

May aortic stenosis be prevented in order to avoid hypertension?

To the Director

Aortic stenosis (AS) is associated with significant cardiovascular morbidity and mortality. Similar to atherosclerosis, in the progression towards AS, classical cardiovascular risk factors take place. (1) But, different from atherosclerosis, no therapeutic modality has shown to be efficient in order to retard the progression of AS.

Giunta et al., in their work published in the Journal, (2) showed the effectiveness of rosuvastatin to ease the development of AS in a model of hypertensive rabbits. This group of researchers from the Favalaro Foundation has developed the AS model generated by hypertension (HPT) using a 2 kidney-1 Goldblatt clip model. (3) The advantage of using the rabbit is in the anatomical similarity of its aortic valve with the one present in the human being.

In order to show that the effect of rosuvastatin is independent from cholesterol decrease, the experiment included a branch of treatment which was enriched with a diet with cholesterol to neutralize the hypolipemiant effect of statins. After six months of treatment, the branch of rosuvastatin alone and the one associated with a diet based on cholesterol were capable of easing hypertension and preventing the reduction of the aortic valve area, aortic valve sclerosis, increase in the transvalvular gradient and ventricular hypertrophy. (2)

The Goldblatt model, originally developed in dogs, results in severe hypertension dependent on the increase of renin. The consequent increase of angiotensin II generates tissue damage through HPT, but also stimulating oxidative stress, nitric oxide deficit, inflammation and fibrosis.

Through the inhibition of HMG-CoA reductase, statins also may inhibit isoprenoid synthesis, lipids that participate in the activation of receptor AT I signaling cascade. (4) Therefore, statins could act favorably in the development of AS due to reduction of cholesterol but also when interfering pro-oxidant, pro-inflammatory, profibrotic and pressor effects of angiotensin II.

Recently, several clinical trials which assessed the potential benefit of statins in the prevention of the disease have concluded in negative results. These results contrast with the epidemiological evidence that shows the association between AS and hypercholesterolemia, and with experimental models, as the one that belongs to Giunta et al. which shows the capacity that different statins have to inhibit their progression. (5)

Other drugs, such as ACE inhibitors, angiotensin II receptor antagonists (6) and bisphosphonates (7) will show their clinical usefulness in patients with AS.

However, the therapeutic opportunity is probably the factor that defines its future in the arsenal in this potentially mortal disease.

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The ST-segment depression which is present during the recovery phase: its contribution to the clinical use of the ergometry

To the Director

We have read carefully Crudo et al.'s work (1) which is related to the behavior of ST-segment during the recovery phase in an ergometry.

The work provides relevant data as regards a diagnostic procedure of easy accessibility, reproducibility and of low cost in comparison with more sophisticated and developed methods. However, we know that its usefulness is limited due to the fact that it presents low sensitivity and specificity in the prediction of risk and it establishes severity and anatomical extension. Several works have also shown the prognostic value of the subendocardial lesion which appears in the effort and remains in the recovery. (2, 3)

This study assesses and correlates the presence of ST-segment depression in three groups: during effort, during recovery and the one which is doubtful during effort and deepens during recovery. In this case, it assesses hemodynamic endpoints and they may be complemented with monitoring clinical variables (mortality, myocardial infarction).

The major risk involves patients from the third group which includes oldest patients and patients with major history of coronary heart diseases. Even so, outcomes confirm the importance and the prognostic value of this ergometric variable in three populations. Outcomes obtained in this work are convincing according to the proposed hypothesis which, in a future, could be assessed by taking into account relevant clinical endpoints.

**Dra. Marcela Cabo Fustaret,
Dra. Graciana M. Ciambrome, Dr. Fedor A. Novo**

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Author's response

We thank doctors Cabo Fustaret, Ciambrome and Novo for the interest in our work. The ergometric response of the ST depression in the recovery phase is of low prevalence, but the diagnostic and prognostic capacity of the coronary heart disease has been shown in previous publications. (1, 2) In our work, we have assessed ST depression that appears in the post-effort (II) and doubtful responses which are intensified during the recovery phase (G-III) and we observe that the correlation with the coronary heart disease was greater than in G-I with significant ST depression during effort, maintaining an appropriate diagnostic specificity (G-I: 74.8%, G-II: 87%, G-III: 94%). This gives a useful value to the response in order to establish the major severity of the coronary heart disease. Lesions of the three vessels and/or the left main coronary artery were prevailing in G-III which gathered oldest patients with a significant statistical difference in presence of dyslipidemia, history of previous myocardial infarction and usual medication with betablockers.

