Emerging Excitatory Role of Cardiovascular Sympathetic Afferents in Pathophysiological Conditions

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Abstract—There is sound experimental evidence that cardiovascular sympathetic afferent fibers mediate cardiovascular reflexes largely excitatory in nature with positive-feedback characteristics. This afferent neural channel is likely to normally participate in the neural regulation of cardiovascular function. The hypothesis, which is the core of this article, is that in some pathophysiological conditions, sympathetic overactivity may be partly due to an emerging excitatory reflex action of cardiovascular sympathetic afferents. In fact, the early phase of congestive heart failure can be characterized by an increase in arterial pressure and heart rate and/or by a diastolic dysfunction, leaving unchanged the cardiac output; in these conditions, in which no baroreceptor deactivation should occur, it is possible that cardiovascular sympathetic afferents with sensory endings in the thoracic low-pressure areas, highly responsive to volume loading, are responsible for mediating the reflex sympathetic excitation. Similarly, during acute myocardial infarction, ventricular sympathetic afferents are likely to mediate a reflex sympathetic overactivity, which is known to facilitate sudden death. Finally, numerous reports have described in essential arterial hypertension an increased sympathetic activity that may be due, at least in part, to the reinforcing action of sympathosympathetic reflexes. Thus, in pathophysiological conditions, cardiovascular sympathetic afferents would mediate a reflex sympathetic overactivity independently of baroreceptive mechanisms, and such an absence of a homeostatic purpose would provide a better rationale for some beneficial effects of therapeutic correction. **(*Hypertension*. 2002;39:63-68.)**

Key Words: heart failure ■ ischemia ■ hypertension, arterial ■ heart rate ■ reflex ■ lung

The present article will attempt to support the hypothesis that in the early phase of congestive heart failure and other pathophysiological conditions, such as myocardial ischemia and arterial hypertension, sympathetic excitation seems devoid of an ultimate homeostatic purpose, and its genesis may be, in part, attributable to an enhanced peripheral excitatory function of sympathetic afferent fibers.

In physiological conditions, the cardiovascular neural regulation is likely to result from a complex interaction of central integration and peripheral inhibitory and excitatory reflexes.[1–3] In this interplay, cardiovascular sympathetic afferent fibers mediate a reflex action that is largely excitatory in nature[1] (Figure). When a sympathetic excitation is part of an integrated physiological pattern with a clear ultimate purpose, such as emotion, the central neural and, in particular, diencephalic mechanisms[4] are likely to play a predominant role. However, the central command is also likely to be reinforced by a synergistic enhancement of peripheral excitatory reflex mechanisms, accompanied by a simultaneous attenuation of mechanisms exerting an inhibitory action.[3,4]

Excitatory Function of Cardiovascular Sympathetic Afferent Fibers

This afferent pathway has traditionally received scarce consideration in respect to cardiovascular neural regulation, inasmuch as it has exclusively been ascribed to the transmission of cardiac pain.[5,6]

Brown[7] first reported recordings of sympathetic nerve afferent multiunit activity being markedly increased during myocardial ischemia. In the following years, numerous more detailed investigations[1,3] have led to the description of the functional properties of the cardiovascular sympathetic sensory endings located in all cardiac chambers and in the large thoracic vessels. These endings appeared to be sensitive to both mechanical[8–10] and chemical[8,11,12] stimuli, acting as low-threshold polymodal receptors.[1,3,6]

On the other hand, it was first found that cardiac sympathetic afferent fibers excited by experimental coronary occlusion were capable of mediating an excitatory sympathosympathetic reflex.[13] This reflex was also present after vagotomy and spinal section or after sinoaortic denervation[3] and, thus, appeared to be independent of baroreflex mechanisms. In addition, it was observed that in conscious dogs,[14] a graded distention of a short segment of the thoracic aorta, within physiological limits (9.6±0.4%), ie, a stimulus simulating a rise in aortic pressure and capable of exciting aortic sympathetic afferents,[1] caused a reflex increase in mean arterial pressure (31±3%) and heart rate (20±3%). This reflex response, in the absence of behavioral changes indicating

