

Letters to the Editor

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Quotation of article in Brazilian Journal of Cardiovascular Surgery (BJCVS)

Dear Dr. Braile,

All through the year we are glad for having intellectual contributions published in BJCS, which you manage honorably. Therefore, we would like to wish you and the Editorial Board success in 2010 and may good publications flourish abundantly.

Furthermore, we would like to report the paper from Tang XN, Yenari MA. Hypothermia as a cytoprotective strategy in ischemic tissue injury. *Ageing Research Reviews*. 2010;9(1):61-8, which refers to an article of our group published in BJCS (Meneghini A, Ferreira C, Abreu LC, Ferreira M, Ferreira Filho C, Valenti VE, Murad N. Cold stress effects on cardiomyocytes nuclear size in rats: light microscopic evaluation. *BJCS*. 2008;23(4):530-3).

We hope we can contribute with more publications throughout the year.

Best regards.

Prof. Dr. Luiz Carlos de Abreu – Physiology - Faculdade de Medicina do ABC, São Paulo/SP

Vitor Engrácia Valenti – PhD student in Cardiology at UNIFESP/EPM, São Paulo/SP

Trends in animal experimentation

"...The conscious admiration and the respect for the creation - of which the man is, at the same time, part and subject, will inspire him with respect and consideration that he owes to his similar, because that is its logical conclusion."
(Carlos B. G. Petcotche)

Comments on the study "Trends in animal experimentation" authored by Full Professor Rosângela Monteiro, published in issue 24.4 of the Brazilian Journal of Cardiovascular Surgery (BJCVS).[1]

The activity of experimental surgery encompasses training in surgery and work in scientific research. In these changing times, on which the "learning curve" of the surgeon in training is no longer permissible, the learning in quality laboratory becomes an issue of renewed importance. [2,3]

I sought data from published literature on experimental surgery in the Journal of the Brazilian College of Surgeons in the years 2007 and 2008, highlighting the periodicity of the journal, its indexing (Latindex, LILACS and SciELO, Scopus, DOAJ and "Free Medical Journals") its circulation (5000 copies) and also because they cover studies in the area of surgery as primary focus. In that period assessed, 177 were original articles and 21 approached experimental study (11.86%). It was observed that in four (19.04%) the records of the study on the ethics committee were cited (date and registration number).

Animal experimentation should follow the recommendations of the "3 Rs", proposed by Russell and Burch (1959): reduction (reduced number of animals under experimentation), refinement (relief of pain and stress, and increasing the welfare of animals under experimentation) and replacement (replacement of animals in research for simulators) [4]. In an editorial, Goldenberg (2007) also highlights three important principles in animal experimentation: gain experience does not mean to cause injury, the practice of art and science must come together and publishing of the experimental study, because non-published knowledge is a lack of knowledge [5].

Regarding an editorial trend to be followed in studies on the experimental surgeries published by BJCVS in species of the phylum Chordata and subphylum Vertebrata, one should contain the recommendations similar to those from the Acta Cirúrgica Brasileira

(www.sobradpec.org.br):

1. following the precepts of the Brazilian College of Animal Experimentation - COBEA (www.cobea.org.br);
2. requesting a copy of the study protocol submitted to the Ethics Committee of the Institution on which the study was performed, as well as presenting these data attached to the Method, when submitting the study to the editor of BJCVS.

Not all ethical issues of the experimental study can be resolved with the recommendations above, but they would

certainly bring fewer hassles in relation to philosophical questions about animal rights or the moral equivalence between all animal species. [6].

