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HYPERTENSION

Understanding baroreflex dysfunction in chronic kidney disease

Patients with chronic kidney disease (CKD) are at risk of cardiovascular mortality attributable to autonomic dysfunction. However, the exact mechanisms involved in this dysfunction are not altogether known. New research in Lewis polycystic kidney (LPK) rats has shown that impaired baroreflex and vascular remodelling of the aortic arch are implicated in this pathologic process.

Using the LPK rats, which are a model of autosomal recessive polycystic kidney disease, Jacqueline Phillips and her team studied changes in blood pressure, heart rate, aortic depressor nerve activity and renal sympathetic nerve activity after pharmacological blood pressure manipulation (with phenylephrine to elevate or sodium nitroprusside to reduce), comparing the results with age-matched control Lewis rats. "We previously demonstrated impaired baroreflex control of heart rate in our model of CKD and wanted to determine if it deteriorated in parallel with the decline in renal function and increase in blood pressure, if there was a comparable impairment of renal sympathetic nerve activity and where within the baroreflex arc the dysfunction occurs," explains Phillips.

Increased renal sympathetic nerve activity was documented in both young LPK rats (7–8 weeks of age) and adult LPK rats (12–13 weeks) compared with controls. "This finding is of particular relevance given the current interest in renal denervation as a treatment of hypertension in patients with CKD," comments Phillips.

"We also found a temporal decline in baroreflex function in our naturally progressive model of CKD and that, in the early phase of the disease, it is due to a deficit in the afferent (sensory) component of the baroreflex arc, but progresses in the adult to also include a decrease in central processing." Only when both the central and the afferent components were impaired was full expression of baroreflex dysfunction evident. That is, these results confirm baroreflex signalling is deficient in CKD and this is a progressive process.

The researchers also examined the histological changes in the aortic arch in the animals, both juvenile and adult. Perhaps unsurprisingly, LPK rats in both age groups have aortic arches with increased wall thickness, reduced elastin content and increased elastin lamellae fractures indicative of the vascular remodelling that is associated with CKD. These features progressed in an age-related fashion and correlated with the decline in baroreceptor afferent function. "Clinically, this is an important finding because hypertrophy and vascular calcification is a prominent feature in CKD," explains Phillips. "Our work suggests that early interventional measures that limit vascular remodelling may well serve to also ameliorate autonomic dysfunction and, therefore, reduce overall cardiovascular risk in these patients."

Overall, the mechanistic findings point to a possible therapeutic strategy. Specifically, preservation of the central component of the reflex might maintain the baroreceptor function in spite of any hypertension or renal failure-induced vasculopathy. "We also hope to examine if and how current therapeutics that target blood pressure control might work to improve sympathetic and heart rate baroreflex function in CKD," concludes Phillips.

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