invited review

Arterial baroreflex function and cardiovascular variability: interactions and implications

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2002;10.1152/ajpregu.00051.2002.—The arterial baroreflex contributes
importantly to the short-term regulation of blood pressure and cardio-
vascular variability. A number of factors (including reflex, humoral,
behavioral, and environmental) may influence gain and effectiveness of
the baroreflex, as well as cardiovascular variability. Many central neural
structures are also involved in the regulation of the cardiovascular
system and contribute to the integrity of the baroreflex. Consequently,
brain injuries or ischemia may induce baroreflex impairment and de-
ranged cardiovascular variability. Baroreflex dysfunction and deranged
cardiovascular variability are also common findings in cardiovascular
disease. A blunted baroreflex gain and impaired heart rate variability
are predictive of poor outcome in patients with heart failure and myo-
cardial infarction and may represent an early index of autonomic acti-
vation in left ventricular dysfunction. The mechanisms mediating these
relationships are not well understood and may in part be the result of
cardiac structural changes and/or altered central neural processing of
baroreflex signals.

baroreflex; autonomic nervous system

THE BAROREFLEXES CONTRIBUTE importantly to neural cir-
culatory control. Abnormalities in arterial baroreflex
function have been linked to derangements in cardio-
vascular variability and to adverse cardiovascular out-
comes. This overview will examine the physiology of
the arterial baroreflex, methods of measuring barore-
flex gain, and physiological and pathologic conditions
that alter baroreflex function. We will also address how
baroreflex function may alter cardiovascular variabil-
ity and vice versa, addressing in addition nonneural
effects of impaired baroreflex function. Last, we will
evaluate the interaction between measurements of
baroreflex gain, cardiovascular variability, and cardio-
vascular disease, examining the possibility that changes
in central neural processing may contribute to the link
between baroreflex dysfunction, impaired variability,
and cardiovascular pathology.

We sought to focus primarily on more recent novel
insights. The literature on the physiological and patho-
logic aspects of baroreflex function, cardiovascular
variability, and cardiovascular disease is vast. We are,
therefore, unable to reference the majority of papers in
the field, but have cited a number of preceding reviews,
which encompass many of the omitted references.

PHYSIOLOGY OF THE BAROREFLEX AND METHODS TO EXPLORE ITS FUNCTION

Physiological aspects of baroreflex. The arterial barore-
flex seeks to regulate the absolute blood pressure and
ultimately to maintain circulation to the brain and
other organs (107). Baroreceptors sense systemic blood
pressure indirectly, by the extent of stretch of receptors
in the walls of the carotid arteries and of the aorta.
Changes in arterial baroreceptor afferent discharge
transmitted to the central nervous system trigger re-
flex adjustments that buffer or oppose the changes in
blood pressure: a rise in pressure elicits reflex para-
sympathetic activation and sympathetic inhibition,

with subsequent decreases in heart rate (HR), cardiac contractility, vascular resistance, and venous return (88). Conversely, a decrease in arterial pressure reduces baroreceptor afferent discharge and triggers reflex increases in HR, cardiac contractility, vascular resistance, and increased venous return. Thus the baroreflex, by affecting blood pressure and HR control, provides powerful beat-to-beat negative feedback regulation of arterial blood pressure that minimizes short-term fluctuations in pressure. However, the arterial baroreflex may not be the only feedback mechanism involved in acute blood pressure control. Endogenous nitric oxide constitutes a second system, which, by acting also through a feedback mechanism, is involved in the short-term regulation of blood pressure (45, 77). Stimulated by the shear stress induced by increases in arterial pressure, this potent vasodilator response is rapidly effective in counteracting the initial rise in blood pressure (77).

Methods of measurement. One index of baroreflex "health" is the degree of change in heart rate or sympathetic traffic for a given unit change in blood pressure (for review, see Ref. 92). This may be quantified as the response of the cardiovascular system to the application of an external stimulus, mechanical (94) or pharmacological (56), in standardized laboratory conditions. An alternative in vivo approach evaluates spontaneous baroreflex modulation of heart rate in a daily life setting by identifying sequences of consecutive beats in which progressive increases in systolic blood pressure (SBP) are followed by a progressive lengthening in pulse interval (or vice versa) (7). The slope of the regression line between SBP and pulse intervals within these sequences is taken as the magnitude of the reflex gain. A third method to assess baroreflex function is provided by cross-spectral analysis of short segments of SBP and R-R or peripheral sympathetic nerve activity to muscle (MSNA). This approach relies on the assumption that a certain frequency band of HR variability, between 0.04 and 0.35 Hz (18), is modulated by the baroreflex. This construct is based on the coherent relationship between SBP and R-R (or MSNA), each of which oscillate at the same frequency in the power spectrum (2, 13, 85). Baroreflex sensitivity is expressed by the gain of the transfer function relating changes in blood pressure to coherent changes in R-R or MSNA (2, 87, 99).

All these methods for computing baroreflex gain assume linearity of the relationship between changes in blood pressure and R-R or MSNA. Simple mathematical models indicate that there is a strong linear coupling between arterial blood pressure and sympathetic nerve activity and/or R-R interval (9, 21). However, there is emerging evidence that the R-R and MSNA responses to blood pressure may be modulated in accordance with nonlinear dynamics (97).

Neural and nonneural mechanisms modulating baroreflex function. Any interpretation of in vivo measurements of HR variability and baroreflex gain must acknowledge the influences of respiration, other reflexes, and central neural mechanisms.

