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COMMENT

Functional insights into the cardiorenal syndrome

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The pathophysiological states of cardiovascular dysfunction are associated with increased morbidity and mortality. There is an increasing recognition that deterioration in cardiac function, leading to a reduction in cardiac output along with the development of hypertension, impacts on the kidney which may be expressed as a reduction in renal hemodynamic function and impaired fluid balance. Conversely, a deterioration in kidney function can itself impact on cardiac function in a positive feedback interaction which is known as the 'cardiorenal syndrome'. The mechanisms underlying this interaction between heart and kidney are unclear but may have either a neural, hormonal or even an immunological basis [1, 2]. Moreover, the exact manner by which deterioration in the function of one organ my influence that of the other has yet to be defined. Interest is increasing in understanding the cardiorenal syndrome and its clinical impact which makes this research area important in terms of developing unexplored therapeutic approaches.

There is a large body of evidence demonstrating that in a range of cardiovascular and renal diseases there is an elevation in the activity of the sympathetic nervous system [2] but whether this is due to peripheral mechanisms being activated or a central dysfunction or both is not clear at this time. Experimental studies have demonstrated that the activation of mechano- and chemo-receptors within the kidney result in inhibitory reno-renal reflexes between kidneys which may rely on both spinal and supra-spinal reflexes. There is also evidence that in some pathophysiological states, these become excitatory reno-renal reflexes which extends into a generalised sympatho-excitation and may contribute to the generation of an hypertensive state. The factors initiating either excitatory or inhibitory reno-renal reflexes may, in part, be dependent on activation of sensory/afferent neurons present within the pelvis and cortex of the kidney [2]. Detailed investigation into the neural control of the heart has firmly established that the sympathetic nervous system exerts an important control of both the chronotropic and ionotropic components of heart function. More recent studies have focused on afferent receptors in the heart that may be involved in autonomic control in that activation of chemo-receptors using epicardial application of capsaicin or bradykinin elicits a sympatho-excitation [3]. It is important to recognize that afferent nerve activity arising from both kidneys and heart passes to the same nuclei in the brain stem and medulla, that is, to the nucleus of the tractus solitarius (NTS), rostral venterolateral medulla (RVLM) as well as the paraventricular nucleus (PVN) where their input signals are integrated in order to generate a patterned sympathetic output. These relationships are outlined in Fig. 1.

Although the basic neurophysiological pathways underlying the cardiorenal syndrome have been described, the question arises as to whether there may be any functional consequences. At a clinical level there is increasing evidence for some interaction between the renal and cardiac sensory systems. A key advance has been the application of novel techniques in man to partially ablate the renal innervation. Initial studies were undertaken in 'resistant' hypertensive patients which showed that such renal nerve ablation led to a small but long lasting reduction in blood pressure [4]. Since the initial studies larger and more wide ranging clinical trials have begun to strengthen the view that sensory information arising in the kidneys can be one factor causing a sympathetically mediated increase in blood pressure. Since these initial studies examining a specific set of resistant hypertensive patients, interest has widened to examine the impact of renal nerve ablation on other patient groups including those with heart failure and metabolic and obese related disorders. Indeed, a recent metanalysis study

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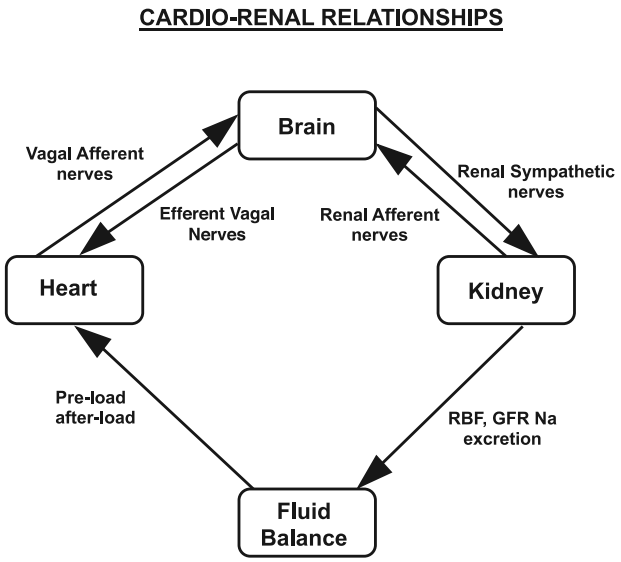

