Author's response to reviews

Title: Fluid Overload in Hemodialysis Patients: A Cross-Sectional Study to Determine its Association with Cardiac Biomarkers and Nutritional Status

Authors:

Marlies Antlanger (marlies.antlanger@meduniwien.ac.at)
Manfred Hecking (manfred.hecking@meduniwien.ac.at)
Michael Haidinger (michael.haidinger@meduniwien.ac.at)
Johannes Werzowa (johannes.werzowa@meduniwien.ac.at)
Johannes Kovarik (johannes.kovarik@meduniwien.ac.at)
Gernot Paul (gernot.paul@wienkav.at)
Manfred Eigner (manfred.eigner@wienkav.at)
Diana Bonderman (diana.bonderman@meduniwien.ac.at)
Walter H Hoerl (walter.hoerl@meduniwien.ac.at)
Marcus D Saemann (marcus.saemann@meduniwien.ac.at)

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Author's response to reviews: see over
Reviewer's report

Title: Fluid Overload in Hemodialysis Patients: A Cross-Sectional Study to Determine its Association with Cardiac Biomarkers and Nutritional Status

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Reviewer: Paul Chamney

Reviewer's report:

MAJOR COMPULSORY REVISIONS
None.

MINOR ESSENTIAL REVISIONS
(1) Page 2, Abstract, Results: The following sentence is a little difficult to understand at first glance: “We detected predialysis fluid overload #15% of extracellular water (ECW) in 95 patients (39%; amount 22.9±4.8% ECW or 4.4±1.5L). Table 2, OH pre-HD [% ECW] offers a figure which appears to be related 22.9+/-4.9% but not accurately transcribed to the abstract. 4.4 +/-1.5 L. is the absolute fluid overload? Could I suggest two sentences for example: “We detected predialysis fluid overload (FO) in 39% of all patients (n=95) in the cases where FO was #15% of extracellular water (ECW). In this fluid overload subgroup the absolute FO was 4.4 +/-1.5 L or 22.9±4.8% of ECW”

Thank you very much for this comment; we agree that this part has previously lacked clarity and have adopted your suggestion. The table was corrected, as the standard deviation is, in fact, ± 4.8% (see page 25).

(2) Background, bottom of page 5: What is meant by “possibly higher intradialytic blood pressure changes” That the intradialytic blood pressure is higher, the blood pressure rises during dialysis?

We are referring to high ultrafiltration rates which are often accepted when patients arrive at the dialysis session with large interdialytic weight gains. Subsequent large withdrawals of extracellular water at these high rates are thought to be associated with blood pressure drops during the dialysis session. Interestingly, high interdialytic weight gains (with associated higher ultrafiltration rates) were not associated with higher mortality in this study, in contrast to chronic fluid overload. This will be discussed in further detail below. As for your remark, we replaced ‘change’ with ‘decline’ to enhance comprehensibility.

(3) Background, Page 6, 3rd paragraph. “All three institutions subsequently participated in the ‘BVM-Reg’ study on dry-weight reduction [27], which investigated whether blood volume monitoring (BVM)-adjusted ultrafiltration rates might reduce intradialytic symptoms associated with a rapid ultrafiltration process
in fluid overloaded hemodialysis patients [28, 29]." Could you explain shortly how
the BVM-Reg studies link in with the current study? It appears that this
manuscript focuses largely on fluid status, whereas the BVM-Reg studies are
aimed at the question of how best to remove the fluid and the impact on
intradialytic symptoms – no symptom data are presented in this manuscript which
could be associated with the prevailing fluid overload in each patient.

It is correct that the BVM-Reg study deals with removing fluid in hemodialysis
patients. The main inclusion criterion for the BVM-Reg study was fluid overload,
which was not only determined clinically, but with bioimpedance analysis (body
composition monitor). Patients exhibiting fluid overload ≥15% ECW (the same
definition used in the current study) were eligible for participation. We here present
the cross-sectional analysis of all participating dialysis centers, while the BVM-Reg
study dealt prospectively with fluid overloaded patients. Results on this matter will be
published soon and were previously presented in the form of an abstract at the ASN
2012 (Hecking et al., "Blood Volume-Monitored Regulation of Ultrafiltration in Fluid
Overloaded Hemodialysis Patients").

