Effects of Myocardial $\alpha_1$-Adrenergic Receptor Stimulation and Blockade on Contractility in Humans

Joel S. Landzberg, MD; John D. Parker, MD; Diane F. Gauthier, RN; and Wilson S. Colucci, MD

Background. Although $\alpha$-adrenergic receptors are present in both normal and failing human left ventricular myocardium and mediate a positive inotropic effect in several other species, it is not known whether stimulation of myocardial $\alpha$-adrenergic receptors exerts a positive inotropic effect or contributes to basal contractile state in vivo in humans.

Methods and Results. We studied 15 patients with angiographically normal coronary arteries (seven with normal left ventricular function and eight with left ventricular failure). To avoid the confounding effects of changes in ventricular loading conditions and systemic reflex mechanisms, the $\alpha$-adrenergic receptor–selective antagonist phentolamine and agonist phenylephrine were infused directly into the left main coronary artery, and the change in contractile state was assessed by measuring left ventricular peak ($+\Delta P/dt$). Phentolamine alone had no effect on left ventricular contractility. Phenylephrine exerted a concentration-related positive inotropic effect in patients with normal as well as those with failing ventricles. The $\alpha$-adrenergic effect of phenylephrine, defined as the component blocked by phentolamine, was significantly less in patients with ventricular failure ($108\pm28$ mm Hg/sec) than in normal subjects ($248\pm54$ mm Hg/sec; $p<0.03$).

Conclusions. Myocardial $\alpha$-adrenergic receptors do not contribute to the maintenance of basal left ventricular contractile state in humans. However, stimulation of myocardial $\alpha$-adrenergic receptors exerts a positive inotropic effect, the magnitude of which may be attenuated in patients with heart failure. (Circulation 1991;84:1608–1614)

Adrenergic modulation of ventricular contractile state is mediated through the action of catecholamines on myocardial adrenergic receptors. Although it is well recognized that $\beta$-adrenergic receptor stimulation markedly increases the contractility of human myocardium, the role of myocardial $\alpha$-adrenergic receptors in mediating the positive inotropic effect of catecholamines in humans is not known.\(^1\) In several animal species, it can be shown that $\alpha$-adrenergic receptor stimulation causes an increase in myocardial contractility.\(^2\) However, despite the identification of $\alpha$-adrenergic receptors by radioligand binding in human myocardium,\(^3\)–\(^5\) in vitro observations on the contractile effect of $\alpha$-adrenergic receptor stimulation in human myocardium have been conflicting.\(^2\)–\(^9\)

Attempts to demonstrate the effects of $\alpha$-adrenergic receptor stimulation or inhibition on myocardial contractility in vivo in humans are hampered by the confounding effects of stimulation and inhibition of vascular $\alpha$-adrenergic receptors on ventricular loading conditions and reflex mechanisms.\(^10\)–\(^12\) One prior in vivo study in humans failed to demonstrate an $\alpha$-adrenergic receptor–mediated positive inotropic response to systemic administration of phenylephrine.\(^12\) Furthermore, there is no information available regarding the contribution of myocardial $\alpha$-adrenergic receptors to the maintenance of basal contractile state in humans. To determine whether myocardial $\alpha$-adrenergic receptor stimulation exerts a positive inotropic effect and/or contributes to basal contractility in humans, we infused the $\alpha$-adrenergic agonist phenylephrine and the $\alpha$-adrenergic receptor–selective antagonist phentolamine into the left main coronary artery of seven subjects with normal left ventricular function. This approach enabled us to

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study the inotropic effect of myocardial \( \alpha \)-adrenergic receptor stimulation while avoiding the effects of systemic \( \alpha \)-adrenergic receptor stimulation or inhibition on ventricular loading conditions and systemic reflex mechanisms.\(^{11,12}\)

In myocardium from patients with end-stage heart failure and downregulation of \( \beta \)-adrenergic receptors, \( \alpha \)-adrenergic receptor density is normal.\(^{3-5}\) Similarly, in animals exposed to excessive adrenergic stimulation, there is attenuation of the positive inotropic response for \( \beta \)-adrenergic\(^{13}\) but not \( \alpha \)-adrenergic stimulation.\(^{14}\)

These observations have led to the suggestion that the \( \alpha \)-adrenergic pathway may be of increased importance relative to the \( \beta \)-adrenergic pathway in patients with excessive sympathetic tone resulting from heart failure.\(^{3,14}\) Therefore, to determine whether \( \alpha \)-adrenergic receptor stimulation contributes to basal contractility and/or exerts a positive inotropic effect in patients with left ventricular failure, we also studied eight patients with congestive heart failure.

