

## Facts and Fiction about Endothelial Function: a New Tool for the Clinician

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The literature from the last decade contains numerous articles about the study of endothelial function. Without looking any further, since 1999, more than 1300 articles related to the endothelium have been published in a single journal that has a great impact on the field of cardiovascular disease. The first question one asks, given such scientific plethora, is, why is there so much interest in studying endothelial function, and, can we really evaluate it in a reliable manner?

The complex function is known, at least in part, of this single layer of cells called the endothelium that separates the vascular wall from the arterial lumen. These cells act like a barrier with selective permeability for the exchange of various substances, and includes cells that allow the endothelium to provide an antithrombotic and anti-inflammatory effect, as well as a vasodilator effect in physiological conditions. Although all the functions of the endothelium can be studied individually, the most commonly studied, and the one on which many authors are concentrating at the present time, is vasoreactivity. For this reason, changes in endothelium-dependent vasoreactivity are often used as a synonym for endothelial dysfunction.

Vasoreactivity studies evaluate the capacity of dilating the artery with nitric oxide freed by the endothelial cell in response to shearing forces (produced by hyperemia) or the administration of acetylcholine. Endothelium-dependent vasodilation (EDV) is always compared with nonendothelium-dependent vasodilation produced by a direct provider of nitric oxide such as nitroglycerine, which acts directly on smooth vascular muscle cells without passing through the endo-

thelium, and the integrity of the muscular cap is proved to be intact.

In the vascular coronary tree, both the EDV in microcirculation (by analyzing the coronary reserve) and in the epicardial arteries can be studied. Quantitative coronary angiography allows the evaluation of changes in the diameter of the epicardial arteries in response to the infusion of acetylcholine, which under normal conditions produces vasodilation, and in the case of endothelial dysfunction, induces vasoconstriction. Initially, all the studies performed on endothelial function focused on coronary vasoreactivity studied with this technique. It has since been shown that endothelial dysfunction is found in very early stages of atherosclerosis, including in patients without heart disease, but with risk factors for it.<sup>1</sup> Researchers also observed that endothelial dysfunction is a reversible phenomenon, at least in part. Thus, hypolipemiant drugs, angiotensin-converting enzyme inhibitors (ACEI), estrogens, and physical exercise, among other regimens, have been shown to improve coronary vasoreactivity.<sup>2,3</sup> Finally, the most important particular of coronary endothelial dysfunction has been recently shown to be its prognostic value. In the broadest and most recent study published to date, Halcox et al<sup>4</sup> showed, in 300 patients (more than half of whom did not have angiographic evidence of heart disease), that coronary endothelial dysfunction of the epicardial arteries and the microcirculation has independent prognostic value for the presence of heart disease; consequently, the degree of EDV allowed identification of 2 groups of patients with different incidence rates for cardiovascular events during nearly 4 years of followup.

Therefore, there seems to be ample evidence that coronary endothelial dysfunction may be evaluated and is of interest as a prognostic factor. What remains to be shown is whether the reversal of such dysfunction results in a significant clinical benefit, although in view of the existing data it seems to be a reasonable conclusion that has probably motivated the intense search for treatments that reverse endothelial dysfunction, with the hope of changing the clinical course of

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cardiovascular illness.

On the other hand, the invasive nature (and therefore not without risks) of coronary angiography techniques and the scarce availability of such resources for studying the coronary endothelial function has limited its application to large population centers and its use as a followup tool, giving rise to a great interest in the use of other methods to study endothelial function. The evaluation of the coronary reserve by noninvasive methods such as nuclear magnetic resonance or positron emission tomography is attractive, but these techniques continue to be laborious and are not always accessible to all medical centers. Given these limitations and the fact the atherosclerosis is a systemic illness, the study of peripheral endothelial function in the forearm has become very popular. This has been evaluated by means of venous occlusion pletismography and 2-dimensional echography of the humeral artery. Due to its non-invasive character and its greater accessibility, the latter is the technique that has been adopted by many groups.

