Baroreceptors, baroreceptor unloading, and the long-term control of blood pressure

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THE SUGGESTION THAT INCREASED sympathetic nerve activity (SNA) could play a role in the development of essential (i.e., primary) hypertension has been considered for a long time (24, 29, 37); however, definitive evidence that this suspicion is true has appeared only relatively recently. Increases in cardiac and renal norepinephrine spillover (an index of SNA to these organs) have been demonstrated in patients with borderline and mild essential hypertension (23). Moreover, direct measurements of muscle SNA via microneurography have indicated increased activity in subjects with essential hypertension (4, 67). The fact that increased SNA is detectable before established hypertension provides a known mechanism in the etiology of the condition; however, the cause of the increase in SNA is not known.

It is generally agreed that essential hypertension arises from a combination of genetic and environmental influences (24). Thus the range of factors that could drive an increase in SNA is enormous. One of the best known and intensely studied of these factors is the reciprocal relationship between arterial baroreceptor input and sympathetic outflow. Experiments in the early part of the 20th century observed that denervation of baroreceptors in the carotid sinus and aortic arch (SAD) in experimental animals produced striking and highly variable increases in mean arterial pressure (MAP, see Ref. 29 for review of the early literature). However, it was recognized as early as 1936 that the characteristics of neurogenic hypertension caused by SAD were sufficiently different from humans with essential hypertension to conclude that the origins were different (48). Nevertheless, the reciprocal relationship between afferent firing by baroreceptors and the control of SNA remains one possible source of the increased sympathetic drive in the development of hypertension.

If altered baroreceptor input is a causative factor in the etiology of hypertension, then by definition, baroreceptors must be involved in the long-term control of MAP. However, this is a contentious proposition, and the arguments against baroreceptor involvement have been succinctly reviewed by Cowley (15). There are three fundamental objections to baroreceptor involvement in the long-term control of MAP: 1) SAD has little effect on the absolute level of MAP chronically; 2) baroreceptors adapt to imposed changes in pressure and therefore cannot provide an error signal to drive a change in MAP; and 3) the gain of the baroreceptor mechanism is insufficient to account for the long-term stability of MAP. And yet, several recent studies have reported evidence that is compatible with the hypothesis that baroreceptors do play a role in setting the long-term level of MAP (see other reviews in this series). Rather than review in detail the author’s recent work or the work presented by others, in this article, I have chosen to look back at earlier studies involving both experimental animals and
BARORECEPTORS AND THE LONG-TERM REGULATION OF MAP

Invited Review

BARORECEPTOR DENERVATION: ANIMAL STUDIES

The earliest attempt to assess the effect of altered input from baroreceptors is the SAD model. Because baroreceptor input tonically inhibits sympathetic outflow, SAD should result in increased SNA and hypertension. The initial observations of MAP in SAD animals supported this hypothesis (29), but eventually, it was realized that the increased MAP was largely an artifact associated with responses to environmental stimuli in animals with no mechanisms to buffer changes in MAP. The classic study by Cowley and colleagues (16) established that when measurements of MAP are made continuously in SAD dogs isolated from activities that normally take place under laboratory conditions, the increase in MAP amounted to 10 mmHg above baroreceptor-intact animals. Thus the striking feature of the SAD condition is not its effect on MAP but on the variability of MAP (16). Today, there is general agreement that SAD has little (56) or no (46, 50) effect on the average MAP in a variety of species.

It’s worth noting that the initial effect of SAD is an acute increase in SNA and hypertension, as predicted from the known properties of the baroreflex mechanism. However, over time, the hypertension dissipates as does the increase in SNA (32). The mechanism that leads to the normalization of SNA is not well understood. It has been proposed that cardiopulmonary receptors may become more important in the control of SNA because combined SAD and cardiopulmonary denervation in dogs causes an increase in MAP when measured under laboratory conditions (47). However, when MAP was measured continuously, it did not differ from baroreceptor-intact dogs (38).

The more likely explanation is that the loss of excitatory input from baroreceptor afferents leads to a reorganization of the neural processing within the nucleus of the solitary tract (NTS) and perhaps other nuclei in the baroreflex pathway. Changes within the NTS after chronic SAD are evident from a study by Schreinhofer and Sved (53). They compared effects of lesioning the NTS on MAP in intact and chronic SAD rats. NTS lesions in baroreceptor-intact rats produced an acute hypertension, as would be expected but had no effect on MAP in SAD rats, indicating that tonic output from the NTS did not inhibit SNA. A later study by Ito and Sved (34) observed that the reorganization involved increased GABA-mediated inhibition of the NTS, as administration of bicuculline into the NTS of chronic SAD rats caused hypotension but little change in MAP in baroreceptor-intact rats.

