Heart rate variability in depressive and anxiety disorders

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Loss of normal autonomic nervous system control of heart rate and rhythm is an important risk factor for adverse cardiovascular events. After myocardial infarction, reduction in beat-to-beat heart rate variability, a measure of cardiac autonomic innervation by the brain, is a strong predictor of death. With loss of vagal innervation, as is noted in patients with severe neuropathy and in heart transplant recipients, there is loss of heart rate variability. It is speculated that decreased parasympathetic innervation exposes the heart to unopposed stimulation by sympathetic nerves. Individuals with high hostility scores and patients with anxiety or depressive disorders have low heart rate variability and may be at increased risk for cardiovascular death associated with coronary heart disease and arrhythmias. After myocardial infarction, depressed patients exhibit higher mortality rates compared with nondepressed patients. Men with "phobic anxiety," a construct that appears to overlap substantially with panic disorder, also have higher rates of sudden cardiac death and coronary artery disease than control populations. The reduction in autonomic nervous system control to the heart may be one link between psychopathology and heart disease. Although tricyclic antidepressants reduce heart rate variability, at least one study has suggested that, in patients with panic disorder, treatment with the selective serotonin reuptake inhibitor paroxetine normalizes heart rate variability. Hence there is potential for the treatment of psychiatric disorders to affect positively the development and course of cardiovascular disease. (Am Heart J 2000;140:S77-83.)

Psychosocial factors may play a clinically significant role in the prognosis of cardiovascular disease. There is accumulating clinical evidence to suggest an association between mood and anxiety disorders and cardiovascular disease.[1] Depression is a major risk factor for the development of cardiovascular sequelae and sudden cardiac death after a myocardial infarction (MI). In patients after MI, depression is associated with increased mortality rate that is similar to that associated with left ventricular dysfunction or a history of previous MI.[2,3] In addition, recent findings suggest that depression is an independent risk factor for progression of cardiovascular disease.[4] Changes in autonomic balance associated with decreased heart rate variability may place depressed patients who have an MI at increased risk for fatal arrhythmias.

Similarly, panic disorder occurs in approximately 4% of the general population and in up to 20% of primary care patients and 14% of cardiology patients.[5-9] Patients with panic disorder or phobic anxiety are at increased risk of cardiovascular disease compared with control subjects.[10,11] Findings from the Epidemiologic Catchment Area (ECA) Program, an epidemiologic study that evaluated the rate of psychiatric disorders in more than 18,000 adults in 5 cities in the United States, demonstrated that patients with panic disorder were at increased risk of high blood pressure, heart attack, and stroke compared with subjects with no psychiatric disorder.[11]

The association between psychiatric disorders and fatal coronary disease is cause for concern, and appropriate diagnosis and treatment of mood and anxiety disorders may lower the risk of coronary heart disease and minimize associated morbidity and mortality.

Heart rate variability

Loss of the normal autonomic nervous system control of heart rate and cardiac rhythm is an important risk factor for adverse cardiovascular events. For example, after MI, reduction in beat-to-beat heart rate variability, a measure of cardiac autonomic innervation by the brain, is a strong predictor of sudden death and ventricular arrhythmias.[12] Heart rate normally varies on a beat-to-beat basis principally because of parasympathetic innervation to the heart, transmitted from the brain by the vagus nerve. With the loss of vagal innervation, as occurs in patients with severe neuropathy and in heart transplant recipients, there is marked attenuation of heart rate variability. It is speculated that such reductions in parasympathetic innervation leave the heart exposed to unopposed stimulation by the sympathetic nervous system. This makes the heart vulnerable to arrhythmia and sudden death and also accelerates development of atherosclerotic coronary artery disease.[13]

Beat-to-beat blood pressure variability is another inter-

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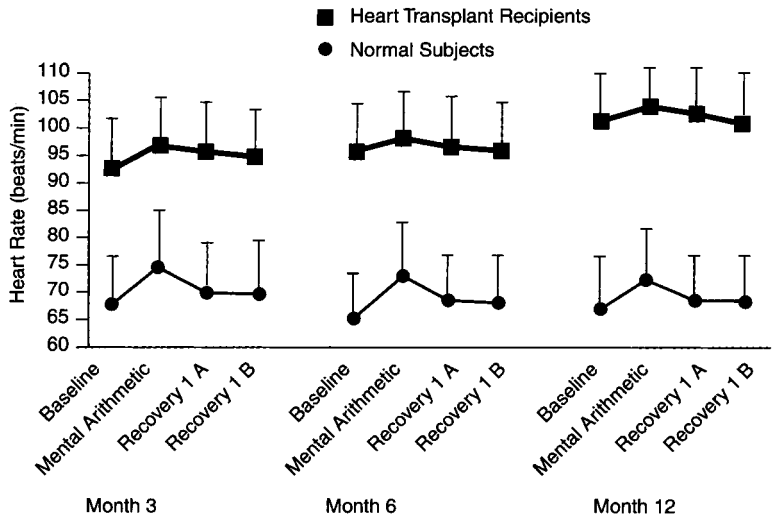
Figure 1