Hélcio Giffhorn, Curitiba/PR

REFERENCES

1. Monteiro R, Brandau R, Gomes WJ, Braile DM. Tendências em experimentação animal. Rev Bras Cir Cardiovasc 2009;24(4):506-513.
2. Hagl S. Cardiothoracic surgery: time for reappraisal! Eur J Cardiothorac Surg 2008;33:759-766.
3. Lang CM and Harrell GT. Guidelines for a Quality Program of Laboratory Animal Medicine in a Medical School. Journal of Medical Education 1972;47:267-271.
4. Tanaka H, Kobayashi E. Education and research using experimental pigs in a medical school. J Artif Organs 2006;9:136-143.
5. Goldenberg S. Citizenship and experimental research. Editorial. Acta Cir Bras 2007;22(2):84.
6. Cohen C. The case for the use of animals in biomedical research. N Engl J Med 1986;315:865-870.

Answer

Dear Dr. Hélcio Giffhorn,

Initially, we would like to thank you for your letter regarding the article “Trends in animal experimentation”, published in issue 24.4 of the Brazilian Journal of Cardiovascular Surgery (BJCVS) [1]. We believe that this is an additional opportunity to comment on other aspects related to animal experimentation.

Some years ago, in the Instructions to Authors of BJCVS, ethics in animal experimentation has been receiving special attention. On the item Research with Humans and Animals is established that “In experimental studies involving animals, the standards established in the *Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Academy of Sciences, Washington, DC, 1996)* and the Ethical principles for animal experimentation of the Brazilian College of Animal Experimentation (COBEA) must be respected, in accordance with the guidelines of the *International Committee of Medical Journal Editors - Vancouver Group*. Moreover, in Instructions to Authors, is established that in the

Methods section of the study must state that “the research was approved by the Research Ethics Committee of its institution”.

Ethical aspects in performing the articles published in BJCVS have been contemplated, including the form of evaluation of manuscripts submitted for publication in BJCVS, in which members of the Editorial Board should determine whether these aspects were contemplated both in studies involving patients – which includes good clinical practices, approval by the Scientific and Ethics Committees, obtaining Written Informed Consent - but also in research using animals, with emphasis on proper management of them.

Finally, we believe that knowledge of physiology and needs of each animal species is essential to ensure not only the reliability of results obtained in the research, but mainly to avoid inadequate handling of animals and the consequent suffering and unnecessary stress.

Sincerely,

Rosângela Monteiro, Ricardo Brandau, Walter J. Gomes, Domingo M. Braile

REFERENCE

1. Monteiro R, Brandau R, Gomes WJ, Braile DM. Tendências em experimentação animal. Rev Bras Cir Cardiovasc. 2009;24(4):506-13.

ROOBY study: A critical view

In a recent article published in The New England Journal of Medicine (NEJM), Shroyer et al. [1], in their study ROOBY Trial, present outcomes quite controversial of coronary surgery when compared to techniques already well established currently, such as coronary artery bypass grafting (CABG) with and without cardiopulmonary bypass (CPB).

The ROOBY study was performed at Veterans Hospitals of the United States of America, against several other previously published studies [2,3], which showed benefit of off-pump CABG surgery over the on-pump technique, in several outcomes in specific subgroups such as elderly and patients with serious coexisting morbidities.

Some comments should be made about the “ROOBY TRIAL”:

1. The study is not double-blind: the surgeon knew which technique would be employed. As the criteria for complete and incomplete revascularization was based on

the number of grafts planned before the operation and the number of grafts really confectioned for each patient, it was enough that the surgeon of the off-pump group overestimated the indication of grafts so that there was a negative influence on the secondary endpoint of the CABG group. After all, it is technically more difficult to make grafts to multiple territories in the same beating heart procedure, compared with the procedure with the heart stopped.

2. The surgeon, to participate in the study, had to prove that previously performed only 20 off-pump CABG surgeries (the experience average was 50 cases). Among these 20 cases, the surgeon should present as evidence, only a few cases he had performed as off-pump CABG in any territory of the heart. This fact will influence the endpoint that analyzes complete myocardial revascularization, which will impair off-pump CABG, in which the technical difficulty is greater, requiring a higher learning curve especially in triple-artery patients (representing 66.1% of the population of the study). Therefore, 20 cases of experience does not seem sufficient for the surgeon is considered allocated on the learning curve plateau of off-pump CABG. On the other hand, are 50 cases, by coincidence, sufficient?

