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Renal Denervation, Blood Pressure and Metabolic Disease: Not a Simple Solution

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Diabetes, obesity, cardiovascular disease and hypertension are frequently grouped together as the 'metabolic syndrome'. The prevalence of these diseases is increasing in the United States and worldwide. In recent years, overactivity of the sympathetic nervous system has been linked to obesity, hypertension, and cardiovascular disease [1]. Promising initial research investigated the role of the sympathetic nervous system in hypertension: renal denervation using catheter-based radiofrequency ablation is an innovative clinical treatment for drug-resistant hypertension, and has been reported to cause sustained blood pressure reduction for up to three years (Symplicity-2 trial) [2]. Animal studies have shown complete reversal of hypertension by renal denervation [3] by lowering the increased renal sympathetic drive. However, more recent studies show much less compelling results.

Negative Results of Renal Denervation

In early 2014 it was announced that the most recent renal denervation trial did not reduce blood pressure 6 months after treatment compared to sham treated controls (Symplicity 3 trial) [4], contradicting previous unblinded trials. Possible reasons for these study differences include bias due to subject selection, medication adherence, lack of statistical power, lack of blinding, or inappropriate controls. Most importantly, *there was no confirmation that the renal vessels were denervated*: some results suggest a correlation between the degrees of nerve injury with the reduction in blood pressure [5], which was not accounted for in either study.

Required Studies

There is a dearth of adequately controlled physiological studies, and recent editorials recommend additional preclinical and clinical studies to optimize treatment efficiency [6].

A recent study demonstrated a heterogeneity in the location of sympathetic peri-arterial renal nerves in human subjects, with more efferent than afferent nerve fibers, more nerves in the proximal location of the artery than distal, and in the ventral rather than dorsal [7]. Thus, the point of contact of the single catheter must be rigorously controlled to ensure nerve ablation, which may not have occurred in previous studies. This has led to the development of other devices using a more complete contact.

Neural regrowth can occur, which may make renal denervation only a temporary treatment, and studies in sheep have demonstrated that responses to stimulation were normal 11 months after denervation, indicating regeneration [8], however the nerve regeneration rate in humans is not clear. It is currently unclear whether the long term hypotensive effect of renal denervation is due to sustained denervation, or other secondary mechanisms.

However, confirming nerve ablation in humans is difficult: some data indicates that renal denervation can cause a reduction in norepinephrine spillover of approximately 40%, but this is highly variable [9], and has so far not been linked to the degree of blood pressure reduction.

Before any clinical application of renal denervation is used as a treatment, knowledge of the mechanisms by which it reduces blood pressure or improves metabolism is required. Recent studies have begun to address the mechanism of the antihypertensive effect of denervation [10], which can include alterations in the renin-angiotensin system, the oxidative stress response, and vascular endothelial function and inflammation [10,11]. More advanced knowledge of the mechanisms by which renal denervation can reduce blood pressure would allow for more effective and perhaps less invasive, treatments to achieve the same outcome.

Still Hope? Metabolic and Cardiac Effects of Renal Denervation

While there is still hope that renal denervation, when performed correctly, may treat hypertension, effects in other organs and systems may again spark interest in renal denervation as a treatment. Sympathetic nervous system activation can modulate metabolism: systemic nervous system inhibition improves glucose metabolism and carotid body denervation prevents the development of insulin resistance and hypertension [12], suggesting an effect of the sympathetic nervous system on glucose metabolism. However, the non-specific action and adverse effects of systemic nervous system inhibition have led to low adherence for therapeutic use, which supports investigation of targeted tissue-specific denervation in clinical treatment.

Surprisingly, clinical renal denervation improved fasting glucose and insulin, and reduced insulin resistance one year after treatment [2] but a longer follow-up schedule has not yet been evaluated. The

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latter study also reported that 8% of patients resolved their diabetes to pre-diabetes, and 11% improved from pre-diabetes to normal glucose tolerance within three months of the procedure. This effect was not supported by a more recent study, which showed no improvement in insulin sensitivity 6 or 12 months after denervation [13], however this study was lacking a control group, and did not demonstrate any reduction in sympathetic nerve activity after denervation. Our own pilot renal denervation data in the obese, normotensive dog model demonstrates improvements in insulin resistance and glucose metabolism, suggesting that renal denervation may improve glucose metabolism without blood pressure changes. Coincident left ventricular hypertrophy and diastolic function was also improved 6 months after renal denervation, without a significant relationship to blood pressure [14], thus there are wide ranging potential cardiovascular and metabolic effects that remain to be clarified. Nevertheless, the mechanism(s) by which renal denervation may improve glucose metabolism or cardiac function remain unknown, one study suggested that beneficial effects of renal denervation on insulin sensitivity or blood pressure are independent of each other [13], which tends to discount the theory that a reduction in sympathetic activity *per se* is responsible for both actions.

Conclusion

Initial promising clinical results for renal denervation have been hampered by poorly controlled studies and a lack of knowledge about renal artery physiology. In addition, a recent study has also discussed the potential of other organ damage by thermal injury with catheter-based ablation [15]. Without appropriate preclinical studies, it is difficult to know the efficiency and percentage of nerve ablation, and the long term effects of renal denervation are still uncertain. Many companies have been developing their own renal denervation devices and procedures in response to the initial promising studies from Symplicity [2] and metabolic benefits may eventually allow these to be repurposed for treating diabetes. However, continuing clinical studies without adequate preclinical data may be premature: it is necessary to unravel the relationship between the sympathetic nervous system, glucose metabolism and general function of a number of organs, as the sympathetic nervous system remains an intriguing target for treatment of cardiovascular and metabolic disease.

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