pressure to end-systolic volume were analyzed by methods validated in our laboratory.\(^14-^18\) To our knowledge, this noninvasive approach has not been used in man; in particular, in subjects with coronary heart disease.

Methods

Volume Loading Study

Fifteen patients constituted the study population, including 14 men and one woman, mean age 54 ± 12 years. All subjects had suffered a myocardial infarction, defined by a typical prolonged history of chest pain in association with elevation of serum creatine kinase and evolutionary electrocardiographic changes. Four patients had experienced an anterior infarction, seven an inferior infarction and four a subendocardial infarction, as defined by their surface ECGs at the time of infarction, an average of 21 ± 9 months (mean ± sd) before this study. On clinical examination before the study, four patients had audible third heart sounds and 13 had fourth heart sounds, but none had mitral regurgitation, pulmonary rales or elevation of the jugular venous pulse. Five patients were receiving chronic oral digoxin therapy (mean digoxin level 1.2 ± 0.4 ng/ml), but none was taking any diuretic, chronic nitrate or \(\beta\)-blocking medication.

Each patient received 15–20 mCi of technetium-99m i.v. after in-vivo labeling of the patient’s red blood cells with stannous pyrophosphate. After adequate intravenous mixing, a portable, single-crystal gamma camera was placed over the supine patient’s thorax in the 45° left anterior oblique projection, with a small caudal tilt to maximize separation of the left ventricle from the left atrium. A modified V\(_5\) electrocardiographic lead was used to gate the scintigraphic data. Blood pressure was taken with the aid of the diaphragm of a standard stethoscope and a Tycos cuff.
adapted to a Baumanometer sphygmomanometer. After baseline scintigraphic data were obtained, 250 ml of normal saline were infused into the patient over 3–5 minutes. A second resting radionuclide study was performed after the first infusion. Then, an additional 250 ml of normal saline were infused, and a third resting scintigraphic study was performed. All resting studies were 3 minutes in duration.

**Atrial Pacing Study**

Twelve patients with chest pain and angiographically documented coronary artery disease were included in this study. Each patient had a temporary bipolar Medtronic transvenous pacemaker inserted through a femoral vein and placed against the lateral wall of the right atrium under fluoroscopic control. Thirty minutes after the completion of a standard cardiac catheterization, performed for evaluation of chest pain (right- and left-heart catheterization, including coronary angiography and contrast ventriculography), each patient underwent atrial pacing at heart rates of 80, 110 and 130 beats/min). Three patients developed chest pain, which was relieved by stopping atrial pacing and administering sublingual nitroglycerin. The radionuclide camera was positioned and data were acquired as in the volume loading study. Each pacing interval was 4 minutes, but radionuclide data were processed only from the last 3 minutes of each pacing stage. Blood pressure was again obtained by cuff sphygmomanometer.

This group included nine men and three women (mean age 48 ± 6 years). One patient had suffered an anterior myocardial infarction and was taking chronic oral digoxin. Two patients were taking furosemide and four were receiving chronic oral nitrate therapy, which was stopped 8 hours before the study. Two patients were taking oral propranolol (60 and 40 mg every 6 hours), which was not given the morning of the study. Eight patients had significant coronary arterial lesions (>70% intraluminal occlusions of a major coronary vessel) involving three vessels, three patients had two-vessel disease, and one patient had a single lesion of the left anterior descending coronary artery. The patient who had had an infarction had a large akinetic segment, but the other patients had predominantly normal or hypokinetic segmental contraction.

**Afterload Stress Study**

Eight patients with coronary artery disease (four with a previous myocardial infarction and four with angiographically proved coronary artery disease) underwent afterload stress. After resting ejection fractions and volume data were obtained, atropine 1–1.5 mg) was given to inhibit the reflex bradycardia after pharmacologic elevation of blood pressure. At this point, phenylephrine (10 mg diluted in 250 ml of normal saline solution) was infused to raise the blood pressure by 15–30 mm Hg. Ejection fraction and volume data were then obtained and blood pressure was measured. The systolic blood pressure was increased by another 15–20 mm Hg and a second study was performed. In six subjects whose systolic blood pressure was less than 150 mm Hg after the second stage, a third set of measurements was performed after the blood pressure was elevated by an additional 15–20 mm Hg.

No patient developed chest pain or shortness of breath during the study. No arrhythmias or new ST changes occurred. (A modified V, lead was monitored.) Two patients were taking oral digoxin and furosemide and no patient had taken propranolol or long-acting nitrates within 72 hours of the study.

