Plasma Levels of Apolipoproteins in a Healthy Population of Argentina: Implications for Cardiovascular Prevention

To the Director

The cross-sectional study of Siniawski et al (1) assesses the levels of apolipoproteins in healthy individuals that attend a general hospital as blood donors. Since Argentina is a country with a high incidence of atherosclerotic vascular disease, it is important to know the levels of these predictors of cardiovascular disease in healthy subjects.

Similar information is available, but it dates back to several years ago, and the variables that modify their levels –like obesity, among others– have changed substantially in recent years; it gives relevance to this new information.

The 463 patients included in the study represent a considerable number; the descriptive tabulation of variables that modify lipid levels is also important. This confirmed that gender, age and weight produced changes in this sample. Exclusion criteria were chosen so as not to assess individuals with vascular disease, diabetes, or lipid therapy.

Measurements of ApoB, ApoA and the ratio between them are performed for the first time on healthy individuals in Argentina, and it is relevant because, in important studies like INTERHEART and AMORIS, these measurements have been excellent predictors of cardiovascular disease.

Alfredo Lozada, M.D.

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Authors' Reply

We thank Dr. Alfredo Lozada's letter, and we agree on his comments. Determining reference values of plasma levels of apolipoproteins in the Argentine population is important. Our study is the first one to provide information for that purpose.

There is consensus as to whether the plasma level of apolipoprotein B (ApoB) and the ApoB/ApoA-1 ratio are better predictors of cardiovascular risk than conventional lipid measurements. (1, 2)

A recently published meta-analysis showed that plasma concentration of triglycerides, adjusted by other lipid variables, has no independent prognostic value. (3) In this context, as mentioned by Dr. Lozada, interesting variations were observed in the distribution of apolipoprotein levels according to body weight. Subjects with a body mass index ≥ 25 had higher ApoB and lower ApoA-1 values than those whose BMI was < 25. Probably, measurement of apolipoproteins may be useful to categorize the cardiovascular risk in overweight or obese individuals.

It was also our intention to suggest ApoB goals –a biomarker that is likely to replace LDL-C progressively– as the treatment objective. Several studies showed that the concentration of ApoB was a better indicator of the clinical benefit of lipid-lowering therapy, and also that the therapeutic response was often not consistent with the reduction of LDL-C. (4)

As referenced in the study, the ApoB value for the 20th percentile of LDL-C (100 mg/dl) was 72 mg/dl, lower than the goal recommended by the Canadian guidelines for subjects with high or very high vascular risk. (5) An ApoB level > 117 mg/dl (80th percentile of LDL-C) could be considered a marker of atherogenic risk, and could be used to select patients for screening of subclinical atherosclerosis.

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Permanent Para-Hisian Pacing. Indications and Follow-Up

To the Director

I have read with great enthusiasm the paper by Dr. Ortega and his group. (1) After their first presentation, *Septal Para-Hisian Pacing. Analysis of Indications and Follow-Up*, (2) in which they showed us the feasibility of this type of pacing, now they demonstrate the 'safety and efficiency' of pacing with this special placement of the catheter. The type of population included made it *unnecessary* for them to use a third catheter in the right ventricular apex to ensure stimulation. Undoubtedly, using a DDD pacemaker reduced costs significantly, and also prevented possible complications.

The idea of starting pacing from a 'more physiologic' location than the tip of the RV is not new, as it has already been experienced in the world, but it is very valuable that they show us their own experience.

It should also be pointed out that measures performed to show the benefits of this type of pacing are commendable, which encourages its use.

I share the view of taking into account the 'special morphology' of the QRS, *"The QRS complex usually shows an initial slow deflection, similar to a delta wave, and this was attributed to depolarization of the septal muscle prior to entering the normal conduction system. For some authors, this is a problem because pacing is not pure hisian; for our group, it is a safe pacing mechanism, because if the His bundle trunk was not depolarized, the impulse could be transmitted through non-specialized muscle"*, and so indications could be extended.

The catheter placement technique implies having special instruments, searching for QRS morphology to appear normal, having a vast previous experience in the use of different catheters, and having more surgical time; however, this new location to pace the ventricle is worth these implications.

By now, the population that can receive this newest position is somewhat limited; however, adverse effects –well proven effects– of RV pacing could be prevented.

Time will tell if this new challenge to achieve a more physiological pacing will have its place in cardiac stimulation.

Mr. Director, allow me to congratulate the authors for their work.

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Usefulness of Intrapericardial Cisplatin for the Management of Malignant Pericardial Effusion

To the Director

I have read with interest the work by Zylberman et al (1) on intrapericardial treatment with cisplatin for cancer patients with cardiac tamponade or severe pericardial effusion.

In my opinion, these publications are important, since they encourage the expansion of the experience with a treatment that, although it seems to be well established –like the use of intrapericardial cisplatin–, still requires to be backed with larger randomized studies.