The plasticity noted in the NTS after chronic SAD (34, 53) is one of probably many changes in medullary reflex pathways that lead to eventual restoration of SNA to control levels (32). However, the fact that these events occur chronically following SAD indicates that this condition is not a good model of chronic baroreceptor unloading. The occurrence of these changes also challenges the argument that “because MAP returns to control following SAD, baroreceptors cannot be involved in setting the long-term level of MAP” (15).

BARORECEPTOR DENERVATION: HUMAN OBSERVATIONS

In the 1960s, carotid body removal was evaluated as a treatment for asthma. Holton and Wood (31) reported observations in two patients before and after bilateral carotid body denervation that clearly included bilateral denervation of the carotid sinus as the adventitia was removed for 2 cm in the area of the carotid bifurcation. Resting blood pressures measured in the horizontal position were normotensive before and became markedly hypertensive for 10–12 wk after carotid denervation (blood pressure measured both by auscultation and direct arterial puncture). The subjects also displayed no heart rate (HR) response to passive tilt from the horizontal to vertical orientation during this period. Restoration of normal responses to passive tilting appeared 12 to 30 wk after surgery and were accompanied by moderation of the hypertension; however, the MAP never declined to preoperative levels more than a year after surgery.

Denervation of the carotid baroreceptors also occurs during surgical resection of tumors associated with the carotid bodies, although the degree of baroreceptor denervation is less clear (i.e., the carotid sinus nerves are damaged but not purposefully cut). Smit et al. (59) studied four female patients who had undergone bilateral carotid body resection and who acutely showed signs of baroreflex failure (large decreases in MAP on standing with incomplete recovery and minimal HR responses and abnormal responses to Valsalva’s maneuver). Ambulatory measurements showed elevated daytime MAP levels in three but normal MAP in the fourth. In all four women, MAP was normal during the nighttime. Reflex responses to orthostatic stress and Valsalva’s maneuver were assessed and the magnitude of the increase in ambulatory MAP correlated with the degree of baroreflex dysfunction. However, the variability of MAP was elevated relative to normal in all four patients at times ranging from 3 mo to 2 yr after surgery. Timmers et al. (64) recorded muscle SNA and HR responses to administration of vasoactive drugs in a group of patients who had bilateral carotid body resection 4–20 years earlier. At the time of the study, none of the patients showed signs of baroreflex failure or were hypertensive, but all showed decreased baroreflex control of HR compared with age-matched controls. Reflex control of muscle SNA in response to sodium nitroprusside-induced decreases in MAP was blunted in the patients but was not different from control during phenylephrine-induced increases in MAP.

Neck irradiation for treatment of various tumors may also alter carotid baroreflex responses. Sharabi et al. (57) studied three patients with baroreflex failure (defined as chronic orthostatic intolerance and labile blood pressure) that developed years after neck irradiation. Baroreflex-mediated changes in HR in response to phenylephrine and nitroglycerine challenges were absent. Twenty-four-hour ambulatory measurements indicated a maintained systolic hypertension in all three patients, and MAP averaged 100 ± 7 mmHg (means ± 1 SE) with no obvious diurnal variation. Average HR levels were also elevated over the 24-h period in two of the patients. Overall, blood pressure variability was markedly increased with frequent episodes of systolic pressures greater than 200 mmHg. The
patients had normal responses to the cold pressor test, suggesting that sympahtetic efferent function was intact, and spectral analysis of HR variability indicated that parasympathetic efferent control of HR was normal. Ultrasound examination of the carotid area revealed atheromatous plaques at the bifurcation and bilateral intimal thickening of the sinus region. Thus the authors concluded that the defect was confined to defective afferent signaling from carotid baroreceptors and suggested that loss of distensibility in the baroreceptive zone caused the defects in the regulation of blood pressure.

There is one report of apparent SAD in a human subject (3). The patient received large doses of radiation in the upper chest and neck area for treatment of cancer. Twenty-four years later, radiation-induced damage to the carotid arteries necessitated insertion of a bypass that effectively destroyed carotid baroreceptors. Shortly afterward, sudden severe increases in MAP together with other indices of increased sympathetic outflow or equally precipitous declines in MAP appeared. Blood pressure in the supine position was 160/105 mmHg and 120/90 standing with no change in HR in either position. A 24-h record of ambulatory blood pressure revealed marked fluctuations in blood pressure but no sustained hypertension. The subject had high resting levels of HR and muscle SNA, but neither variable changed in response to increases or decreases in MAP induced by administration of vasoactive drugs, suggesting loss of afferent baroreceptor input. Thus apparent SAD in a human patient produced cardiovascular consequences similar to those observed in SAD animals, that is, increased variability of MAP but not a sustained increase in MAP.

