Cardiac Autonomic Control Buffers Blood Pressure Variability Responses to Challenge: A Psychophysiologic Model of Coronary Artery Disease

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This article presents a model that identifies effects of blood pressure variability (BPV) as a possible mechanism by which psychological/psychiatric factors and health behaviors confer increased risk of coronary artery disease (CAD) and acute coronary syndromes. Recent research in vascular biology and dynamics of coronary artery blood flow suggests that BPV may have pathogenic effects on the coronary endothelium, plaque formation, and plaque stability. Thus, BPV may be a risk factor for cardiovascular disease independent of mean arterial pressure. The model proposes that autonomic control of the heart exerts a buffering or inhibitory influence on oscillations in blood pressure. Established psychological/behavioral risk factors for CAD, such as depression, hostility, and anxiety, as well as physical deconditioning and aging, are associated with diminished autonomic control of the heart, which may disinhibit pathogenic BPV. Together, these data suggest a coherent, testable psychophysiological model of CAD. In this article, we review these data and make recommendations for research to examine the model. **Key words:** coronary artery disease, psychological factors, blood pressure variability, heart rate variability.

BPV = blood pressure variability; CAD = coronary artery disease; HR = heart rate; HP = heart period; BP = blood pressure; HPV = heart period variability; HF = high frequency; MI = myocardial infarction; LF = low frequency; VLF = very low frequency; MAP = mean arterial pressure; CVP = central venous pressure; LVM = left ventricular mass; SBP = systolic blood pressure; DBP = diastolic blood pressure; PRA = plasma renin activity; DBPV = diastolic blood pressure variability; SBPV = systolic blood pressure variability; ΔBPV = change in BPV; ANS = autonomic nervous system.

PSYCHOLOGICAL FACTORS AND HEART DISEASE: AN OVERVIEW

The relationship of mental and emotional factors to heart disease has been a subject of intellectual and practical interest in medicine for hundreds of years. Strong emotion in general, and fear, anger, and grief in particular, have been associated with angina pectoris, myocardial infarction, and sudden cardiac death. As scientific study of these relationships has proceeded, associations between emotional state and physical health have drawn strong empirical support from epidemiological studies and, more recently, prospective studies. However, the mechanisms by which psychological/behavioral factors contribute to the development of cardiac disease have not been elucidated fully. Over the last several years, we have drawn on studies in autonomic nervous system physiology, pharmacology, cardiology, and vascular biology to develop a model that links mental and emotional factors to the development and expression of coronary artery disease. Simply put, the model, depicted in Figure 1, holds that psychological/behavioral factors have in common the effect of reducing the capacity for cardiac autonomic modulation, that this reduction in cardiac autonomic control is, in turn, associated with an increase in the BPV in response to challenge, that increased BPV responses to challenge promote increased BPV throughout the day, and that this increased BPV is harmful to the coronary arteries, contributing to plaque formation, plaque rupture, and acute coronary events.

THE PATHOGENESIS OF CORONARY ARTERY DISEASE AND ACUTE CORONARY SYNDROMES

Atherosclerotic coronary heart disease is believed to result from a series of dynamic processes affecting the coronary artery endothelium. In the so-called response-to-injury model (1–3), damage to the coronary endothelium results in plaque formation, characterized by cellular proliferation, lipid and calcium deposition, and macrophage in-migration. This atherosclerotic plaque is covered by a fibrous cap. Damage to the fibrous cap material exposes underlying plaque material to the lumen of the coronary artery, stimulating platelet aggregation and thrombus formation. Occlusion of the coronary artery by thrombus precipitates cardiac tissue hypoxia and the acute coronary syndromes of unstable angina and myocardial infarction. Both the initial endothelial damage and rupture of the

