

## “Monkey see, monkey do”, or the contribution of mirror neurons to learning

### To the Director

The motivating letter by Dr. Hernán Doval, published in this year's first issue of the *Revista*, (1) excites the interest in trying to clarify the underlying concepts and theories in the teaching process of clinical medicine. In addition to recommending the reading of that essay, I thought it appropriate to mention the discovery of mirror neurons, in this case as a conceptual tool for transmitting and teaching motor skills.

Giacomo Rizzolatti, from the University of Parma, identified for the first time the so-called mirror neurons when he implanted electrodes on the premotor cortex (area F5) of the Macaque nemestrina (belonging to the Rhesus monkey family, but more docile). (2)

This area F5 consists of a group of motor neurons that control hand movement. According to one of the anecdotes about the first observation of a mirror neuron, in the eighties, there was a monkey sitting in the laboratory and waiting to be assigned the next task, when one of the experimenters –who was opposite the monkey– took something with his hand, and immediately the computer that was connected to the electrodes of the animal indicated a neuronal discharge activity from area F5. To the experimenter's surprise, the monkey remained sitting quietly, without trying to grab anything; however, this motor neuron associated to the prehensile act had been activated without any movement of the animal's hand. (3) In light of traditional knowledge, there is no reason why motor neurons anatomically connected to the muscles that move the hands should be activated when they are at rest and the animal does nothing but observe the movement another one does. Later on, through these observations it was discovered that 80% of the neurons from the area F5 are motor neurons, and the rest corresponds to this special type of mirror neurons, whose characteristic is to behave partly as motor neurons and partly as perceptive neurons; this contradicts the notion that action and perception are independent processes. Somehow, the existence of mirror neurons suggests that neither monkeys nor humans can observe the movement performed by another individual without invoking in the brain the motor plans necessary to perform the action by themselves. In further experiments performed on humans, using functional magnetic resonance imaging and transcranial magnetic stimulation, it was found that the activation of mirror neurons with the simple observation of a hand action induced in the observer a muscle activity recorded from electrodes placed in the hands, even though that observer was not performing any action.

This form of learning by imitation through mirror neurons seems to be the fastest and most effective way the brain has to learn new tasks or modify those

already learned. Observation is the natural form of learning in virtually all mammals, not because they memorize the movements observed but because they feel them in the brain as their own. Beyond the importance of cognitive function in the teaching and learning process in medicine –which allows to plan and select the motor behavior–, the conception of mirror neurons justifies an empiric observation made by our teachers throughout the years. On many occasions, any young applicant to surgeon has received the indications “concentrate on surgery and do not get distracted”, “because you're learning all the same even if you don't move your hands and you perform the surgery”, or “watching is learning”. And from the perspective of current knowledge about mirror neurons, these indications are much more justified. Proper attention to the movements of the surgeon (if skillful, much better) would induce the training of the observer's hand through the activity of mirror neurons. Although manual practice is essential for the general practitioner's training, particularly the surgeon's training, the discovery of mirror neurons provides a scientific framework for the use of certain tools for the technical teaching of medicine. With this approach, some pedagogical experiments may be proposed, in which learners are repeatedly exposed to watching films about a certain technique, and then they can be evaluated according to the acquisition of more or less skill, depending of the prior exposure to learning mediated by mirror neurons.

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## Is Cold Pressor Test Useful to Predict Cardiovascular Events in Patients with Not Documented Coronary Artery Disease?

### To the Director

I have read with great interest the work *Is Cold Pressor Test Useful to Predict Cardiovascular Events in Patients with Not Documented Coronary Artery Disease?*, by Pautasso et al. (1)

In this regard, I would like to share with my colleagues some concerns arisen from this elegant material. To begin with, the authors included a significant number of apparently healthy individuals who were referred by their primary care physicians to be performed a perfusion study. Here is the first question: Why was a perfusion study used

as diagnostic option? I can only speculate that it was requested because only 22% of the population admitted was asymptomatic. Or maybe because 50% had precordialgia, as reported in Table 1. If this was the case, perhaps the individuals were 'hiding' some clinical issue.

The second question requires a methodological explanation: Why was the population not performed an imaging study of the vascular tree? If the title announced "with not clinically documented coronary artery disease", I would not ask such question. However, considering the detailed demographic characteristics, it is hard to affirm in its real name that patients do not have atherosclerotic disease on the vessel wall. Thus, if a multi-slice computed tomography had been performed, it would have confirmed such hypothesis. In our work published in the Revista that you well run, and in another foreign one, we find a significant number of non-obstructive atherosclerotic plaques in an apparently healthy population with similar characteristics of age, weight and risk factors. (2, 3)

The authors make no mention about it in any segment of their work. To my mind, it is hard to understand these biological phenomena without health documentation about the parietal structures, at least using this or other invasive technologies such as coronary ultrasound or optical coherence tomography.

