The Chicken and the Egg
Sympathetic Nervous System Activity and Left Ventricular Diastolic Dysfunction

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In this issue, Grassi et al describe an elegant study in which they measured sympathetic nerve traffic by microneurography in 17 untreated hypertensive subjects with left ventricular (LV) diastolic dysfunction but without LV hypertrophy. The control groups were 20 age-matched normotensive subjects and 20 subjects with hypertension but without LV diastolic dysfunction. Microneurography is a technique in which a microelectrode is inserted into the peroneal nerve posterior to the head of the fibula and is a method of quantifying sympathetic nerve activity, which the Milan group has used to produce some outstanding research in the past. The main finding in this study was that muscle sympathetic nerve traffic was greater in the 2 hypertensive groups than in the normotensive group. In addition, if they compared hypertensive subjects with the same degree of BP elevation, there was a greater increase in sympathetic nerve traffic in those with than in those without LV diastolic dysfunction. They conclude that, “The results of the present study document for the first time that, in essential hypertensive patients, the presence of left ventricular diastolic dysfunction enhances sympathetic nerve traffic in the subjects with LV diastolic dysfunction, not the other way around.”

The science is excellent, but the inference is, at least, open to debate. Which caused which: the LV diastolic dysfunction causing the sympathetic activation or the increased sympathetic activation causing the diastolic dysfunction? There is often the problem of ascribing causality where there is a correlation between 2 variables; which is the cause and which the consequence? This is the old chicken-and-egg conundrum. Modern biology has answered the question: it must have been the egg, because the only way that the species could have evolved is by a mutation in the germline first manifest in an egg laid by the closest ancestor of a chicken. The question of which came first, sympathetic nerve activity or LV diastolic dysfunction, is more difficult but can probably also be settled, in my view, on the basis of modern knowledge of the pathophysiology of heart failure. It is more likely to be the sympathetic nerve activity causing the LV diastolic dysfunction, not the other way around.

Increased activity of the sympathetic nervous system may be an important contributory factor in the development of arterial hypertension. In turn, hypertension, because of the greater-than-normal impedance to LV output, imposes a mechanical load on the left ventricle, which will activate many of the pathophysiologic mechanisms that result in stiffer ventricles. These include myosin isoform changes, myocyte hypertrophy, increased LV collagen concentration, and interstitial fibrosis.

Another interpretation of these effects is possible, namely, that both hypertension and LV diastolic dysfunction (and hypertrophy) are induced or enhanced by the common factor of an increase in sympathetic drive. Sympathetic stimulation, as well as being an important factor in chronic blood pressure elevation, can also induce, via activation of β-adrenoceptors, both the structural and functional changes of cardiac decompensation. These changes include proinflammatory cytokine expression, reversion to the fetal phenotypes of myosin and troponin I, and alterations in the sarcoplasmic reticulum, plasma membrane, and cytoskeletal proteins. In experimental animals, sympathoinhibition prevents the development or delays the progression of diastolic dysfunction.

There are, therefore, 2 equally plausible scenarios, one in which sympathetic stimulation causes hypertension, which, in turn, causes the abnormalities in the myocardium characteristic of heart failure, and the other where sympathetic activation produces both hypertension and the heart failure myocardial phenotype. Both concepts are equally credible, and it is likely that both apply. Both are consistent with what we know about the effects of both afterloading and of an increase of sympathetic activity on the left ventricle. How then do we explain, in the Grassi et al study, the greater sympathetic nervous efferent activity in the subjects with LV diastolic dysfunction compared with those with normal LV diastolic function? After all, both groups had hypertension. It may be that, whereas sympathetic activity is increased in hypertension, a quantitatively greater sympathetic drive produces both hypertension and LV dysfunction.

What is more difficult to understand is the obverse idea, namely, that LV diastolic dysfunction can cause an increase in sympathetic nerve activity. What could the mechanism be? In diastolic dysfunction, ejection fraction is, by definition, normal, cardiac output is usually normal, and blood pressure is often elevated. None of the stimuli, low cardiac output or low blood pressure, which unload the carotid baroreceptors and, thus, reflexly activate the sympathetic nervous system, are present in this scenario. The only persuasive explanation...
is that a stiff ventricle might be expected to reduce the
difference between end-diastolic and end-systolic cardiac
stretch, as well as the rate of atrial and ventricular mechanoreceptor unloading with each cardiac cycle. Thus, the stiffer myocardium is associated with reduced unloading of cardiac mechanoreceptors, blunting the ability of these cardiopulmonary baroreflexes to limit sympathetic outflow.\(^8\) It would have been nice to have some experimental verification of this sequence of events to support the clear implication from the Grassi et al.\(^1\) report that the LV dysfunction causes sympathetic activation. What they did find was an impairment of baroreflex function in hypertensive individuals with diastolic dysfunction, another interesting phenomenon that is hard to explain.

Whichever way round it is, chicken or egg, this is a significant contribution from a distinguished group of investigators who have made the role of the sympathetic nervous system in hypertension such a fruitful area of study.

**Disclosures**

None.

**References**

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