Impairment of Autonomically Mediated Heart Rate Control in Patients with Cardiac Dysfunction

By Robert E. Goldstein, G. David Beiser, Morris Stampfer, and Stephen E. Epstein

ABSTRACT
Patients with cardiac disorders have defective parasympathetic control of heart rate. To evaluate the possibility of similar changes in sympathetic control of heart rate, we compared reflex chronotropic responses to 80° upright tilt and nitroglycerin-induced hypotension in 31 cardiac patients and 7 normal individuals before and after partial parasympathetic blockade with atropine. Tilting revealed an attenuation of the normal heart rate increase in patients; the magnitude of this defect was greatest in patients with more severe symptoms (class III) and evidence of left ventricular dysfunction (the heart rate increase averaged 25 ± 3 beats/min in normal subjects, 12 ± 2 beats/min in class I-II patients, and 7 ± 1 beats/min in class III patients). Class III symptoms due to mechanical causes (mitral stenosis), however, were not associated with this defect. A marked reduction in heart rate rise with hypotension was seen only in those class III patients without mitral stenosis (0.4 ± 0.1 beats min⁻¹ mm Hg⁻¹ vs. 3.0 ± 0.5 beats min⁻¹ mm Hg⁻¹ in normal subjects). This abnormality also persisted after atropine administration, thus confirming a defect in the sympathetic as well as the parasympathetic component of baroreceptor-mediated reflex heart rate control in patients with cardiac dysfunction. Infusions of isoproterenol produced equivalent rises in heart rate in patients and normal individuals, excluding a reduction in beta-receptor responsiveness as a cause of impaired sympathetic influence. Norepinephrine depletion, however, is a well-recognized concomitant of cardiac failure. It is possible that the reduction in sympathetically mediated heart rate responses results in part from depletion of the sympathetic neurotransmitter.

KEY WORDS
heart failure  baroreceptors  atropine  nitroglycerin  sympathetic nervous system  postural change

Baroreceptor reflexes play an important role in modulating circulatory responses of normal individuals. Recent observations indicate, however, that patients with disordered cardiac function may have significant impairment of reflex circulatory control. Eckberg and co-workers (1) have demonstrated a marked attenuation of reflex cardiac slowing mediated by the parasympathetic nervous system in patients with a variety of cardiac disorders. In contrast, relatively little is known about the influence of heart disease on human cardiac reflexes mediated by the sympathetic nervous system. We therefore evaluated reflex heart rate responses to head-up tilt and to vasodilator-induced hypotension before and after parasympathetic blockade in normal individuals and in patients with various degrees of functional limitation due to cardiac disease. To characterize sympathetic influence on heart rate more completely, we also measured the chronotropic response to maximal exercise and to the beta-adrenergic agonist isoproterenol.

Methods
A total of 31 patients, 13 women and 18 men ranging in age from 15 to 61 years, was studied. Twenty-four had valvular heart disease, 5 had dilated cardiomyopathy, and 2 had a previously repaired atrial septal defect. None of the subjects in this study had hypertension or a history of hypertension. All subjects were in normal sinus rhythm.

PATIENTS WITHOUT OVERT CARDIAC DYSFUNCTION
Twelve patients (median age 40 years) were in either functional class I or class II (New York Heart Association). All 9 of these patients evaluated by cardiac catheterization had normal right and left ventricular end-diastolic pressures and cardiac output at rest except for 2 patients with mild mitral disease, who had cardiac indexes just below 2.5 liters min⁻¹ m⁻², the lower limit of normal for our laboratory.

PATIENTS WITH CARDIAC DYSFUNCTION
The remaining 19 patients (median age 43 years) were in functional class III. In the 13 patients with mixed
stensosis and insufficiency of the aortic and mitral valves or with primary myocardial disease, cardiac catheterization
documented elevated end-diastolic pressures in the right ventricle (≥ 6 mm Hg) or the left ventricle (≥ 14
mm Hg), often with a decreased cardiac index. Thus, each of these 13 patients manifested some degree of
ventricular dysfunction.

