Clinical Kidney Journal

ckj

OXFORD

Leading European Nephrology

Clinical Kidney Journal, 2017, vol. 10, no. 6, 776–777

doi: 10.1093/ckj/sfx095
Advance Access Publication Date: 9 October 2017
Editorial Comment

EDITORIAL COMMENT

Renal artery intervention utilizing carbon dioxide angiography

Alan A. Sag, MD[1], Baris Afsar, MD[2] and Mehmet Kanbay, MD[3]

[1]Division of Interventional Radiology, Department of Radiology, Koc University School of Medicine, Istanbul, Turkey, [2]Division of Nephrology, Department of Medicine, Suleyman Demirel University School of Medicine, Isparta, Turkey and [3]Division of Nephrology, Department of Medicine, Koc University School of Medicine, Istanbul, Turkey

Correspondence and offprint requests to: Mehmet Kanbay; E-mail: mkanbay@ku.edu.tr, drkanbay@yahoo.com

Abstract

Carbon dioxide angiography is an established non-nephrotoxic option for imaging of the infradiaphragmatic arteries and veins. Safe performance of the technique once required a somewhat cumbersome system, however, recent innovations have simplified implementation and expanded the user base for this technique. As such, patient access has also increased. In this issue, Hameed *et al.* provide initial feasibility data regarding carbon dioxide angiography and renal denervation therapy. This experience may be translated into future renovascular interventions in patients with limited renal reserve.

Key words: angiography, carbon dioxide, denervation, digital subtraction, hypertension

In this issue of *Clinical Kidney Journal*, Hameed *et al.* [1] present feasibility data for carbon dioxide (CO_2) angiography during renal denervation in 11 patients with estimated glomerular filtration rates <45 mL/min/1.73 m^2. In brief, the image guidance is safe and effective. Given the homogeneity of renal denervation patients (owing to strict inclusion criteria), the external generalizability of this study to renal denervation patients is already valid. However, the majority of resistant hypertensive patients will have some component of renovascular atherosclerosis and the external generalizability of CO_2 to the renovascular hypertensive population at large will need further testing in larger trials including atherosclerotic patients. This information should not be expected from the current study because it was not part of its design.

Inclusion criteria were as expected for a renal denervation trial. Of note, patients had to be hypertensive and resistant to three antihypertensive medications. Although this is consistent with other studies on the matter, it would have been ideal to know the proportion of thiazide-resistant patients who were also resistant to angiotensin-converting enzyme (ACE) inhibitors. These two pathways are purported to be interrelated [2] and it is possible that renal denervation may be most useful for patients resistant to both of these medications in that sequence. This is specific to renal denervation–eligible patients but may apply to patients with renovascular atherosclerosis as well. Specifically, the purported ischaemic effects of constant microembolic burden from haemodynamically significant atherosclerotic plaques may confound the underlying crosstalk of physiologic pathways and the external generalizability of combined resistance to thiazides and ACE inhibitors may therefore be questioned.

Calcific atherosclerosis was an exclusion criterion since it precludes adequate catheter–true vessel wall contact and limits energy delivery to the sympathetic nerves therein. It is noteworthy that the pre-procedure evaluation of these patients employed non-contrast computed tomography (CT). CT is

Received: July 15, 2017. **Editorial decision:** July 16, 2017

useful for identifying calcified plaque, however, it cannot reliably determine the presence of non-calcified intimal plaque, which has a higher chance of causing intraprocedural embolization and may also hamper energy delivery into the vessel wall. One significant improvement to this study would have been rigorous documentation of non-calcific atherosclerotic burden of the treated vessels as detected by CO_2 angiography. This finding may have correlated with treatment success as well and will certainly be an important determinant of whether CO_2 can be used safely. Stated differently, if CO_2 does not provide enough resolution to adequately assess the burden of non-calcified atherosclerosis in the renal artery, then it will likely not be superior to traditional contrast angiography and will remain a niche modality for patients with tenuous renal function.

