Beneficial Effect of Salbutamol on Cardiac Function in Severe Congestive Cardiomyopathy

Effect on Systolic and Diastolic Function of the Left Ventricle

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SUMMARY The effects of Salbutamol (a "selective" beta, agonist) were studied in 12 patients with congestive cardiomyopathy in a dose of 0.5 µg/min/kg. In Study A (n = 6), pressures and cardiac index (CI) were measured at rest and during supine exercise. Study B (n = 6) was specifically designed to observe the effects of Salbutamol on the indices of left ventricular performance and diastolic pressure-volume relationships. The results of Study A revealed Salbutamol infusion significantly (P < 0.001) increases CI from 1.8-3.9 l/min/m² in the resting state; the exercise CI improved from 3 to 4.5 l/min/m² (P < 0.005); there was a marked decrease in left ventricular end-diastolic pressure at rest from 27-13 mm Hg (P < 0.001) and during exercise from 39-20 mm Hg (P < 0.001). There was no significant change in heart rate and blood pressure. In Study B, there was a significant reduction in left ventricular end-diastolic pressure index from 210-183 ml/m² (P < 0.05) and left ventricular end-systolic volume index from 159-102 ml/m² (P < 0.001) with a significant increase in ejection fraction from 28% to 46% (P < 0.01). Indices of myocardial performance showed significant improvement in LV dp/dt max (P < 0.02), V pm (P < 0.001), V max (P < 0.01), V ce (P < 0.01), V i (P < 0.02) and V o (P < 0.05). Salbutamol infusion significantly decreased end-diastolic circumferential wall stress (P < 0.001), total passive diastolic stiffness (P < 0.02), elastic stiffness (P < 0.001), and increased total left ventricular diastolic compliance (P < 0.01). This study indicates that Salbutamol produces significant improvement in overall cardiac function and in both systolic and diastolic function of the left ventricle.

SYMPTOMATIC AND HEMODYNAMIC improvement with rapidly acting parenteral vasodilators and inotropic agents in congestive heart failure and low cardiac output states has been well-established.1-5 No single available oral agent has proven to be consistently effective for the long-term management of these patients. Among the currently used drugs for the management of congestive heart failure are vasodilators in sublingual, chewable, oral and topical forms. The chief drawbacks of their use include unpredictable hypotension, flushing, and headache, methemoglobinemia, occasionally tachyphylaxis, and potential increase in myocardial ischemia created by a coronary steal effect.6 Other nonparenteral agents that have been studied on a limited basis include the alpha-adrenergic blocking agents phenoxybenzamine, the direct arteriolar dilating agents hydralazine7 and prazosin.8 However, the search for safe, effective and long-acting nonparenteral agents is continuing in order to make long-term therapy practical. Salbutamol, allegedly a selective beta, agonist developed for obstructive bronchial disease, belongs to the isoproterenol family of drugs and has been reported to improve cardiac function in nonfailing hearts.9 This study was designed to investigate the cardiovascular effects of Salbutamol in patients with severe heart muscle disease (congestive cardiomyopathy) whose clinical condition warranted further therapeutic support despite adequate digitalis and diuretic therapy.

Patients and Methods

Twelve patients, clinically suspected and later confirmed by cardiac catheterization to be suffering from severe heart muscle disease (congestive cardiomyopathy), were studied. The average age of the group was 45 years (range 32-65). At the time of the study, despite intensive conventional anti-heart failure treatment, all patients were in residual refractory heart failure, and all had dyspnea. Paroxysmal nocturnal dyspnea and ankle edema were present in four patients: the jugular venous pressure was raised at least 4-5 cm above the sternal angle in the 45° supine position in all. The liver was enlarged 3-5 cm below the costal margin in the mid-clavicular line in eight patients. On auscultation, a third heart sound was audible in six, and a fourth heart sound in 11 patients. None had evidence of ischemia, valvular heart disease, hypertension or diabetes mellitus. All the patients had been adequately treated with digoxin and diuretic therapy before the study.

