

IJC 00279

Assessment of dysfunction in aortic regurgitation by stress-shortening relationship

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(Received 9 April 1984; revision accepted 11 February 1985)

Weiss RJ, Buda AJ, LeMire MS, Pitt B. Assessment of dysfunction in aortic regurgitation by stress-shortening relationship. *Int J Cardiol* 1985;8:475–486.

Some patients with aortic regurgitation develop irreversible left ventricular dysfunction. The purpose of this study was to noninvasively examine left ventricular function in patients with aortic regurgitation by determining the end-systolic stress-shortening relationship using M-mode echocardiography. Ten normal volunteers and 10 patients with chronic, isolated aortic regurgitation were studied at rest and following load and inotropic alteration by cold pressor testing. The baseline ejection phase indices of ejection fraction and percent fractional shortening did not distinguish between normals and patients with aortic regurgitation ($74.6\% \pm 2.8\%$ versus $67.0\% \pm 4.2\%$, $P = \text{NS}$ and $37.6\% \pm 2.4\%$ versus $31.6\% \pm 2.7\%$, $P = \text{NS}$, respectively.) End-systolic stress was significantly greater in patients with aortic regurgitation both at rest (107.8 ± 11.6 dynes/cm² $\times 10^{-3}$ versus 68.4 ± 4.8 dynes/cm² $\times 10^{-3}$, $P < 0.005$) and after cold pressor intervention (122.8 ± 13.0 dynes/cm² $\times 10^{-3}$ versus 80.1 ± 4.0 dynes/cm² $\times 10^{-3}$, $P < 0.005$). Normals showed increased fractional shortening in the presence of increasing end-systolic stress. Patients with aortic regurgitation showed decreased fractional shortening during increased stress. This response suggests either left ventricular dysfunction with increasing stress or decreased myocardial contractile reserve after cold pressor inotropic stimulation. End-systolic stress-percent fractional shortening relationship may be a sensitive indicator of early left ventricular dysfunction in patients with aortic regurgitation.

(Key words: aortic regurgitation; echocardiography; myocardial function)

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Introduction

There has been considerable controversy concerning the assessment of the degree of left ventricular dysfunction in patients with chronic aortic regurgitation. Physical examination [1–3], cardiomegaly on chest X-ray [4], left ventricular dimensions as measured by echocardiography [5,6], and abnormal ejection phase indices such as ejection fraction and percent fractional shortening as measured by catheterization [7–9] radionuclide ventriculography [10,11] or echocardiography [5,6,12] have all been used to describe both clinically apparent and inapparent left ventricular dysfunction. Recently, Suga, Sagawa, and co-workers have suggested that the preload-insensitive relationship of end-systolic stress and end-systolic volume–dimension relation may better define myocardial contractility [13,14] particularly in volume overload states [15]. The purpose of this study was to attempt to define left ventricular function noninvasively by M-mode echocardiography in patients with chronic aortic regurgitation as compared to a group of normal volunteers. Ejection phase indices and the end-systolic stress-percent fractional shortening relationship were determined. Cold pressor testing which has been shown to both increase afterload and have a direct inotropic effect [16,17] was used to noninvasively alter this relationship.

Materials and Methods

Patient Population

Ten normal volunteers were compared to 10 consecutive patients with chronic aortic regurgitation. Eight of the patients were asymptomatic with 2 (patients 4 and 8) having New York Heart Association Class III congestive heart failure. All patients had idiopathic aortic regurgitation except for patient 8 who had Marfan's syndrome with chronic aortic dissection and patient 3 who had a history of rheumatic fever. Four patients underwent cardiac catheterization (patients 1, 2, 5, 10). None of the patients had other associated valvular lesions or coronary artery disease. Patients 5 and 6 had rest and exercise radionuclide ventriculograms with a normal increase in ejection fraction, while patients 2 and 8 had a fall in ejection with exercise [11]. Only patients 4 and 8 had echocardiographic end-systolic diameters > 55 mm, a suggested sign of myocardial dysfunction [5]. Thus, based on symptoms, angiocardiology, radionuclide ejection fraction response to exercise, and echocardiographic end-systolic diameter, only 4 of the 10 patients were predicted to have decreased myocardial function.