Thus complete denervation of carotid baroreceptors does produce a sustained increase in MAP and pressure lability in humans, even though aortic baroreceptors are presumably functioning normally (31, 57, 59). In contrast, less than complete sinus denervation decreases baroreflex sensitivity and increases MAP variability but does not result in an elevated MAP (59, 64). These observations differ from animal studies that show no chronic effect of carotid sinus denervation on either the level of MAP or the variability of MAP (33, 45, 56). In animal studies, it is presumed that aortic baroreceptors provide sufficient afferent input to the baroreflex to stabilize MAP at normal control levels without increased variability. Therefore, the question arises as to why aortic baroreceptors apparently did not provide redundant control of MAP in the human subjects with denervated carotid baroreceptors. One possibility is that the aortic nerves might have been damaged by the radiation or during surgery to remove tumors on the carotid bodies. Another possibility is that aortic baroreceptors in humans, particularly middle-aged to elderly subjects, may not be sensitive enough to effectively buffer changes in MAP. Finally, it may be that human subjects are simply more active and alert for longer periods of time during a 24-h day compared with animals under normal housing conditions. Smit et al. (59) provided figures of the 24-h recordings of blood pressure annotated with periods of activity, supine relaxation, and sleep for each of the four subjects studied. The records show that MAP was generally higher during the light phase and markedly elevated during periods of activity compared with the period of supine rest and during sleep in the denervated subjects. The sleep plus supine rest periods totaled 9 h vs. 15 h of light to moderate activity. In contrast, housing conditions for laboratory animals typically provide for a 12:12-h light-dark cycle, and dogs, for example, sleep during the light, as well as during the dark phase of the cycle. Thus the average MAP over a 24-h period that includes 25% more time for activity may explain the higher MAP in human subjects after carotid sinus denervation.

BARORECEPTORS AND VASCULAR COMPLIANCE

A key argument against baroreceptor participation in determining the level of MAP is that they adapt to the prevailing pressure over time and thus, could not provide a sustained error signal to reflex mechanisms controlling SNA (15). However, this argument may be circumvented if the vascular wall in which the receptors are embedded becomes stiffer. Under this condition, there will be less deformation of the receptors in response to the same pressure wave and, therefore, reduced afferent signal to reflexively inhibit sympathetic outflow. There have been a number of experimental approaches to alter the relationship between the baroreceptors and the vessel wall, and these will be considered next.

Crandall et al. (17) devised a circular plastic clamp with channels to accommodate the common carotid, external carotid, and the internal carotid plus the occipital artery together. Applied bilaterally, the clamps compressed the arteries and thus reduced the increase in vascular radius during cardiac systole. Because the sinus nerve runs between the internal carotid and occipital arteries, it was not denervated in most of the dogs studied (based on ventilatory responses to sodium cyanide). Control MAP averaged 126 ± 8 mmHg (mean ± standard deviation) from Table 1 minus the three dogs identified as carotid sinus denervated) and increased to 167 ± 10 mmHg 9 to 47 mo after placing the clamp on the carotid sinus area. The principal weakness of this and many studies of its time (1950s) is that MAP was measured by direct femoral artery puncture, necessitating some restraint of the animal; hence, the elevated control levels of MAP. A principal criticism of the early reports is that SAD caused hypertension is based on the observation that the stress associated with measuring the MAP by puncture caused the hypertension rather than denervation of the baroreceptors themselves (15). The same criticism does not apply to the data of Crandall et al. (17) because even if there were some damage to the sinus nerves, the aortic baroreceptors should have remained functional. They also studied a group of SAD dogs and reported control pressures of 117 ± 7 mmHg before and 189 ± 16 mmHg after SAD. Note that the SD changed little after constricting the carotid sinus area but more than doubled after complete SAD, as would be expected. Six months after constricting the carotid sinus area, three of the dogs, were given a 6-mo course of pheonoxbenzamine treatment. During treatment, their MAP fell to control levels and after cessation of treatment, MAP increased again.