Respiration modulates the influence of the baroreflex on cardiac vagal motoneurons: inspiration decreases and expiration enhances the cardiac vagal responses to baroreflex activation (22). Hyperventilation impairs baroreflex modulation of HR and sympathetic nerve traffic (115). A change in respiratory pattern, for example during resistive load breathing, may itself affect respiratory sinus arrhythmia, independent of the arterial pressure changes accompanying respiration (11).

Other mechanisms, of reflex or central origin, may contribute to coherent R-R-SBP variabilities independent of the baroreflex pathways. Low-pressure receptors activated by respiration-related changes in blood volume and central venous pressure may induce changes in R-R independent of SBP. These R-R changes in turn elicit SBP variation through the Frank-Starling mechanism.

Further insights have been obtained from the analysis of SBP and R-R sequences that are in opposition to the expected baroreflex-mediated response. Reflexes operating with a positive feedback (i.e., hypertensive/tachycardic and hypotensive/bradycardic) and suspected to be physiologically active in humans (58) may interact with and oppose the negative feedback dynamic operated by the baroreflex (58). Pathological activation of reflex mechanisms may also oppose baroreflex responses. Activation of these reflexes may be mediated, for example, by the stretch of the thoracic aorta (86), or of mechanosensitive vasodepressor afferents in the inferoposterior wall of the left ventricle (1). During vasovagal syncope, bradycardia and hypotension induced by ventricular mechanoreceptors overwhelm the reflex compensatory vasoconstrictor and tachycardic action of baroreflexes (1). Finally, central inhibitory or excitatory influences on baroreflex responses to pressure changes might also contribute to the state-related differential baroreflex sensitivity reported during sleep (96, 117). This state-related modulation of baroreflex function during sleep is crucial in permitting simultaneous reductions in HR, blood pressure, and MSNA during non-rapid eye movement (REM) sleep (111) (Fig. 1). Similarly, rapid increases in blood pressure, HR, and sympathetic activity during intrinsic changes in brain state, as is evident during REM sleep, as well as in response to external stimuli that may induce an alerting or arousal response from sleep, relate directly to central modulation of baroreflex control. Intermittently, during REM and during arousal, the rapid transition from a condition of slow HR, low blood pressure, and low sympathetic activity, to conditions permissive of simultaneous tachycardia, sympathetic activation, and pressure surges, speaks to the plasticity of baroreflex dynamics (both gain and set point) and the magnitude of the influences of changes in consciousness and central neural processing on baroreflex control characteristics.

Given the complexity of neural circulatory control mechanisms in the intact organism, the baroreflex is not always effective in overcoming nonbaroreflex influences on blood pressure. As a result, in physiological conditions, the baroreflex sequences are often inter-
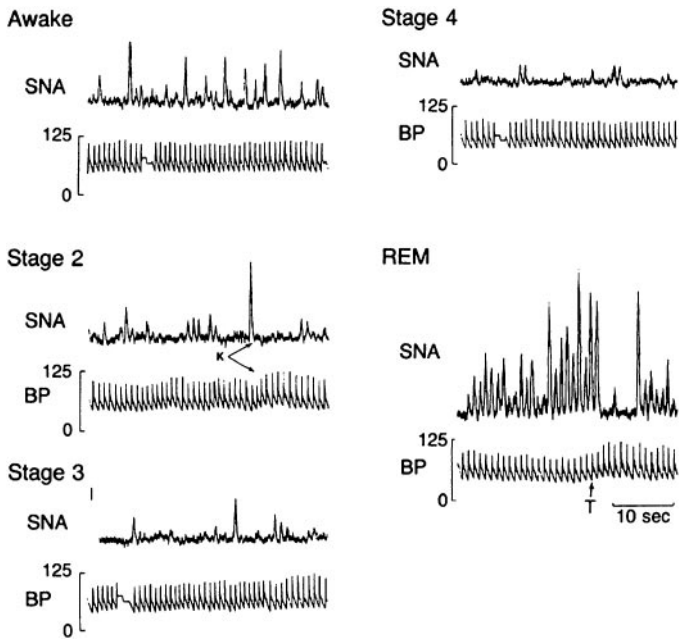
Fig. 1. Recordings of sympathetic nerve activity (SNA) and mean blood pressure (BP) in a single subject while awake and while in stages 2, 3, 4, and rapid eye movement (REM) sleep. As non-REM sleep deepens (stages 2 through 4), sympathetic nerve activity, heart rate, and blood pressure gradually decrease together, suggesting a sleep-related modulation of the baroreflex. By contrast, heart rate and blood pressure are labile during REM sleep, together with a profound increase in both the frequency and the amplitude of sympathetic nerve activity. [Reproduced with permission from Somers et al. (111).]

spersed with SBP changes that are not coupled with reflex changes in R-R modulation. Moving from this observation, a new index has been proposed to quantify baroreflex activation in modulating HR, the baroreflex effective index (19). With the use of this approach, in normal subjects, it has been shown that the arterial baroreflex induces beat-to-beat changes in pulse interval in response to only 21% of all the ramps in blood pressure. This effectiveness is particularly low during the night, when, by contrast, baroreflex gain is particularly high (Fig. 2). Baroreflex effective index and baroreflex sensitivity are not redundant measures, but rather provide data on different aspects of baroreflex control of the heart. Baroreflex effective index quantifies the number of times the baroreflex is clearly effective in driving the sinus node, whereas baroreflex sensitivity quantifies the power of the reflex when this drive is effective (19).