Echocardiographic Examination

All subjects underwent M-mode echocardiographic examination with a 2.25 MHz transducer in the left lateral position. Blood pressures were obtained by sphygmomanometer with the stethoscope diaphragm over the brachial artery. All blood pressures obtained in each study were done by the same investigator. Posterior

wall thickness (PWT_s) was measured by the leading edge to leading edge method. Left ventricular internal dimension in diastole ($LVID_d$) was measured from the interventricular septal endocardium to the posterior wall endocardium at the peak of the electrocardiogram R wave. Left ventricular internal diameter in systole ($LVID_s$) was measured from the septal endocardium to the posterior wall endocardium at the smallest ventricular dimension. The percent fractional shortening ($\% \Delta D$) was calculated from the equation: $LVID_d - LVID_s / LVID_d \times 100\% = \% \Delta D$. The ejection fraction (EF) was calculated using the cube method [18]: $(LVID_d)^3 - (LVID_s)^3 / (LVID_d)^3 \times 100\% = EF$. Systolic blood pressure (SBP) measured in mm Hg was converted to dynes/cm² by multiplying by a factor of 1332 dynes/cm² mm Hg. The end-systolic meridional stress (ESS) was calculated by the equation: $ESS = 0.334 \times SBP \times LVID_s / PWT_s \times (1 + PWT_s / LVID_s)$ [19,20].

Cold Pressor

Cold pressor testing was performed by placing the subject's hand in ice water for 1 min with blood pressures obtained at baseline, 30 sec, and 60 sec. Continuous M-mode echocardiograms were obtained. Blood pressure, end-systolic stress, ejection fraction, and percent fractional shortening at baseline and after one minute of immersion in the cold water were compared.

Statistical Analysis

Student's *t*-test was used to analyze the data. A statistically significant difference was defined as $P < 0.05$.

Results

Normals

Normal subjects (Table 1) had an ejection fraction of $74.6\% \pm 2.8\%$ (mean \pm standard error of mean) at rest which changed to $80.9\% \pm 1.4\%$ after 1 min of cold pressor testing ($P < 0.05$). Resting percent fractional shortening was $37.6\% \pm 2.4\%$ compared to $43.0\% \pm 1.5\%$ after cold pressor ($P < 0.025$). End-systolic stress was 68.4 ± 4.8 dynes/cm² $\times 10^{-3}$ at baseline and 80.1 ± 4.0 dynes/cm² $\times 10^{-3}$ after intervention ($P < 0.05$). The average increase in blood pressure was 12.6 ± 1.3 mm Hg (121 ± 3 mm Hg to 134 ± 4 mm Hg, $P < 0.025$). The heart rate increased slightly from 68 ± 3 to 76 ± 4 .

Aortic Regurgitation

Patients with chronic aortic regurgitation (Table 2) had an ejection fraction of $67.0\% \pm 4.2\%$ at rest which was not significantly different from the control population. The ejection fraction after cold changed to only $65.4\% \pm 3.9\%$ which was not significantly different from baseline. This lack of an increase in ejection fraction

TABLE 1
Normal subjects before and after cold pressor testing.

Subject	Before cold pressor testing					After cold pressor testing						
	LVID _s (cm)	PWT _s (cm)	BP _s (mm Hg)	ESS (dynes/cm ² × 10 ⁻³)	%ΔD	EF%	LVID _s (cm)	PWT _s (cm)	BP _s (mm Hg)	ESS (dynes/cm ² × 10 ⁻³)	%ΔD	EF%
1	3.0	1.4	138	65.9	26.8	60.8	2.7	1.3	160	75.0	37.2	75.2
2	2.7	1.4	132	56.7	44.9	83.2	2.5	1.0	146	87.1	49.0	86.7
3	2.4	1.3	106	43.6	46.7	84.8	2.7	1.0	120	79.0	47.0	83.3
4	2.8	1.0	118	81.2	44.0	82.2	2.6	1.0	130	81.1	46.9	85.1
5	3.7	1.3	123	86.6	27.4	61.8	3.5	1.5	138	75.2	36.4	74.2
6	2.9	1.2	118	67.5	35.6	73.2	2.6	1.0	128	80.6	42.2	80.7
7	2.8	1.2	117	63.8	33.3	70.4	2.5	0.9	126	86.0	44.4	82.9
8	2.4	1.1	132	66.3	46.7	84.8	2.3	0.9	140	86.0	46.5	84.7
9	2.3	1.0	118	63.4	35.3	71.6	1.8	0.7	128	79.1	43.8	82.2
10	2.9	0.9	108	89.4	35.6	73.2	3.0	1.2	120	71.6	36.2	74.0
Mean	2.8	1.2	121	68.4	37.6	74.6	2.6	1.1	133	80.1	43.0	80.9
±SEM	±0.1	±0.1	±3	±4.8	±2.4	±2.8	±0.1	±0.1	±1	±4.0	±1.5	±4.0

BP_s = systolic blood pressure; %ΔD = percent fractional shortening; EF% = ejection fraction; ESS = end-systolic stress; LVID_s = left ventricular internal dimension at end-systole; PWT_s = posterior wall thickness at end-systole; SEM = standard error of the mean.

