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EDITORIAL COMMENT

Stress Echocardiography, Carotid Arteries, and More

Its Versatility for Our Imaging Times*

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Stress echocardiography (SE) has been used clinically for >30 years (1,2). It originated from the pivotal concept that identification of physiologically significant epicardial coronary artery stenosis is the main diagnostic target in ischemic heart disease (3) (**Figure 1A**). It has stood the test of time, and we can confidently say that a theoretical model of extraordinary originality (the noninvasive detection of coronary flow reserve–limiting stenosis) generated a diagnostic model of extraordinary success (functional cardiac testing with regional wall motion and/or perfusion imaging) (4). SE now has an undisputed role in general cardiology guidelines.

In the last 10 years, the diffusion of SE has received a further boost from 2 disruptive changes that affected the use of cardiac testing in the era of sustainable medical imaging (5): 1) the need to justify the use of radiology (along with the need to encourage radiation-free techniques for an effective primary prevention of cancer) (6); and 2) the principle of responsible use of healthcare resources, which avoids, whenever possible, any testing with substantially higher direct cost and a long-term environmental burden (7). Yet, we are missing something. The diagnostic and therapeutic approach to coronary artery disease has clinically and conceptually focused on coronary stenosis (8). This now appears to be increasingly inadequate and dangerously reductionist compared with the complexity of being a cardiovascular patient with different sources of vulnerability, within and beyond the stenosis—for instance, at the level of the left ventricle (myocardial vulnerability), coronary microcirculation (small vessel vulnerability), and alveolar–capillary barrier (lung edema vulnerability) (9). Within this framework, the study by Amhadvazir et al. (10) in this issue of *iJACC*, is both timely and important, because it shows the feasibility and incremental prognostic value of carotid ultrasound (CU) simultaneously applied with SE in patients referred for known or suspected coronary artery disease.

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BEYOND SE: CAROTID PLAQUE PRESENCE (AND VULNERABILITY)

Although conceptually different and frequently performed by separate subspecialists, both SE and CU can provide insight into the atherosclerotic vulnerability of the individual patient. As shown by Amhadvazir et al. (10), the presence of carotid plaque indicates a significant atherosclerotic burden and makes a negative SE less benign and a positive SE more malignant.

As frequently happens with original work, there were some unavoidable limitations. The study was from a single center, and hard events were relatively few. The information provided by CU was relatively unsophisticated and failed to include plaque morphology, which is also important. Hypoechoic (lipid-rich) plaques with textural heterogeneity contour irregularities, and signs of intraplaque neovascularization with contrast-enhanced ultrasound are probably at higher risk of subsequent cardiovascular events than low-risk stable plaque with regular contours, homogeneous texture, hyperechoic structure, and no signs of intraplaque neovascularization (11).

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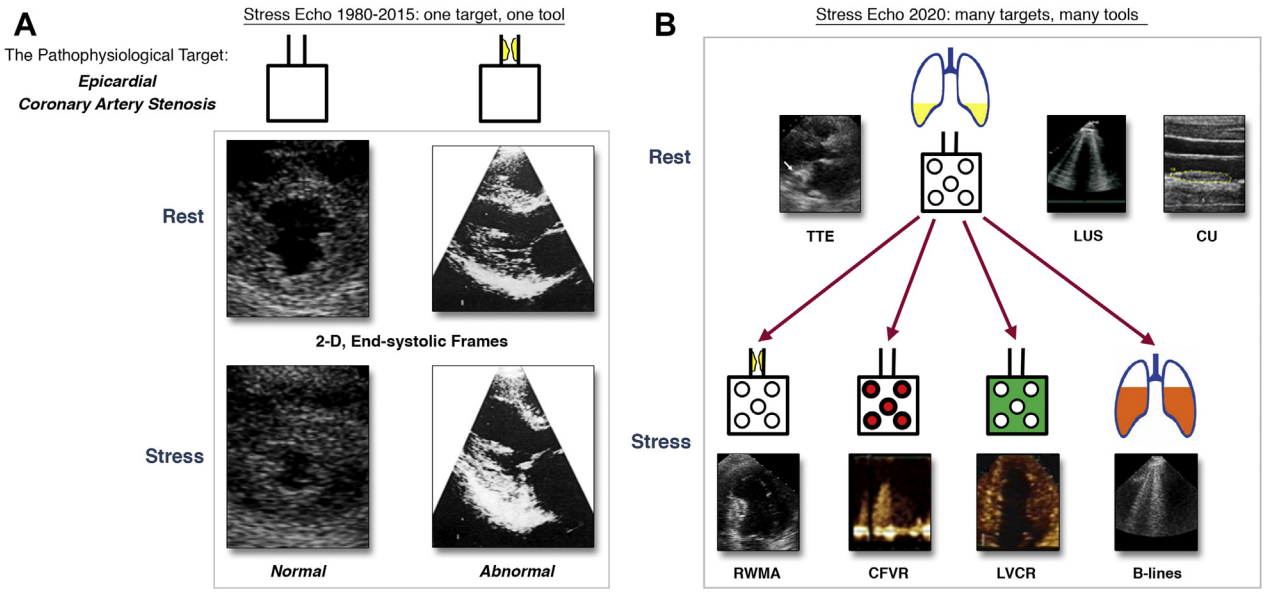
FIGURE 1 SE Evolution to Versatility