Six other patients in functional class III had pure
mitral stenosis without evidence of ventricular failure.
Hence, low cardiac output, when it was present in these
patients, reflected mechanical obstruction at the mitral
valve rather than myocardial dysfunction. Because of
this difference, the results obtained in these 6 patients
were evaluated separately from those obtained in class
III patients without mitral stenosis. Subjects in this
study were regularly receiving no other drugs except
digoxin and diuretics; there was no difference between
class I-II patients and class III patients with respect to
the frequency of use or the dosage of these drugs. In
addition to the 31 patients, a group of 7 normal men,
aged 21-24 years, was studied in a similar fashion.

STUDY PROTOCOL

All studies were performed in the postabsorptive state.
Brachial arterial blood pressure was measured using a
Cournand needle and a Statham 23 Db transducer. Zero
reference level was set at the estimated level of the right
atrium. The electrocardiogram was monitored continu-
ously, and no arrhythmias were observed.

The protocol for evaluating heart rate responses was
given by measuring base-line values of heart rate and
arterial blood pressure (mean and phasic) with the
subject at supine rest on a tilt table. In 13 patients and 5
normal subjects isoproterenol was infused intravenously;
the rate of infusion of the drug was increased every 4
minutes until heart rate rose at least 20 beats/min above
base line or until mean arterial blood pressure fell more
than 5 mm Hg. The heart rate response of each subject
was measured at every infusion rate. Because of the
approximately linear nature of the heart rate response,
however, the isoproterenol response was characterized as
the maximal change in heart rate from control divided by
the corresponding rate of isoproterenol infusion.

Following recovery from the effects of isoproterenol, all
subjects were tilted to the 80° upright position; heart
rate and arterial blood pressure were allowed to stabilize
(a process taking 1-2 minutes) and then recorded.
Repeat measurements were made in both the supine and
the upright positions until reproducible values for heart
rate and arterial blood pressure were obtained for each
position.

The baroreceptor-mediated heart rate response to
lowered arterial blood pressure was then determined
while the subjects remained in the 80° head-up tilt
position. Mild arterial hypotension was induced by
sublingual administration of nitroglycerin, 0.4–0.8 mg.
Heart rate and arterial blood pressure were recorded
continuously until mean blood pressure fell at least 10
mm Hg from the control level. Measurements of heart
rate and blood pressure were recorded after these param-
eters were stable for at least 30 seconds; the subjects were
then returned to the supine position. These maneuvers
did not produce severe hypotension (systolic arterial
blood pressure below 80 mm Hg) in any subject.

The effects of nitroglycerin were allowed to dissipate
completely (45–60 minutes). Heart rate and arterial
blood pressures were then recorded in the supine position
before and 5 minutes after the intravenous administra-
tion of 3 mg of atropine sulfate in 24 of the patients and
in all of the normal subjects. Shortly after atropine was
given, the subjects were again tilted to the 80° upright
position, and a repeat assessment of the heart rate
response to the nitroglycerin-induced blood pressure
reduction was conducted, this time in the presence of
partial parasympathetic blockade.

On a separate occasion, the heart rate response to
maximal exercise was obtained in 27 of the 31 patients
and in all of the normal subjects. The subjects exercised
on a motor-driven treadmill at progressively increasing
grades and speeds until they were stopped by dyspnea or
fatigue. Grades and speeds were chosen individually to
produce dyspnea or fatigue after 5–10 minutes. The heart
rate during the peak level of exertion was recorded.

Results

HEART RATE RESPONSE TO POSTURAL CHANGE AND BLOOD
PRESSURE REDUCTION

Consistent blood pressure changes were not ob-
served in any group shortly after 80° upright tilt.
However, heart rate rose by an average of 25 ± 3
(SE) beats/min with 80° upright tilt in the normal
group compared with an average increase of 12 ± 2
beats/min (P < 0.001) in the class I-III patients
(Fig. 1 and Table 1). The response of each of these
two groups was significantly greater than that seen
in the class III patients, who manifested an in-
crease of only 7 ± 1 beats/min. Thus, in these three
groups, the heart rate increment with upright tilt
was inversely related to the extent of functional
impairment. In contrast, heart rate increased with
upright tilt an average of 20 ± 3 beats/min in class
III patients with mitral stenosis, a change that was