One has to be highly critical of observations published 60 years ago, in part, because some methods used in that time are not adequate by the standards of today (e.g., femoral artery puncture to measure MAP) and because of the use of inappropriate statistics to analyze data. Nevertheless, there does not appear to be a fundamental flaw in Crandall and colleagues’ basic observations. Interestingly, they argued that it was the alteration in cerebral blood flow that most likely caused the increase in MAP rather than altered carotid baroreceptor sig-
naling. They tested the effects of reduced blood flow in a group of four dogs by constricting the external and internal carotid arteries and the occipital artery above the sinus area without apparent effect on MAP. Furthermore, an earlier study by Taylor and Page (61) observed that ligating both common carotids and vertebral arteries in the dog did not result in a sustained increase in MAP due to rapid development of new vessels and anastomotic connections. Thus the results of Crandall et al. (17) appear compatible with the hypothesis that decreased stimulation of the carotid baroreceptors, imposed by placing the sinus in a rigid chamber, led to an increase in MAP.

A later study by Burstyn et al. (12) reported the effects of casting the carotid sinus area in dental cement on systolic pressure in the rabbit. They observed that systolic pressure increased 38% above control and was sustained for 50 days after casting the carotid sinus compared with an increase of 9% in a control group in which the cast was placed on the internal carotid above the sinus. The integrity of the sinus nerves was verified at the conclusion of the experiment by demonstrating a normal pressor response to common carotid occlusion compared with the control group. In contrast, the bradycardia in response to acute increases in MAP was reduced in the group with sinus casts compared with the control animals. In two animals, there was no response to carotid occlusion on either side, indicating that the casting procedure destroyed the sinus nerves; there was also no change in systolic pressure in these two animals. The authors presumed that the sinus cast limited the expansion of the vessel in response to a pressor agent, thus explaining the reduced reflex effect on HR, while allowing a normal response to carotid occlusion. Therefore, these results support the hypothesis that a stiff wall in the baroreceptor area leads to an increase in MAP.

It should be noted in both Crandall et al. (17) and Burstyn et al. (12) studies, the manipulation affected only the carotid baroreceptors, and aortic baroreceptors should have been functioning normally. Because denervation of carotid baroreceptors alone does not lead to changes in MAP (33, 45, 56), presumably because aortic baroreceptors provide sufficient input to inhibit increased SNA, the question arises as to why MAP increases if afferent signals from carotid baroreceptors are simply reduced, as opposed to being eliminated. One could speculate that as long as there is a pulse synchronous input, albeit reduced in magnitude, from carotid baroreceptors that arrives together with input from aortic baroreceptor afferents at a common pool of neurons in the NTS, the net response is an increase in SNA. This would lead to an increase in MAP that, if sustained, could cause upward resetting of the aortic baroreceptors and eventually reach a new steady state. However, there is no available evidence to support such a mechanism.

Two studies by Angell-James used dietary means to decrease the distensibility of arteries. In one (10), rabbits were fed high levels of vitamin D that caused medial sclerosis and calcification of the large arteries, including the arch of the aorta and carotid bifurcation. Over a period of weeks to months, the rabbits became hypertensive. In the other (8), rabbits were fed a cholesterol- and lipid-rich diet to induce atherosclerosis. Over time, these rabbits also became hypertensive, and at death, atheromatous plaques were found throughout the aortic arch region, as well as in the coronary and renal arteries. In both studies, pressure volume studies of the excised aortic arch region indicated a marked decrease in the distensibility of the vessels. Angell-James also recorded from baroreceptor afferents in these studies, and these results are discussed below.

BARORECEPTOR RESETING

The first evidence that baroreceptors reset appeared in 1956 in a classic paper by McCubbin et al. (42). Whole sinus nerve and aortic nerve recordings in dogs with established renal hypertension revealed that the pressure threshold to induce firing and the pressure at which firing became continuous (i.e., saturation pressure) were both markedly elevated compared with normotensive control dogs. In a separate group of dogs, they measured pressor responses to carotid occlusion (CO) before and weekly during the development of renal hypertension. There was no diminution of the pressor response to CO as the hypertension progressed, indicating that baroreflex arc remained functional throughout. The simplest explanation for this finding is a shift in the operating characteristics of the baroreceptors to higher pressures, and the nerve recordings showed that is exactly what happened. Thus these results gave rise to the concept that in hypertension, the baroreceptor mechanism resets to a higher operating pressure and therefore acts to maintain rather than suppress the hypertension. In a later study, McCubbin (41) provided evidence that resetting, based on the whole nerve response, could be detected within 2 days after constricting the renal artery, and that on the basis of the response to CO, the resetting may never be complete. These seminal studies set into motion a decades-long search for the mechanism(s) that causes resetting of baroreceptors. Later studies in rabbits (9) and dogs (58) confirmed that resetting reflected a shift in the threshold of the baroreceptors based on recordings from single units in the aortic depressor nerve and carotid sinus, respectively.