Finally, the authors argue that 32.4% (166) of the cases studied had a positive cold pressor test. However, only 12 patients had events during their follow-up. What are the authors' arguments to explain why the events did not occur in the remaining 154 subjects?

These questions do not detract the research. However, they may contribute to a better understanding of this fascinating process.

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## Authors' reply

We thank Dr. Enrique Gurfinkel for his interest in our work *Is Cold Pressor Test Useful to Predict Cardiovascular Events in Patients with Not Documented Coronary Artery Disease?*

One of the inclusion criteria of this work was

to have a normal rest-stress myocardial perfusion study, so it was essential to include this test for these patients. Physicians were never asked to refer patients to this protocol; moreover, many of them got to know it when we found a patient that met these criteria, and the primary care physician could accept or reject his inclusion. Only when patients were included, symptoms were analyzed. A significant proportion had precordialgia, coronary risk factors or nonspecific ECG alterations. Given that the rest-stress myocardial perfusion test was normal in all cases, it may be accepted that, despite the population was not fully healthy, its cardiovascular risk was relatively low.

Coronary atherosclerotic disease is an asymptomatic entity for a long period of time, which clinically expresses itself in the presence of myocardial ischemia. When we say that our group of patients does not have documented coronary artery disease, what we mean is that no myocardial ischemia was observed in any of them; in fact, when mentioning the goals of our work, we referred to patients with not documented ischemic heart disease. Perhaps a more accurate title should have included "with no ischemic heart disease documented by rest-stress myocardial perfusion studies".

On the other hand, we believe that, in this population, there may be patients with coronary atherosclerosis but no ischemia documentable by stress testing. Cold pressor test was positive in 32.4% of the patients; this suggests the presence of endothelial dysfunction, which represents an early stage of cardiovascular disease. This issue has been developed in the sections "Discussion" and "Interpretation of the cold pressor test result".

Knowledge of the coronary tree anatomy was not included in the design of our study, and this is why performing a multi-slice computed tomography in the 511 study individuals was not justified. We have attempted to analyze the incidence of cardiovascular events occurred in patients with positive cold pressor test, versus those with a negative test.

During follow-up, a low incidence of events was observed (as expected in this low-risk population): 14, in a total of 12 patients. What was most relevant in the study was the significant increase of events in the group with positive response versus those with negative response, as pointed out in Table 5 and Figure 1. This observation is consistent with other authors' findings (1, 2) whose responses were comparable under the effect of intracoronary acetylcholine, which was also commented on in the discussion of our publication.

We are available for any comments or suggestions, because we believe this exchange is useful for cardiology today.

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**Long-Term Outcome of Atherosclerotic Renovascular Disease in Patients Treated with Angioplasty**
**To the Director**

The diagnostic and therapeutic management of atherosclerotic renovascular disease is still controversial, or at least there is no clear systematization, even in the light of new data like those provided by the ASTRAL and CORAL studies. Dr. Gerardo Nau et al. (1) provide a valuable descriptive study of the evolution of a large series of patients with atherosclerotic renovascular disease (ARD) treated with stent-assisted angioplasty. The results are consistent with the similar series published by Felipe Ramos, Carol Kotliar et al. in the year 2000, (2), who also observed the predictive value of baseline creatinine or glomerular filtration (higher baseline renal impairment, greater response of blood pressure and post-intervention renal function). This goes in line with other similar studies that suggest the benefit of indicating coronary artery bypass with this method in the presence of renal impairment, defined by AHA as symptomatic ARD. (3) The follow-up of Nau et al in their series (median 1.7 years) shows improved evolution of most of the parameters, compared with the evolution reported by Dorros et al (4) in a 4-year follow-up. It is likely that, if the authors manage to continue with the follow-up, they will find deteriorating rates of blood pressure control. We believe the most important fact dealt with in the work is the greater benefit in terms of blood pressure drop and improved renal function in patients with bilateral lesions of the renal arteries, in whom renal functional impairment is greater. Also, these patients usually present more complications, particularly heart failure episodes. Probably, improvement of these patients is related to the fact that coronary artery bypass – along with improved renal blood flow– causes a better management of extracellular volume and sodium with the resulting benefit, particularly in patients with heart failure. But also, as we have recently noticed, (5) patients with bilateral ARD show extremely high levels of aldosterone, and their coronary artery bypass is associated with its notorious decrease. This would contribute to better management of the renal volume, and most probably it would interfere with the tissular and fibrotic stimulus of aldosterone, and the reversal of this effect would be the basis of the clinical improvement reported by the authors.

The amount of antihypertensive drugs at baseline and at follow-up seems suboptimal, given the characteristics of the risks for the population involved;

this gives rise to new research questions about the prior management and the magnitude of the response found.