This research was observational with a reduced number of cases as a limitation and with no monitoring to determine the prognosis.

The ergometry still has an important role in the diagnostic process and in the assessment of the coronary heart disease.

**Dra. Norma Crudo, Dr. José Luis Castellano^{MTSAC},
Dr. Alfredo Piombo^{MTSAC}, representing authors**

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The cultural and humanistic training of the doctor

To the Director

Dear Dr. Carlos Tajer,

I have read with attention and satisfaction your essay about the cultural and humanistic training of the doctor. (1)

You have dealt in it with some important problems about the training of the doctor during postgraduate course.

From my experience as a Dean of a Faculty of Medicine, I may assure that the problems you mentioned in your article begin with the degree course and they continue after residencies.

The Universidad Abierta Interamericana, in which I hold my activities, favors the value formation without overlooking the professional part. We have to take into account that a doctor (or any professional) that flaunts "no values" may not be useful to patients or society.

In a survey that we carried out with the aim of fitting our degree curriculum to community needs, for most of the 900 inhabitants from Capital Federal who participated: communication (94.9%), containment (82.6%), guidance (89.9%) and the monitoring of the indicated treatment up to obtain the complete rehabilitation (97.6%) were the most valued capacities.

The controversy that rises when designing a curriculum for a degree or postgraduate course is the use of students' time and their preferential dedication on technical-professional or humanistic topics. In a workshop that I led about humanistic subjects, the audience conclusion (medicine teaching staff of different careers) was that the student's difficulty to face those topics was due to their professors' demand on the main subjects.

On the other hand, you referred to the risk of converting the learning of values in strict subjects and, although this is possible, a theoretical and practical base should be reinforced in all career subjects. Students listen to what we say, but they learn what we do. Attitudes and values are assimilated according to students' models of coexistence.

Students, before graduation and independently of some specific subjects (Philosophy and History of Medicine, Medical Ethics, Anthropology, Oral and Written Communication, Current World Situation), go to the Ability Laboratory where they interact with "actors" that officiate as patients in the career of Medicine in our University. A clinical interview with

an appropriate script, which is filmed, is performed. It is used by students to do a self and co-assessment (I attach some photos). Before being filmed, students agree on an informed consent.

In the same Laboratory, we work on a seminar named "How to give bad news"; about a guide which is read by students (attached material) and with specialized tutors.

All these experiences are assessed in a constant way and students take a portfolio with their reflections about their stay in the Laboratory.

To obtain the degree, students carry out a final career assessment (OSCE format) in which attitudes and the relationship with those "actors" are taken into account.

The training in values by subjects, which is essential to know the teaching efficiency and the learning quality, is carried out.

As regards the postgraduate course, the decision of this Deanship in keeping with the University authorities is that postgraduate careers will include a subject named "Values in the Health Field". The first subject with such contents was Specialization in Cardiology, subject that is given by Dr. Rafael Porcile (I attach the subject syllabus); specialization that shares its qualification with the Argentine Society of Cardiology (UAI-SAC, through an agreement). In the training of these professionals, workshops about narrative medicine were carried out. They were in charge of Lic. Isabel del Valle (Maine Humanities Council).

Important efforts are carried out in order to achieve the "Humanization of Medicine".

I will appreciate the publication of this article in the Argentine Journal of Cardiology in order to show some instruments that will help us to achieve the objectives you mentioned in your essay.

Yours sincerely,

Prof. Dr. Roberto Cherjovsky

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NOTE FROM THE RAC: The aforementioned attached materials are available on the online version of the Website.