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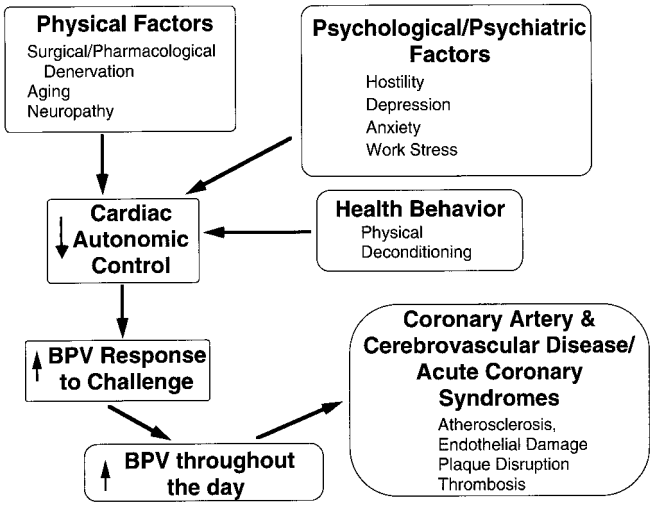

Fig. 1. A proposed psychophysiological model of coronary artery disease and acute coronary syndromes.

fibrous cap may be precipitated by shearing forces associated with blood flow changes in the coronary artery and with toxic effects of circulating factors, including catecholamines, serotonin, neuropeptides, and corticosterone. The stiffness of the fibrous atherosclerotic cap is a function of the frequency of oscillatory stressors (4).

CARDIAC AUTONOMIC CONTROL, CORONARY ARTERY DISEASE, AND CARDIAC MORBIDITY AND MORTALITY

Over the past 15 years, methods of quantifying cyclical oscillations in HR or HP and BP have yielded indices of autonomic control of the cardiovascular system. Fourier or autoregressive analysis of HPV partitions total variability of HP into components that reflect different autonomic influences on HP and BP. The "HF band" ($\sim$ 0.25 Hz) of the heart period power spectrum has been used to estimate cardiac vagal control (5). HPV in this band is linked to respiratory influences and has been referred to as "respiratory sinus arrhythmia" (6). HP oscillations at lower frequencies are less well understood. Most investigators believe that they represent mixed sympathetic-parasympathetic and thermoregulatory influences on HP (5, 7–9). Some, however, hold that when power in the 0.04- to 0.15-Hz frequency band is normalized relative to total power, it represents pure sympathetic tone to the heart (10, 11).

Reduced HPV is associated with CAD. Severity of coronary atherosclerosis correlates negatively with HF-HPV (12–14). Kleiger et al. (15) found an inverse association in patients after MI between a 24-hour SD of RR intervals and subsequent mortality, even after controlling for the presence of heart failure and arrhythmias in the early post-MI period. Bigger et al. (16, 17) showed that HPV measured in the frequency domain was inversely related to mortality after MI. Recently, two prospective studies have shown that low HPV predicts cardiac mortality in a normal population (18, 19). We know of no comprehensive theory that accounts for the association between reduced HPV, increased CAD, and mortality.

PSYCHOLOGICAL AND PSYCHOPHYSIOLOGICAL FACTORS LINKED TO THE DEVELOPMENT OF CAD

The contribution of psychological and psychophysiological characteristics to the development of CAD has been the focus of decades of research. The Western Collaborative Group Study (WCGS) (20) was the first of several prospective studies to find a strong association between a behavior pattern characterized by drivenness, impatience, hostility, and competitiveness (Type A) and subsequent CAD. Since the WCGS, there have been several positive and several negative studies (21). Attempts to refine the concept of the Type A Behavior Pattern (TABP) to improve prediction of risk and to find the "toxic core" of Type A have focused especially on the personality trait of hostility. In addition, evidence suggests that anxiety and depression are associated with CAD.

Hostility

Reanalyses of data from several large studies originally designed to evaluate the impact of the TABP on CAD have shown that hostility predicts the development of CAD (21). Most recent studies confirm the relationship between hostility and heart disease (22–25), although at least one cross-sectional study did not (26). Hostility also is associated with increased cardiovascular reactivity to psychological challenge (21, 27–33), which may contribute to CAD as described below.

Depression

Many studies have shown that depression is a significant risk factor for CAD, myocardial infarction, and cardiac mortality (34–37). Patients who are depressed after MI have significantly greater mortality compared with patients without depression (38, 39). Negative affect, measured at enrollment, predicted progression of carotid atherosclerosis after a 3.3-year follow-up in hypertensive men (40). In the Cardiac Arrhythmia Pilot Study, depression predicted the development of

cardiac events in post-MI patients with significant ventricular ectopy (41).

