In this issue of the Journal, Hays et al. (1) report the use of noninvasive magnetic resonance imaging (MRI) to evaluate vasomotor responses of epicardial coronary arteries to isometric handgrip exercise. Normal increases in luminal area, peak diastolic flow velocity, and derived values of coronary flow in healthy subjects were reduced systematically in patients with coronary artery disease. The degree of reduction appeared to vary with the severity of disease in individual arteries. The noninvasive MRI methodology is thought to expand opportunities for evaluating coronary endothelial function and for risk-stratifying persons with and without known coronary disease.

Accentuated importance of vasomotion in conduit coronary arteries in coronary artery disease. Although epicardial coronary arteries are subject to a variety of vasoactive stimuli, they normally constitute a small portion of coronary vascular resistance and cause minimal reductions in coronary pressure. However, their susceptibility to vasoactive stimuli becomes important when coronary artery disease is present. Because of the nonlinear relationship between pressure drop and flow across a stenosis, the magnitude of the additional resistance imposed by an epicardial stenosis increases disproportionately, and progressively more rapidly, as the degree of stenosis increases (2). Thus, even small increases in the severity of a clinically important stenosis can cause the stenosis to become flow limiting. Similarly, interventions that increase flow through a stenosis of fixed severity increase the trans-stenotic pressure gradient exponentially.

Influences of endothelial factors. Vasomotor responses in human conduit arteries are influenced by both vasodilating and vasoconstricting products of local endothelium. Epicardial arteries dilate in response to at least 3 agents, as well as pharmacologic stimuli such as nitroglycerin and acetylcholine. The most extensively studied agent is nitric oxide (NO), which causes vasodilation as it diffuses into adjacent vascular smooth muscle. Endothelium-derived hyperpolarizing factors (EDHF) act by opening calcium-activated potassium channels in vascular smooth muscle. Prostacyclin, a cyclooxygenase product, may play a lesser role than NO and EDHF in epicardial arteries. The most prominent vasoconstricting agent is endothelin-1, a small peptide that activates specific receptors (ET\textsubscript{A}) on vascular smooth muscle cells.

Endothelial production of vasoactive agents is regulated by the shear stress generated by local blood flow. Endothelial dysfunction is usually identified as a reduction in “flow-mediated dilation,” namely, a reduction in the expected degree of conduit artery dilation and/or flow increase in response to a flow-stimulating intervention. Interactions among endothelium-derived agents, and their relative importance in specific situations, remain incompletely understood. Increased production of NO plays an important role in flow-mediated dilation of epicardial arteries; EDHF may compensate partially when endothelium becomes dysfunctional.

Gori et al. (3) have suggested that endothelial-mediated effects can be evaluated more completely by combining measures of radial arterial caliber during inflow blockade with those during flow-mediated vasodilation. They postulate that EDHF and cyclooxygenase products contribute primarily to resting vasomotor tone and that their production is decreased when shear stress is reduced markedly. Similarly, Spieker et al. (4) have shown that ET\textsubscript{A} receptor blockade can blunt radial artery constriction during inflow blockade.

Influences of neural factors. As reviewed by Konidala and Gutierrez (5), conduit coronary arteries can also be affected importantly by their sympathetic and parasympathetic innervation. Sympathetic effects are complex, involving alpha-1 and -2 receptor-mediated vasoconstriction of vascular smooth muscle; vasodilator effects of beta-1 and -2 receptor activation; alpha-2 receptor-mediated release of NO from endothelium; and alpha-2 receptor-mediated pre-junctional inhibition of norepinephrine release. The usual net result is a moderate vasoconstriction. As discussed in the following text, epicardial artery constriction sufficient to cause myocardial ischemia has been reported during isometric handgrip exercise in the setting of a flow-limiting stenosis (6).

Parasympathetic stimulation produces vasodilation by cholinergically activating endothelial muscarinic receptors. In the presence of endothelial dysfunction, acetylcholine reaching vascular smooth muscle can result in smooth muscle contraction rather than the usual vasodilation (7).

Isometric handgrip exercise. Cardiovascular effects of sustained isometric exercise have been studied since the late 1960s. These include modest increases in heart rate, cardiac
output, and systemic systolic and diastolic arterial pressure. In the early 1970s, it became evident that handgrip exercise could sometimes induce angina and/or left ventricular dysfunction. Sustained handgrip exercise was explored as a cardiac stress test (8). Martin et al. (9) demonstrated that the procedure activated important autonomic mechanisms, namely, vagal withdrawal and sympathetic vasoconstriction. Other studies demonstrated elevations in plasma epinephrine and norepinephrine levels (10).

In the early 1980s, Brown et al. (6) used quantitative coronary arteriography to study responses of epicardial coronary arteries in patients with coronary disease. Handgrip exercise reduced luminal area of both stenotic (−35%) and remote (−14%) portions of diseased arteries. The latter value is comparable to that reported by Hays et al. (1) in arteries containing >60% stenoses as shown in Figure 4 of their paper. Brown et al. (6) attributed their findings to reflex vasoconstriction (at a time when systematic studies of endothelial dysfunction were just beginning). The vasoconstriction could be prevented by intracoronary nitroglycerin and was thought to be an important mechanism in the development of ischemic manifestations during handgrip exercise.

Direct comparisons of responses of epicardial arteries to handgrip exercise with responses to more selective endothelial stimuli are not available. However, Gordon et al. (11) have demonstrated that bicycle exercise and intracoronary acetylcholine evoke similar responses in arteriographically smooth (vasodilation) and diseased (vasoconstriction) epicardial arteries (11). Thus, endothelial function no doubt has important impact on responses to handgrip exercise.

The question of whether, and to what degree, neural and neurohumoral responses to handgrip exercise in other human vascular beds (e.g., Shibaski et al. [12]) are operative in epicardial arteries remains unsettled.

**MRI assessment of epicardial artery vasomotion.** The current study by Hays et al. (1) benefited from careful application of state-of-the-art 3.0-T MRI technology by a group experienced in coronary imaging. As outlined in the text, meticulous attention was paid to maintaining slice orientation perpendicular to the artery being studied throughout each voxel’s 8-mm slice thickness. Only proximal or mid-arterial segments that were straight over a distance of 2 cm were examined. Imaging planes were located at least 2 cm distant from known stenoses to avoid partial volume effects and bias due to turbulent flow. That was intended to ensure that observations reflected effects on portions of epicardial arteries that did not include areas of clinically important stenosis.

In addition to its noninvasive nature, the current study is notable for the use of an exercise stimulus in the MRI setting. The direct examination of human coronary arteries also avoids uncertainties in extrapolating findings in other species and other peripheral beds to the coronary bed.

It remains difficult to judge the degree to which the present observations were influenced by factors other than endothelial dysfunction. As outlined in the preceding text, handgrip exercise is a complex intervention that increases myocardial oxygen demand and activates neural and neurohumoral as well as endothelium-produced stimuli. In addition, atherosclerosis may alter catecholamine-mediated as well as endothelial responses. Although the design of studies capable of isolating effects of specific stimuli remains challenging, the ability to evaluate changes in epicardial artery caliber and flow velocity noninvasively is a welcome addition to current options.

**References**


**Key Words:** cardiac MRI • coronary artery innervation • coronary endothelial dysfunction • dynamic stenosis severity • handgrip exercise.