The authors have decided to use cisplatin –which seems to be the most used drug nowadays– because it is a safe treatment, with a low rate of adverse effects, and apparently effective in preventing recurrence of pericardial effusion. (2)

A controversy has been raised over whether the use of cytostatic drugs –especially cisplatin– is a better choice due to its possible healing effect on the root cause of pericardial effusion, or if, instead, it is better to use less cytostatic agents but with sclerosing effect, as is the case of bleomycin or thiotepa, considering that, in up to 30% of the cases, cytology is negative and effussion may be due to other ethiologies, such as actinic pericarditis or other opportunistic infections. In this regard, only one randomized study compared bleomycin versus single pericardiocentesis, and although there was a trend to lower recurrence of effusion in the bleomycin group, the difference was not statistically significant. (3) The objection raised to the use of sclerosing agents is the lower efficiency as a cytostatic and the higher frequency of pericardial constriction. (2)

The presence of clinical signs of tamponade represents an absolute indication to perform pericardiocentesis, but this situation should be avoided. In this regard, the echocardiographic indicators of hemodynamic compromise resulting from the 2D echocardiography and Doppler used by the authors help to make an early decision, although they should be used with caution, and taking the clinical context into account. While there is no uniformity of criteria regarding the definition of severe pericardial effusion, the authors take 10 mm gap between sheets to define severe effusion, which impresses me because it is a very low cut-off point. The scarce pericardial fluid makes pericardiocentesis more difficult and risky regarding complications. Although diastolic collapse of the right atrium is very sensitive, it is unspecific and highly load-dependent, and the venous plethora or decreased inspiratory collapse of the inferior vena cava can also respond to significant tricuspid regurgitation or pulmonary hypertension.

Finally, I would like to ask the authors which is the strategy of ultrasound-guided pericardiocentesis they used, since, according to the techniques described by the Mayo Clinic group, the sonographer must indicate the site with greatest separation between pericardial sheets and the shortest-distance point between the pericardial effusion and the skin surface. This usually determines better access at parasternal or apical level, but not at subxiphoid level. Contrary to what is usually believed, echocardiography generally does not permit visualization of the puncture needle or the progress of a catheter.

Echocardiographic guidance is also used for injection of physiological salt solution through the pericardiocentesis catheter, and in this way, be assured of being in the pericardial space prior to instillation of the cytostatic agent, particularly in cases of hemorrhagic effusions. (4)

Dr. Gabriel Scattini, M.D.

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Authors' Reply

We are very grateful to Dr. Scattini's letter about our work *Usefulness of Intrapericardial Cisplatin for the Management of Malignant Pericardial Effusion*.

Regarding the questions he poses, we believe that the following comments may be useful:

We chose cisplatin because when we started using it, in 2005, we based on the experience from other authors to suspect about its low toxicity (1, 2) compared with that of the sclerosing agents. (3)

As expressed by Dr. Scattini, the decision to prescribe this treatment depends on clinical judgement. On the one hand, we always try to show the malignant infiltration of the pericardium; on the other hand, we have treated patients with no tamponade but with progressive effusion but no expectations to other systemic therapies.

Regarding the surgical approach to the pericardium, we have followed the protocol guidelines in the Spanish (1) and German (4) groups using the subxiphoid route. While our group is experienced in evacuation via the parasternal route, it has not been necessary to use it for this group of patients.

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Treatment of Critical Lower Limb Ischemia

To the Director

With reference to the article by Jozami et al, (1) I think endovascular treatment for critical lower limb ischemia should not be considered as the only possible treatment, since this condition is too varied to be solved with a single therapeutic approach.

Marston (2) reported a subgroup of patients with extense but stable and non-complicated loss of tissue, who were not candidates for revascularization due to comorbidity or anatomic considerations; they were treated with wound-healing techniques. 38% required amputation per year.

The BASIL (Bypass versus Angioplasty in Severe Ischemia of the Leg) trial compares bypass surgery first strategy to a balloon angioplasty first strategy in patients with infra-inguinal disease. Survival rate without amputation, rates of mortality from all causes, and rates of life quality were similar in both groups.

A recent meta-analysis reviewed angioplasty or popliteal to distal vein bypass. While primary and secondary patency favored bypass, there was no difference with the limb salvage rate.

Conte et al (3) pooled data from three multicenter, prospective trials (PREVENT III, CIRCULASE II and BASIL), and found out that the combination of age > 80 years and tissue loss was associated with a 3.1-fold increased risk of major adverse events.

TASC identified the following indications for primary amputation: non-reconstructible arterial occlusive disease, necrosis in significant foot support areas, irreversible flexion contracture of the leg, terminal illness, very short life expectancy.