(A) Upper row: the classical paradigm of ischemia-producing coronary artery stenosis. The **box** represents the myocardium, and the **parallel lines** represent the coronary epicardial artery. Stress echocardiography (SE) is focused on only 1 target (the hemodynamically significant coronary artery stenosis) with only 1 tool (RWMA by 2-dimensional [2D] echocardiography). The end-systolic frames are shown: **left**, a normal response and **right**, an abnormal response with septal RWMA [from Picano et al. (2)]. **(B) Upper panel**, the examination at rest takes 3 steps: transthoracic echocardiography (TTE) (including assessment of cardiac calcification, a proxy of coronary calcification); LUS (for assessment of extravascular lung water, which is important in heart failure); and carotid ultrasound (CU) (for carotid plaque). **Lower panel**, the stress is made by multiple imaging with each parameter focused on a different target: the coronary artery stenosis **(yellow)** mirrored in regional wall motion abnormalities (RWMA); the coronary microcirculation **(red)** in coronary flow velocity reserve (CFVR); the myocardial function **(green)** in left ventricular contractile reserve (LVCR) (which can be impaired in the absence of RWMA); and B-lines (a sign of acute backward left heart failure) by lung ultrasound (LUS). This "next generation" SE imaging is currently under evaluation in and beyond coronary artery disease in the effectiveness, large scale, multicenter SE 2020 study (13).

Despite these limitations, the study teaches an important lesson. Atherosclerosis is a systemic disease, and SE and CU offer 2 complementary views of the same process, in 2 different territories that may be clinically uncoupled but share the same basic background (the risk factors) and the same outlook (the prediction of events). Similar information might be obtained with a combination of other techniques based on computed tomography or single-photon emission computed tomography, but because cost and radiation-induced, long-term risks have to be introduced in the risk–benefit balance of imaging, the integrated "one-stop shop" provided by CU provides similar clinical dividends without the cost and radiation exposure of a fragmented multi-imaging approach based on ionizing techniques.

TABLE 1 Risk Stratification of Atherosclerotic Patients by Ultrasound

	What We Have	What We Need
Pathophysiology model	Ischemia-producing stenosis	+ Small vessels, LV, ACB
Rest ultrasound	TTE	TTE, LUS, CU
Stress echocardiographic parameters	RWMA	RWMA, CFVR, LVCR, B-lines
Approach	Monolithic	Omnivorous
Risk stratification	Black-or-white	Shades of grey
Effectiveness studies	Present	Missing

ACB = alveolar-capillary barrier; CFVR = coronary flow velocity reserve; CU = carotid ultrasound; LUS = lung ultrasound; LV = left ventricle; LVCR = left ventricular contractile reserve; RWMA = regional wall motion abnormalities; TTE = transthoracic echocardiography.

The full translation of this study to the clinic will require additional cultural, technological, and scientific steps. Separate competence is required for echocardiographers who want to practice vascular sonography, with appropriate education, training, and certification. The strict standardization of acquisition and analysis of carotid intima-media thickness and plaque imaging is required, possibly with the assistance of software that will control variability through semi-automated reading of wall thickness and plaque texture. The clear definition of patients more likely to benefit most from additional imaging is required; likely candidates are those with negative SE, who may still be at significant risk. This

needs to be proven with future prospective, large-scale longitudinal studies with the combination of the 2 techniques (CU and SE) applied in the same patients.

SE: BEYOND REGIONAL WALL MOTION

CU focuses on arterial vulnerability with structural markers, and SE relies on myocardial vulnerability with functional markers, and both are useful for cardiovascular risk assessment. SE based on regional wall motion abnormalities (RWMA) remains the cornerstone of diagnosis, but today we have the unprecedented possibility of supporting RWMA with newer indexes that provide extra information, with a minimal increase in imaging and analysis time, such as coronary flow velocity reserve on the left anterior descending coronary artery (9), extravascular lung water (12), and left ventricular contractile reserve as the stress/rest ratio of systolic arterial pressure/end-systolic volume (9) (**Figure 1B**). Effectiveness studies are already beginning for the next generation of SE, with the aim of recruiting >10,000 patients with >100 SE laboratories from >10 countries in 10 separate projects, in and beyond coronary artery disease, in the "SE 2020" study (13) to fill the evidence gap in the field (**Table 1**).

We see the analogy of SE as a smart-phone with myriad potentialities, being used as an old-fashioned landline telephone, based only on RWMA. A "smart SE" application is possible, and will continue to emphasize how the versatility of this technique is truly unique.

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