Are Arterial Pressure and Deformation the Sole Determinants of Baroreceptor Activity?  
Importance of Humoral and Endothelial Modulation in Normal and Disease States

Mark W. Chapleau

Arterial baroreceptors located in the carotid sinuses and aortic arch play a major role in control of circulation and regulation of arterial pressure. Increased arterial pressure triggers increased frequency of baroreceptor discharge, which leads to reflex adjustments that buffer the rise in pressure. It is established that baroreceptors are not activated by increases in arterial pressure directly but instead are activated by the increased vascular stretch or strain that accompanies the rise in pressure. Mechanical deformation of the baroreceptor nerve endings is usually considered the primary or even the sole determinant of the frequency of baroreceptor discharge. Are there other factors besides deformation that are important in activation of baroreceptors?

In this issue of Hypertension, Wang et al.\(^1\) report that exposure of the vascularly isolated carotid sinus in anesthetized dogs to the hormone aldosterone suppresses activation of baroreceptors without a change in vascular stretch as measured with sonomicrometer crystals. What is the mechanism of aldosterone-induced suppression of baroreceptor activity? Wang et al.\(^1\) demonstrate that the inhibitory effect of aldosterone is dependent on the presence of intact endothelium and is blocked by the aldosterone receptor antagonist spironolactone. The simplest scenario is that aldosterone binds to its receptor in endothelial cells and alters the release of a diffusible mediator that acts directly on baroreceptor neurons to modulate their sensitivity. This study is the first to show that aldosterone modulates baroreceptor activity and adds to the growing evidence that humoral and endothelial factors modulate to a significant extent the sensitivity of baroreceptors.

Evidence for Humoral/Endothelial Modulation of Baroreceptor Activity

Numerous studies dating back as far as the 1950s have demonstrated that various neurohumoral factors act locally in the carotid sinuses and aortic arch to modulate baroreceptor activity.\(^2\) The majority of these studies, particularly earlier ones, attributed the effects of various agents on baroreceptor discharge to vasoconstriction or vasodilatation and accompanying changes in vascular distensibility.\(^2\) More recent studies that used simultaneous measurement of baroreceptor discharge and vessel diameter in isolated carotid sinus and aortic arch preparations have demonstrated that certain neurohumoral factors modulate baroreceptor activity independent of changes in vessel diameter and calculated wall strain. For example, norepinephrine appears to act directly on baroreceptor neurons to increase their sensitivity.\(^3^\^4\)

In recent years there has been a tremendous interest in endothelial cell biology and release of vasoactive factors from endothelium in response to both chemical and mechanical stimuli. Recent studies, including the present study by Wang et al.,\(^1\) suggest that factors from endothelium are important paracrine modulators of baroreceptor sensitivity.\(^1^\^2^\^3^\^5\^6\) Prostanoids such as prostacyclin released from carotid sinus endothelium increase baroreceptor sensitivity without altering distensibility of the carotid sinus.\(^5^\^6\) Evidence in support of an inhibitory influence of endothelium on baroreceptors has also been obtained. Cultured endothelial cells activated with calcium ionophore suppress baroreceptor activity, which cannot be explained by changes in vessel diameter or strain.\(^7\) Endothelin in the isolated carotid sinus suppresses baroreceptor activity at high vascular pressures.\(^9\)

Significance and Pathophysiological Implications

One might ask: What is the purpose or significance of humoral and endothelial modulation of baroreceptor sensitivity? There is no reason to assume that the transduction of increased pressure and vascular stretch to increased baroreceptor discharge should be mediated only by deformation of the nerve endings. Vascular stretch is known to modulate the release of factors such as prostanoids from endothelium that may influence baroreceptor sensitivity. Thus, endothelial factors may be involved in the local transduction of changes in pressure to changes in nerve activity. Clearly, baroreceptors are activated by stretch in the absence of endothelin,\(^1^\^2^\^3\) indicating that endothelial factors are not solely responsible for baroreceptor activation but instead act as modulators of activity.

Vascular endothelium is in an ideal location to sense changes in the circulation. Endothelial cells possess receptors for multiple circulating hormones and respond to chemical and mechanical stimuli, including
changes in shear stress. Communication from endothelium to baroreceptor could provide the central nervous system with information not directly accessible to baroreceptors located in adventitia. Indeed, increased flow and shear stress in the carotid sinus increase baroreceptor activity without an increase in carotid sinus diameter. Thus, baroreceptors or other types of receptors in carotid sinus or aortic arch may function as "rheoreceptors" that sense changes in carotid blood flow or cardiac output and trigger appropriate reflex adjustments.

Various pathological states are associated with both impaired function of endothelium and decreased baroreceptor sensitivity. Evidence suggests that impaired formation of prostanooids and loss of their sensitizing influence contribute to decreased baroreceptor sensitivity in atherosclerosis and in chronic hypertension. The contribution of endothelial dysfunction to altered baroreceptor reflex control in other diseases such as diabetes and heart failure remains to be determined.

