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Mechanisms of Blood Pressure Reduction by Prolonged Activation of the Baroreflex

Radu Iliescu and

Department of Physiology and Biophysics at the University of Mississippi Medical Center, Jackson, MS 39211, USA (phone: 601-815-1813, fax: 601-984-1817)

Thomas E. Lohmeier

Department of Physiology and Biophysics at the University of Mississippi Medical Center, Jackson, MS 39211, USA

Radu Iliescu: riliescu@physiology.umsmed.edu; Thomas E. Lohmeier: tlohmeier@physiology.umsmed.edu

Abstract

Recent technological advances have made activation of the afferent limb of the baroreflex a viable therapeutic approach for lowering blood pressure. Experimental studies demonstrate sustained reductions in blood pressure in response to electrical baroreflex activation and initial results from clinical trials using device-based therapy for drug-resistant hypertension are promising. The mechanisms involved in the blood pressure lowering effect of baroreflex activation have not been completely defined and experiments designed to investigate them often challenge preconceived notions and even dogmas. This paper is a brief overview of our current understanding of these mechanisms.

Despite the wide availability of numerous pharmacological tools to treat hypertension, adequate blood pressure reductions are often not achieved and the prevalence of resistant hypertension remains high.[1]. Early experimental attempts to lower blood pressure in hypertensive animals and human subjects by electrical stimulation of the afferent limb of the baroreflex demonstrated proof of concept and suggested a potential therapeutic use of this technique [2]. Unfortunately, with the technical limitations inherent in these early devices and the emergence of antihypertensive agents, interest with this approach waned. However, over time, technical limitations have been overcome. Recent technological advances have led to the design of a new device (CVRx, Minneapolis, MN) that produces sustained and controllable reductions in arterial pressure by electrical stimulation of the carotid sinus [3;4].

Clinical trials are now underway in Europe and USA using this new device to test the efficacy of prolonged baroreflex activation as a therapy for drug-resistant hypertension. Platinum electrodes embedded in a thin sheet of biocompatible silicone are implanted perivascularly around the carotid sinuses. Optimal lead placement is determined by reflex-induced decreases in blood pressure during surgery. The leads are attached to an implanted pulse generator, which is programmable via a wireless external system that allows control over the amplitude, frequency, pulse duration and temporal pattern of electrical impulses delivered to the electrodes [5]. Recent results from clinical trials indicate the effectiveness of this procedure for blood pressure reduction in resistant hypertension [5].

The mechanisms by which baroreflex activation lowers blood pressure are still a subject of debate and active experimental investigation. An understanding of these mechanisms is required for defining and guiding the use of electrical stimulation of the carotid sinus in clinical practice. Since much of the insight into the role of baroreflexes in blood pressure regulation has been inferred from acute studies, the technology for baroreflex activation

described above provides a novel approach for understanding long-term control of blood pressure. In the following, we present an overview of studies aimed at understanding the mechanisms that account for the blood pressure lowering effect of the baroreflex activation.

Normotensive dogs were chronically implanted with electrodes around both carotid sinuses [6]. After control measurements, the conscious dogs were subjected to baroreflex activation for 1 week, using the device described above. Mean blood pressure was promptly reduced by ~ 20 mmHg and remained at this low level for the entire activation period. Heart rate decreased in parallel with blood pressure. Circulating norepinephrine concentration decreased by ~ 35%, indicating that baroreflex activation is capable of chronically suppressing sympathetic outflow. Seminal systems analysis studies by Guyton et al. [7] indicate that a reduction in blood pressure can only be sustained if the kidney function is altered to increase the excretion of water and electrolytes. The renal sympathetic nerves promote sodium retention and, therefore, a reduction in renal sympathetic nerve activity during baroreflex activation was suggested to play a role in the observed blood pressure reduction. Furthermore, as plasma renin activity did not increase in response to the fall in blood pressure, it was suggested that suppression of renal sympathetic nerve activity counteracted the pressure stimulus for renin secretion. In the absence of this inhibitory effect on renin secretion, increased plasma levels of angiotensin II would be expected to attenuate the effect of baroreflex activation to lower blood pressure.

To test whether increased plasma levels of angiotensin II might attenuate the blood pressure lowering effects of baroreflex activation, dogs were made hypertensive by chronic infusion of angiotensin II [8]. The same carotid sinus stimulation protocol was used that produced a ~ 20 mmHg reduction in mean arterial pressure in normotensive animals, as indicated above. However, after 1 week of baroreflex activation, mean arterial pressure decreased by only ~ 5 mmHg during angiotensin II-hypertension. One explanation for this intriguing finding is that angiotensin II has direct effects on the central nervous system to stimulate sympathetic outflow, which may attenuate the effects of baroreflex activation. Another possibility is that high levels of angiotensin II directly enhance sodium and water retention by the kidneys and, therefore, oppose the direct actions of renal sympathoinhibition to enhance sodium excretion and decrease blood pressure. Regardless of the precise mechanisms, this study supported the hypothesis that suppression of the renin-angiotensin system during baroreflex activation is one of the major mechanisms involved in lowering blood pressure.

