Author's response to reviews

Title: When the Chimney is Blocked: Malignant Renovascular Hypertension after Endovascular Repair of Abdominal Aortic Aneurysm

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Version: 2 Date: 14 February 2013

Author's response to reviews: see over
Editor, BMC Nephrology

Dear editor,

Re: resubmission of manuscript 2942676978512872 entitled "When the Chimney is Blocked: Malignant Renovascular Hypertension after Endovascular Repair of Abdominal Aortic Aneurysm"

Thank you very much for your kind e-mail of January 7th, 2013 containing your editorial letter together with the valuable comments of the reviewers.

As requested, we have edited the manuscript and are now submitting the revisions. Please see below our response to the points raised by the reviewers. We have highlighted all the changes in the manuscript by crossing through deleted items in blue and marking additions in underlined red. We trust that we can now satisfy the reviewers’ and your requests.

Thank you very much for considering the publication of this work in BMC Nephrology.

Sincerely,

Gil Chernin M.D

Director, Nephrology Clinic

Tel-Aviv Medical Center
Reviewers' comments:

Reviewing: 1

1. Throughout the article, "GC" is used multiple times, however "CG" should be used as abbreviation for Chimney Graft.

Response: We corrected the abbreviations throughout the manuscript.

Abstract:

2. Please delete "to open the occluded stent" to enable correct interpretation by the reader.

Response: We have changed the whole sentence and it now (p.2, line 17): "Any attempt to recanalize the covered stent or revascularize the left kidney was rejected and conservative treatment was chosen."

Introduction:

3. line 4: change "patient" to "patients".

Response: As requested, we changed to patients.

4. line 22: change "placing of a parallel stent grafts" to "placing of parallel stent Grafts".

Response: As requested, we changed to "placing of parallel stent Grafts".

5. line 23: change "aneurism" to "aneurysm"

Response: As requested, we changed to "aneurysm".

6. line 24: change "involves a standard" to "involves standard"

Response: As requested, we changed to "involves standard".
7. line 25: change "cover to one" to "coverage of one"

Response: As requested, we changed to "coverage of one".

Case presentation:

8. **Please provide more technical details. What type and size of main body endograft was used for the aorta? What size Adventa stent was used for the chimney graft? Please state explicitly if this was a self-expanding or balloon-expandable stent and if this was a covered or bare metal stent.**

Response: We have added (p.6, line 4): "Thirteen months before admission, an elective endovascular aneurysm repair (EVAR) operation was performed to repair a rapidly expanding AAA with a diameter of 5.3 cm. EVAR with Endurant endograft (Medtronic, Minneapolis, MN) was combined with a Chimney procedure into the left renal artery, using a balloon expandable covered stent-graft (7x38 mm Advanta V12; Atrium Medical Corp). The Chimney technique was used due to irregular aortic neck with posterior ulceration and high difference of right renal artery origin, 10mm above the left renal artery origin. Antiplatelet therapy with clopidrogel (75 mg/day) was initiated after the surgery. During the 6th month follow-up an abdominal computed-tomography (CTA) revealed a well functioning aortic stent and a patent CG (Figure1 A-B).

9. **Was there any kinking of the stent apparent, if not, please state so.**

Response: We have added (p.7, line 8): "However, a total occlusion of the CG to the left renal artery was noted (Figure1 C-D) without stent kinking."

10. **Last paragraph: change "as antihypertensive medications" to "as antihypertensive medication"**
Response: As requested, we changed to "as antihypertensive medication".

Conclusions:

11. *Should physicians have a higher threshold before stopping antiplatelet medications on these patients on the basis of your data? Please discuss in more detail.*

Response: We have extended the discussion and added (p.10 last 3 lines): "We believe that a reasonable approach before elective operation for patients with EVAR and GC, is to stop antiplatelet therapy, one week prior to elective surgery and to temporarily initiate anticoagulation treatment (e.g. subcutaneous Enoxaparin). Anticoagulation will be stopped, one day before the procedure, and antiplatelet therapy will be re-initiated in the second post-operative day."