Recently, other methods have been proposed addressing the "causality" in the estimate of the spontaneous baroreflex, i.e., only selecting the fraction of R-R variability driven by changes in SBP. Among them, one method is based on the analysis of the statistical dependence "Z" between SBP and HR, where the baroreflex is determined only for selected values of SBP and HR that are characterized by a strong probability of dependence (14, 55). Another approach, the causal parametric method (95), evaluates the baroreflex by fixing the temporal direction of the influences of SBP

on R-R and "disentangles the baroreflex pathway from mechanisms driving R-R interval independently of SBP" (95). These approaches have been validated in animal models. However, their relevance and application to human cardiovascular disease condition remains to be defined.

ARTERIAL BAROREFLEX AND CARDIOVASCULAR VARIABILITY

Linear and nonlinear dynamics of cardiovascular variability. Cardiovascular variability comprises a very complex interaction between hemodynamic, humoral, and electrophysiological variables, integrated by a sophisticated system of controllers within the autonomic and central nervous systems (33, 121, 122).

Linear and nonlinear dynamics have been demonstrated within the variability of the cardiovascular system (for reviews, see Refs. 29, 63, 66, 85, 112, 121, 122). In addition to the periodic oscillatory behavior observed in arterial blood pressure, R-R interval, and peripheral sympathetic activity (66, 85, 112), a less specific variability occurs with nonperiodic behavior, which can be described by methods based on nonlinear system theory ("chaos theory and fractal analysis") (29, 63, 121, 122). Although the physiological basis for this nonharmonic beat-to-beat behavior, which extends over a wide time scale range (seconds to hours), is still unsettled, evidence is increasing that this fractallike variability may encode clinically relevant information (10, 29, 40, 64).
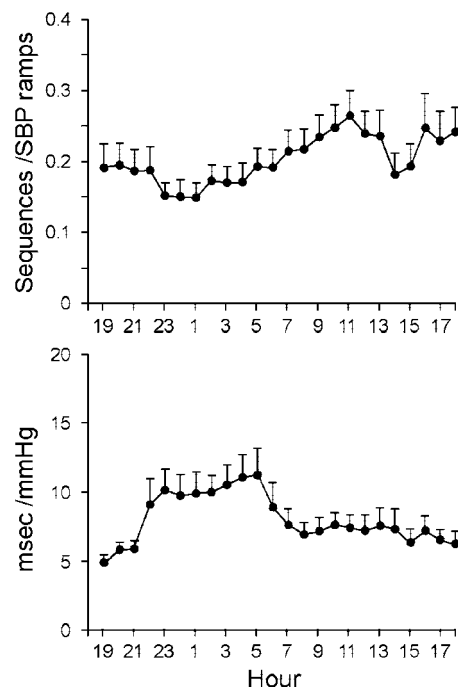

Fig. 2. Hourly profile of baroreflex effectiveness index over 24 h (*top*) and hourly profile of baroreflex sensitivity (*bottom*) in healthy control subjects. These different aspects of baroreflex function do not have similar profiles through the day. SBP, systolic blood pressure. [Reproduced with permission from Di Rienzo et al. (19).]

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More detailed information is available on the oscillatory behavior observed in arterial blood pressure, R-R, and sympathetic activity, ranging, in humans, between 0 and 0.5 Hz. These oscillations are affected significantly by the autonomic nervous system (66, 85, 101, 112), acting in part through the arterial baroreflex.

During normal quiet breathing there is a strong temporal relationship between respiration and autonomic outflow. The consensus of opinion is that the high-frequency (HF) respiratory component of R-R interval variability ($\sim$0.2–0.3 Hz) primarily reflects respiration-driven vagal modulation of sinus arrhythmia (112). Administration of atropine or other parasympathetic blocking agent virtually abolishes this component of HR variability (4). Nonneural mechanical mechanisms, linked to respiratory fluctuations in cardiac transmural pressure, atrial stretch, and venous return, are also determinants of HF power, and may become especially important after cardiac denervation (6). The relative contribution of the arterial baroreflex to this HF component is still not fully accepted (16, 23, 94). A further caveat is that in any assessment of relative power distribution on low-frequency (LF) and HF components, it is crucial to ensure that the respiratory pattern is limited to the HF component (8). LF components in respiration diminish the values of the LF component of cardiovascular variability in helping to understand the autonomic characteristics of cardiovascular control.

Although the primary source (or sources) of the slower nonrespiratory oscillation ($\sim$0.1 Hz) is still controversial (for review, see Refs. 48, 66), current evidence suggests that the baroreflex contributes substantially to LF oscillations in blood pressure, R-R interval, and MSNA variability (2, 13, 18, 20, 108). LF oscillation in the R-R interval has been related to cardiac sympathetic modulation resulting from the baroreflex response to the LF blood pressure oscillations (feedback theory) (108). It has been also proposed that the LF oscillation arises from the interaction of slow sympathetic and fast vagal responses, where baroreflex buffering of the HF respiratory-induced blood pressure oscillations results in resonant LF oscillations due to the delay in the slow conducting sympathetic control loop of the baroreflex (18). Indeed, baroreceptors, stimulated by changes in blood pressure, induce fast responses to the heart and slow sympathetic withdrawal to the vessels. The delay in the sympathetic branch of the baroreflex in turn determines a new oscillation, which is sensed by the baroreflex, which induces a new oscillation in the HR.