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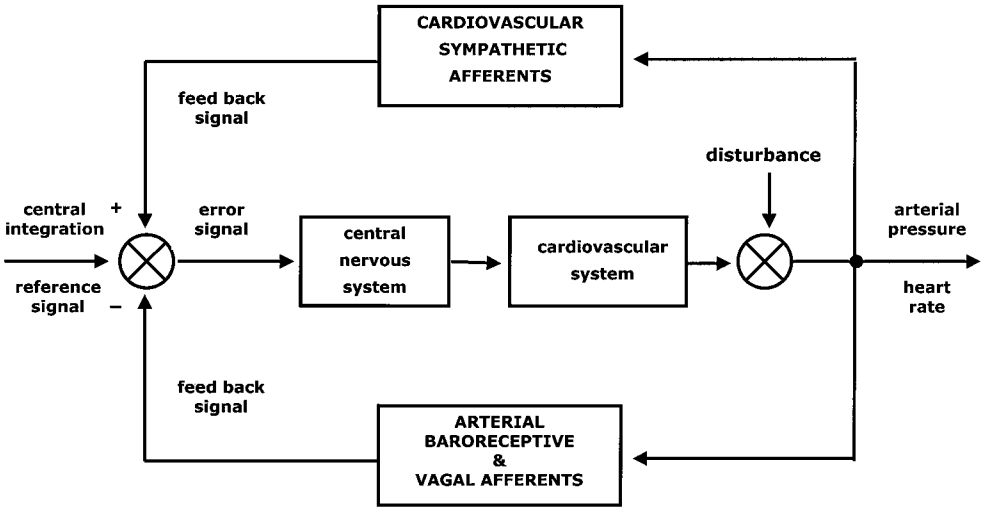

Schematic representation of opposing feedback mechanisms that, in addition to central integration, subserve the neural control of the cardiovascular system (see text).

pain perception, suggested a positive-feedback mechanism.[1,3,14] As anticipated by a previous electrophysiological study,[15] it was also found that this sympathetic pressor reflex could blunt (57±7%) baroreceptor sensitivity, assessed as the slope of the RR interval on systolic arterial pressure rise induced by phenylephrine.[16] Thus, in these experimental conditions, a reduction in baroreceptor sensitivity was the consequence and not the cause of a reflex sympathetic excitation.[1,3]

In general, cardiac structures and thoracic large vascular areas seem to possess both vagal and sympathetic sensory innervations that project to the brain stem and to the spinal cord, respectively. Afferent vagal and arterial baroreceptive fibers transmitting to supraspinal structures their information on hemodynamic events seem to exert largely inhibitory influences acting through negative-feedback mechanisms.[17] Afferent sympathetic fibers impinging on the spinal cord seem to mediate mainly excitatory influences with positive-feedback properties[1,3,14,18,19] (Figure).

The crucial point is that the same normal hemodynamic events are likely to activate both afferent pathways.[18] In resting conditions, the influence of the inhibitory negative-feedback circuit appears to prevail,[17,18] as exemplified by the bradycardic response induced by phenylephrine injection.[16] However, also in this specific case, the cardiovascular sympathetic afferents may exert a restraining influence on the reflex bradycardia. Accordingly, Gnecchi Ruscone et al[20] found that the reflex bradycardia induced in decerebrate cats by elevations in arterial pressure was significantly increased (from 21±4% to 34±4%) after dorsal root (from C8 to T6) section. This intervention, by interrupting a large contingent of cardiovascular sympathetic afferent fibers, diminished their reflex excitatory action.

On the other hand, it is well known that states of sympathetic excitation are accompanied not only by vagal withdrawal, leading to the concept of sympathovagal balance,[2] but also by parallel blunting of negative-feedback responses.[4]

Congestive Heart Failure

In the early investigations, it was found that circulating levels of catecholamines were increased in heart failure in proportion to the severity of the disease.[21] Recently, it has been reported that in mild to moderate heart failure, the cardiac adrenergic drive (assessed with norepinephrine spillover) is excited in the absence of an augmented sympathetic outflow to the kidney and skeletal muscle.[22] In addition, it has also been known for years that the reflex cardiac slowing accompanying a pressor stimulus is greatly reduced in humans[23] and in dogs[24] with heart failure.

Regarding the mechanism leading to sympathetic excitation, an enigmatic ensemble of contradictory elements has to be envisaged. On the one hand, a compensatory baroreceptor reflex is still interpreted as the main cause of an excitatory release phenomenon, assuming a priori the occurrence of a reduction in cardiac output.[25] On the other hand, the congestion of thoracic low-pressure areas and the consequent activation of vagal afferents, known to play an inhibitory role,[17] should oppose this sympathetic excitation.

