Stress Echocardiography: Need to Optimize its Appropriate Use in Suspected Angina and a Review of Available Additional Tools for its Clinical Application in 2018: First do no Harm! Second do it at the Highest Possible Accuracy

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Abstract

There is a need to reassess the most appropriate indications for stress echocardiography in the current era, in patients with suspect or known coronary artery disease (CAD), and also the most helpful additional parameters that can be easily calculated in clinical practice to increase the known suboptimal sensitivity for obstructive CAD of this test. The current review tries to clarify what is and what should be the proper role for functional testing in general, but specifically regarding modern stress echocardiography in the current practice, for suspected CAD and/or atypical chest pain. Few candidate additional parameters beyond wall motion assessment are here suggested to improve diagnostic accuracy of stress echocardiography, and pertinent literature is briefly reviewed, together with a more personal view of the author regarding the characteristics of each parameter, as far as ease of acquisition, cost, and true diagnostic or prognostic clinical usefulness are concerned. The reviewed additional parameters, which can be acquired during stress echocardiography, are Doppler coronary flow reserve in the left anterior descending artery, cardiac calcium score, global longitudinal strain, ventricular elastance, and contrast myocardial perfusion. Each of them finds a potential place in the current practice or may find a place in the future practice of stress echocardiography.

Keywords: Contrast echocardiography, elastance, longitudinal strain, stress echocardiography, ultrasound calcium

Living a Historical Turning Point in Revascularization for Stable Coronary Artery Disease: Need to Reassess Our Use of Stress Echocardiography and Other Stress Tests

We are in the midst of a paradigm shift in cardiology as far as coronary artery disease (CAD) is concerned although the coronary angiogram will remain a key diagnostic information in stable CAD (in the future probably mostly noninvasively assessed as a first step); revascularization is recognized as an important but complementary therapy for a significant part of stable patients with CAD, in whom medical therapy should first be maximized,[1] something that remains difficult to “accept” for most of our cardiologic community. There still remains a substantial fanatical push to extend diagnostic functional testing as some type of screening test, without any proactive clinical control, to screen and search for any type of AD, as if that information could radically change “per-se” the outcome of stable patients, mainly based on the false idea that such finding will possibly trigger some “lifesaving” revascularization procedure (“if there is a blockage, we will fix it!”). Since now, we know this is clearly not the case, and revascularization in stable CAD is only one of the therapeutic options, and at least there is no agreement on whether it may impact on the outcome, we should also adapt our attitude toward the diagnostic “crusade”, our unnecessary quest for
stable CAD detection in otherwise mildly symptomatic or often asymptomatic individuals.

**Don’t Screen for Coronary Artery Disease in Substantially Asymptomatic Individuals, Search Instead for Real Cardiac Symptoms First, and then, If They Are Present, Calculate Pretest Probability!**

A prototypical case of a useless functional stress test is a stress echocardiogram inappropriately requested for suspected CAD in a young female patient with no risk factors and costal pain at palpation, who typically bears around 1% pretest probability (PTP) of CAD. Such case is not rare in modern echolabs, and this should trigger some action by the cardiology community aiming to minimize such cases, in whom a wise cardiologist should clearly recommend “no further testing.”

Such low risk of CAD patients is often forced to take a day off, maybe from work, for something which they expect to represent some kind of warranty for their future, but instead won’t change by any means their future living, apart from a possible false sense of safety, which can on the contrary obstacle the adoption of healthier lifestyle habits.

**What is and What Should Be the Proper Role for Functional Testing in General and Stress Echocardiography in Current Practice for Suspected Stable Coronary Artery Disease or Atypical Chest Pain?**

The ESC guidelines[2] clearly recommend against stress testing in patients with suspected CAD at <15% PTP according to the CAD consortium score.[5] In a recent retrospective study (unpublished data), from my own center in Parma and the Modena center, we found that as much as >1/3 of individuals without prior CAD who were undergoing single-photon emission computed tomography or stress echocardiography for suspected chest pain, and were tested either with exercise or dipyridamole, were low risk (<15% PTP of CAD), and importantly, the stress test results did not associate significantly with 5-year outcome of myocardial infarction (MI) or death, in a remarkable sample (n = 900 individuals) and 6 years median follow-up time; these data reinforce the guidelines in that >1/3 of such stress tests (all individuals at low PTP) are of little use and they should not be performed.