Atrial fibrillation was present in one patient, and T wave inversion with or without ST depression indicative of some digitalis effect was present in all patients. The chest radiographs revealed cardiomegaly; the average cardiothoracic ratio of the group was 64% (range 62-70%). Selective angiography revealed a large dilated left ventricle with generalized hypokinesis and normal coronary arteries in each case, confirming the diagnosis of congestive cardiomyopathy in all. The nature and purpose of the treatment and associated study was explained to each
TABLE 1. Indices of Myocardial Performance at Rest in Patients with Congestive Cardiomyopathy and Effect of Salbutamol Infusion (Study B)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal values† (n = 6)</th>
<th>Congestive cardiomyopathy Control (n = 6)</th>
<th>Subsalbutamol infusion (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF %</td>
<td>66 ± 3 P &lt;0.001</td>
<td>28 ± 5 P &lt;0.001</td>
<td>47 ± 4</td>
</tr>
<tr>
<td>dp/dt max. mm Hg/sec</td>
<td>1200 ± 140 P &lt;0.02</td>
<td>850 ± 130 P &lt;0.02</td>
<td>1100 ± 150</td>
</tr>
<tr>
<td>Vpm = peak (dp/dt)/P1sec-1</td>
<td>55 ± 6 P &lt;0.001</td>
<td>17 ± 2 P &lt;0.001</td>
<td>31 ± 3</td>
</tr>
<tr>
<td>Peak (dp/dt)/Pdsec-1 (Pd = developed pressure)</td>
<td>102 ± 8 P &lt;0.02</td>
<td>75 ± 17 NS</td>
<td>88 ± 13</td>
</tr>
<tr>
<td>Vce = peak (dp/dt)/KPdsec-1 (K = 28)</td>
<td>1.9 ± 0.2 P &lt;0.001</td>
<td>0.6 ± 0.67 P &lt;0.001</td>
<td>1.1 ± 0.12</td>
</tr>
<tr>
<td>Vce at developed pressure</td>
<td>3.8 ± 0.2 P &lt;0.05</td>
<td>2.7 ± 0.6 NS</td>
<td>3.1 ± 0.5</td>
</tr>
<tr>
<td>Vmaxsec-1 = (dp/dt)/P at zero pressure</td>
<td>108 ± 5 P &lt;0.001</td>
<td>39 ± 3 P &lt;0.01</td>
<td>53 ± 4</td>
</tr>
<tr>
<td>Vsec-1 = (dp/dt)/P5</td>
<td>90 ± 7 P &lt;0.02</td>
<td>63 ± 12 P &lt;0.02</td>
<td>81 ± 13</td>
</tr>
<tr>
<td>Vsec-1 = (dp/dt)/P40</td>
<td>58 ± 3 P &lt;0.001</td>
<td>18 ± 3 P &lt;0.05</td>
<td>27 ± 4</td>
</tr>
</tbody>
</table>

Data collected for comparison from normal controls.
Data expressed as mean ± sem.
Abbreviations: P5 and P40 = developed pressure of 5 and 40 mm Hg, respectively; EF = ejection fraction; LV = left ventricular.

Design of Investigation

The study was designed in two parts. The hemodynamic effects of Salbutamol infusion at rest and during mild supine exercise were studied in the first six patients (Study A). In the next six patients (Study B), the effects of Salbutamol infusion on the indices of left ventricular (LV) systolic performance and diastolic pressure-volume relationships (DPVR) were investigated. Digitalis and diuretics were continued throughout both studies.

TABLE 2. Pressure-Volume Data; Indices of Left Ventricular Diastolic Compliance Before and After Salbutamol Infusion in Congestive Cardiomyopathy (Study B)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal values Rest (n = 6)</th>
<th>Control (n = 6)</th>
<th>Congestive cardiomyopathy (n = 6)</th>
<th>Subsalbutamol infusion (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (mm Hg)</td>
<td>9 ± 1 P &lt;0.001</td>
<td>28 ± 3 P &lt;0.01</td>
<td>13 ± 2</td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume (LVEDV) ml/m²</td>
<td>84 ± 5 P &lt;0.001</td>
<td>210 ± 10 P &lt;0.05</td>
<td>183 ± 9</td>
<td></td>
</tr>
<tr>
<td>LV end-systolic volume (LVESV) ml/m²</td>
<td>30 ± 2 P &lt;0.001</td>
<td>150 ± 6 P &lt;0.001</td>
<td>102 ± 8</td>
<td></td>
</tr>
<tr>
<td>Total LV diastolic compliance Index-(ΔV/Δp)/LVESV</td>
<td>0.196 ± 0.01</td>
<td>0.022 ± 0.05 P &lt;0.01</td>
<td>0.109 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>LVEDP/LVEDV ratio mm Hg/ml/m²</td>
<td>0.062 ± 0.009</td>
<td>0.097 ± 0.008 P &lt;0.02</td>
<td>0.075 ± 0.007</td>
<td></td>
</tr>
<tr>
<td>Total passive diastolic stiffness Index-(ΔV/Δp)/p</td>
<td>0.014 ± 0.004</td>
<td>0.035 ± 0.009 P &lt;0.02</td>
<td>0.017 ± 0.009</td>
<td></td>
</tr>
<tr>
<td>LV volume mass ratio VED/VW ratio</td>
<td>0.94 ± 0.04 P &lt;0.01</td>
<td>1.46 ± 0.10 NS</td>
<td>1.36 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>Mid circumferential end-diastolic wall stress (em) dyne/cm² X 10⁸</td>
<td>12.2 ± 1.2 P &lt;0.001</td>
<td>86 ± 5 P &lt;0.001</td>
<td>46 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>Peak systolic stress dyne/cm² X 10⁸</td>
<td>350 ± 20 NS</td>
<td>370 ± 30 NS</td>
<td>380 ± 25</td>
<td></td>
</tr>
<tr>
<td>Stiffness constant K (K = 3 + 3 log 2.33 (LVEDP))</td>
<td>14.3 ± 3 NS</td>
<td>19.9 ± 4 NS</td>
<td>19.3 ± 3</td>
<td></td>
</tr>
<tr>
<td>Elastic stiffness (Em) × 10⁸ dyne/cm² (Em = K-em)</td>
<td>205 ± 22 P &lt;0.001</td>
<td>1710 ± 392 P &lt;0.001</td>
<td>890 ± 275</td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as mean ± SEM.
Abbreviations: LVEDP = left ventricular end-diastolic pressure; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.
Protocol for the Patients (n = 6) in Study A

