Reviewer's report

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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Reviewer: Shukri Khuri

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This manuscript describes a study in 16 patients in whom myocardial pH was continuously measured in the anterior and posterior LV walls throughout a CABG procedure that was performed with interrupted aortic clamping and ventricular fibrillation. After characterizing the myocardial pH changes during and following a total of 50 periods of aortic clamping, the authors concluded 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.

This study has two major strengths:
1. It describes for the first time in the clinical setting the myocardial pH changes, and hence the spectrum of ischemic changes, during repeated aortic clamping and reperfusion of the fibrillating heart. There is much to be learned from a proper analysis of these changes, since the ischemic insult incurred during this type of myocardial management has not been quantified before, and its clinical significance has not yet been elucidated. The lack of such specific information is what fuels the controversy between the advocates of repeated clamping and those of other myocardial management techniques. The finding that that the patients varied in the recovery of normal pH after reperfusion is a very important one. It should not be dismissed as clinically insignificant, as the authors unfortunately implied (see below). On the contrary, it should prompt advocates of repeated aortic clamping to devise pH-guided myocardial management techniques that would result in a more uniform return of post-reperfusion pH to normal in all patients undergoing this operative management technique.
2. The study validates, for the first time in a clinical setting, what has been previously demonstrated in the animal laboratory: the metabolic diminution of the ischemic insult during a second period of aortic clamping, suggestive of a protective effect rendered by the initial period of aortic clamping. The authors may have thus documented, for the first time clinically, a salutary metabolic effect of ischemic preconditioning. It has been demonstrated in animal studies of repeated regional coronary occlusions that the rise in myocardial tissue pCO2 (References 1-3 below) and in myocardial tissue hydrogen ion concentration (Reference 4), was diminished after the second occlusion, similar to what the authors described in their patients. These animal studies were published well before ischemic preconditioning became recognized. It would strengthen the manuscript if reference to these studies is made in the discussion.

However, the study has two major weaknesses which seriously compromise its scientific credibility:
1. Inadequate analysis of the myocardial pH variables.
   a. For each patient, the magnitude of ischemia was assessed by averaging the corresponding anterior and posterior myocardial pH values. This can be misleading and may lead to inaccurate conclusions considering that the ischemic insult that is encountered intraoperatively during CABG is regional in nature, and its clinical correlates and effects (histologic and functional damage) are also regional in nature. To date, all the publications that have elucidated meaningful relationships between intraoperative myocardial pH to postoperative events and outcomes (such as references # 7,8 and 9 in the manuscript, and reference 5 below) have used the lower of the anterior or posterior myocardial pH value as an index of patient specific ischemic damage, thus adhering to the regional concept of intraoperative damage.
   b. The authors have not used an important functionality of the Khuri Myocardial pH Monitoring System, which is the ability to integrate the myocardial pH values over specific periods of time. Considering that in studies where single periods of aortic clamping were employed (references # 7,8 and 9 in the manuscript, and reference 5 below), the integrated mean pH during the period of aortic clamping was found to be an important predictor of short and long term postoperative outcomes, it would be worthwhile in this study to calculate the integrated pH during individual periods of aortic clamping as another variable to be analyzed. One may consider adding the integrated pH values derived from each electrode throughout all the periods of aortic clamping in a single patient. This would quantify the total regional ischemic load recorded for that patient, which may turn out to be an important prognostic variable.
   c. It is uncertain on what basis did the authors choose to dichotomize the reperfusion pH at a pH 6.8 threshold. If this was not performed on the basis of recursive partitioning, the authors may consider
analyzing this variable as a continuous variable. I suspect that the reperfusion pH will be a very good indicator of the adequacy or lack of protection, since it can quantitate the no-reflow phenomenon that is observed with reperfusion injury. The authors are encouraged to explore this further, and, hopefully underscore this variable as an indicator in devising intraoperative management techniques that would eliminate reperfusion injury during the repeated aortic clamping technique.

2. Inadequate methodology and lack of power for the elucidation of clinical significance of the myocardial pH changes observed. The manuscript, based on the data provided, cannot make any claim relating the myocardial pH changes to outcomes.
   a. First and foremost, a total of 16 patients is a woefully small number of patients to provide enough statistical power for outcome analysis. Studies that have found statistically significant relationships between intraoperative myocardial pH and outcomes have all exceeded 250 patients in the least.
   b. As discussed above, the authors used unvalidated myocardial pH variables, and did not use variables and statistical analyses that had been shown previously to relate to postoperative patient outcomes.
   c. The study did not report or analyze important outcome variables that relate to postoperative myocardial damage such as pre and postoperative ejection fraction and wall motion abnormalities, postoperative cardiac enzymes, pre and postoperative EKG changes, specific heart-related postoperative adverse outcomes, etc. The variables they used (ICU and hospital stay, inotrope usage, atrial fibrillation, resternotomy) are woefully inadequate to adequately characterize the impact of intraoperative myocardial protection on patient outcomes.

In summary, this is an important work, but, as submitted, this study has many weaknesses and is inadequate to relate myocardial pH to postoperative outcomes. I suggest a major revision that takes into account the strengths of this study as identified above, and that would eliminate the part that relates the pH changes to postoperative outcomes.

References:


What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.