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Pressure to change? Re-evaluating the role of baroreceptors in the long-term control of arterial pressure

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A CLEAR CONCEPTUAL FRAMEWORK for the long-term control of arterial pressure is required for a full mechanistic understanding of normal cardiovascular regulation as well as changes in arterial pressure that occur in such states as primary and secondary hypertension, congestive heart failure, and pregnancy. For the purpose of this editorial focus, long-term control is defined as those mechanisms that set the average level of arterial pressure of an unstressed individual at rest, though it is recognized that there is no clear consensus on this "theoretical" definition; normal daily routines can alter this level, and the 24-h mean pressure is sometimes used operationally to define the set point. Despite a considerable amount of research over many years, there is much that remains unclear. One key area of dispute is whether brain control of the autonomic nervous system or renal control of sodium balance forms the long-term arterial pressure control, although their role in control of arterial pressure may be interrelated. A long-standing argument against a critical role of the brain and the sympathetic nervous system in the long-term control of arterial pressure has been that the predominantly short-acting control system that adjusts sympathetic activity and heart rate in response to pressure perturbations, the baroreflex, cannot be involved. Two key pieces of evidence are typically evoked to support this contention. First, the average level of arterial pressure in dogs and other experimental animals housed in a standard controlled environment is chronically unaltered by baroreceptor deafferentation. Second, arterial baroreceptors, in particular myelinated A-fibers, adapt or reset to sustained changes in arterial pressure in the direction of the pressure change. Importantly, this baroreflex resetting refers to an action of a change in pressure per se on the afferents, and possibly also within the brain, such that the initial changes in baroreflex afferent or efferent activity wane with time. Abundant evidence indicates that complete resetting of baroreflex control of heart rate occurs in human and experimental hypertension (although whether there is complete resetting of sympathetic activity throughout the vasculature is unclear).

Despite these two sizeable pools of data and the long-heralded view that the baroreflex is only involved in short-term control of arterial pressure, recent experiments from the laboratories of Thrasher, Lohmeier, and Malpas, have revitalized an interest in understanding the potential role of baroreflex in long-term control of arterial pressure. The four Invited Reviews that follow (3, 23, 36, 42) examine the evidence in favor of a role of baroreceptors in the long-term control of arterial pressure as well as opposing views. Obviously, this issue of the role of baroreceptors in the long-term control of arterial pressure is far from settled, and it is hoped that these reviews will stimulate further discussion and experimentation in this important area.

The renewed discussion of this issue revolves around three new experimental approaches. A key approach used by Lohmeier and colleagues has been chronic electrical stimulation of carotid baroreflex afferent nerve fibers in dogs. They find that with the stimulation parameters they use there is a decrease in arterial pressure, accompanied by a decrease in plasma norepinephrine concentration that presumably reflects a decrease in sympathetic activity, which is maintained for at least 7 days (24). Conversely, Thrasher has shown that chronic unloading of carotid baroreceptors (with other carotid and aortic baroreceptors surgically removed) increases arterial pressure for at least 7 days in dogs (41). Thus, both of these preparations suggest that increasing or decreasing the activity of baroreceptors can lead to decreases or increases in arterial pressure, respectively, for at least 1 wk and therefore support the hypothesis that altered baroreceptor function can chronically alter arterial pressure. A third approach, used by Malpas and colleagues, has been chronic recording of renal sympathetic nerve activity (RSNA) during chronic increases in arterial pressure with ANG II infusion in rabbits. They find that ANG II infusions for a week, which result in sustained increases in arterial pressure, produce sustained reductions in RSNA (4). Lohmeier et al. also have indirect data to suggest that ANG II infusion chronically reduces RSNA in dogs (25). The observations are most readily consistent with baroreceptors contributing to the chronic control of arterial pressure and RSNA. Another older observation that is being interpreted as supporting a role for baroreceptors in the long-term control of blood pressure is that sinoaortic baroreceptor-denervated (SAD) rats fed a diet with a high salt content show an increase in arterial pressure (19, 35). Thus, in contrast to previous research, these data seem, at face value, to make a strong case in favor of baroreceptors contributing to the long-term control of arterial pressure. The key issue would then seem to be how the recent observations from the laboratories of Lohmeier, Malpas, and Thrasher can be reconciled with the numerous views that follow (3, 23, 36, 42) that the predominantly short-acting control system that adjusts sympathetic activity and heart rate in response to pressure perturbations, the baroreflex, cannot be involved.

1 These four reviews stem from presentations made at the Experimental Biology 2004 meeting in a symposium entitled “Do Baroreflexes Play a Role in Long-Term Control of Arterial Pressure” that was sponsored by the Water and Electrolyte Homeostasis Section of the American Physiological Society.
studies documenting that animals lacking arterial baroreceptor afferents exhibit normal blood pressure. Moreover, if the baroreflex chronically represses sympathetic outflow in animals with hypertension, then why is arterial pressure not even higher in hypertensive animals subjected to sinoaortic denervation (13)? Indeed, in one model (chronic NOS blockade), hypertension was actually reversed by sinoaortic denervation (37).

