PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A Retrospective Morphometric Study of the Suitability of Renal Arteries for Renal Denervation According to the Symplicity HTN2 Trial Criteria
AUTHORS	Schönherr, Elisabeth; Rehwald, Rafael; Nasseri, Parinaz; Luger, Anna; Grams, Astrid; Kerschbaum, Julia; Rehder, Peter; Petersen, Johannes; Glodny, Bernhard

VERSION 1 - REVIEW

REVIEWER	Prof Murray Esler Baker IDI Heart and Diabetes Institute Melbourne Australia I have received research grants, honoraria and meeting travel support from Medtronic related to renal denervation
REVIEW RETURNED	27-Jul-2015

GENERAL COMMENTS	The authors have performed a detailed morphometric analysis of human renal arteries, based on retrospective, consecutive formal analysis of renal CT angiograms generated during during abdominal CT angiography. This was done because of the relevance of anatomical knowledge of this type to the catheter-based denervation of the renal nerves as a treatment for patients with resistant hypertension. The study group was not patients with severe hypertension, or patients scheduled for renal denervation. The authors document an influence of laterality on renal artery dimensions (typically shorter left main renal artery, but with larger diameter) and of gender (smaller dimensions in women). They report a substantially greater number of instances of main renal artery length less an 2 cm, and diameter less than 4 mm than were reported in the Symplicity HTN trials; these dimensions are relevant, having been exclusions in Symplicity HTN2 (Lancet 2010;376:1903-1909). The authors suggest that some patients, in error, may have been included in the Symplicity HTN trials, rather than being excluded as per experimental protocol. This leads them to conclude (page 11) that in catheter-based renal denervation trials "the lack of success of denervation can be attributed to the absence of the required anatomical conditions". This, I believe, is untenable. Other reasons than this have been substantiated for failure to lower blood pressure in renal denervation trials, most notably in Symplicity HTN 3 (J Am Soc Hypertens 2014;8:593-598). Further, it is helpful to recall why these particular renal artery dimensions (less than 2 cm length, less than 4 mm diameter) were

	chosen as criteria for exclusion from the Symplicity HTN trials. The intention was to deliver spirally placed, spaced doses of radiofrequency energy, to ensure circumferential energy delivery to ablate all nerves of passage, but not on a single vessel circumference, to minimize artery damage subsequently leading to stenosis or aneurysm. A main renal artery length of 2 cm would allow 5 RF doses, 5 mm apart, thought to be adequate for denervation. A diameter of 4 mm was chosen to minimize vascular risk from over-heating. It was never established experimentally that trial inclusion of main renal arteries less than 2 cm long, or less than 4 mm in diameter would cause renal denervation failure. In a sense the renal denervation field has move on, so that the precise anatomical findings of the authors are now less pertinent that they once would have been. New experimental research establishes that FR energy should be delivered into the renal artery divisions and the distal main renal artery. The length of the main renal artery is of less concern. Further, the need for spiral, spaced energy delivery, which was always conceptual only, was probably overstated; secondary artery stenoses are very uncommon and aneurysms unknown. The introduction of multi-electrode denervation catheters, which are more tolerant of anatomical deviations, also somewhat undercuts the clinical relevance of the morphometric renal artery findings reported here. I also have more additional, specific comments for the authors. 1. The authors suggest explicit informed consent was not required, for this retrospective use of CT angiographic data which was available, and generated independently for clinical purposes. I have sympathy with their position, but others might dispute it. 2. No mention seems to have been made of renal artery atherosclerosis which might have influenced derived vessel diameters. 3. The referencing of the introduction could have been better. Earlier surgical sympathectomy for hypertension did not specifically target the renal nerves (a theory of their importance in hypertension pathogenesis did not exist). Surgical denervation results in experimental hypertension were the important specific antecedent. The Lancet reference (reference 18) was actually of an accompanying editorial, rather than the positive France-based DENERHTN trial. 4. The conceptualization that an ellipsoid renal artery cross section might influence catheter placement, torque and success or otherwise of attempted denervation (page 10) is novel and interesting.