![Heart rates measured at supine rest and following 80° head-up
tilt are shown for normal individuals (left), class I-II patients
(middle), and class III patients (right). Paired data from each
individual are connected; circled bars denote mean values. The
magnitude of the heart rate rise with upright tilt decreased
progressively with the extent of functional impairment.](http://circres.ahajournals.org/)

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Heart Rate Responses to Exercise, Tilt, Atropine, Nitroglycerin, and Isoproterenol

<table>
<thead>
<tr>
<th>Maximal exercise (beats/min)</th>
<th>Tilt (ΔHR)</th>
<th>Atropine (ΔHR)</th>
<th>Nitroglycerin Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control study</td>
<td>Atropine study</td>
<td>Control study</td>
</tr>
<tr>
<td>A. Normal subjects 184 ± 2</td>
<td>3.0 ± 0.5</td>
<td>2.2 ± 0.2</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>P(A vs. B)</td>
<td>&lt; 0.02</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>B. Class I-II patients</td>
<td>170 ± 4</td>
<td>12 ± 2</td>
<td>28 ± 4</td>
</tr>
<tr>
<td>P(B vs. C)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C. Class III patients</td>
<td>128 ± 4</td>
<td>7 ± 1</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>P(C vs. D)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D. Class III-MS patients</td>
<td>137 ± 5</td>
<td>20 ± 3</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td>P(D vs. B)</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

All values are means ± se. ΔHR = change in heart rate (beats/min) occurring with each intervention, ΔMABP = change in mean arterial blood pressure (mm Hg) in 80° upright position following sublingual administration of nitroglycerin, ΔPP = change in pulse pressure (mm Hg) following sublingual administration of nitroglycerin, ΔHR/dose = change in heart rate per ng/kg min⁻¹ of isoproterenol infusion, MS = mitral stenosis, and NS = not significant (P > 0.05).

Heart rate responses to hypotension were significantly different in each of the groups: heart rates averaged 86 ± 4 beats/min in the normal group, 83 ± 3 beats/min in the class I-II patients, 85 ± 4 beats/min in the class III patients, and 87 ± 4 beats/min in the class III patients with mitral stenosis. The reflex increase in heart rate following the nitroglycerin-induced reduction in arterial blood pressure averaged 3.0 ± 0.5 beats/min for each 1 mm Hg drop in mean arterial blood pressure in the normal group, 3.1 ± 0.3 beats min⁻¹ mm Hg⁻¹ in the class I-II patients, and 2.7 ± 0.5 beats min⁻¹ mm Hg⁻¹ in the class III patients with mitral stenosis (Fig. 2 left, Fig. 3 left, and Table 1). Thus, heart rate responses in these three groups were not significantly different. In marked contrast, the increase in heart rate following nitroglycerin administration averaged only 0.4 ± 0.1 beats min⁻¹ mm Hg⁻¹ in the class III patients, a mean response that was significantly different (P < 0.001) from that of each of the other three groups.

Because of the importance of pulse pressure as well as mean pressure in determining baroreceptor-mediated responses, heart rate increments were related to the change in pulse pressure (ΔHR/ΔPP) as well as to the change in mean pressure (ΔHR/ΔMABP) (Table 1). The results obtained with this index were qualitatively similar to those just described.
pretreatment values. Hence, the heart rate increment after atropine administration, like the heart rate increment with upright tilt, varied inversely with the degree of functional impairment in the three groups tested. The number of patients with pure mitral stenosis given atropine was insufficient for statistical evaluation of their performance. It is noteworthy, however, that two of three patients with mitral stenosis had a rise in heart rate of 20 beats/min or more despite their class III status.

