Published in final edited form as:

Auton Neurosci. 2012 December 24; 172(1-2): 1–3. doi:10.1016/j.autneu.2012.10.010.

Afferent Baroreflex Failure

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Keywords

Baroreflex; Heart Rate; Blood Pressure; Autonomic System

The Arterial Baroreflex

The baroreceptor and cardiopulmonary reflexes represent a crucial integrative neuronal negative feedback system which confines excessive blood pressure fluctuations into physiologically normal ranges. It includes a) the arterial baroreceptors (high pressure baroreceptors), with sensory nerve endings within the aortic arch, at the origin of the right subclavian artery, and within the carotid sinuses and b) pressure-sensitive receptors located in the walls of cardiopulmonary veins and right atrium (low pressure baroreceptors). Carotid baroreceptor input transmits through the glossopharyngeal nerve to the first synapse located in the *nucleus tractus solitarius* (NTS) in the brainstem. Baroreceptor input of the aortic arch transmits through the aortic depressor nerve, which joins the vagus nerve, and ascends to the NTS. Cardiopulmonary receptors in the heart and lungs project through the vagal nerve to the same nuclei in the NTS (Figure 1).

Baroreceptors respond to vascular wall stretch with increase of baroreceptor discharge frequency, which inhibits sympathetic activity and enhances parasympathetic activity. This is accomplished via NTS projections to those hindbrain nuclei at the caudal ventrolateral medulla (CVLM) and sympathetic pacemaker neurons at the rostral ventrolateral medulla (RVLM) with an efferent path to the intermediolateral columns of the spinal cord (IML). Parasympathetic activity is modulated in the nucleus ambiguus (NA) and the dorsal motor nucleus of the vagus (DMNV). Blood pressure increases stretch in the vascular wall producing an increase in the frequency of firing, leading to a decrease in sympathetic

activity and an increase in parasympathetic activity, with the final integrated response of a reduction in blood pressure and heart rate (Figure 1) (Ertl et al., 2003).

The Importance of Arterial Baroreflex

The role of arterial baroreflex in short-term blood pressure regulation has been investigated by many researchers for centuries. Increases of blood pressure of up to 300 mmHg after carotid sinus denervation demonstrate the power of arterial baroreceptors in human blood pressure regulation (Kezdi, 1953)(Figure 2). A heroic self-experiment where Wallin and colleagues studied sympathetic outflow after local anesthesia of the glossopharyngeal and vagal nerve demonstrate that the loss of arterial baroreceptor input initially increases muscle sympathetic nerve activity unrelated to heart beat and blood pressure fluctuation, but rather, elicited by emotional cortical and other exogenous stressors (Fagius et al., 1985). But it seems that the baroreflex resets quickly and the blood pressure is normalized after a short period of time (Figure 2). The carotid baroreceptors are responsible for short-term blood pressure regulation (seconds to minutes) and less important for long-term blood pressure regulation. However, recent studies in animals suggest that baroreceptor resetting may not be as rapid or complete as previously thought. Thrasher et al. clearly demonstrate that unloading baroreceptors in a single carotid sinus can cause neurogenic hypertension for at least 7 days duration and he suggest that the role of baroreceptors in the long term control of mean arterial pressure needs to be revisited (Thrasher, 2006).

Afferent Baroreflex Failure and its Clinical representation

The importance of baroreflex mechanisms in the regulation of blood pressure is most evident when they fail. Abnormalities may originate in the afferent, central, and efferent pathway. Afferent baroreflex failure has been described as a patient group with loss of afferent baroreceptor and neural pathways, nuclei or interneurons in the brainstem, which cause diminished or absent buffering capability to prevent blood pressure from rising or falling excessively after removal of a paraganglioma and carotid body (Robertson et al., 1993), endarterectomy (Timmers et al., 2004), radiation therapy (Timmers et al., 2002, Sharabi et al., 2003), or central nervous system damage (Biaggioni et al., 1994). This patient entity is characterized by volatile blood pressure fluctuations during the day with hypertensive episodes accompanied by tachycardia or hypotensive episodes with bradycardia. Higher norepinephrine level, no heart rate response to vasoactive drug and pronounced hypotensive effect to clonidine are common for these patients. It is important to distinguish these patients from the broader group of patients with other forms of autonomic failure or patients with pheochromocytoma (Robertson et al., 1993, Biaggioni et al., 1994, Jordan et al., 1997, Ketch et al., 2002).

Novel Therapeutic Approaches

Recent non-pharmacological approaches to reduce resistive hypertension by stimulation of the afferent pathways from the carotid sinus (Heusser et al., 2010) (Jordan et al, in this issue) and kidney (Esler et al., 2010) showing promising results in the reduction of blood pressure.

But not every patient responds to proposed renal ablation intervention (Brinkmann J et al. 2012 in press).

Do we even yet know enough about the baroreflex mechanism and its role in blood pressure and volume regulation? Does the phenotype always play the major role in blood pressure control? To what extent does genotype also contribute importantly predict the response to therapy?

Learning from Baroreflex Failure

Interruption of baroreceptor inputs from the carotid sinus and aortic arch to areas of central integration in the brainstem produces profoundly labile blood pressure. In consequence, central disturbances, whether initiated by exogenous psychological, physical stressors, or endogenous neural perturbations translate into alterations in cardiac and vascular function, which are often greatly amplified. This provides an opportunity to elucidate mechanisms whose contributions would have been obscured in the presence of a functioning baroreflex. It is an opportunity to learn about the mechanisms of high blood pressure and how to optimized novel strategies for its management.

The present issue summarizes new trends in the field of baroreflex failure research: from the baroreceptor cell (Shild et al, in this issue), genetic factors (Jordan et al, in this issue), its representation in familial dysautonomia (Norcliffe-Kaufmann et al., in this issue), about influence of gender and exercise on baroreflex properties (Fisher et al, in this issue), and recent results using electrical carotid sinus stimulation in treatment of resistant arterial hypertension {Jordan, in this issue}. We also update you about longterm and heterogeneous consequences of baroreflex impairment as experienced in a family with genetically mediated susceptibility to paragangliomas (Robertson et al., 1993). Enjoy this issue.

Acknowledgments

Authors DR and AD are supported by the National Heart, Lung, And Blood Institute of the National Health under Award Number NIH 2P01HL056693-19. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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FIGURE 1.

Simplified anatomical and functional scheme of baroreflex function demonstrating the baroreflex response to hypotension

Abbreviations:

BP Blood pressure;

IX Glossopharyngeal nerve;

X Vagus nerve;

NTS Nucleus Tractus Solitarius;

NA Nucleus Ambiguus;

CVLM Caudal Ventrolateral Medulla;

RVLM Rostral Ventrolateral Medulla;

DMV Dorsal motor nucleus of the vagus;

IML intermediolateral column of the spinal cord).

FIGURE 2.

Heart rate and blood pressure response to external pressure (PRESSURE) on left (L) and right (R) carotid sinus receptors and total pharmacological blockade (BLOCKADE) in normotensive and hypertensive subjects (modified from Kezdi et al. 1953)