Author’s response to reviews

Title: The atrial uremic cardiomyopathy regression in patients after kidney transplantation. The prospective echocardiographic study

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Author’s response to reviews:

Dear Professor Mitra Mahdavi-Mazdeh

Thank you for kind consideration for publication of our manuscript (BNEP-D-19-00002) in the BMC Nephrology. Accordingly to suggestions enclosed in Reviewers commentary we revised the manuscript and we made some changes as follows:

Farrokhlagha Ahmadi (Reviewer 1):

1. You evaluated only atrial but not ventricular function.

ad 1. We assessed the function of the left atrium (LA) and left ventricle (LV). For clarity in the original version we have limited the number of parameters represents only the parameters on the left atrium. The LV parameters were not included in the analysis that too much data does not obscure the tasks set for aim of study – so we wrote in limitations in the original version. However, on the Reviewer’s suggestion, we have expanded the data regarding the LV in time intervals such as those given in the parameters of the left atrium. Data on LV therefore also have taken into account in subsequent analyzes: correlation analysis LAVI with echocardiographic parameters of LV and independent echocardiographic parameters related to LAVI. Therefore, we
have also added a description of the LV parameters methodology and relevant references in the literature (red font). LV parameters were also included in statistical analyzes and the results described in the text and tables (red font).

2. In the methods you should explain protocol of immunosuppressant

ad 2. The immunosuppressive protocol has been described in more detail in separate paragraph with the data given in the table 1 (red font). It also provides literature on the principles applied immunosuppression (reference number 21,22) (red font).

3. How was your patients serum cr after transplantation

ad. 3. Creatinine values after transplantation are supplemented in Table I. In addition, a figure is provided changes of creatinine level over 3-years of observation in patients before and post-KTx (figure 1). A similar figure showing the changes in eGFR was added (figure 2)

4. We need laboratory parameter before and after transplantation

ad. 4. The laboratory parameters were given in table 1 in the original version. According to the Reviewer's suggestion, the table was extended and parameters were introduced after kidney transplantation.

5. How was use of medication after transplantation, as ACE inh, ARB, diuretic

ad. 5. The use of pharmacological treatment is given in the appropriate table with baseline characteristics of the study population (table 1) (red font). Consideration was not given to the use of drugs in subsequent stages in order to avoid too much data, which would limit the clarity of the presentation. This was included in the limitations of the study. However, the use of drugs during the observation period probably had no significant effect on echocardiographic parameters, as pharmacotherapy was not significantly modified in the majority of patients. This also applies to immunosuppressive therapy, where only the dosage of the initially programmed treatment has been modified to maintain the therapeutic level of the drug in the blood serum (red font).

6. What is necessary of atrial function evolution before transplantation, and it is a exclusion criteria? because routinely we consider ventricular function before transplantation
ad 6. The reviewer rightly noticed that the function of the left ventricle is routinely assessed before qualifying for kidney transplantation. This is mainly the left ventricular systolic function. The diastolic function is often, though falsely omitted. In this context, the possible usefulness of the assessment of selected parameters of the left atrium should be considered. The LAVI value is an expression of left ventricular diastolic function and is known as a marker of the severity of its diastolic failure. Therefore, the value of LAVI can be an indicator of left ventricular diastolic function in patients before renal transplantation. This comment is attached to the text (red font).

Adarsh Babu, MBBS,MRCP. (Reviewer 2):

1. If available, would be better to have baseline ECHO before transplantation. Although, the authors have clearly demonstrated the improvement in left atrial parameters, from a renal transplant prescriptive it would be helpful to have clinical correlation. Pre-transplant left atrial parameters may help to choose patients who would benefit most from transplant.

ad. 1. Pre-transplant echocardiographic information has not been given because that they were not complete and available for all patients. Transplants for obvious reasons were performed urgently. Recipient came to transplantation is often outside of our center, from all over the country. Echocardiography examination what they had covered only the basic parameters, and especially not stated the parameters relating to the left atrium. Therefore, it could not be included in the study. As soon as possible after the transplant (after a satisfactory post-operative wound healing in order to avoid complications) was performed echocardiography according to a uniform protocol prepared for this project. Practically, it took place within a few days after the transplantation. Therefore, the heading in column 2 has been changed from: 1 month after KTx to: immediately after KTx. we can therefore believe that echocardiographic parameters before transplantation were similar to those obtained immediately after the execution. Uniform study protocol is also essential for the quality of follow-up data. Additionally, as you can see from the presented parameters, they required tedious and accurate echocardiography. It was not possible and not advisable for two reasons. First, studies to obtain reliable results of the study were conducted using high-quality echocardiographic devices by experienced echocardiographers familiar with the study protocol in detail. Both high-quality echocardiographs and experienced echocardiographers were not available in emergency at the time just before the kidney transplant. Secondly, as mentioned, numerous indicators of the left atrium, not assessed in daily practice, were evaluated. This required a large commitment of time, which was impossible because of the need to carry out a number of other tests required prior to the transplant. Detailed assessment of the left atrium is not necessary before kidney transplantation. However, knowledge about the size of the heart cavity, left ventricular contractility and heart valve function is necessary. Therefore, all patients undergoing transplantation had a standard echocardiographic examination
before the transplantation (most often performed in the hospital that was preparing for the transplant). However, without a detailed evaluation of the left atrium, and therefore no data are available on the left atrium. This explanation was also added to section limitations (red font).