To determine whether an impairment of sympathetic reflexes contributed to the reduced heart rate response to lowered arterial blood pressure, studies of the heart rate response to hypotension were repeated after partial vagal blockade by atropine. When a blood pressure reduction was again induced (by nitroglycerin and 80° upright tilt) after atropine administration, heart rate increments per unit blood pressure decrement averaged 2.2 ± 0.2 beats min⁻¹ mm Hg⁻¹ in the normal group, 2.4 ± 0.4 beats min⁻¹ mm Hg⁻¹ in class I-II patients, and 0.4 ± 0.1 beats min⁻¹ mm Hg⁻¹ in class III patients (Fig. 2 right and Fig. 3 right). Thus, the marked attenuation in the heart rate response of class III patients relative to that of normal individuals and class I-II patients was equally apparent before and after atropine administration (Fig. 3): the difference between class III patients and either the normal group or the class I-II patients remained highly significant (P < 0.001) after atropine administration. The heart rate increment per unit blood pressure decrement (∆HR/∆MABP) after atropine administration was somewhat less than that which occurred in the absence of atropine in both the normal group (mean -27%) and the class I-II patients (mean -23%), but neither of these decreases achieved statistical significance on paired analysis. When data from the normal group and the class I-II patients were pooled, however, a significant difference became apparent (mean -25%, P < 0.05), indicating that both increased sympathetic drive and withdrawal of vagal tone contributed to the heart rate response to hypotension. The low level of ∆HR/∆MABP in class III patients was unaffected by atropine administration.

Only two patients with severely symptomatic mitral stenosis were studied after atropine administration. Both of these patients maintained values of ∆HR/∆MABP after atropine administration that were nearly equal to the means of the normal group and the class I-II patients, indicating that sympathetically mediated baroreceptor reflexes to the sinus node were intact despite their class III status.

Results using ∆HR/∆PP after atropine administration, like the results obtained before atropine was given, were very similar to those obtained using ∆HR/∆MABP.

HEART RATE RESPONSE TO EXERCISE AND TO ISOPROTERENOL

The peak heart rate response to a maximal level of exercise averaged 184 ± 2 beats/min in the normal subjects and 170 ± 4 beats/min in the class...
Peak heart rates during treadmill exercise are related to patient age for members of each group. Class III patients with or without mitral stenosis (MS) had lower peak heart rates compared with those of age-matched normal individuals and class I-II patients.

I-II patients (Fig. 5 and Table 1). If the normal linear decrease in heart rate at maximal exercise with increasing age is taken into consideration (2, 3), the lower heart rates of the class I-II patients can be related entirely to their greater age. In contrast, the peak heart rate averaged $128 \pm 4$ beats/min in class III patients and $137 \pm 5$ beats/min in class III patients with mitral stenosis. These values are significantly lower than those seen in the normal subjects ($P < 0.001$) and the class I-II patients ($P < 0.001$), and the differences are not attributable to differences in age.

With the exception of one patient in the class III group, the heart rate response to an infusion of isoproterenol at increasing concentrations was essentially the same in each of the four groups (Fig. 6 and Table 1). These increments averaged $0.66 \pm 0.18$ beats/min per ng/kg min$^{-1}$ of isoproterenol in the normal group, $0.70 \pm 0.02$ in the class I-II patients, $0.58 \pm 0.11$ in the class III patients, and $0.93 \pm 0.15$ in the class III patients with mitral stenosis. It should be noted that the heart rate rises observed with isoproterenol were never accompanied by blood pressure reductions in excess of 5 mm Hg.

**Discussion**

Previous studies in man have demonstrated that parasympathetic control of heart rate is impaired in patients with cardiac dysfunction (1). The results of the present investigation confirm these findings and further demonstrate that cardiac dysfunction also leads to severe derangement of sympathetic control of heart rate. Our conclusions are based on several findings. First, in patients with cardiac disease, the normal increase in heart rate that occurs after atropine administration is diminished; the degree to which this response is impaired relates directly to the degree of cardiac dysfunction (Fig. 4). Eckberg and co-workers (1) have reported similar findings. Thus, it appears that under relatively basal conditions, vagal tone is diminished in patients with cardiac disease. Moreover, Eckberg and co-workers have also shown a diminution in the vagally mediated cardiac slowing normally following transient elevations of arterial blood pressure, indicating an additional defect in the parasympathetic component of baroreceptor regulation of heart rate.