The most common definition of baroreceptor resetting is a shift in the pressure threshold of a receptor in the direction of the prevailing MAP (40). However, there appear to be two different forms of resetting. Rapid or acute baroreceptor resetting can be induced by increasing or decreasing the conditioning pressure to which the receptors are exposed for as short as 20 min or less (14, 20, 44). The initial shift in pressure threshold (Pth) is stable for at least an hour, occurs without a change in the sensitivity of the receptors, and is fully reversible (44). In chronic resetting, as observed in various models of hypertension, the Pth is shifted in the direction of the pressure change as above, but the sensitivity of the receptors is reduced, and these changes are not readily reversible (58). Thus the mechanism that causes the acute change in Pth is not the same as that underlying the chronic change in Pth.

Whether the acute resetting phenomenon plays a role in the chronic resetting of baroreceptors is also uncertain. The reason is that exposing the baroreceptors to a pulsatile pressure instead of a static pressure eliminates resetting at pressures near physiological levels and attenuates resetting at higher pressures (13). In addition, the receptors that display the phenomenon of rapid resetting appear to be associated with myelinated fibers (55). However, many of the baroreceptors communicate via unmyelinated axons, and these receptors appear to lack the property of rapid resetting (54). There is evidence that receptors with unmyelinated fibers do reset in models of chronic hypertension but not to the same extent as receptors with myelinated fibers (35). Finally, there is uncertainty as to
whether baroreceptor resetting is complete, at least in the sense that the receptor threshold shifts by the same magnitude as the change in MAP ($\Delta P_{th}/\Delta MAP$). Munch et al. (44) performed a retrospective analysis of $\Delta P_{th}/\Delta MAP$ obtained from 18 published papers and determined that the mean was about 0.5. Furthermore, there was no obvious correlation between the duration of the change in MAP and $\Delta P_{th}/\Delta MAP$ as ratios <0.5 were found in both models of chronic hypertension, as well as experiments observing resetting in response to acute changes in MAP.

A number of mechanisms have been proposed to account for the resetting that is observed in chronic models of hypertension. These include destruction of receptors (1, 2), decreased distensibility of the vascular walls in which the receptors are embedded (10, 28, 39, 52), an alteration in the coupling between the receptors and the vascular walls (11), and an intrinsic property of the receptors themselves (6, 7, 11). Evidence in favor of the latter possibility has been obtained in the spontaneously hypertensive rat (SHR) model. Brown et al. (11) observed a significant increase in $P_{th}$ and a decrease in sensitivity of aortic baroreceptors of 16- to 20-wk-old hypertensive SHR compared with normotensive rats of the same age. However, the distensibility of the aortas from the two strains of rats was similar, indicating that reduced vascular compliance was not a necessary condition for resetting. However, a later study from the same laboratory (7) compared baroreceptor responses over time in SHR and Wistar-Kyoto (WKY) rats and concluded that the receptors were different as early as 5 wk of age, at a time when MAP is similar. This observation suggests that there is a genetically related difference in the properties of the receptors independent of both the distensibility of the wall and the exposure to elevated MAP in the SHR model.

Andresen (5) compared baroreceptor function in elderly SHR and WKY averaging 76 and 115 wk of age, respectively. As expected, aortic baroreceptor $P_{th}$ and sensitivity in the SHR differed significantly from WKY rats. However, observations in the WKY rats provided an important insight concerning the properties of baroreceptors. Decreased aortic distensibility in the aged WKY rat did not increase the $P_{th}$ compared to younger rats studied previously (6, 7), but the pressure sensitivity was significantly reduced in the aged rats. Furthermore, the baroreceptors of both the aged WKY and SHR rats still responded to changes in conditioning pressure by acutely resetting the $P_{th}$ without a change in pressure sensitivity. On the basis of this study and previous studies from the same laboratory (6, 7), Andresen proposed that wall distensibility was an important determinant of the suprathreshold sensitivity of the baroreceptors but that other factors were involved in determining the threshold for baroreceptor activation (5). This interpretation is compatible with earlier observations by Sapru and Krieger (51). They prevented hypertension in SHR until about 44 wk of age and then withdrew drug treatment for 2 wk and assessed baroreceptor function. The $P_{th}$ was elevated in the SHR rats that experienced short-term hypertension, but there was no change in either the sensitivity of the receptors or the distensibility of the aorta compared with control rats. In contrast, in untreated SHR, the $P_{th}$ was increased, and both the sensitivity of baroreceptors and aortic compliance were decreased. Finally, in another group of SHR exposed to a brief period of hypertension, resumption of vasodilator treatment restored the $P_{th}$ to control levels. Thus the shift in threshold appears to be most directly related to the pressure to which the receptors are exposed, whereas the sensitivity of the receptors is related to the distensibility of the vessel wall.