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Vagus nerve and heart disease

To the Director

The surprising work presented by Buchholz et al. in our Journal (1) contradicts the current knowledge about the role of parasympathetic nervous system in cardiovascular pathophysiology. Effectively, the vagus nerve is a "great protector", although in some occasions "it is too clever by half", as when it modulates the

triggering of atrial fibrillation or when it participates in most of syncope. In this case, in spite of authors' findings, as regards ischemic heart disease, the vagus nerve reduces the incidence of lethal arrhythmias and sudden death against myocardial infarction; so this should be clear within the medical community. This was proved in basic and clinical researches in several opportunities. Peter Schwartz (3) published his famous test with conscious dogs. They were separated into two groups and Schwartz induced myocardial infarction and subsequent ischemia by means of exercise on them. He assessed the susceptibility of generating ventricular fibrillation with and without carotid vagus nerve stimulation through electrical stimulation, and he showed that the incidence of lethal arrhythmia was significantly minor in those that were "protected" by the vagus nerve. Even when this incidence was reverted by atropine. This has been previously observed in anesthetized animals.

Buchholz et al.'s work is referred to another topic, such as the increase in size of the myocardial infarction with vagus nerve stimulation, and it does not contradict clinical evidence. This comment is a look from the rhythmologist's angle and the objective is to keep the clinical concept of vagal "protection". Schwartz's tests were subsequently confirmed with the assessment of baroreceptor sensitivity through phenylephrine infusion which showed that the most sensitive patients had a minor mortality during monitoring. This clinical characteristic was shown in ATRAMI study (4) in more than 1,200 patients. The assessment of the vagal tone, through baroreceptor sensitivity and heart rate variability tests, was observed on them. And also its role in the reduction of the risk of sudden death which is independent from ventricular function in patients that carry myocardial infarction.

The vagal tone may be increased through physical exercise, with smoking cessation and stress reduction, among other steps.

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Which is the right methodology for vagus nerve stimulation in a study to reduce or increase the myocardial infarction size?

To the Director

Within subspecialties, electrophysiology is one of the cardiovascular branches that has generated more interest within the medical scientific community; its advances may be observed in the equipment of anatomical navigation for complex ablations and different stimulation studies, having into account places and ways of stimulation.

Nowadays, chronic vagus nerve stimulation (SVN) could be a potential treatment for several clinical conditions, such as epilepsy, depression, anxiety, cognitive disorders, Alzheimer's disease, migraines, involuntary movements and other neuropsychiatric disorders. (1)

Buchholz et al. (2) did not achieve the activation of preconditioning mechanism and the reduction in ischemic area, in an experimental model of ischemia in rabbits with previous SVN, with rectangular electric pulses (0.1 ms, 10 Hz) applied with the intention of inducing the liberation of acetylcholine. Contrary to this, myocardial infarction size is increased and such effect is reverted with the administration of atropine or beta blockers.

In the methodology proposed by several authors (3, 4), several exits with respect to voltage and pulse width are used to analyze studies of vagus nerve stimulation, in search of different cardiovascular responses, as an approach to the treatment for modulation of nodal conduction in patients with supraventricular arrhythmias, such as atrial fibrillation with a high ventricular response. One of the most used methods was carried out with exits of up to 10 volts, width 1 ms and 50 Hz, with biphasic waveform. (4) Progressive increases in stimulation exits show an increase in the vagal tone. (3) The use of a cardiac pacemaker may benefit those patients, achieving a decrease in ventricular response, proving in that way the increase in the vagal tone.

We agree with Dr. Piñero (1) when he considers that results from Buchholz et al.'s work should be corroborated in order to modify variables such as intensity, pulse width, frequency, duration of on and off periods and the moment of SVN.

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Author's response

I appreciate Dr. Alberto Giniger and Dr. Elibet Chávez González's contributions to our work "Preischemic efferent vagal stimulation increases myocardial infarction size in rabbits". We also thank Dr. Piñero's editorial, he has interpreted the essence of our study. (2)

Vagus nerve stimulation is a technique that has awakened researchers' interest, (3) initially to study its physiological effects on different organs and recently to understand the role of the vagus nerve in the physiopathology of several diseases. The discipline that has developed this technique in depth is neurology; so much so that vagus nerve stimulation is used in clinical practice for the complementary treatment of some neurological diseases as epilepsy, depression and demency. (3) Moreover, initial clinical trials have been developed to assess the effects of this technique in the context of heart failure. (4) However, mechanisms responsible of their effects are not clear.

