Author’s response to reviews

Title: The improvement of QRS-T angle as a manifestation of reverse electrical remodeling following renal transplantation in end-stage kidney disease patients on haemodialysis

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Author’s response to reviews:

Thank you very much for taking your time to review our paper “The improvement of QRS-T angle as a manifestation of reverse electrical remodeling following renal transplantation in end-stage kidney disease patients”. I was glad to hear that you will be willing to consider a revised version of my paper for publication in BMC Nephrology.

I found the Reviewers comments exceptionally helpful. I did my best to address all their concerns in the paper as well as in responses to their particular questions, which are enclosed with the manuscript.

Here are my responses to the comments by the Reviewers:

Reviewer 1:

MAJOR COMMENTS

The study by Jaroszynski and Colleagues is quite interesting, enlightening the potential usefulness of an easy to obtain parameter to assess cardiac muscle remodeling in transplanted patients. However, there are some pitfalls that need to be pointed out.
1. First of all, it is mentioned in Methods section that QRS-T angle was evaluated in 60 controls, with gender distribution and age range similar to the group of patients. However, no other information is given about this control group. What were the baseline characteristics of the controls? What was the mean value of QRS-T angle in this group and was it different from the patients group? Did they undergo the same follow-up? These points need to be clarified before considering the manuscript for publishing.

We have now provided more detailed information about the control group both in the methods and results sections. In Figure 2 we have also added the QRS-T angle values in the control group.

The QRS-T angle was also evaluated in 60 healthy controls (hospital employees) controls; who came for routine physical check-ups, having no abnormalities detected by physical examination, ECG, and laboratory analysis. The group’s gender distribution and age range were similar to the group of patients. In the control group, the QRS-T angle was evaluated at the same intervals as in patients.

The QRS-T angle was lower in controls (51.4±11.3 ) compared with RTRs at the beginning of the observation and throughout the entire observation as well as after 1 year, when the nadir of the QRS-T angle values was observed (p<0.001 in all both cases). In the control group, no significant changes in QRS-T angle values were observed during observation (Figure 2).

2. No data are given about the pharmacological treatment of patients during the follow-up. Data about the therapy are shown only for the period prior RT. In the analysis shown in Table 5 beta blockers were considered: is it reffered to a therapy instituted after RT or before (in this case, was it continued during the whole folloe-up)? As treatment such as beta blockers, ACE inhibitors and aldosterone receptors antagonists can have a strong impact on cardiac remodeling, treatment history should be detailed.

We thank the Reviewer for pointing out this issue. We have provided analysis of pharmacological treatment both in a result section as well in a Table 3. We did not analyzed relation between QRS-T angle and aldosterone receptors antagonists because only 2 patients were treated with aldosterone receptors antagonists.

We did not find significant relations between drug treatment and QRS-T angle changes (except the relation between beta-blockers and QRS-T angle change in univariate logistic regression analysis).

The analysis of drug treatment is shown in Table 3. During observation, a reduction in the use of calcium channel blockers was observed. We did not observe differences in the use of both beta-blockers and angiotensin-converting enzyme inhibitors/aldosterone receptors blockers.
3. Patients' data such as ECG, electrolytes and blood pressure should have been obtained even before renal transplantation, as changes in those parameters could have been happened even 1 week after transplantation.

We did not decide to include biochemical data obtained before renal transplantation because all patients were dialyzed prior to transplantation in their HD centers. Thus almost all biochemical parameters were approximately normal ranges. In addition, given the effects of mental stress associated with kidney transplantation, blood pressure results would probably be overestimated.

MINOR COMMENTS

4. Methods: "unstable graft function" should be defined.

In the methods section we defined „unstable graft function”

Unstable graft function was defined as delayed graft function of more then 3 days, acute graft rejection, and acute kidney injury defined by the RIFLE criteria.

5. What was dialysis vintage of patients? As a longer time on dialysis could influence negatively cardiac remodeling, it would be interesting to check if there were differences in the study outcome according to different dialysis vintage.