(4) Figure 3. Linear correlations are problematic with these data, even if the
direction of correlations are consistent with the findings elsewhere. Obviously,
some parameters such as NT-proBNP have a very wide range and thus the
influence of outliers can be significant. Could I suggest you try grouping the data
in box plots using appropriate cut-off ranges? See for example the publication
“Optimal fluid control can normalize cardiovascular risk markers and limit left
ventricular hypertrophy in thrice weekly dialysis patients.” Velasco N et al.,
Hemodial Int. 2012 Oct;16(4):465-72

We completely agree with your comment. The issue of the distribution range of
NTpro-BNP has been discussed in detail prior to submission.
At your request, we have now additionally applied the method proposed above and
calculated the median (which showed to be higher than in the publication by Velasco
et al., but was comparable to the work by Sommerer et al., Eur J of Clin Invest,
2007). We then compared the resulting groups' mean percental fluid overload. A
highly significant difference could be shown (p<0.001), which is now reflected in the
newly introduced Suppl. Fig. 1.

(5) Subjects & methods, Page 8, paragraph “Bioimpedance monitoring”. At the
end of this paragraph please include a short description of the difference
between absolute fluid overload (in litres) and the relative fluid overload (in %) as
both quantities are used throughout the manuscript. E.g Pre-HD fluid overload
may be described in terms of the absolute fluid overload (FO) in litres whereas relative fluid overload is the expansion of the extracellular water calculated as Rel FO = FO/ECW x 100 %. Also please use a different term such as “>15% Rel FO” in place of “(#15% of ECW)” in the manuscript as the later could be more difficult to interpret. Please also ensure consistency of terms, replacing OH with FO and ‘replacing ‘overhydrated’ with fluid overloaded’.

At your request, we inserted a short explanation of currently applied standards for the body composition monitor as well as cut-off values for fluid overload in hemodialysis patients (page 7, first paragraph). An article by Hecking et al. dealing with this exact issue in an in-depth review about fluid overload and interdialytic weight gain has recently been published in the American Journal of Nephrology. The term overhydration (OH) was completely eliminated from the manuscript in order to preserve consistency.

(6) Subjects & methods, Page 8 “As part of the quarterly blood draws” English: a clinician draws blood, but ‘blood draws’ might imply a selection from a random sample. Suggested sentence “As part of the quarterly blood sampling strategy/policy....”

Thank you for this suggestion, which was inserted in the revised manuscript.

(7) Subject and methods, Page 9, Outliers “Prior to statistical analyses, patients exceeding percental fluid overload of three standard deviations above or below the mean were excluded (n=1 patient).” If I understand correctly, you found the mean of the population (in terms of relative fluid overload (FO/ECW) and excluded patients +/- 3 SD of this mean? Any reason for excluding the one patient found to be outside this criteria – not consistent with the clinical situation, measurement error?

The one excluded patient showed extreme values (a relative 'dehydration' of -36%), which seemed unlikely when compared with this patient's clinical status, as she exhibited pretibial edema. Other than with this patient, data obtained with the BCM were consistent with the respective patient's clinical status. We regarded an exclusion cut-off of >3 standard deviations as plausible and useful in order not to exclude patients with truly large amounts of fluid overload or dehydration.

(8) Subjects and Methods, Page 10 Statistical analysis, 1st paragraph. “Dehydrated patients with <-10% ECW were thus included into the normohydrated group, as in a prior study [2]. How many subjects were below the
dehydration criteria? If this subgroup was sufficiently large, it would have been interesting to observe the levels of NT-pro BNP, CRP, TnT and D-Dimer in this subgroup.

Only two patients had values below -10%. We therefore did not specifically analyze this group.

(9) Results, Page 11, 3rd paragraph. “These results corresponded well to percental ECW values.” Please omit this sentence as the fluid overloaded and normohydrated groups were formed on the basis of the 15% Rel FO criteria, as a good correspondence with absolute FO should be expected in any case where the same method is employed.

Thank you for this comment, the sentence was removed.