**Methods**

**Study Population**

The study population consisted of 15 subjects. All subjects were in normal sinus rhythm and without angiographically evident coronary artery lesions. Two groups of subjects were defined. One group (normal subjects) comprised seven patients, (five men and two women) with a mean age of 48±4 years. These patients had no evidence of left ventricular dysfunction or symptoms of congestive heart failure and were undergoing diagnostic catheterization for investigation of a chest pain syndrome \((n=4)\) or before electrophysiological evaluation \((n=3)\). Three patients were receiving \( \beta \)-adrenergic antagonists, which were discontinued the evening before catheterization.

The second group (congestive heart failure patients) comprised eight patients with idiopathic \((n=5)\), peripartum \((n=1)\), ethanol-related \((n=1)\), or muscular dystrophy-related \((n=1)\) dilated cardiomyopathy. There were three men and five women with a mean age of 44±4 years. These patients were in New York Heart Association functional class II \((n=2)\), III \((n=3)\), or IV \((n=3)\) despite treatment with digoxin \((n=6)\), diuretics \((n=8)\), and converting enzyme inhibitors \((captopril, n=6; enalapril, n=1)\). These medications were withheld on the day of catheterization. All patients had evidence of moderate-to-severe left ventricular dysfunction by echocardiographic evaluation \((\text{mean left ventricular ejection fraction}, 23\pm5\%)\).

The study protocol was approved by the Committee for the Protection of Human Subjects From Research Risks at the Brigham and Women's Hospital, and written informed consent was obtained from all subjects.

**Hemodynamic Measurements**

All patients initially underwent routine diagnostic left and right heart catheterization using the femoral approach. Coronary arteriography was performed with nonionic contrast, and left ventriculograms were not performed until after the drug infusion protocol was completed. After the diagnostic procedure, at least 20 minutes elapsed before the beginning of this investigation. An 8F micromanometer-tipped catheter (Millar Industries, Houston, Tex.) was then placed in the left ventricle. Femoral arterial pressure was monitored via a 9F side arm sheath (Cordis Laboratories, Miami, Fla.). A 7F L-4 Judkins catheter (Cordis Laboratories) was placed from the opposite femoral artery and advanced to the ostium of the left main coronary artery as would be done for routine contrast injection.

The electrocardiogram, femoral arterial pressure, left ventricular pressure, and the first derivative of left ventricular pressure (continuous electronic differentiation, model 2203A amplifier, Electronics for Medicine, Honeywell, Inc., Pleasantville, N.Y.) were recorded on a strip-chart recorder. Heart rate, mean arterial pressure, and left ventricular end-diastolic pressure \((\text{LVEDP})\) were recorded as the averages of measurements made on at least 15 consecutive beats. Left ventricular peak \((+\text{dP/dt})\) was the average of measurements made on at least 45 consecutive beats under each experimental condition.

**Infusion Protocol**

Drugs were infused into the left main coronary artery via the 7F Judkins catheter, using a Harvard pump (Harvard Apparatus, South Natick, Mass.) as previously described.\(^{11,15,16}\) Unless otherwise noted, each drug infusion and control period was of 5 minutes' duration with hemodynamic measurements made during the fifth minute. The sequence of infusions and control periods was as follows. First, 5% dextrose in water \((\text{D5W})\), the vehicle for intra-coronary drug infusion, was infused at a rate of 2 ml/min. Second, dobutamine diluted in D5W was then infused at a rate of 25 \(\mu\)g/min. Assuming a left main coronary artery blood flow of 125 ml/min, the estimated dobutamine concentration in the coronary artery at this infusion rate is approximately 200 \(\mu\)g/l, a level similar to that achieved during intravenous infusion at a rate of 14 \(\mu\)g/kg/min.\(^{15}\) Third, this was followed by a recontrol period of D5W infusion until \((+\text{dP/dt})\) had returned to the baseline value, which generally occurred 3–5 minutes after discontinuation of dobutamine. Fourth, the \( \alpha_1 \)-adrenergic agonist phenylephrine was then infused at rates calculated to yield final coronary artery concentrations of \(10^{-7}\), \(5\times10^{-7}\), and \(10^{-6}\) M, which in general correspond to the serum concentrations expected with intravenous phenylephrine infusion at rates of 20–200 \(\mu\)g/min, the recommended dosage range used in the treatment of vasodilatory hypotension.\(^{18}\) In the first three subjects, \(10^{-8}\) M phenylephrine was also infused but had no hemodynamic effect. Fifth, phenylephrine infusion was followed by a recontrol period during which D5W was infused for 5 minutes. Sixth, phenotolamine was then infused at a rate of 0.2 mg/min to
yield a calculated coronary artery concentration of approximately $5 \times 10^{-6}$ M. Seventh, after hemodynamic measurements were recorded for the phentolamine infusion, phentolamine infusion was continued, and phenylephrine ($10^{-6}$ M) was infused concurrently with phentolamine (0.2 mg/min) to determine the “phenolamine-sensitive” (i.e., α-adrenergic) component of the phenylephrine response. Last, after completion of the drug infusion protocol, radiographic contrast was injected to confirm the continued position of the J4 catheter in the left main coronary artery ostium. All 15 subjects received phenylephrine; 14 received phentolamine and phentolamine concurrently, and 12 received phenolamine alone.