In the first place, we coincide with Dr. Chávez González's comments, as well as Dr. Piñero's editorial, as regards the need of performing more studies to assess the effects from vagus nerve stimulation modifying stimulation parameters; due to structural and functional complexity of the vagus nerve, its stimulation with different electrical parameters should generate varied responses. In this sense, as Dr. Chávez mentioned, benefits using high frequency stimulations in the context of supraventricular arrhythmias were observed. (5) On the other hand, using stimulation parameters similar to those used in our work, beneficial effects of vagus nerve stimulation on the lesion due to ischemia and reperfusion have been pointed out. (6) On the contrary, in the study published in the Argentine Journal of Cardiology, we have shown that after an appropriate vagus nerve stimulation, an increase in the myocardial infarction size was produced, and such harmful effect is due to the coactivation of the sympathetic nervous system, since it was abolished using esmolol and atenolol. In a complementary way, and supporting these data, in another work published recently we show that vagus nerve stimulation increases plasmatic levels of catecholamines and it is also associated with an increase in the myocardial oxygen consumption. (7) Such variables may increase the myocardial infarction

size. Nevertheless, in a subsequent study, our group has shown that vagus nerve stimulation is capable of activating mechanisms of myocardial protection, reducing the myocardial infarction size, but this effect is evident only when ischemia and reperfusion are carried out in an isolated heart (a denervated one) perfused in a Langendorff system. (8) All our findings show that vagus nerve stimulation is capable of blending the ischemic preconditioning in the isolated organ, while in the in vivo animal there are systemic mechanisms which are activated and that generate an additional damage to the one produced by the own ischemia, and they are capable of increasing the myocardial infarction size.

The complexity of the vagus nerve stimulation study is shown when considering Schwartz et al.'s work, (9) mentioned by Dr. Giniger, who also show beneficial effects in the vagus nerve stimulation when antagonizing the sympathetic system. Their object of study is the onset of sudden death in a temporal framework away from acute ischemia, when the myocardial infarction is healed up. This situation differs from the initial moment of the myocardial infarction studied in our work, and our object of analysis, the myocardial infarction size after an acute episode of ischemia-reperfusion, is a different variable from the one considered by Schwartz et al.. Likewise, making a generalization of the effects is not convenient when studying vagus nerve stimulation; that is why each situation and each variable of study in particular should be considered.

Secondly, we want to point out the methodological aspect. There are clear differences in the cardiac nervous system in different species of animals. These differences involve variants in the anatomical individuality of sympathetic and parasympathetic nervous systems from the cervical level up to the formation of the intrinsic cardiac nervous system and the distribution of nerve fibers and receptors in different cardiac cavities. (3) In this way, the efferent stimulation of the tenth pair of cranial nerves is not always accompanied by a "subtle and beneficial" increase of the vagal tone at the cardiac level. The effector response after the stimulation is definitively more complex than that and it implies the participation of a great quantity of variables that are going to be studied.

Lastly, data published in the Argentine Journal of Cardiology may not contradict the concept about benefits of the increase in the vagal tone in different heart diseases, although a first analysis could suggest the contrary. Nevertheless, vagus nerve stimulation applied in certain conditions does not generate beneficial responses, but, on the contrary, it produces harmful effects. In this sense, reactive oxygen species are considered compounds that caused cell damage, and although this concept is still present, different studies have shown that they participate in signals which activate ischemic preconditioning. In 1986,

Murry et al. showed that if ischemic episodes are short and multiple, the heart goes to a preconditioning state and protects itself. (10) Our work, applying scientific methodology in a particular experimental model, allowed us to obtain results that clarify possible effects and underlying mechanisms. This is relevant, since, vagus nerve stimulation is been applied in patients and we need to find an ideal way of beneficial vagus nerve stimulation, reducing the possibilities of collateral effects.

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Multivessel coronary disease: and the non-invasive option?