REVIEWER	Sebastian Ewen UKS Homburg Klinik für Innere Medizin III Germany
REVIEW RETURNED	29-Jul-2015

GENERAL COMMENTS	Schönherr et al. analyzed in a retrospective cohort study the renal arteries of 126 patients undergoing high-contrast CTAs. The authors summarized that based on these measurements, the anatomical situation as a reason for exclusion of denervation appears to be significantly more common than previously suspected. Since this can be the cause of the failure of treatment in some cases, further development of catheters or direct percutaneous approaches may

	improve success rates. This is an interesting paper. However, I have some major concerns which should be addressed before publication. 1. The authors should combine their data with procedural outcome to prove their theses. 2. The authors state that they included 126 consecutive patients. Please be more specific and explain the number of patients enrolled more precisely. 3. How many investigators performed the analysis of the CTAs? 4. Did the CTA analyses with the procedural parameters of the RDN? 5. Did any parameter predict the outcome of the RDN procedure?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Prof. Murray Esler
Baker IDI Heart and Diabetes Institute, Melbourne, Australia
Please state any competing interests or state 'None declared':
I have received research grants, honoraria and meeting travel support from Medtronic related to renal denervation
Please leave your comments for the authors below

Comments to the Author
Item #1-1
The authors have performed a detailed morphometric analysis of human renal arteries, based on retrospective, consecutive formal analysis of renal CT angiograms generated during abdominal CT angiography. This was done because of the relevance of anatomical knowledge of this type to the catheter-based denervation of the renal nerves as a treatment for patients with resistant hypertension. The study group was not patients with severe hypertension, or patients scheduled for renal denervation.

This is a correct description of what we did, and therefore does not entail any changes in the manuscript.
Item #1-2
The authors document an influence of laterality on renal artery dimensions (typically shorter left main renal artery, but with larger diameter) and of gender (smaller dimensions in women). They report a substantially greater number of instances of main renal artery length less an 2 cm, and diameter less than 4 mm than were reported in the Symplicity HTN trials; these dimensions are relevant, having been exclusions in Symplicity HTN2 (Lancet 2010;376:1903-1909).
This is a correct summary of parts of our results, and the comparison we undertook between our data, and the frequency of the application of the exclusion criteria having been adopted for the Symplicity HTN2-Study (Lancet 2010;376:1903-1909). The statement does not entail any changes in the manuscript.
Item #1-3
The authors suggest that some patients, in error, may have been included in the Symplicity HTN trials, rather than being excluded as per experimental protocol. This leads them to conclude (page 11) that in catheter-based renal denervation trials "the lack of success of denervation can be attributed to the absence of the required anatomical conditions".
This, I believe, is untenable.
We fully agree with the reviewer, that the statement "the lack of success of denervation can be attributed to the absence of the required anatomical conditions" is untenable.
In order to address the criticism of the reviewer, we took different measures.
In a first step, we removed the conclusion that in catheter based renal denervation trials "the lack of

success of denervation can be attributed to the absence of the required anatomical conditions" from the manuscript. Changes occurred in the discussion part of the manuscript: The sentence "the lack of success of denervation can be attributed to the absence of the required anatomical conditions", which was enclosed in the manuscript at two locations (discussion) disappeared from the manuscript.
In a second step we clarified our suggestion, that some patients in error may have been included in the Symplicity HTN trials, rather than being excluded as per experimental protocol (page 9, line 30 – page 10 line 5 and following). We quoted the Symplicity HTN2-Study (Lancet 2010;376:1903-1909): "Before randomization, patients underwent "renal artery anatomical screening with renal duplex", computed tomography, MRI, or renal angiography to confirm anatomical eligibility" (page 10, line 5 – line 6), and discussed, that especially duplex sonography underestimates the number of renal arteries, quoting Zhang et al, (Zhang HL, Sos TA, Winchester PA, Gao J, Prince MR Renal artery stenosis: imaging options, pitfalls, and concerns Prog Cardiovasc Dis, 2009; 52 (3): 209–219; page 10, line 7-line 9), and that this may be another cause for the remarkable low frequency of multiple renal arteries reported in HTN-2.
Moreover, the existence of additional renal arteries is not even taken into account in the most studies, and the method is "notoriously operator-dependent" (Vasbinder GB, Nelemans PJ, Kessels AG, Kroon AA, de Leeuw PW, van Engelshoven JM. Diagnostic tests for renal artery stenosis in patients suspected of having renovascular hypertension: a meta-analysis. Ann Intern Med. 2001 Sep 18;135(6):401-11); page 10, line 9 – line 10).
The two new references have been inserted into the manuscript as reference 30, and reference 31 (page 10, line 8, 9, and 10). They can be found in the reference list on page 16, line 26 – line 31.
Moreover, the technical specifications for the Duplex-Sonographies MR-angiographies, and the CT-angiographies that were required for the inclusion or exclusion of patients were not defined, or are not available any more (The link to the online-information of HTN-2 leads to the Ardian website, which does not contain the information any more). In a short sentence in the discussion section we inserted the statement, that the detection rate of renal arteries depends on the imaging technique, the image quality, and appropriate assessment of the examinations (page 10, line 13 – line 17), and that, for example, some artifacts, or unsatisfactory contrast opacification may result in a detection failure (page 10, line 15 – line 17). The changes found their way into the paragraph 2 on page 10 dealing with the possible explanations for the low frequencies indicated for multiple renal arteries in the HTN-2 study (Lancet 2010;376:1903-1909)