Although phenylephrine is a relatively selective agonist for α-adrenergic receptors, particularly of the α1-subtype, this drug may also stimulate β-adrenergic receptors. Therefore, the highly α-adrenergic receptor-selective antagonist phentolamine was used in this protocol to define the portion of the phenylephrine response that is sensitive to α-adrenergic blockade. Because phentolamine is a competitive blocking agent, this phenolamine-sensitive component of the phenylephrine response probably underestimates the portion of the phenylephrine response that can be attributed to α-adrenergic receptor stimulation. The phenolamine-sensitive component of the phenylephrine response was defined as the change (relative to the preceding control infusion) in $(+\Delta P)$ with $10^{-6}$ M phenylephrine infusion minus the change (relative to the preceding control infusion) in $(+\Delta P)$ with concomitant infusion of $10^{-6}$ M phenylephrine and phenolamine (0.2 mg/min).

Statistical Methods

The effect of each drug infusion was compared with the immediately preceding control period. Thus, for dobutamine and phenylephrine infusions, the control period was the preceding D5W infusion. For the combined phenolamine and phenylephrine infusion, the control period was the preceding infusion of phenolamine alone. Multiple observations on repeated measures were tested for significant change by analysis of variance. Comparisons of individual observations were made by paired or unpaired two-tailed Student’s $t$ tests, as appropriate, and the statistical significance of differences was tested using the Bonferroni correction for repeated measures, such that a probability of less than 0.05 was required for statistical significance.

**Results**

**Baseline Hemodynamics**

Patients in the congestive heart failure group had elevated right and left heart filling pressure and heart rates with depressed ejection fractions and stroke volume indexes compared with the normal group (Table 1). The peak rate of left ventricular pressure rise [$(+\Delta P)/dt$] was significantly lower in the patients with congestive heart failure.

**Hemodynamic Responses to Intracoronary Infusions**

In the normal subjects (Table 2), heart rate, LVEDP, and mean arterial pressure did not change in response to any of the intracoronary drug infusions. In the patients with congestive heart failure (Table 2), heart rate and LVEDP also did not change in response to any of the drug infusions. In this group, mean arterial pressure increased from 88±3 to 96±4 mm Hg with the maximal phenylephrine infusion rate ($10^{-6}$ M) but did not change with the other intracoronary drug infusions.

**Effects of Intracoronary Dobutamine on $(+\Delta P)/dt$**

Baseline $(+\Delta P)/dt$ was stable throughout the protocol, with no significant differences among the three control (D5W) conditions (Table 2). Intracoronary dobutamine infusion at a rate of 25 μg/min significantly increased $(+\Delta P)/dt$ in each group. The dobutamine-stimulated increase in $(+\Delta P)/dt$ was significantly ($p<0.02$) smaller in the patients with congestive heart failure ($299±33$ mm Hg/sec) than in the normal subjects ($1,081±273$ mm Hg/sec).

**Effects of Intracoronary Phenylephrine on $(+\Delta P)/dt$**

Intracoronary phenylephrine caused a dose-related increase in $(+\Delta P)/dt$ in both normal subjects and patients with congestive heart failure, with significant increases over baseline at concentrations of $5 \times 10^{-7}$ and $10^{-6}$ M (Figure 1). At both $5 \times 10^{-7}$ and $10^{-6}$ M phenylephrine, the increase in $(+\Delta P)/dt$ was significantly smaller in the congestive heart failure group.