So why are we wasting our time, patients’ time, and health resources to do something that current ESC guidelines clearly state we should not do?

You would never behave similarly in the field of invasive cardiology; the first problem with stress tests is in fact that they are perceived as tests at negligible risk, and this is particularly true for stress echocardiography, which is extremely safe and does not imply long-term biohazard from ionizing radiation,[4-6] and hence, their indication is somehow liberally extended to any medical problem which is found otherwise difficult to address, just to “order a test,” something intended to appease the patient and buy some time for the physician.

It is usual practice that patients themselves admit they are happy to undergo some type of testing, but that they would have never undergone testing if they knew that inappropriate and possibly leading to more downstream unnecessary testing, rarely also invasive testing, due to a significant probability of a false positive test.

And here is the second issue, in which physicians and/or researchers are partially responsible, since we always push to propose our preferred diagnostic methods, maybe our research focus, as if such methods were the holy grail, so good to be independent of the clinical context of utilization, which is obviously not the case.

Testing low PTP patients with functional tests is instead particularly useless and in my view probably deleterious due to false reassurance of the patient, explaining the first part of the current article title: “First do no harm!” but what about the second part “…do it with the best possible accuracy”?

**If You Finally Opt for Stress Echocardiography, Do It at Its Best Possible Accuracy**

Once we have appropriately selected patients at reasonable >15% PTP for CAD, we will then use our preferred, or reasonably available method for stress testing, hopefully in conjunction with imaging, and at its best possible accuracy. In fact, it has been recently clearly demonstrated that most functional tests have in general a very limited sensitivity if the diagnosis of stable obstructive CAD is the endpoint, and focusing our discussion more into stress echocardiography, we should definitely combine the “good old” standard wall motion assessment, in itself a marker with very high specificity but low sensitivity, with everything else we may have available in our lab, at least a second additional variable, to make the test not only robust and specific, but also reasonably sensitive, beyond inherently limited diagnostic sensitivity of standalone wall motion assessment.[7]

**Which Are the Most Useful Parameters to Add on Top of Wall Motion Assessment during Stress Echocardiography?**

There is a wealth of parameters (Doppler coronary flow reserve [CFR], contrast myocardial perfusion imaging, ultrasound cardiac calcium score, left ventricle global longitudinal strain, elastance for contractile reserve, and few others) that may help to increase stress echocardiography diagnostic and prognostic accuracy, but only few of them are already routinely used at least in few laboratories around the world in clinical practice, not only for research, mainly
CFR and contrast echocardiography, although the second is generally used limited to better wall motion assessment (very few centers use contrast for myocardial perfusion imaging). Both assessments bear the limitation that they require some specific skills and a learning curve, with CFR in the distal left anterior descending coronary artery (CFR-LAD) having the clear advantage that its measurement does not require the use of consumable materials, such as microbubble contrast media, while contrast echocardiography (only if used for myocardial perfusion assessment) has the clear advantage that it may significantly improve diagnostic sensitivity in all 3 coronary territories and not only in the LAD territory, which is to date the only territory easily interrogated with Doppler CFR-LAD. Since the use of contrast for better wall motion assessment is to be considered a “feasibility or reproducibility-enhancing” application, more than an “accuracy-enhancing” application, this specific application is not comprised in Table 1, which encompasses only the candidate parameters to improve diagnostic and/or prognostic accuracy of current stress echocardiography clinical practice, with their characteristics graded in comparison one to the others. Unfortunately, few laboratories use at the same time more than one of such additional parameters so that comparison studies are rare.[9] All variables we can additionally assess on top of wall motion during stress echocardiography have a borderline zone between frankly normal or abnormal and we suggest to discard such ancillary information (and the clinician stick to wall motion data), when the variable is not clearly normal or abnormal, since an additional variable should never be further confounding on clinical grounds.[9]

A recently established registry (Stress Echo 2020) is prospectively enrolling thousands of patients in hundreds of echolabs around the globe and will assess the diagnostic and prognostic yield (and importantly the feasibility and reproducibility) of such additional parameters in several clinical settings, the typical suspected CAD setting being one of them.[10,11]

Table 1 shows several comparable characteristics of additional parameters to be used on top of wall motion during stress echocardiography.