TABLE 2
Patients with chronic aortic insufficiency before and after cold pressor testing.

Subject	Before cold pressor testing					After cold pressor testing						
	LVID _s (cm)	PWT _s (cm)	BP _s (mm Hg)	ESS (dynes/cm ² × 10 ⁻³)	%ΔD	EF%	LVID _s (cm)	PWT _s (cm)	BP _s (mm Hg)	ESS (dynes/cm ² × 10 ⁻³)	%ΔD	EF%
1	3.0	1.7	180	66.3	40.0	78.4	3.1	1.7	190	74.6	38.0	76.2
2	4.0	1.6	145	86.5	32.0	68.8	3.7	1.6	180	97.2	38.0	76.5
3	3.5	1.4	138	82.3	30.0	65.7	3.6	1.3	188	127.9	28.0	62.7
4	5.8	1.5	150	153.7	25.6	58.9	5.8	1.5	160	164.0	25.6	58.9
5	3.2	1.4	155	82.2	41.8	80.3	3.2	1.3	150	88.1	39.6	80.3
6	2.9	1.2	190	108.8	40.4	82.7	3.2	1.3	196	115.1	38.5	76.7
7	5.1	1.2	121	138.5	17.7	44.3	5.1	1.0	128	181.7	20.3	49.4
8	6.2	1.2	124	179.8	30.3	66.2	6.4	1.2	124	184.1	28.1	62.8
9	4.4	1.5	130	95.1	20.0	48.8	5.2	1.6	130	107.7	17.5	43.8
10	3.6	1.1	100	83.4	37.9	76.1	3.6	1.1	104	87.5	30.8	66.8
Mean	4.2	1.4	143	107.7	31.6	67.0	4.3	1.4	155	122.8	30.4	65.4
±SEM	±0.4	±0.1	±9	±11.6	±2.7	±8.6	±0.4	±0.1	±10	±13.0	±2.5	±3.9

BP_s = systolic blood pressure; %ΔD = percent fractional shortening; EF% = ejection fraction; ESS = end-systolic stress; LVID_s = left ventricular internal dimension at end-systole; PWT_s = posterior wall thickness at end-systole; SEM = standard error of the mean.

after cold-induced inotropic stimulation and an increase in afterload was markedly different from the increase in ejection fraction noted in the control group ($P < 0.005$). The percent fractional shortening at baseline in the group with aortic regurgitation was $31.6\% \pm 2.7\%$ which was also not significantly different from controls. After cold pressor, the percent fractional shortening stayed basically constant at $30.4\% \pm 2.5\%$ which was highly significantly different from the response of the normal control population ($P < 0.0005$). The end-systolic stress at rest in the patient group was 107.8 ± 11.6 dynes/cm² $\times 10^{-3}$ which was significantly different from the resting control value ($P < 0.005$). With cold pressor testing, the end-systolic stress rose to 122.8 ± 13.0 dynes/cm² $\times 10^{-3}$ which was also significantly different from the control group's post-cold pressor value ($P < 0.005$). The only resting difference between the patient group and normal controls was in the end-systolic stress (68.4 ± 4.8 dynes/cm² $\times 10^{-3}$ vs. 107.7 ± 11.6 dynes/cm² $\times 10^{-3}$, $P < 0.005$) and left ventricular thickness to diameter ratio (0.43 ± 0.02 vs. 0.36 ± 0.03 , $P < 0.05$). The average rise in blood pressure was 12 ± 6 mm Hg (141 ± 8 mm Hg to 151 ± 10 mm Hg, $P = \text{NS}$) which was not different from the response of the normal control group. Heart rate increased slightly from 72 ± 5 to 79 ± 6 . Neither the heart rate in the basal state, or after the cold pressor intervention, nor the degree of increase in the heart rate differed between the two groups.