Again, the radionuclide, camera positioning and data acquisition were the same as used in the pacing and volume infusion studies. Blood pressures were obtained with a Tyco cuff adapted to a Baumanometer sphygmomanometer and a standard stethoscope with the diaphragm placed over the right brachial artery.

**Radionuclide Data Processing**

Data recording and processing were performed using a general nuclear medicine computer (Medical Data Systems, PAD). Several hundred heart beats were integrated during the acquisition period to construct multiple, identically phased composite images. The RR interval from each cardiac cycle was divided into 28 equal time frames. Usually, 2000–5000 counts could be accumulated within the left ventricular region of interest at end-diastole (counts corrected for background activity).

A left ventricular time-activity curve was generated from a rectangular region of interest placed around the ventricle at end-diastole. An edge-detection algorithm using second-derivative count rate change as well as simple count rate threshold outlines the ventricle in each frame during the cardiac cycle. An automatically assigned background region of interest was located outside the lower left quadrant of the left ventricle in the end-systolic frame to correct for non-cardiac activity. A composite left ventricular volume curve was then produced. Ejection fraction was calculated as:

\[
EF = \frac{EDC - ESC}{EDC}
\]

where EDC = background-corrected end-diastolic counts and ESC = background-corrected end-systolic counts. In a recent study from this laboratory involving 76 patients who underwent both radionuclide and contrast ventriculography, this method had an excellent correlation (r = 0.93), and interobserver, intraobserver and serial variability were all less than 0.04 ejection fraction units.18

Left ventricular end-systolic and end-diastolic volumes were calculated using a previously described method.15, 16, 18 Briefly, the counts at the end-diastolic and end-systolic data point were corrected for frame time, the total number of processed heart beats and
blood radioactivity obtained from a 4-ml blood sample drawn at the midpoint of each study. Whole blood was used to calculate the radioactivity “concentration,” rather than plasma as previously described, to enable the use of red-cell-labeled radionuclides. This modification of our original technique also provided arbitrary volume units that correlated well with contrast ventriculography ($r > 0.91$). Absolute volumes were obtained from the least-squares fit linear regression relationship between the radionuclide volume units and contrast volumes.

The serial variability (hour by hour) of ventricular volumes in eight patients studied four times over 4 hours was ±7.5% using these techniques. Ejection fraction variability on an hourly basis was 0.03 ± 0.02 ejection fraction units. Intraobserver variability, interobserver variability, serial variability in counts/cycles has been reported on a number of occasions and found to be less than 4%,15-19

To obtain a noninvasive representation of the ratio of the peak systolic pressure to end-systolic volume, systolic blood pressure and radionuclide end-systolic volume were used. We have shown that this noninvasive ratio correlates well ($r > 0.92$) with the ratio of peak systolic left ventricular pressure to end-systolic volume determined angiographically14 and that the variability of this ratio is less than 5%. In that study, as well as in the present study, patients with systemic hypertension or peripheral vascular disease (as evidenced by clinical examination of the peripheral pulses) were excluded.

Statistical Analysis
All serial data points were evaluated by performing a repeated-measures analysis of variance20 or, when appropriate, a $t$ test for unpaired data. Linear correlations were performed using a least-squares linear fit. Data are mean ± SD unless otherwise stated.

Results

Volume Infusion Study
No patient developed additional clinical signs or symptoms of congestive heart failure.

Vital Signs
The mean heart rate in this study group declined from 77.3 ± 13 to 72.3 ± 12 beats/min ($p < 0.05$) after the complete infusion of 500 ml of saline. The heart rate response in each patient varied widely, from an increase in 10 beats/min to a decline of 11 beats/min. The systolic blood pressure increased slightly (118.3 ± 6.3 to 123 ± 7.1 mm Hg, $p < 0.05$), although the diastolic pressure did not change significantly (74.6 ± 5.3 to 73.2 ± 5 mm Hg). The intermediate determinations for heart and blood pressure (after 250 ml of saline) were not significantly different from baseline.