Studies on sinoaortic denervation confirm the considerable contribution of the baroreflex in the strength of the LF oscillation of cardiovascular variability, by showing a consistent reduction in LF power in R-R and blood pressure variability after baroreceptor deafferentation (13, 20). However, a residual variability is still present in both R-R and blood pressure, organized in a definite LF peak that is eliminated with ganglionic blockade. Therefore, the baroreflex may not be the only determinant of the LF rhythm.

A number of studies suggest that the LF component in the cardiovascular system is a marker of sympathetic modulation of central origin (for reviews, see Refs. 65, 73). In anesthetized, vagotomized, and sinoaortic-denervated cats, both LF and HF components have been detected in the discharge variability of medullary neurons localized in areas involved in the regulation of sympathetic nerve activity (72). In humans, an increased LF component in R-R variability has been documented in various conditions known to decrease baroreflex gain and increase sympathetic outflow (tilt, mental stress, exercise). An oscillatory component in the LF range can be observed in blood pressure and R-R variability during apnea, i.e., in absence of peripheral inputs (90). Finally, in patients with severe heart failure, restoring hemodynamic function by the implantation of a left ventricular device may also restore the LF component in R-R variability of the native heart, even in the absence of any organized blood pressure variability pattern (17). Because in this model the native HR variability is uncoupled from blood pressure variability, the restoration of the LF oscillation independent of any oscillation in blood pressure suggests that this LF rhythm may be a fundamental property of central autonomic outflow (17).

An LF rhythm, which could be independent from neural inputs, has also been described in the vasomotor tone in animals as well as in humans (98, 118). In conditions of baroreflex unloading, such as with sodium nitroprusside, increases in sympathetic activity and R-R interval are accompanied by clear increases in LF power of these measurements (118). In the same experiment, during hypotension after α_1-selective blockade (by phentolamine), LF power in cardiovascular variability is attenuated, despite the reflex tachycardia and increased sympathetic nerve traffic, suggesting that α-adrenergic transmission within the baroreflex loop appears to contribute importantly to LF oscillation. However, phentolamine did not suppress completely the LF oscillations in cardiovascular variability, suggesting the possibility that LF vasomotor oscillations may persist even in the absence of intact neurovascular transmission. These neural-independent oscillations could either indicate the presence of "autoregulatory" properties (98) or be an expression of the modulation operated by the nitric oxide system (79), as described below.

Further insights from baroreflex denervation. Baroreflex deafferentation by sinoaortic denervation results in an increase in average arterial blood pressure and large fluctuations in blood pressure variability (102). As mentioned above, animal studies report that arterial baroreceptor denervation induces selective changes in the spectrum of R-R and blood pressure variabilities (13, 20, 45). There is a consistent reduction in LF power in R-R variability, with or without reduction in HF and with or without changes in the overall R-R interval variance (markedly decreased in cats, unchanged in rats and in dogs). Conversely, the overall blood pressure variance increases, because of an increase in the very low frequency (VLF) components

(<0.03 Hz), whereas the faster fluctuation in LF appears to decrease. HF respiratory-related fluctuations do not change. These findings suggest that in several species the baroreceptor reflex exerts its major buffering effect on fluctuations occurring in the VLF band.

Baroreflex, nitric oxide, and cardiovascular variability. Blood pressure variability is also affected by the nitric oxide system (45, 77, 79). Blockade of nitric oxide synthesis leads to an increase in blood pressure variability due to an increase in the variability at higher frequencies (45, 79). The combination of nitric oxide blockade and infusion of nitroprusside (the latter infused to restore the values of blood pressure and HR to physiological levels and reduce consequent baroreflex activation) elicited a marked increase in blood pressure variability in the frequency range between 0.2 and 0.6 Hz (79), corresponding to that frequency that seems mainly influenced by the sympathetic nervous system in rats (44).

Therefore, the arterial baroreflex and the nitric oxide system are both involved in the short-term regulation of blood pressure, modulating the average value and variability of arterial blood pressure. However, although the baroreflex and nitric oxide both show similar strength in buffering blood pressure fluctuations, they show differences in the frequency range of their actions.

PHYSIOLOGICAL CHANGES IN BAROREFLEX FUNCTION

A multitude of physiological factors may influence baroreflex function. These influences will be exemplified below by a focus on effects of aging, physical deconditioning, and physical training. The important effects of sleep were addressed earlier.

Effects of aging. Aging is associated with significant cardiovascular modifications (for review, see Ref. 24). Arterial baroreflex modulation of HR and sympathetic activity may be decreased in older individuals (26, 70). In rats, an impaired baroreflex control of cardiac vagal function in response to both loading and unloading of baroreceptors, and depressed renal sympathetic activity during unloading of baroreceptors, have been reported (42). Preservation of the bradycardia produced by electrical stimulation of the vagus nerve, as well as by acetylcholine injection, supports the hypothesis that the impaired cardiac-vagal baroreflex control in aged rats does not reflect dysfunction in the efferent branch, but possibly in the sensory or central components of the reflex arc (42). Vascular compliance is an important determinant of the magnitude of deformation and, hence, activity of the baroreceptors. In the presence of a high compliance, the same pulse pressure can result in increased baroreceptor firing (50). A large cohort study in sedentary humans suggests that carotid artery compliance may play an important mechanistic role in the age-associated reduction in cardiovagal baroreflex sensitivity (70).