The presumed lack of clinically relevant atherosclerosis provides a relatively level playing field for CO_2 angiography to perform since no detailed stenosis or gradient pressure measurements are necessary for renal denervation, as would be for an atherosclerotic case [3]. As expected, this limits the external generalizability of this study to atherosclerotic intervention, since renal denervation is not as imaging intensive as angioplasty and stenting of an ostial renal artery plaque, for example. One purported benefit of CO_2 would be that imaging can be repeated with no nephrotoxic repercussions. However, one downside would be technical limitations with imaging during detailed stent placements, specifically for cases in which operators prefer to inject contrast via the side port to 'check' the vessel as they are deploying the stent.

The clinical follow-up of post-interventional patients was quite successful in this study. As such, the secondary aim of this article was to report on short-term outcomes after renal denervation in the context of severe renal failure. Severe renal failure purports a significant reduction in the reserve of salvageable nephrons. Despite this limited reserve, this study was able to demonstrate trends towards reduced albuminuria and improved blood pressure in the face of a stable (not worsening) creatinine level. While the data would have been more solid if these trends had reached statistical significance, given the small sample size, achieving statistical significance was unlikely and the lack of statistical significance does not detract from the value of such a pilot study, rather it is hypothesis generating and spurs the need for a more significant follow-up study.

Given the success of this pilot study, the next step would be to repeat the study with a larger data set. It is possible that nephrotoxic contrast agents cause harm to the nephrons we are trying to salvage. CO_2 and renal denervation may prove to be a valuable combination therapy for the niche of renovascular hypertensive patients with severely limited renal function. Future advances in imaging may help quantify this hidden 'penumbra' of nephron reserve and help guide appropriate therapy in such patients [4]. Specifically, it would be interesting to determine whether only cortex penumbra is important or whether the presence of medullary penumbra helps in the selection of patients who will respond favourably to therapy. Although these patients should always be followed for the most relevant clinical endpoint of blood pressure reduction, secondary endpoints of blood pressure stabilization and renal function stabilization should also be included in the statistical analyses from such studies.

The detailed natural history of hypertension and kidney injury in non-atherosclerotic renovascular hypertensive patients undergoing renal denervation therapy is not yet well known, and the underlying mechanism of renal denervation success may relate to a complex network of post-intervention crosstalk. As such, the post-interventional course, outcomes and treatment durability may not overlap completely with patients undergoing successful intervention for global renal ischaemic atherosclerotic renovascular hypertension. For example, it is possible that the non-atherosclerotic patient population from the current study would have more penumbra (both cortex penumbra and medullary penumbra) than the average atherosclerotic patient who has had a protracted prodrome of atherosclerotic cholesterol microemboli. Future concepts may include tailored sympathetic intervention where one or both kidneys are treated based on split renal function physiologic testing in the context of penumbra, similar to the atherosclerotic paradigm of bilateral renal intervention for global renal ischaemia secondary to atherosclerotic plaque causing renovascular hypertension.

Conflict of interest statement

None declared.

References

1. Hameed SMA, Freedman JS, Watkin R *et al*. Renal denervation using carbon dioxide renal angiography in patients with uncontrolled hypertension and moderate to severe chronic kidney disease. *Clin Kidney J* 2017; 10: 776–777.
2. Sag AA, Sal O, Kilic Y *et al*. The concept of crosstalk-directed embryological target mining and its application to essential hypertension treatment failures. *J Clin Hypertens (Greenwich)* 2017; 19: 530–533
3. Sag AA, Sos TA, Benli C *et al*. Atherosclerotic renal artery stenosis in the post-CORAL era part 2: new directions in transcatheter nephron salvage following flawed revascularization trials. *J Am Soc Hypertens* 2016; 10: 368–377
4. Sag AA, Inal I, Okcuoglu J *et al*. Atherosclerotic renal artery stenosis in the post-CORAL era part 1: the renal penumbra concept and next-generation functional diagnostic imaging. *J Am Soc Hypertens* 2016; 10: 360–367