Hemodynamic Results
The resting left ventricular ejection fraction was 0.49 ± 0.12 at rest, 0.50 ± 0.12 after 250 ml of saline were infused ($p = \text{NS}$) and increased to 0.55 ± 0.12 after a total of 500 ml of saline was infused (an increase of 12%, $p < 0.05$ vs baseline). The ratio of systolic blood pressure to end-systolic volume increased slightly but not significantly (1.73 ± 0.95 mm Hg/ml at rest, 1.76 ± 0.86 mm Hg/ml after 250 ml of saline and 1.80 ± 0.94 mm Hg/ml after 500 ml of saline were infused) (fig. 1).

Figure 2 illustrates the changes in left ventricular size. End-diastolic volume increased from 150 ± 47 ml at rest to 165 ± 52 ml (10% increase) after the 500-ml infusion ($p < 0.05$). The intermediate end-diastolic volume was not significantly different from the resting value. The end-systolic volume did not change after the saline infusion (78 ± 41 ml at rest to 77 ± 39 ml, and finally, 77 ± 40 ml). Thus, stroke volume increased, from 72 ± 26 ml to 88 ± 33 ml ($p < 0.05$), as did cardiac output, from 5.56 ± 1.1 to 6.36 ± 1.4 l/min ($p < 0.05$).

Atrial Pacing Study
All 12 subjects underwent right atrial pacing at sequential heart rates of 80, 110 and 130 beats/min. Three subjects developed angina pectoris during the peak pacing rate in association with ≥ 1 mm ST-
segment depression on a modified V₆ electrocardiographic lead. The other nine patients had neither pain nor electrocardiographic changes. Systolic blood pressure did not change in these patients, but in the three subjects who developed angina, systolic pressure declined by a mean of 10 mm Hg compared with resting levels. The ejection fraction declined from 0.58 ± 0.04 at a paced rate of 80 beats/min to 0.55 ± 0.09 at 110 beats/min (p = NS) and to 0.52 ± 0.04 at 130 beats/min (p < 0.05 vs baseline) (fig. 3). Patients who developed angina showed a decline in ejection fraction, but this response did not clearly separate them from the patients who did not develop angina, four of whom also had decreased ejection fractions. Interestingly, all pain-free patients increased their pressure-volume ratio, while those with pain showed a marked decline (fig. 3). The volume response is shown in figure 4. End-diastolic volume declined from 176 ± 11 ml at 80 beats/min to 136 ± 9 ml at 110 beats/min (p < 0.05) to 119 ± 11 ml at 130 beats/min (p < 0.01 vs baseline). Most subjects showed a continual decline in end-diastolic volume at each paced rate. When angina resulted, end-diastolic volume actually increased. Similar results were seen for end-systolic volume in both anginal and nonanginal patients. Stroke volume decreased by 39% (p < 0.01), but the response was similar in anginal and nonanginal patients. Cardiac output was unchanged at each paced rate.

Figure 2. With saline infusion, end-diastolic volume and stroke volume increased significantly, with little change in end-systolic volume.

Figure 3. The ejection fraction and pressure-volume ratio response are shown at atrial pacing rates of 80, 110 and 130 beats/min. Note the increase in the pressure-volume ratio, except when angina intervened. The mean ejection fraction gradually declined, and angina did not clearly alter the response.

Phenylephrine Infusion Study

All subjects had an increase in systolic blood pressure of at least 30 mm Hg (mean increase of 44.6 ± 11.9 mm Hg, range 33–70 mm Hg). Heart rate did not decrease more than 4 beats/min (after 1.5–2.0 mg of i.v. atropine) after the infusion was initiated. No patient developed clinical evidence of pulmonary congestion and none complained of chest pain. No subject developed arrhythmias, ST-segment depression or any other physical complaint.

Ejection fraction (baseline obtained after atropine infusion) decreased from a mean of 0.52 ± 0.18 to 0.41 ± 0.13 (p < 0.01) at the peak blood pressure. The pressure-volume ratio also declined from 2.31 ± 1.64 to 1.46 ± 0.67 mm Hg/ml (p < 0.05; fig. 5). Simultaneously, there were increases in end-diastolic volume (mean increase 64 ± 36 ml, from 155 ± 53 to 218 ± 70 ml, p < 0.001), end-systolic volume (mean increase 49 ± 21 ml, from 79 ± 46 to 128 ± 56 ml, p < 0.005), and stroke volume (14 ± 23 ml, from 76 ± 26 to 90 ± 27 ml, p < 0.05). The relationship between
systolic blood pressure and end-systemic volume was linear, with all r values ≥ 0.91 (fig. 6).

