Patients with low output congestive heart failure have less-than-normal slowing of heart rate during pharmacologic increases of arterial pressure, indicating impairment of the arterial baroreceptor–heart rate reflex. The mechanism underlying this abnormality is not fully understood and could involve one or more components of the reflex arc, including an afferent limb (generation and transmission of baroreceptor neural impulses), central neural processing of afferent neural impulses (most importantly in the nucleus tractus solitarius), and an efferent limb that includes transmission of neural impulses in efferent pathways and end-organ responses to these efferent impulses. In this issue of Circulation, Wang et al present results from studies in an animal model of low output congestive heart failure that provide new insight into the mechanisms of arterial baroreceptor reflex impairment in congestive heart failure.

In the present study, Wang et al recorded single-unit baroreceptor activity from the vascularly isolated carotid sinus during stepwise increases in carotid sinus pressure (CSP) in normal dogs and in dogs with congestive heart failure produced by chronic tachypacing. Several abnormalities were found in dogs with heart failure. First, the lowest CSP at which carotid sinus baroreceptors discharged (threshold pressure) was higher than in normal dogs. Second, the ratio relating change in baroreceptor firing rate to change in CSP (baroreceptor gain) was lower than in normal dogs. Finally, the peak carotid sinus baroreceptor discharge rate at any pressure was markedly lower than in normal dogs. These findings establish that there are profound abnormalities in the afferent limb of the arterial baroreceptor reflex in congestive heart failure.

To investigate a possible mechanism for this abnormality in baroreceptor function, these investigators perfused the isolated carotid sinus with ouabain, a digitalis glycoside that inhibits Na,K-ATPase. In normal dogs, there were no effects on carotid sinus baroreceptor behavior. In dogs with heart failure, however, ouabain reduced the threshold pressure and augmented baroreceptor gain, indicating a partial normalization of baroreceptor behavior. Perfusion of the carotid sinus with a lowered concentration of potassium (which also inhibits Na,K-ATPase) also resulted in a decrease in threshold pressure in heart failure dogs, although baroreceptor gain was unaffected. These findings suggest that augmented Na,K-ATPase activity may be responsible for impairment in baroreceptor function seen in congestive heart failure. They also suggest a mechanism by which digitalis glycosides may improve circulatory control in heart failure.

In a recently published study, Dibner-Dunlap and Thames also showed that arterial baroreceptors are impaired in dogs with tachypacing-induced congestive heart failure. In these experiments, multunit baroreceptor activity was recorded from the aortic depressor nerve during ramp changes of arterial pressure produced by intravenous boluses of phenylephrine and nitroglycerin. In dogs with heart failure, baroreceptor gain (change in baroreceptor firing rate per mm Hg change in mean arterial pressure) was significantly reduced compared with that in normal dogs. To determine if there are abnormalities of the central component of the arterial baroreflex, these investigators recorded simultaneously efferent renal sympathetic and aortic depressor nerve traffic. By comparing levels of afferent baroreceptor activity and efferent sympathetic nerve activity, they could estimate the central gain of the baroreflex (change in renal sympathetic nerve activity divided by change in aortic depressor nerve activity). Interestingly, although there was decreased aortic baroreceptor sensitivity, changes of renal sympathetic nerve activity in response to changes of mean arterial pressure were similar in normal dogs and dogs with heart failure. These findings suggest that the central gain of the baroreflex is preserved in congestive heart failure.
and may, in fact, be augmented and compensate for abnormalities in the afferent limb.

These studies show that in congestive heart failure, abnormal arterial baroreflexes (the entire reflex arc) may result from abnormal baroreceptors (the afferent limb). As shown by Dibner-Dunlap and Thames, however, augmented gain of the central component of the reflex may mask abnormalities at the level of the baroreceptor, at least with respect to baroreflex modulation of renal sympathetic nerve activity. It should be emphasized that baroreflex modulation of sympathetic nerve activity may be normal even when baroreflex control of heart rate is abnormal. Wang et al.2 further suggest that digitalis glycosides may restore arterial baroreceptor sensitivity in congestive heart failure by inhibition of Na,K-ATPase. This sensitizing effect of digitalis glycosides has been suggested in previous studies of arterial and cardiopulmonary baroreceptors.5,6 Wang et al have extended these observations by demonstrating that a second intervention that inhibits Na,K-ATPase (lowered carotid sinus potassium concentration) also tends to normalize baroreceptor function in heart failure.

Augmentation of baroreceptor sensitivity may occur in patients with heart failure treated with digitalis glycosides; this may be one mechanism by which this drug improves circulatory function in humans. This concept is supported by a recent study by Ferguson et al.,7 which showed that intravenous deslanoside (a digitalis glycoside) reduces efferent muscle sympathetic nerve activity in patients with heart failure before any detectable change in arterial pressure. This is consistent with sensitization of arterial or cardiopulmonary baroreceptors leading to increased afferent baroreceptor nerve traffic at any given level of pressure and resultant inhibition of sympathetic outflow. This sympathoinhibition did not occur during an infusion of dobutamine that increased cardiac output to a similar extent.

Although the cellular basis for abnormal baroreceptor activity may reside in heightened activity of Na,K-ATPase, the mechanistic link between impaired ventricular function and impaired baroreflexes remains elusive. Patients with other forms of cardiovascular disease, notably hypertension, also have impaired arterial baroreflex control of heart rate,8 and it is possible that a common mechanism mediates baroreflex abnormalities in different pathologic states. These baroreflex abnormalities are reversible, in both congestive heart failure and hypertension, and this suggests that permanent structural abnormalities in the components of the baroreflex arc are not present in these disease states. Ellenbogen et al.9 demonstrated normal slowing of the native sinus node during pharmacologic increases of arterial pressure in heart transplant recipients who had advanced congestive heart failure before transplantation. Mancia et al.10 showed that blunted cardiopulmonary baroreflexes in patients with hypertension were restored toward normal after antihypertensive treatment that produced regression of left ventricular hypertrophy.

Finally, recent studies have shown that carotid sinus baroreceptors may respond to changes of blood flow independent of changes in mean arterial pressure11 and that these changes in baroreceptor behavior may be mediated by release of endothelium-derived factors.12 These considerations raise the interesting possibility that endothelial cell dysfunction that accompanies various cardiovascular diseases may be involved not only in abnormal local vascular regulation but also in abnormal reflex neural control of the circulation.

References


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