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 sympathetic nervous system nitroglycerin 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
stens 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 Gournand needle and a Statham 23 Db transducer. Zero reference level was set at the estimated level of the right atrium. The electrocardiogram was monitored continuously, and no arrhythmias were observed.

The protocol for evaluating heart rate responses was begun 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; 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.

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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 parameters 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 administration of 2 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 observed 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-II 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 increase 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
TABLE 1

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

<table>
<thead>
<tr>
<th>Heart Rate Studies</th>
<th>Nitroglycerin Administration</th>
</tr>
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<tbody>
<tr>
<td>Maximal exercise (beats/min)</td>
<td>AHR/ΔMABP</td>
</tr>
<tr>
<td></td>
<td>Control study</td>
</tr>
<tr>
<td>A. Normal subjects 184 ± 2</td>
<td>3.0 ± 0.5</td>
</tr>
<tr>
<td>(A vs. B)</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>B. Class I-II patients 170 ± 4</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>(B vs. C)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C. Class III patients 128 ± 4</td>
<td>0.4 ± 0.1</td>
</tr>
<tr>
<td>(C vs. D)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>D. Class III-MS patients 137 ± 5</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td>(D vs. B)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

All values are means ± se. AHR = 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, AHR/dose = change in heart rate per ng/kg min⁻¹ of isoproterenol infusion, MS = mitral stenosis, and NS = not significant (P > 0.05).

not significantly different from that of the normal group.

Before the administration of nitroglycerin, mean heart rates during 80° head-up tilt were indistinguishable 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.

SUPINE AND UPRIGHT HEART RATES AFTER ATROPINE ADMINISTRATION

Following the intravenous administration of 2 mg of atropine sulfate, heart rate in the supine position increased an average of 53 ± 6 beats/min in the normal subjects compared with 28 ± 4 beats/min (P < 0.001) in the class I-II patients (Fig. 4 and Table 1). Supine heart rate increased even less after atropine administration in the class III patients, averaging only 10 ± 1 beats/min above
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 $2.2 \pm 0.2$ beats min$^{-1}$ mm Hg$^{-1}$ in the normal group, $2.4 \pm 0.4$ beats min$^{-1}$ mm Hg$^{-1}$ in class I-II patients, and $0.4 \pm 0.1$ 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 ($\Delta HR/\Delta MABP$) 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 $\Delta HR/\Delta MABP$ 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 $\Delta HR/\Delta MABP$ 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 $\Delta HR/\Delta PP$ after atropine administration, like the results obtained before atropine was given, were very similar to those obtained using $\Delta HR/\Delta MABP$.

HEART RATE RESPONSE TO EXERCISE AND TO ISOPROTERENOL

The peak heart rate response to a maximal level of exercise averaged $184 \pm 2$ beats/min in the normal subjects and $170 \pm 4$ 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 ± 4 beats/min in class III patients and 137 ± 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 ± 0.18 beats/min per ng/kg min⁻¹ of isoproterenol in the normal group, 0.70 ± 0.02 in the class I-II patients, 0.58 ± 0.11 in the class III patients, and 0.93 ± 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.

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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 Covel and his associates (6) that the heart rate response to stellate 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 in the normal subjects 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 (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

6. Covell JW, Chidsey CA, Braunwald E: Reduction of the
cardiac response to postganglionic sympathetic nerve
stimulation in experimental cardiac failure. Circ Res
19:51–56, 1966
7. Chidsey CA, Kaiser GA, Sonnenblick EH, Spann JF Jr,
Braunwald E: Cardiac norepinephrine stores in experi-
mental heart failure in the dog. J Clin Invest
43:2386–2393, 1964
8. Spann JF Jr, Chidsey CA, Braunwald E: Reduction of
cardiac stores of norepinephrine in experimental heart
9. Vogel JHK, Jacobowitz D, Chidsey CA: Distribution of
norepinephrine in failing bovine heart: Correlation of
chemical analysis and fluorescence microscopy. Circ Res
24:71–84, 1969
10. Chidsey CA, Braunwald E, Morrow AG, Mason DT:
Myocardial norepinephrine concentration in man: Effects
269:653–658, 1963
11. Chidsey CA, Braunwald E, Morrow AG: Catecholamine
excretion and cardiac stores of norepinephrine in congest-
12. Higgins CB, Vatner SF, Eckberg DL, Braunwald E:
Alterations in the baroreceptor reflex in conscious dogs
13. Epstein SE, Beiser GD, Stampfer M, Robinson BF,
Braunwald E: Characterization of the circulatory re-
sponse to maximal upright exercise in normal subjects
and patients with heart disease. Circulation
35:1049–1062, 1967
14. Han J: Mechanisms of ventricular arrhythmias associated
with myocardial infarction. Am J Cardiol
24:800–813, 1962
Impairment of autonomically mediated heart rate control in patients with cardiac dysfunction.
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