Assessment of Plasmatic Levels of Endothelial Progenitor Cells in Patients with Chronic Coronary Disease

To the Director

I have read with great interest the paper "Assessment of Plasmatic Levels of Endothelial Progenitor Cells in Patients with Chronic Coronary Disease" by Gagliardi et al. (1)

The relationship between the regular practice of exercise and the development of collateral circulation by progenitor cells in patients with chronic coronary artery disease (CAD) reaffirms that exercise is important for these patients. As the prevalence of these patients is high, there are a great number of them who are not eligible for revascularization.

Physical fitness might reduce myocardial ischemia and increase coronary reserve as it reduces myocardial oxygen requirements. A double product (DP) greater than the ischemic threshold reached during the exercise stress test results in an increase in coronary blood flow and it might be suggestive of collateral circulation or angiogenesis. Previous treatment with heparin produces an increase in DP as a factor related to VEFG before the exercise (2) suggesting the presence of collateral vessels.

In this study, maximal double product showed no modifications and there are no references to double product break point, thus it could be assumed that coronary blood flow did not increase; nevertheless, the active group of patients trained during 12 sessions presented a greater expression of progenitor cells, and the incidence of coronary risk factors was similar to that of the habitual treatment group.

Exercise might act as a constant stimulus to improve endothelial function and promote the development of collateral circulation to ischemic areas. This mechanism might result beneficial to a greater number of patients, even those with a poor control of their coronary risk factors.

Therapies focused on the development of angiogenesis are promising; meanwhile, patients' possibilities of accessing cardiac rehabilitation programs and remaining in them are still the most important challenges. This study is an incentive to increase our efforts in that sense.

My congratulations go to the authors for conducting a study with a great clinical value, which is distinctive of a work team that was graced with the presence and the contribution of the unforgettable Dr. Carlos Bertolasi.

Dr. José Luis Castellano

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Answer from the authors

We are thankful to Dr. Castellano for his concepts.

The double product (DP) break point showed no modifications as the protocol design established that 12 exercise sessions would be enough to assess the increase in progenitor cells. It is well-known that DP break point is modified by exercise only after 3 months in a rehabilitation program.

Probably the increase in progenitor cells is a previous issue to the modifications of exercise parameters.

Further studies will enable us to have a better understanding of physiologic mechanisms which explain the improvement of patients with chronic coronary artery disease in a programmed exercise plan.

Dr. Juan Gagliardi[MTSAC]

Cinefluoroscopic Assessment of Bivalve and Single-Leaflet Mechanical Heart Valve Prosthesis Implanted in the Argentine Republic

To the Director

I had the pleasure to read the study "Cinefluoroscopic assessment of eight models of bivalve mechanical heart valve prosthesis implanted in the Argentine Republic: its value as a complementary method to colour-Doppler echocardiography" (1) and the brief communication: "Cinefluoroscopic assessment of five models of single-leaflet mechanical heart valve prosthesis implanted in the Argentine Republic: its value as a complementary method to colour-Doppler echocardiography" (2) published by Cianciulli et al in the *RAC*, volume 76, 1. It should be emphasized the meticulous work the authors have carried out to characterize the different types of prostheses and the clinical relevance of this communication for subsequent consultations. It is very frequent that cardiologists in charge of performing echocardiography do not know the type of prosthetic heart valve implanted to the patient that is being assessed. In these cases, normal prosthetic valves are assessed with the help of reports from valve gradients considered "normal"; however, these records do not include all the models of pros-

theses implanted in our country. Nevertheless, the problem arises when gradients are "high" and poses the diagnosis of prosthetic obstruction versus mismatch. According to Cianciulli et al, cinefluoroscopy would be useful to establish the type of prosthesis and to assess prosthetic function. It should be taken into account that although this is an economical and accessible method, it would only be available in institutional facilities with radiology sections. Even more, the procedure should be performed by cardiologists with experience in prosthetic heart valves. Cinefluoroscopy is a method that was used 20 years ago, before the development of Doppler echocardiography, to assess pericardial calcifications (especially at the atrioventricular sulcus) in case of suspected constrictive pericarditis, calcifications of the coronary arteries, enlarged pulmonary hilum with hyperdynamic vasculature in cases of suspicion of atrial septal defect, and less frequently, to differentiate between valvular calcification and/or annular calcification versus valvular vegetation in elder patients. For this reason I consider the revaluation of this technique useful. In summary, I believe that Cianciulli et al have performed a significant contribution to the assessment of prostheses implanted in Argentina, and this paper will be frequently consulted.

