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Conference Report

The Importance of Depression in Cardiovascular and Cerebrovascular Disease

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Gary J. Kennedy, MD

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Introduction

Heart disease and stroke are the leading causes of death and disability among older Americans,^[1] despite advances in the identification of modifiable risk factors and improvements in the treatment of hypertension, coronary artery disease, cardiac arrhythmias and cardiomyopathies. Recent studies provide compelling evidence that the onset and outcome of both heart attack and stroke are influenced by depression. Antidepressants must be carefully chosen in these patients to avoid promoting cardiac arrhythmias or fostering dangerous drug interactions.

This report on the interaction between depression and cardiovascular and cerebrovascular disease summarizes selected presentations on this topic delivered at this year's American Association for Geriatric Psychiatry Annual Meeting, held in San Francisco, California.

Cardiology Overview

The Aging Heart

Kennedy and colleagues^[2] described the heart as a dual-chambered, rate-responsive pumping mechanism designed to sustain the organism's hemodynamic equilibrium. It is also a sense organ that is capable of responding to changes in motor performance, mental effort, and emotional states through central and peripheral neurohumoral inputs. There are several mechanisms underlying this relationship that are affected by advanced age. First, the major pumping chamber, the left ventricle, loses elasticity and exhibits greater impedance to ejection. The result is impaired left ventricular diastolic relaxation, poorer compliance, and less cardiac output. Second, there is a reduction in the number of sinoatrial pacemaking cells that jeopardizes the maintenance of cardiac rhythm. Third, there is a loss of neurohumoral sensitivity particularly to beta-adrenergic stimuli. Finally mitochondrial adenosine triphosphate production capacity is reduced such that cardiac energy reserves are more tenuous. Although 80% of cardiac output may be preserved into old age by vigorous exercise, the delicate balance of heart rhythm and energy expenditure becomes more precarious. Thus both ischemic and arrhythmic events are thought to be the proximate cause of cardiac mortality.

Heart Rate Control

The chief regulators of cardiac rhythm are the intrinsic pacemakers located in the upper and lower chambers of the heart. The sinoatrial (SA) node initiates the pacing signal, which is propagated through a specialized line of cells forming the bundle of His in the ventricular septum. There is an auxiliary atrioventricular (AV) node, which is capable of sustaining pacemaker function should the SA node fail. However the intrinsic rate of the AV node is too slow to prevent hemodynamic collapse in older adults. The pacemaking signal emanates from the cellular action potential and is represented on the surface electrocardiogram. The depolarizing atrium, represented by the P wave, signals the ventricle to contract in a twisting fashion which is seen as the QRS complex. The QRS is followed by the T wave, representing the repolarization of the ventricle. The interval between the Q wave (or first deflection of the R wave) to the end of the T wave is the QT interval. To provide a uniform measure, the QT interval is corrected for heart rate to yield a QTc value. QTc values above 450 msec are dangerous, those above 500 msec are considered pathological.

QTc pathology. Within the repolarization phase, when the ventricle is electrophysiologically recharging in preparation for another organized contraction, there is an absolute refractory period during which the cellular action

potential cannot be propagated. This refractory period allows the cells to regain equilibrium so that the pacemaking signal may be propagated with uniform velocity and direction. There is also a relative refractory period during which a sufficiently strong or errant stimulus will cause the ventricle to contract prematurely. As the QTc interval is prolonged, the relative refractory period becomes lengthier and thus more available to aberrant stimuli and arrhythmic response. Structural damage from ischemic or myopathic disease can cause the normally spent pacing signals to reenter the pacing pathway and fall within the relative refractory period hence short circuiting the system. The response may lead to a premature ventricular depolarization that, if repeated, becomes ventricular tachycardia (VT) which is usually self-limiting. However VT may decay into ventricular fibrillation (VF), which is fatal unless converted by electrophysiologic means. Torsade de pointes differs from VT in that it is a more unstable arrhythmia with a variable rate and wave form unlike the repetitive R waves of VT or the paroxysmal chaotic quiver of VF. Although not as malignant as VF, torsade de pointes is more deadly than VT.

Autonomic influences. There are also subtle, but important, variations in heart rate that are not detectable with routine electrocardiography. Heart rate variability, a measure of the moment-to-moment change in cardiac rhythm, reflects the balance between sympathetic and parasympathetic tone as well as the hemodynamic effects of inspiration and expiration. Heart rate increases imperceptibly with expiration and slows with inspiration. The respiratory effect on heart rate variability is reflected in the spectrum or distribution of frequencies that emerge with computer analysis of continuous rhythm monitoring. The frequency associated with parasympathetic tone appears to protect against the emergence of arrhythmias. Loss of heart rate variability is associated with life-threatening cardiac arrhythmias.