Anxiety

In a quantitative review, both depression and anxiety were associated with CAD (28). The Epidemiologic Catchment Area study has shown an association between panic disorder and cardiovascular events, even after control for demographic differences (42). Anxiety predicted the development of CAD in two long-term prospective studies (43, 44). Anxiety early after myocardial infarction is associated with increased risk of ischemic events and arrhythmias (45). Mental stress during daily life, including feelings of tension and sadness, significantly increased the risk of myocardial ischemia in the subsequent hour (46). Cognitive behavioral stress management in patients with evidence of transient myocardial ischemia, either during 24-hour monitoring or in response to laboratory stressors, reduced the rate of clinical coronary events at 4-year follow-up compared with exercise training or standard care (47).

AUTONOMIC MECHANISMS LINKING PSYCHOLOGICAL RISK FACTORS TO CAD

Hostility, depression, and anxiety each have been shown to be associated with autonomic dysregulation. We have shown that in normal subjects under age 40, HF-HPV is inversely related to hostility, but only during daytime hours (48). This is consistent with Smith's transactional hypothesis, which holds that hostile individuals interact with their environment in ways that create interpersonal conflict, something that would occur only during waking hours (27). In a small study of adolescents, HF-HPV was marginally lower in aggressive subjects than in normal controls or anxious subjects (49). In a larger study of 7- to 11-year-old boys, measures of psychopathology were inversely related to HF-HPV (50). In normal subjects, hostility was associated with reduced vagal antagonism to β-adrenergic effects (51) and diminished vagal reactivity to a vagomimetic stimulus (52). Carney and others have shown that depression is associated with significantly reduced HPV (53–56). In addition, successful treatment of depression resulted in increased HPV (57).

Anxiety, too, is associated with dysregulated cardiac autonomic activity. Panic patients are characterized by low cardiac vagal modulation and sympathetic dominance, and reflect this disordered cardiac autonomic control in analyses of HPV (58–60). Phobic anxiety also is associated with reduced HPV (61).

AUTONOMIC REGULATION AND BLOOD PRESSURE VARIABILITY

Like heart period, blood pressure oscillates at high (0.15–0.50 Hz, HF) and lower frequencies (0.02–0.15 Hz). Some authors conclude that high frequency BPV is produced by high frequency HPV (62). Others conclude the opposite: that high frequency HPV is produced by respiratory-driven high frequency BPV through the influences of the baroreflexes (63). Lower frequency BP oscillations, however, appear to be mediated by vascular sympathetic activity. Unlike the dually innervated sinus node, the blood vessels of the heart receive only sympathetic fibers, and the slower response characteristics of the sympathetic system (SNS) (64, 65) are consistent with these low frequency oscillations (5). Other evidence also suggests a relationship between lower frequency BPV and the SNS. Power in the 0.04- to 0.15-Hz frequency band decreases during the night and increases in the early morning (66), as does activity of the SNS. Infusions of nitroglycerin resulting in hypotension produce reflex increases in this band (67). Tilt, which activates the SNS, also leads to an increase in this band (68).

Evidence of the involvement of the SNS in lower frequency BPV also comes from animal studies. Abolition of the baroreflex by denervation of the arterial baroreceptors located in the aortic arch and carotid sinuses (sinoaortic denervation (SAD)) repeatedly has been shown to increase BPV, generally with little change in MAP. In rats, SAD slightly increases MAP and markedly increases BPV, measured as the SD of BP values collected once/minute for 1 hour (69). These increases in BPV are partially reduced by ganglionic blockade and return to normal levels with ganglionic blockade in combination with angiotensin-converting enzyme inhibitors, suggesting the importance of the SNS in the production of this variability. SAD also increased overall MAP variability in rats, measured as total spectral power, and power in the VLF band (0.0195–0.25 Hz), whereas power in the LF band (0.27–0.74 Hz) decreased (70). Ganglionic blockade by chlorisondamine significantly decreased MAP variability in SAD rats but not in controls. These findings suggest that the arterial baroreflex exerts a buffering influence on spontaneous BPV and the effect of ganglionic blockade implicates the SNS in BPV.