In the study by Wang et al, the suppression of baroreceptor activity by aldosterone was concentration-dependent and occurred over a range (50–500 pg/ml) that can be found in various clinical states including heart failure, hyperaldosteronism, and renal hypertension. Does the elevation of aldosterone in plasma contribute to decreased baroreceptor sensitivity in these diseases? Considering the multiple factors that may contribute to impaired baroreceptor function in these diseases, additional studies are required to answer this question.

**Future Directions for Research**

The interesting results of Wang et al raise several questions worthy of further investigation. If indeed an endothelial factor is responsible for aldosterone-induced suppression of baroreceptor activity, what is the identity of the factor? I am unaware of any studies that demonstrate an influence of aldosterone on release of substances from endothelium. One candidate is the "inhibitory factor" released from cultured endothelium activated with calcium ionophore that suppresses baroreceptor activity. The influence of aldosterone on activity of single baroreceptor fibers is remarkably similar to that of this inhibitory factor: pressure threshold is increased and maximum baroreceptor discharge frequency is decreased without a change in the peak slope or gain of the pressure–activity curve. Could the factor be endothelin or a related peptide? Our recent studies demonstrate a significant inhibitory effect of endothelin on carotid baroreceptor activity, particularly at high levels of pressure.

An alternative explanation is that aldosterone may decrease the spontaneous release of an "excitatory factor" such as prostacyclin from endothelium and consequently decrease baroreceptor activity. What is the mechanism of aldosterone's proposed action on endothelial cells? The well-known effects of aldosterone on the function of kidney tubule cells usually require 45 minutes to a period of hours to become evident. As with other steroid hormones, gene expression and protein synthesis are required for aldosterone-mediated influence. Baroreceptor activity was suppressed after only 15 minutes of exposure of the isolated carotid sinus to aldosterone. Approximately 60 minutes were required to restore baroreceptor activity after removal of aldosterone from the carotid sinus. Is protein synthesis required for aldosterone to decrease baroreceptor activity?

Evidence suggests that increased activity of Na⁺,K⁺-ATPase on baroreceptor nerve endings contributes to decreased activity of carotid baroreceptors after acute hypertension and in dogs with pacing-induced heart failure. In the study by Wang et al, exposure of the isolated carotid sinus to ouabain in the presence of aldosterone did not restore baroreceptor activity. Thus, the inhibitory influence of aldosterone on baroreceptor activity does not appear to involve increased Na⁺,K⁺-ATPase activity and consequently does not fully account for the decreased baroreceptor sensitivity observed in heart failure.

A possible mechanism that should be considered for aldosterone's action on endothelium is increased turnover of membrane phospholipid fatty acids that has been observed within 20–30 minutes of treatment in toad urinary bladder. It should be emphasized that the study by Wang et al only examined the acute influence of aldosterone on baroreceptor activity, and the results cannot necessarily be extended to conditions associated with chronic increases in aldosterone. Chronic administration of fludrocortisone, a mineral corticoid, for 7 days in humans causes a sustained suppression of muscle sympathetic nerve activity and preservation of baroreceptor reflex function (Reference 14 and D. Mion, personal communication, October 1991), responses not consistent with suppression of baroreceptor activity.

Two major questions remain concerning the significance and importance of modulation of baroreceptor activity by aldosterone and the role of endothelium in general in modulation of baroreceptor activity. First, essentially nothing is known concerning the cellular mechanisms by which humoral and endothelial factors modulate sensitivity of baroreceptors. The conclusion that endothelial factors act directly on baroreceptor nerve endings rather than through an indirect mechanical effect is usually based on the absence of a change in the pressure–diameter relation of the carotid sinus. The possibility that local mechanical changes in the region of the nerve endings may account for the changes in nerve activity cannot be discounted. The inability to measure mechanical changes at the level of the nerve endings and the inaccessibility of the nerve endings for electrophysiological measurements prevent a solution to the problem at this time. New methods must be developed to enable investigation of mechanoelectrical baroreceptor transduction at the cellular level. Preliminary reports suggest that study of baroreceptor neurons in culture may be a feasible approach to this problem.

The second major question relates to the physiological and pathophysiological significance of humoral and endothelial modulation of baroreceptor activity. The phenomena have largely been demonstrated in vitro or in situ preparations. It is now clear that numerous factors have the potential to modulate baroreceptor sensitivity. What is the relative contribution of the various factors both in normal and pathological states? This question will have to be approached not only in vitro but also in vivo in experimental animals and in
humans. For example, does specific blockade of aldosterone receptors with spironolactone restore baroreceptor activity in animals with chronically elevated levels of aldosterone or animals with heart failure?

In summary, the study by Wang et al. provides additional evidence in support of the concept that humoral and endothelial factors modulate sensitivity of arterial baroreceptors. Further work in this area should enhance our understanding of control of the circulation in both normal and pathological states.

References

KEY WORDS • baroreceptors • carotid sinus • endothelium • prostanoids • aldosterone • aldosterone-induced hypertension • blood pressure
Are arterial pressure and deformation the sole determinants of baroreceptor activity?
Importance of humoral and endothelial modulation in normal and disease states.
M W Chapleau

doi: 10.1161/01.HYP.19.3.278

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/19/3/278.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org/subscriptions/