To sum up, the study by Nau et al is a very valuable contribution that, despite the limitations of its retrospective design, reinforces the concept that some selected patients may indeed benefit from angioplasty, and those patients with bilateral stenosis –especially with CRF in stages III and IV– seem to be included among them.

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**Is There Any Room for Adenosine Test in Syncope of Unknown Origin?**
**To the Director**

We have read with interest the article published by Albina et al (1) about the use of the adenosine test in the diagnostic algorithm of the syncope of unknown origin. In this regard, we would like to discuss some points to be considered when using this test in daily practice. The adenosine is an endogenous nucleoside with different actions in different organs and systems. In the heart, through the A1 receptor binding, it acts on the atrial tissue and the sinus and atrioventricular nodes, particularly on the outward inwardly rectifying potassium currents  $I_{KAdo}$  and  $I_f$  current, among others, with negative chronotropic and dromotropic effects. (2) The positive adenosine test (bolus IV infusion of 20 mg of adenosine in the presence of asystole  $\geq 6$  seconds or transitory total AV block  $\geq 10$  seconds, regardless of the presence of ventricular escape rhythm) was first described by Brignole and Flammang in the syncope of unknown origin. Several works with different designs have attempted to include or discard this diagnostic test in the algorithm

for the syncope of unknown origin. Detractors argue that adenosine-dependent mechanisms are involved in the vasovagal syncope, in which a positive result is a neurocardiogenic equivalent, and not a conduction system disorder. (3) On the other hand, supporters of this method are based on the chances to reduce the rate of syncopes of unknown origin with this test, and some studies mention the high sensitivity and specificity of the method in detecting patients with unclear syncope and need for permanent cardiac pacing. (4)

However, the numerous works by detractors and supporters of the method compare different groups –both in age and underlying conditions–, leading to different outcomes for and against both lines of thought. But still there is not a clear answer to two key questions: 1) Does the positive adenosine test unmask a hidden conduction system disorder, or it simply shows a neuromediated response related to the vasovagal syncope? 2) What is the value of this test in the diagnostic algorithm for the syncope of unknown origin?

The merit of the work presented by Albina et al. lies in having achieved a defined and homogeneous sample: patients with malignant syncope (with facial trauma but no prodromes), without organic pathology, without obvious disorders in the conduction system, and with normal cardiac tests (including negative tilt test and normal electrophysiology study). And the merit also lies in having achieved a long-term follow-up with or without evidence of recurrence of the syncope, with the record of events in patients who were under pacing.

Regarding the first question, it is surprising that those patients who had a positive adenosine test and were implanted a dual-chamber pacemaker (working as VVI 40 bpm) had no recurrence of syncope, and their rate of stimulation was < 1%. At this point, a parenthesis should be added, since the brands of the implanted pacemakers are not mentioned in the article. This is not a minor detail, since in the devices manufactured by certain companies, the information displayed as 1% rate of stimulation would fall within the statistical error of the device, and it could actually be 0% stimulation. If this were the case, would it be a placebo effect of the pacemaker implantation? And would it support the neurocardiogenic mechanism of syncope sensitive to adenosine? Also, the two patients with positive adenosine test and recurrence of syncope had the longest pauses in the diagnostic test. Will that be statistically significant in a larger patient sample? Should we define new cut-off values for the adenosine test in order to find higher correlation with a masked conduction system disorder? Either way, larger samples and new studies are needed to respond to these concerns.

Regarding the second question, the opinion based on the experience of our group matches the one given by Albina et al. The adenosine test is a useful diagnostic method in the algorithm for the malignant

syncope of unknown origin, which shows a high negative predictive value, when no other possible causes are found after a thorough examination. However, the article does not define a course of action to take with positive-test patients; it only includes hygiene and dietary measures for vasovagal syncope, or the pacemaker implantation.

Based on the above findings in this and other similar works from the bibliography, we believe that the need for a pacemaker in these patients (syncope with normal neurological and cardiologic tests, with positive adenosine test) still remains uncertain.

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## Authors' reply

We thank Juan P. Montes', Emilio Logarzo's y Nicolás Mangani's interest and comments on our article "Is There Any Room for Adenosine Test in Syncope of Unknown Origin?"

The adenosine test began to be used as a predictor of cardioinhibitory responses in vasovagal syncope. Later, it was found that patients with negative tilt test and positive adenosine test had certain clinical differences, and this even led to include a new category within the etiology of syncope: the adenosine-sensitive syncope. However, the subsequent correlation of positive adenosine test with extreme bradycardia and –more precisely– with paroxysmal AV block at the time of the syncope was not good, resulting in a class III classification in the European Task Force. This categorization was grounded on observations drawn from unselected populations without distinguishing between patients with positive or negative tilt test, so it might be considered a bit hasty.