Julien et al. (71) suggest that vasoconstrictor tone is necessary for the expression of BPV, providing sufficient background tone for transient vasodilatory influences to generate variability. Vasodepressor actions seem to generate most of the variability (71). Specifically, variability appears to be due to short-lasting depressor responses, usually induced by physical ac-

tivity, and immediately followed by BP increases. That is, high levels of BPV do not characterize the quiet resting state but emerge from reactions to external and internal events.

CARDIAC AUTONOMIC CONTROL AND BPV

Many studies have demonstrated the role of the baroreflexes and sympathetic vasoconstrictor tone in BPV. Modulation of SNS activity is too slow to alter the cardiac arm of the baroreflex. However, several groups have demonstrated cardiac modulation of BPV: atropine, which dramatically reduces power in the HF-HPV band, also increases BPV in rats (70, 71). In humans, atropine increases total MAP variability (72). Because there is virtually no parasympathetic regulation of vascular activity, the BPV effect of parasympathetic blockade must be mediated by changes in vagal modulation of the heart, which, in turn, affects the blood pressure control system. Recently, Veerman et al. (73) concluded that "heart rate variations exert an antioscillatory influence on the variability of blood pressure" (p. 125) during challenge of exercise but not at rest, consistent with the finding that increased BPV characterizes responses to events, not the quiet resting state (71). In humans, atropine led to slightly reduced MAP variability when subjects were supine but substantially increased BPV when subjects were walking (74). Thus, evidence strongly suggests that cardiac autonomic activity buffers BPV responses to challenge.

Dramatic demonstration of this buffering effect during challenge appears in two elegant studies in humans. Taylor and Eckberg (75) recently showed that elimination of HPV by transesophageal pacing led to a reduction in BPV in supine, resting subjects. However, in the same subjects during the challenge of 40-degree head-up tilt, BPV increased when HPV was reduced by pacing. Triedman and Saul (76) manipulated BPV by varying CVP by random fluctuation of lower-body negative pressure in the 0.067- to 1.0-Hz frequency range while subjects breathed at a fixed frequency of 0.30 Hz. After administration of atropine and propranolol, induced fluctuations in CVP below 0.10 Hz led to substantial increases in BPV in the same frequency range, compared with the effects of CVP fluctuations in intact subjects. Pharmacological blockade without fluctuations in CVP slightly reduced BPV compared with the intact condition. In both conditions, HF oscillations in CVP were filtered and did not appear in BP.

To summarize, evidence suggests that interruption of the afferent limb of the baroreflex loop dramatically increases total BPV. Disruption of the cardiac arm of the baroreflex by atropine has the same effect. The frequencies at which these BPV effects are seen vary, dependent upon differences in species, signal processing, and measures of variability. Nevertheless, the weight of this evidence strongly suggests that an intact, autonomically mediated, cardiac control system, including the baroreflexes, acts to buffer fluctuations in blood pressure, especially in response to challenge.

THE CLINICAL SIGNIFICANCE OF BLOOD PRESSURE VARIABILITY

Several streams of evidence suggest that BPV is associated with cardiovascular disease outcomes. Both clinical studies and laboratory studies in vascular dynamics provide relevant data.

Clinical Studies

The strongest evidence comes from studies, mostly cross-sectional, of patients with hypertension. Three general classes of outcome variables have appeared in these studies: 1) early indicators of heart disease, eg, urinary albumin excretion, plasma renin activity, and LVM; 2) target organ damage, eg, left ventricular hypertrophy and retinopathy; and 3) cardiovascular morbidity, eg, death, coronary artery bypass surgery, and myocardial infarction.