### Table 1: Effectiveness of additional parameters

| Additional parameter | Easy | Low cost | Diagnosis | Prognosis | Literature |
|----------------------|------|----------|-----------|-----------|------------|
| CFR-LAD              | +++  | ++++++   | ++        | +++       | +++        |
| Cardiac calcium score| ++++ | ++++:+*:**| +++       | +++       | ++*        |
| Global strain        | +++  | +++      | ++        | +         | +          |
| Elastance            | +++  | +++:++:* | ++        | +         | +          |
| Myocardial perfusion | ++   | +++      | ++        | +++       | +/++       |

Number of + indicates how much effective is a given parameter for a specific aim. *Only 2 points regarding the specific literature for incremental information during stress echocardiography, while calcium literature for prognosis is much more relevant. **Calcium score and elastance do not require top machines or specific probes, differently from CFR-LAD, which only for this reason has 4 points and not 5 points. CFR-LAD=Coronary flow reserve-left anterior descending

### Doppler coronary flow reserve on the left anterior descending

Doppler CFR on the LAD does not need a long review in this context since this is an excellence from Italian echocardiography research, thanks to our Italian colleagues we are grateful to for first pioneering and then implementing this technique in the workflow of real-world echolabs. Consequently, at least in Italy, few stress echocardiographers are not aware of this technique and of its potent capability to stratify prognosis, due to the possibility to interrogate at the same time the epicardial coronary artery and the downstream microcirculatory function of a vastly dominant myocardial territory, such as the one subtended by LAD.[12] Its use is instead not fully satisfactory purely as a CAD diagnostic tool, with few studies demonstrating its possible incremental value for purely diagnostic purposes on top of wall motion although some benefit can effectively be observed through an increase in diagnostic sensitivity, obviously in exchange with a decrease in specificity.[13,14] This exchange between an increase in sensitivity and a decrease in specificity is typical for all parameters added on top of wall motion, but it is generally virtuous, only slightly decreasing the very high starting specificity of wall motion, in exchange for a higher significant increase in sensitivity. Coronary flow is consequently a very good candidate to be routinely chosen in addition to wall motion assessment to increase diagnostic sensitivity and mostly, prognostic stratification value of stress echo, and for this reason, it is in fact already endorsed by the EACVI guidelines on stress echocardiography.[14]

### Ultrasound calcium scoring

Ultrasound calcium scoring is a surprising parameter: it is easy, it does not require top level echo machines, it is available at no additional cost, and it has recently demonstrated significant incremental value both for diagnostic and prognostic purposes in patients undergoing stress echocardiography,[15,16] although in this stress echocardiography setting, the literature is limited. Cardiac calcium is more robustly proven as a parameter acquired outside of this stress echocardiography setting, during standard rest echocardiography, when it has an incredible long-standing “career” since the first 1999 NEJM outcome paper in which, specifically for the aortic valve,[17] the association between cardiac calcium and mortality became first widely known, and this association in general for cardiac calcium also assessed in the mitral valve or other sites remained valid both for diagnostic and prognostic purposes in primary prevention prospective studies.[18-23] Several types of scores have also been built and tested assessing the grade of sclerosis-calcification of the aortic valve, mitral valve, ascending aorta, and sometimes papillary muscles, but, in general, some structured assessment of echogenicity and thickening of at least aortic and mitral valves is enough, and the presence of zero cardiac calcium versus moderate-severe calcium does help to stratify the absence or presence of obstructive CAD or future cardiovascular events. Importantly, this variable or score adds incrementally to wall motion behavior assessed during stress echocardiography, which
makes ultrasound cardiac calcium scoring another good candidate as an additional parameter in this context. In case of only trace or low cardiac calcium score, the clinician should be very cautious and simply skip this parameter, considering it as a neutral information, similarly to all other borderline ancillary parameters. Figure 1 shows calcium (arrow) on the mitral annulus, on the left imaged using standard echocardiography or on the right using a dedicated setting at low mechanical index, which was originally conceived to be used with contrast echocardiography, a setting that better highlights the presence of calcium or fibrotic tissue versus normal myocardial tissue.

**Global longitudinal strain assessment during stress echocardiography**

Global longitudinal strain assessment during stress echocardiography has been associated with possible incremental diagnostic accuracy for the presence of CAD on top of wall motion assessment, although only in few studies,[24-28] but for some reason, the excellent and consistent results obtained with global or segmental deformation parameters using imaging at rest have not been translated to their variation between peak and rest phases during stress echocardiography (technical reasons?) as was expected, leading to conclude, according to most authors, that it may basically substitute, rather than add incrementally to visual wall motion assessment, which makes this parameter not very useful at this time in clinical practice as an add-on to standard wall motion assessment. Figure 2 shows an example of global longitudinal strain measurement.