Further evidence of an impaired autonomically mediated reflex heart rate response in patients...
with heart disease was found in our investigation of the effects of upright tilt. This maneuver normally results in a baroreceptor-actuated reflex increase in heart rate, a change mediated by alterations in both parasympathetic and sympathetic stimulation to the heart: parasympathetic tone is withdrawn and sympathetic stimulation is increased (4). In patients with heart disease, cardiac speeding in response to upright tilt is progressively impaired with increasing degrees of cardiac dysfunction (Fig. 1). Thus, the ability of the autonomic nervous system to speed the heart in response to postural alterations, through either sympathetic stimulation, parasympathetic withdrawal, or both, appears to be considerably diminished in patients with heart disease.

The possibility that the sympathetic component as well as the parasympathetic component of reflex control of heart rate is impaired in cardiac patients was evaluated by determining the heart rate response to a vasodilator-induced decrease in arterial blood pressure before and after partial blockade of parasympathetic influence by atropine. In these studies, we found a marked attenuation of normal cardiac speeding during an arterial blood pressure reduction in those patients with evidence of severe myocardial dysfunction. The persistence of this impairment after parasympathetic blockade (Figs. 2 and 3) confirms the dual nature of the defect in autonomically mediated heart rate control: a deficiency in sympathetic cardioacceleration accompanies a deficiency in parasympathetic cardiac slowing (1).

The precise mechanisms responsible for the impaired sympathetic component of baroreceptor action on heart rate are uncertain. Our data demonstrated that the chronotropic response to isoproterenol was essentially indistinguishable in patients and normal subjects (Fig. 6). Therefore, it is unlikely that the reduced heart rate response to blood pressure decreases could have been caused by a diminution of the sensitivity of beta-receptors to the chronotropic actions of norepinephrine released by sympathetic nerve endings. Alternatively, it is possible that the sensitivity of the carotid or aortic arch baroreceptors is reduced. In heart failure, sodium and water contained in the arterial wall increase (5), and the resulting change in arterial wall compliance could lead to a diminished sensitivity of the afferent limb of the baroreceptor reflex. However, the demonstration by Covall and his associates (6) that the heart rate response tostellate ganglion stimulation is reduced in dogs with chronic heart failure implies a defect of the efferent limb of the reflex. Norepinephrine, the sympathetic neurotransmitter, is either absent or present in reduced amounts in the cardiac sympathetic nerve endings of animals (7-9) or patients (10, 11) with heart failure. When all of this evidence is considered, it appears likely that the marked attenuation of sympathetically mediated chronotropic baroreceptor reflexes in patients with myocardial dysfunction is related, at least in part, to depletion of the sympathetic neurotransmitter, norepinephrine. This condition, in turn, might result in release of less neurotransmitter at any given level of neural activity and thereby cause the observed derangement of sympathetically mediated control of heart rate.

The mechanisms responsible for the defect in parasympathetic control of heart rate are even less clear. The sinoatrial node reacts normally to stimulation of the vagus nerves in dogs with experimentally induced heart failure (12), a finding suggesting that the efferent limb of the reflex is not impaired. Whether there is a decrease in the sensitivity of the carotid or aortic arch baroreceptors or an abnormality in the function of centers within the central nervous system which govern the baroreceptor reflex remains to be determined.

Despite their class III functional status, it is noteworthy that the six patients with pure mitral stenosis had relatively normal heart rate responses to upright tilt, atropine administration, and blood pressure reduction in contrast to the markedly attenuated responses of class III patients with other cardiac diseases. This latter group generally had evidence of left ventricular dysfunction (as opposed to the mechanical obstruction to left ventricular filling responsible for the symptoms in the patients with pure mitral stenosis). Thus, left ventricular failure per se (rather than symptomatic impairment or left atrial or pulmonary arterial hypertension) appears to constitute the determining stimulus leading to attenuation of baroreceptor-mediated sympathetic reflexes. Whether right ventricular failure alone can produce similar changes cannot be determined from our data.