Veerman et al. (77) have reported that in 33 untreated hypertensive patients, daytime diastolic blood pressure variability, measured as SD of ambulatory DBP measured every 15 minutes, was a significant predictor of left ventricular mass index and that beat-to-beat DBPV, measured as the SD of all beats during a 20-minute recording period, was a significant predictor of urinary albumin excretion. Palatini et al. (78) found that increased daytime systolic BPV, measured as the SD of readings taken every 7.5 to 10 minutes during daytime, was associated with more severe target organ damage, independent of mean daytime BP in 728 subjects whose blood pressure status ranged from normotensive to severely hypertensive. Among 25 elderly male hypertensive subjects, left ventricular mass was associated with increased 24-hour ambulatory SD of SBP and DBP measured every 15 minutes during the daytime and every 30 minutes at night (79). Daytime SBPV, measured as the SD of SBP recorded every 15 minutes, predicted carotid atherosclerosis in both hypertensive ($N = 208$) and normotensive subjects ($N = 216$), even after control of other risk factors (80). Among 231 men over the age of 45 years, diastolic BPV, measured as the SD of BP measured every 15 minutes during daytime, and the level of PRA are closely related (81). PRA is associated with risk of myocardial infarction (82, 83).

In addition to the above cross-sectional studies, sev-

eral longitudinal studies exist. Frattola et al. (84) studied 73 hypertensive subjects with intraarterial ambulatory BP monitoring and 7 years later, evaluated LVM. SD of mean blood pressure for all 30-minute epochs of the 24-hour recording was the best predictor of LVM. Blood pressure level was not a significant predictor. Pickering and James (85) reported that among 729 patients with mild hypertension, observed for an average of 5 years, daytime diastolic BPV (SD of all daytime values of DBP), age, male gender, and serum cholesterol were significant predictors of cardiovascular morbidity (death, myocardial infarction, stroke, and coronary artery bypass surgery or angioplasty). Daytime SD of DBP was a better predictor than all others. They conclude that these findings are consistent with the failure of antihypertensive treatment to prevent MI while succeeding in preventing stroke and with its success in lowering BP but not BPV, as shown by Mancia (86). Finally, in rats, increased SD of BP, produced by baroreceptor denervation and measured on a beat-to-beat basis, was associated with greater atherosclerosis compared with rats with sham denervation (87). As expected, the groups did not differ in mean BP.

Some studies have failed to find a relationship between BPV and heart disease outcomes. Using 24-hour SD as the measure of BPV, neither Rizzoni et al. (91 subjects, 68 of whom were hypertensive) (88) nor Drayer et al. ($N = 12$) (89) found a relationship between SD of SBP or DBP with LVM. However, neither group reported relationships between daytime or nighttime BPV and LVM. Rizzoni et al. (88) did find that all measures of BPV were significantly related to vascular resistance, an index of vascular structural changes. In another study, however, BPV, measured as 24-hour, daytime only, and nighttime only SD, was not related to left ventricular hypertrophy in 40 hypertensive subjects (90). Finally, in a study of 124 hypertensive patients, Sokolow et al. (91) found no relationship between daytime BPV (SD of all pressures recorded at 30-minute intervals) and hypertensive complications. However, due to equipment limitations at the time the study was conducted, BP was not recorded automatically but required the subjects to activate the device for each recording. This makes the findings of this study difficult to interpret, because the conditions under which recordings were made may have been subject to psychological and logistical factors that either inclined or disinclined subjects to record their pressures precisely on schedule.

Comparison of these positive and negative studies suggests some important differences. First, most of the positive studies showed relationships between daytime measures of BPV and outcomes, whereas two of the negative studies reported only 24-hour BPV. Second, in four of the positive studies, the numbers of subjects were 231, 424, 728, and 729, whereas in only one of the negative studies did the number exceed 100. Finally, either because of restrictions in age range or large sample size, most of the positive studies included large numbers of subjects 45 years of age or greater. In the negative studies, this was not the case.

Studies in Vascular Physiology

Recent evidence from studies in vascular biology also may be consistent with a relationship between CAD and BPV. In a model of the human carotid bifurcation, Ku et al. (92) demonstrated that oscillations of wall shear were highly correlated with intimal thickness. In the human aorta, oscillatory shear and intimal thickness were highly correlated (93). Oscillatory shear stress also is highly correlated with the focal atheromas in the human left coronary artery (94). In these studies, the oscillatory stress index expresses the amount of shear stress oscillation the arterial wall experiences. Although its relationship to BPV is unknown, oscillations in BP are likely to produce oscillations in flow and, correspondingly, shear stress.