At the level of the humeral artery and using 2-dimensional echography, an abnormal response to hyperemia has been described; in other words, endothelial dysfunction in almost all cases in which it has been described at the coronary level—in patients with risk factors, in menopausal patients, in patients with cardiac insufficiency, etc.<sup>5</sup> Similarly, peripheral endothelial dysfunction is also reversible, at least partially, and improves with certain treatments (ACEI, estrogens, hypolipemiant) at the coronary level.<sup>6,7</sup> In addition, although there are few studies on the subject, there seems to be a correlation between coronary and peripheral endothelial dysfunction.<sup>7,8</sup> Finally, an association has also been shown between peripheral endothelial dysfunction and heart disease.<sup>9</sup> What is less clear is the prognostic significance of peripheral endothelial dysfunction, although data clarifying this process are just recently being published. Thus, using pletismography and intraradial infusion of acetylcholine, it has been shown that patients with a better response to peripheral vasodilation have less adverse events during followup; this factor is independent of the number of diseased coronary vessels present.<sup>10</sup> Another small study also showed that endothelial dysfunction was a predictive factor for cardiac events in patients undergoing vascular surgery.<sup>11</sup>

Similarly, in this issue of *REVISTA ESPAÑOLA DE CARDIOLOGÍA*, Novo García et al<sup>12</sup> have published a provocative study concerning the possible usefulness of EDV of the humeral artery in the followup of patients with heart disease to monitor the efficacy of secondary preventative treatment. The authors evaluated endothelial function with vascular echography in 665 patients with established heart disease, in association with followup pharmacological treatment, which was always monotherapy. They observed that EDV was

significantly better in the group treated with ACEIs and also tended to be better in the group treated with statins; nonendothelium-dependent vasodilation, mediated by nitroglycerine, was not different for the different groups. Treatment with ACEI and statins was, together with age, an independent predictor of normalization of endothelial function. This labor-intensive and far-reaching study confirms previous findings on the beneficial effect of statins and ACEI on endothelial function, but above all makes an interesting contribution by suggesting that the noninvasive study of endothelial function may be one more tool for monitoring vascular risk in patients with heart disease.

The baseline heterogeneity of the various groups comprising the study population has an inevitable limitation, in part compensated for by the large sample size and by the multivariate analysis. Nevertheless, it is still a fact that their findings coincide with other studies in which statins and ACEI, but not calcium antagonists, have been shown to improve EDV. More controversial is the effect of beta-blockers, which have been shown in other studies to have a beneficial effect on endothelial function.<sup>13</sup> What seems to be clear is that the beneficial effect of various drugs on the mortality and morbidity of patients with heart disease may be due in part to such medications effect on endothelial function. Another question is whether or not the drugs that did not specifically have an effect on endothelial function are efficacious in the prevention of sudden death, as is the case with beta-blockers. Therefore, in spite of the fact that in the study by Novo García et al beta-blockers did not reverse endothelial dysfunction, there is no doubt that their efficacy has been shown as a secondary preventative measure in patients with heart disease.

Conversely, the use of vascular echography of the humeral artery is undoubtedly attractive for evaluating EDV due to its noninvasive character, and it is apparently easy and repeatable for followup studies. Nevertheless, it must be pointed out that there are also limitations to its use, especially in view of the large number of groups and studies that have used this technique in recent years. There is notable biological variation in the baseline artery diameter and, particularly, there can be great variability with regard to the echography technique used that, in part, depends on the technician. Slight changes in the diameters of arteries that are already very small have been evaluated, and therefore, it is of primary importance that the technique be standardized as much as possible, and that it be rigorously and meticulously practiced when used. Groups that have a great deal of experience, such as Novo García et al, may be conscious of the great variability than can occur if a standardized technique is not used. To this end, an international study group<sup>14</sup> has recently published guidelines for performing these studies. Each laboratory must be responsible for main-

taining adequate internal control, but without a doubt, all the measures implemented to decrease variability, such as the use of a specific process for the measurement of 1 continuous arterial segment and compliance with uniform criteria for performing the technique, must be praised. What all this means is that at present this technique is probably adequate for interventional studies or comparisons between groups of patients; nevertheless, its impact on categorizing individuals and on the normalization of endothelial function is still in the incubation stage, particularly in light of the variability of the normal EDV values described. Although the cutoff point of 4% proposed by Novo García et al coincides with that previously described by other authors, higher normal values have also been published, especially when the occlusion is performed on the arterial segment studied.<sup>15</sup>

Finally, as the authors conclude in their article, this technique may be an additional tool for following patients with heart disease and monitoring the effect of the therapies used. Nevertheless, caution is in order at present, as studies are still needed to confirm the prognostic value of peripheral endothelial dysfunction as evaluated by vascular echography, independently of heart disease; even more importantly studies are needed to evaluate whether or not reversal of peripheral endothelial dysfunction translates into an improved clinical prognosis. Most likely in the future when these points have been clarified, the use of this technique for measuring vascular risk will help the clinician to categorize the individual risk of each patient and even be useful in designing therapies or drug regimens. In the meantime, our efforts should also be directed to the refinement of this technique and to making it sufficiently reproducible so that the evaluation of EDV by vascular echocardiography can be a clinically useful measurement of individual cardiovascular risk.

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