During the control period patients were studied at rest and during supine pedaling exercise. The cardiac output (CO) and intracardiac pressures were measured simultaneously at rest as well as during the final 2 minutes of exercise. After 20 minutes of rest following exercise, control resting measurements of CO and pressures were made at 5 and 10 minutes before the infusion of Salbutamol. Then a continuous intravenous infusion of Salbutamol was given to each patient using an electromechanical pump (Harvard) in a dose of 0.5 μg/min/kg body weight. Resting cardiac outputs and simultaneous pressures were measured at 5, 10, 20, 30 and 40-minute intervals during infusion of Salbutamol. Supine bicycle exercise was then repeated 40 minutes after the resting data had been collected while patients were still on continuous Salbutamol infusion.

Normal Controls

Six patients referred for suspected heart disease were studied at rest in a similar manner to patients with congestive cardiomyopathy in Study B, except none of the patients in this group received Salbutamol infusion. None were found to have hemodynamic or electrocardiographic abnormality at rest. All had normal coronary arteries and normal LV angiograms, and none had mitral or aortic valve lesions. Thus, all were considered to have normal LV function and were used as controls. Data from these patients on myocardial performance and DPVR are given in tables 1 and 2.

Hemodynamic Methods

Study A

Right and left heart catheterization was performed with the standard technique using the fluid-filled catheter system. Zero level was set 10 cm above the table top. Cardiac outputs were measured in triplicate in each instance by the dye dilution technique using a Gilford Densitometer (Gilford Instruments). Only five of six patients could manage mild supine leg exercise for 6 minutes, and in these patients, recording of the pressure and CO was made between 4–6 minutes of exercise.

Study B Simultaneous Recording of High Fidelity Pressure and Volume Employing Long Sheath Technique

By nature of their construction, Millar catheters may be difficult to introduce into an artery and to advance across the aortic valve in order to record LV pressure. To overcome this problem, a thin-walled teflon tubing (Becton, Dickinson, UK Ltd) was used as a long sheath in the following manner: The femoral artery was punctured percutaneously by the standard Seldinger technique. The Teflon-coated guide wire was introduced through the needle and the needle was withdrawn over this guidewire. After using a dilator over the guidewire, a long sheath (9F × 110 cm), already mounted on a multilumen “pigtail” angiographic catheter (Ducor, Cordis; 7F), was retrogradely negotiated into the left ventricle (fig. 1). The pigtail catheter was then withdrawn, leaving the long sheath well-placed in the left ventricle. The proximal end (femoral arterial end) of the long sheath was connected to a Y-connection. Through one limb of this Y-connection a Mikro-tip catheter (4F) was introduced.
into the ventricle, leaving its tip outside the long sheath. The other limb of the Y-connection was used for the calibration of Millar catheter with fluid-filled system and also for the calibration of the contrast material for left ventriculography. This technique has been found to be safe, easy and reliable. There has been no incidence of local thrombosis or excessive hemorrhage in any patient studied. By this long sheath technique, LV pressure and volume were recorded simultaneously using only one percutaneous arterial puncture. Another Mikro-tip catheter (4F) was also placed through a long sheath (6F × 100 cm) into ascending aorta via percutaneous brachial artery puncture for the simultaneous recording of aortic pressure.