However, in terms of clinical knowledge, it is well known that during acute heart failure accompanied by pulmonary congestion, an increase in both arterial pressure and heart rate frequently occurs. The patient is usually sweating and, on the whole, furnishes one of the most dramatic examples of sympathetic overactivity that cannot be attributed, in its early phase, to chemoreceptor stimulation or to baroreceptor deactivation.

In a quite recent article, Gandhi et al[26] have provided evidence that hypertensive patients during pulmonary edema usually present a marked hypertensive crisis (200±26 versus 139±17 mm Hg before and after treatment, respectively) and a significant tachycardia (83±14 versus 72±12 bpm, respectively). Despite the marked difference in blood pressure, the left ventricular ejection fraction during the acute episode (0.50±0.15) was similar to that measured after treatment (0.50±0.13) and was normal in half of the patients. Gandhi et al concluded that diastolic dysfunction was likely to have

caused acute heart failure, but no hypothesis was provided to explain the "increased β-adrenergic tone during acute pulmonary edema."

We have hypothesized for numerous years[27] that the increase in filling pressures and the congestion of the low-pressure thoracic vascular areas would therein activate cardiovascular sympathetic sensory endings, which are extremely sensitive to such changes.[1,28] The consequent excitatory reflex[29] would further aggravate heart failure.

On the other hand, an increasing evidence supports by now[30] the beneficial effects of chronic administration of β-blockers, and this, in turn, suggests an untoward role of such a sympathetic overactivity, contradicting its presumed homeostatic and compensatory nature.

Pathophysiological Predominance of Reflex Excitatory Mechanisms

However, in the congested areas, why the excitatory reflex mechanism mediated by sympathetic afferents would prevail over the inhibitory mechanism mediated by vagal afferents still remains a puzzle. Yet a corollary hypothesis seems attractive. Afferent vagal fibers from the atria, for an example, normally display a burst of impulses per each cardiac cycle, in correspondence with atrial systole in the case of type A receptors.[31] Rhythmic afferent bursts can produce in central structures sequences of excitatory and inhibitory postsynaptic potentials.[4] During volume loading, type A atrial vagal receptors also discharge during diastole,[32] and this more continuous firing may blunt the capability of generating inhibitory postsynaptic potentials in the central circuitry. Similar changes in firing patterns may characterize the majority of vagal cardiopulmonary receptors, thus explaining their reduced efficacy in exerting an efficient reflex restraint on the sympathetic outflow. Conversely, cardiovascular sympathetic afferent fibers do not display, in normal conditions, bursts of impulses but rather a more sparse spontaneous activity with, at most, 1 action potential per cardiac cycle.[1] Thus, an increased afferent sympathetic barrage, independent of its rhythmic relationship with the cardiac cycle, would retain its capability of exciting the sympathetic outflow.

Some aspects of these abnormal responses can also be detected in the course of human pathophysiological investigation. As an example, a paradoxical increase in forearm vascular resistance has been observed in patients with mild heart failure during saline load.[33] This suggests that the reflex excitatory response is due to the stimulation of cardiovascular low-pressure receptors rather than to the deactivation of some negative-feedback reflexogenic area.

It is also quite interesting to point out that Ando et al[34] have reported that patients with heart failure and pulsus alternans present a correlated alternation in the discharge of the muscle sympathetic nerve activity as well, clearly indicating that brisk baroreflex mechanisms are also operative in an advanced phase of the disease. Thus, some of the observed blunting of supraspinal negative-feedback responses, such as the reduced reflex bradycardia, may depend on the activation of sympathetic afferents mediating a reflex increase in cardiac sympathetic drive and a simultaneous decrease in cardiac vagal efferent activity.[15]

This new perspective is also supported by numerous experiments on dogs with sinoaortic denervation, bilateral cervical vagotomy, and heart failure. In these animals, the observed increase in sympathetic efferent activity, potentiated by volume loading, could be mediated only by cardiovascular sympathetic afferents.[35]

Frequency Domain Analysis

Spectral methodology[2,3,36] should offer an appropriate tool to investigate the abnormal neural mechanisms occurring in the early phase.