The end-systolic stress-percent fractional shortening relationship after cold pressor was remarkably different between normal volunteers and patients with aortic regurgitation (Fig. 1). As stress increased in the normal group, the percent fractional shortening increased. Thus, the point defining the relationship moved upward and to the right. There was no change in end-diastolic diameter between the control state or

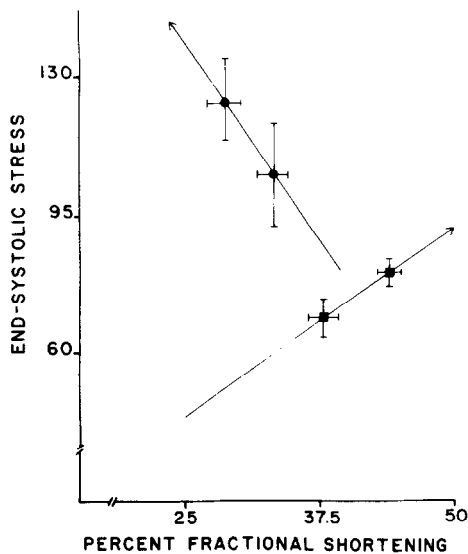


Fig. 1. Relationship between end-systolic stress (dynes/cm² $\times 10^{-3}$) and percent fractional shortening before and after cold pressor testing in normal subjects (■) and in patients with aortic insufficiency (●).

after cold pressor. This increase in percent fractional shortening likely represents increased contractility. In 7 patients with aortic regurgitation, the increased stress seen after cold pressor testing was associated with a decrease in percent fractional shortening, and in one patient there was an unchanged percent fractional shortening. Thus, the point defining the relationship moved upward and to the left. In only 2 cases, the percent fractional shortening increased with an increased end-systolic stress. Again, there was no change in end-diastolic diameter.

Discussion

Left ventricular function in chronic aortic regurgitation has been difficult to evaluate. Evaluation of ejection phase indices such as resting ejection fraction, regurgitant fraction, and end-diastolic volume have not proved to be predictive of left ventricular function during stress [21–23]. Some studies have suggested that ejection fraction is predictive of left ventricular functional recovery after aortic valve replacement [24,25]; whereas others have not [21,26]. Ejection fraction may remain normal due to the increased preload seen in states such as aortic regurgitation despite significant left ventricular dysfunction [26], and thus may not reflect changes in left ventricular function during acute alterations in loading conditions [27–29].

End-Systolic Stress

The degree of left ventricular contraction can be defined by the ventricle's force–length relationship. End-systolic stress represents the load that terminates left ventricular ejection [15]. Thus, end-systolic stress, or force, is directly related to end-systolic volume or length; is load independent, and can be used as a measure of myocardial contractility [13,14,19]. In this study, we did not elect to determine left ventricular volumes by M-mode echocardiography due to the inherent inadequacy of that calculation, particularly in large hearts [30–32]. Myocardial contractility, as measured by end-systolic pressure–volume relationships, has been used to evaluate normals [33] and patients with aortic regurgitation [20,34]. In those studies, contractile function, as determined by that relationship, only appeared depressed in patients with aortic regurgitation and congestive heart failure. The asymptomatic group was no different compared to the control population; this was also true in our study using this parameter. However, end-systolic pressure does not take into account changes in left ventricular wall thickness which occur in patients with chronic volume overload [8,35].

That end-systolic stress can be accurately estimated from M-mode echocardiographic measurements has been repeatedly validated against angiographically-determined end-systolic stress [19,20,36]. Wilson et al. [20] simultaneously performed echocardiograms and high-fidelity left ventricular pressure recordings in patients with aortic regurgitation. They found an excellent correlation between measured end-systolic stress and calculated end-systolic stress ($r = 0.99$, $P < 0.001$), and between end-systolic pressure and peak pressure ($r = 0.98$, $P < 0.01$). They also showed that systolic blood pressure obtained by the cuff method correlated well with

peak systolic aortic pressure ($r = 0.95$, $P < 0.01$) [20]. Furthermore, it has been suggested that the echocardiographically determined values may be more accurate than the angiographic because the injected contrast material may significantly affect the invasively obtained values [36].

Stress-Shortening Relationship

Borow et al. [37] studied alterations of stress–fractional shortening relationships in normals using echocardiography. Afterload was altered by the infusion of methoxamine and contractility was altered by the infusion of dobutamine. Linear inverse relationships were defined between stress and shortening. There was no strong correlation between stress and dimension in the control state, however, positive inotropic stimulation always shifted each individual's stress-dimension curve to the right. This suggested that smaller dimensions for any given stress indicated an increase in contractility. Positive inotropic intervention resulted in a higher percent fractional shortening for any end-systolic stress and the change was more discriminating than that of the end-systolic stress-dimension relation. In the present study, all but one of the normal group increased their percent fractional shortening as the stress increased. This increase in percent fractional shortening, despite the increased afterload caused by the cold pressor, suggested an increase in myocardial contractility due to the cold pressor test. In our patients with aortic regurgitation, only two showed an increase in percent fractional shortening as end-systolic stress rose. This suggested decreased myocardial contractility, or a decrease in the ability of the left ventricle in these patients to respond to this inotropic stimulus with simultaneously increased afterload. Heart rate changes were equal in both groups so that changes in the force–frequency relationships did not account for changes in contractility [38]. In the present study, there was no difference in the resting state between the two groups when the ejection phase indices of ejection fraction and percent fractional shortening were compared.