**Effects of Intracoronary Pentolamine on Baseline and Phenylephrine-Stimulated $(+\Delta P)/dt$**

Phentolamine infusion had no significant effect on baseline $(+\Delta P)/dt$ in either normal subjects ($-6±27$ mm Hg/sec) or patients with congestive heart failure.
TABLE 2. Hemodynamic Effects of Intracoronary Drug Infusions in Normal Subjects and in Patients With Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Heart rate (beats/min)</th>
<th>Left ventricular end-diastolic pressure (mm Hg)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Left ventricular (+dP/dt) (mm Hg/sec)</th>
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</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Control (DSW)</td>
<td>7</td>
<td>72±4</td>
<td>11±1</td>
<td>100±8</td>
<td>1,346±152</td>
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<tr>
<td>Dobutamine (25 μg/min)</td>
<td>7</td>
<td>78±8</td>
<td>9±2</td>
<td>98±8</td>
<td>2,425±388*</td>
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<tr>
<td>Recontrol (DSW)</td>
<td>6</td>
<td>71±5</td>
<td>11±2</td>
<td>98±9</td>
<td>1,309±162</td>
</tr>
<tr>
<td>Phenylephrine (10⁻⁷ M)</td>
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<td>72±5</td>
<td>10±1</td>
<td>99±8</td>
<td>1,410±154</td>
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<tr>
<td>Phenylephrine (5×10⁻⁷ M)</td>
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<td>71±6</td>
<td>10±1</td>
<td>102±8</td>
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<td>Phenylephrine (10⁻⁶ M)</td>
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<td>69±6</td>
<td>11±2</td>
<td>109±10</td>
<td>1,926±232*</td>
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<td>Recontrol (DSW)</td>
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<td>68±5</td>
<td>11±2</td>
<td>94±6</td>
<td>1,327±205</td>
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<td>Phenylephrine (0.2 mg/min)</td>
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<td>70±5</td>
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<td>Phenylephrine (10⁻⁶ M)+phenotolamine</td>
<td>6</td>
<td>74±8</td>
<td>9±2</td>
<td>98±4</td>
<td>1,694±234*</td>
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<td>Patients with congestive heart failure</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control (DSW)</td>
<td>8</td>
<td>98±4</td>
<td>26±4</td>
<td>88±3</td>
<td>822±121</td>
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<tr>
<td>Dobutamine (25 μg/min)</td>
<td>8</td>
<td>103±6</td>
<td>20±4</td>
<td>89±3</td>
<td>1,121±170*</td>
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<tr>
<td>Recontrol (DSW)</td>
<td>8</td>
<td>97±4</td>
<td>26±4</td>
<td>89±3</td>
<td>832±118</td>
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<tr>
<td>Phenylephrine (10⁻⁷ M)</td>
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<td>25±3</td>
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<td>25±3</td>
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<td>921±142</td>
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<tr>
<td>Phenylephrine (10⁻⁶ M)</td>
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<td>97±5</td>
<td>25±3</td>
<td>96±4*</td>
<td>1,029±153*</td>
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<tr>
<td>Recontrol (DSW)</td>
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<td>95±5</td>
<td>27±3</td>
<td>91±3</td>
<td>774±122</td>
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<tr>
<td>Phenotolamine (0.2 mg/min)</td>
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<td>100±4</td>
<td>27±4</td>
<td>87±3</td>
<td>878±136</td>
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<tr>
<td>Phenylephrine (10⁻⁶ M)+phenotolamine</td>
<td>8</td>
<td>100±4</td>
<td>26±4</td>
<td>90±3</td>
<td>966±152*</td>
</tr>
</tbody>
</table>

DSW, 5% dextrose in water. *p<0.0083 vs. prior control.

(+54±23 mm Hg/sec). Phenotolamine infusion significantly reduced the (+dP/dt response to phenylephrine in both normal subjects and patients with congestive heart failure (p<0.01 versus phenylephrine alone, both groups), thereby defining a phenotolamine-sensitive component that can be attributed to α-adrenergic receptor stimulation (Figure 1B). The α-adrenergic component of the phenylephrine response was significantly reduced (p<0.03) in the congestive heart failure group (108±28 mm Hg/sec) compared with normal subjects (248±54 mm Hg/sec) (Figure 1B). Patients were divided by left ventricular ejection fraction into those with 20% or less (mean, 14±3%; n=4) and those with more than 20% (mean, 32±7%; n=4). The α-adrenergic component of the phenylephrine-stimulated increase in (+dP/dt was smaller (55±29 mm Hg/sec) in the group with ejection fractions of 20% or less than in the group with ejection fractions of more than 20% (162±31 mm Hg/sec, p=0.045).