The Reciprocity of Depression and Vascular Disease

Glassman^[3] reported that cardiovascular mortality has been linked to a variety of mental disorders and behavioral and psychological attributes, including sedentary lifestyle, hostility, cynicism, personality type (time urgency), smoking, alcohol abuse, and bereavement. However, depression appears to be the more enduring predictor of mortality. Only recently has the magnitude of the interaction between heart disease and depression been appreciated. The relationship between depression and heart disease is reciprocal, with each condition contributing excess, potentially avoidable, morbidity and mortality to the other. The acute disability following myocardial infarction is associated with a substantial incidence of major depression. And the loss of social roles and independence due to cardiomyopathy and arrhythmia may also cause depression. Similarly, apathy, lack of physical activity, inability to stop smoking, alcohol abuse, and hypercortisolemia associated with depression also predispose the individual to heart disease. Depression following heart attack or stroke interferes with physical rehabilitation, return to sexual function, and adherence to the therapeutic regimen (eg, antiarrhythmia medications and anticoagulants). The majority of studies in patient populations with cardiovascular disease, showed a significant relationship between depression and mortality, but inferences were confounded by treatment and the effects of associated behaviors. More recent epidemiologic studies demonstrate that even when the effects of smoking are controlled, depression remains a significant independent predictor of mortality among heart patients and stroke survivors according to Glassman^[3] and Robinson.^[4]

Disease-Causing Mechanisms

Several speakers described diverse mechanisms by which depression's physiologic effects promote stroke and heart attack. Depression increases the cardiotoxic neurohumoral effects of emotional stress. Elevated cortisol described in major depression amplifies the cardiotoxic effects of catecholamines and accelerates arteriosclerosis. Depression and cardiac arrhythmias are linked through the autonomic nervous system seen in the measurement of heart rate variability. Some depressed persons exhibit decreased heart rate variability that has been related to arrhythmia vulnerability. Whyte and colleagues^[5] reported on a comparison of indices of platelet activation (platelet factor 4 and beta-thromboglobulin) between depressed and nondepressed elderly subjects. The serotonin transporter protein and the serotonin transporter-linked promoter region are shared by platelets and brain neurons so that both central and peripheral effects would be expected. Platelet activation was significantly elevated among the depressed group both in the presence and absence of ischemic heart disease. These results suggest a common pathway to ischemic events both in the brain and the heart through which depression, via physiologic rather than behavioral effects, increases mortality.

Psychotropics and the Vascular System

As reviewed by Roose,^[6,7] antidepressants have significant cardiovascular effects. Several antidepressants (eg, tricyclics, trazodone, nefazodone, venlafaxine) affect blood pressure through adrenergic-receptor activity to

mechanically alter cardiac pump function. Tricyclic antidepressants promote arrhythmias by altering cardiac conduction at the sinoatrial and ventricular pacemaking nodes. Their activity is similar to the class Ia antiarrhythmics, such as quinidine. Tricyclics slow the pacemaking cell's sodium ion channel, altering depolarization, repolarization, the relative refractory period, and propagation of the cardiac action potential. Also, the protective parasympathetic frequency seen in measures of heart rate variability is diminished by tricyclic antidepressants. Selective serotonin reuptake inhibitors (SSRIs) and the newer antidepressants appear to have no influence on cardiac condition or heart rate variability. Antipsychotics, most notably thioridazine and mesoridazine, can prolong QTc through alterations in the potassium rectifier in the cell membrane. Olanzapine prolongs QTc somewhat as well, but the weight gain and increases in serum glucose and lipid levels that raise concerns about its use in patients with vascular disease.

SSRIs complicate anticoagulant therapy via drug interactions with the cytochrome P450 family of enzymes. The SSRIs also have the capacity to reduce platelet aggregation that is a significant contributor to coronary artery disease and stroke. However Greenblatt and colleagues^[8] reported that select SSRIs may have effects on antiarrhythmics as a result of the inhibition of the cytochrome system. Levels of some antiarrhythmics and beta-blockers may be elevated by the CYP2D6 inhibitors fluoxetine and paroxetine. In contrast, buspirone, trazodone, and nefazodone, which are complete substrates for CYP3A, will be elevated in patients on calcium antagonists diltiazem or verapamil. Greenblatt and colleagues suggested that sertraline, citalopram, venlafaxine, and mirtazapine are at low risk for interactions with cardiovascular drugs. The finding that select SSRIs inhibit platelet activation without the risk of drug interactions is a promising avenue for reducing poststroke and post-MI mortality. Nonetheless, Robinson and colleagues^[9] found nortriptyline to be superior to fluoxetine in the reduction of poststroke depression.

Conclusion

Although routine screening for depression in primary care settings is controversial, the incidence and effects of depression among heart patients and stroke survivors are persuasive arguments for screening among these subgroups. The introduction of antidepressants that do not promote arrhythmias, lower blood pressure, or interfere with anticoagulant therapy has changed the threshold at which primary care physicians choose to treat depression in patients with cardiovascular disease. The effects of new antidepressants on cortisol, catecholamines, heart rate variability, platelet aggregation, and arteriosclerosing lipids are only now being appreciated. The choice of antidepressants was formerly determined by avoidance of cardiovascular side effects. In contrast, newer generations of antidepressants may also offer protective effects for both the heart and brain. However for optimum effects, antidepressant medication should be combined with lifestyle counseling and psychotherapy for both the depressed patient and his or her spouse or partner. Both behavioral and mental health interventions will be required to fully reduce the excess morbidity and mortality of heart disease and stroke complicated by depression.

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