3. More than half of the procedures in both groups were performed by resident physicians. It is obviously that this fact does not deserve too much comments as their positions in the learning curve. This impaired the outcomes of the ROOBY Trial. It impaired mainly the off-pump CABG group, in which the technical difficulty is greater.

4. The study was composed of more than 99% of male patients, which was not possible to extrapolate the results for women.

5. There was cross-over three times higher in the off-pump CABG group, or that is, there was a higher conversion of procedure intraoperatively in this group. This difference also represented statistical significance. Despite the cross-over, patients who were converted from one procedure to another continued being evaluated as originally planned. This means that patients randomized to the off-pump CABG group who underwent surgery using CPB (by conversion) had all their complications and negative outcomes computed in the off-pump CABG group, when they should have been evaluated as participants of the on-pump CABG group.

6. In the analysis of the grafts patency, through catheterization, it was not performed follow-up of 35.6% of patients. So we do not know how it would be a real comparison of outcomes compared to the initial group. This implies that the risk analysis of loss of permeability should have been examined in the light of an analysis of clinical pre-trial characteristics only of the group analyzed in terms of arterial patency (or that is, those who performed catheterization). With this, a new comparative analysis of pre-intervention clinical characteristics should have been

performed (identifying possible differences between on-pump and off-pump CABG groups only from patients who have undergone catheterization, making statistical analysis using logistic regression, with removal of the influence of risk factors for loss of patency if there were significant differences (diabetes, hypertension, smoking, etc.). This was not performed in the study, since the authors took into account the clinical characteristics of the initial total (without loss of 35.6% for assessment by catheterization), in which there were no significant differences between groups, which mistakenly led to non-compliance of the need for further analysis of pre-intervention clinical characteristics, and subsequent analysis with logistic regression.

7. The population evaluated with cardiac catheterization accounted for only 64.4% of the total population of the randomization. One hundred and twelve (8.1%) patients received radial artery grafts - not specified to which territories; sixty (4.3%) had used left mammary to territory different from the anterior descending. The study does not specify which groups received these grafts and in which percentage. Any differences in the concentration of these grafts in one of the groups influence the outcomes. These percentages influence the patency and certainly in mortality from cardiac causes. And in this data are only counted patients who were evaluated by cardiac catheterization. As for the remaining who did not undergo catheterization (35.6%), it is not mentioned in the study the pattern of graft used. Again, this part that is not approached in the study certainly influences the outcomes negatively or positively to one of the groups, or also the possibility of influence nil. This is a gap that the study misses.

8. Regarding neurocognitive assessment, similar phenomenon occurred to the evaluation of graft patency, and less than half of the patients was assessed from this point of view. Or that is, once again there was the mistake of not evaluating the patients in light of the pre-intervention clinical characteristics that affect the outcomes. The patients were assessed as if they were homogeneous groups, when in fact we do not have this information, because this comparison of the groups that were really assessed (only those who underwent follow-up of the the secondary outcome in question - neurocognitive function) was not performed.

9. It was demonstrated higher mortality in the off-pump CABG group. This probably was the result of two aspects: a) lower graft patency in the off-pump CABG group and b) increased number of incomplete revascularization in the off-pump CABG group. Both aspects are influenced directly by the surgeons skill. Clearly, in this study the ability of surgeons who operated in the off-pump CABG group was not in scale worthy of trust, considering that the average of off-pump procedures was of only 50 procedures

performed. The same may be applicable to the on-pump CABG group, however, we must not forget that the technical difficulty of making a bypass without CPB is higher compared to on-pump, especially for surgeons who have not reached the plateau in the learning curve.