To the Director

I have read with great interest the controversy between Roberto Battellini and Jorge Belardi about the controversial topic: percutaneous treatment (PT) versus surgical treatment (ST) in patients with multivessel coronary disease (MVD). (1) Motivated by this excellent discussion, as well as for the great setting that the Argentine Journal of Cardiology represents, I will carry out some considerations from

the perspective of a clinical cardiologist.

In the first place, as Belardi points out, the controversy shows that evidences may have different interpretations on the part of clinical, interventionist and surgical cardiologists. (1) Precisely, the last European and American guidelines recognize the need of reaching a consensus about MVD decisions in the Heart Team (multidisciplinary team). (2, 3) The European guideline recommends that in complex cases, revascularization should not be performed immediately after diagnostic angiography so that the Heart Team will arrange the time to assess the available information, reach a consensus, explain and discuss findings with the patient. (3) However, is this recommendation carry out in the practice?

Second, although the objective of the controversy was not the analysis of the optimal medical treatment (OMT) versus the PT and ST, (1) indirectly there are authors' statements that may lead readers (non-expert ones) to conclude that the OMT could not be a good option in the MVD. In this sense I am "agonist" of recommending the OMT as a first option due to the following reasons:

1. Atherosclerosis is a systemic disease. That is, the vascular risk does not only depend on coronary revascularization and there could be other vascular comorbidities in patients with MVD.
2. Three quarters of thrombi related to myocardial infarction are developed in plaques that cause mild or severe stenosis, from the angiographic point of view. (4)
3. The OMT is capable of causing regression of the atherosclerotic plaque. (6)
4. In the PT and ST not always a complete revascularization is achieved. (1, 2)
5. The cost and availability of PT and ST, elements that are intensified in "Third World countries" where 80% of the worldwide mortality due to cardiovascular diseases takes place.
6. Ischemic heart disease and the ascending prevalence of MVD with age and population aging. There is no doubt that diagnosed MVD is just the tip of the iceberg.
7. Complications that may take place in the PT and ST at short, mid and long-term. Several "minor" adverse events, which in practice may have great clinical impact for patients, as arrhythmias, peripheral vascular disease, sepsis, kidney damage, cognitive disorders, pleuropericardial effusions, are not taken into account in clinical trials. Consequences that may cause high radiation doses after revascularization at long term are not considered. For example, the effective dose of an angioplasty may vary between 6.9 mSv and 13 mSv, value that is equivalent to 345 and 650 chest x-rays respectively. (6)
8. Patients with personal background of coronary interventionism and/or surgery have the worst prognosis for a new revascularization. (1, 7)
9. The medical treatment may stimulate protective factors as atherogenesis and collateral circulation. (8)
10. Results from COURAGE study and other researches, in which a significant difference in the survival between the medical treatment and interventionism was not observed; although in such studies, all present OMT potentialities were not used. (2, 9)

The importance of applying an OMT is not sufficiently recognized, in part due to present interests are led to analyze the more appropriate type of interventionism, forgetting huge benefits that derive from a good fulfillment in the medical treatment. (11) In this sense, the community waits with interest results from FREEDOM study, in which patients have been treated very aggressively from the medical point of view, with a multidisciplinary approach led to modify drastically risk factors. (10)

Lastly, I congratulate the Argentine Journal of Cardiology for promoting the controversy which will always be a favorable exercise for science.

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Author's response

I appreciate the discussion provided by Dr. Morales Salinas. We believe that decisions about patients with MVD which are analyzed in the Heart Team are not carried out. In the year 2005, Dr. Robert Califf published an article named "Stenting or Surgery, an opportunity to do it right" (1) which was mentioned in point 4 from the conclusions of my controversy. (2) According to Califf angioplasty should not be performed at the moment of the diagnostic CCG.

As regards the optimal medical treatment that is suggested by Dr. Salinas, in general surgeons receive patients who underwent this treatment; may we say the same about patients who underwent an angioplasty? The subject of the controversy is surgical treatment versus angioplasty, so no surgeon may be against OMT.

