

31294-Reply to reviewers

Dear Dr. Xiu-Xia Song;

On behalf of all of our colleagues, we want to express our thanks to the editors and reviewers of this report. We appreciate the comments of the reviewers. They have been very helpful in addressing areas of our report that needed improvement. We made changes in the text addressing these areas. Here we will provide our replies to the comments of the reviewers:

Reviewer 00420421: First we express our thanks to the reviewer for his favorable reception of this report. The reviewer's comments about the last two sentences in the Introduction are critical in understanding the whole topic. We provide here the following detailed reply: Although changes in renal function and peritoneal membrane transport characteristics will change temporarily the amount of creatinine excreted by each of these routes, if muscle mass remains stable total creatinine excretion will not change in the steady state unless there is a substantial change in the serum creatinine concentration. Our study addresses only steady state creatinine excretion. Creatinine excretion is an index of muscle mass only in the steady state, in which the rates of creatinine production and removal are exactly equal. Continuous peritoneal dialysis (PD) is considered a steady state. For example, the equations used to calculate urea and creatinine clearance in PD are steady state equations, in contrast to the equations used in hemodialysis which of course is not a steady state. The steady state approach in PD has worked well despite the fact that in a strict sense PD does not represent a steady state (in each PD exchange, both peritoneal clearance and peritoneal quantitative removal of azotemic substances are maximal at the beginning of a cycle, right after intraperitoneal instillation of the dialysate, when the concentrations of these substances in the infused peritoneal dialysate are zero, and decrease progressively as these concentrations increase during the dwell time). The reason that the steady-state approach is not flawed overall is that over a longer period of time –for example over 24 hours- all the creatinine and urea produced is removed, as indicated by the stability of their serum values in PD patients. We added in the Methods section the information that serum creatinine at each measurement of creatinine excretion differed from its values one month prior and one month following the clearance study by less than 0.3 mg/dL in all patients. Thus we did appear to deal with steady states. If creatinine production is unchanged, total creatinine removal will also be unchanged in the steady state, but that does not mean that creatinine removal through individual sites (i.e. the urine, the peritoneal dialysate or the GI tract) will necessarily remain unchanged. Indeed, in PD patients on an unchanged prescription of the procedure, as in our study, creatinine removal through the urine decreases progressively while creatinine removal

through the peritoneal route increases –at least for patients with no loss in their muscle mass- as total creatinine clearance decreases in parallel with the decrease in renal creatinine clearance. Peritoneal creatinine removal increases in this case even without a change in the prescription of PD because serum creatinine rises as total creatinine clearance decreases (the amount of creatinine removed through PD is the product peritoneal clearance times serum creatinine). The findings in our patients (Tables 3-5) clearly indicate these changes. If a steady state exists, changes in renal creatinine excretion caused by drugs (please see the related comment of reviewer 00503199) or in peritoneal membrane function will affect the fractions of creatinine removed by the renal and peritoneal routes and the serum creatinine concentration, but will not affect significantly total creatinine excretion, unless the rise in serum creatinine is large enough to produce a significant increase in the amount of creatinine removed through the GI tract. This has also been addressed in the Discussion of this report. To summarize: The main purpose of this report was to evaluate total creatinine removal, which in the steady state will not change significantly if muscle mass is maintained. We made changes in the last part of the Introduction to stress the steady state point. Again, we thank the reviewer for giving us the opportunity to clarify this critical point. Because of the length of the manuscript we did not add many comments. However, this point (the steady state) is critical. If the editors request it, we are willing to expand the comments addressing this issue in the report.

Reviewer 00503339: Please accept our thanks for the favorable grading of this report. Serum creatinine concentration levels will decrease progressively in patients on PD under one of two circumstances: (a) No change in muscle mass and creatinine production, but a progressive increase in total creatinine clearance – usually meaning an increase in the prescription of PD that exceeds the drop in renal function. We had encountered exactly this sequence in a previous study (reference 17). We added a comment in the Discussion about this sequence, which led to an increase in the removal of creatinine through the kidneys and the peritoneum in the steady state. Sustained increased creatinine excretion in the steady state is due to either decreased removal of creatinine through the gut (by far the most probable mechanism) or improved muscle mass. (b) A progressive loss in muscle mass and decrease in creatinine production relatively greater than the loss of renal function and total creatinine clearance. In this second case measured creatinine excretion will decrease. We did not add any information about decreases in serum creatinine level in long-term PD, given the length of the manuscript and the absence of patients with progressive decrease in serum creatinine in our study. However, we are willing to add some comments in a new revision if the editors consider them necessary.

Reviewer 00503199: Thank you very much for the useful suggestions. Drugs that block tubular creatinine excretion will of course decrease urinary creatinine excretion in PD patients, as will the progressive loss of renal function, but will not affect total creatinine excretion in the steady state (please see response to reviewer 00420421), again unless the rise in serum creatinine level is substantial leading to significant increases in creatinine removal through the gut. Anyway, our patients were not on cimetidine or trimethoprim. Drugs causing increased creatinine production will increase creatinine excretion in the steady state and could have major effects on our study. We reported one such case in reference 20 of this report. However, this study does not include patients receiving drugs causing rises in creatinine production. This information was added to the Methods section. Months on PD were added to Tables 3-5. Finally, information about lean body mass from creatinine production estimates is relevant to this report because it links directly creatinine production and muscle mass and information about measured/predicted creatinine excretion and non-compliance is relevant because sudden correction of non-compliance is one of the recognized causes of changes in total creatinine excretion. With these thoughts in mind, we decided to keep the sections devoted to these two items in the Introduction and Discussion, but shortened them, with omission of one reference (reference 28 in the original version).

Reviewer 00503272: Thank you very much. Your comments were useful. We made the indicated changes.

Reviewer 00503254: Thank you very much for a very careful reading of the report. We made all the requested changes.

Dr. Xiu-Xia Song, we are submitting the revised report as well as the other items requested for retrospective studies. If you need further revisions or other documents, please be assured that we are willing to comply with your requests.

Thank you again

Best regards

Xu Zhi

Antonios H. Tzamaloukas