**Discussion**

The influence of sequentially induced, acute alterations in preload, afterload and heart rate on noninvasive measurements of left ventricular performance have received little systematic study in patients with coronary heart disease, partly because of difficulties in the serial noninvasive evaluation of patients with asynchronous regional ventricular contraction. Because recent advances in radionuclide imaging have facilitated the evaluation of left ventricular function and size without use of geometric assumptions regarding cardiac chamber shape,16 these variables can be serially evaluated in patients with coronary heart disease. In this study, we evaluated the response of left ventricular ejection fraction and volumes to atrial pacing, volume infusion and afterload stress. Similarly, because of the recent interest in the slope and simple ratio of the end-systolic pressure-volume relationship,13, 14, 21-25 we also investigated the response of systolic blood pressure/end-systolic volume.

In animal studies, volume infusion produces increases in heart rate (depending on the rapidity of the infusion) along with small increases in ejection phase and isovolumic phase indexes of left ventricular performance.9-27 In our patients, heart rate declined slightly but not significantly (although several patients showed increases of up to 10 beats/min) with increases in end-diastolic volume (10%), stroke volume (22%) and cardiac output (13%). A “Bainbridge” response was not seen in these subjects, probably because of the modest amount of volume infused. When more fluid has been administered, heart rate increases have been reported, although usually in subjects under general anesthesia.28 The ejection fraction increased significantly (12%), while the ratio of systolic blood pressure to end-systolic volume showed an increase that was not statistically significant. The response of end-diastolic volume and end-systolic volume was similar to the animal data reported by Karliner et al.28

Recent work by Ricci et al.29 has shown that in conscious man, increases in heart rate represent a positive inotropic stimulus, independent of other factors influencing ventricular performance, such as autonomic influences. They found that the velocity of circumferential shortening increased linearly with the increase in paced heart rate. Similar data were found in normal subjects by DeMaria et al.1 In the latter study, however, fractional shortening declined, while velocity indexes increased. In the present study, atrial pacing induced a reduction in end-diastolic, end-systolic and
stroke volumes, with little change in cardiac output or systolic pressure. The ratio of systolic blood pressure to end-systolic volume increased by 23%, but the ejection fraction declined by 10%. Only three patients developed angina (all in association with ST depression), and in all three of them, the ratio of systolic blood pressure to end-systolic volume declined during pain.

Our data suggest that the change in ejection fraction alone during atrial pacing does not reflect changes in contractile state, similar to conclusions reached by DeMaria et al. However, the changes in the pressure-volume ratio response appears to correspond to findings in both clinical and animal studies. In the latter study, Mahler et al. demonstrated increases in dP/dt with atrial pacing, which was not altered by β blockade. As heart rate increased, so did dP/dt.

The responses of left ventricular function and size to afterload stress have been analyzed in a series of clinical studies involving patients with symmetric ventricular contraction and normal subjects. The linearity of the relationship of systolic blood pressure and end-systolic volume has been examined in only one study, and the constancy of the pressure-volume ratio has never been studied. Additionally, patients with coronary heart disease were excluded because of the inherent limitations of M-mode echocardiography in evaluating these patients. We have previously shown the excellent correlation between the ratio of systolic blood pressure to end-systolic volume determined by radionuclide techniques and the ratio of peak left ventricular systolic pressure to end-systolic volume determined by contrast angiography. Using this noninvasive technique in the present study and altering systolic pressure by infusing phenylephrine, we found that the relationship between end-systolic volume and systolic blood pressure is linear in patients with coronary heart disease. During phenylephrine infusion, end-diastolic volume, end-systolic volume and often stroke volume increase, but the ejection fraction and the ratio of systolic pressure to end-systolic volume declined in equal proportions.

We conclude that the ratio of systolic pressure to end-systolic volume is a useful index of left ventricular function that appears relatively independent of preload but is predictably dependent on afterload. We have also presented a model for the analysis of the pressure-volume relationship that can be easily performed noninvasively using systolic blood pressure and equilibrium radionuclide angiography. Similar to the animal data presented by others, this relationship is linear in patients with coronary heart disease. Finally, equilibrium radionuclide angiography can be used to evaluate a variety of pharmacologic and physiologic interventions in patients with coronary heart disease.

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The response of left ventricular function and size to atrial pacing, volume loading and afterload stress in patients with coronary artery disease.
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_Circulation_. 1981;63:864-870
doi: 10.1161/01.CIR.63.4.864
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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