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 intracoronary 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...
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 conduitance
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 vasodiator 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 coronaryography 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
dipyridamole alone, in 6 with cold pressor test and in
8 with both procedures. That is why, the mismatch
pattern between dipyridamole 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
dyldlipidemia, 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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