Effects of physical deconditioning. A major cardiovascular effect of deconditioning after prolonged bed rest or microgravity in spaceflight is the predisposition to orthostatic intolerance (for review, see Ref. 37). Among the potential mechanisms contributing to orthostatic intolerance associated with deconditioning (including hypovolemia, inadequate maintenance of stroke volume, and vascular dysfunction) is altered autonomic function (46, 68, 105). After bed rest or spaceflight, baseline arterial baroreflex regulation of HR is reduced (46). In rats, after 14 days of hindlimb unloading, sympathetic activation to muscle, renal, and lumbar vascular beds during a hypotensive stimulus appears to be blunted (68). In humans, after 14 days prolonged bed rest, postural hypotension in orthostatic intolerant subjects is associated with blunted responses of MSNA (Fig. 3) and total peripheral resistance during 60° head up tilt (105). Taken together, these findings suggest an impairment of reflex mechanisms, cardiac and peripheral, to compensate for the diminished stroke volume. Arterial baroreflex dysfunction could be due, at least in part, to changes in central nervous processing of baroreceptor afferent input (possibly involving altered function at the level of the rostral ventrolateral medulla), rather than to compromise in the baroreceptors themselves (69).

One of the key adaptations to bed rest is a reduction of plasma volume, which may itself alter baroreflex sensitivity (43). The arterial cardiac baroreflex appears to be similarly impaired after head-down bed rest (chronic hypovolemia plus deconditioning) and after acute hypovolemia, suggesting that the reduced cardiac baroreflex gain may be due primarily to a reduction of plasma volume. By contrast, a different and opposite behavior is shown at the level of SBP variability, which reflects the influence of vascular sympathetic drive and which is increased during hypovolemia and unchanged after bed rest. An interesting aspect is that an altered response of the peripheral circulation to mental stress has also been described after head down bed rest in healthy subjects (47). Although the sympathetic drive (MSNA) in response to mental stress was higher, the responses of blood flow (increased) and
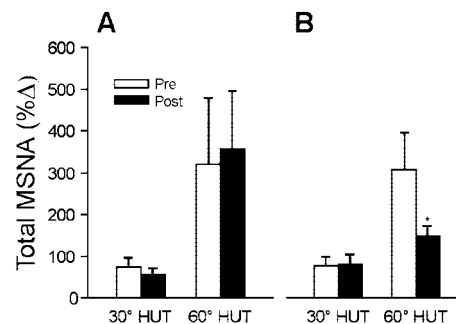

Fig. 3. Effect of 14 days head-down bed rest on percent increase in total mean sympathetic nerve activity (MSNA) between supine and 30° and 60° of head-up tilt (HUT). Comparisons are between subjects who were orthostatically tolerant (*A*) and intolerant (*B*) after prolonged bed rest. Orthostatic intolerance was associated with a blunting of the sympathetic response to 60° HUT. *Significantly different from pre-bed rest condition ($P < 0.05$). [Reproduced with permission from Shoemaker et al. (105).]

vascular resistance (decreased), observed before head down bed rest, were abolished after head down bed rest. A direct involvement of an alteration in baroreflex function was not documented. The possible invoked mechanisms responsible for this altered vasomotor function, including cardiovascular remodeling, are only speculative.

Effects of physical training. Exercise training improves endothelial function (12, 106), the major determinant of arterial compliance, and reduces sympathetic activation (15, 33), another possible factor affecting the distensibility of the arteries. The subsequent enhanced mechanoelastic properties of the carotid artery and aorta that may occur after training (49) could theoretically favor an increase in the baroreflex gain.

In spontaneously hypertensive rats, also characterized by a depressed baroreflex and high sympathetic cardiovascular tone, exercise training has been shown to attenuate the sympathetic drive to the heart and to produce an antihypertensive effect, which results from the reduction in HR and cardiac output rather than from decreased peripheral resistance (106; for review, see also Ref. 54). A marked improvement in baroreflex sensitivity is also documented in accounting for some of these benefits (106). In normotensive rats, an improvement was observed only in the baroreflex hypotension/tachycardia axes, whereas, by contrast, the hypertension/bradycardia reflex was attenuated (81). Moreover, although physical training seemed to be effective in reducing the baseline sympathetic activity to the kidney, baroreflex modulation of renal sympathetic activity appeared to be attenuated (81).

In humans, the effect of exercise training on baroreflex sensitivity and HR variability seems to be variable, depending on the category of subjects considered.

In sedentary normal subjects, exercise training has been reported to improve the baroreflex modulation of sympathetic nerve activity (33, 51), whereas the effect on the cardiac axis of the reflex is controversial (33, 51, 61).

Conversely, aerobic exercise can modulate the baroreflex depression associated with aging (71) and hypertension (87, 110). In patients with borderline hypertension, an endurance training program is not only accompanied by prolongation of R-R and lower daytime ambulatory intra-arterial blood pressure but also by prolongation of the R-R interval during sleep with marked increases in R-R variability (110) (Fig. 4). Remarkably, blood pressure during sleep is not lowered by endurance training. The simultaneous blood pressure reduction accompanied by a slowing of HR is accompanied by an increase in measurements of baroreflex gain using the phenylephrine bolus technique. Thus the tachycardia, higher blood pressures, decreased R-R variability, and lower baroreflex gain that are thought to characterize early hypertension (8, 74) are all opposed and reversed in part by endurance training.

