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Editorial

Vascular function of the peripheral and coronary circulation: worthwhile to assess their relation?

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In this issue of the journal, Scholtens et al[1] report of an absence of any correlation (r = 0.13, SEE = 54; P = .36) between hyperemic myocardial and peripheral blood flows during pharmacological vasodilation with adenosine in a heterogenous group of patients and healthy volunteers as determined with 13N-ammonia PET. The study is unique in that it concurrently measured the blood flow increase or vasomotor response during pharmacologically induced vasodilation of the arteriolar resistance vessels in the myocardium and upper limb muscle. The current investigation agrees with earlier observations from Bottcher et al[2] but extends them now also to the same stimulus to induce flow increases in the coronary and peripheral circulation. Bottcher et al[2] were first to describe that the peripheral arterial flow responses to transient forearm ischemia did not correlate with dipyridamole-induced hyperemic myocardial blood flow increases. Thus, the current and previous investigations[2] strongly suggest different regulatory mechanisms of the coronary and peripheral microcirculations in the diseased and normal vascular states. Extrapolations between findings in the two vascular beds therefore may not necessarily apply. At the first sight, the results from Scholtens[1] and those from Bottcher et al[2] may indeed contrast the reported association between vascular function of the brachial and epicardial artery from a previous investigation conducted by Anderson et al.[3] In the latter study, the stimuli to provoke the vasomotor response in the peripheral and coronary circulation were different and a different vascular bed was examined, i.e. conductance arteries. Alterations of epicardial artery diameter in response to intracoronary acetylcholine infusion were determined with quantitative coronary angiography (QCA), while the change in brachial artery diameter in response to reactive hyperemia in the peripheral circulation was determined with vascular ultrasound. Thus, endothelial function of the epicardial artery was specifically tested with acetylcholine stimulation of the muscarinergic receptor, whereas flow-mediated brachial artery response was determined in response to hyperemic flow increases. In both the instances, the endothelial vasoreactivity of the conduit vessels of the periphery and coronary circulation was tested. This may explain the observed statistically significant but rather weak correlation between endothelium-dependent vasomotor responses at the site of conduit vessel of the peripheral and coronary circulation in patients with and without angiographically determined CAD (P = .36, P\.01) (Figure 1)[3]. Interestingly, this weak correlation appeared to be driven by patients without evidence of structural CAD. Conceptually, if these patients without evidence of structural CAD were taken out of the analysis, no association between peripheral and coronary endothelial function would probably exist. Thus, the results from Anderson et al[3] suggest that CADrelated advanced structural alterations may actually dissolve the described association of endothelial function between the peripheral and coronary circulation. The prognostic value of the assessment of endothelial or vascular dysfunction of the peripheral and coronary circulation is well established.[4-6] In particular, the power of peripheral and coronary endothelial dysfunction in re-

