EDITORIAL

Clinical Usefulness of Cold Pressor Test in Patients with Risk Factors and Not Documented Coronary Artery Disease

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Nowadays, it is possible to diagnose an ischemic myocardial muscle with great precision through different bloodless methods, especially if this ischaemia implies some risk degree in the patient's evolution; for instance, to suffer from some major event as myocardial infarction or death.

The more recent pathophysiological finding that may produce myocardial ischaemia is the one related to the endothelial function. It is known that the endothelium infiltrated by atherosclerosis is significantly altered in its function and it is also known that dyslipidemia, nicotine poisoning, hypertension and/or menopause may produce functional alterations in the endothelium without damaging its structure. (1)

The endothelium is the biggest and more active paracrine organ of the body, which produces powerful vasoactive, anticoagulant, procoagulant and fibrinolytic substances. (2)

The endothelium, then, sensor and transducer of several chemical (acetylcholine, serotonin, thrombin) and physical (*shear* stress) stimuli, not only regulates the caliber of conductance vessels, but also modulates the tone of resistance vessels which determine the flow and the appropriate tissue perfusion for metabolic needs.

The response of a healthy endothelium, when facing an intracoronary infusion of acetylcholine, is the liberation of nitric oxide, which has a coronary vasodilator effect. When there is a functional or anatomical change in the endothelium, the response to acetylcholine is vasoconstriction, that is, the endothelium loses the capacity to release vasodilator substances, and the effect of vasoconstrictor substances predominates.

HOW CAN THE DIAGNOSIS OF ENDOTHELIAL DYSFUNCTION BE DONE?

By invasive method

Acetylcholine (ACh) is a drug used by intracoronary administration. The physiological response of acetylcholine is the production of coronary vasodilation through the liberation of nitric oxide, by endothelial stimulation.

When the endothelium is damaged, functional or anatomically, the response to ACh is converted into vasoconstriction due to the endothelium inability to produce nitric oxide.

In this way, the form of showing endothelial dysfunction in the coronary territory is based, nowadays, in the invasive study with quantitative angiography where the vasomotor response of intra-arterial ACh is evaluated. (3, 4)

May this flow decrease be converted into perfusion defects?

In a study, we have correlated perfusion defects and vasoconstriction in different coronary arterial territories through the use of intracoronary ACh and intravenous injection of mibi at the moment of highest action of ACh. We studied 11 patients from which 33 arteries were analyzed, 23 of them received ACh, 13 normal arteries or with obstructions lower than 50%, 3 arteries with intermediate lesions between 50% and 69% and 7 arteries with serious lesions > 70%. We observed that 31% of the analyzed arteries had positive response to ACh and perfusion defect in the corresponding arterial territory, 31% of normal arteries, 33% of arteries with intermediate lesions and 85% of arteries with serious lesions. (5)

These preliminary results suggest that myocardial perfusion with ^{99}Tc-sestamibi may identify coronary arterial territories with an abnormal response to ACh as it was determined by the angiography. There were coronary arteries with intermediate lesions or with no lesions which had abnormal response to ACh and this fact is very important since arterial territories with functional abnormalities would be identified, not necessarily with significant coronary obstructions, which may have an important role in the development of myocardial ischaemia. It is interesting to mention Hasdai et al.'s work, (6) who studied patients with normal coronary arteries or with lesions lower than 50% in which the intracoronary infusion of ACh was done and images of myocardial perfusion with sestamibi were analyzed. They also measured the arterial diameter with intracoronary Echo-Doppler and the flow of the anterior descending artery which was object of study.

These authors observed in 21 studied arteries: 7 with normal response to ACh and no perfusion

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defects, 7 arteries had abnormal response to ACh with decrease of the arterial diameter but with preserved flow where perfusion defects were not observed and 7 arteries with abnormal response to ACh, decrease of the arterial diameter, significant decrease of the flow and perfusion defects in the territory of the anterior descending artery. This study shows that the preserved endothelial function in the conductance vessels is important, and also the fact that a change in the endothelium of the resistance vessels is expressed with perfusion defects (myocardial ischaemia).