Discussion

The present study demonstrates that α-adrenergic receptor stimulation increases contractility in both normal and failing human myocardium in vivo. Intracoronary infusion of phenylephrine caused an infusion rate–related increase in (+dP/dt in both normal subjects and patients with congestive heart failure. Although phenylephrine is relatively selective for α-adrenergic receptors, it may also stimulate β-adrenergic receptors. Therefore, to define the α-adrenergic effect of phenylephrine, we determined the component of the phenylephrine response that was blocked by intracoronary phenotolamine, a highly α-adrenergic receptor–selective antagonist. The concurrent infusion of phenotolamine significantly reduced the response to phenylephrine by 46%, thereby defining the part of the phenylephrine response that is secondary to myocardial α-adrenergic receptor stimulation. Interestingly, although α-adrenergic receptor stimulation increased contractility, the intracoronary infusion of the α-adrenergic antagonist phenotolamine alone did not significantly decrease basal (+dP/dt. This suggests that endogenous myocardial α-adrenergic tone does not play a role in maintaining the basal state of left ventricular contractility in humans. Because our subjects were resting in the supine position, it is possible that this finding would be different in states of greater sympathetic tone. Phenotolamine is a nonselective antagonist for α₁- and α₂-adrenergic receptors and might
increase endogenous cardiac sympathetic tone by blocking presynaptic α1-adrenergic receptors that regulate neurotransmitter release. However, this does not appear to have occurred, since neither heart rate nor (+) dP/dt increased in either normal subjects or patients during phenolamine infusion.

α1-Adrenergic receptors have been demonstrated by radioligand binding to be in the myocardium of many species, including humans. In most animal species, α-adrenergic stimulation increases myocardial contractility. In rabbit, rat, cat, and bovine myocardium, α-adrenergic receptor stimulation causes an unequivocal increase in contractility. In contrast, in vitro muscle bath experiments with canine myocardium fail to show an α-adrenergic receptor–mediated positive inotropic response despite the demonstration of receptors by radioligand binding. In vitro muscle bath studies of human ventricular myocardium have yielded inconsistent findings. Although some investigators have concluded that α-adrenergic receptor stimulation exerts a substantial positive inotropic effect in human ventricular myocardium, others have found little or no response; in one study, a response could not be detected in myocardium from five of 14 patients.

A positive inotropic effect of myocardial α-adrenergic receptor stimulation has not previously been shown in vivo in humans. The demonstration of a positive inotropic effect of myocardial α-adrenergic receptor stimulation is hampered by the fact that most measures of ventricular contractility are sensitive to the marked changes in heart rate and ventricular loading conditions that occur with the systemic administration of α-adrenergic agonists or antagonists. Curiel et al infused the α-adrenergic agonist methoxamine systemically to patients and used noninvasive methods to measure Emax, a load-independent index of contractility. Although Emax was significantly higher with methoxamine than with angiotensin II, phenolamine did not significantly diminish the effect of methoxamine on Emax, suggesting that α-adrenergic receptor stimulation may not have been responsible for the observed effect of methoxamine.

A major advantage of the intracoronary infusion technique used in the present study is that it allows the relatively selective stimulation and inhibition of myocardial α-adrenergic receptors, thereby in large part avoiding the confounding effects of the systemic administration of potent vasocostritor and vasodilator agents on ventricular loading conditions, reflex mechanisms, and heart rate. Under these conditions, the peak rate of left ventricular pressure rise [(+dP/dt)] provides a reliable index of changes in inotropic state.
Patients with congestive heart failure have evidence of adrenergic hyperactivity with increased circulating norepinephrine levels and sympathetic nerve activity.\(^{22,23}\) Myocardial $\beta$-adrenergic receptor density and the positive inotropic response to $\beta$-adrenergic receptor stimulation are reduced in patients with severe heart failure.\(^{22,24}\) In contrast, myocardial $\alpha_1$-adrenergic receptor density is not decreased in heart failure.\(^{3-5}\) Our data show that the positive inotropic response that can be attributed to $\alpha$-adrenergic receptor stimulation was reduced in the congestive heart failure group and was most reduced in the patients with the lowest left ventricular ejection fractions. This finding is consistent with a number of possibilities. First, it may indicate that myocardial $\alpha$-adrenergic responsiveness is decreased in heart failure. A reduction in $\alpha$-adrenergic responsiveness without a reduction in $\alpha$-adrenergic receptor density might reflect reduced efficiency of receptor coupling, a phenomenon shown to occur in vitro.\(^{25,26}\) Second, it might reflect a higher coronary blood flow in the patients with heart failure. Third, it could be due to a decrease in the overall contractile capacity of the failing heart and thus not be specific for the $\alpha$-adrenergic response. A reduced $\alpha$-adrenergic response in failing myocardium might help to explain the conflicting results reported with $\alpha$-adrenergic receptor stimulation in in vitro studies of human myocardium, since some studies used myocardium from patients with end-stage congestive heart failure,\(^7\) whereas others used nonfailing myocardium from patients undergoing routine cardiac surgery.\(^6\)