Item #1-4
Other reasons than this have been substantiated for failure to lower blood pressure in renal denervation trials, most notably in Symplicity HTN 3 (J Am Soc Hypertens 2014;8:593-598).
We fully agree with the referee.
We included the paper the referee quoted: "Esler M. Illusions of truths in the Symplicity HTN-3 trial: generic design strengths but neuroscience failings. J Am Soc Hypertens. 2014 Aug;8(8):593-8. doi: 10.1016/j.jash.2014.06.001. Epub 2014 Jun 12.", and described briefly the key points from the paper in our discussion section:
The failure to lower blood pressure in renal denervation trials, most notably in Symplicity HTN 3 may have been due to
- The paucity of experience of cardiologists with renal denervation technique in the beginning, and the fall of their learning curve during the trials
- The fact that "one-third of operators performed one procedure only",
- "the failure to apply a confirmatory test for renal denervation"
- If a tests was applied, "denervation was found to be incomplete and nonuniform between patients", and therefore
- "it is probable that the degree of denervation has typically been suboptimal in renal denervation trials".
These explications can be found on page 11, second paragraph, line 13 – line 23 now and the publication "Esler M. Illusions of truths in the Symplicity HTN-3 trial: generic design strengths but

neuroscience failings. J Am Soc Hypertens. 2014 Aug;8(8):593-8. doi: 10.1016/j.jash.2014.06.001. Epub 2014 Jun 12." has been inserted as reference 38 (page 11, line 14 and line 38), and added to the literature list on page 17, line 9 – line 10. The Symplicity HTN-3 Study has been quoted as well (page 11, line 14), and found its way into the references list as reference 39 (page 17, line 12 – line 13).
Additionally, a statement was inserted into the discussion section of the manuscript, that the central proposition of Esler explaining the failure of the renal denervation trials, namely, "denervation was found to be incomplete and nonuniform between patients" is in perfect accordance with a hypothesis in the present paper, that some arteries may have been missed unintentionally, and unwittingly due to the fact that they may have been underestimated prior to the inclusion of the patients into the studies. This point, which was already included in our manuscript, has been emphasized on page 11, line 21 – line 23.
Item #1-5
Further, it is helpful to recall why these particular renal artery dimensions (less than 2 cm length, less than 4 mm diameter) were chosen as criteria for exclusion from the Symplicity HTN trials. The intention was to deliver spirally placed, spaced doses of radiofrequency energy, to ensure circumferential energy delivery to ablate all nerves of passage, but not on a single vessel circumference, to minimize artery damage subsequently leading to stenosis or aneurysm. A main renal artery length of 2 cm would allow 5 RF doses, 5 mm apart, thought to be adequate for denervation. A diameter of 4 mm was chosen to minimize vascular risk from over-heating. It was never established experimentally that trial inclusion of main renal arteries less than 2 cm long, or less than 4 mm in diameter would cause renal denervation failure.