When in our study, we analyze the percentage of decrease in the arterial caliber in patients who had a positive response to ACh, we observe that in some of them vasoconstriction of great vessels was not significant; however, there was a perfusion defect that probably was due to an abnormal response of microcirculation (7) to ACh, as Hasdai et al. observed.

MAY THE DIAGNOSIS BE DONE IN A COMPLETELY NON-INVASIVE WAY?

Cold pressor test

Another vasodilator stimulus is the cold pressor test, which increases the flow in the coronary sinus due to a mechanism that releases nitric oxide, through the adrenergic stimulation.

As it happens with ACh, the physiological response is maintained while the endothelium is unharmed; when the endothelium function is altered, the response to cold pressor test is vasoconstriction.

It is an easy test to do: a hand is introduced in cold water (4°C approximately) during 3-4 minutes with blood pressure monitoring and electrocardiography and before taking out the hand from the cold water, the perfusion agent (^{99m}Tc-mibi o ^{201}Tl) is injected.
Nabel et al. (8) proved that arteries with significant stenosis during the cold pressor test showed vasoconstriction in the coronarography and that normal arteries suffered vasodilation. These findings are particularly important for non-invasive techniques of imaging diagnosis, since through this procedure endothelial dysfunction may be observed in a bloodless way.

In a study, we evaluate endothelial dysfunction with perfusion SPECT studies triggered with two different procedures in the same patient: dipyridamole and cold pressor test. Since dipyridamole is a vasodilator drug through a non-dependant mechanism of the endothelium, it is interesting for the study of fixed obstructions. And the cold pressor test may diagnose the sick endothelium.

In this experience in 15 patients with known coronary disease, we analyzed the behaviour of 300 segments with both procedures and we observed development of ischaemia in 25 segments with dypiridamole alone, in 6 with cold pressor test and in 8 with both procedures. That is why, the mismatch pattern between dypiridamole and cold pressor test could show different physiological mechanisms in the origin of myocardial ischaemia. Reversible defects associated to cold pressor test could involve the endothelial dysfunction as the main mechanism of myocardial ischaemia. (9)

Based on this new knowledge about the mechanism and the treatment of atherosclerosis, it is necessary to revise our use of the traditional diagnostic tools. Following this line of reasoning, the development of a totally non-invasive study to detect endothelial dysfunction in the coronary territory could be very useful.

In this way, the endothelial dysfunction expresses a new challenge for nuclear cardiology. With the non-invasive results we could intervene in two moments: one, the diagnosis of endothelial dysfunction and the other, the evaluation of therapeutics to correct the endothelial dysfunction.
This new scene expresses a new line of investigation in primary and secondary prevention in ischemic heart disease.

Pautasso et al.'s work, "Could the cold pressor test predict the onset of cardiovascular events in patients with no proved coronary disease?", which is published in this issue of the *Journal* (10) expresses a new contribution to the understanding of endothelial dysfunction as a prognosis element in patients with endothelial disease, but with no known coronary disease, in the remote monitoring of this population.
Using the cold pressor test as a procedure in 464 patients over a total of 511, they found 32,4% with abnormal perfusion studies (166 patients with positive cold pressor test). They completed a 24 ± 13 month-monitoring in 441 patients, 12 of them suffered from events (7). Among these events, the most frequent one was unstable angina and a patient died suddenly. The multivariable analysis showed that males and the highest body mass index were the clinical variables associated to a positive test.

The poor relationship between the positive test and dyslipidemia, hypertension and above all diabetes calls the attention, since this last group of patients has a high incidence of endothelial dysfunction and constitutes a risk group in itself.

The authors' contribution was of great value, due to the important number of studied patients and the long-term monitoring. This allows us to know the prognostic use of a test or evaluate the effect of a drug. Nowadays, we may approach the population risk in a precise way; however, knowing the individual risk is very difficult. This study is a step forward, but in science every step is very important.

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