OVERALL SYNTHESIS

Based on this evidence, we propose that attenuated cardiac autonomic control, principally cardiac parasympathetic modulation, is a significant contributor to CAD and acute coronary events. The effect of this attenuation is the reduction of the capacity to buffer fluctuations in blood pressure (BPV) in response to challenge both in the laboratory and throughout the day, which may confer risk of CAD independent of MAP. This hypothesis is consistent with the fact that subjects with psychiatric/psychological risk factors for CAD also have diminished cardiac autonomic control, with the recognized cardioprotective effect of aerobic conditioning, and with the effect of aerobic conditioning on autonomic control of the heart.

TESTS OF THE MODEL

Each arm of the model lends itself to empirical verification. The literature reviewed above indicates that some of these relationships already have been supported, eg, the relationship between psychological/psychophysiological risk factors for CAD and autonomic control of the heart. Cardiac denervation virtually eliminates HPV (95–97) and aerobic conditioning increases HPV (98–101). Limited empirical support exists linking BPV throughout the day and heart dis-

ease outcomes. Below, we review data which address the central relationship of the model: that autonomic control of the heart buffers BPV responses to challenge.

BPV Responses to Psychological and Orthostatic Challenge

We tested the hypothesis that lower frequency BPV responses are buffered by cardiac autonomic control by examining the BPV response to psychological and orthostatic challenge in 23 normal subjects differing in cardiac control due to differences in aerobic capacity as measured by VO_{2max}. In this cross-sectional study, cardiac control, operationalized as HPV, and BPV were measured noninvasively on a beat-to-beat basis during a quiet baseline period and in response to mental arithmetic, the Stroop color-word matching task, and 70-degree head-up tilt.

As expected, VO_{2max} and HPV were positively correlated, ie, that subjects high in aerobic capacity had greater cardiac autonomic control. For both the psychological and tilt tasks, as predicted, there was a significant negative correlation between changes in BPV and baseline HPV. The effects were strongest for DBPV. The correlations between ΔBPV to psychological stress and ΔBPV to tilt generally were substantial and significant (102, 103).

A baroreflex mechanism may account for the finding of a stronger inverse relationship between baseline HPV and ΔDBPV but not ΔSBPV (63). On any given cardiac cycle, a higher systolic pressure will lead to a correspondingly higher diastolic blood pressure. However, this higher SBP would lead to compensatory lengthening of the current RR interval through the baroreflexes. This prolonged RR interval extends the diastolic runoff period, thereby decreasing the next diastolic pressure. Thus, diastolic pressure oscillations are dampened by baroreflex activity. The extent of this alteration in RR interval in part may be a function of prevailing levels of cardiac autonomic activity as measured by HPV. Because the alteration of RR interval takes place within a given cardiac cycle, only the parasympathetic system is likely to be involved. Thus, in subjects with greater levels of baseline HPV, the diastolic buffering effect is greater than in subjects with lower levels.

Cardiac Autonomic Control and BPV Throughout the Working Day

Another approach to studying the relationship between cardiac autonomic control and BPV involves the use of ambulatory blood pressure monitoring. We have conducted a pilot study of the relationship between resting HPV and BPV during a stressful working day (104). Subjects were nine New York City Traffic Enforcement Agents. Traffic Agents spend their workdays traveling by foot throughout the streets issuing summons for parking and other vehicular violations. Correspondingly, they encounter frequent verbal harassment and even physical assault from the public and report relatively high levels of burnout and stress on the job (104).

HR and HPV (SD) were measured while subjects rested quietly at the workplace before the beginning of the workday. On another day, BP was recorded every 15 minutes throughout the working day with an Accutracker ambulatory BP monitor and the SD of these values was taken as the measure of BPV.

As predicted, BPV (SD of all workday measurements) was inversely related to resting HPV ($r = -.54$, $p = .14$, and $r = -.77$, $p = .01$, for SBP and DBP, respectively). Data are depicted in Figure 2. These results support the hypothesis that increased levels of cardiac control are associated with diminished BPV and extend results from our laboratory studies to the more relevant everyday work environment.

Although the number of subjects was small, these findings are consistent with the view that diminished cardiac buffering of blood pressure oscillations during the workday may be a mechanism by which psychological factors contribute to the development of CAD. The stronger effect on DBPV is consistent with the findings from our studies of the effect of aerobic conditioning and BPV responses to psychological and orthostatic challenge.