Dr. Roberto Battellini

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I appreciate Dr. Morales Salinas for his interest in the controversy "Multivessel coronary disease. Surgical treatment versus angioplasty", developed together with Dr. Roberto Battellini.

As Dr. Morales Salinas mentioned, although the aim of the controversy was not to assess the medical treatment (MT), "the treatment of patients with multivessel coronary disease (MVD) is based mainly on an appropriate medical treatment, oriented to lessen symptoms and to modify intensively coronary risk factors, plus a revascularization strategy at the right moment" is clear at the beginning of the controversy.

The universe of patients with MVD is heterogeneous, from patients with problems in the three vessels with focal lesions up to patients with severe lesions of the left main coronary artery, so generalizations are difficult to apply. In this way, treating patients with MVD and disease of the left common trunk (LCT) with evocative tests of high risk ischemia only with MT would be medically inadequate, without indicating a revascularization strategy, although patients are clinically stable. The risk of each patient to indicate an appropriate therapeutic behavior should be stratified.

On the other hand, I do not agree with comments about COURAGE study, since the MT in both study branches was very aggressive and current, achieving a successful control of risk factors (BP < 130/85, LDL 60-85 mg/dl, HDL > 40 mg/dl and triglycerides < 150 mg/dl, HbA1c < 7%, smoking cessation), with a high adherence rate, plus an intense exercise plan, that is why I think that the OMT is sufficiently recognized and it constitutes the cornerstone of the treatment of patients with coronary heart disease, in the diagnosis and also during the monitoring after the implementation of a coronary revascularization procedure, with CA or MRS.

Finally, the importance of handling these patients through a multidisciplinary or individualized approach is highlighted in the conclusions; through the Heart Team which is the way of discussing these patients in our Center from the moment this controversy was published.

Dr. Jorge Belardi^{IMTSAC}

Blood pressure pattern assessment during the sleep-wake cycle in patients with metabolic syndrome

To the Director

There is a strong association between metabolic syndrome (MS) and the damage on the target organ, cardiovascular disease (CVD), cerebrovascular accident (CVA) and cardiovascular mortality. In the general population and among patients with hypertension (HPT), a high night blood pressure (BP) predicts a higher probability of damage on target organs and of CVD. Even more, the lack of nocturnal blood pressure fall (a 10% decrease in the average BP in nocturnal rest in relation to the average ambulatory pressure during daytime activity) and the increase of the ambulatory pulse pressure, among other factors related to the circadian rhythm pattern of BP, are associated with an increase in cardiovascular morbimortality.

In a study of the University of Vigo, Spain, the prevalence of MS was 40.7% in 2,045 non-complicated hypertensive patients with higher systolic pressure of 24 hours and lower diastolic pressure of 24 hours than patients without MS. Moreover, the presence of an alteration in the circadian rhythm of BP with non-dipper pattern was significantly higher among hypertensive patients with MS (48.4% vs. 36.1; $p < 0.001$). (1)

Patients with MS and alteration of nocturnal blood pressure fall have high values of cardiovascular risk markers. (2)

Leal et al.'s work (3) shows in a little sample (125 patients) of the adult population native from Venezuela (55 ± 12 years), the high prevalence of MS in primary health care with predominance of women (65%) and it realizes that 44% of patients with MS have lack of nocturnal fall of BP, higher daytime, nocturnal

and pulse BP than patients that don't have MS. The logistic regression model used in this work showed that the increase in the abdominal circumference was capable of predicting a non-dipper pattern with a power of prediction of 81.6%. On the other hand, the study shows the limited reproducibility of the circadian rhythm of BP measured by ambulatory blood pressure monitoring (ABPM) (83 patients excluded due to lack of reproducibility over a total of 208 analyzed patients, 39.9%) and the analysis was performed on 125 patients with two studies with good reproducibility of ABPM and the circadian rhythm of BP.

The work shows alterations in the circadian rhythm of BP with non-dipper pattern as well as in Hermida et al.'s work. (2) However, other studies (4) with a more numerous population have observed that the most frequent pattern among patients with MS is the one that corresponds to hyper-dippers (average nocturnal blood pressure fall > 20%), finding in the Greek population a decrease in the prevalence of dippers.

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