Cold Pressor Testing

Cold pressor testing was used in this study to evaluate a truly noninvasive method of altering contractility and afterload. Cold immersion causes an acute increase in both systemic blood pressure and heart rate. The average increase in blood pressure in this study was consistent with that found previously [16,39]. This pressor effect is most likely due to an increase in peripheral vascular resistance mediated by the sympathetic nervous system [17,39,40]. Cold pressor testing is also believed to cause an increase in myocardial contractility that is not related to changes in diastolic volume [16]. Studies in normals showed an increase in ejection fraction as measured by radionuclide ventriculography after cold pressor testing without an increase in end-diastolic volume. Patients with ischemic heart disease, or cardiomyopathy, had no increase in ejection fraction despite an increase in end-diastolic volume. It has been suggested that the lack of an increase in ejection fraction after cold immersion represents the inability of abnormal myocardium to increase its contractility during

an increase in afterload [16]. In the present study, 8 of the 10 patients with aortic regurgitation failed to increase their percent fractional shortening after cold pressor testing. This was in marked contradistinction with the ability of nine of the ten normals to increase their percent fractional shortening in the presence of increased end-systolic stress.

The markedly increased end-systolic stress seen in this study, both at rest and after cold pressor in patients with chronic aortic regurgitation, is likely due to inadequate hypertrophy of the left ventricle. This increase in end-systolic stress has been suggested to be predictive of a poor prognosis after aortic valve replacement [41,42]. The importance of "adequate" hypertrophy, and therefore normalized end-systolic stress for any given percent fractional shortening, has been implicated indirectly in several studies which found that patients with a high end-diastolic radius-to-wall-thickness ratio did poorly after aortic valve replacement, and did not show significant improvement in left ventricular function, or a decrease in left ventricular internal dimensions [29,43,44]. This index has been suggested to be insensitive, although specific, in identifying patients with a poor prognosis [5,45]. Gaasch et al. [46] have recently used systolic pressure times the ratio of left ventricular radius to wall thickness to predict which patients would have a postoperative return towards normal in their left ventricular dimensions and mass. This is very similar conceptually to using the end-systolic stress. The relationship between increased end-systolic stress and poor left ventricular function has also been suggested in hypertensive patients [35]. An inverse relationship between end-systolic stress and left ventricular performance was noted. These investigators also suggested that "inadequate" hypertrophy accounted for the increased stress, and therefore decreased ventricular function [35].

The present study suggests some degree of left ventricular dysfunction in most patients with chronic aortic regurgitation. This is in agreement with experimental data in dogs [47]. All foxhound puppies which had aortic regurgitation produced at four months had increased end-diastolic diameters, a decreased rate of left ventricular contraction and expansion after 2 and 6 months. Our results also agree with those recently reported by Branzi et al. [48]. In their study, they examined end-systolic pressure-volume relationships using M-mode echocardiography during angiotensin infusion in 16 asymptomatic or mildly symptomatic patients with chronic severe aortic regurgitation. They found that the end-systolic pressure-volume relationship was abnormal in 75% of their patients whereas other traditional ejection phase indices were often normal.

The end-systolic stress-percent fractional shortening relationship, as determined by M-mode echocardiography, can noninvasively detect early myocardial dysfunction in most patients with chronic aortic regurgitation. The value of this parameter in detecting early left ventricular dysfunction in patients with chronic aortic regurgitation, and the prognostic implications of the index, need to be examined in a prospective long-term study. Present decisions on the need for valve replacement are still largely based upon symptoms and the load-dependent indices of left ventricular function, such as changes in ejection fraction during exercise and/or left ventricular end-diastolic diameter. However, these have not correlated well to outcome after

valve replacement. Only by further prospective, long-term study before and after valve replacement will the full value of the end-systolic stress-dimensional relationships be known.

Acknowledgement

The authors gratefully acknowledge the assistance of Mrs. Sharon Haglund in the preparation of this manuscript.

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