**VASCULAR DISTENSIBILITY AND BAROREFLEX SENSITIVITY**

It is well known that the sensitivity of the reflex control of HR in response to vasoactive agents is altered independently by hypertension and by aging in both animal models (27), and in human subjects (22, 26, 49). A consequence of both hypertension and aging is a reduction in vascular distensibility, although the mechanisms are not identical. The demonstration that reduced baroreceptor sensitivity could be accounted for by reduced aortic compliance observed in both aged normotensive rats (5) and hypertensive rats (51), as discussed in the previous section, may provide an explanation for the decreased baroreflex control of HR in hypertensive subjects and aged normotensive humans.

For example, Monahan et al. (43) measured baroreflex control of HR and carotid compliance in 47 healthy sedentary men ranging from 19 to 76 years of age. Monahan and colleagues reported a progressive decline in baroreflex sensitivity with increasing age. The decline in baroreflex sensitivity correlated significantly with carotid compliance, percentage of body fat, diastolic blood pressure, and resting HR. However, stepwise multiple regression analysis indicated that carotid compliance was the strongest physiological correlate of baroreflex sensitivity. They also studied a group of older sedentary men (averaging 56 yr old) before and 13 wk after initiating an aerobic exercise program. They reported that regular exercise significantly increased both baroreflex control of HR and carotid artery compliance, and the two variables were strongly and positively correlated. Thus this study provides experimental evidence in human subjects that increased stiffness of the vessel wall in baroreceptive regions can account for a large component of the age-related decrease in reflex control of HR.

On the basis of the association between aging, decreased vascular compliance, and impaired baroreflex control of HR, one would predict a similar reduction in the baroreflex control of SNA. However, evidence supporting this prediction is not conclusive. Ebert et al. (21) measured muscle SNA in subjects ranging from 18 to 71 yr of age during acute increases and decreases in MAP induced by vasoactive agents and observed baseline muscle SNA was higher in older subjects, but no difference could be found in the slope relating the change in pressure to muscle SNA. They also measured SNA in response to neck pressure in a small group of young and old subjects. Although changes in SNA in response to increased neck pressure were not significantly different between groups, the mean response in the older men was only 50% of that observed in young men and much more variable. Davy et al. (18) recorded muscle SNA in young (average age = 25) and old (average age = 69) healthy normotensive men during sustained infusion of phenylephrine. Baseline SNA (expressed as bursts/min) in older subjects was twice the level recorded in younger subjects, and both groups displayed significant inhibition of SNA during baroreceptor stimulation. There was no age-related difference between the change from baseline in muscle SNA. However, the percent decrease in SNA per millimeters Hg increase in MAP was significantly smaller in the older men. Perhaps more importantly, the actual level of muscle SNA...
achieved in the older group during baroreceptor stimulation was still higher than the baseline levels recorded in the young men. Grassi et al. (25) compared control of muscle SNA in elderly hypertensive and age-matched normotensive subjects and observed decreased baroreflex control of HR in the hypertensive subjects but no difference in muscle SNA between the two groups. Thus the studies by Ebert et al. (21) and Davy et al. (18) both concluded that baroreflex control of muscle SNA did not decrease with age, and yet both studies contained evidence suggesting an age-related decline in sensitivity. The study by Grassi et al. (25) reported no difference in baroreflex control of muscle SNA between elderly normotensive and hypertensive subjects but did not compare either group to a group of young subjects.

In contrast, a recent study using a new technique to estimate baroreflex control of MAP in human subjects concluded that it is markedly reduced in aged men (36). The technique compared the rise in MAP in response to either bolus and infused doses of phenylephrine before and after ganglionic blockade with trimethaphan. The rise in MAP was greater in the older group before ganglionic blockade and significantly less after ganglionic blockade compared with the young group, indicating a much reduced ability to buffer increases in MAP. Thus the question of whether there is an age-related or hypertension-related reduction in baroreflex control of SNA in human subjects will require additional studies to resolve.