Mean heart rate during baseline, mental arithmetic, and recovery periods in heart transplant recipients 3, 6, and 12 months after the transplantation compared with normal subjects. *Error bars* represent SD. Reprinted from Shapiro PA, Sloan RP, Bagiella E, et al. Heart rate reactivity and heart period variability throughout the first year after heart transplantation. Psychophysiology 1996;33:54-62. Reprinted with the permission of Cambridge University Press.

esting cardiovascular effect that has been evaluated as a prognostic indicator in cardiac disease. There is an indirect correlation between heart rate variability and blood pressure variability in which increased heart rate variability is associated with decreased blood pressure variability.[14] Parasympathetic influences on the heart limit blood pressure variability. However, heart transplant recipients demonstrate significant blood pressure variability because of the absence of parasympathetic influences on the heart. Increased blood pressure variability is an independent and powerful risk factor for the development of coronary artery disease. Coronary artery disease tends to develop at an accelerated rate in patients who have received a heart transplant, and it is hypothesized that beat-to-beat blood pressure variability is partially responsible.

Heart rate response during stress

The mechanisms responsible for increased heart rate and blood pressure during psychological stress are incompletely understood. It is known that sympathetic activation leads to increased catecholamine release during periods of acute stress, which subsequently increases heart rate. However, another factor in stress-induced tachycardia is the direct innervation from the brain to the heart. Understanding the mechanisms of stress-induced reactivity may elucidate the methods by which the central nervous system regulates cardiovascular function and may clarify the association between cardiovascular disease and psychiatric disorders. The ability of the heart to respond to mental stress depends on both direct autonomic innervation and the effect of circulating catecholamines.

Jiang et al[15] have shown that mental stress–induced ischemia is a predictor of increased rates of fatal and nonfatal cardiac events. In an analysis of 136 patients with coronary artery disease, 5 mental stress tests were conducted to evaluate stress-induced ischemia. The incidence of adverse cardiac events was 2-fold greater in patients with stress-induced ischemia compared with patients who did not exhibit increased ischemia. The risk associated persisted even after controlling for ischemia during exercise.

Cardiac reactivity to psychological stress has also been evaluated with the mental arithmetic test, in which patients are asked to perform a series of stressful mental calculations. Shapiro et al[16] investigated central versus peripheral influences on cardiovascular reactivity to psychological stress. Twenty ambulatory heart transplant recipients were compared with 2 groups of normal subjects who were age-matched to the transplant donor and the heart recipient, respectively. All patients participated in the mental arithmetic test, which is associated with β-adrenergic activation and vagal withdrawal, and the reaction time test, which primarily measures β-adrenergic activity. Subjective stress ratings were increased in all subjects. However, heart rate reactivity was significantly attenuated in heart

Table I. Conditions associated with reduced heart rate variability

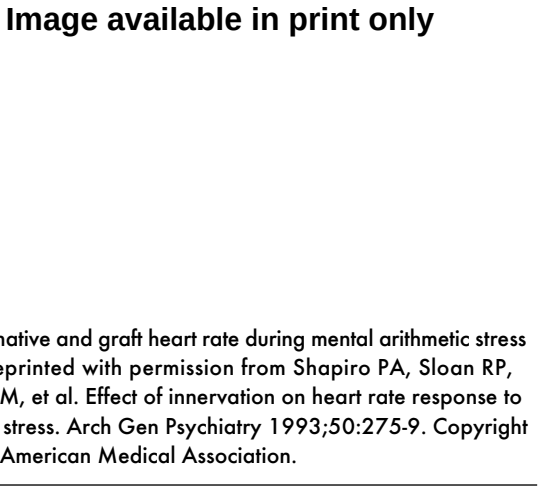
- Cardiac transplantation
- Diabetic neuropathy
- Normal aging
- TCA treatment
- Dysphoric emotional state
  - Behavioral inhibition
  - Anger/hostility
  - Stress
  - Panic disorder
  - Depression

transplant recipients compared with both groups of normal subjects, indicating that loss of direct neural modulation significantly blunted the capacity of the heart to respond to stress. Heart rate increase was also significantly slower in transplant recipients, suggesting that the delayed reactivity was associated with circulating catecholamine levels. Overall, in normal patients with innervated hearts, central nervous system effects were more important than catecholamines in mediating the immediate cardiac response to psychological challenge.