Dr. Ricardo Migliore[MTSAC]

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Aquaporin-2 Abundance Modulation in the Kidney of the Rat: the Effect of Nitric Oxide During the Hypovolemic State

To the Director

My congratulations to the authors of the study that demonstrated the association between the nitric oxide system with the progressive reduction in the expression of aquaporin-2 water channels, which contribute to the alteration in the capacity of urine concentration as a response to hemorrhagic shock.

The hypothesis of the paper "Aquaporin-2 Abundance Modulation in the Kidney of the Rat: the Effect of Nitric Oxide During the Hypovolemic State" by Fellet et al (1) was that the production of NO induced by hemorrhagic shock might be associated with an alteration in aquaporin-2 expression; this protein participates in water management after an acute bleeding. In this way, the objective of the authors was to assess if the inhibition of the nitric oxide system alters aquaporin-2 expression and/or location in the collecting-duct systems in kidneys of anesthetized bleeding rats.

NO modulates renal hemodynamics and might be involved in sodium and water reabsorption in specific segments of the nephron, contributing to diuresis and natriuresis in different hydration states. (2) In addition, it is well-known that vasopressin is one of the factors involved in the adaptation of renal function in response to volume depletion and this has an effect on water channels abundance and expression in the renal collecting-duct system. (3) Nevertheless, a relationship between NO system and the regulation of aquaporin-2 expression after a hypovolemic state induced by acute bleeding has not been described yet. (4)

The authors have demonstrated that bleeding increased the expression of the aquaporin-2 channels, 120 minutes after hemorrhage induction. Immunolocation showed aquaporin-2 inside the cytoplasm of collecting-duct main cells in kidneys of bleeding rats. In addition, the inhibition of the NO system increased the protein levels of aquaporin-2 which were associated with the apical membrane and with the subapical region. Rates previously treated with L-NAME showed an increase in aquaporin-2 expression induced by bleeding.

This study demonstrates that NO might be involved in the expression of aquaporin-2 water channels, as well as in their rearrangement in response to hypotension induced by acute bleeding in anesthetized rats. It may be taken for granted that NO system might have a negative effect on the expression and translocation of aquaporin-2 membranes in the renal collecting-duct system, suggesting that a relationship exists between renal NO and antidiuresis induced by vasopressin during the hypovolemic state.

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Pedro Cossio. The Nobel Prize Never Honored

Dr. Jorge Carlos Trainini

Firstly, I would like to congratulate you for your book "Pedro Cossio – The Nobel Prize Never Honored", which constitutes a valuable effort to communicate the actions carried out by an important man and Argentinean professional who has not been completely recognized for his preeminent merits. Nevertheless, I would like to supply some historical data that is not intended to weaken the international importance of Dr. Cossio, who performed the third cardiac catheterization in a human being. I think it necessary to highlight a historical truth: the second cardiac catheterization was performed in Madrid in 1930.

I shall not make any comment on the first well known self-performed catheterization by Forssman; however, as a disciple of Dr. Carlos Jiménez Díaz, I want to emphasize that he performed the second procedure of this type. Dr. Jiménez Diaz was a Professor at the Complutense University of Madrid, who, having heard about Forssman's work, immediately thought about the possibilities of injecting drugs directly into the cardiac chambers in order to obtain an instant effect as well as to measure intracardiac pressures. He commented this idea to López Brenes, a cardiologist who tried to persuade him because he thought that the technique was not exempt from risks and it would not contribute with innovative information. Nevertheless, he found in Dr. Baldomero Sánchez Cuenca, who was head of the Section of Allergy, an enthusiastic collaborator who helped him throughout the whole project.

The procedure was performed with thin and long catheters on a volunteer patient who suffered from terminal leukemia. X-Rays were taken in different positions and the presence of the catheter in the cardiac chambers was demonstrated. No complications were recorded at the electrocardiogram. The result of this study was subsequently published at the "Archives of Cardiology and Hematology" under the heading "Right Heart Catheterization".

In 1970, The Nobel Prize Laureate Professor Andre Cournand opened the II Commemorative Lectures - Carlos Jiménez Díaz- with these words: "I have been honored with the affectionate friendship of the great clinician, humanist and generous good man, whose memory is honored by these lectures, since we first met more than ten years ago. The subject of this lecture "History of Cardiac Catheterization" is an opportunity to highlight that the name of Jiménez Díaz is associated with the second catheterization performed in the world and with the early development of this technique in man". In that opportunity, Cournand emphasized the importance of Dr. Cossio's studies in the subsequent development of cardiac catheterization.