Clearly the answers are not yet available, and the four reviews present the approaches and biases of four laboratories that have been important contributors to this area. In doing so, the authors cover many, if not all, of the points that should be raised in discussion of this issue. Obviously we are not going to resolve this issue here and clearly much research lies ahead. Nevertheless, three general points come to mind that apply to any evolving issue in science. First, it is always important to continue to think about and evaluate old observations in light of new data. In this regard, how do the two key observations that seem to argue strongly against the baroreceptor involvement in long-term control fit in? Each of the reviews comments on this, and we offer our own views. Second, newer is not always better. What are the critical issues that must be considered in evaluating the newer data? And third, always keep an open mind.

One possible explanation for why chronic sinoaortic denervation fails to support a long-term role for the baroreceptors, in contrast to the newer approaches, is that the complete loss of afferent information secondary to baroreceptor denervation causes changes in brain function differently than does afferent input that is reduced but pulsatile. There are ample data to support this position. For example, Balkowiec and Katz (2) have shown that stimulation of cultured nodose ganglion cells increases the expression of brain-derived neurotrophic factor, but only if the stimulation is pulsatile and not static. Furthermore, the degree of acute resetting is less if the pressure input is pulsatile rather than static (11). Apparent differences in animals with complete SAD versus incomplete SAD also highlight this issue (38). For example, Ito and Sved (20) have shown that processing of cardiovascular information through the nucleus tractus solitarius (NTS) is markedly different between complete and partial SAD rats; with partial SAD rats, pulsatile baroreceptor input is partially sustained, which is rather similar to baroreceptor-intact rats. Finally, Thrasher’s most recent study (43) indicates that whereas complete adaptation to loss of afferent input occurs in SAD dogs studied at rest (pressure returns to control), sustained albeit modestly increased arterial pressure results from occlusion of the one remaining innervated carotid sinus.

Another concern in the interpretation of findings from animals subjected to sinoaortic denervation is that the average daily pressure in chronically denervated animals may be dependent on whether predominantly dynamic hypertensive or hypotensive stimuli or static influences are experienced. For example, in the study by Osborn and Hornfeldt (35), higher levels of arterial pressure were achieved only during the dark phase, when the SAD rats were actively consuming food with excess salt, but not during the light phase when they were resting. Thus, in this model the baroreceptors appear to be acting in the classical sense, by buffering the rapid changes in pressure that follow ingestion of a salty meal, rather than by determining the pressure operating point around which reflex changes occur. This result underscores the importance of showing circadian pressure data from telemetry experiments. It also suggests another potential mechanism of chronic hypertension. Decreased baroreflex gain appears to precede hypertension (15, 34). If the decreased gain allows greater pressure swings, in particular hypertensive swings, then repeatedpressor insults could lead to hypertension similarly to the transient sympathoexcitatory and pressor episodes of individuals with sleep apnea that lead to hypertension.

In an attempt to reconcile recent findings with the long-held view that the baroreflex is unimportant in long-term pressure control, another dichotomy that must be explained is the clearly established acute and chronic resetting of baroreceptors versus the results from the Lohmeier, Thrasher, and Malpas labs indicating little, if any, resetting. One explanation that has been put forth in the reviews that follow is that while the more reactive myelinated A-fibers do reset, unmyelinated C-fibers reset to a lesser degree if at all, and it is activity from these C-fiber afferents that maintain changes in sympathetic activity and arterial pressure.

A second issue related to baroreceptor resetting that requires additional attention is its time course. Acute resetting clearly occurs within seconds to minutes, yet the time required for chronic resetting to be fully established is less clear. In this regard, it is noteworthy that the more recent experiments were usually conducted over 5–7 days. A study in rats is frequently cited to suggest that chronic resetting is complete within 2 days (21). However, the approach used to document resetting was indirect, comparing the systolic pressure at which the aortic nerve began firing (SPth), to the basal diastolic pressure. As these were equivalent before hypertension and became equivalent again within 2 days following hypertension induction, complete resetting was inferred. However, because whole nerve activity was quantified, the assessment (comparison of SPth to diastolic pressure) relied on the activity of the fiber that was activated first as pressure rises (SPth), which may not accurately represent the threshold and degree of resetting of all afferents. Moreover, the results from individual animals indicated that while the average SPth was similar to the average diastolic pressure in control and 48-h hypertensives, the difference between these pressures in individuals was quite variable (range, 50 mmHg). In contrast, other research indicates that chronic resetting continues to occur over a longer time frame. Studies of carotid single fibers in the dog suggest that resetting continues to occur even after 5 days of hypertension (39). In ANG II-infused hypertensive rabbits, chronic resetting was suggested by the tendency for heart rate and/or plasma norepinephrine concentration to increase as blood pressure fell immediately after terminating the infusion. While no chronic resetting of heart rate and norepinephrine was apparent within the first week of hypertension, distinct resetting occurred after 9–14 days of hypertension (6–8). Studies of baroreflex control of RSNA in renal hypertensive rabbits also suggest that baroreflex relationships between pressure and RSNA continue to shift further to the right as the hypertension progresses over several weeks (5, 18). Additionally, Thrasher’s recent report indicates that the initial 7-day hypertensive effect of carotid baroreceptor unloading produced by carotid occlusion is not sustained, with arterial pressure falling back toward control levels during the second and third week of occlusion (43). Thus, one explanation for the sustained suppression of RSNA in the studies of Lohmeier et al. (25, 26) and Barrett et al. (4) may be that
insufficient time was allowed for chronic resetting to be completely engaged.