The study also did not analyze the parameters of the left atrium in terms of prognostic. This was not the purpose of the work. The analysis included only those patients who survived the entire period of observation and have a good function of the transplanted organ, requiring no re-use of renal replacement therapy or repeat transplant. This explanation was also added to section limitations (red font).

2. It would be better to include Pulmonary artery pressure as it is used in ESRD patients and in their renal transplant evaluation.

ad 2. As the Reviewer rightly pointed out, it would undoubtedly be an additional useful parameter for monitoring patients after transplantation. However, measurement of this parameter requires tricuspid valve regurgitation. In the study group did not include it in the assessment of patients for several reasons. First, about half of the patients did not have enough tricuspid regurgitation for reliable PASP calculations. Secondly, some patients with tricuspid regurgitation had unsatisfactory imaging quality to reliably calculate this sensitive and quality-dependent imaging index. This gave the number of less than 20 patients to a potential PASP analysis, which would make statistical analysis unreliable for methodical reasons.

3. It would be helpful to include renal function and at the same points as ECHO.

ad 3. According to the Reviewer's suggestion, data regarding renal function were included in the same time intervals as echocardiographic examinations were performed. These data were placed in the expanded table I. (red font). In addition, figures are provided changes of creatinine level and eGFR over 3-years of observation in patients before and post-KTx (figures 1 and 2).

4. Authors need to include a paragraph on future studies that may help nephrologists.

ad 4. The reviewer rightly pointed out the desirability of adding a paragraph on future research that could help nephrologists. We have partially signaled this in the results.

However, we pay close attention to two pathophysiological conditions useful for the management of patients in the future. First, the use of monitoring the size of the left atrium (especially LAVI) for the assessment of left ventricular diastolic function. LAVI reflects the long-term exposure of LA to elevated left ventricular filling pressure. LAVI is a valuable parameter enables long-term haemodynamic monitoring of patients. By analogy, it can be stated
that LAVI is in heart failure what glycated hemoglobin in monitoring patients with diabetes. This is particularly important and very useful in patients with volume overload that can accompany kidney disorders including monitoring the process of organ rejection. When qualifying for transplantation, we evaluate mainly the left ventricular systolic function (ejection fraction). Diastolic function is usually ignored. This is wrong because of the possibility of heart failure with preserved ejection fraction (HFpEF). HFpEF are highly prevalent in patients with end stage renal disease. And this form of heart failure also have prognostic significance in patients on hemodialysis and planned to transplant [1].

Secondly, the size of the left atrium is important in the context of the risk of atrial fibrillation (vicious circle: atrium enlargement - atrial fibrillation and vice versa - reduction of the size of atrium after transplantation - lower risk of arrhythmia). This is of particular importance in the context of potential anticoagulant therapy, including the currently preferred therapy with new oral anticoagulants (NOAC). These drugs require more careful monitoring of renal function in order to avoid bleeding complications.

Reference


Minor

1. Selection of patients with both graft and patient survival may contributed to selection bias.

ad 1. The study included only patients who survived until the end of the observation. Also we enrolled only patients who had good graft function until the end of the observation. The aim of the study was not to assess the atrial indexes for survival. This was a prospective echocardiographic study exclusively on the left atrium, which is included in the title of the work and to study. Also included in limitations paragraph. (red font)

2. Table 1 Please change the characteristic and the value in parenthesis for example: the characteristic parenthesis represents units and in value's parenthesis it has Standard deviation.

ad 2. Changed, as suggested by the Reviewer. (red font)

Substantive corrections have been marked in red font. While the language and spelling correction, introduced by a native speaker, were not marked in a different color font.
We hope that our changes have improved quality of presented manuscript and thereby you will be able to consider this version of paper for publication in the BMC Nephrology

With compliments –

Tomasz Zapolski, Jacek Furmaga, Andrzej Jaroszyński, Anna Wysocka, Sławomir Rudzki, and Andrzej Wysokiński