Before ending, I would like to comment that the first physicians that thought about the possibilities of developing this technique were Forssman, an urologist, Jiménez Díaz, an internist and Sánchez Cuenca, a specialist in Allergy, and the first professionals with a solid cardiology background were Cossio, Padilla and Berconsky, who established the diagnostic and therapeutic possibilities of this procedure.

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Hospital Costs Analysis of Heart Failure with Preserved versus Depressed Systolic Function

To the Director

The article by Giorgi et al (1) published in the last issue of the *RAC* about hospital costs of heart failure generates some reflections.

Firstly, my congratulations to the authors for advancing in a field with too many opinions and quotes from foreign data and few (or none) own figures. Heart failure generates high health care system costs, particularly during hospital stay. It would be helpful for decision making, in order to estimate health care costs related to treatment of heart failure, to perform a similar analysis taking into account other cardiovascular and non-cardiovascular conditions.

Cost reduction is an issue as complex as the definition of heart failure and the election of an adequate perspective are (for the funder, the State, the health care provider and the society). Clearly, that the figures presented are only indicators which may differ from those presented by other funders, institutions and health care providers. This study serves us to awaken our consciousness in the search of more information.

It would have been interesting to include data about previous admissions for heart failure. For a long time we have been stating that our mistakes are more evident in patients with prior hospitalizations. Where have we failed if a patient that has been discharged is readmitted? Even in the absence of this piece of information, it is worthwhile to point out some characteristics of the population (which does not differ from other populations): 66% of patients had previous CHF; however less than 40% of patients were receiving loop diuretics and only about 20% beta blockers; in addition, only 50% of patients admitted with systolic dysfunction were on ACE inhibitors. Approximately 30% of patients had AF and only 10% were taking anticoagulant drugs (this may be probable related to the prevalence of old-aged patients). Each of the aforementioned treatments has demonstrated a reduction in admissions and, in consequence, in costs. It appears

that this is an issue which will never be insisted enough on.

Differences in costs between depressed and preserved systolic function may be partially explained by more medications and longer hospitalizations, as the authors have pointed out. Some questions to go further into this subject: Are diagnostic studies the same? In which proportion are they prescribed in one group and the other? Can the duration of the entire hospitalization be attributed to heart failure? Do 30% of patients admitted need inotropic support? And last, and going further from this paper in particular: if an additional day in hospital is necessary to adjust the medication more efficiently, the patient will be discharged in a better clinical status and there will be less probabilities of readmissions; so, is it right to analyze only the admission rate costs?

The study by Giogi et al is an excellent gate to knowledge. We should surpass it.

Dr. Jorge Thierer[MTSAC]

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Answer from the authors

Firstly, we would like to thank Dr. Thierer for his words and we coincide with his critical comments on the paper. They stay as teachings for the future. We were exactly interested in making the first step in the field of economic evaluation of health care, and especially in heart failure. As any first step, our study has evident limitations. If we had compared costs in heart failure with costs in other conditions, we would have given a frame of reference to the net cost in heart failure. We must clarify that we only had access to data of this disease. The use of inotropic drugs (30%) in the group of patients with preserved systolic function included renal-dose dopamine, as we have previously mentioned. The low incidence of treatments in patients with previous HF, as Dr. Thierer has pointed out, does not differ significantly with other published data. The causes of low adherence to treatment should be investigated further. This is another challenge we should deal with. Finally, the type of database design prevents us from answering Dr. Thierer's questions.

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Effects of Late Reperfusion in Myocardial Infarction on Morbidity, Mortality and Left Ventricular Function: a Meta-Analysis of Randomized Trials

To the Director

Treatment of patients with acute ST-elevation myocardial infarction presenting late after symptom onset is still a challenge for Medicine as this condition has high morbidity and mortality rates. (1) The result of the meta-analysis by Mariani et al (1) suggests that late angioplasty performed to post-infarction stable patients who do not have large areas of ischemia does not supply any additional benefit on survival. In addition, ventricular function showed a discreet and controversial improvement. This would mean the collapse of the open-artery hypothesis. There may be some physiopathological reasons to explain this absence of a net benefit. Patients who are stable and asymptomatic at 8.3 days (time since the onset of symptoms to angioplasty) after a myocardial infarction might not benefit from angioplasty probably because the amount of viable myocardial tissue is not significant. Even more, the impact of opening the infarct-related artery decreases over time. Nevertheless, there is increasing evidence of the benefit of performing an angioplasty within the first 48 hours after the onset of an acute ST-elevation myocardial infarction. (2, 3)

