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Beyond postural tachycardia syndrome

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Twenty years ago physicians dusted off a phrase Rosen and Cryer¹ employed a decade earlier in reference to a carefully studied hyperadrenergic patient, and used the term 'idiopathic postural orthostatic tachycardia syndrome' or 'postural tachycardia syndrome' (POTS) to describe symptomatic patients with excessive tachycardia on standing,² thereby rechristening a number of older, poorly differentiated entities such as orthostatic intolerance,³ idiopathic hypovolaemia,⁴ effort syndrome, mitral valve prolapse syndrome, vasoregulatory asthenia and neurocirculatory asthenia. Defined by Phillip A Low, Ron Schondorf and their colleagues in clear and thoughtful terms,⁵ the postural tachycardia syndrome soon became a home for many poorly understood conditions presenting as orthostatic intolerance.

Bringing these together under the POTS rubric had a number of important consequences. By focussing on heart rate rather than blood pressure (which is usually not abnormal in POTS), it created a new benchmark which had not been the diagnostic focus in previous incarnations of these disorders. That led to increased recognition because many physicians and patients noticed the tachycardia and it became the organising principle in diagnosis. Large numbers of patients began to be diagnosed as having POTS. In recent years the number of such patients continues to grow, particularly in North America but also in Europe. Some estimates place the prevalence of POTS as high as 1 in 600 in the USA, with a 5:1 predilection for women of childbearing age.³

These developments spawned a major effort in autonomic centres to elucidate the pathophysiology of POTS. In general, this effort was quite productive. Several new aetiologies have emerged, including partial neuropathy, hypovolaemia,⁶⁷ norepinephrine transporter (NET) dysfunction,⁸ deconditioning⁹ and autoantibodies to the ganglionic nicotinic receptor.¹⁰ The pace of research in POTS has quickened in recent years as new investigators entered the field.

In this issue, Haensch and colleagues¹¹ use the radionuclide ¹²³I-MIBG (¹²³I-meta-idobenzylguanidine) to study the neuronal uptake of norepinephrine (NE) in 20 patients with well characterised POTS (*see page 339*). The focus of this scintigraphic study is the synaptic junction; it utilises ¹²³I-MIBG as a substrate and false neurotransmitter that shares characteristics (uptake, storage and release) with NE, the major neurotransmitter of the sympathetic nervous system. ¹²³I-MIBG was originally designed to image and thereby diagnose catecholamine containing tumours such as pheochromocytoma and other neural

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crest tumours, which possess NET in high quantities, and therefore accumulate the radionuclide tracer.¹¹

It has been adapted in recent years to study accumulation of the radionuclide to permit visualisation and density of noradrenergic nerve fibres in tissues such as the heart. ¹²³I-MIBG myocardial washout rate has also been used along with heart/mediastinum ratio to evaluate sympathetic innervation of the heart. It generally reflects turnover of NE attributable to sympathetic drive.¹² Reduction in the density of NET can lead to increased NE spillover into the plasma which accounts for the abnormal ¹²³I-MIBG washout in certain disease states. Furthermore, high levels of circulating NE can compete with the radiotracer resulting in its impaired accumulation.^{13,14}

The heart is richly innervated by sympathetic neurons, with cardiac tissue NE levels about the same as those in the brain. Because these noradrenergic fibres have multiple roles in the heart, disease processes involving this autonomic innervation can impair cardiac function. Already, the ability of the ¹²³I-MIBG test to differentiate between innervated and denervated myocardium is proving useful to differentiate Parkinson's disease from multiple system atrophy early in the disease, as the former, but not the latter, often has loss of sympathetic neurons in the heart.¹⁵ This is so even though standard tests of cardiac autonomic function, for example, using heart rate variability analysis, fail to distinguish between Parkinson's disease and multiple system atrophy.

In this study,¹¹ the investigators found reduced cardiac MIBG accumulation in four of 20 patients with POTS. They propose that this finding implies cardiac denervation. While there is a theoretical possibility that an abnormality in the function of the NET itself might give similar findings in the four patients who failed to accumulate MIBG, the rarity of NET dysfunction encourages the view that they have identified the partial noradrenergic dysfunction which they propose. A different radiotracer, 6-[¹⁸F] fluorodopamine, has shown generally normal labelled noradrenergic innervation in POTS^{15,16} but there were gradations in the individual data and, given the heterogeneity of POTS, this current study is not inconsistent with these earlier findings.

It is noteworthy that plasma NE tends to be raised in the presence of NET blockade or impaired NET function, and while it was not statistically significant in the small number of subjects in the study, there was a trend for higher plasma NE level in the subgroup with reduced MIBG uptake but NE levels themselves do not seem high enough to have produced this finding. Certainly, the observations in this study argue for more aggressive efforts to diagnose neuropathy in individuals with POTS. Different centres have different experiences but estimates of partial dysautonomia in POTS range all the way from <10% to >50% of POTS patients.

The results of this study¹¹ underscore the heterogeneity of POTS. With all this heterogeneity, what are we to think of the POTS diagnosis we make in clinic? Probably we should view the POTS diagnosis as a starting place for discovery of the cause of the patient's problem rather than a final answer as to what the patient actually has. These considerations introduce an element of uncertainty into the diagnosis and management of these patients but experienced clinicians will not be surprised at developments like this as such heterogeneity is widespread in disorders throughout all disciplines of medicine. If we view the POTS syndrome simply as a final common pathway by which a myriad of genetic and acquired pathophysiologies may present to the physician, we should in time acquire the capabilities to ascertain these individual pathophysiologies. That should make our therapeutic efforts more highly tailored for, and optimally beneficial to, the patient we are caring for in the clinic that day. The results of Haensch and colleagues,¹¹ encourage us to begin to bring the MIBG scan

into the research clinic to facilitate this process of discovery but we must be realistic and recognise that the road to genuine aetiological diagnosis will be long and circuitous.

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