Author’s response to reviews

Title: Case report: Bilateral renal artery stenosis as a cause of refractory intradialytic hypertension in a patient with end stage renal disease.

Authors:
Zachary Wolfmueller (zaw917@mail.usask.ca)
Kunal Goyal (kunalgoyal@yahoo.com)
Bhanu Prasad (bprasad@sasktel.net)

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Author’s response to reviews:

Dear Dr. Henderson,

Thanks for the opportunity to respond back to the suggestions of the reviewers. I am responding on behalf of all the co-authors. Please see my responses after individual questions.

Peter Van Buren, MD, MSCS (Reviewer 1):

1. I think it is necessary to provide more specific objective information on blood pressure data and weights throughout the course of management. For example, prior to the intervention, it would be useful to see the pre and post dialysis blood pressure and weights during the period of dry weight reduction. This same information is necessary regarding the post intervention period. This detailed information is necessary to fully understand the magnitude of the impact that the intervention presumably induced.

Answer: Thanks for the suggestion and we apologize for the oversight. The patient’s weights and blood pressure data are now included in the case description.
2. The potential for RAS and FMD to induce the overall hypertensive state is explained in the discussion, but what is not addressed is how this would affect the intradialytic rise in blood pressure. This is the defining criteria of intradialytic hypertension and still remains poorly understood.

Answer: The potential for RAS and FMD to induce IDH is reviewed in the last paragraph of the case discussion. We hope the changes are acceptable to the reviewer.

Eiji Ishikawa, M.D., M.P.H. (Reviewer 2):

1. I could not see the data of patient's body weight or body mass index on case report. Was this patient obese or not? Lower dry weights are known to risk of intradialytic hypertension.

Answer: The patient’s body weight, dry weight and BMI are now included in the case description.

2. Volume overload plays a significant role in poorly controlled blood pressure in hemodialysis patients. I could not understand the patient's dry weight was appropriate because no data about dry weight such as human atrial natriuretic peptide level or cardiothoracic rate on chest X-ray were shown on case report.

Answer: Thanks for raising this important clinical point. We based our judgement of fluid status based on clinical examination. There was no peripheral edema and the lungs were clear on auscultation. We did not measure BNP or organize a CXR prior to her intervention. Clinically, we were confident that she was euvolemic.

3. I could not find several clinical data for blood pressure on hemodialysis patients such as ESA dose, use of NSAIDs for rheumatoid arthritis and Ca concentration of dialysate. The dose of antihypertensive drugs are also unknown.
Answer: The contents of the patient’s dialysate bath, ESA dose, NSAIDs and antihypertensive doses are now included in the case description. We apologize for the oversight.

4. Even in the same patient, it is known that blood pressure fluctuation differs for each dialysis session. So by averaging blood pressure during three consecutive dialysis and graphically showing time transition before and after the renal angioplasty, we will be able to better understand the IDH and antihypertensive effect of the renal angioplasty.

Answer: The patient’s average blood pressures over 3 sessions pre and post treatment have now been included in the case description. No graph has been included.

5. I could not find whether antihypertensive effects developed from just after the renal angioplasty or not.

Answer: We have phrased the case report in such a way to make it clear that the blood pressure improved by 30 systolic points post intervention. We hope that the revision meets the reviewers approval.

6. Why did intradialytic hypertension improve by bilateral renal angioplasty? Information should be needed on how humoral factors such as renin, aldosterone and catecholamines changed after the procedure. The authors should also show how much improvement in renal artery pressure difference before and after renal angioplasty.

Answer: We have now added a few lines in the last paragraph of the discussion. The patient still had a residual urine output and we were aware of the need to restrict the use of contrast to preserve her urine output. Pressure studies are not commonly done in our institution in patients with CKD or ESRD with urine output due to the potential of additional contrast exposure influencing adverse outcomes.
3rd reviewer (Dr. Sarafidis):

1. Report of all available definitions of IDH in a very short introductory paragraph is clearly superfluous. Apart from the two first, the others are obviously wrong and are not used currently. Again, citing all these studies is not necessary. I suggest describing the two most prevalent definitions and citing this review from Inrig et al, along with the most recent comprehensive review in the field, from Georgianos et al. Hypertension. 2015 Sep;66(3):456-63. Doi

Answer: As suggested, we have limited the definitions of IDH. There was overlap between the 2 papers and we have cited Ingrid et al.