The timing of each cine film exposure during ventriculography was electronically integrated with pressure by means of a battery operated photo cell device, so that a calculated volume could be related to a time of the cardiac cycle and instantaneous pressure (Fig. 2). Left ventriculograms were performed in 45° right anterior oblique plane during inspiration at a camera speed of 48 frames/sec.

Measurements, Calculations and Statistical Analyses

Mean systolic pressure was estimated by planimetric integration of the pressure and aortic pressure pulse component over five cardiac cycles. LV stroke work was calculated as the product of stroke volume and mean systolic pressure. Oxygen uptake was derived as the product of atrioventricular (AV) difference of oxygen content and CO. Systemic and pulmonary vascular resistances were calculated with response to surface area.

The LV volumes were calculated from the first three beats during angiography by the area length method. In addition to frame-by-frame analysis of volume, measurements were made of the long axis, and midwall internal radius and midwall external radius. Ejection fraction (%) was calculated as

\[
\frac{LVEDV-LVESV}{LVEDV} \times 100
\]

where LVEDV and LVESV are left ventricular end-diastolic and left ventricular end-systolic volumes, respectively.

The measurements and calculations of the pressure-related indices of myocardial performance —

\[
\frac{LVEDP}{VPM, Vce, Vmax, \text{Peak (dp/dt)}}
\]

Peak dp/dt, V₈ and V₄₀ were made as shown in appendix A₇—A₈. The total diastolic compliance index (ΔV/ΔP/LVESV) where ΔV equals diastolic volume changes measured as stroke index and ΔP equals changes in the LV diastolic pressure measured from the lowest early diastolic pressure to left ventricular end-diastolic pressure (LVEDP). The first three beats were analyzed for ΔV/ΔP for each patient before and during Salbutamol. Since initial volume affects the functional passive volume curve, the value for observed compliance was normalized by dividing by LVESV. Total passive diastolic stiffness index (ΔP/ΔV)/P is the reciprocal of ventricular compliance. Previous studies in canine heart have shown that instantaneous first derivative (dp/dv) related to the simultaneous LV pressure (p) is a linear function, the slope of which provides a quantitative index of LV stiffness, independent of volume and largely dependent of ventricular geometry. The approach has been ex-

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** A record of high fidelity left ventricular (LV) pressure (high gain and low gain), aortic pressure, cineangiographic frame maker, electrocardiogram at a paper speed of 125 mm/sec. Cine frame maker has been shown to drop down 1 mV, which indicates the time of the contrast injection. Pressure 0-25 for high gain LV pressure and 0-150 for low gain LV and aortic pressures. A = atrial wave; b = post A wave (where LV end-diastolic pressure has been measured; b to c = isovolumic contraction phase; c to d = ejection phase; e-early diastolic pressure of the left ventricle.)
tended to the relation of ΔP/ΔV to mean LV pressure (p).\textsuperscript{17} The LV volume mass ratio (Ved/Vw), mid-circumferential wall stress (Em) and elastic stiffness were calculated as shown in appendix A\textsubscript{7}–A\textsubscript{10}. Volume mass ratio was calculated because elastic stiffness (Em) has been shown to be dependent on it.\textsuperscript{18} The Em constant K, calculated as shown in the appendix, is a simplified expression for constant K in the clinical situation.\textsuperscript{19}

Probability of statistical significance within the group was calculated by the Student t test for paired data, and statistical significance in between the group was calculated by the unpaired t test.

**Results**

Each patient’s electrocardiogram was continuously monitored throughout the study and did not reveal any arrhythmias or any other change during or after Salbutamol infusion. No side effects of the drug were observed in any of the patients studied.

**Hemodynamic Changes in Study A (table 3 and 4)**

**At Rest (fig. 3)**

Individual hemodynamic characteristics in this group of patients were similar. Before Salbutamol infusion, patients with cardiomyopathy had a low resting cardiac index (1.8 ± 0.2 l/min/m\textsuperscript{2}) and high heart rate (91 ± 2/min), LVEDP (27 ± 2 mm Hg), and pulmonary artery mean pressure (35 ± 6 mm Hg), indicating severe heart failure. Responses to intravenous Salbutamol were similar in all patients. There was a significant increase in stroke volume (P < 0.005) and CO (P < 0.001), a consistent fall in LVEDP (P < 0.001), with a concomitant reduction in the pulmonary artery mean pressure (P < 0.05). Although there were individual variations in the heart rate and systemic arterial pressure, there was no significant change in these two factors as a group during Salbutamol infusion. Since there was no change in the aortic dynamic and mean pressure, the significant fall in the calculated systemic (P < 0.001) and pulmonary vascular resistance (P < 0.02) primarily reflected changes in the CO. These changes were maintained throughout the 40-minute period of Salbutamol infusion.