10. CABG is itself a procedure that demands a lot of technical skill. The key to success of this surgery is graft patency. Confirmation of graft patency before and after protamine administration requires an objective documentation, using available technologies, such as Flowmeter [4]. Subjective evaluations, such as digital palpation, normal electrocardiogram or hemodynamic stability are unreal. The graft can already be performed occluded during the closure of the chest. Accordingly, coronary angiography performed as follow-up shows occlusion of the graft, which could be attributed to technical failure during the closure of the chest, rather than poor rate of graft patency related to a technique or another. In this study, Shroyer et al. [1] have not reported the need to objectively verify the graft patency after the procedure. In our view, this is the biggest flaw of this study, which invalidates the results and conclusions. CABG without CPB may be more difficult technically than surgery with CPB, however, when comparing results of grafts patency, the starting point is its determination prior to closure of the chest, which should be the same in both techniques. If different, it indicates that the surgeon is inexperienced with either technique.

Finally, we expect the ROOBY study, published in a journal of high global impact (NEJM), is read and interpreted in the light of reality and faults committed by their authors. Also, we expect that such study does not impair the use of a surgical procedure as important as the off-pump CABG surgery and thus hindering its use and benefits to our patients.

REFERENCES

1. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, et al. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med.* 2009;361(19):1827-37.
2. Lima R, Diniz R, Césio A, Vasconcelos F, Gesteira M, Menezes A, et al. Revascularização miocárdica em pacientes octogenários: estudo retrospectivo e comparativo entre pacientes operados com e sem circulação extracorpórea. *Rev Bras Cir Cardiovasc.* 2005;20(1):8-13.
3. Iglésias JCR, Lourenção Jr. A, Dallan LAO, Puig LB, Oliveira SA. Revascularização do miocárdio no paciente idoso: com ou sem circulação extracorpórea? *Rev Bras Cir Cardiovasc.* 2003;18(4):321-5.
4. Gwozdziwicz M. Cardiomed coronary flow meter for

prevention of early occlusion in aortocoronary bypass grafting. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2004;148(1):59-61.

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Cystatin C and Glomerular Filtration Rate

Dear Editor,

I have read the recent publication by Felicio et al. (RBCCV/BJCVS 24.3) with a great interest. Felicio et al. [1] reported on the comparative usage of “Cystatin C and glomerular filtration rate in the cardiac surgery with cardiopulmonary bypass”. Felicio et al. [1] concluded that “The cystatin C and the Cys-GFR showed significant changes after cardiac surgery when compared with the creatinine and respective GFR calculated by the Cockcroft-Gault and MDRD formulas”. Indeed, the use of cystatin C is accepted in cardiac surgery [2,3]. However, there is a considerable concern on cost of cystatin C. Momeni et al. [3] noted that “In patients with normal preoperative renal function undergoing coronary artery bypass graft, measured creatinine concentration remains a cheap and easy way of estimating renal function.” It will be a good information if Felicio et al. could provide more data on the comparative cost effectiveness of the studied alternative approaches.

Professor Viroj Wiwanitkit – Bangkok/Thailand

REFERENCES

1. Felicio ML, Andrade RR, Castiglia YMM, Silva MAM, Vianna PTG, Martins AS. Cystatin C and glomerular filtration rate in the cardiac surgery with cardiopulmonary bypass. *Rev Bras Cir Cardiovasc.* 2009;24(3):305-11.
2. Zhu J, Yin R, Wu H, Yi J, Luo L, Dong G, et al. Cystatin C as a reliable marker of renal function following heart valve

replacement surgery with cardiopulmonary bypass. *Clin Chim Acta*. 2006;374(1-2):116-21.

- Momeni M, Baele P, Jacquet L, Mourad M, Waterloos H, Wallemacq P. Cystatin C in cardiac surgery. *Acta Anaesthesiol Belg*. 2007;58(2):107-12.