(10) Results, Page 11 4th paragraph. “Furthermore, no significant difference between the two groups could be observed regarding interdialytic weight gain (IDWG), represented by ultrafiltration volume on the day of the BCM measurement after a short interdialytic interval (1.31 ± 0.99 L vs. 1.59 ± 1.08 L, p=0.144). If I understand correctly, this refers to weight gain in normohydrated and fluid overloaded groups? Please re-word as this is another key result which underlines the difference between fluid overload and weight gain as you point out in the background, e.g. “When comparing short interdialytic intervals, there was no significant difference in the IDWG between the fluid overloaded and normohydrated groups (1.31.....).”

We slightly modified your suggestion, but think we have enhanced the significance of this finding in the current version of the manuscript with your remark. Specifically, we stated that " Furthermore, when comparing short interdialytic intervals, there was no significant difference in the interdialytic weight gain (IDWG) between the fluid overloaded and normohydrated groups, represented by ultrafiltration volume on the day of the BCM measurement (1.31 ± 0.99 L vs. 1.59 ± 1.08 L, p=0.144)."

(11) Discussion, Page 13, 2nd paragraph “This state of higher morbidity was also reflected by significantly lower average body mass in patients dialyzing at the University-based hemodialysis unit.” Could you explain the link here?

Several studies in hemodialysis patients (beyond others by Kalantar-Zadeh et al.) have shown clear associations of higher body mass, higher blood pressure and higher albumin levels with lower cardiovascular mortality rates as well as decreased inflammation (Kalantar-Zadeh et al., JACC, 2004; Kalantar-Zadeh et al., AJKD, 2005;
Suliman et al., NDT, 2007. Therefore, higher blood pressure (up to a certain level) as well as obesity seem to confer a survival advantage in this special set of patients. As many patients with significant pre-existing conditions (such as malignancies, prior heart and lung transplants, etc.) remain to be treated at the University clinic, we associated their lower body mass indices and higher fluid overload detected on standardized BCM measurements with this apparent higher morbidity. However, we were unable to comment on potentially higher mortality rates compared to other patients from the Viennese hemodialysis population.

(12) The association shown in Fig 2 is weak. Nevertheless to further support the observation of higher fluid overload in low BMI patients, it would be useful to see additionally the association of BMI with NT-proBNP and TnT. This might be best achieved with box plots for Rel FO, NT-proBNP and TnT and in each case generate boxes for 3 BMI ranges i.e. ‘low’, ‘normal’ and ‘high’. It would be ideal if these results could be presented allowing a stronger case to be argued in the discussion as to why this association might be observed at all.

Thank you for this important suggestion. We divided patients according to their body mass index and set cutoff values at 18.5 kg/m² and 30 kg/m² resulting in three groups conforming to the WHO standards 'underweight', 'normal and overweight without the need for intervention' and 'obese'.

As expected, obese patients had significantly lower percental fluid overload than others (p<0.001); underweight patients had higher values than patients of normal weight but the significance was not as strong (p=0.05).

For NT-proBNP, an even stronger result was seen: underweight patients had extremely elevated values (mostly above the upper level of detection), while those of normal weight and obese patients were in a significantly lower range. These results did not confer to troponin T, which was evenly distributed in all three groups. We implemented these calculations into a new Suppl. Fig. 2.

(13) Discussion Page 15, 3rd paragraph. Blood pressure was not different between the groups, but this can be difficult to interpret appropriately. Firstly the number of antihypertensive is clearly a crude indicator and of course the dose of antihypertensive is a major influence. Secondly, chances are that there may be patients in your cohort with cardiac impairment who present normal to low blood pressure, despite the presence of fluid overload. Thirdly, in dehydrated patients a very wide range of BPs can be encountered for different clinical reasons. See reference “Towards improved cardiovascular management: the necessity of combining blood pressure and fluid overload.” Wabel P, Moissl U, Chamney P,
Thank you very much for this remark; we agree that this finding has previously not received the appropriate recognition in the submitted paper. It is indeed an important finding that blood pressure and objectified fluid overload do not correlate. As blood pressure regulation in hemodialysis patients is an extremely complex issue influenced by many confounding factors such as ejection fraction/systolic function, diastolic dysfunction and arterial stiffness, the renin-angiotensin-system, the sympathetic nervous system etc., it seems hard to correlate a single factor with higher/lower blood pressure values. We have now given this matter more attention in the manuscript and have added the following paragraph (page 16, first paragraph): “It has previously been shown that, regardless of fluid overload, blood pressure values vary widely. As other factors besides fluid overload, such as sympathetic nervous activity, the renin-angiotensin system, cardiac function and potentially the interdialytic weight gain, also contribute to the genesis of arterial hypertension in hemodialysis patients, it appears challenging to associate the volume status with blood pressure [41, 42].”