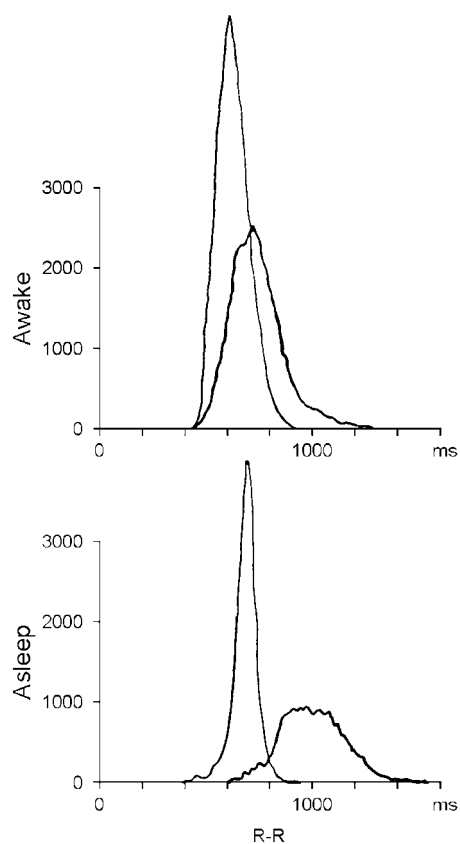After myocardial infarction, a slight improvement in cardiac vagal responsiveness seems to be a spontane-

Fig. 4. Frequency histograms of R-R intervals in a single subject before and after training. Thick lines, fit; thin lines, unfit. With increased fitness, mean R-R is prolonged and R-R variability increased during waking hours (*top*) and especially during sleep (*bottom*). These increases in R-R and R-R variability are accompanied by increases in baroreflex gain (not shown). [Reprinted with permission from Elsevier Science (110).]

ous phenomenon, independent of the intervention of training (60). By contrast, in post-coronary surgery patients, the significant increase in functional capacity after a short but intense training program is associated with a considerable improvement in baroreflex gain (41).

In patients with chronic heart failure, the improvement in peripheral hemodynamics appears to be a major factor responsible for the beneficial effects of physical training (for review, see Ref. 113). Data in trained heart failure patients show a correction of the endothelial dysfunction (35) and an improvement in artery compliance (89) with a decrease of peripheral vascular resistance and an increase in muscle blood flow (35). There is also evidence that physical training attenuates sympathetic overactivity and improves HR variability and its vagal components (15). These mechanisms have been invoked, among others, in the improved outcome after physical training (5).

Any analysis of the effects of endurance training on baroreflex characteristics must take into account the potential confounding effects of acute exercise (109). Immediately after exercise, HR is faster and blood pressure is higher. Bolus phenylephrine measurements of baroreflex gain show marked suppression of baroreflex

sensitivity. By 30–45 min after cessation of exercise, HR approaches baseline levels and blood pressure is normal or even lower. At this time, baroreflex gain is markedly increased. It is therefore important that baroreflex gain in association with endurance training is not measured shortly after an acute bout of exercise because exercise alone may confer a short-term improvement in baroreflex gain, even in individuals studied before undergoing an endurance training regimen. It is important that measurements of baroreflex gain reflect the effects of training rather than effects of a single bout of exercise.

Baroreflex and the kidney: neural and humoral interactions. Neural mechanisms contribute importantly to acute changes in arterial blood pressure, whereas humoral (renin-angiotensin-aldosterone system) and autoregulatory mechanisms (i.e., vascular stress-relaxation, capillary fluid shift, and kidney excretory function) have slower and more sustained effects on blood pressure control (34). However, neural and humoral mechanisms are closely linked. For instance, increased levels of brain ANG II, such as occurs in Dahl salt-sensitive rats during high sodium intake, affect the tonic level of sympathetic activity as well as the magnitude of baroreflex-induced changes in sympathetic traffic (39, 80). In humans with mild to moderate hypertension, the marked increase in plasma renin activity induced by a low-sodium diet has been shown to also be associated with a blunted baroreflex modulation of sympathetic neural drive (31).

Renal function is crucial to long-term blood pressure regulation (34). The average level of blood pressure as well as the dynamic fluctuations of blood pressure can both influence the excretory function of the kidney (78). Experimentally induced blood pressure fluctuations in the renal artery at 0.1 Hz (corresponding to the frequency of oscillations in the cardiovascular system influenced by the baroreflex) have been shown to change renal fluid and sodium excretion, thus potentially modulating longer-term blood pressure (78). Among the possible mechanisms involved, an attenuation in the activity of the renin-angiotensin system was reported, as evidence of the importance of the LF oscillatory component in renal perfusion in preventing marked increases in renin release.

BAROREFLEX AND CARDIOVASCULAR DISEASE

Hypertension. Baroreflex gain may be reduced in hypertensive subjects (74). Although it is not possible to establish the causal role of the baroreflex abnormality in essential hypertension and in any associated sympathetic activation, a depressed baroreflex gain and the resulting increased fluctuations in SBP variability may contribute to increased end-organ damage and adverse outcome (28).

