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Mechanisms of Blood Pressure Reduction by Prolonged Activation of the Baroreflex

Radu Iliescu and Thomas E. Lohmeier

Abstract— **Recent technological advances have made the 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. Although theoretically obvious at first glance, the mechanisms involved in the blood pressure lowering effect of baroreflex activation elude precise quantification, and experiments designed to investigate them invariably 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 [1]. Initial studies have shown that, at least acutely, activation of arterial baroreflexes leads to reductions in sympathetic outflow, which in turn tend to lower blood pressure. Early experimental attempts to lower blood pressure by electrical stimulation of the afferent limb of the baroreflex indicated the applicability of this approach and suggested the potential therapeutic use of this technique [2]. Unfortunately, with technical limitations related to the construction of the early devices used to deliver electrical impulses to baroreceptor afferent nerve fibers, as well as surgical implantation difficulties, the interest with this approach waned. However, over time, these limitations have been overcome. Recent technological advances have allowed the design of a new device (CVRx, Minneapolis, MN) whereby electrical stimulation of the carotid sinus can produce sustained and controllable reductions in arterial pressure [3;4].

Clinical trials are now underway in Europe and USA using this new device to test the efficacy of prolonged baroreflex activation in the therapy of drug-resistant hypertension. Platinum electrodes embedded in a thin sheet of biocompatible silicone are surgically placed around the carotid adventitial surface at the level of the two carotid sinuses. Adequate electrode placement is tested during the surgical procedure in terms of the magnitude of blood pressure and heart rate reduction during acute stimulation. The electrode leads are tunneled subcutaneously and connected to an implantable pulse generator. The pulse generator is programmable via a wireless external system which allows control over the amplitude, frequency, pulse duration and temporal pattern of electrical impulses delivered to the electrodes [5]. Recent results from the 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 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 mechanisms. 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 have a sustained, direct antinatriuretic effect on the kidney 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 levels did not increase, which would normally be expected when blood pressure is decreased, 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

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Radu Iliescu is with the Department of Physiology and Biophysics at the University of Mississippi Medical Center, Jackson, MS 39211, USA (phone: 601-815-1813, fax: 601-984-1817, email: riliescu@physiology.umsmed.edu).

Thomas E. Lohmeier is with the Department of Physiology and Biophysics at the University of Mississippi Medical Center, Jackson, MS 39211, USA (email: tlohmeier@physiology.umsmed.edu).

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 way of chronic angiotensin II infusion [8]. The same carotid sinus stimulation protocol was used that produced a ~20 mmHg reduction in mean arterial pressure in normotensive animals. However, during angiotensin II – induced hypertension, mean arterial pressure decreased by only ~ 5 mmHg after 1 week of baroreflex activation. One explanation for this intriguing finding is that angiotensin II has direct effect on the central nervous system to stimulate sympathetic outflow, which may have attenuated 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 suppression renal sympathoinhibition to enhance sodium excretion. Regardless of the precise mechanism, 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 rendered 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. Plasma norepinephrine concentration decresed in parallel with the blood pressure. These findings indicate that baroreflex activation is able to chronically suppress the sympathoexcitation associated with obesity, thereby abolishing 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. After renal denervation there were no differences in blood pressure. Moreover, there were similar decreases in blood pressure in response to baroreflex activation in the presence or absence of the renal nerves. Plasma norepinephrine and renin activity also decreased by the same amount under both conditions. 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 enhance natriuresis at a lower pressure in the absence of the renal nerves. The nature of these mechanisms is unclear to date, but one can speculate based on the current knowledge of cardiovascular regulation and some experimental observations. Measurements of daily urinary sodium excretion throughout the experimental period showed that during the initial day after baroreflex activation there was sodium retention and thereafter sodium balance was achieved. The amount of sodium retained initially was slightly higher in the absence than in the presence of the renal nerves. Considering that an isosmotic amount of fluid was retained in parallel with the sodium, and that a similar increase in arterial conductance was achieved by baroreflex activation in both cases, then a higher amount of fluid was conceivably sequestered in the high capacitance compartment of the circulation, such as the veins. This would lead to an increase in the atrial volume and pressure, which would trigger the release 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, when the baroreflex is activated. In addition, a significant increase in the volume of blood in excess of the total volume of the venous compartment, despite the large capacitance of this vascular bed, would lead to an increase in venous pressure. An increase in renal venous pressure would in turn increase renal interstitial pressure, which opposes sodium reabsorbtion [11] and therefore provide 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 baroreflex activation-induced natriuresis and attendant lowering of blood pressure changes when one of the systems is inactivated, 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]. Most of the cardiovascular and renal effects of the sympathetic nervous system are mediated via peripheral alpha1- and beta1,2 – adrenoreceptors. The hypothesis was tested that central suppression of sympathetic outflow may have an effect to decrease blood pressure beyond the reduced activation of these adrenoreceptors. Dogs were treated chronically with alpha1- and beta1,2- adrenergic antagonists. As a result, blood pressure decreased significantly (~20 mmHg), while plasma norepinephrine levels increased, presumably due to unloading of the baroreceptors. Subsequent activation of baroreflex during adrenergic blockade led to an additional fall in blood pressure (~10 mmHg) which was associated with suppression of plasma norepinephrine concentration to control levels. Since activation of peripheral, post-junctional

alpha2 adrenoreceptors has vasoconstrictor effects, it is possible that activation of these receptors during the increases in sympathetic outflow associated with adrenergic blockade may partially counteract the blood pressure lowering effect of alpha1 and beta1,2-adrenergic antagonism. Indeed, administration of an antagonist to peripheral alpha2-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 alpha1-and beta1,2- adrenoreceptors. Therapeutic use of other antihypertensive drugs may also be associated with sustained sympathetic activation presumably due to baroreceptor unloading. In these instances, electrical activation of the carotid baroreflex may allow for a more powerful effect 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. Although some of the mechanisms involved in the cardiovascular response to baroreflex activation are theoretically obvious, their relative contribution escapes precise quantification by yes-or-no experimental approaches, probably due to their redundant nature. 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 therapeutic use of current technology for baroreflex activation.

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