**During Exercise (fig. 4)**

Only five of six patients were able to perform light supine leg exercise. The hemodynamic findings in these patients and their response to exercise, before and during Salbutamol infusion, were again...
remarably consistent. In the control study the exercise cardiac index (3 ± 1/min/m²) and stroke index (25 ± 4 ml/beat/m²) were severely impaired. The LVEDP (39 ± 4 mm Hg) and pulmonary artery mean pressure (48 ± 6 mm Hg) were raised significantly. Salbutamol infusion during exercise resulted in no significant change in the heart rate and systemic arterial pressure compared with the control exercise data. The rise in the LVEDP in response to exercise during Salbutamol infusion was significantly less marked (P < 0.001) than the values obtained during the control exercise study. There was also significant increase in cardiac index (P < 0.001) and stroke index (P < 0.01) and a significant fall in pulmonary artery mean pressure (P < 0.01) and pulmonary resistance (P < 0.02) during Salbutamol infusion in these patients.

Effect on Modified Frank-Starling Left Ventricular Function Curve

The relationship between LV stroke work and LVEDP before and during Salbutamol infusion is illustrated in figure 5. Infusion of Salbutamol was followed by a large reduction in end-diastolic pressure (both at rest and during exercise P < 0.001) and a significant increase in stroke work output (rest P < 0.001; exercise P < 0.01) without significant change in the heart rate and systemic arterial pressure, indicating significant improvement in the LV function.

**Figure 3.** All patients had low cardiac output and significantly raised left ventricular end-diastolic pressure (LVEDP) during control period. During 40 minutes of Salbutamol infusion there was sustained improvement in cardiac output and LVEDP without significant change in the heart rate and systemic arterial pressure.
HAEMODYNAMIC EFFECTS OF SALBUTAMOL INFUSION DURING EXERCISE IN PATIENTS WITH HEART FAILURE

FIGURE 4. Patients with congestive cardiomyopathy in Study A showed a significant increase in cardiac output (CO) and a decrease in left ventricular end-diastolic pressure (LVEDP) with no significant change in the heart rate (HR) and mean aortic pressure (MAP) during Salbutamol infusion.

Effect of Salbutamol on the Pressure-Related Parameters of Myocardial Performance
(table 1, fig. 6)

In Study B, ejection fraction and LV dp/dt max were severely depressed, indicating myocardial disease. During Salbutamol infusion these values rose significantly (P < 0.001 and P < 0.02, respectively). The total LV pressure-related parameters of contractility (Vpm, Vce and Vmax) were severely depressed during the control rest period and rose significantly during the Salbutamol infusion (P < 0.001, P < 0.001, and P < 0.01, respectively). Similarly, the values of force velocity parameters related to the LV developed pressure (Peak dp/dt, Vce, V5 and Vw) were far lower than normal values. Of these parameters there was statistically significant improvement in V5 and Vw (P < 0.02 and P < 0.05, respectively). Thus, in Study B patients all the parameters of contractility measured were depressed during the control resting period, indicating severe heart muscle disease. Also, there was significant improvement in the majority of myocardial contractility parameters during Salbutamol infusion without significant change in the heart rate and systemic arterial pressure.

Effect of Midcircumferential Wall Stress (table 2, fig. 7)

In Study B, the end-diastolic midcircumferential wall stress at rest was significantly elevated (86 ± 5 dyne/cm² × 10⁹), as compared to the normal values (12.2 ± 1.2 dyne/cm² × 10⁹). Salbutamol significantly lowered this stress (P < 0.001) in these patients. The midwall peak systolic circumferential stress was normal at control rest and did not change significantly during Salbutamol infusion. However, when LV wall stress (tension) was plotted against time during systole, these patients showed an abnormal response. Instead of the usual normal rapid fall in wall stress during the mid and late ejection period, four patients showed sustained or increasing wall stress throughout the ejection period. During Salbutamol infusion this abnormal response was abolished in all four patients.