In the denervated heart of a heart transplant recipient, reinnervation does not occur within the first year after transplantation, and the cardiovascular response to mental stress remains blunted. In one study, 20 heart transplant recipients were challenged with the mental arithmetic stress test to measure heart rate reactivity 3, 6, and 12 months after transplantation. During each of the study periods, heart rate reactivity of the transplant recipients remained blunted compared with normal subjects (Figure 1).[17] Because cardiac and hemodynamic response to mental stressors may be influenced by the immunosuppressive medication regimens of heart transplant recipients, Sloan et al[18] compared psychophysiologic reactivity of heart transplant recipients with kidney transplant recipients and normal controls. Patients with transplanted hearts clearly had hemodynamic reactivity in response to psychological stress. However, compared with kidney transplant recipients and normal controls, heart transplant recipients exhibited blunted heart rate reactivity that was most likely influenced by cardiac denervation. Kidney transplant recipients had similar responses compared with normal controls, indicating that immunosuppressive medications did not alter the hemodynamic effects observed in heart transplant recipients.

Many recipients of heart transplants exhibit dual P waves on the electrocardiogram (ECG). One P wave is the result of the native sinoatrial node that remains responsive to direct autonomic innervation and functions independently from the grafted heart. The other P wave represents the electrical activity of the transplanted heart, which controls the rate and variability of the contractions.[17,19] The heart transplant patient provides a unique model for evaluating the impact of autonomic control of the cardiovascular system because both the native and graft sinus nodes are exposed to circulating catecholamines and medications. However, direct neural actions still affect the native node, serving as an internal control to evaluate cardiac response to mental stress in the denervated heart. As expected, in heart transplant recipients, the increase in the native P wave in response to a mentally stressful arithmetic test is greater than that of the graft P wave. Thus, centrally mediated direct autonomic innervation is responsible for the acute increase in heart rate in response to psychological stress (Figure 2).[19] Studies in transplant recipients with denervated hearts provide evidence that circulating catecholamines are not primarily responsible for increased heart rate during mental stress. Direct innervation of the heart by the brain clearly has the more important role in heart rate reactivity.

Figure 2

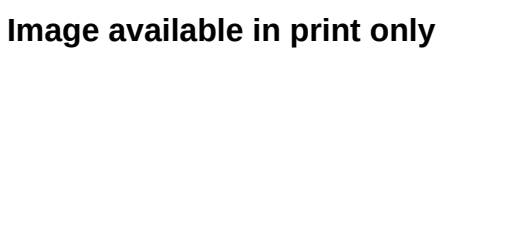


Mean native and graft heart rate during mental arithmetic stress test. Reprinted with permission from Shapiro PA, Sloan RP, Horn EM, et al. Effect of innervation on heart rate response to mental stress. Arch Gen Psychiatry 1993;50:275-9. Copyright 1993, American Medical Association.

Heart rate variability and psychiatric disorders

The findings of several studies suggest that patients with mood and anxiety disorders, as well as individuals prone to dysphoric emotional states, may be at increased risk of cardiovascular disease as a result of decreased heart rate variability.[1,10,20,21] There are a number of psychiatric situations in which heart rate variability

Figure 3



Sympathetic components of heart rate variability in patients with panic disorder before and after paroxetine (20 mg/d). Reprinted with permission from Tucker P, Adamson P, Miranda R, et al. Paroxetine increases heart rate variability in panic disorder. J Clin Psychopharmacol 1997;17:370-6.

becomes abnormally low (Table I).[13] For example, men with hostility as a personality trait have lowered heart rate variability associated with decreased vagal modulation and sympathetic predominance. Sloan et al[22] noted a significant inverse relation between hostility and daytime levels of high-frequency power, a measure of vagal modulation of R-R intervals, in normal healthy men younger than 40 years. A positive relation between low-frequency to high-frequency power ratio and hostility was also observed. Increased sympathetic predominance has been observed during periods of stress in healthy subjects undergoing 24-hour continuous ECG monitoring.[23]

Although the sympathetic nervous system is involved in the pathogenesis of panic disorder, it is not globally activated in response to stress or during panic attacks.[24] When panic attacks are induced in the laboratory with either placebo or lactate infusion, subjects have a sudden increase in heart rate, in the order of 15 to 20 beats/min, that corresponds with the panic attack.[25] The acute increase in heart rate during panic attacks is not associated with circulating catecholamines, as shown in patients pretreated with large doses of intravenous propranolol who continue to exhibit increased heart rate in response to lactate infusions.[26] Because lactate infusions significantly attenuate vagal tone and increase heart rate in normal volunteers,[27] it is postulated that reductions in central parasympathetic activity may contribute to decreased heart rate variability and increased heart rate during periods of anxiety.