Dialysis vintage is shown in Table 1 (time on dialysis until RT). We did not found relations between dialysis vintage and QRS-T angle changes.

6. In Results, it is stated that an abnormal QRS-T angle was found only in 18.5% of patients. The mean baseline value, according to Figure 1, was 88.3±16.2°, which is not far from the mean of a healthy population, according to other published reports. Please discuss, also clarifying the abnormality cutoff in the introduction (was it considered different for men and women?).
As stated in the methods section in our paper the normal values for the spatial QRS-T angle are below 116 and 130 for women and men, respectively. In an analysis on the relationship between the spatial QRST angle and survival in dialysis patients these cut-off values were used to demonstrate a significant prognostic value of the spatial QRST-angle [de Bie M et al. Europace 2013, 15, 290-296]. In controls the QRS-T value was 51.4±11.3 and was lower (p<0.001 in all cases) compared to patients (Figure 2). We have clarified in the discussion that the cut-off values of the QRS-T angle are strongly dependent on method of the QRS-T angle calculation, and that there is no consensus on the methods for the calculation of the QRS-T angle.

It provides greater prognostic value than any of the commonly utilized ECG indicators [8, 9, 17, 27], however, that there is no consensus on the methods for the calculation of the QRS-T angle and the cut-point value that defines abnormal QRS-T angle depends on the method of QRS-T angle estimation. It may cause difficulties in comparing results of different studies.

Reviewer 2:

Kenneth A. Andreoni (Reviewer 2): This is a very interesting manuscript by the authors as they look at the QRS-T angle and Echocardiogram changes in cardiac function after renal transplant. Their data suggests that improved volume status results in both improvements in ECHO findings as well as QRS-T angle changes after renal transplant.

Suggestions to improve the manuscript for the reader:

1. Can you give the reader a diagram showing the QRS-T angle as most of the readership may not be knowledgeable about what this is exactly.

We have added a diagram showing the method of QRS-T angle calculation (Figure 1)

2. Can you please show the number of patients in each time point in the Tables and in Figure 1. Is this 54 patients at each time point in all tables and figure?

We have added the number of patients in Figure 2 as well as in Tables 1-3.

3. Figure 1: Could you label the Figure more clearly. I believe from reading the text and the prior Tables that the first point is 1 week after RT, then 3 mos, 6 mos, 1 yr, and 3 yrs, but the exact details are unclear. A figure should be understandable by itself without needed to read the text.
Figure 2 is labeled more clearly. In Figure 2 we entered data for the control group.

4. None of the control data is shown in the Tables or the Figure, though it is discussed in the text. The control group is also not defined well except to say it was 60 pts with gender and age similar to study patients - that may be all that is necessary, but please check. Can you show the control values more clearly, especially when you state in 'results' that the QRS-T angle was higher in the RTRs than controls at each evaluation. Putting the Control QRS-T angle values in the Figure may be helpful to the reader.

We have now provided more detailed information about the control group both in the methods and results sections. In Figure 2 we have also added the QRS-T angle values in the control group.

The QRS-T angle was also evaluated in 60 healthy controls (hospital employees) controls; who came for routine physical check-ups, having no abnormalities detected by physical examination, ECG, and laboratory analysis. The group’s gender distribution and age range were similar to the group of patients. In the control group, the QRS-T angle was evaluated at the same intervals as in patients.

The QRS-T angle was lower in controls (51.4±11.3 ) compared with RTRs at the beginning of the observation and throughout the entire observation as well as after 1 year, when the nadir of the QRS-T angle values was observed (p&lt;0.001 in all both cases). In the control group, no significant changes in QRS-T angle values were observed during observation (Figure 2).