Post-myocardial infarction. In the post-myocardial infarction phase, both depressed HR variability and impaired baroreflex control of cardiac function have been reported as predictors of cardiac mortality (40, 52, 56) and life-threatening arrhythmias (57, 64). This prognostic value is independent of other important indicators, such as electrical instability (as expressed by the presence of non-sustained ventricular tachycardia) and impairment of left ventricular ejection fraction (40, 57). The integration of traditional risk stratifiers, such as nonsustained ventricular tachycardia and left ventricular ejection fraction, with autonomic markers, has been, therefore, suggested as providing better identification of patients at risk for cardiac and arrhythmic mortality who might benefit from aggressive strategies such as an implantable cardiac defibrillator.

A mathematical model capable of producing normal and pathological patterns after ventricular premature beats suggests that baroreflex function (and dysfunction) has a primary role in the genesis of HR turbulence (i.e., fluctuations of sinus-rhythm cycle length after perturbations such as ventricular premature beats). This turbulence may have predictive value for mortality after myocardial infarction (103) and may be an indirect reflection of baroreflex gain (76).

The mechanisms mediating depressed HR variability and decreased baroreflex sensitivity after myocardial infarction are unknown (62). Altered responsiveness of sinus node pacemaker cells to autonomic influences, changes in central neural processing, and alterations in cardiac afferent neural inputs due to cardiac remodeling may be implicated. Why these abnormalities worsen prognosis is even more difficult to say. A depressed HR variability and depressed baroreflex gain are both expressions of, among other things, reduced parasympathetic cardiac control. Therefore, their abnormality may reflect the inability to counterbalance sympathetic activation, which, in the presence of electrical instability, such as a ventricular premature beat, can induce life-threatening arrhythmias. Recently, it has been suggested that the fractallike variability of R-R is even more sensitive than traditional measures of R-R variability in predicting overall cardiac and arrhythmic death after myocardial infarction. Although the mechanistic basis for this beat-to-beat behavior is still unclear, the loss of the dynamic complexity of the variability signal may be an index of loss of adaptability to the continuously changing environmental requirements (29, 63).

Heart failure. Depressed HR variability and deranged baroreflex sensitivity are commonly observed in patients with heart failure (114) and have been described even in early stages of ventricular dysfunction (32). The severity of the impairment appears to be related to the degree of functional compromise (75, 114) and the level of sympathetic activation (27, 116). Impaired baroreflex function is an attractive candidate mechanism to explain the heightened sympathetic activation in heart failure. However, some studies suggest that, although the arterial baroreflex control of HR (2) and cardiac norepinephrine spillover (82) are impaired, the arterial baroreflex control of peripheral sympathetic outflow is preserved and rapidly responsive in human heart failure (3; for review, see Ref. 25). These studies suggest that factors other than barore-

flex dysfunction may be implicated in the sympathetic over-activation in heart failure.

In these patients, despite direct evidence of high levels of sympathetic activation (increased cardiac and total norepinephrine spillover and MSNA) (36, 59), there is a blunting or absence of the LF component of R-R and SNA (83, 116). The observed dissociation between sympathetic drive and LF power in the power
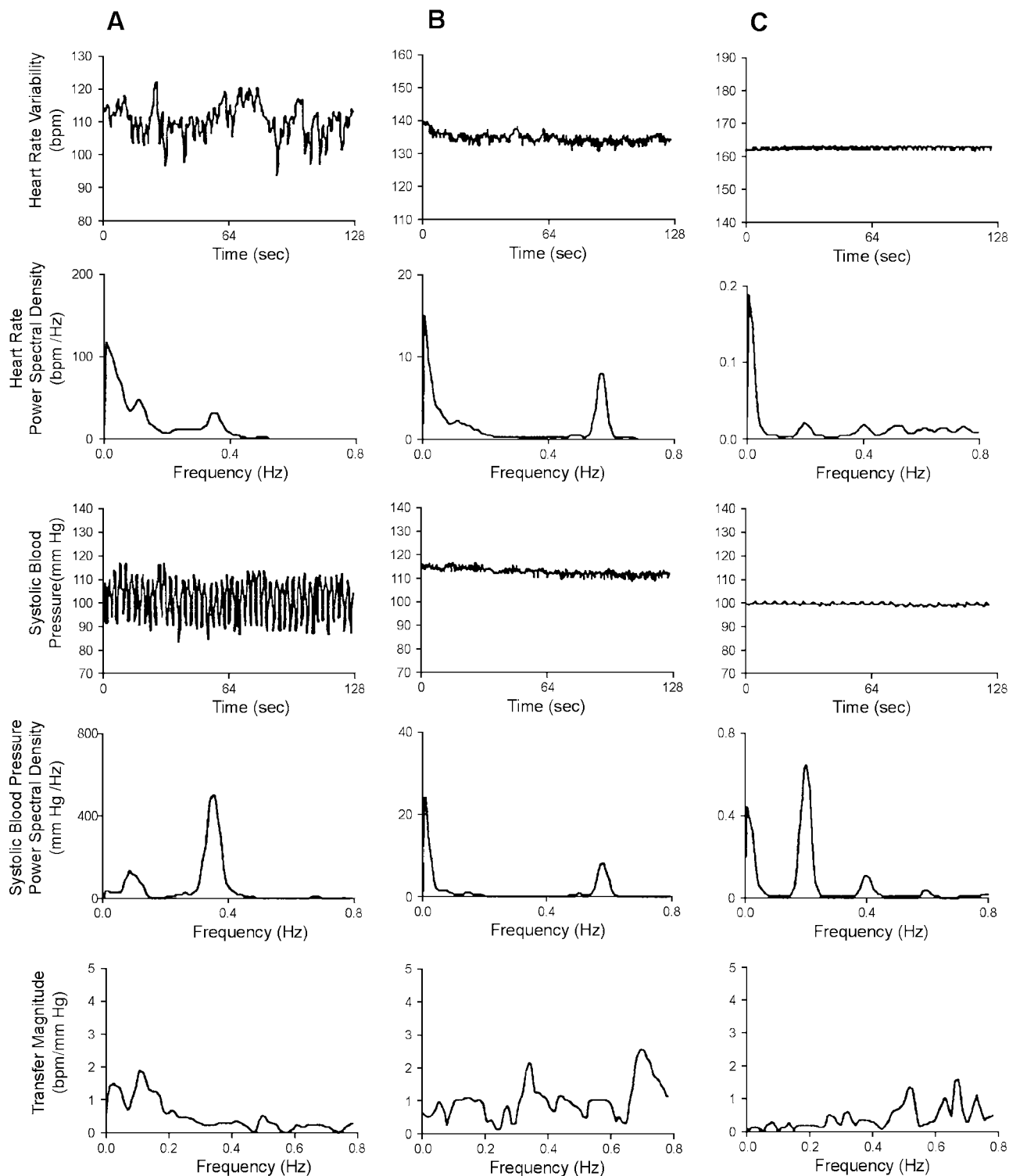