CONCLUSIONS

The model we propose holds that psychological/psychiatric/behavioral characteristics identified as risk factors for CAD and acute coronary syndromes have their effect through reduced autonomic control of the heart which in turn disinhibits pathological BP

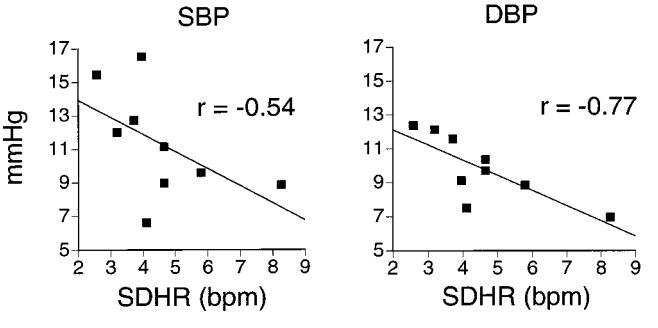

Fig. 2. Scatterplot of ambulatory systolic and diastolic blood pressure variability and resting SD of HR.

oscillations. To date, evidence supports 1) the link between physical factors, eg, denervation, neuropathy, and ANS control of the heart, 2) the relationship between indices of negative affect (depression, hostility, and anxiety) and ANS control of the heart, and 3) the direct relationship between physical conditioning and cardiac autonomic control. Preliminary evidence supports the central feature of the model: that increased cardiac autonomic control buffers BPV responses to challenge. Preliminary evidence also supports the link between increased BPV and heart disease outcomes. The proposed inverse relationship between cardiac autonomic control and BPV throughout the day is supported only in a small pilot study. Each of these findings requires replication.

Measurement of BPV

Although BPV is central to the model described in this paper, there are no standards for its measurement and as the various studies cited indicate, it is conceived of and measured in many different ways. Variability can be due to cyclical increases and decreases in pressure at a fixed period. The diurnal BP rhythm, which in normal subjects is characterized by reductions in BP at night, is an example of a cyclical oscillation with a period of 24 hours.

Variability can be pseudoperiodic, with cycles centered around a specific frequency but varying to some degree. Examples of this pseudoperiodicity include spectrally defined variability in the low-, mid-, and high-frequency bands reported by many studies cited in this article. Variability in these frequency bands is not perfectly periodic, inasmuch as each band contains many individual frequencies. However, they are usefully aggregated in bands of varying width, depending (usually) on their physiological significance. Finally, variability in BP can be irregular, the product of pressor or depressor events which may be associated with events ranging from emotional arousal to changes in posture. In these cases, variability increases as the number of BP-provoking events increases, regardless of their periodicity.

Variability in the BP signal can be quantified in many ways. The most straightforward metric is the SD of values of a specified time interval. Because the various sources of variability (periodic, pseudoperiodic, irregular) can be concurrent, the SD reflects the total effects of all three. Even in the simple case of SD, there are variants. For example, Frattola et al. (84) measured the long- and short-term SD of their 24-hour intraarterial BP recordings. The long-term measure was defined as the SD of the ½ hour mean values of BP. The short-term measure was the average SD for each ½ hour of the 24-hour record. These measures reflect dramatically different processes. For example, the short-term SD would not reflect the circadian rhythm of BP generally seen in normal subjects, whereas the long-term SD would.

Variability can be quantified in the frequency domain by using spectral analysis. Following this approach, the constituent regularly occurring frequencies in a series of blood pressure measurements can be identified. Typically, this requires beat-to-beat recording. In cardiovascular physiology, the frequencies usually studied are in the 0.003- to 1.0-Hz range, ie, they have a period of 1 to 300 seconds.

The clinical data on BPV are based only on SD. As the above discussion suggests, SD could be elevated due to circadian changes, increases in specific BP frequencies, or increased frequency of pressor and depressor events throughout the day. Currently, there is no information on these matters, nor is there information on the relationship between SDBP throughout the day and resting BPV measured in the frequency domain over short-term recordings.