sponse to various stimuli in the prediction of cardiovascular events appears to be comparable.[5] Cardiovascular events therefore may occur remotely from the site of endothelial dysfunction identified. These observations strongly suggest a systemic nature of vascular dysfunction and its central role in predicting future cardiovascular events. Vascular dysfunction has been appreciated as a useful integrating index of the overall stress burden by various cardiovascular risk factors on the arterial wall, taking into account the cumulative risk of cardiovascular risk factors and as yet unknown variables and genetic predispositions.[4,5,7] Despite this, it is important to keep in mind that forearm conduit and resistance vessels do not develop atherosclerotic disease. [7] Currently, no systematic investigations of both the forearm and the coronary circulation have been performed, and therefore the relation between vasomotor function in the forearm and coronary circulation remains poorly understood. In this direction, the observations from Scholtens et al[1] shed some new light in that they did not observe an association between vasomotor function of the resistance vessels in the periphery and the coronary circulation when assessed concurrently with adenosine-induced hyperemic flow increases. Conversely, their study does not provide any mechanistic insight about the mechanisms underlying the vasoreactivity in the upper limb microcirculation in response to adenosine stimulation. Intravenous adenosine infusion caused a much lower flow increase in the upper limb than in the myocardium, which may be related to effectively lower adenosine arriving in the peripheripheral circulation and, at least in part, different mechanisms underlying peripheral vasoreactivity.[1] As regards the hyperemic myocardial blood flow increase during pharmacologically induced vasodilation of the arteriolar vessels, vascular smooth muscle-relaxing substances like adenosine, dipyridamole, or, more recently, adenosine receptor agonists decrease resistance to flow at the site of the coronary arteriolar resistance vessels and, thereby, cause a maximal or submaximal hyperemic myocardial blood flow increase.[8,9] The resulting hyperemic coronary flow increase is considered to represent predominantly an endotheliumindependent flow response as the aforementioned substances increase hyperemic flow increases through vascular smooth muscle cell relaxation at the site of the coronary arteriolar vessels.[8,10] Blocking the endothelial nitric oxide synthase (eNOS) by intravenous infusion of NG-monomethyl-L-arginine, however, results into a significant loss of adenosine-induced MBF increases by 20%-25% as measured with PET.[9,11,12] It may be concluded that shear-sensitive components of the coronary endothelium contribute in part through a flow-mediated and, thus, nitric oxide-mediated coronary vasodilation to the overall hyperemic MBF increase during pharmacologic vasodilation.[7,8,13] Such a myocardial flow response has also been appreciated as total integrated coronary circulatory function.[8,9,14] The complexity of the mechanisms underlying hyperemic MBF increases during pharmacologic vasodilation may also explain, at least in part, the absence of any correlation between hyperemic myocardial and peripheral blood flows during pharmacological vasodilation with adenosine

as determined with 13N-ammonia PET.1 Overall, the investigation by Scholtens et al1 add further to the consideration that vascular (dys)function in the peripheral and coronary circulation may indeed reflect different features and stages of vascular disease. Given that the forearm circulation does not develop atherosclerotic disease,7 systemic comparative investigations of endothelial, or circulatory dysfunction of both the forearm and the coronary circulation and its response to pharmaceutical intervention15-19 could possibly contribute to better identify and characterize pathophysiological mechanisms favoring the initiation and progression of the CAD process and/or possible protective responses within the arterial wall aiming to counterbalance the adverse effects of various cardiovascular risk factors. Such an emerging concept certainly deserves further investigations.

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Figures:

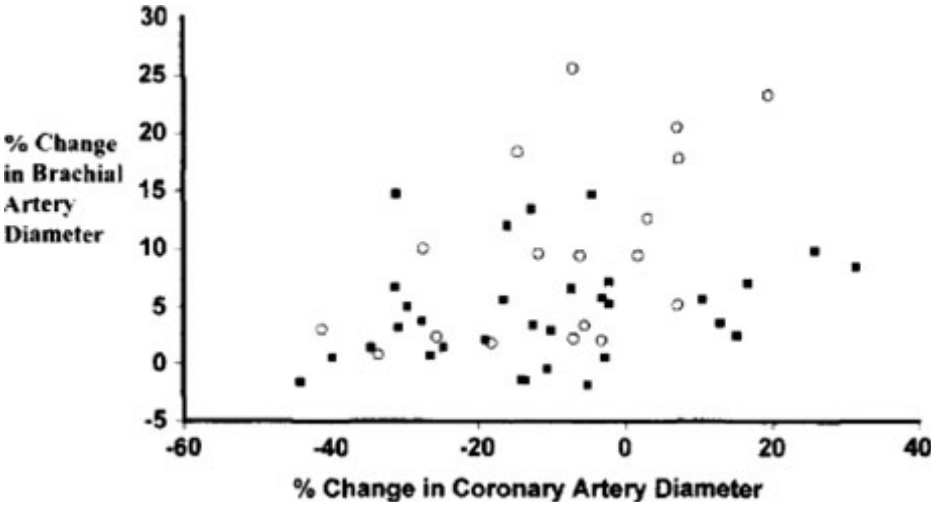

Figure 1. Brachial dilator response to reactive hyperemia as a function of the coronary response to acetylcholine in patients without (circles) and with (squares) coronary artery disease (r = 0.36, P = .01) (with kind permission from Anderson et al3).