Author’s response to reviews

Title: Coronary bypass grafting using Crossclamp Fibrillation does not result in reliable reperfusion of the Myocardium when the crossclamp is intermittently released: A prospective cohort study.

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Response to reviewers

Response to reviewer 1, Shukri Khuri

We would like to thank Professor Khuri for his very positive review, and it is indeed an honour to have a review from the world authority and creator of the Intramyocardial pH probe, which we feel is a truly remarkable device for guiding myocardial protection and an outstanding research tool.

We echo Prof Khuri’s views on the major strengths of our study, and thank him for his view that this is the first clinical demonstration of ischaemic preconditioning. He also agrees that this is the first study to validate animal laboratory findings many of which he performed. We thank Prof Khuri for his additional references and we have added them to the discussion.

Professor Khuri points out 2 weaknesses:

1. We used the average of the anterior and posterior probe values rather than the lowest of the two, as he has done in his studies. He recommends that we use this value instead.

   OUR RESPONSE:

   The difference between our study and Professor Khuri’s research is that whereas he gives cardioplegia down the aortic root which passes into the left main stem and right coronary artery, he is interested in the anterior and posterior pH values which may reflect the quality of protection afforded by cardioplegia down these two routes. Cross clamp fibrillation initiates ischaemia globally and therefore we were not looking to identify areas of regional ischaemia. Rather we were aiming to document the dynamic reduction of global myocardial ischaemia, and thus we found the averaged pH to be most meaningful.

   We have of course looked at the anterior and posterior probe data alone and they are not significantly different and always correlated, and therefore the lowest reading rather than average reading does not change our results.

   We agree that an integrated pH would provide a good measure of ‘ischaemic load’ that could in the future be used to see if this correlated with outcome. However we would not like to imply that our study was large enough to make any conclusions with regard to outcomes.

   Our study is simply a small pilot study that has some very interesting but small number findings. Future studies would certainly be greatly assisted by using the integrated pH and we thank him for this suggestion.

2. Prof Khuri was uncertain as to the reasons for choosing a pH of 6.8 for dichotomising the results and made some suggestions for future research

   OUR RESPONSE:

   In our manuscript we have added a section explaining the reasons for deciding on a pH cut-off of 6.8. It is not possible to determine this cut-off by recursive partitioning as we do not have an outcome variable by
which recursive partitioning could be asked to predict. It was simply an observation that there seemed to be a difference here, and we hope that we have not built up the importance of these groups more than a mechanism of highlighting some of the interesting findings in our study. We have a passage in the discussion playing down the importance of the two groups.

We agree with Prof Khuri that there are many opportunities to try to determine a myocardial pH guided management technique for cross clamp fibrillation in the future from this initial pilot study.

We would like to point out to the editors however that the Khuri Myocardial pH probe has recently been withdrawn from clinical use and therefore it will not be possible to repeat our study in the near future. Thus it may be that our study will be a unique study for many years to come, until the technical issues around the probe are overcome.

REVIEWERS COMMENT

Prof Khuri points out that this study is too small to make any conclusions regarding clinical outcome and we did not look at any other markers of ischaemia.

OUR COMMENTS:

We entirely agree that our study is far too small to make any comments about clinical outcome. We inserted a small table on clinical outcomes (Table 3) but made very little comments about clinical outcome in the text. The only reason for including this is because we thought that readers would want to see this table. We have however deleted all references to clinical outcomes from the abstract and conclusion.

Secondly we would very much have liked to have taken a number of other biochemical markers to correlate with the probe, but we were not allowed to do this in this pilot study. Our study required no change in practise and no additional blood tests other than those required clinically. Thus if we were in the future able to carry out further research in this area we would try to do this but we were unable to do this for this pilot study.

Prof Khuri makes the comment that we cannot come to any conclusion about clinical outcomes. I am sure he is referring to out conclusion that 'Crossclamp fibrillation does not result in reliable reperfusion of the myocardium between periods of crossclamping, but failure to reperfuse does not result in any clinical evidence of myocardial injury.' Our assertion that failure to reperfuse does not result in any clinical evidence of myocardial injury was not based on our research but on the fact that multiple cohort studies have shown the equivalence of cross clamp fibrillation and cardioplegic techniques. However we agree that we cannot make any clinical outcome statements and therefore we have removed this assertion.

IN SUMMARY

Prof Khuri asks us to concentrate on our considerable strengths, and to delete our assertions relating to post-operative outcomes. We have deleted our assertions to post-operative outcomes as requested and we thank Prof Khuri for his review. Furthermore we wonder whether it would be appropriate to ask Prof Khuri to write a short editorial to accompany our article in your journal.

REVIEWER 2: Mr Fabri.