One type of BP variability, the nocturnal reduction in BP seen in normal subjects, has been shown to be related to cardiovascular disease outcomes in some studies (105). Specifically, among hypertensive patients, "nondippers," ie, those whose pressure does not fall at night, seem to be at greater risk than "dippers." However, at least one study failed to find this relationship (106). We should note that other things being equal, nondippers should have less BPV, measured as the 24-hour SD, than dippers and, therefore, this is contradictory to the model we propose. However, Roman et al. (106) have shown that daytime SD of DBP was greater in nondippers than in dippers. Palatini et al. (78) report that increased daytime systolic BPV, measured as SD, and reduced day-night differences in DBP, were associated with target organ damage.

The model makes several assumptions which have not been tested. Data on the clinical significance of BPV come from studies in which BP is measured by ambulatory monitoring, usually three to four times per hour. BPV in the laboratory is measured on a short-term, beat-to-beat basis and is analyzed either in the time or frequency domain. The relationship between short-term BPV in the laboratory and intermittently measured BPV in the field has not been established.

Correspondingly, there is no human clinical information linking disease outcomes and short-term spectrally defined BPV. In rats, however, short-term BPV measured in the time domain was associated with the development of coronary atherosclerosis (87). Finally, the impact of HPV on BPV reactivity to laboratory

stressors has been demonstrated only in a small number of subjects and only cross-sectionally (102, 103).

Causality

Much of the clinical literature is cross-sectional and the limitations of cross-sectional studies are well-known. Foremost among these short-comings is the inability to draw causal inferences. Thus, a cross-sectional association between BPV and heart disease is as consistent with an effect of CAD on BPV as it is with an effect of BPV on CAD. Some clinical studies, however, prospectively examined the relationship between BPV and outcomes (84, 85). Moreover, the one animal study to examine this issue has shown that experimental increases of BPV by baroreceptor denervation led to greater atherosclerosis compared with rats with normal BPV (87). Thus, although the issue is not resolved, our working hypothesis is that increased BPV is causally related to heart disease outcomes.

Although the model may be substantially correct, it does not specify the extent to which coronary artery disease outcomes are determined by psychological factors. Psychological factors may contribute to CAD outcomes in ways other than those described by the model. The effects of generally recognized coronary risk factors, such as hypertension, hypercholesterolemia, diabetes, smoking, and the genetic risk implied in a positive family history of coronary disease, presumably may be largely independent of the psychophysiological mechanisms proposed here. These factors together do not account perfectly for the observed variance in coronary disease outcomes; however, our model provides several specifically testable hypotheses regarding mechanisms linking the brain and the cardiovascular system, which may improve predictive power and risk stratification.

Even if the model proves correct, its impact on therapeutics is uncertain. Whether blood pressure variability can be modified through "treatments" for anxiety, depression, hostility, or "stress," or through aerobic conditioning programs, and whether such treatments affect coronary disease outcomes, either through effects on blood pressure variability or independent of them, is unknown. It also is possible that treatments aimed "downstream" on the physiological pathway from the brain to the heart could reduce risk in those with psychological factors leading to increased blood pressure variability, without any effect on the psychological factors.

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ANNOUNCEMENT

Psychosomatic Medicine Mentoring Program

The goal of this program is to provide assistance to young investigators and students wishing to submit articles for publication in ***Psychosomatic Medicine***, journal of the American Psychosomatic Society, and to encourage scholarly activities in psychosomatic medicine and related fields. The participating mentors are experienced scholars who are volunteering their services. The assistance may take the form of advice on the substance of the work such as design, concepts, and methods or on language, style, format, and overall suitability of presentation. Mentors may also be willing to offer comments or advice on future research plans, work in progress, career issues, or general questions about psychosomatic medicine. Each mentor will decide whether or not to assist on a particular request and on the manner of providing assistance.

With a further goal of fostering international scholarly communication, the program is intended for scholars outside the United States, but anyone needing assistance for any reason is invited to participate. It is assumed that the person seeking assistance will be writing in English. Mentors will not assist in translation from another language, but may make suggestions on grammar, syntax, and clarity of writing.

For ease of correspondence, the program is limited to those who can communicate by electronic mail. The name, areas of interest, and c-mail address of each participating mentor will be sent on request by e-mail.

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