Fig. 1 The kidney has both afferent and efferent sympathetic innervation which underly the neural basis of reno-renal reflexes, both inhibitory and excitatory. These reflexes regulate renin secretion, glomerular filtration rate, renal blood flow and sodium and water excretion which determine the level at which fluid volume is set. Similarly, the heart, innervated by both vagal afferent and efferent nerves, ensures that blood pressure is regulated appropriately in response to everyday activity. The volume of fluid in the circulatory system will itself impact on heart function and provide a link between the heart and kidney which underlies the cardiorenal syndrome

[5] reported that the reoccurrence of atrial fibrillation following pulmonary vein isolation was substantially reduced if renal nerve ablation was also performed. There are now increasing reports of similar beneficial effects of renal nerve ablation in other forms of heart failure [6].

The publication of Honetschlägerová and co-workers [7] attempts to add further information and understanding of the functional impact on heart and kidney of renal denervation in a rat model of heart failure with reduced renal function. This model had been previously developed by this group and was one having a high output cardiac failure and hypertension with an elevated expression of the endogenous renin-angiotensin system, a reduced renal function together with a sympatho-excitation as reflected by raised intrarenal norepinephrine levels.

The model involved construction of an aortico-caval anastomosis in the heterogeneous REN-2 transgenic rat (REN-2 TGR) strain [8] and undertaking functional studies three weeks later as the model moved from a compensated to a decompensated phase in which there was increasing mortality. The impact of bilateral renal denervation on cardiovascular and renal functional characteristics was investigated. It is important to note that in these studies, the creation of the aortico-caval anastomosis itself reduced blood pressure compared to the hypertensive level in the sham operated group. Nonetheless, bilateral renal denervation caused a further significant reduction in blood pressure in the heart failure group compared with the heart failure group with an intact renal innervation. A significant point arising from experimental scenario would be that afferent information arising from the kidney was contributing to the sympatho-excitation and raised blood pressure in the REN-2 TGR model. A significant feature was that renal denervation of the heart failure group had minimal impact on either renal blood flow or glomerular filtration rate compared to the heart failure group with an intact renal innervation. By contrast it became evident that in terms of fluid handling, urine flow, absolute and fractional sodium excretion, these variables were much lower in the heart failure compared to the sham control REN-2 TGR. However, those REN-2 TGR subjected to bilateral renal denervation, water and sodium excretion was elevated compared to the intact REN-2 TGR heart failure group. This again would suggest that a raised renal sympathetic nerve activity was exerting an antidiuretic and antinatriuretic influence on tubular fluid reabsorption.

To further evaluate how in heart failure the neural control of kidney function might be disturbed, studies were undertaken to examine whether autoregulation of renal haemodynamics and pressure diuresis and natriuresis relationships were impacted. It was evident that in the heart failure REN-2 TGR, renal denervation resulted in a slightly higher renal blood flow compared to rats with an intact renal innervation at all pressure levels but particularly at or below the autoregulatory limit. By contrast, glomerular filtration rate in the heart failure REN-2 TGR was well maintained over the greater part of the autoregulatory curve, unlike the decreased observed in the sham operated REN-2 GFR. Thus, a raised sympathetic outflow to the kidney which occurs in heart failure would impair maintenance of renal blood flow, but not glomerular filtration rate, particularly at lower pressures. The mechanisms underlying this differential impact on renal blood flow versus glomerular filtration rate is unclear but does point to other intrinsic mechanisms within the kidney possibly related to the renin-angiotensin system or other signalling mechanisms regulating glomerular filtration pressure. An essentially similar pattern was observed in relation to the pressure diuresis and natriuresis relationships in the REN-2 TGR in that in the absence of the renal innervation, fluid excretion was higher at all renal perfusion pressure levels tested. Together, these observations would suggest that removal of the influence of the renal innervation would offer a better chance of fluid mobilisation in a state of heart failure.

The importance of this report [7] is that it does provide a functional framework underlying the experimental neurophysiological evidence for the cardiorenal syndrome. Furthermore, it does add weight to the clinical studies focused on the value of renal denervation in man which may reduce

mortality and morbidity in heart failure. A note of caution has to be raised in that the experimental model utilised is one of high output heart failure which may not accurately reflect the situation in the patient cohorts with cardiac disease. Nonetheless, this report does represent an important step in our knowledge base in understanding the basis of the cardiorenal syndrome pointing to renal nerve ablation as a potential effective therapeutic avenue.

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Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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