The difficulty in demonstrating impaired baroreflex control of SNA in aged human subjects is surprising, as there is clear evidence of the phenomenon in animal studies. For example, Hajduczok et al. (27) compared baroreflex control of renal SNA in old vs. young beagles and observed a marked reduction in the aged group. There is always the possibility of a species difference underlying the divergent results between human subjects and dogs. However, other possibilities exist. In the dog study, the animals were anesthetized, and the stimulus was delivered via the isolated carotid sinus preparation. This allowed a much larger range of pressure steps compared with the human studies. It is also possible that renal SNA activity is a better index of the overall control of SNA. It would indeed be surprising if the input-output relationships between baroreceptor input and SNA were markedly different as a function of aging in animals vs. humans.

The dependence of baroreceptor sensitivity on arterial compliance vs. the dependence of Pth on the pressure to which the baroreceptors are exposed (5) raises an interesting question. In models of hypertension such as the SHR rat or renal artery constriction, for example, the increase in MAP precedes the change in vascular distensibility, the latter occurring presumably as an adaptive response to increased vessel wall stress. Under these conditions, baroreceptor resetting probably follows a parallel path to the increase in MAP. Therefore, is it possible to have an increase in MAP without a change in baroreceptor Pth? There appear to be two examples where this has occurred experimentally, both reported by Angell-James (8, 10). Baroreceptors in rabbits made hypertensive by ingestion of a high-cholesterol diet were significantly less sensitive compared with normotensive rabbits, but their Pth was not different from control rabbits. Baroreceptor sensitivity was also reduced in rabbits made hypertensive by calciferol ingestion, but their Pth was actually reduced compared with control rabbits. Angell-James noted that in both models, the baroreceptive areas of the aortic arch (and presumably the carotid sinus) were heavily lesioned with atheromatous plaques or calcification. The reduced Pth in the calciferol model was explained by the extreme degree of calcification of the aortic wall such that the crystalline structure prevented a decrease in vessel radius at low pressures. She also noted that the variability of MAP, measured in the conscious state, was increased, particularly so in the calciferol-treated rabbits, as would be expected. Thus, in these two examples, hypertension was produced without resetting or resetting in the opposite direction to the pressure change. Therefore, it is experimentally possible to induce hypertension by loss of vascular compliance in the baroreceptive areas of the circulation.

HUMAN CAROTID DISTENSIBILITY AND ATHEROSCLEROSIS

Atheromatous lesions occur frequently in humans, particularly in the area of the carotid bifurcation and the aortic arch (28, 60). The progressive enlargement of the atheroma in the carotid sinus area can lead to significant obstruction to flow and cerebral ischemia; hence, a procedure termed carotid endarterectomy was developed to remove the plaque. This is a common procedure and would appear to be the ideal model in which to test the hypothesis that decreased distensibility of the vascular wall containing the carotid baroreceptors can alter MAP. Unfortunately, most of the studies in the literature were not focused on long-term effects of the procedure on MAP. Nevertheless, some of the findings are germane to the question of baroreceptor involvement and chronic regulation of MAP.

Tyden et al. (66) calculated the closed loop gain of the carotid occlusion reflex before and immediately after unilateral carotid endarterectomy and reported that it doubled, suggesting increased sensitivity of the receptors. However, they also determined that improvements in reflex gain were gone 2 mo after the procedure (65). Hirschl et al. (30) determined baroreflex sensitivity before and 3–4 days after unilateral carotid endarterectomy in 16 normotensive and 34 hypertensive patients. There was no change in baroreflex sensitivity in the normotensive group, but a significant improvement in the hypertensive patients 3 days after surgery. There was no change in MAP (measured via direct arterial cannula) in the normotensive or hypertensive patients, but 21 of the 34 hypertensive patients required a reduction in their antihypertensive therapy to maintain preoperative MAP levels. Interestingly, there was a significant improvement in baroreflex sensitivity in the subgroup of hypertensive patients with reduced antihypertensive medication following surgery but no change in the subgroup that did not show a fall in MAP. The authors noted that 80% of the patients had plaques in the opposite carotid sinus (thus it is likely that plaques were also present in the aortic arch). Therefore, the reduction in MAP in 62% of hypertensive patients (i.e., those whose antihypertensive medication was reduced) after plaque removal from one baroreceptive field together with improved baroreflex sensitivity suggests baroreceptor involvement in their hypertension. Unfortunately, there was no apparent follow-up to determine the chronic effects of the surgery on MAP.