Reviewer 3:
Sandawana William Majoni, MBChB, MRCP, FRACP, MMedStats, MClinicalMed, FRCP
(Reviewer 3): Comments for authors:

In this study, the authors aimed to a) assess the effect of renal transplantation on the QRS-T angle and b) evaluate the possible factors influencing QRS-T changes in a group of selected renal transplant recipients. The study was performed in a single centre in Poland. Although not stated, they were testing the hypothesis that an improvement in the QRS-T angle is a manifestation of reverse electrical remodelling following renal transplantation in patients with end stage kidney disease. From their results, it was concluded that renal transplantation resulted in biphasic reverse electrical remodelling as assessed by the narrowing of the QRS-T angle. Although this is a reasonably well explained study, there are some issues which will need to be addressed.
MAJOR COMMENTS:

ABSTRACT

1. There are some spelling errors and grammatical errors which will need revision

Spelling and grammatical errors have been corrected

2. In the objectives and methods section, the objective is not clearly stated. Could the authors please explicitly state the objective of the study?

We have specified the aim of the study more precisely.

The study aimed to assess the influence of the RT on QRS-T angle and to evaluate factors influencing QRS-T changes in renal transplanted recipients (RTRs).

3. This statement in the results section "The dynamics of the indices changes behaved, however, individually" is difficult to understand. Could the author word this so it easier to understand?

The statement has been reformulated to make it easier to understand

The dynamics of changes in individual parameters were, however, variable.

THE MAIN MANUSCRIPT

1. It appears from their manuscript that the authors studied patients who were on haemodialysis before they got a kidney transplant so, the title should specify that this was end stage kidney disease patients on haemodialysis.

We have changed the title of our paper according to the Reviewer suggestion.

The improvement of QRS-T angle as a manifestation of reverse electrical remodeling following renal transplantation in end-stage kidney disease patients on haemodialysis

2. In the background page 3 in line 18, the authors should specify that they are referring to adverse cardiac events rather than just cardiac events.
Many studies have confirmed that QRS-T angle is a powerful and independent risk stratifier that predicts adverse cardiac events either in the…..

3. In the methods section they need to specifically provide more information on the 60 controls so that it will be clearer to make comparisons with the studied group. Were the controls also dialysis or CKD patients for example?

We have now provided more detailed information about the control group both in the methods and results sections. In Figure 2 we have also added the QRS-T angle values in the control group.

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4. In the results section, the authors mention that all patients had undergone RT from unrelated donors, were these living or deceased donors? It is not clear in the manuscript.

We have adjusted the text in order to clarify this point.

All patients have undergone RT from unrelated deceased donors.

5. There are also several grammatical and spelling errors in the manuscript which will need to be addressed.

Spelling and grammatical errors have been corrected

6. They authors clearly described some limitations of this study, but it is not clear whether they have done anything in their analysis to mitigate some of these limitations.
Owing to the fact that it is a preliminary study we did not assess outcome data, and we can not mitigate this limitation. We emphasized this issue in the limitations section.

Exclusion criteria were limited exclusively to conditions/confounders that could certainly interfere with the results of the study, thus in this case we also could not mitigate this limitation.

The third limitation was the small numbers of patients. We have included all available patients who had a kidney transplant in the last 3 years in our center. We have adjusted the results in order to clarify this point.

Of the total of 92 available RTRs patients that were transplanted in the last 4 years in our center....

7. The authors need to list all the abbreviations in the manuscript as they have left some of them.

We have now listed all the abbreviations in the manuscript

8. Table 4: The authors need to provide the specific p-values not a range of <0.05 or <0.001. They can provide additional columns in the table for the exact p-values. This will provide the readers with an understanding of the level of significance. For example, although both p=0.01 and p=0.044 are less than 0.05, their level of significance is different.

We have reported the exact p-values in Table 5.

9. In figure 1 the authors need to label the axes.

We have labeled the axes in Figure 2.

MINOR COMMENTS:

1. A minor comment on the statistical analysis section is for the authors to specify whether the p-values were two-tailed or one-tailed, I assumed that it was two-tailed.

The p-values were two-tailed
2. A minor comment for table 1, could the authors write the names of the treatments in full, for example sartans should be angiotensin 2 receptor blockers or add a foot note below the table to explain these. They should also use international nomenclature for units of measurement, for example, mg/dl should be mg/dL, mmol/l should be mmol/L, g/l should be g/L.

We have adjusted Table 1 according to the Reviewer suggestion