Editorial

Transient myocardial ischaemia: new questions about autonomic responses

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This editorial refers to “Changes in autonomic nervous system activity: spontaneous versus balloon-induced myocardial ischaemia”1 by O. Manfrini et al. on page 1502

In this issue of the Journal Manfrini et al.,1 demonstrate that radically different autonomic profiles accompany episodes of spontaneous myocardial ischaemia compared to myocardial ischaemia in the same patient. Practicing cardiologists have known for decades that the location of myocardial ischaemia determines the pattern of autonomic response. For example, acute transmural anterior wall myocardial infarction is often accompanied by sympathetic activation, sinus tachycardia, and relative hypertension, while inferior wall infarction is accompanied by sinus bradycardia and hypotension. Given that heart rate variability is assumed to shed insight into the balance between vagal and sympathetic tone,2 this led to a number of animal and clinical studies of heart rate variability during myocardial ischaemia.3,4 Manfrini et al., now use this method to show that not only the location of ischaemia but also the mechanism of coronary artery occlusion determines the heart rate variability response. They report that ischaemia that occurs apparently spontaneously is accompanied by heart rate variability changes thought to reflect sympathetic dominance, while ischaemia induced by balloon angioplasty of the left anterior descending artery is accompanied by heart rate variability changes thought to accompany parasympathetic dominance.

Before considering the implications of this striking finding, we should first consider the study itself, which included several strong methodological features. The authors limited their study population to patients with single vessel disease with a significant stenosis of the left anterior descending artery, preserved coronary flow at rest, normal left ventricular function, and normal regional wall motion. The ischaemic events lasted a mean of only 2–4 min, which limits the kinds of responses that need to be considered. Finally, they report autonomic changes during both clinical and induced ischaemia. This is a robust study with a clean and simple population with which to study autonomic neural patterns that accompany ischaemia, and the authors are to be congratulated.

As is often true, strong physiologic methodology may limit generalisability to real-life clinical scenarios. The study subjects were younger than most coronary artery disease patients, having a mean age of only 55 years and a range of 43–63 years. Also, only 3/14 subjects were smokers. Autonomic reflexes change with the progression of age and structural heart disease, and therefore the results in this population may not be cleanly and simply transferable to the usual patient population, composed of older patients who are often smokers with multi-vessel disease and previous myocardial damage.

The authors report that episodes of spontaneous ischaemia are associated with heart rate variability changes consistent with sympathetic activation and parasympathetic withdrawal. This is not surprising, and is in accord with earlier findings.5 However the unexpected finding was that transient ischaemia induced by balloon coronary artery occlusion provoked heart rate variability changes consistent with sympathetic withdrawal and increased vagal tone. What is the physiologic link between balloon occlusion and reflex changes? Our ability to link this kind of study with animal studies is limited by the outcome measure: Manfrini et al., detected substantial changes
in heart rate variability but only trivial changes in heart rate and blood pressure, which in turn are important measures in animal studies. The major possibilities appear to be chemoreflexes, coronary artery mechanoreceptors, and ventricular mechanoreceptors. There are chemosensitive receptors in the left ventricle, and through them non-physiological agents such as veratridine cause substantial reflex hypotension and bradycardia. Given that sensory neurites are affected by locally-released purines and oxygen-free radicals, it might be that chemoreflexes that respond to locally produced ischaemic metabolites and ATP also cause the change in heart rate variability. However these chemoreceptors are conventionally thought to mainly be localised in the infero-posterolateral wall, and Manfrini et al., occluded the left anterior descended artery.

A second possibility is that local dyskinesis in the ischaemic region might stimulate ventricular mechanoreceptors, thereby triggering reflex hypotension and bradycardia and hypotension. Again, these receptors are usually located in the infero-posterolateral wall, and the authors caused anterior wall ischaemia in all subjects and a reduction in low frequency heart rate variability, a presumed measure of sympathetic tone, in 13/14 subjects and a reduction in low frequency heart rate variability. However these chemoreceptors are conventionally thought to mainly be localised in the infero-posterolateral wall, and Manfrini et al., occluded the left anterior descended artery.

This latter notion, is in turn, questioned by the recent report by Wright et al., who used changes in intraluminal and intracavitary pressures in highly controlled terminal dog preparations to demonstrate the presence of coronary artery mechanoreceptors. Stimulation of these by increases in perfusion pressure caused reflex vasodepression. The coronary artery receptors are much more sensitive to changes in pressure and much more effective in causing vasodepression than were the ventricular mechanoreceptors. Indeed, changes in perfusion pressure within the physiologic range reduced vascular resistance by 35%. Wright et al., did not determine whether the mechanoreceptors were in epicardial arteries or in smaller distal branches. Taken together, these data suggest that changes in heart rate variability induced by balloon angioplasty are mediated by stimulation of coronary artery mechanoreceptors that respond to locally increased intra-luminal pressures.

This article also provokes the question of how the responses are mediated. Related experiments in a porcine model suggested that the afferent stimuli are carried by epicorony sympathetic nerves. Although it is conventionally assumed that reflexes such as these are mediated by the brainstem, ample evidence has been accrued in the past 15 years that there are complex reflexes mediated by intra-cardiac and intra-thoracic ganglia. The intrinsic cardiac nervous system includes local afferent and efferent neurons and local interconnecting neurons. These respond to a variety of physiologically important stimuli including circulating neurohormones, metabolic products, ischaemia, and pressure, and can modulate myocyte function. Whether they modulate changes in heart rate variability due to balloon angioplasty is unknown, but this possibility cannot be ignored.

A final issue is whether the heart rate variability that was measured by Manfrini et al., truly reflects what they assumed it did, that is the sympathetic and parasympathetic tone and its balance. There is substantial and unresolved debate about this. The arguments that low frequency heart rate variability reflects sympathetic tone include its partial susceptibility to adrenergic blockade, its correlation with muscle sympathetic nerve traffic, and its variable but generally increased level during orthostatic stress. In fact, the power in the low frequency band of heart rate variability appears to be derived from power in the low frequency band in blood pressure variability. The cause of these fluctuations in blood pressure is unresolved. The effect of blood pressure fluctuations on heart rate is mediated by arterial baroreceptors, and indeed baroreceptor tone is often estimated by comparing the power in these two systems. Accordingly, the striking reduction in low frequency heart rate variability power during balloon occlusion might be due to either a novel regulation of blood pressure regulation, or a novel regulation of arterial baroreceptor function.

Therefore this simple and methodologically sound study of heart rate variability during myocardial ischaemia has produced not just an apparently paradoxical result, it has brought a number of interesting possibilities about cardiovascular autonomic physiology to the clinical domain, and has given us the tools to address these questions.

References