The effect of baroreflex activation was next studied in an experimental model of hypertension with direct relevance to human hypertension [9]. Dogs were made obese by feeding a high fat diet. After 4 weeks of the high fat diet, mean arterial pressure increased ~ 15 mmHg in association with a 50% increase in body weight. Plasma norepinephrine concentration increased significantly, consistent with sympathetic activation in obesity hypertension. After 4 weeks of weight gain, activation of the baroreflex for 1 week in these obese dogs resulted in marked reductions in mean pressure to levels even lower than control. The lowering of blood pressure occurred concomitantly with reductions in plasma norepinephrine concentration. These findings indicate that baroreflex activation can have sustained effects to suppress the sympathoexcitation associated with obesity and, therefore, abolish obesity-induced hypertension.

Based on these studies, the critical link between the baroreflex and the kidneys was then investigated. Since the renal nerves are the obvious direct neural link between the brain and the kidneys, experiments were performed to test whether their presence is required for baroreflex activation to lower blood pressure [10]. Normotensive dogs were subject to baroreflex activation before and after renal denervation. Renal denervation had no effect on blood pressure prior to baroreflex activation. Moreover, there were similar reductions in

plasma norepinephrine concentration and blood pressure during baroreflex activation before and after renal denervation. Astonishingly, this study indicates that although suppression of renal sympathetic nerve activity may normally contribute to the fall in blood pressure in response to baroreflex activation, the renal nerves are not an obligate requirement for this response. Taking into consideration the fundamental role of the kidneys in the chronic regulation of blood pressure by altering salt and water excretion, other mechanisms must come into play to increase renal excretory function at a lower pressure in the absence of the renal nerves. The nature of these mechanisms is unclear to date but, based on current knowledge of cardiovascular regulation and experimental observations, several possibilities emerge. Daily measurements of urinary excretion throughout the experimental period indicated an initial retention of sodium on day 1 of baroreflex activation that was slightly higher in the absence than in the presence of the renal nerves. Assuming that reflex suppression of sympathetic activity leads to comparable increases in vascular capacitance in the presence and absence of the renal nerves, then greater fluid retention after renal denervation might result in greater increases in atrial volume and pressure and, consequently, greater secretion of atrial natriuretic peptide (ANP). An increase in ANP is therefore a likely candidate as one of the natriuretic forces that allow the kidneys to achieve sodium balance at a lower pressure in the absence of the renal nerves during baroreflex activation. In addition, a significant increase in the volume of blood in excess of the total volume of the venous compartment would lead to an increase in venous pressure. An increase in renal venous pressure would, in turn, increase renal interstitial pressure, which opposes sodium reabsorption [11]. Therefore this might be an additional natriuretic force that may contribute to the blood pressure lowering effect of baroreflex activation in the absence of renal nerves. The quantitative importance of these apparently redundant mechanisms is still unclear but it is likely that their relative contribution to natriuresis and attendant lowering of blood pressure during baroreflex activation increases when one of the systems is impaired, such as after renal denervation.

Since baroreflex activation is consistently associated with reductions in sympathetic outflow, we also investigated the postjunctional mechanisms involved in the blood pressure reduction in this setting [12]. Established dogma indicates that the cardiovascular and renal effects of the sympathetic nervous system are mediated via peripheral α_1 - and $\beta_{1,2}$ -adrenoreceptors. The hypothesis was tested that central suppression of sympathetic outflow may have an effect to decrease blood pressure independent of these adrenoreceptor mechanisms. Dogs were treated chronically with α_1 - and $\beta_{1,2}$ -adrenergic antagonists. As a result, blood pressure decreased significantly (~ 20 mmHg), while sympathetic activity (plasma norepinephrine concentration) increased, presumably due to unloading of the baroreceptors. Moreover, subsequent activation of the baroreflex during adrenergic blockade led to an additional fall in blood pressure (~ 10 mmHg) that was associated with suppression of plasma norepinephrine concentration to control levels. Since activation of peripheral, post-junctional α_2 adrenoreceptors causes vasoconstriction, we tested the hypothesis that activation of these receptors during the increases in sympathetic outflow associated with adrenergic blockade may partially counteract the blood pressure lowering effect of α_1 and $\beta_{1,2}$ -adrenergic antagonism. Indeed, administration of an antagonist to peripheral α_2 -adrenoreceptors further reduced blood pressure during adrenergic blockade, and this effect was abolished during simultaneous baroreflex activation. This study suggests that suppression of central sympathetic outflow can reduce blood pressure more than blockade of peripheral α_1 - and $\beta_{1,2}$ -adrenoreceptors as a result of diminishing activation of postjunctional α_2 -adrenoreceptors. Because therapeutic use of other antihypertensive drugs may also produce sustained sympathetic activation by unloading baroreceptors, electrical activation of the carotid baroreflex may enhance the efficacy of the antihypertensive therapy.

In summary, these studies, together with the promising results from clinical trials suggest that prolonged baroreflex activation is an effective tool to achieve sustained reductions in blood pressure. Many questions remain unanswered and further studies are necessary in order to fully elucidate the role of the baroreflex in the control of blood pressure and expand the theoretical basis for the use of baroreflex activation in the treatment of hypertension and possibly other cardiovascular diseases.

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