We fully agree with the reviewer.
As it is actually helpful to recall why these particular renal dimensions were chosen as criteria for exclusion from the Symplicity HTN trials in our discussion section as well, we take the following measures in order to include this information into the manuscript.
In a first step we stated that the criteria (longer than 2 cm, with a diameter greater than 4mm) had been chosen arbitrarily in the beginning, in order to ensure circumferential, spirally placed energy delivery to ablate all nerves of passage, but not on a single vessel circumference in order to minimize artery damage. This statement has been inserted into the discussion section on page 11, line 24 – line 25. We clarified, that the criteria were never established experimentally prior to the initiation of the Symplicity studies (page 11, line 25 – line 26), and that it was never established, that inclusion of renal arteries falling below a length of 2cm, or a diameter of 4mm, results in denervation failure (page 11, line 33 – page 12 line 1).
In a second step, we inserted the initial rationale for these criteria, that "A main renal artery length of 2 cm would allow 5 RF doses, 5 mm apart, thought to be adequate for denervation", and "a diameter of 4 mm was chosen to minimize vascular risk from over-heating". These two sentences can be found on page 11, line 26 – line 30.
Then we stated that a shortfall below the inclusion criteria does not imply denervation failure necessarily, but rather smaller magnitudes of success, or, in some cases, even the same magnitude of success (page 11, line 34 – page 12 line 1).
Item #1-6

In a sense the renal denervation field has move on, so that the precise anatomical findings of the authors are now less pertinent that they once would have been.

Again, we fully agree with the reviewer.
We inserted this estimation into the discussion section, behind the causes for it, which are subject to the following Item #1-7 of the same reviewer. It can be found on page 13, line 3 – line 5.
Item #1-7

New experimental research establishes that FR energy should be delivered into the renal artery divisions and the distal main renal artery. The length of the main renal artery is of less concern. Further, the need for spiral, spaced energy delivery, which was always conceptual only, was probably overstated; secondary artery stenoses are very uncommon and aneurysms unknown. The introduction of multi-electrode denervation catheters, which are more tolerant of anatomical deviations, also somewhat undercuts the clinical relevance of the morphometric renal artery findings reported here.

This issue corresponds to Item #1-6 of the same reviewer, and the measures taken in order to reflect it found their way into the manuscript together with those described above (Item #1-6).
As this point is the cause of the estimation regarding the importance of anatomical conditions of renal arteries in renal denervation, which is subject to Item #1-6 of the same reviewer, the changes made in order to include these important points into the manuscript were placed behind of the estimation itself (page 13, line 3 – line 5), on page 13, line 6 – line 16.
First, the findings that the radiofrequency energy should be delivered into the renal artery divisions, and the distal main renal artery, and that the length of the main renal artery is of less concern found their way into the manuscript (page 13, line 9 – line 13).
Secondly, we stated that the habit to deliver energy at several different points with a distance of at least 5mm, arranged in a convoluted pattern was conceptual in order to avoid complications such as stenoses or aneurysms, which are very seldom (stenoses), or completely unknown (aneurysms). This can be found on page 11, line 26 – line 32. These safety measures may have been overstated (page 11, line 32). Moreover, the development and introduction of new catheters such as multi-electrode denervation catheters “somewhat undercuts the clinical relevance of the morphometric renal artery findings” (page 13, line 3 – line 5), “so that the precise anatomical findings of the authors are now less pertinent that they once would have been”, a statement which found its way into the manuscript on page 13, line 4 – line 5 (see Item #1-6 of the same reviewer).
However, this does neither resolve the problem of the frequency of multiple renal arteries (multiple renal arteries are much more frequent than reported in the renal denervation studies, see Item #1-2 of reviewer 1), nor the problem of the sometimes very small diameters of additional renal arteries, which are, nevertheless, accompanied by renal nerves as well.
The problem of frequency of additional or accessory renal arteries has been addressed above (Item #1-2).
In order to illustrate the latter issue, we inserted a sentence into the results section of the manuscript stating how many arteries were smaller than 3 mm at 2 cm distal their origin, how many were smaller than 2 mm, and how many were smaller than 1.5 mm (page 8, line 32 – page 9, line 2). Moreover, we inserted a short sentence into the discussion section on how many patients exhibit additional arteries smaller than 3, or 2 mm, or 1.5 mm at 2 cm distally to their orifices, precluding treatment even with newest devices (page 12, line 2 – line 4).
Item #1-8
I also have more additional, specific comments for the authors.
1. The authors suggest explicit informed consent was not required, for this retrospective use of CT angiographic data which was available, and generated independently for clinical purposes. I have sympathy with their position, but others might dispute it.