**Elastance or contractile reserve**

Elastance or contractile reserve is technically easy, based on easy end-systolic pressure–volume relationship, and it has been proved as a diagnostic and a prognostic tool, in particular it may be incrementally diagnostic and prognostic in wall motion-negative stress echocardiograms. As of now, it is supported by very limited literature,[29,30] but the diagnostic data from the ongoing stress-echo 2020 registry,[9] some soon available (unpublished yet), will hopefully shed more light on its practical usefulness on top of wall motion, particularly as a sensitivity enhancer. More is expected with the publication of the full diagnostic data of the Stress-Echo 2020 registry, in late 2018.

**Contrast myocardial perfusion**

Although contrast echocardiography has long been considered one of the most promising new diagnostic techniques, as of today, it has not reached widespread diffusion and it has not ultimately entered routine clinical practice: multiple reasons may be adduced for this research/practice mismatch and some of them are inherent to the lack of appropriate guidelines clearly supporting its use and clarifying how to use it and for which specific clinical indications.

The 2017 EACVI recommendations for the clinical practice of contrast echocardiography have recently been released so that we can briefly focus on the chapter regarding recommendations for stress echocardiography.[31]

According to the new guidelines, stress echocardiography for the assessment of regional wall motion abnormalities for the detection of myocardial ischemia should be performed with contrast agents when two or more contiguous segments are not adequately visualized at rest (Class I, Level A) or during deep inspiration mimicking cardiac motion during stress (Class IIa, Level C). In patients in whom <2 segments are not well visualized, contrast agents should be given only when myocardial perfusion is assessed in addition to left ventricular wall motion, using low MI contrast imaging.

Low MI contrast-specific imaging modalities should be used for stress-echocardiography (see contrast imaging modalities section), irrespective of whether only wall motion or both wall motion and perfusion are assessed (Class I, Level C).

The threshold for the use of contrast for better endocardial visualization in this recommendations is lowered to at least two not well-visualized segments at rest or during deep inspiration, a phenomenon we know is frequent in clinical practice, and is further lowered to even <2 segments (meaning 1 segment or none) if myocardial perfusion is to be assessed.

This is an almost revolutionary aspect of such new recommendations, tackling a long time-debated application of contrast echocardiography, myocardial perfusion, with a very “light” attitude, which I fully agree with, introducing the first acknowledgement of contrast myocardial perfusion, simply giving it for granted. In fact, myocardial perfusion [Figure 3] is not easy to perform and interpret compared with the simpler technicality required for endocardial border enhancement (just click the appropriate setting and inject contrast), and no ultrasound contrast agent has a specific European Medicines Agency (EMA) or Food and Drug Administration (FDA) approval (nor a contraindication) for such utilization in the context of perfusion imaging. It is usually argued that
the absence of a specific indication or contraindication by regulatory bodies does not mean you cannot use that method, since, for example, gadolinium-containing contrast media for cardiac magnetic resonance are also not specifically EMA or FDA approved for myocardial perfusion, although they are widely used for this indication. This lack of specific approval for perfusion, with 20-year existing approval and proof of very high safety of contrast media for cardiac and noncardiac similar indications, does not appear as a real problem, once the approval of such use of contrast media is recognized and now endorsed by pertinent medical societies, which is in fact what now happens in this new EACVI guideline, and this may be a game changer for future wider clinical use. Only few adequately powered studies addressed the key issue of the potential incremental diagnostic value of contrast use during standard stress echocardiography using myocardial perfusion on top of standard wall motion assessment and the same is true for prognosis, but it appears that for both aims myocardial perfusion imaging is very useful.

This encourages new generations of stress echocardiographers that contrast echocardiography is out of the research field, it is safe, and can be used anytime the images are not ideal or, if they learnt the basic skills to do that, to assess myocardial perfusion.

**Conclusions**

There is still plenty of room for clinically oriented stress imaging and specifically for stress echocardiography in individuals with suspected CAD, but preselection based on estimated risk is a must, and additional sensitivity enhancing variables should always be collected in conjunction with wall motion assessment.

This combination of less inappropriate use with some sensitivity enhancing parameters will surely revitalize stress echocardiography for many more decades.

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