Late angioplasty offers some additional benefits due to the coexistence of coronary artery disease with myocardial impairment and necrosis, extensive inflammation and microvascular edema. In this context, angioplasty may be associated with distal embolization of atherothrombotic material that could potentially increase myocardial damage. These factors, added to ventricular dysfunction, might explain the increase of the rate of reinfarction seen in the meta-analysis.

Biologic processes are complex, and different variables – some well-known and others still unknown – play a role in preserving viable tissue. Some of these factors might be age, diabetes, smoking habits, overweight, collateral circulation, the amount of compromised tissue and its location, the size of the culprit vessel and the characteristics of the lesion, multiple vessel disease, ventricular function and renal function, as well as the outcomes of the coronary intervention. It might also be probable that some marginal benefits, such as an increase in ejection fraction, might start to be evident at late follow-up and are not taken into account during the analysis of clinical trials.

These results make us keep on sharpening the physiopathological way of thinking and the clinical judgment

in order to identify some post-infarction patients who might benefit from coronary revascularization.

Indeed, our efforts should focus on developing strategies in order to treat all patients with acute myocardial infarction with reperfusion therapies during the first hours after the onset of symptoms. These strategies should include teaching programs in high-risk populations, early diagnosis, availability of reperfusion therapies, possibility of referring certain groups of patients for angioplasty to tertiary centers, and a decrease in hospital timing to preserve a greater proportion of myocardium and reducing the risk of infarction.

Dr. Fernando Cura

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Effects of Late Reperfusion in Myocardial Infarction on Morbidity, Mortality and Left Ventricular Function: a Meta-Analysis of Randomized Trials

To the Director

We have read with profound interest the study by Mariani et al published at the *Revista* about the "effects of late reperfusion in myocardial infarction on morbidity, mortality and left ventricular function". The aforementioned study has encouraged us to communicate some reflections. The retrospective nature of meta-analysis has demonstrated to be a useful tool to generate hypothesis. In addition, when the evidence available is not enough, we are convinced that meta-analysis may provide objective answers to the questions posed during our clinical practice when they are performed with an adequate method of selection. Late opening of the infarct-related artery without a previous assessment of muscular status is an unfounded concept. The conclusions of the meta-analysis are consistent with this statement. Firstly, late angioplasty (PTCA) does not reduce total mortality or cardiovascular mortality. The study by Zeymer was a prospective and unblinded trial that reported favorable outcomes with late angioplasty; however, only 30% of patients presented occlusion of the infarct-related artery (versus 85% in OAT or DECOPI studies) and when this sub-group of patients was analyzed, PTCA did not show any additional benefit. Even more, total mortality related to PTCA was 4% after 4.5 years of follow-up, which means that the risk of the study population was extremely low compared to that reported by other series. The OAT study represents half of the evidence, and this might neutralize the differences appeared after the individual analysis, explaining why there was no significant heterogeneity among the studies. Secondly, PTCA increased the risk of reinfarction during follow-up (OAT: 7 versus 5.3%; HR: 1.36) and as a direct adverse outcome during the procedure (pooled data from TOMIIS, TOAT, OAT and DECOPI trials: 11 events versus 1 event; OR 5.4, 95% CI, 2-17; p: 0.003). The procedure may produce coronary vascular failure with subsequent new ischemic events instead of protecting myocardial viability.

Finally, PTCA does not reduce the incidence of heart failure during follow-up. Undoubtedly, the mechanisms involved in the physiopathology of postinfarction ventricular dysfunction are more complex than the simple equation open artery or occluded artery. In fact, the mechanisms responsible of postinfarction vascular and myocardial failure are as follows: an increase in parietal stress and oxidative stress, a greater inflammatory and neurohumoral activity, a high insulin resistance, the development of a prothrombotic state, and apoptosis. The effect of PTCA on EF showed some discrepancies among the studies; even more, pharmacologic treatment was inadequate in most studies.

Finally, the value of this meta-analysis may help us to build a more solid medical criterion, especially in the absence of a large randomized and prospective trial which might guide our medical behaviors. Individual medical experiences are valuable, though not always reproducible.

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