It should be pointed out that a positive test does not mean alteration of the conduction system but individual susceptibility to the negative dromotropic effect of adenosine in AV node; in fact, these patients have normal electrophysiology study.

Through our observation, we have been able to demonstrate the excellent progress of patients with negative adenosine test in a population with unexplained syncope, without prodromes, with severe trauma and without obvious heart disease. However, given the low incidence of clinical events, it was impossible for us to evaluate the positive predictive value of the test.

The brands of implanted pacemakers were different, and we agree that  $< 1$  does not necessarily mean 0% pacing; however, no conclusions can be drawn about the usefulness.

For now, systematic permanent pacemaker implantation cannot be recommended for positive-test patients; however, given the good clinical outcome of these patients, it will be possible to determine the actual usefulness of the positive test in future studies with no therapeutic intervention.

For all this we thank Dr. Montes, Dr. Logarzo, and Dr. Mangani once again for their interest in trying to find the meaning and value of the adenosine test in unexplained syncope with no obvious heart disease, which is defined as the one that remains undiagnosed after a thorough clinical examination and lab tests.

Gastón Albina, M.D.<sup>MTSAC</sup>

## Drug-Induced Long QT Syndrome

### To the Director

We present the case of a 59-year-old woman with diabetes, who was admitted in our center with chills, fever, diarrhea, and a sharp pain on one side with productive discharge, hemodynamically stable, with a four-day treatment with levofloxacin prior to admittance.

On admittance, a cardiologist was consulted for nonspecific chest pain that changed with breathing. Its coronary origin was ruled out, but the ECG showed a prolonged corrected QT (QTc) (Figure 1) of 660 msec, so the patient was referred to ICU for treatment. In 2009, the AHA defined the maximum QTc interval in 460 msec. (1)

At the admittance laboratory, abnormal potassium of 2.5 mEq/L (NV 3.5-5.2) was confirmed. Treatment was performed with drug discontinuation and administration of calcium, potassium, and IV magnesium, with corrected QTc at discharge.

### DISCUSSION

Prolongation of the QT interval is a rare condition, but the delay in (congenital or acquired) repolarization increases the risk of torsade de pointes (TdeP) and sudden death. (2, 3) Its multiple causes include the drug effect –like quinolones therapy, especially with levofloxacin–, (4) which prolongs the QT per se or due to predisposing factors like cardiovascular disease, hypokalemia, hypomagnesemia, bradycardia, age, old women, and/or the use of multiple medications such

as class IA and III antiarrhythmic drugs, which should be monitored in patients with probable heart disease, according to their warnings for use. It should be used with caution when combined with other agents that prolong the QT interval, or in situations like those described above. (5)

QTc is a poor predictor of risk of arrhythmia in an individual patient. (6) Most of the drugs that induce TdeP belong to the group whose QTc is prolonged beyond 500 msec. (7) However, while it is unusual that some drugs that prolong the QTc cause TdeP, other agents that cause minor changes in QTc are considered to have stronger proarrhythmic effect. These findings are associated with factors that go beyond the QTc, which are relevant in the genesis of TdeP (like transmural repolarization dispersion and genetic factors). (8) Despite these significant limitations as a marker, the QTc interval is still the best predictor of proarrhythmic drugs. (9-11)

This case is presented due to the widespread use of this medication in clinical medicine, sometimes without warning about the possible side effects or associations with concomitant pathology, as was the case of our patient, who, in addition to her bronchial condition, she had hypokalemia due to diarrhea.

### SUMMARY

Prolongation of the QTc interval has been associated with proarrhythmia resulting from a potentially fatal form of polymorphic ventricular tachycardia called torsade de pointes and sudden death.

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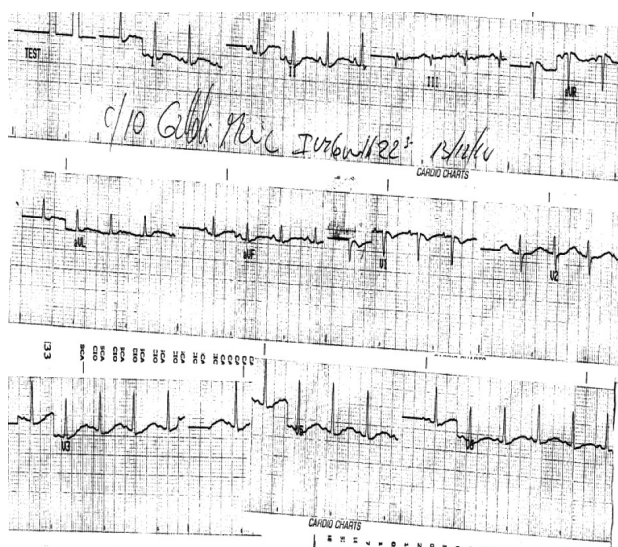


Fig. 1. Corrected QT interval on admittance: 0.66 seconds.

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