In their recently published paper, Velasco et al. used a value similar to fluid overload (time-averaged fluid overload, TAFO) for 30 patients who underwent bioimpedance assessments at three consecutive dialysis sessions. Additionally, these patients underwent cardiac MR imaging in order to quantify left ventricular hypertrophy. The clear association of higher TAFO with higher left ventricular mass index confirms previous assumptions. As is mentioned in the study limitations section, these patients might have represented a study population 'above the mean', as they underwent HDF with few hypotensive episodes; additionally, the measured BNP levels were rather
low compared to a previous study by Sommerer et al. This comment was now inserted on page 15, second paragraph.

(15) Discussion, General comment: The negative correlation of fluid overload with albumin is an interesting finding. Could you comment whether this might be an acute phase response, reflects a state of malnutrition or possibly a dilution effect due to expanded plasma volume?

We actually regard the apparent negative correlation of albumin with fluid overload as a combination of several contributing factors. Sicker patients certainly exhibit lower levels of albumin (especially those suffering from congestive heart failure), similarly to low sodium levels, a laboratory parameter also associated with higher mortality in hemodialysis patients. Up to a certain degree, this state of illness leads to fluid retention and a dilution effect, as you commented. As these exact patients are also the ones with a poor nutritional status, this also contributes to low albumin levels (page 14, second paragraph).

DISCRETIONARY REVISIONS
(1) Background, Page 6, 2nd paragraph. “These methods allow for the important differentiation between chronic fluid overload [2, 25] and interdialytic weight gain [1, 26].” This is a key point, especially as weight gain is often used inappropriately as a surrogate marker of fluid status. It would be useful to elaborate further on the differences between fluid overload and weight gain.

We have now additionally inserted the work by Hecking et al.; AJN 2013, as an important reference in the manuscript. This review extensively discusses the differences between these terms and various assessment forms. Further, a brief description of IDWG and FO were inserted in the manuscript on page 5, second paragraph: "These methods allow for the important differentiation between chronic fluid overload (the amount of residual postdialysis volume overload) [2, 26] and interdialytic weight gain (the amount of fluid gained between the end of the dialysis session and the beginning of the next) [1, 19, 27]."

(2) Results, Page 11, last paragraph. You state that the relationship between Rel FO and BMI is strong. I would not agree. On the contrary, the data indicate a rather weak relationship, irrespective of the statistics. At best the data ‘suggest’ that a negative relationship might be present, but certainly it would be worth
proposing some possible explanations in the discussion.

While we agree that the term 'strong' is exaggerated, we still consider it significant and noteworthy. In the newly created Suppl. Fig 1, results are confirmed for the various created BMI groups and especially overweight patients exhibited significant results with regard to lower fluid overload as most of these were in the normal range < 15% ECW.

(3) Discussion, Page 14, 3rd to 5th paragraph. Are underweight patients really more susceptible to fluid overload or is this in part a reflection of the limitation of clinical methods for dry weight determination? Your suggestion of clinical misclassification is likely to be on the right track and it is one of the subtle issues frequently overlooked. No doubt you have also encountered patients of low weight who do not wish to reduce their weight further, particularly when the difference between excess fluid and normally hydrated body tissue is not apparent. Is it not for such reasons (dry weight management policy) that relationships between fluid overload and BMI can be misleading? Indeed, are there any specific clinical reasons why the majority of underweight/ malnourished patients cannot achieve normohydration status? You may wish to elaborate further on the issue of clinical misclassification and how this may influence the apparent observations regarding FO and BMI.

We agree with you on this matter. During the present study and especially during the ensuing BVM-Reg study which has dealt with dry weight reduction in fluid overloaded hemodialysis patients, we have often encountered the slim (male) patient not willing to further reduce his dry weight, as many psychological issues are closely interrelated with a patient's physique. Fortunately, bioimpedance assessments of the fluid status such as the BCM offer relatively objective methods to quantify and reproduce fluid overload in this unique set of patients where fluid overload (but also underhydration) are often hard to detect. Nevertheless, we still think that dry weight reduction is extremely challenging especially in malnourished, oftentimes very sick patients, as they do not seem to tolerate rapid dry weight reductions well. This will be dealt with in extensive detail in the upcoming BVM-Reg study.