Patients with anxiety disorders, such as panic disorder, also exhibit chronically reduced heart rate variability. Patients with panic disorder have reduced parasympathetic innervation to the heart compared with normal adults.[28-30] In one analysis of resting ECG recordings from 10 patients with panic disorder compared with 14 control subjects, patients with panic disorder exhibited significantly decreased high-frequency peaks, associated with reduced parasympathetic activity, on the power spectrum analysis.[28] Yeragani et al[29] evaluated heart rate variability as a measure of autonomic responsiveness in 21 patients with panic disorder compared with 21 normal subjects. In the standing position, patients with panic disorder had decreased absolute low-frequency power (0.01 to 0.05 Hz) and increased mid-frequency power (0.07 to 0.15 Hz) compared with the control group. These findings suggest that patients with panic disorder have increased adrenergic and decreased cholinergic responsiveness.

Heart rate variability is also reduced in patients with depression.[1] Frasure-Smith et al[2] evaluated the effect of depression on 6-month survival in 222 patients after MI. Depression was an independent risk factor for death and a significant predictor of cardiac death. Depressed patients had a 5-fold higher mortality rate than nondepressed patients. The authors postulated that decreased heart rate variability in depressed patients may be associated with the occurrence of fatal arrhythmias.[2] In a subsequent evaluation of depression and 18-month survival rate in 222 patients after MI, depressive symptoms after an acute MI were significantly associated with cardiac death within the 18-month period.[3] Depression may increase the risk of ventricular arrhythmias after MI because of a decrease in vagal tone and an increase in sympathetic drive.

Heart rate variability is clearly reduced in individuals with hostile personalities and patients with anxiety and depressive disorders. These findings have significant implications because low heart rate variability is a powerful predictor of sudden cardiac death.[12,13,31] In a study evaluating death after MI, Bigger et al[12] studied the association between heart period variability and mortality rate in 715 patients 2 weeks after an MI. Heart period variability was evaluated with 6 frequency domain measures. Ultra-low frequency, very low frequency, and 24-hour total power were significantly associated with all-cause mortality, cardiac death, and arrhythmic death. When parasympathetic activity to the heart is reduced, sympathetic tone is unopposed, which may place the heart at risk for developing lethal arrhythmias.

There is a clear association between cardiac death and anxiety disorders. Men with high levels of phobic anxiety have a 3-fold greater risk of fatal coronary heart disease compared with men with lower levels of anxiety.[10,20] In a 6-year study of more than 1400 men in London, Haines et al[20] noted that men with high initial scores for phobic anxiety were at increased risk for major ischemic heart disease. Phobic anxiety was associated with fatal ischemic heart disease but not with death from other causes. Kawachi et al[32] prospectively

examined the effects of anxiety with 5 items from the Cornell Medical Index anxiety scale. Men with 2 or more anxiety symptoms had an increased risk of fatal coronary heart disease and sudden cardiac death compared with men who reported no anxiety symptoms. Kawachi et al[21] also noted that as the phobic anxiety score increased on the Crown-Crisp index (a diagnostic self-rating scale for common phobias), heart rate variability decreased. Men with higher levels of phobic anxiety also had lower levels of heart rate variability. The strong causal relation between phobic anxiety and the development of fatal coronary heart disease suggests that patients with high levels of anxiety are at increased risk for fatal coronary sequelae.

Treatment options

The importance of finding safe and effective agents to treat psychiatric conditions in patients with cardiac disease is paramount. Treatment with tricyclic antidepressants (TCAs), medications with powerful anticholinergic effects, blocks parasympathetic innervation to the heart and diminishes heart rate variability.[33-35] The adverse cardiovascular effects associated with TCA overdose are well-established, and these agents may exhibit untoward cardiovascular effects even when taken in therapeutic doses.[36] The effect of imipramine treatment (mean dose 70 mg/d) on heart rate variability measures was evaluated in 12 depressed patients and 6 patients with panic disorder. After 3 weeks of treatment, all patients had reduced heart rate variability as measured by mean consecutive differences and the standard deviation of the mean consecutive difference of the R-R intervals for supine and standing postures.[35] Consequently, TCAs may not be an appropriate choice for the management of mood and anxiety disorders in patients at risk for coronary heart disease.[37]