2. As above, a sentence on the most important pathophysiology mechanisms is essential in the first paragraph

Answer: We have added a couple of sentences about the pathophysiology of IDH earlier in the discussion.

3. Please report the ESRD cause of the pts brother. Is it APKD?

Answer: We have added the cause of ESRD in the manuscript.

4. What about her mother? could it be intracranial aneurysm rupture ? Complications of hypertension is too general

Answer: She died in Ethiopia and had no access to medical facilities. The patient is certain being informed that her mother died of complications of blood pressure, but cannot remember any specifics. We cannot add any further information in the manuscript.
5. Maternal transmission of what??

Answer: The statement has been amended.

6. Details of IDH prior to operation are absolutely necessary – graph of BP with ABPM or at least pre- and postdialysis BP for 6 sessions, as we report herein IDH and not only uncontrolled BP.

Answer: We note an overlap with a similar question from one of the other reviewer. We have added data on three consecutive dialysis pre intervention and six sessions post intervention. The data supports that there was an improvement in blood pressures post intervention.

7. The paper would be greatly improved by addition of details of the current status of the pt – i.e. time after the procedures, BP with ABPM or at least home BP or at least pre- and postdialysis BP for 6 sessions, as we report herein IDH.

Answer: Thank you for the suggestion. We have added the necessary information.

8. Discussion The paper needs addition of recent data on treatment of patients with IDH are added. The first RCT in this important field has just published (Bikos et al, J Hypertension 2018) and should be cited. Until that, using β-blockers or RAS blockers came from empirical evidence.

Answer: Thanks again for making us aware of this important paper that addresses the issue of pharmacotherapy in ESRD. We have included the citation Bikos et. al in the case discussion on the management of IDH.

9. The paragraph of RDN should be removed this was note done – RDN is now not indicated in any patient – data for ESRD are very scarce and ambiguous.
Answer: We concur with the reviewer and the paragraph has now been removed from the discussion.

10. Further, the authors jumped to RDN without first checking for SECONDARY CAUSES of hypertension, which is a mistake. If the pt had adequate diuresis, there could have been also other secondary causes involved – though on such cases it is clear that underlying RAS is the cause. We have experience of at least 10 pts with secondary causes in dialysis, among which 3 with exactly this problem.

Answer: We concur with the reviewer. The discussion suggests that we jumped to RDN but in practice all the secondary causes were excluded. While the non contrast CT of the abdomen failed to identify an adenoma -- it also did not comment on the stenosis of the renal arteries. We thus assumed that she didn't have renal artery stenosis and jumped to RDN, which as documented was a rookie mistake.

11. Given the wrong pathway the authors took, it is of utmost importance to clearly discuss the possibility of a secondary cause as above. This would help the readership going through this interesting case. The should refer to and cite the recent position statement Sarafidis et al Hypertension in Dialysis – NDT or J Hypertens 2017

Answer: We agree with our mistake and we apologize for the wrong clinical path. Sarafidis et al has been cited in the case discussion on secondary causes of hypertension.

12. The possibility of RAS as a cause of both ESRD and uncontrolled hypertension should be also discussed. The authors should cite Sarafidis PA. Blood Press. 2016;25(2):123-8

Answer: We have addressed the issue in the discussion. We have also cited Sarafidis PA. Blood Press. 2016;25(2):123-8. We thank him for the suggestion and guidance in completing this manuscript.
We hope that the manuscript if accepted will be of value to your readers.

Bhanu Prasad, MRCP, FRCPC

(On behalf of all the co-authors).