Austin Journal of Cardiovascular Disease and Atherosclerosis

Open Access

Austin Publishing Group

Editorial

Does Renal Denervation Inhibit Atherosclerosis in Humans?

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Received: May 28, 2015; **Accepted:** August 27, 2015; **Published:** September 25, 2015

Editorial

Renal sympathetic nerve activity in hypertensive patients is increased [1]. Renal Denervation (RDN) may decrease blood pressure in humans by decreasing renal sympathetic nerve activity. This hypothesis was first tested by the proof-of-principle Symplicity HTN-1 trial (N=45) [2] which showed that RDN lowered office systolic blood pressure by 22 mm Hg at 6 months in patients complicated with resistant hypertension. Later, the randomised but not sham-controlled nor blinded Symplicity HTN-2 trial (N=106) confirmed the effectiveness of RDN in lowering blood pressure [3]. Subsequently, RDN has become a standard treatment option for patients with resistant hypertension in many countries. RDN was then regarded as the possible cure for resistant hypertension [4], and may significantly decrease the morbidity and mortality of cardiovascular diseases including myocardial infarction and stroke [5], diseases with atherosclerosis being a major underlying cause.

A large number of clinical trials showed that RDN decreased blood pressure; however a few clinical trials with a small sample size did not demonstrate the blood-pressure-lowering effect of RDN [6,7]. In 2014, the Symplicity HTN-3 trial (N=535), the first trial on RDN with a single-blinded and sham-controlled design, failed to show a blood-pressure-lowering effect of RDN [8]. The disappointing results from the Symplicity HTN-3 trial prompted widespread re-evaluation of the efficacy of RDN in humans.

Evidence Against the Application of RDN in Humans

Several lines of evidence argue against the application of RDN in humans

(1) RDN does not consistently decrease blood pressure. The Symplicity HTN-3 trial [8] and a few other trials [9,10] failed to show a blood-pressure-lowering effect of RDN. In addition, even in the studies which showed that RDN decreased blood pressure, the non-responder rate (defined as a reduction of systolic blood pressure <10 mm Hg) was still substantial. For example, the non-responder rate was 15% at 12 months after RDN in the Symplicity HTN-1 trial [11]. In addition, the results from 10 European Expert Centres (N=109) [12] showed that office systolic blood pressure was increased in 22.9% of patients six months after the procedure. It has been reported that RDN could occasionally lead to hypertension crisis [13], indicating that RDN is not beneficial for every patient with resistant hypertension.

(2) RDN may promote renal artery stenosis [14]. RDN is generally regarded as a safe procedure [2,3,8]. The Symplicity HTN trials reported that the rate of renal artery stenosis after RDN was low, ranging from 0.3% to 2.2% [2, 3, 8]. However, some studies with small sample sizes reported that renal artery stenosis occurred at a higher rate, ranging from 2.8% to 18.2% [12, 15, 16].

(3) Long-term beneficial effects of RDN are yet to prove. The Symplicity HTN-1 trial is the clinical trial on RDN which has longest follow-up, *i.e.* 3 years [11]. After a 3-year follow up, patients in this trial would not continue to be formally followed up. In that 3-year report of the Symplicity HTN-1 trial [11], estimated glomerular filtration rate (eGFR) was decreased (P=0.05) and the creatinine concentrations in the serum were increased (P=0.05) [11]. Whether the decline in renal function in those renal denervated patients was due to natural history or due to RDN is not known, as this trial lacks a control group. Therefore, long-term beneficial effects of RDN need to be established [17, 18].

Evidence Supporting the Application of RDN in Humans

Several lines of evidence support the application of RDN in humans

(1) RDN, if done properly, decreases blood pressure. The Symplicity HTN-3 trial failed to show the efficacy of RDN in lowering blood pressure. This may be resulted from multiple reasons [19], among which incomplete sympathetic denervation may, at least in part, explain the failure of the Symplicity HTN-3 trial [20].

(2) RDN may have other benefits beyond its effect on blood pressure. For example, Mahfoud et al [21] reported that RDN improved glucose metabolism and insulin sensitivity. In this report (N=37 for the RDN group and N=13 for the control group), fasting glucose was reduced from 118 mg/dL at baseline to 108 mg/dL (P=0.039) at 3 months after RDN. Similarly, insulin levels were decreased from 20.8 μIU/mL to 9.3 μIU/mL (P=0.006), and insulin resistance decreased from 6.0 to 2.4 (P=0.001). There were no significant changes in metabolic markers in the control group [21]. RDN may also provide benefits for patients complicated with heart failure, myocardial hypertrophy, arrhythmias and chronic renal disease [22].

RDN Inhibits Atherosclerosis in Mice Whereas its Anti-Atherosclerotic Effect in Humans is Yet to be Investigated

Another line of evidence supporting the application of RDN in humans is the recent report that RDN inhibited atherosclerosis in mice [23]. Wang el al performed RDN/sham surgery in apolipoprotein

Citation: Wang Y. Does Renal Denervation Inhibit Atherosclerosis in Humans?. Austin J Cardiovasc Dis Atherosclerosis. 2015; 2(1): 1013.

E-deficient mice fed on a Western diet (N=8 in the RDN group and N=8 in the sham control group) to investigate the effect of RDN on atherosclerosis [23]. The authors found that RDN had no effect on blood pressure (101.0 mm Hg for the sham control group versus 97.5 mm Hg for the RDN group; P=0.25). However, atherosclerosis was smaller in the aortic tree (including the aortic arch, brachiocephalic arteries, common carotid arteries, and subclavian arteries) of the denervated mice compared with that in the sham control group, as assessed by oil-red-O staining. It showed that the oil-red-O staining positive area (%) was 4.2% in the RDN group; whereas it was 6.3% in the sham control group (P<0.05). In addition, similar results were obtained from the lesion area in the aortic root (normalised to the respective media area of the aorta). The reduction in lesion size was associated with reduced aldosterone levels (206.8 pg/mL for the RDN group versus 405.5 pg/mL for the sham control group, P<0.05), monocyte chemoattractant protein-1 (51.7 pg/mL for the RDN group versus 91.7 pg/mL for sham control group, P<0.05), and 8-isoprostane, a marker of oxidative stress (331.9 pg/ mL for the RDN group versus 468.5 pg/ mL for the sham control group, P<0.05).

It is worthwhile to note that the sample size (N=8) of the study by Wang et al [23] is relatively small. In addition, these mice in Wang et al's study [23] are normotensive, which is different from the clinical setting that most of the patients undergoing RDN are hypertensive. Moreover, the mode of renal denervation in mice is different from the clinical setting, and in the latter setting radio frequency energy is most commonly used to destroy nerves in the renal artery. Therefore, whether RDN reduces atherosclerosis in humans needs to be explored. If RDN is proved to inhibit atherosclerosis in humans, it will benefit a large proportion of aged patients who are at higher risk of atherosclerosis.

Summary

The disappointing results from the Symplicity HTN-3 trial prompted widespread re-evaluation of the efficacy of RDN in humans. There exist several lines of evidence either against or supporting the application of RDN in humans. The recent finding that RDN inhibited atherosclerosis in mice gives new hope for the application of RDN in humans as RDN may inhibit atherosclerosis in humans independent of its effect on blood pressure. However, clinical trials are needed to investigate this hypothesis.

Acknowledgement

The author is funded by a grant from the National Health and Medical Research Council (1062671).

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