Given that chronic resetting does occur with time, a critical question is whether the resetting is complete. There are several lines of evidence that suggest it is not. First, as reviewed in a paper by Munch et al. (33), the increase of the pressure threshold for activation of arterial baroreceptor afferents is generally not as great as the blood pressure shift. Second, as discussed by Lohmeier et al. (23), studies of the expression of the early immediate gene, c-fos, indirectly suggest that both the NTS and the caudal ventrolateral medulla (CVLM) continue to be activated during established hypertension in dogs (27, 28), presumably due to continued baroreflex activation; however, other studies in rats find the opposite (22). Finally, Thrasher’s study of prolonged carotid sinus occlusion reveals that even after four weeks of occlusion, a modest elevation of arterial pressure is maintained (43).

A question that logically follows is if resetting of baroreceptors is not complete, then why is baroreflex control of heart rate completely reset in, for example, hypertension and pregnancy. One explanation, provided by Barrett and Malpas (3), is that heart rate is not a representative sympathetic efferent response, as it is often regulated differently than sympathetic activity throughout the peripheral vasculature. There are abundant examples to support this idea, but in the case of the ANG II-induced hypertension model, it is possible that changes in RSNA differ from sympathetic nerves controlling other vascular beds. Indeed, while RSNA may be suppressed (4, 10, 25), splanchnic (30) and cardiac nerve (44) activities appear to be increased, which would likely reflect a resetting of the baroreflex curve as is seen with heart rate. Moreover, baroreflex control of RSNA in renal hypertension (5, 18), and muscle sympathetic nerve activity in human hypertension (16) are reset to higher pressures. Other examples of differential long-term control of various sympathetic nerves exist (17) and suggest that either different afferent control different efferents or variable processing of afferents occurs in the brain. Thus, even if changes in baroreceptor input can be sustained, this input clearly can be modified either at the baroreceptors themselves by hormones or other factors (12) or at some site downstream. Additionally, although resetting of the pressure threshold of baroreceptor afferents may not be complete in hypertension, because the slope (i.e., gain) of the pressure versus afferent activity relationship becomes depressed (1), the actual basal activity of the baroreceptors may be closer to normal than if the shift were a parallel one.

Third, as previously proposed (9, 14, 40), and reiterated in the review of Osborn et al. (36), hormones regulated in response to changes in arterial pressure and other afferent information, including changes in body temperature, osmolality, or metabolism, infection, psychological stress, and exercise, can alter the baroreflex relationship between pressure and sympathetic activity independently of changes in pressure (i.e., pressure-independent resetting). Moreover, these inputs can alter the levels of heart rate and of individual sympathetic nerves variably. One good example of this may be the changes in heart rate and RSNA that occur during ANG II-dependent hypertension. While ANG II causes a right shift (resetting) in the relationship between pressure and heart rate, this entire shift is pressure independent for the first week of the hypertension, with a pressure-dependent component developing thereafter (6, 7). Similarly, although baseline RSNA is suppressed by ANG II infusion and the baroreflex-RSNA relationship does not appear to be shifted (4), at least part of this suppression of RSNA may be due to a central effect of angiotensin, independently of the rise in pressure, to suppress RSNA. Evidence to support this mechanism is that the decrease in RSNA caused by intracerebroventricular ANG II infusion appears to be independent of the arterial and cardiopulmonary baroreceptors and is prevented by lesions of the lamina terminalis (31, 32). Thus it is important to be careful in generalizing from increases in arterial pressure produced by ANG II to increases in arterial pressure in general.

Given that other afferent signals can modulate baroreflex relationships, then much remains to be resolved, including where and how these interactions occur within the baroreflex pathway. The experiments of Lohmeier and Thrasher in which the activity of baroreceptor afferents are chronically altered, along with other experiments, indicate that chronic changes in sympathetic outflow can alter the long-term level of arterial pressure, at least for a few weeks. Another key unanswered question then is which sympathetic nerves are crucial in this action: only renal nerves, as argued by Lohmeier et al. (23), or nonrenal nerves, or both? And, if renal nerves are crucial, is it via actions on renin secretion or on sodium excretion or both? This seems to us to be a critical issue that has not received nearly enough attention. The answers to these questions await further study, but we applaud these investigators for their use of novel approaches to address old questions and look forward to the progress that can be produced and appreciated only with an open mind.

REFERENCES