LVEDP-Volume Relation and Ventricular Compliance (table 2 and fig. 8)

At rest the average LVEDV in normal subjects was 84 ± 5 ml/m² (average ± SEM). The average LVEDV in patients with congestive cardiomyopathy (210 ± 10 ml/m²) was significantly higher (P < 0.001) than normals. During Salbutamol infusion the average value of LVEDV (183 ± 9 ml/m²) was significantly lower
(P < 0.05) than control value. The average LVEDP for the cardiomyopathy group was 28 ± 3 mm Hg (P < 0.001), which was significantly higher (P < 0.01) when compared to the normal group (table 2). In patients with congestive cardiomyopathy, the average value of LV diastolic compliance index (0.022 ± 0.05) was significantly reduced (P < 0.02) when compared with the average value in normals (0.196 ± 0.01), indicating significant reduction in ventricular distensibility in patients with congestive cardiomyopathy. During infusion of Salbutamol this index of ventricular distensibility was nearly normal (0.109 ± 0.04).

The total passive diastolic compliance index, \( \frac{\Delta P}{\Delta V} \), was significantly higher in patients with congestive cardiomyopathy (P < 0.01) when compared with the values obtained in normal subjects. During the infusion of Salbutamol the average value of this stiffness index decreased significantly (P < 0.02). There was no significant difference between the normal value and the value obtained during Salbutamol infusion in patients with congestive cardiomyopathy. The LVEDV-mass ratio (Ved/Vw) was significantly higher in cardiomyopathic patients (P < 0.01) and did not change significantly during the infusion of Salbutamol.

The stiffness constant K during the control rest in patients with congestive cardiomyopathy was 19.9 ± 4. This was not significantly different from the value achieved during Salbutamol infusion (19.3 ± 3) and the normal group (14.3 ± 3). Em was markedly elevated (1710 ± 392 dyne/cm² × 10⁶) in patients with congestive cardiomyopathy (P < 0.001) and was significantly reduced (890 ± 275 dyne/cm² × 10⁶) during Salbutamol infusion (P < 0.001), yet remained significantly higher than normal value (205 ± 22 dyne/cm² × 10⁶). In figure 8, Em was plotted against end-diastolic stress. This indicated that patients with congestive cardiomyopathy, before and during Salbutamol infusion, were operating at different stress levels of the same stiffness-stress curve.

**Discussion**

An assessment of myocardial function apart from studying the performance of the heart as a pump is of continuing interest to clinical cardiologists. Various compensatory mechanisms may mask pump failure until late in the course of the disease. Therefore, the knowledge of both systolic performance and diastolic properties is important for an accurate diagnosis of myocardial dysfunction, and for the evaluation of the mechanisms of action of a particular therapeutic agent. Study B was specifically designed for this purpose. Data from this study indicate that patients with congestive cardiomyopathy have depressed myocardial contractility, decreased LV compliance, increased end-diastolic stress and elevated Em. These findings are in agreement with the pressure-volume data reported by Gaasch et al.\(^9\)

Salbutamol infusion in patients with congestive cardiomyopathy improved cardiac function (at rest as well as during mild supine exercise), increased LV diastolic compliance and decreased Em. Also, Salbutamol decreased end-diastolic wall stress and improved the stress-time curve relationship during systole. With this improvement in myocardial function, Salbutamol infusion in a dose of 0.5 g/kg/min did not significantly change heart rate and systemic arterial pressure in these patients. Previous studies have shown Salbutamol infusion to produce an improvement in patients with valvular heart disease without heart failure\(^8\) and cardiogenic shock.\(^20\) This study has indicated its further usefulness in severe heart muscle disease.
The claims for increased myocardial contractility may be questioned because there are disadvantages attached to all the various measurements of cardiac contractility. In order to overcome some of these objections, this study was designed to influence many accepted derived parameters of contractility. The majority of these indices (Vpm, Vce, Vmax, V40 and V5) have shown consistent unidirectional changes before and during Salbutamol infusion. Vpm, which is regarded as one of the reliable indices of contractility and is independent of changes in preload, afterload, and CO,21 was found to be consistently low in the control period and consistently increased during Salbutamol infusion. The decision of whether a given therapeutic agent is an inotropic agent or a vasodilator can be difficult when a study is carried out in

**Figure 7.** Effect of Salbutamol on midwall stress time curve in a patient with congestive cardiomyopathy.

**Figure 8.** Elastic stiffness \((Em)\) has been plotted against end-diastolic wall stress before and during Salbutamol infusion in patients with congestive cardiomyopathy.
man. Since heart rate, preload and afterload, if not controlled, can be affected equally by both agents, these simple, easily obtainable parameters cannot be used reliably to distinguish a vasodilator from an inotropic agent. Although concomitant vasodilator effect is difficult to exclude, Salbutamol has been shown to increase stroke volume, ejection fraction and other direct indices of myocardial contractility. Salbutamol has also been shown to increase those indices of myocardial contractility which are known to be least affected by preload and afterload. Other sensitive and reliable indices of contractility, as described in the literature, are maximum rate of change of aortic blood flow and maximum rate of change in LV power. Recently, other investigators in this field have studied the effect of Salbutamol and nitroprusside on these two parameters in nine patients after cardiac surgery and demonstrated that Salbutamol significantly augments the maximum acceleration of aortic blood flow and maximum rate of change in LV power, while nitroprusside does not change the acceleration and reverses the effect of Salbutamol on maximum rate of change in LV power. Thus, from this and other studies, it may be suggested that Salbutamol enhances the inotropic state of the left ventricle.