Thank you very much for this advice. It’s correct, explicit informed consent was not required. We used CT angiographic data, which were generated independently for clinical purposes. Data were de-identified. No patient records were viewed, and therefore clinical data are missing. This information was not changed, as it is correct.
We simply clarified in the material and methods section that data were de-identified (page 5, line 5, and page 6 line 14), and added the clause, that clinical data were not used (page 5, line 14 – line 15).
Item #1-9

2. No mention seems to have been made of renal artery atherosclerosis which might have influenced derived vessel diameters.

In order to address this comment, we took the following measures.
All data sets were retrieved again, and subjected to an assessment of the Friesinger Score, which was proposed by Friesinger et al in 1970 (Friesinger GC, Page EE, Ross RS. Prognostic significance of coronary arteriography, Trans Assoc Am Physicians, 1970; 83: 78–92). Initially the method was used to subjectively classify the degree of atherosclerosis in human coronary arteries, but, however, it can be applied in other territories like the renal arteries as well.
The method was mentioned and explained in the material and methods section, which can be found on page 7, line 11 – line 16 now, and the reference was inserted as reference 27 (page 7, line 16).
The reference itself can be found in the references section on page 16, line 17 – line 18.
The results found their way into the results section of the manuscript, and can be found on page 8, line 5 – line 6 now. Overall, there was only little atherosclerosis in the 300 renal arteries observed. An influence on the derived vessel diameters could not be observed. The statistical analysis was done as follows: A spearman rho was determined for the relation between the vessel diameters and the Friesinger score.
The Correlation Analysis method was inserted into the “statistical analysis” section (page 7, line 22–line 24), and the analysis itself can be found on page 9, line 10 – line 12.
The results have been discussed briefly in one sentence, which can be found in the discussion section on page 12, line 23 – line 26.
Item #1-10

3. The referencing of the introduction could have been better. Earlier surgical sympathectomy for hypertension did not specifically target the renal nerves (a theory of their importance in hypertension pathogenesis did not exist). Surgical denervation results in experimental hypertension were the important specific antecedent.

In order to address this comment of the reviewer exhaustively, we took the following measures.
Only in order to clarify a point: we did not quote publications regarding “Earlier surgical sympathectomy for hypertension”, as was stated by the referee.
However, as we fully agree with the referee, we removed the quotations regarding supra- and infradiaphragmatic splanchnicectomies, combination procedures, and non-selective, open surgical renal denervation which were performed beginning in the 1930s of the last century in a first step. This is acceptable, because the history of surgical renal denervation does not greatly matter in the context of the modern catheter based endovascular renal denervation procedures. So ultimately, references 10, 11, 12, 13, 14, and 15 have been removed from the manuscript. All following references have got new numbers, accordingly.
We, of course, fully agree with the reviewer regarding the surgical denervation results in experimental hypertension which were the important specific antecedent of the endovascular renal denervation procedures.
Therefore, in a second step, we inserted this literature into the manuscript. As the literature regarding surgical renal denervation procedures in different experimental hypertension animal models, as well as in different normotensive animals is so comprehensive, we inserted the following important and outstanding original and review papers into the manuscript:
- Schlaich MP1, Sobotka PA, Krum H, Whitbourn R, Walton A, Esler MD. Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. Hypertension. 2009 Dec;54(6):1195-201. doi: 10.1161/HYPERTENSIONAHA.109.138610. Epub 2009 Oct 12.
- Bravo EL, Rafey MA, Nally JV Jr. Renal denervation for resistant hypertension. Am J Kidney Dis. 2009 Nov;54(5):795-7. doi: 10.1053/j.ajkd.2009.07.005. Epub 2009 Sep 6
- DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. Am J

