Endothelium in polycythemia secondary to obstructive lung disease

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THE ROLE OF ENDOTHELIAL FUNCTION in the regulation of the normal and diseased cardiovascular system has been one of the most popular areas of investigation in the past decades. This is justified by the importance of the substances released from the endothelium in normal and abnormal conditions. Just to quote a few examples, nitric oxide (NO), i.e., the most important vasodilator substance released by endothelial cells, importantly contributes to maintenance of vital organ perfusion at rest and under a variety of environmental stimuli (9, 10). Also, a reduced release of NO (and perhaps an increased secretion of endothelin and other endothelial products with a vasoconstrictor effect) may be involved in the initiation of hypertension as well as in the maintenance of elevated blood pressure values after hypertension appears (5). Finally, an abnormal balance between NO and endothelin secretion represents the first step in the cascade of events that leads to atherosclerosis (7), i.e., the anatomic lesion primarily responsible for coronary heart disease, stroke, and peripheral artery disease, and thus for the leading position of cardiovascular disease as the first cause of death worldwide (11).

Studying endothelial function and dysfunction in humans has always been a demanding task, however (6). First, methods based on the vasodilator response to infusion of selective endothelial stimulators (acetylcholine, bradykinin, etc.) require cannulation of the brachial artery, which severely limits their use in conditions other than the strictly experimental ones. Second, noninvasive methods such as the forearm vasodilation or the increase in radial artery diameter in response to the hyperemia generated by release of a previous ischemia may be unable to precisely quantify the stimulus as well as to properly identify the timing of the response (which is characterized by a highly dynamic profile), with resulting limited within- and between-laboratory reproducibility (3). Third, administration of substances that block the baseline release of NO, such as N-monomethyl-L arginine (L-NMMA), although addressing a number of substances that block the baseline release of NO, such as N-monomethyl-L arginine (L-NMMA), although addressing a crucial issue such as the tonic contribution of endothelium to cardiovascular regulation, can only be used by expert investigators, given the potential risk of generalized or local vasoconstrictor effects. Finally, in humans endothelial function when studied in skeletal muscle and skin tissues, leaves the question whether the results reflect endothelium-dependent vascular modulation in the viscera unanswered (7). These are some of the reasons that current guidelines on cardiovascular prevention do not yet include endothelial function among the markers of organ damage to search for in quantifying the baseline cardiovascular risk as well as their modifications by treatment (8).

The study of Boyer et al. (1) in this issue of the Journal of Applied Physiology has two merits. First, endothelial function was studied in individuals with polycythemia secondary to obstructive lung disease, a condition not commonly addressed by cardiovascular investigators, although its presence is associated with a clearcut increase in cardiovascular risk (2). Second, the authors made use of virtually all techniques available in humans to determine endothelium-dependent modulation of vascular tone, an unusual effort that differentiates this study from most other studies so far published. The results provide evidence that in polycythemic patients with obstructive lung disease the forearm vasoconstriction induced by L-NMMA administration was not reduced compared with controls, while the brachial artery dilatation in response to postischemic hyperemia was increased. This suggests that in this condition the endothelium exerts a tonic and phasic vascular modulation that it is not less than that seen in individuals with normal blood cell counts and no lung disease. In other words, these patients can still count on the endothelial component of cardiovascular regulation.

Does this allow one to conclude that in patients with obstructive lung disease and polycythemia endothelial vascular modulation is not at all impaired? Our opinion, perhaps not entirely in line with that of the authors of the present study, is that this remains an open question. First of all, the present study is based on a relatively small number of subjects, which limits the statistical power to see between-group differences. Second, as pointed out by the authors, patients had a relatively mild degree of polycythemia, which does not allow one to exclude that endothelial dysfunction occurs when obstructive lung disease, and secondary alterations in hematocrit and blood viscosity, are more severe. Third, the different methods used to quantify endothelial function did not produce entirely consistent results. That is, while polycythemic subjects showed an unaltered vascular response to L-NMMA and a greater brachial artery vasodilation to postischemic hyperemia [possibly, however, because polycythemia is associated with a greater wall shear stress for a given increase in blood flow (4)], their ability to vasodilate during acetylcholine infusion was markedly impaired, although, surprisingly, this did not occur with other substances, such as bradykinin, also stimulating NO release from the endothelium. This inconsistency, however, has important methodological implications because it directs attention to the difficulty of studying endothelial function with current methods, and the risk of giving only a partial view when a single method is used. It is a further merit of the present study to focus investigators’ attention on this important methodological issue via the data provided by a demanding protocol.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