As you have brought up a very important issue, we have addressed it in the limitations section on page 16/17 as following: " Further, for many patients psychological issues interrelated with their physique and dry weight might lead to clinical misclassifications regarding their ideal weight as cachectic patients do not wish to further reduce it whereas obese patients might insist on further lowering it."
Using baseline characteristics of 244 hemodialysis patients at three hemodialysis facilities in Vienna, the authors tried to make links between fluid overload measured by BCM and parameters for cardiovascular, inflammatory and nutritional status.

Major Critics
1. Comorbid conditions of these patients should be described deliberately. Patients would be prone to fluid overloading due to their comorbidities (e.g. CHF or DM). The reasons of being more fluid-overloaded for patients receiving dialysis in University Hospital might not always be due to more comorbidities, but due to more academic and less clinical activities for University Hospital-based Nephrologists. The authors need to show the data of comorbid conditions in details.

Thank you very much for this crucial input. In order to conform with your suggestions, we calculated the Charlson comorbidity index for each patient from the University-based hospital to offer a numerical representation of their associated diseases. On page 11, second paragraph the results are now presented as following: "Similarly, patient comorbidities represented by the Charlson comorbidity index (CCI) [31], showed a significant association with fluid overload, as the CCI was significantly lower in patients exhibiting normohydration (mean 4.06 ± 2.04) compared to those with percental fluid overload (mean 4.96 ± 2.27 (p=0.024))."

We disagree with the notion that this set of patients receives less clinical care as, in fact, at the time of study conduction, no other cross-sectional or prospective (as in the case of the associated BVM-Reg study) clinical trials were conducted at this center. Further, clinical rounding occurs for all patients at every single dialysis visit, where all medical problems are routinely discussed and therapies are regularly evaluated.

2. The cardiovascular, inflammatory and nutritional makers were shown to be related to comorbid burden by many publications. Although not well-validated in ESRD patients, Charlson comorbidity index or USRDS index (Liu et al, KI 2010) could be used to measure the total comorbidity burden. Personally, I think the effects of comorbidity on these markers would be greater than fluid status. A multivariate regression model containing the comorbidity index was needed to
illustrate the independent effects of fluid overloading.

As mentioned above, the Charlson comorbidity index was calculated for every patients. Indeed, morbidity correlated significantly with fluid overload, with a mean CCI of 4.06 ± 2.04 in patients below 15% relative fluid overload compared to a CCI 4.96 ± 2.27 (p=0.024) in patients who had fluid overload on BCM measurement. A multiple regression analysis was run to predict NT-proBNP from percental fluid overload and comorbidities represented by the Charlson Comorbidity Index. These variables statistically significantly predicted NT-proBNP, $F(2,115)=13.665$, $p<0.001$, $r=0.438$. Only fluid overload added statistically significantly to the prediction with a $p<0.001$ ($p=0.059$ for CCI). See page 11, second paragraph.

3. The lack of association between fluid status and blood pressure needs more investigation. Dialysis vintage and heart function (at least ejection fraction or diastolic function) should be provided to help explain the exceptional finding.

We now also provided data on hemodialysis vintage in our patients, which interestingly did not show to associate with fluid overload (figure provided below).
We can retrospectively report on 56 transthoracic echocardiograms of our study patients. Interestingly, no association could be shown for normal versus reduced systolic function and percental fluid overload (13.9±9.1% vs. 17.7±9.4%, p=0.198). Similar results were obtained for normal/abnormal diastolic function (12.5±4.3% vs. 15.9±10.1%, p=0.466).

4. In terms of the inverse association between fluid status and BMI, lean body mass would be a better marker of nutrition status. The information of lean body mass could be easily obtained from the BCM.

Unfortunately, we are unable to provide results with regard to our patients' lean body mass due to our documentation system of the BCM measurements. Consistent with numerous other publications on the matter of fluid overload, we have primarily focused on fluid status-associated variables. We apologize for not being able to provide the suggested supplementary notes, but hope the BMI along with serum albumin levels is accepted as valuable enough for this question.