Studying patients in New York Heart Association (NYHA) class II in controlled laboratory conditions, Guzzetti et al[37] observed an increased normalized low frequency component of RR variability, a marker of sympathetic modulation.[2,36] No further enhancement of the normalized low frequency component occurred during tilt, suggesting a background sympathetic predominance with a decreased responsiveness to physiological stimulation. This shift in sympathovagal balance toward sympathetic predominance, in the absence of significant changes in arterial pressure, was thus likely to be independent of baroreceptive deactivation.[37]

Patients in NYHA classes III and IV, together with a progressive reduction in variance, also presented decreased absolute values of spectral components, as already reported by Saul et al,[38] suggesting an altered responsiveness of sinus node pacemaker cells.[3,39]

Quite interestingly, patients who present a reduced or undetectable low frequency component in RR and arterial pressure variability[37,40–42] also seem to have the worst clinical state and prognosis.

Testing the Hypothesis

To test this hypothesis in the clinical setting of heart failure is quite a difficult task. At this moment only some indirect reasoning seems feasible. For instance, although cardiac transplantation produces a limited interruption of cardiovascular sympathetic afferent fibers, its influence on the autonomic profile during heart failure may provide some interesting findings.

This hypothesis, however, is not intended to oversimplify the reality but rather to add a further facet to the complexity. In the early phase of pulmonary edema, an excitation of central neural structures that is due to respiratory distress, an initial chemoreceptor activation, a potentiation of peripheral excitatory, and a reduction in the efficacy of peripheral inhibitory mechanisms may well coexist. In addition, the role of other factors, such as the renin-angiotensin system, influencing the sympathetic activity at both central and peripheral levels[43] should not be dismissed. With the progression of the disease, when arterial baroreceptor deactivation truly occurs, the sympathetic overactivity would become even more marked, being usually accompanied by a β-adrenergic receptor downregulation.[39]

Ischemic Heart Disease

Most deaths from acute myocardial infarction occur within 1 hour from the onset of symptoms. In the pioneering work by Pantridge's group (Webb et al[44]), an autonomic disturbance

was present in 92% of the patients seen within the first 30 minutes and consisted in a pattern of vagal or sympathetic overactivity. Reflexes from the heart, of depressor[45] or pressor[13] nature, were considered to cause these 2 opposite patterns, unrelated to pain or pump failure but related to the infarct location. Vagal overactivity was more frequent in inferior infarction and sympathetic overactivity in anterior infarction,[44,46] as a possible consequence of a preferential distribution of vagal afferents to the inferoposterior wall of the left ventricle.[47] Autonomic disturbance appeared to facilitate life-threatening arrhythmias, and its pharmacological correction was highly rewarding.[46] This practically unduplicated attempt has clearly evidenced the involvement of abnormal neural mechanisms in the early phase of myocardial infarction.

In experimental animals, dorsal root section was shown to decrease the absolute number of ectopic beats during coronary occlusion.[48] The deleterious effects of sympathetic reflexes from the heart during acute myocardial ischemia[13] seem now to be widely accepted. On the other hand, increases in heart rate and arterial pressure are the most frequent accompaniments of transient myocardial ischemia, whether or not pain is present.[6]

In patients after myocardial infarction, the work by La Rovere et al[49] has demonstrated the prognostic value of a depressed reflex bradycardia during phenylephrine-induced arterial pressure elevations. In view of the unlikeliness of a primary alteration in arterial baroreceptor functional properties, the reduced baroreceptive slope was convincingly attributed to an increased afferent sympathetic barrage from the heart, secondary to the abnormal mechanical conditions of ventricular wall.[50]

Testing the Hypothesis

In the case of myocardial ischemia, rather than proving the participation of cardiac sympathetic afferents in eliciting the reflex sympathetic excitation,[13] which appears by now to be a recognized mechanism, the challenge would be that of interpreting the remarkable therapeutic efficacy of chronic β-blockade in patients after myocardial infarction.[51] This may partly consist of the attenuation of sympathetic excitatory reflexes during eventual ischemic episodes,[6] leading to the reduction of life-threatening arrhythmias and reinfarctions.[51] The noninvasive power spectrum analysis[2,36] of heart rate variability may furnish the appropriate tool to monitor whether episodes of transient myocardial ischemia are accompanied by surges of sympathetic excitation.