Only one study followed patients chronically after carotid endarterectomy (19). Blood pressure was measured before and 6 mo after surgery in 25 patients, and there was no significant change in MAP. Baroreflex sensitivity was also determined
BARORECEPTOR UNLOADING IN THE DOG

A recent variation on the theme of altering the afferent signal from the baroreceptors was developed in the author’s laboratory (62). Chronic baroreceptor unloading (CBU) is accomplished by ligating the common carotid artery proximal to a single innervated sinus (the opposite sinus is denervated, and aortic baroreceptors are denervated via stripping the aortic arch and brachiocephalic and subclavian trunks). This technique results in a rise in MAP of 20–30 mmHg that was sustained for 7 days and that returned to control levels after removal of the ligature. We have argued that the increase in MAP in response to CBU is due to a reflex increase in sympathetic activity to restore pressure in the innervated sinus distal to the ligature to control levels. And in fact, mean carotid sinus pressure (CSP) is not statistically different from levels measured before placing the ligature on the common carotid, but pulse pressure in the sinus is chronically decreased. Evidence of increased SNA is indirect and is based on two observations. Plasma renin activity (PRA) increases for a few days after CBU, even though systemic and, thus, renal perfusion pressure are significantly increased. Furthermore, the initial renal response is sodium retention and not a pressure natriuresis, as would be expected. After a few days, PRA declines to control levels but not below control, and sodium balance is restored even though systemic MAP remains significantly elevated. An increase in SNA to the kidneys is the only plausible explanation for the PRA responses during increased renal perfusion pressure. And the initial sodium retention under the same conditions of increased MAP can only be explained by resetting the pressure natriuresis mechanism to a higher level. Two known factors that could alter the pressure natriuresis mechanism are increased renal SNA acting on proximal tubule sodium retention and increased ANG II due to increased renin secretion.

The results obtained in the CBU model also address the third principal argument against the participation of baroreceptors in the long-term control of MAP, that is, “the gain of the baroreceptor mechanism is insufficient to account for the long-term stability of MAP” (15). Cowley et al. (16) estimated the reflex gain of the system to be about “1” based on the increase in variability of MAP in SAD dogs compared with baroreceptor-intact dogs. In contrast, the gain of the reflex calculated from the steady-state change in systemic MAP to the change in CSP during CBU was greater than 11 (62). Thus the gain of the baroreceptor reflex based on the CBU model indicates that the system is fully capable of ensuring long-term stability of MAP.

We have repeated the CBU study described above using implanted telemetry sensors to record MAP continuously with the dog in its home cage and extended the period of observation to 5 wk after ligation of the carotid (63). The increase in MAP during the first week following CBU was similar to that reported previously, but the increase was not sustained; MAP gradually declined over the succeeding 2–3 wk and stabilized about 10 mmHg above control during the final 2 wk of observation. Nevertheless, the final level of MAP was significantly different from the control levels, suggesting that a long-term change in MAP had occurred. The two most likely explanations for the subsequent decline in MAP are resetting of the baroreceptors and vascular adaptations that improve delivery of the cardiac impulse to the carotid baroreceptors. In terms of resetting, even though there was no statistically significant difference in CSP during CBU compared with control, it was clearly 1–3 mmHg less in all dogs (62). Thus it is impossible to rule out some small degree of resetting during CBU. In contrast, the capacity of the dog’s vascular system to adapt to insult is enormous, as noted previously (61). In the dogs with CBU, there is an obvious increase in the diameter of the external carotid distal to the innervated sinus, and there are many new small vessels around the sinus area. That these vascular adaptations are important is evident from the observation that CSP distal to the ligature remains near control levels rather than declining in step with systemic MAP. It may be that the ability of the dog’s vasculature to adapt to insult limits the usefulness of the CBU model to study the role of baroreceptors in the long-term control of MAP.

SUMMARY AND CONCLUSIONS

In summary, experimental conditions under which baroreceptors appear to be implicated as the cause of a change in MAP include decreased distensibility of vessels in reflexogenic areas of the circulation by mechanical means or dietary manipulations and the CBU model in which a permanent obstruction is placed between the heart and the receptors. These experimental models either alter the normal relationship between the distensibility of the vascular wall and the receptor elements contained therein or, in the CBU model, protect the receptors from the consequences of a reflex increase in SNA. There is also clear experimental evidence that decreased vascular distensibility is an important factor in determining the sensitivity of the baroreceptors and, hence, the variability of MAP. Thus disordered baroreceptor function may play an important role in the pathogenesis of hypertension in subjects with atherosclerosis or other conditions associated with decreased arterial compliance. However, whether decreased arterial compliance plays a role in most cases of primary hypertension remains unclear.

ACKNOWLEDGMENTS

The author acknowledges the excellent technical assistance of Cassandra Smith and Sarah Muncie in the studies cited from the author’s laboratory.

GRANTS

This article was supported by grant HL-67329 from the National Heart, Lung, and Blood Institute of the National Institutes of Health.
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