Fig. 5. Heart rate and blood pressure variability, power spectral density, and transfer function magnitude plots for 3 patients with different degrees of neurological injury. *A*: normal. *B*: moderate injury. *C*: brain death. Note changes in *y*-axis scales among graphs and near-zero levels for all variables during brain death. [Reproduced with permission from Goldstein et al. (30).]

spectra of cardiovascular variability implies that the traditional paradigm linking increased sympathetic drive to increased LF power in normal subjects cannot simply be extrapolated to include pathological conditions such as severe heart failure, where all homeostatic mechanisms are mobilized at close to maximum levels with little or no reserve to maintain variability. In particular, how this dissociation between LF power and sympathetic activation relates to any baroreflex abnormalities in patients with heart failure remains unclear.

Importantly, blunted or undetectable LF components in R-R variability are associated with worsening clinical status and poorer outcome (75, 116). We can speculate that attenuated or absent LF oscillation in the cardiovascular system and, thereby, in renal perfusion (78), could contribute to the marked increase in renin-angiotensin activity observed in heart failure.

CENTRAL NEURAL CONTRIBUTIONS TO BAROREFLEX DYSFUNCTION

Many central neural structures are involved in the regulation of the cardiovascular system and contribute to the integrity of the baroreflex. Acute brain injuries may induce baroreflex dysfunction and impair cardiovascular variability. The severity of neurological injury and the outcome are related to the change in cardiovascular variability and blunted baroreceptor sensitivity (Fig. 5) (30). Brain death is characterized by attenuated variability and baroreceptor sensitivity. Extensive unilateral infarction of the brain stem in the region of the nucleus of the solitary tract may result in baroreflex dysfunction, increased sympathetic activity, and paroxysmal neurogenic hypertension (93). Among the supramedullary structures, the insular cortex (the dorsal section of the rhinal sulcus) seems to be importantly involved in cardiovascular regulation (for review, see Ref. 120). Although the precise role of this nucleus is not clearly understood, animal studies report that *1*) unilateral lesions of the insula elicit myocardial damage and cardiac arrhythmias (84); *2*) focal cerebral ischemia leads to transient elevations in blood pressure and HR only if the insula is involved (91); and *3*) blockade of synaptic transmission through the insula (by local injection of lidocaine) significantly decreases the slope of baroreflex gain as evaluated by the reflex bradycardic response to phenylephrine (100). These findings suggested the speculation that baroreflex dysfunction could be a potential mechanism involved in the cardiac effects observed after a stroke in this region.

In cardiovascular disease conditions, particularly those that have been associated with severe hypotension or syncopal episodes, either brief ischemia or brief profound hypotension may conceivably contribute to abnormalities in cardiovascular control and abnormal variability on a central neural basis, rather than because of a direct and selective dysfunction of the baroreflex. Moreover, in patients with ischemic heart disease and/or heart failure who also have baroreflex dysfunction and impaired cardiovascular variability, we cannot exclude that damage in the brain, such as lacunar infarction and other ischemic changes in cardiovascular control areas, might be implicated in the associated autonomic and hemodynamic abnormalities.

SUMMARY

The baroreflex is an important contributor to short-term blood pressure control and to cardiovascular variability patterns. Although rapid and dynamic physiological functions, such as breathing, importantly affect baroreflex function, other influences such as aging and physical deconditioning must be recognized when interpreting changes in baroreflex function and cardiovascular variability. Baroreflex effects may feed back into changes in baroreflex function through nonneural mechanisms such as sodium retention and consequent changes in intravascular volume. Cardiovascular disease overall has been linked to baroreflex dysfunction and variability abnormalities. Some of the abnormality in variability and baroreflex function may be secondary to dysfunction at a central neural level. Last, we need to consider the possibility that the prognostic information provided by baroreflex dysfunction and impaired variability may, at least in part, be the result of "nonneural" consequences of impairments in baroreflex function and cardiovascular variability, such as sodium retention and activation of the renin-angiotensin system.

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