12. *It could be worthwhile to discuss in more detail treatment strategies for occluded renal chimney grafts. What determined your decision to not perform an open or endovascular thrombectomy (I would assume the small kidney size)? Where would be your threshold for intervention? When thrombolysis and when open surgery? Please comment.*

Response: We have added (p.9 line 5): "The pathophysiology of renovascular hypertension, involves increased activation of the renin-angiotensin axis. Therefore, medical treatment was initiated and maintained with the angiotensin converting enzyme inhibitor, ramipril (14). Any attempt to recanalize the covered stent or revascularize the left kidney was rejected. The rational for our conservative approach was that the symptoms of malignant hypertension persisted for several days before presentation and that the left kidney was found to be small. We believe that revascularization of occluded renal artery
CG, should be considered in acute events without signs of prolonged ischemia to the affected kidney (15). Different invasive approaches of revascularization are possible, such as percutaneous endovascular therapy or distal bypass. There is lack of sufficient data to indicate which method of revascularization is preferable."
Reviewing: 2

MAJOR COMPULSORY REVISIONS

BACKGROUND

1. LINE 2-3: "to treat suprarenal and juxtarenal abdominal aortic aneurysms". Not only these types but also thoracic and thoracoabdominal aneurysms with supraortic branches orifice involvement. Moreover, common iliac artery aneurysms with or without internal iliac artery involvement can be included.


Response: We have added in the abstract (p.2 line 4) "... Other indications for the use of CG placement include thoracic and thoracoabdominal aneurysms with supraortic branches orifice involvement and cases of common iliac artery aneurysms with or without internal iliac artery involvement."
We also added in the Introduction section (p.5, line 6) "Possible indications for the use of CGs, other than treating suprarenal and juxtarenal abdominal aortic aneurysms, include thoracic and thoracoabdominal aneurysms with supraortic branches orifice involvement and suitable cases of common iliac artery aneurysms with or without internal iliac artery involvement (7,8).

2. **LINE 4: “fixation-zones”. You should better say “fixation and / or sealing zones.”**

By the way we all know that the term fixation has to do mainly with anchoring and the ability of the device - stent graft not to move (migrate). The term sealing mainly has to do with the ability of the stent graft to firmly attach against the wall to avoid blood flow towards the aneurismal sack. On the other hand chimney technique intents to solve issues of inadequate sealing and or fixation by simply translocating the sealing and or fixation zone more proximal or more distal (as branched endografts do). Fenestrated endografts do not translocate they only transform the unfavorable proximal (short neck, para, juxta) or distal landing zone into favorable.

Response: As suggested we have added "...and/or sealing zones".

3. **LINE 6: "to renal or other visceral branches" should be altered to "to renovisceral or supraortic branches."

Response: We have changed to "to renovisceral or supraortic branches."

**INTRODUCTION**

4. **LINE 1-3: support it with 1 reference**

Response: As suggested, we have added a reference.

5. **Line 6-7: "There is no consensus about the method of choice to repair suprarenal or juxtarenal AAA with complex proximal neck anatomy". These two**
types of AAA, do not have complex neck anatomy, to be honest they have no
neck at all, at least the way you imply in the phrase. If you have a suprarenal AAA
you do not have a neck problem, since you do not have an infrarenal neck at all.
You should always translocate or transform the chimneys or fenestrations or
branches, or hybrid techniques.

The definition of these aneurysms:

Infrarenal AAA with unfavorable infrarenal neck (short < 10mm, conical, bulged, calcified, thrombus (...)
*Juxtarenal AAA: arise distal to the renal arteries but in very close proximity to them.

Pararenal AAA: involve the origin of one or both renal arteries

Suprarenal AAA: encompass the visceral aortic segment containing the superior mesenteric and celiac arteries, and specifically are termed type IV thoraco-abdominal aneurysms if they extend upward to the crus of the diaphragm.

*)Definition by Crawford ES, Beckett WC, Greer MS. Juxtarenal infrarenal abdominal aortic aneurysm: special diagnostic and therapeutic considerations.

I believe you should alter your phrase to "There is no consensus about the method of choice to repair suprarenal or juxtarenal AAAs."

Response: As suggested, we have changed the text.
6. **LINE 9:** "...low risk patients." Support with 1 reference. You will use it later in the text in discussion.

Response: As suggested, we have added a reference.

7. **LINE 9:** "The standard EVAR procedure for suprarenal or juxtarenal AAA.". I don't think there is a "standard" procedure for these kind of AAAs. The "standard " EVAR for infrarenal AAAs is not intended for these aneurysms by the main indications of the technique (length of infrarenal neck, diameter, contour of the neck, angulation,...etc). Please rephrase or use the following proposal: " The standard EVAR procedure for infrarenal AAAs cannot be applied to suprarenal or juxtarenal AAAs since it is accompanied by high rate of adverse events including proximal endoleak, migration and mainly aortic side branches occlusion with possible renovisceral ischeamia ".

Response: As suggested, we have used the above proposal (thank you).

8. **LINE 14:** "..as a possible alternative that would...". "..alternative to open repair or standard EVAR techniques that would "....