From the nationwide Finnish vascular registry (Finnvasc), Biancari et al (4) developed a risk scoring method to better predict immediate post-surgical outcome after femoral endarterectomy, femoropopliteal bypass, or infrapopliteal bypass. The risk factors validated by the multivariate analysis were: diabetes, ischemic heart disease, gangrene of the foot, and urgent intervention. One point was assigned to each risk factor.

Schanzer et al (5) developed a model to predict amputation free survival using the PREVENT III trial cohort. Five predictive factors were identified and a risk score was assigned to each of them: dialysis in chronic kidney failure, 4 points; tissue loss –defined as non-healing ulcer or gangrene– 3 points; age > 75 years, 2 points; hematocrit < 30%, 2 points; ischemic heart disease, 1 point. One-year amputation free survival, in vein bypass, 86% in patients with score < 3, 73% between 4 and 7 points, and 45% in patients with > 8 points.

Goodney et al (6) analyzed the ability to predict which patients will be on ambulatory status one year after bypass. If no risk factor was present (age, inability to walk before surgery, not self-sufficient, patency of the bypass), the possibility of death or inability to

ambulate was < 5%, while those with three or more risk factors had 50% possibilities of death or inability to walk in a year.

Tang et al (7) developed a biological/biochemical binary system of logistic regression, Vascular Biochemistry and Hematology Outcomes Model (VBHOM), to predict death after amputation. The equation includes gender, mode of admission, age at admission, urea, sodium, potassium, hemoglobin, white blood cell count, creatinine.

Treatments based on genetics and cell therapy can be helpful in the future, but further research is needed.

At present, the treating physician may find it useful to assess the following:

– If the patient can perform independent daily activities, has neither significant coronary heart disease nor renal failure requiring dialysis, and is younger than 75 years of age, he/she should undergo open or endovascular bypass.
– If, in contrast, the patient has limited life expectancy, is dependent, does not ambulate, presents significant necrosis in foot support areas or increasing infection, amputation should be considered.
– If tissue loss is stable and non-complicated, medication and lesion healing could be a valid option for subjects with little hope for surgical resolution, taking into account the limitations of this procedure.

Emilio Turco, M.D.

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Cardiac Myxomas. Clinical Presentation, Surgical Outcomes, and Long-Term Prognosis

To the Director

We have read with great interest the recent paper published by Enzo González et al, from the Favaloro Foundation University Hospital. (1)

To begin with, the large caseload is remarkable, with 59 patients undergoing surgery in a 14 years period, compared with a very rare disease with a late post-surgical follow-up, which is only comparable –in design and outcomes– to the one recently published by Kurouzynski et al (2), with 57 patients from a single center, who were followed-up for 22 years.

We highlight the important contribution of echocardiography by revolutioning its objectification in clinical practice, which was exclusive resort of pathology.

Moreover, clinical examination objectivates nonspecific mitral murmurs, and we point out a fact hightlighted by the authors as the "tumor plop", well known in the past, which, like all semiotic signs in today's cardiology –dependent on complementary tests–, is no longer relevant.

Embolism was another form of presentation, with its usual involvement of the brain area; however, unusual clinics such as inferior AMI due to coronary artery embolism, ischemia in lower limb, and even renal failure were also mentioned. In the caseload, there are even unusual patients whose tumor was located in the mitral valve system, with a high percentage of embolism secondary to valve motility. Coincidental with what Gabe et al reported, (3) García Zubiri et al (4) positively associated embolism with the smallest tumor diameter, and those with the largest tumor diameter being responsible for the symptoms in the elderly.

According to what has been described in classic works on echocardiography, (5) it is usually located in the left atrium, with pedicle attached to the interatrial septum, then the right atrium, the biatrial location, and finally the ventricular location (in younger patients). The intraoperative transesophageal echo allowed to examine the heart anatomy accurately and rule out masses in other cavities.

Surgical resection was the overall therapy, focusing on septal reconstruction with pericardial patches, and even the electrofulguration of the bed to avoid recurrence.

Only one patient died during surgery (1.7% mortality); as in most series, this procedure presented a very low mortality rate. (2, 4) The most common complications were complete AV block and supraventricular arrhythmias.

Since surgery is currently the only therapeutic option, we would like to mention the recent advances in molecular biology, trying to find the critical molecular pathways involved in the pathogenesis of myxomas, as well as the attempt to decode the molecular profile, which is a promising process to guide the treatment and determine a prognosis for this disease. (6)

Recurrence occured in only one patient with a family history of myxoma and skin lesions (Carney syndrome); high proliferative activity was confirmed through flow cytometry of the resected tumor.

It is particularly gratifying that, in our sphere, a late follow-up of almost 80 months can be carried out in 95% of the surgical patients.

We congratulate the authors on their detailed description of their caseload and the update of a very sporadic disease.

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