Physiol Regul Integr Comp Physiol. 2010 Feb;298(2):R245-53. doi: 10.1152/ajpregu.00647.2009. Epub 2009 Dec 2. Review.
- Hendel MD, Collister JP. Renal denervation attenuates long-term hypertensive effects of Angiotensin ii in the rat. Clin Exp Pharmacol Physiol. 2006 Dec;33(12):1225-30.
- Katholi RE, Winternitz SR, Oparil S. Decrease in peripheral sympathetic nervous system activity following renal denervation or unclipping in the one-kidney one-clip Goldblatt hypertensive rat. J Clin Invest. 1982 Jan;69(1):55-62.
They found their way into the manuscript at the place from which the former references 10, 11, 12, 13, 14, and 15 have been removed. We stated briefly, according to the suggestion of the reviewer, that "Surgical" renal "denervation results in experimental hypertension were the important specific antecedent" to the modern possibilities of catheter based renal denervation procedures. This can be found on page 4, line 15 now. The newly inserted references have the numbers 10, 11, 12, 13, and 14 (page 4 line 15), and can be found in the references section on page 14, line 40 – page 15 line 12

Item #1-11
The Lancet reference (reference 18) was actually of an accompanying editorial, rather than the positive France-based DENERHTN trial.
Thank you very much for finding this glitch, the erroneous quotation of the accompanying editorial to the France based DENERHTN trial. We corrected the quotation and inserted the correct one:
Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, Midulla M, Mounier-Véhier C, Courand PY, Lantelme P, Denolle T, Dourmap-Collas C, Trillaud H, Pereira H, Plouin PF, Chatellier G; Renal Denervation for Hypertension (DENERHTN) investigators. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet. 2015 May 16;385(9981):1957-65. doi: 10.1016/S0140-6736(14)61942-5. Epub 2015 Jan 26. PMID: 25631070,
which can be found on page 4, line 18 as reference 18 now, and in the reference section on page 15, line 26 – line 29.

Item #1-12

4. The conceptualization that an ellipsoid renal artery cross section might influence catheter placement, torque and success or otherwise of attempted denervation (page 10) is novel and interesting.

Thank you very much for this assessment!
This comment did not entail any changes in the manuscript.

Reviewer #2: Dr. Sebastian Ewen
Universitätsklinikum des Saarlandes und Medizinische Fakultät der Universität des Saarlandes
Innere Medizin III - Kardiologie, Angiologie und internistische Intensivmedizin
Please state any competing interests or state 'None declared': Nothing to declare
Please leave your comments for the authors below

Comments to the Author
Item #2-1
Schönherr et al. analyzed in a retrospective cohort study the renal arteries of 126 patients undergoing high-contrast CTAs.

That's exactly what we did.
Item #2-2

The authors summarized that based on these measurements, the anatomical situation as a reason for exclusion of denervation appears to be significantly more common than previously suspected.

Correct.
Item #2-3
Since this can be the cause of the failure of treatment in some cases, further development of catheters or direct percutaneous approaches may improve success rates. This is an interesting paper. However, I have some major concerns which should be addressed before publication.

Thank you very much for this assessment ("This is an interesting paper")!
The conclusions from our work have been have been described correct. There's nothing to change upon these comments.
Item #2-4
The authors should combine their data with procedural outcome to prove their theses.

As was already stated in the manuscript, there was no procedural outcome of any intervention. This information was clarified on page 5, line 9 now.
However, we further clarified this issue by repeating the statement that no renal denervation was done by us (contained in the discussion section of the manuscript on page 13, line 22 – line 23) explicitly and immanently in the first paragraph, page 11, line 6 for example, and in other locations throughout the manuscript.
Item #2-5
The authors state that they included 126 consecutive patients. Please be more specific and explain the number of patients enrolled more precisely.