In addition, our observations during exercise suggest that the defect in sympathetic mechanisms may not be limited to reflexes involving only the baroreceptor system. Exercise-induced tachycardia normally is mediated largely by increased sympathetic and decreased parasympathetic activity (4). Since vagal tone is minimal, even at rest, in patients with heart failure, our finding that heart rate at maximal exercise is reduced in class III patients (Fig. 5) is compatible with the concept
that the ability of the sympathetic system to speed the heart during exercise (an attribute presumably not mediated by baroreceptor mechanisms) is also impaired in these individuals. It should be noted that a generalized defect in sympathetic function would be expected if the abnormality in heart rate control is caused by depletion of cardiac stores of norepinephrine. Caution must be observed, however, in interpreting the exercise results in this manner. The class III patients with mitral stenosis, who otherwise manifested relatively intact reflex heart rate responses, exhibited a marked reduction in heart rate at maximal exercise similar to that observed in the other class III patients.

It is possible that the reduction in heart rate at maximal exercise reflects, at least in part, a tendency of certain patients to terminate exercise because of dyspnea or fatigue before the sympathetically-induced tachycardia can become fully manifest. That this explanation is not satisfactory, however, is indicated by the results of a previous study (13) in which we characterized the circulatory response of patients with various types of heart disease to intense levels of treadmill exercise. The circulatory stress produced by exercise was judged independently of symptoms by measuring mixed venous (i.e., pulmonary arterial) oxygen saturation. During an exhausting level of exercise, all normal subjects extracted oxygen at a rate that produced a pulmonary arterial oxygen saturation of 30% or less. At this maximal level of exercise, heart rate averaged 171 beats/min. Similarly, when they were performing exhausting exercise, seven patients in functional class II or class III with pure mitral stenosis and normal sinus rhythm achieved pulmonary arterial oxygen saturations of 30% or less (average 25.8%). This degree of pulmonary artery desaturation indicates that the exercise was sufficiently intense and prolonged to produce substantial circulatory stress and demonstrates that the patients were not stopped prematurely by symptoms. At this maximal exercise, heart rate averaged 139 beats/min, significantly less (P < 0.05) than that in normal subjects. Five of the seven patients had heart rates less than 160 beats/min (143, 134, 129, 126, and 115 beats/min), the slowest heart rate observed when maximal exercise was performed by normal subjects. Likewise, heart rate averaged 145 beats/min in seven patients whose cardiac reserve was decreased as a result of cardiomyopathy, mitral regurgitation, aortic regurgitation, or mixed valvular disease (P < 0.05 compared with normal subjects), and six had heart rates less than 160 beats/min (156, 154, 153, 132, 127, and 124 beats/min) during exercise that reduced pulmonary arterial oxygen saturation to less than 30% (the seventh had a heart rate of only 168 beats/min). These differences in heart rate in conjunction with the results of the present investigation indicate that heart rate is reduced during maximal exercise in patients with cardiac dysfunction and that this reduction is not simply the result of symptom-induced premature termination of exercise.

In conclusion, cardiac dysfunction appears to be associated with a marked impairment of autonomically mediated control of heart rate. That a sympathetically mediated increase in heart rate constitutes an important compensatory mechanism for augmenting cardiac output in patients with heart disease has been well documented, and it seems probable that any condition interfering with such a mechanism will contribute to a reduction in cardiac reserve. If defective sympathetic neural control of the sinus node is associated with defective sympathetic neural control of the ventricle, then the myocardial contractile response to stress would also be impaired, thereby leading to a reduction of another important reserve mechanism of the heart. On the other hand, stimulation of sympathetic nerves to the ventricle decreases ventricular electrical stability (14). It is therefore possible that sympathetic denervation of a ventricle that is intrinsically irritable from underlying disease might enhance ventricular electrical stability and decrease the risk of arrhythmic death. Thus, although our findings indicate that patients with abnormal left ventricular function suffer from impaired sympathetic as well as parasympathetic neural regulation of the sinus node, further studies are necessary to define both the full extent of alterations in autonomic regulation of the heart in the presence of cardiac dysfunction and the clinical and physiological implications of these alterations.

References

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