Arterial Hypertension

For years, there has been an enduring effort to demonstrate the existence of an increased sympathetic activity at least in the early phase of human hypertension.[3] Among the first probative findings, one should mention the consistent elevation of plasma norepinephrine observed in younger hypertensive patients[52] and the signs of an excited sympathetic discharge, detected from direct peroneal nerve recordings,[53,54] recently corroborated by single-unit sympathetic detection.[55] Signs of a moderately enhanced cardiac sympathetic modulation were also found with spectral methodology in untreated hypertensive patients; these signs were associated with a clearly reduced sympathetic responsiveness to an orthostatic stimulus[56] or to a blunted circadian oscillation.[57]

The cause of this sympathetic overactivity has been mainly attributed to central neural mechanisms, including emotional, cognitive, and other factors. Yet, in all these instances, a reinforcing action of sympathosympathetic reflexes appears plausible.[1,3]

However, the strongest argument in favor of the likeliness of linking the state of central excitation also to peripheral positive-feedback mechanisms has to be found in the similarity existing between the organization of the somatic and of the autonomic nervous systems.[1,3] The mechanisms that produce a sustained increase in sympathetic activity may be similar to those that, in the decerebrate animal, are responsible for spasticity. Sherrington[58] observed that spasticity was abolished by dorsal root section. Thus, it was proved that an augmented central command was not, per se, capable of causing a sustained increase in the postural tone but that a peripheral spinal loop was necessary for the maintenance of the phenomenon.

On pathophysiological grounds, it is essential to recall that tetraplegic patients during gentle manipulations of the abdomen, such as those facilitating bladder emptying, can undergo sudden and sometimes dramatic hypertensive crises,[59] which perhaps indicate the full potential of spinal reflexes.[1,3] In decerebrate vagotomized cats, with a subsequent spinal section, a rise in aortic pressure can increase 4-fold the sympathetic discharge to the heart. A subsequent dorsal root section, by interrupting cardiovascular sympathetic afferents, abolishes this positive-feedback excitatory reflex.[60]

Moreover, it is interesting to mention that propranolol, given during acute episodes in animal experiments, was capable of reducing the responsiveness of aortic and pulmonary vein sympathetic afferents to elevations in arterial pressure.[61] This effect was independent of its membrane-stabilizing properties because DL-propranolol was active, whereas D-propranolol, possessing only this stabilizing property, was ineffective. This observation suggests the second corollary hypothesis that the largely unexplained decrease in systemic vascular resistance induced by chronic β-blockade[30] may, in part, depend on the reduced afferent discharge of cardiovascular sympathetic afferents.

Testing the Hypothesis

Tarazi's group (Estafanous et al[62]) interpreted the arterial hypertension immediately after myocardial revascularization by coronary bypass surgery as resulting from a sympathetic reflex elicited by coronary artery distension.[8] In fact, Tarazi et al[63] found that unilateral stellate ganglion block led to rapid and sustained control of arterial pressure in 18 of 27 patients in whom a successful lidocaine infiltration was achieved. The reduction in arterial pressure was associated with a significant decrease in total peripheral resistance and heart rate but no significant changes in cardiac output. The hemodynamic pattern as well as the effectiveness of a unilateral approach led the authors suggest that stellate block reduced arterial pressure by interrupting the afferent limb of a pressor reflex from the heart. Their study indicates the difficulty in gather-

ing definitive evidence on the role of cardiovascular sympathetic afferents in the course of human diseases and, at the moment, provides an excellent model for further testing this hypothesis in a peculiar clinical setting.

Limitations and Conclusions

Very often a new hypothesis is the result of laboratory models that seem to clarify human pathophysiology.[64] On the other hand, a hypothesis is just a tool for further investigation and surely is never unique.

The main limitation of the present hypothesis is that it is centered on a mechanistic excitatory role of sympathetic afferents, emerging in pathophysiological conditions, whereas the essence of neural regulation is its integrative structure.[58] A further limitation is that it cannot be tested as a whole in human pathophysiology. Hence, peculiar examples, when adequately analyzed, are more likely to probe its usefulness.

The main contribution of this hypothesis is to counterbalance the concept of homeostasis with that of instability and the concept of compensatory sympathetic excitation with that of an excitation deprived of a homeostatic purpose in pathophysiological states of paramount importance.[3] Primary conditions of sympathetic overactivity[65] may very well be more numerous than is usually appreciated. In all these instances, the recognition of abnormal neural mechanisms deprived of an ultimate function may be important in monitoring their relevance and progression and the need for a therapeutic correction.

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