Done as requested.
Briefly, we looked through all computed tomographic abdominal angiographies which had been made between 1.1.2010 and 5.6.2014. In order to ensure good segmentability, we sought for examinations with high radiation dosages, and high contrast medium dosages at the same time. As both preconditions are usually avoided by radiologists in order to respect the ALARA principle, dosage "as low as reasonably possible", 126 high irradiation dosage examinations with a contrast opacification of more than 300 hounsfield units in the aorta, as described in the manuscript (page 5, 3rd paragraph, line 17 – line 26) could be identified. Moreover, computed tomographies of the body during an arterial contrast medium phase do not require irradiation dosages as high as in parenchymal contrast medium phases due to the high contrast discrimination brought about with the dense opacification.
In order to fulfill this request of the referee, we inserted the time interval in which we searched for the examinations into the manuscript, which can be found on page 5, line 22, and inserted the number of examinations which had been ruled out due to motion artifacts, incomplete depiction of the kidneys and the aorta in the arterial phase, and irradiation dosage which have been too low for segmentation of the renal arteries. These numbers can be found on page 5, line 21 – line 24 in the material and methods section of the manuscript now.
As the technical parameters indicated in the text were used as inclusion criteria as well, the order of the inclusion and exclusion criteria section, and the technical parameters section has been interchanged, because the order seemed to be more logical after insertion of the new information on the frequency of exclusions. The technical parameters section can be found on page 5, last paragraph, and page 6, first paragraph, the inclusion and exclusion criteria section can be found as third paragraph on page 5
Item #2-5
How many investigators performed the analysis of the CTAs?

The analyses of the CTA's were performed by two investigators in consent, after initial assessment of the anatomic situation by a third investigator. After the segmentation process, the result was checked by a third investigator, as well as the documentation of the segmentation process. The approximately 60.000 measured values have been transferred to an excel sheet, de-identified, and checked by a third one, as well as prior to the statistical analysis by another one.
The assessments of pathologies were done by two board certified radiologists in consensus. These informations have been included into the manuscript and can be found on page 6, line 15.
Item #2-6
Did the CTA analyses with the procedural parameters of the RDN?

This point corresponds to Item #2-1 of the same reviewer.
No RDN had been performed in these patients, an information which was already included in the manuscript. However, due to this misunderstanding, this issue has been clarified as outlined in the answer for Item #-2-1.
The new passage can be found in the materials and methods section on page 5, line 15 – line 16.
Item #2-7

Did any parameter predict the outcome of the RDN procedure?

As clarified above, no RDN procedures had been performed. The clarification can be found in the manuscript on page 5, line 15 – line 16.
Usually, radiation dosages as high as they were applied in the present patients are not necessary in computed tomographic angiographies prior to renal denervation, and therefore we are facing the dilemma, that in patients treated with renal denervation no CT angiography is available, which is at least nearly sufficient for the segmentation process, and that in patients with high-quality (high irradiation dosage) CT-angiographies of the kidneys (mostly due to other indications, regarding the parameters up to the individual decision of the radiologist on duty) no renal denervations have been done.
In terms of exactness, there is no alternative to the CT-angiography studies.
Performing high dose CT-angiographies as used here (which were available due to other clinical problems) prior to renal ablations on purpose seems to be unethical; we disapprove making such an application proposal.
However, we included the statement that a prospective observational study using standard CT-angiographic technique or MRI angiographic technique performed prior to renal denervation procedures should be performed, even if the vessels cannot be segmented from the data sets – the informations will possibly be extractable from these examinations too, when a loss of exactness is accepted.

This proposal can be found on page 13, line 13 – line 16.

Correction of (minor) mistakes (The authors)
1. On the former page 5, second last line, we found the following mistake: "The tube voltage was 0.6 seconds",
This mistake was corrected:
"The tube voltage was 120 KV, the period of revolution was 0.6 seconds…"
This change can be found on page 6, line 6.
2. In the abstract, two mistakes have been corrected, these were transmission errors from the excel sheet to the word document.

Mistake 1: Length of the first right artery must be "45.9 ± 15 mm"
This change can be found on page 2, line 10.

Mistake 1: Diameter of the first right artery must be “4.9 ± 11.2 mm”
This change can be found on page 2, line 11.

Correction of typing errors, grammar, inauspicious style, and wrong tenses
The manuscript has been corrected by a native English speaker. The minor changes that were made are highlighted in the red-line version, but not enumerated here, as they were of minor importance, without changing the sense in any location of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Murray Esler Senior Director Baker IDI Heart and Diabetes Institute Melbourne, Australia I have received research grant support, honoraria and travel support from Medtronic. I am a recipient of payment for laboratory procedures from Kona Medical
REVIEW RETURNED	15-Sep-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Dr. Sebastian Ewen Klinik für Innere Medizin III; 66421 Homburg; Germany
REVIEW RETURNED	17-Sep-2015

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.