Author's response to reviews

Title: Hemodialysis and hemodiafiltration differently modulate left ventricular diastolic function

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Author's response to reviews: see over
Dear Professor Henderson,

We would like to thank you for the suggestions which have contributed immensely to the improvement of our paper entitled „Hemodialysis and hemodiafiltration differently modulate left ventricular diastolic function”, Manuscript MS: 1736514151847771.
We have corrected the manuscript with the help of your suggestions and we hope that you will find it worth publishing in BMC Nephrology.

We provide a detailed point-by-point response to each of the referees' concerns, describing exactly how we responded to each point and where you can find the amendment in the revised manuscript.

Thank you very much for your patience and kind help.

Yours sincerely,

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Authors’ response to Reviewer I

We are highly grateful for your pieces of advice and remarks which have contributed to the improvement of the academic standards of our paper entitled „Hemodialysis and hemodiafiltration differently modulate left ventricular diastolic function”, Manuscript MS: 1736514151847771.

In the following we give detailed answers to your comments.

1. The transition zone between abnormal relaxation and restrictive filling is termed pseudonormalization and it is characterized by normal diastolic filling values \(E/A\), but \(E/A\) is not higher than 1.5. In order to differentiate between the normal and pseudonormal pattern, evaluation of the transmitral flow at peak Valsalva maneuver is advised. In the case of pseudonormal filling the trace reverts from normal to an abnormal relaxation pattern. Failure to revert reflects normal filling conditions. Moreover, velocities measured during tissue Doppler imaging \(E_a\) are less dependent upon preload and in addition to transmitral flow are useful in the evaluation of diastolic function. An \(E/E_a \leq 8\) in most circumstances predicts normal filling pressures. Deceleration time in the case of pseudonormalization has to be greater than 140 msec. Thus, in all subjects where \(E/A\) ratio was proved to be normal (between 1-1.5) and deceleration time was found to be above 140 msec, the possible pseudonormalization was evaluated with the measurement of \(E/E_a\) ratio, furthermore Valsalva maneuver was performed. Patients with pseudonormalization (relaxation pattern occurring during Valsalva maneuver and \(E/E_a \geq 10\) were not involved in the study.


The missing information was inserted to the text on page 6, lines 15-19.

During our investigations we established three categories according to the severity of diastolic left ventricular dysfunction. At the time of randomization 7 of our patients belonged to the severe group, 15 belonged to the medium, and 8 to the mild group.

The missing data has been inserted into the manuscript on page 6, lines 13-15.
2. Changes in E/Ea are depicted in Table 1. It was shown, that E/Ea decreased in both hemodialysis and hemodiafiltration. However, no statistically significant difference was found between the two renal replacement methods (p=0.37). Thus, it was concluded that in our study population hemodiafiltration did not bring better improvement of E/Ea compared to hemodialysis.

Regarding E/Ea measured before the beginning of the sessions we did not find statistically significant differences (12.56±3.56 vs. 11.65±4.49, p=0.14)

The missing data were inserted into the text on page 8, lines 1-4 and on page 11, lines 1-2.

3. Any condition or process that leads to stiffening of the left ventricle can lead to diastolic dysfunction. Most of our patients suffered from hypertension, hypertensive heart disease, ischaemic heart disease or previous myocardial infarction which are common in end stage renal failure and may lead to diastolic dysfunction.

**Exclusion criteria:** Any impulse generation or conduction disease which could affect echocardiographic findings, or makes it impossible to measure certain echocardiographic parameters. Thus, atrial fibrillation, where no atrial contraction appears and A wave cannot be detected during Doppler examination was an exclusion criterion. In the case of atrial flutter the evaluation of late diastolic transmittal velocity may not be easy to measure, so patients suffering from this type of arrhythmia were also excluded. Furthermore, patients with amyloidosis, sarcoidosis, carcinoid, hemochromatosis, and pericardial constriction were not involved in the study. Diabetes mellitus was also an exclusion criterion, since we intended to measure electrocardiographic parameters in our study population as well. Diabetes mellitus may cause autonomic dysregulation, and thus affect certain parameters of the surface electrocardiogram.

**Inclusion criteria:** Patients suffering from end stage kidney disease (Stage 5) participating in regular hemodialysis program in our center, who were willing to give their informed consent to take part in the study.

The missing information has been inserted into the manuscript on page 5, lines 1-10.

4. Our original aim was to examine changes in echocardiographic parameters during renal replacement therapy sessions. Since the follow up time was three years at this phase of our study we are unable to give a definitive answer about the long term effects of
hemodiafiltration on cardiac function and mortality. We would like to thank the referee for the reference (Ohtake et al). The results of this study are in accordance with our findings.

This reference was inserted into the text on page 10, line 23 and to our list of references on page 17, lines 3-5.

We plan to follow our study population for a longer period of time so, possibly, later additional data would clarify the role of hemodiafiltration on the cardiovascular outcome and echocardiographic features of our patients.

5. We have provided detailed data on laboratory results of NO and ADMA. The following table was inserted into the manuscript as Table 2.