Response: As suggested, we added"... to open repair or standard EVAR techniques.."

9. **LINE 15:** "...to the aortic side branches in possible stent-graft sealing zone ".

Rephrase to "...to the aortic side branches since the sealing and or fixation zone is translocated proximal or distal away from the target vessels ".

Response: We have changed the text as requested.

10. **LINE 16:** "stents" change to "endografts" or "stent grafts", since the covered stents that are used are easily available.

Response: We have changed to "stent grafts".
11. LINE 25-28: "Intentional....proximal seal". Do not report it here in the introduction. Move it to the discussion -conclusions.

As Suggested, we moved this paragraph to (page 8, line 10): "It is important to remember that intentional coverage of one of the renal arteries is sometime considered in cases with the need of CG into the superior mesenteric artery because of the risk that placing more than two CGs might compromise the proximal seal (10).

CASE PRESENTATION

12. LINE 18-24: readers would prefer a table I suppose.

Response: as suggested, we generated Table 1 with laboratory values.

13. LINE 25-27: "CTA demonstrated an endovascular stent of the aorta that was patent without a leak, dissection or migration." It would be better to say "CTA demonstrated an abdominal stent graft that was patent without endoleak, migration or dissection.

Response: As suggested, we have changed the text.

14. LINE 30: Ramipril is an ACE inhibitor. Was there any potential danger for renal insufficiency due to renal artery occlusion, and increased amount of iodine used in CTAs? Was that Medicine invaluable? Please explain.

Response: We believe that the pathophysiology of the severe hypertension in this case, involved increased activity of the renin-aldosterone axis. It is Similar to the pathophysiology that we see in hypertension due to unilateral renal artery stenosis.

Declining kidney functions after the initiation of ace-I, is a concern but with a contra-lateral normal kidney in imaging, we expect to have a process of compensation. Kidney functions were monitored regularly after the presentation without further elevation of
serum creatinine. We added in the conclusions (p.9, line 3) "The pathophysiology of renovascular hypertension, involves increased activation of the renin-angiotensin axis. Therefore, medical treatment was initiated and maintained with the angiotensin converting enzyme inhibitor, ramipril (14)."

As for the use of CTA- we agree that MRA would have reduced the risk of contrast-induced nephropathy. However, MRA was not available at presentation. The patient was treated with a rapid protocol of fluids to reduce the risk of nephropathy and serum creatinine levels were not elevated after the procedure. We added at the Case Presentation section (p.7, line 14): " and serum creatinine levels of 1.5 mg/dL. "

15. Since it is a case report please offer to readers more details and images concerning the morphology of the AAA before CG implantation. We should be able to understand if CG was invaluable for that morphology.

Response: We have added (p.6, line 5): " Thirteen months before admission, an elective endovascular aneurysm repair EVAR operation was performed to repair a rapidly expanding AAA with a diameter of 53 mm. EVAR with Endurant endograft (Medtronic, Minneapolis, MN) was combined with a Chimney procedure into the left renal artery, using a balloon expandable covered stent-graft (7x38 mm Advanta V12; Atrium Medical Corp). The Chimney technique was used due to irregular aortic neck with posterior ulceration and high difference of right renal artery origin, 10mm above the left renal artery origin. Antiplatelet therapy with clopidrogel (75 mg/day) was initiated computed-tomography after the surgery. During the 6th month follow-up an abdominal angiography (CTA) revealed a well functioning aortic stent and a patent CG (Figure1 A-B).
CONCLUSIONS

16. LINE 1-4: "The newer techniques of EVAR, such as the fenestrated, branched or CG techniques, can pose an increased risk of renal injury because of several mechanisms, including higher doses of nephrotoxic contrast media and instrumentation of the renal arteries, which can lead to emboli and inadequate revascularization". There are other reasons for potential renal injury as well:

(1) mechanical stenoses or kinking, (2) in-stent restenoses due to neo intimal hyperplasia. Please add and make it clear to the reader.

Response: We have added these causes of renal injury (p.8; line 5): "Other potential causes of renal injury are mechanical stenoses or kinking and in-stent restenoses due to neo intimal hyperplasia (4,8)."

17. LINE 11: "necessitating...". What are the indications for intervention according to your team or to the authors that you refer to?? It is important to know (and you should discuss it) when to operate on CG occlusion according to your team and to other authors. Also how to operate (distal by pass, thrombectomy, endoluminal??). This is very important apart from just reporting a case.

