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EDITORIAL COMMENT

Coronary Flow: How Far Can We Go With Echocardiography?*

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The possibility of directly observing arterial flow in vivo has been the dream of scientists for centuries (Fig. 1), but more than that, both noninvasive imaging of coronary flow and measurement of flow reserve have been considered a chimera.

The study by Hirata et al. (1), along with many other similar reports published in the last four years (2–8), shows that, using a simple bedside tool such as echocardiography, the chimera can be turned from a frightening mythological monster to a friendly companion of our work.

Hormones and the microcirculation: Does the "storm" affect women's hearts? Gender differences in vascular reactivity have been postulated for years, and common experience teaches that difficult days during the menstrual cycle are often associated with mood instability. Whether these changes are due to a direct hormonal effect or to a generalized microcirculatory instability involving the heart and the brain is not known.

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The interaction between microvascular flow and sex hormones is complex and incompletely understood. It is supposed that the vascular tree is targeted by the cyclic hormonal variations during the menstrual life and that hormones influence peripheral vascular reactivity, as endothelial-dependent vasodilation is clearly reduced during the menstrual phase and after menopause (9–12). In fact, microvascular involvement is often cited to explain cyclic chest pain and positive stress tests in fertile women with normal epicardial coronary arteries. In addition, estrogens increase the ischemic threshold in premenopausal women with coronary artery disease (13), and they attenuate coronary reactivity in postmenopausal women with angina pectoris and normal coronary angiograms (14). The role of progestins is still controversial (15,16), and their association with estrogens to protect against vascular stiffness has yielded conflicting results (17,18).

However, despite the previous belief that sex hormones might play a protective role for cardiovascular disease, at least for primary prevention (19,20), recent randomized trials surprisingly showed no benefit of hormonal therapy replacement for secondary prevention (21–24).

Focusing the target: From brachial to coronary arteries. There has been considerable interest in the brachial artery as a surrogate target to measure microvascular dysfunction. The main reason for this interest is that this artery is very easy to image by two-dimensional Doppler ultrasound because of its proximity to the skin. The brachial artery has been considered a mirror of other inaccessible arteries, and it has been used to measure vascular reactivity during cyclic hormonal phases and to evaluate the efficacy of hormone replacement in postmenopausal women (10,13). Hormones may affect endothelial and microvascular function both in brachial and coronary circulation. However, these two territories are very different in terms of flow pattern, resistances, metabolism, receptor population and microvascular architecture. In this view, the great merit of Hirata and colleagues (1) was to abandon the surrogate target to focus our attention on the real target, the coronary circulation.

Angle correction: Essential or superfluous? In most of the studies dealing with noninvasive coronary Doppler, the theta angle between the incident beam and direction of flow is corrected. However, coronary flow reserve is not an absolute measure, but rather is the ratio between hyperemic and baseline flow velocity, and it is not affected by the actual flow velocity. Therefore, angle correction during the study is unnecessary because this additional maneuver may prolong adenosine infusion and may potentially introduce a bias when strong corrections are used.

Microvascular flow, coronary stenosis and the "magic number." Adenosine is the key drug to measure coronary flow reserve, because it produces maximal arteriolar dilation with little or no effect on the epicardial artery (25). Coronary flow is the product of velocity multiplied by the cross-sectional area of the vessel. Because the diameter of the epicardial artery does not significantly change during adenosine infusion (25), any change in velocity translates into an increase in flow. In the absence of coronary stenosis, as described by Hirata and colleagues (1), microvascular dysfunction may reduce coronary flow reserve. The situation is more complex in the presence of a flow-limiting stenosis, which by definition establishes a new resistance to flow that is considerably higher compared to that produced by the microcirculation (4). In other words, the "stop" produced by the stenosis is dominant, and microcirculatory dysfunction can hardly affect the "magic number" of 2 or 2.5 that has been adopted to detect significant coronary artery disease. In addition, adenosine may not be the ideal drug to study pure microvascular dysfunction because its potent dilating effect probably overwhelms vasoconstriction due to other causes. Acetylcholine is the ideal drug; unfortunately, it cannot be used intravenously.

The "third dimension" of Doppler. Time and velocity are the most commonly used parameters to extrapolate clinically

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Figure 1. John Marshall's double microscope for viewing the circulation of the blood (from Harris's *Lexicon Technicum*, 1704, Figure 103, and W.B. Carpenter, *The Microscope and Its Revelation*. 7th ed. London: J & A Churchill, 1891;135–8.

useful data from Doppler spectra. However, there is a third potentially useful but neglected piece of information in the Doppler spectrum: the intensity of the reflected signal (3). Doppler intensity is proportional to the number of scatterers and is a measure of blood volume crossing the Doppler sample volume. Doppler intensity can be used to detect coronary vasomotion as it significantly decreases during handgrip in patients with coronary artery disease while it increases or remains unchanged in normals. Doppler intensity, expressed in gray levels or decibels, may be implemented in the velocity data to compensate for potential changes in lumen diameter during adenosine infusion, due to flow-mediated vasodilation (25).