However, the selective serotonin reuptake inhibitors (SSRIs) appear to be safe for use in patients with cardiovascular disease and may be particularly beneficial in this population.[34,37] Unlike the TCAs, SSRIs are very rarely fatal in overdose and are infrequently associated with cardiac effects.[38] Studies suggest that in addition to efficacy in the management of psychiatric conditions, treatment with SSRIs may improve heart rate variability and exert beneficial effects on cardiac function in patients with panic disorder.[34,39,40] The effect of paroxetine (10 to 30 mg/d) on heart rate variability was evaluated in 8 patients with panic disorder who were successfully treated for their panic symptoms. Holter records of ECG were used to monitor variability before and after treatment with paroxetine. After treatment, relative low-frequency power was significantly decreased ($P < .05$) and relative ultra-low-frequency power was increased during sleep in patients with panic disorder ($P < .01$).[40]

Tucker et al[39] compared heart rate variability with power spectral analysis in 17 patients with panic disorder and 16 control patients who were not taking medication. Patients with panic disorder were analyzed before and after treatment with paroxetine 20 mg/d for 4 weeks. Before therapy, patients with panic disorder had higher sympathetic activity compared with controls. After treatment with paroxetine, patients with panic disorder had decreased total sympathetic activity in both the reclining and standing positions (Figure 3). The sympathetic baroreflex response also normalized and parasympathetic activity increased after paroxetine treatment in the patients with panic disorder. Additionally, 53% of patients with panic disorder had a reduction in panic attacks.

In a comparison of antidepressant medications in 81 clinically depressed patients with ischemic heart disease, Roose et al[34] evaluated the efficacy and safety of paroxetine (20 to 30 mg/d) compared with nortriptyline (dosed to a therapeutic plasma level of 50 to 150 ng/mL). Depression improved in 61% of patients treated with paroxetine and in 55% of nortriptyline-treated patients. Treatment with paroxetine did not affect heart rate, rhythm, or heart rate variability in depressed patients. However, patients who received nortriptyline had a significant increase in heart rate ($P < .001$) and reduction in heart rate variability ($P < .01$).

Fluoxetine (mean dose 50 mg/d) also appears to be safe for use in depressed patients with serious cardiovascular disease. In patients with impaired baseline cardiac conductivity, ejection fraction improved during treatment with this SSRI.[34]

Because psychiatric conditions often are comorbid with cardiac conditions, patients may require pharmacotherapy that will affect both disorders. Treatment decisions for these patients must be individualized to minimize the occurrence of adverse effects. Important factors to consider include the severity of the psychiatric and cardiac illness as well as the cardiovascular effects associated with antidepressant medications. Appropriate intervention in depressed and anxious patients with cardiovascular disease may significantly decrease rates of morbidity and mortality. As suggested by Williams and Chesney[41] it would be unfortunate not to treat psychosocial factors in patients with cardiovascular diseases, and the SSRIs as a class are safe for use in patients with cardiovascular disease.

Summary

Dysregulated autonomic control of the cardiovascular system may be associated with fatal arrhythmias and coronary artery disease. Parasympathetic innervation increases heart rate variability, whereas sympathetic innervation decreases heart rate variability. Lowered parasympathetic innervation or increased sympathetic effects may increase the risk for arrhythmias. Also, disruption of direct parasympathetic innervation, as noted

in heart transplant recipients, disrupts the inhibition of blood pressure variability and increases the risk for cardiovascular disease.

Psychosocial factors clearly affect the development and prognosis of cardiovascular disease. The role of the autonomic nervous system in psychiatric and cardiovascular disorders is being investigated by psychiatrists and cardiologists. Decreased heart rate variability, a predictor of cardiac health and adaptability, may provide some explanation for the association between cardiovascular disease and panic disorder. Depression, panic disorder, hostility, and other dysphoric emotional states are associated with decreased heart rate variability, which may increase the risk of fatal arrhythmias and coronary artery disease.

Early and appropriate treatment of anxiety and depressive disorders may prevent the development of comorbid cardiac conditions and may lower morbidity and mortality rates for patients with both conditions. Treatment with SSRIs appears to normalize some aspects of cardiac function in patients with comorbid psychiatric and cardiac illness. These findings suggest that psychosocial and pharmacologic therapies have the potential to improve cardiac health and to enhance patients' quality of life. Prospective clinical trials are needed to evaluate the efficacy of pharmacotherapy for depression and anxiety in patients with cardiovascular disease.

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