Response: We have added (p.9, line 6): "Any attempt to recanalize the covered stent or revascularize the left kidney was rejected. The rational for our conservative approach was that the symptoms of malignant hypertension persisted for several days before presentation and that the left kidney was found to be small. We believe that revascularization of occluded renal artery CG, should be considered in acute events.
without signs of prolonged ischemia to the affected kidney (15). Different invasive approaches of revascularization are possible, such as percutaneous endovascular therapy or distal bypass. There is lack of sufficient data to indicate which method of revascularization is preferable."

18. **Also it would be interested to know the endoleak rate of CG technique (from the references you report) which is the major drawback, I believe. Please add a short paragraph.**

Response: We have added (p.5, line10): "A potential major drawback of the EVAR procedures is the presence of endoleaks (*i.e.* persistent flow of blood into the aneurysm sac after device placement). Endoleaks were reported to complicate up to 25% of EVAR operations with CG placement. However, endoleak repair was not necessary in most cases (1)."

**MINOR ESSENTIAL REVISIONS**

**BACKGROUND**

19.LINE 7: "GC" should be "CG"

Response: We corrected the abbreviations of CG throughout the manuscript.

**CASE PRESENTATION**

20. LINE 5-6: "Conservative therapy was chosen without invasive intervention to open the occluded stent". Invasive intervention is not a term that is usually used. *it might be better to rephrase "Any attempt to recanalize the covered stent or revascularize the renal was rejected and conservative treatment was decided".*
Response: We have changed to "Any attempt to recanalize the covered stent or revascularize the left kidney was rejected and conservative treatment was chosen."

**INTRODUCTION**

21. **LINE 13**: "The so-called fenestrated...". *Erase the term "so-called"*

Response: As suggested we erased "so-called".

22. **LINE 22**: "...of a parallel stent grafts..." *It is stent graft.*

Response: We have changed to pleural: "...placing of parallel stent grafts...".

23. **LINE 30**: "Hereby we present a case of malignant hypertension that was caused by occlusion of a CG to the renal artery, as a novel etiology of renovascular hypertension." *You repeat the same word twice (hypertension).*

*Change it for" Hereby we present a novel etiology of malignant renovascular hypertension caused by a renal artery CG occlusion ".*

Response: As suggested, we have changed the phrase.

**CASE PRESENTATION**

24. **LINE 2**: "...were first noted...". *May be "...were initially noted..."*

Response: As suggested, we have changed the phrase.

25. **LINE 5**: "endovascular aneurysm repair (EVAR)". *You have explained the term above, so use only "EVAR" or full phrase without EVAR.*

Response: We have changed the phrase.
26. **LINE 6:** the same with abdominal aortic aneurysm (AAA).

Response: We have changed the phrase.

27. **LINE 5:** use repair instead of treat.

Response: We have changed the phrase.

28. **LINE 7:** it is Advanta not Adventa

Response: We have corrected to Advanta.

29. **LINE 7:** "and therapy with...", replace with "and clopidogrel was initiated 75 mg/day".

Response: As suggested, we replaced the sentence.

30. **LINE 9:** "A follow-up computed-tomography angiography (CTA) of the abdomen that was performed, five months before presentation with hypertension.....", You should better replace with "During the 6th month follow up an abdominal computed-tomography angiography (CTA) revealed ...."

Response: As suggested, we have replaced the text.

31. **LINE 10:** replace "A month" by "One month"

Response: As suggested, we have changed to "One month",

32. **LINE 11:** "...prior to an elective...". You could replace with "...in order to undergo an elective ..."

Response: As suggested, we replaced the sentence.

33. **LINE 25:** not " to the left renal" "into"

Response: As suggested, we replaced to "into".

34. **LINE 27:** erase "novel" and replace "complete" with " total" 

Response: As suggested, we replaced the sentence.
35. **LINE 28:** "In comparison with the previous CTA, the left kidney was small with poor enhancement by contrast material and hypodense wedge-areas. The lesions in the left kidney were compatible with the appearance of new foci of infarcts". It would be simple to rephrase "The left renal parenchyma was smaller compared to the previous CTA, with decreased contrast media uptake and hypodense wedge areas, indicative of multiple infarcts".

Response: As suggested, we replaced the sentence.

**CONCLUSION**

36. **LINE 7:** *not medium , better say "mid-term "*

Response: As suggested we have changed to "mid-term".

**AUTHOR CONTRIBUTION**

37. *"participated aas", it id "as "*

Response: We have corrected the typo.
Editorial points --

1. Acknowledgement Section

Following from the Authors' Contributions section, please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

Response: We have added a section for Acknowledgement.