The squaring of the circle: The posterior descending artery. The left anterior descending coronary artery is at our fingertips, and its flow reserve can be measured noninvasively in virtually every patient without the need of a contrast agent (4). Despite the prominent importance of measuring anterior descending flow, the evaluation of other coronary territories is desirable. As 95% of the infarctions are either anterior or inferior, we have recently concentrated on the posterior descending coronary artery regardless of its origin from the right or circumflex coronary artery (7) (Fig. 2). In a preliminary survey, we have found it feasible to measure resting flow velocity and coronary flow reserve in 75% and 50% of the patients, respectively. This lower

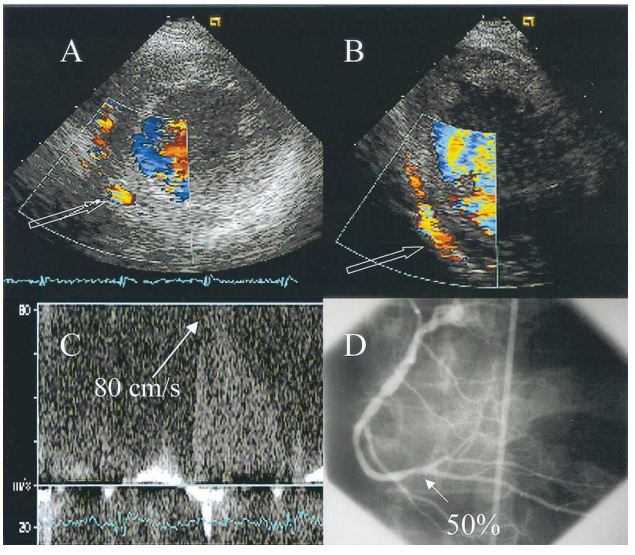

Figure 2. Transthoracic color Doppler echocardiography. Imaging of the posterior descending coronary artery arising from a dominant right coronary artery. **Panels A** and **B** show the short axis **(A)** and long axis **(B)** color Doppler imaging of the artery in the posterior interventricular groove. Pusled Doppler **(C)** shows inappropriate flow acceleration at the site of a 50% posterior descending stenosis **(D)**. Flow acceleration is a mechanism to compensate for lumen loss and maintain normal flow at rest.

success rate compared to the left anterior descending coronary artery depends on two main factors: 1) adenosine-induced hyperventilation interferes more with posterior than with anterior descending imaging; and 2) whereas the anterior descending artery has a dedicated transducer, the posterior descending artery is studied by a conventional transducer. Therefore, the feasibility of imaging the posterior descending artery can be improved in two ways: 1) the use of specific A_{2A} adenosine receptor agonists producing

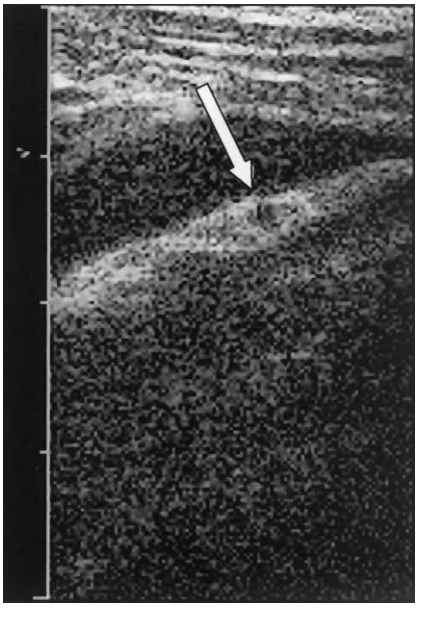

Figure 3. High-resolution transthoracic echocardiography by an 8-MHz linear probe shows the short-axis of the distal left anterior descending (LAD) coronary artery in the anterior interventricular groove.

little or no hyperventilation (26); and 2) the design of specific probes and software. Considering that A_{2A} receptor agonists are being tested in clinical trials (26), most of the investment should be done by the ultrasound companies. This money seems to be very little, compared with the huge investments of computed tomography or magnetic resonance imaging, but it may nevertheless produce an even more accurate tool to study coronary flow pathophysiology.

Coronary morphology: Beyond function. High-frequency transducers allow us to directly image in 2D the mid- and distal tract of the left anterior descending coronary artery from the chest (27) and to measure its cross-sectional area (Fig. 3). This method has the potential to show plaque morphology and measure coronary vasomotion and the effect of drugs on lumen diameter. Finally, computerized transesophageal echocardiography may allow reconstruction of long tracts of the coronary arteries, with direct imaging of coronary lesions and stents (Zotz, personal communication), and may potentially compete with computed tomography and resonance imaging to detect coronary atherosclerosis.

Conclusions. What was believed to be impossible yesterday seems to be easy today. But the "impossible" can be achieved only with effort, motivation and love. Echocardiography is like the agile David sculptured by Bernini in the Galleria Borghese; echocardiography can compete with the giants of radiology, and will bring us very far in the adventure of coronary flow imaging.

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