Alterations in LV compliance are affected by many factors other than elastic properties of the myocardium. Most accepted factors related to the left ventricle itself altering compliance are ventricular geometry, initial volume, hypertrophy, wall thickness, ventricular filling rate, and ventricular stiffness. Changes in the behavior of the anatomical constraints to the LV distension, including right ventricular chamber, the pericardium and the pleural cavity associated with altered pressure and volume-loading conditions, have also been suggested to contribute to the observed displacement of the LV pressure-volume curves. Another constraint to the LV pressures, volume and shifting pressure-volume relationship, without directly altering ventricular stiffness, is the perfusion pressure within the coronary vascular bed. However, in this study it is unlikely that the compliance changes with Salbutamol infusion have been produced by the changes in the ventricular geometry or hypertrophy. Although pleural pressures were not measured, Alderman et al. did suggest that changes in the pleural pressure may slightly affect pressure-volume relations between patients, but individual patients under identical respiratory conditions have pleural pressures which are similar and would not account for a significant shift of pressure-volume relation. Thus, with Salbutamol infusion an improvement in the pressure-volume relationship may be attributed to changes either in the elastic properties of the myocardium or to alteration of the physical constraints to the LV distension produced by the right ventricle, pericardium and/or perfusion pressure within the coronary vasculature. Since myocardial contractility in itself does not directly affect ventricular compliance, it might be suggested that an improvement in the LV diastolic dysfunction could be due to an action of Salbutamol, independent from its inotropic action.

The acute effects of an inotropic agent on LV diastolic compliance in congestive cardiomyopathy have not been well-documented. Although previous clinical observations suggested an improvement in the pulmonary hemodynamics in congestive heart failure after the use of an inotropic agent, this may be related to improved compliance with consistent alteration in passive pressure-volume relation in addition to enhancement of cardiac contractile property. Changes in ventricular compliance related to ischemia may be corrected, and observations in LV compliance and chronic volume overload may at least be partially reversible, as shown in children after closure of a VSD and in certain patients after surgical correction of aortic regurgitation. This study suggests that Salbutamol infusion has acutely improved the long-standing and profoundly abnormal pressure-volume characteristics of the diseased left ventricle of congestive cardiomyopathy.

The potential of Salbutamol as a therapeutic agent for heart failure or congestive cardiomyopathy has not been established. This study indicates Salbutamol infusion may be an effective means of improving pump failure, abnormal wall stress, ventricular compliance and Em properties of the left ventricle. Oral preparations of this drug, currently used in the treatment of obstructive airways disease, should be investigated further. Combined therapy with such an inotropic agent and vasodilator drug may be a potent therapeutic combination for severe intractable heart failure.

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Appendix

1. Calculation of the Pressure-Related Parameters of Myocardial Contractility:

   Maximum rate of pressure rise in the left ventricle (LV dp/dt max) was determined by the R-c differentiating circuit connected to the left ventricular LV pressure. By simultaneously recording LV pressure with its derivative and aortic pressure, the following indices were calculated in Study B:

   \[ V_{pm} = \text{Peak } \left( \frac{dp}{dt} \right)_{\text{Sec}^{-1}} \frac{1}{p} \quad A_1 \]

   Where \( p \) is the instantaneous LV pressure.

   \[ V_{ce} = \text{Peak } \left( \frac{dp}{dt} \right)_{\text{Sec}^{-1}} \frac{1}{K_p} \quad A_2 \]

   Where \( K \) is the series elastic constant. A value of 28 mm sec muscle-length was used for \( K \) appropriate to the previous studies in isolated heart.

   \[ V_{max} = \frac{dp}{dt} \frac{1}{P_o} \quad A_3 \]

   \( dp/dt \) at LV zero pressure (Po) was obtained by computer extrapolation of the descending limb of \( \frac{dp}{dt} \) curve to zero pressure employing an exponential curve fit to the formula \( y = a + \frac{b}{c} \) where \( a, b \) and \( c \) are constants determined from a nonlinear regression analysis.