Mr Fabri comments that this paper ends up as 'an observational report'

OUR RESPONSE

Our study set out to be an observational report. Our protocol determined that we would make no modifications to the usual clinical treatment of each patient and therefore we are very happy to call our study an observational report. We called it a prospective cohort study which is also another correct nomenclature for our study, as it was a group of patients that we studied from the outset.

REVIEWERS COMMENT:

That the probe has been around a long time and has recently been withdrawn.

OUR RESPONSE

Prof Khuri invented the probe around 20 years ago, but has found it extremely useful for research purposes. The fact that it has recently been withdrawn makes our study all the more important as it will not
be possible to investigate the intramyocardial pH of patients undergoing cross clamp fibrillation again in the near future.

REVIEWERS COMMENTS
The review states that we failed to achieve either of our aims of determining a safe ischaemic time or to measure ischaemic preconditioning in clinical practise.

OUR RESPONSE
We do not see it as a weakness that we could not determine a safe ischaemic time, in fact it could be a warning to readers that there may not be a single safe time. We think that to state the reasons for our study but then to document our true findings which could not determine a safe ischaemic time is a true reflection of the study and an important finding.

With regard to the assertion that we did not achieve our aim of demonstrating ischaemic preconditioning, we would refer to Professor Khuri’s review, where he seems more than happy with this part of the paper and asserts that this is the first time that this has been seen in clinical practise.

REVIEWERS COMMENT:
How did we determine maximal recovery?

OUR RESPONSE:
The reviewer is correct that the maximal recovery was the pH just before the Cross clamp was reapplied. We have added an explanation of this in the methods.

REVIEWER COMMENTS
Was it valid to average the pH values?

OUR COMMENTS
We have addressed this issue in the responses to Prof Khuri, but the results are no different if just anterior, or posterior, or lowest pH is used, and adding this data in addition to the average pH we feel would just complicate our paper which is just a small pilot study report.

REVIEWER COMMENTS
There are no clinical, ECG or biochemical markers measured.

OUR COMMENTS
As addressed previously we were unable to measure any markers not being measured during the patients routine clinical care due to study constraints. We did not consider looking at Pre and post operative ECGs, but as Prof Khuri correctly states, our study is far too small to make any conclusions about clinical outcome measures.

REVIEWER COMMENTS
Further queries were raised about the possibility of there being some observation of ischaemic preconditioning. There was a query as to how it only occurred in one of the groups.

OUR RESPONSE
There is a very simple answer as to why ischaemic preconditioning did not occur in the non-recoverers: the reason is that they did not recover after cross clamp removal! Therefore all the pH values stayed at very low levels for the whole case, and the pH traces were flat essentially for the second and third cross clamp episodes. Thus there is no way that you can measure the slope of those lines.

However the recoverers did go back to a baseline and then the pH fell when the cross clamp was applied. We could then look at the slope of these curves and they reduced. This is why Prof Khuri agreed that this is an interesting and important result.

REVIEWER WRITES:
The reviewer writes that 'In the discussion the authors 'hypothesise' on why some patients did not show recovery in pH after X-clamp release. They consider this is due to lack of adequate perfusion of the native coronaries either because of the non-pulsatile, 'lower' aortic pressure during cardiopulmonary bypass (BUT wouldn't this be the same for both groups?), or the cardioplegia pressure (BUT CARDIOPLEGIA WAS NOT USED IN THESE PATIENTS!!) or because of increased resistance from 'twisted or compressed' vessels!!! Why in that case was no attempt made to improve the perfusion pressure and see whether this resulted in an improvement in pH?'

OUR RESPONSE
We hypothesised that perhaps the lack of perfusion was due to a lower aortic pressure on cross clamp release. The reviewer asks whether this would be the same in both groups. It obviously would be the same in both groups, however the stenotic lesions may not be the same and therefore this lower pressure may be enough to push some blood down the coronary arteries in the recoverers but not enough pressure to push blood down the coronaries of non recoverers. 

The reviewer misunderstood our comment regarding cardioplegia. Of course we did not use cardioplegia in this study, but our comment was meant to imply that the reason that there is no problem getting blood down the coronaries in cardioplegic cases is that the cardioplegia pressure is around 150-250mmHg. However in contrast, when you remove the crossclamp in cross clamp fibrillation, the pressure pushing blood down the native coronaries or the new graft is 60mmHg. Thus with low pressure blood going down twisted coronaries with stenotic lesions it is perhaps more surprising that there is any reperfusion at all !! We have added a small passage to clarify this comment.

We were also not allowed to make any modifications to the patient's operation and thus we were not able to improve the perfusion pressure, as the surgeon was required to be blinded to the probes results.

OUR CONCLUSION
Both we and Prof Khuri disagree with this reviewer's conclusion that because the study is small, it is of no value. This is the first time that intramyocardial pH has been measured in real time during cross clamp fibrillation and these results will not be repeated again in the near future and thus we highlight some important concerns regarding cross clamp fibrillation.