Answer

Dear Professor Viroj Wiwanitkit,

Thank you for your interest and considerations about the article "Cystatin C and glomerular filtration rate in the cardiac surgery with cardiopulmonary bypass" [1]. Although creatinine measurement is a method widely used to assess renal function, it is known to be limited as serum creatinine concentration can be influenced by several factors [2]. Moreover, serum creatinine is considered to be a specific marker, but it is not very sensitive as its level does not significantly rise until glomerular filtration rate falls below 50% of normal values [3]. The never-ending search for the best (and early) marker of acute kidney injury has given rise to several studies of alternative renal function evaluation methods, cystatin C measurement among them. In our study, cystatin C was a better marker of renal function after cardiac surgery than creatinine.

Indeed, Momeni et al. [4] report that in patients undergoing coronary artery bypass graft, measured creatinina concentration is a cheap and easy way of estimating renal function. However, our results were not consistent with those obtained by Momeni et al. [4]. This probably occurred because, in Momeni's observation time was shorter, only the first 72 hours following surgery. In this period, patients are still found to be suffering the effect of considerable hemodilution, and with this the rise in serum cystatin C levels are not sufficient to be meaningful, as the cystatin C is also hemodiluted. Evidence of hemodilution after surgery was the drop in serum albumin concentration, a high molecular weight protein. In the Momeni study, plasma proteins value went from $7.1 \pm 0.33\text{g/dl}$ (before surgery) to $4.1 \pm 0.49\text{g/dl}$ (after surgery) and in our study were from $3.5 \pm 0.6\text{g/dl}$ to $2.5 \pm 0.3\text{g/dl}$ ($P=0.000$). One of the limitations of ours and Momeni's study is the number of patients observed. I believe the cystatin C method would be even more effective if a larger sample were used.

Cystatin C measurement is a simple method that can be routinely performed. As a matter of fact, this kind of testing is already available in some clinical laboratories.

Regarding costs, every new diagnostic method has a higher initial cost. Nonetheless, as the number of studies in the literature increases [4-8] and the use of the method in clinical practice spreads, costs tend to drop. I believe cystatin C is important because it is a marker that rises early and thus allows us to develop strategies to control and treat acute kidney injury.

Sincerely,

Dr. Marcello L. Felicio - Department of Cardiovascular Surgery - College of Medicine of Botucatu – São Paulo State University/Brazil

REFERENCES

- Felicio ML, Andrade RR, Castiglia YMM, Silva MAM, Vianna PTG, Martins AS. Cystatin C and glomerular filtration rate in the cardiac surgery with cardiopulmonary bypass. *Rev Bras Cir Cardiovasc*. 2009;24(3):305-11.
- Schrier RW, Wang W, Poole B, Mitra A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. *J Clin Invest*. 2004;114(1):5-14.
- Mahon P, Shorten G. Perioperative acute renal failure. *Curr Opin Anesthesiol*. 2004;19(3):332-8.
- Momeni M, Baele P, Jacquet L, Mourad M, Waterloos H, Wallemacq P. Cystatin C in cardiac surgery. *Acta Anaesthesiol Belg*. 2007;58(2):107-12.
- Zhu J, Yin R, Wu H, Yi J, Luo L, Dong G, et al. Cystatin C as a reliable marker of renal function following heart valve replacement surgery with cardiopulmonary bypass. *Clin Chim Acta*. 2006;374(1-2):116-21.
- Zahran A, El-Husseini A, Shoker A. Can cystatin C replace creatinine to estimate glomerular filtration rate? A literature review. *Am J Nephrol*. 2007;27(2):197-205.
- Ling Q, Xu X, Li JJ, Chen J, Shen JW, Zheng SS. Alternative definition of acute kidney injury following liver transplantation: based on serum creatinina and cystatin C levels. *Transplant Proc*. 2007;39(10):3257-60.
- Heringlake M, Wernerus M, Grünefeld J, Klaus S, Heinze H, Bechtel M, et al. The metabolic and renal effects of adrenaline and milrinone in patients with myocardial dysfunction after coronary artery bypass grafting. *Crit Care*. 2007;11(2):R51.