   Similarly, \( \text{Peak } \left( \frac{dp}{dt} \right) \frac{1}{P_d} \) and \( \left( \frac{dp}{dt} \right) \frac{1}{KP_d} \) were calculated employing developed pressure (Pd) in the left ventricle which in turn was calculated as instantaneous LV pressure minus LV end-diastolic pressure.

Since \( V_{max} \) at zero developed pressure-approached infinity the following measurements were made:

   \[ V_5 = \left( \frac{dp}{dt} \right)_{\text{Sec}^{-1}} \frac{1}{P_5} \quad A_5 \]

   \[ V_{40} = \left( \frac{dp}{dt} \right)_{\text{Sec}^{-1}} \frac{1}{P_{40}} \quad A_6 \]
Where \( P \) and \( P_a \) are developed pressure of 5 and 40 mm Hg during isovolumic systole.

2. Calculation of LV Volume-Mass Ratio. \((V/V\omega)\), Midcircumferential Wall Stress (\(\sigma_m\)) and Elastic Stiffness:18

\[
\text{Volume-mass ratio } \frac{V_e}{V_w} = \frac{V_e}{4\pi (b^2-a^2)} \quad (1 + b^3) \\
2R^3
\]

where \( P \) is LV pressure, \( V \) is instantaneous LV volume, \( b \) is external radius and \( R \) is the aorta.

Midcircumferential wall stress (\(\sigma_m\)) = \( P \frac{V}{V_w} \)

Elastic Stiffness (Em) = \( K \sigma_m \)

where \( K \) is elastic stiffness constant which in turn is calculated as:19

\[
K = 3 + 3 \log_e 2.33 (LVEDP)
\]

Aortic Input Impedance in Heart Failure

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SUMMARY The input impedance of the systemic circulation was calculated from recordings of pulsatile pressure and flow in the ascending aorta of 20 patients. Ten patients had clinical and hemodynamic evidence of heart failure. The other 10 subjects had no clinical evidence of heart failure and were used as a control group. In the heart failure patients, both input resistance and characteristic impedance (index of aortic distensibility) were significantly increased compared to pressure and age-matched control subjects. Oscillations of impedance moduli, represented by the difference between maximum and minimum modulus, were also significantly increased in the heart failure patients compared with the control subjects. The increased characteristic input impedance in these heart failure patients suggests that the human aorta is stiffer in heart failure, and the larger oscillations in the impedance spectrum indicate an increase in pressure and flow wave reflections. From reflected wave theory in elastic tubes, reflected pressure waves add to the amplitude of incident pressure waves at the entrance of the system, whereas reflected flow waves subtract from the magnitude of the forward flow. Thus, changes in aortic distensibility could have an important influence on the pulsatile function of the failing left ventricle.

THE AORTA AND LARGE ARTERIES of the systemic circuit are not rigid pipes, but constitute a distensible elastic buffering chamber. These elastic properties permit a damping mechanism through which pulsatile blood flow waves ejected from the left ventricle are converted to a near-constant blood flow for resistance vessels to distribute to systemic capillaries. Elastic properties of these large vessels can be modified by autonomic nervous effects on vascular smooth muscle cells with only minor changes in vessel dimensions.1 Recent studies in our laboratories suggest that age and the presence of atherosclerosis may also be important in modifying the elastic properties of large vessels.2

In heart failure, previous studies have emphasized abnormal ventricular and peripheral hemodynamic responses.3, 4 The peripheral responses consist of abnormal vasoconstriction both at rest and during exercise.5 The latter changes were thought to be compensatory and possibly important in maintaining regional blood flow.5, 6 Recent interest in these so-called "compensatory" changes in vascular resistance has emerged due to the application of vasodilator therapy in patients with heart failure.7 These studies suggest that the failing ventricle's pump performance is markedly influenced by alterations of the mean component of the total resistive load. Alterations of aortic distensibility also have the potential to alter the dynamic or pulsatile component of the vascular load.5, 8-10 This alteration could be deleterious in the patient with a failing ventricle. A study of this part of the ventricular afterload in patients with heart failure has not been reported. In this investigation we studied the total impedance spectrum at the input to the systemic arterial system in patients with heart failure. These findings were compared to measurements made in age-matched subjects with similar aortic pressure who had no evidence of heart failure. These findings may also be useful in providing a basis for future investigation of agents designed to reduce the pulsatile component of afterload.
Beneficial effect of salbutamol on cardiac function in severe congestive cardiomyopathy.
Effect on systolic and diastolic function of the left ventricle.
B Sharma and J F Goodwin

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