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>HDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>NO (µmol/L)</td>
<td>30.3±7.6</td>
<td><strong>12.23±5.7</strong></td>
</tr>
<tr>
<td>ADMA (µmol/L)</td>
<td>0.69±0.2</td>
<td><strong>0.55±0.16</strong></td>
</tr>
</tbody>
</table>

6. The requested study limitation section has been inserted into the manuscript on page 12, line 17 as follows:

**Study limitation** The number of the studied patients is relatively small, however all patients suitable for clinical investigations were enrolled from our center. A larger study population would help to clarify the role of different renal replacement therapies on left ventricular diastolic function. The determination of the long term effects of hemodiafiltration on cardiac function was not possible during the present study, so further investigations are needed to get a clearer picture on this issue. Our results apply only to
our selected group of patients without rhythm abnormalities and a low frequency of coronary artery disease.

7. The text of our manuscript was rewritten in order to improve the style of the paper. All the changes are detailed as follows and highlighted in yellow colours in the revised paper.

1. Page 1, line 1: The word “differentially” was corrected to “differently”.
2. Page 2, line 4: Abbreviations NO and ADMA were clarified.
3. Page 2, line 4: “Clarified” was corrected to “clear”.
4. Page 2, line 6: “Were” was corrected to “was”.
5. Page 2, line 7: “Were receiving” was corrected to “received”.
6. Page 2, line 7: “For” was corrected to “over a period of”.
7. Page 2, line 8: Missing comma was inserted.
8. Page 2, line 12: “Left” was corrected to “the left”.
9. Page 2, line 13: “Left” was corrected to “the left”.
10. Page 3, line 4: “The dialyzed” was corrected to “these dialyzed”.
11. Page 3, line 5: “Adverse cardiac failure” was corrected to “heart failure”.
12. Page 3, line 8: “If” was corrected to “when”.
13. Page 3, line 9: “CKD patients” was corrected to “patients with chronic kidney disease”.
14. Page 3, line 19: Missing “an” was inserted.
15. Page 4, line 17: “Are” was corrected to “is”.
16. Page 4, line 23: “Another” was corrected to “further”.
17. Page 5, line 21: Missing “a” was inserted.
18. Page 5, line 21: Missing “and a” was inserted.
19. Page 7, line 13: “Made” was corrected to “carried out”.
20. Page 7, line 14: Missing “finally” was inserted.
21. Page 7, line 17: “Breathing” was corrected to “breathed”.
22. Page 7, line 17: “Did not talk” was corrected to “were not talking”.
23. Page 7, line 17: First appearance of NO was corrected to nitric oxide.
24. Page 7, line 19: Missing “an” was inserted.
25. Page 8, line 19: “At the 30th minute” was corrected to “after 30 minutes”.
26. Page 8, line 19: Missing “the” was inserted.
27. Page 8, line 21: “Reach the border of significance” was corrected to “had reached a significant level”.


28. Page 9, line 2: “At the 15th minute” was corrected to “after 15 minutes”.
29. Page 9, line 4: “Did not reach” was corrected to “had no”.
30. Page 9, line 5: “The diastolic values showed an increase” was corrected to “there was an increase in diastolic values”.
31. Page 10, line 5: Missing “a” was inserted.
32. Page 10, line 5: Missing “an” was inserted.
33. Page 10, line 22: “Could” was corrected to “were able to”.
34. Page 11, line 4: Missing “the” was inserted.
35. Page 12, line 2: Missing “the” was inserted.
36. Page 12, line 8: “CKD” was corrected to “chronic kidney disease”.
37. Due to a previous error the number of the sponsor was corrected on page 14, line 11

Once more, we would like to express our sincere gratitude for all the assistance given to us.
Authors’ response to Reviewer II

We are highly grateful for your pieces of advice and remarks which have contributed to the improvement of the academic standards of our paper entitled „Hemodialysis and hemodiafiltration differently modulate left ventricular diastolic function”, Manuscript MS: 1736514151847771.

In the following we give detailed answers to your comments.

1. According to the request the following sentence has been inserted into the study limitation section on page 13, lines 1-2: “Our results apply only to our selected group of patients without rhythm abnormalities and a low frequency of coronary artery disease.”

2. Most of our patients (17 subjects, 56% of our study population) refused to undergo kidney transplantation. Thirteen patients were on the transplantation list but did not get a transplant kidney. In 2009, when the randomization was started Hungary was not a member of Eurotransplant Group. This possibly led to the low frequency of transplantations at that time. Since 2011, four of these thirteen patients have been transplanted.

3. During hemodiafiltration 15.16±5 liters of ultrafiltrate was removed. The substitution fluid was prepared on-line from dialysis solution through a set of two membranes to purify it before infusing it directly into the blood line. The replacement solution was manufactured on-line from ultrapure water and consisted of 138 mmol/L sodium, 2 or 3 mmol/L potassium (in 13 cases 2 mmol/l in 17 cases 3 mmol/l), 1.5 mmol/L calcium, 0.5 mmol/L magnesium, and 1 g/L glucose. The blood flow was 338±11.6 ml/min and did not differ significantly during the respective procedures (p<0.05). The missing data have been inserted into the manuscript on page 6, line 23.

4. The hemodiafiltration technique was introduced in our hemodialysis center in May 2008. As we randomized our patients in March 2009, the average time of hemodiafiltration before starting our study was 11 months.
5. The text of our manuscript was rewritten in order to improve the style of the paper. All the changes are detailed as follows and highlighted in yellow colours in the revised paper.

1. Page 1, line 1: The word “differentially” was corrected to “differently”.
2. Page 2, line 4: Abbreviations NO and ADMA were clarified.
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