A potential limitation of the present study is the use of peak $(+)$dP/dt to quantitate changes in inotropic state, since this index can be affected by changes in heart rate and loading conditions.\(^{11}\) However, $(+)$dP/dt is relatively insensitive to small changes within the physiological range\(^{22};\) to minimize changes in loading conditions and activation of reflex mechanisms, phenylephrine and phenotolamine were infused via the intracoronary route. There were no significant changes in heart rate or LVEDP with phenylephrine infusion in either group. Mean arterial pressure was not changed by phenylephrine in the normal subjects and was increased by only 7 mm Hg at the peak infusion rate of phenylephrine in the patients with congestive heart failure. Because even a much larger, 25–30 mm Hg change in mean arterial pressure causes less than a 10% change in $(+)$dP/dt,\(^{28}\) we feel it is unlikely that the small change in mean arterial pressure in the congestive heart failure patients could account for the observed change in contractility. A second limitation of the present study is that all of the patients had normal coronary arteries. Therefore, the effect of $\alpha$-adrenergic stimulation seen in our heart failure patients may not reflect the response in patients with heart failure resulting from ischemic disease, in whom the coupling relation between receptor and response may differ.\(^{29}\)

It should be emphasized that these data may underestimate the maximum potential effect of myocardial $\alpha$-adrenergic receptor stimulation. The $\alpha$-adrenergic effect of phenylephrine ($10^{-6}$ M) was defined as that part of the response that was blocked by phentolamine. Thus, the part of the phenylephrine response that is not blocked by phentolamine may be due to the $\beta$-adrenergic effect of this agent. However, because phentolamine is a competitive antagonist, it is also possible that the intracoronary concentration of phentolamine achieved in the present study was not sufficient to fully block $\alpha$-adrenergic responses. In addition, in vitro studies of human myocardium have shown that the maximum $\alpha$-adrenergic receptor response to phenylephrine requires concentrations in excess of $10^{-7}$ M. Because of concerns about excessive coronary vasoconstriction, we infused phenylephrine at rates achieving a maximal concentration of only approximately $10^{-6}$ M. Therefore, the response to $10^{-6}$ M phenylephrine probably underestimates the maximum possible $\alpha$-adrenergic receptor response. The concentrations used in the present study are, nevertheless, pertinent to the systemic concentrations achieved with clinical infusions of phenylephrine.

**Summary**

The data show for the fist time in vivo in humans that stimulation of myocardial $\alpha$-adrenergic receptors increases contractility. Because $\alpha_1$-adrenergic receptor stimulation acts through a mechanism that is not cyclic AMP dependent, most likely involving stimulation of phospholipase C,\(^1\) it is possible that the positive inotropic effect of $\alpha_1$-adrenergic receptor stimulation will complement that caused by $\beta$-adrenergic receptor stimulation. The demonstration that myocardial $\alpha_1$-adrenergic receptors are functionally active in humans may also have implications for other actions of the myocardial $\alpha_1$-adrenergic receptor. In vitro and in vivo studies in animals have shown that stimulation of myocardial $\alpha_1$-adrenergic receptors can play a role in mediating myocyte hypertrophy\(^{30,31}\) and modulating the degree of contractile dysfunction after brief periods of myocardial ischemia\(^{32}\) and can be of importance in the genesis of ischemia- and reperfusion-related ventricular arrhythmias.\(^{33,34}\) It will be important to learn whether $\alpha_1$-adrenergic receptors in human myocardium also play a significant role in these or other pathological processes.

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**References**


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