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DOI: 10.5603/KP.a2019.0002

Article type: Review

Submitted: 2019-01-08

Accepted: 2019-01-08

Published online: 2019-01-08

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Left ventricular contractile reserve in stress echocardiography: the bright side of the force

Eugenio Picano, Tonino Bombardini², Tamara Kovačević Preradović², Lauro Cortigiani¹, Karina Wierzbowska-Drabik⁴, Quirino Ciampi⁵

¹Institute of Clinical Physiology, National Council Research, Pisa, Italy
²School of Medicine, University Clinical Center of The Republic of Srpska, Banja-Luka
³Cardiology Division, San Luca Hospital, Lucca, Italy
⁴Chair and Department of Cardiology, Medical University of Lodz, Lodz, Poland
⁵Fatebenefratelli Hospital of Benevento, Viale Principe di Napoli, Benevento, Italy

Address for correspondence:
Eugenio Picano, MD, PhD, Institute of Clinical Physiology, National Council Research, Via Giuseppe Moruzzi 1, Pisa 56124, Italy, tel: +39-050-315 2398, fax: +39-050-315 2374, e-mail: picano@ifc.cnr.it

Abstract

Stress echocardiography (SE) is based on the detection of regional wall motion abnormalities (RWMA) mirroring a physiologically critical epicardial artery stenosis determining subendocardial underperfusion. Recently the core protocol of SE was enriched by adding left ventricular contractile reserve (LVCR) based on Force. An altered Force can be due to microvascular and/or epicardial coronary artery disease, but also to myocardial scar, necrosis and/or sub-epicardial layer disease.

LVCR is calculated as the stress/rest ratio of force (systolic arterial pressure by cuff sphygmomanometer/end-systolic volume, ESV, from 2D echo). Differently from ejection fraction, Force is not dependent from changes in preload and afterload. Cutoff values for a preserved LVCR are >2.0 for dobutamine or exercise and >1.1 for vasodilators, which are weaker inotropic stimuli. Patients with "strong" heart (normal LVCR) have a better outcome than patients with "weak" heart
(reduced LVCR), and this is the prognostic bright side of the Force, incremental over RWMA and outperforming LVCR based on ejection fraction.

Force addition to standard SE based on RWMA increases the spectrum of risk stratification without any significant inflation in imaging time and only trivial increase in analysis time. In ischemic (with RWMA) and non-ischemic (without RWMA) hearts, the preserved Force is associated with a more benign prognosis. The prospective multicenter international stress echo 2020 trial started in September 2016 has already recruited >5,000 patients with dual RWMA-Force imaging and will systematically test the Force impact within and beyond coronary artery disease, including heart failure and hypertrophic cardiomyopathy.

**Key words:** end-systolic volume, force, left ventricular contractility, stress echocardiography, wall motion abnormalities

**ADDING FORCE TO STRESS ECHO**

Stress echocardiography (SE) based on regional wall motion abnormalities (RWMA) is a technique well established for diagnosis and risk stratification in several cardiovascular conditions, within and beyond coronary artery disease (CAD) [1-5]. In recent years, the new cost-conscious and radiation-conscious climate [6,7,8,9] was the main driver of the observed relative growth of SE over competing cardiac stress imaging techniques [10,11]. As an example, in Mayo Clinic of Rochester, USA, the myocardial perfusion imaging /stress echo utilization ratio was 10 to 0 in 1999 and 1 to 5 in 2012 [12].

In spite of the increasing use of SE based on RWMA, the technique has limitations in contemporary populations. The positivity rate dropped-off for SE in the last decades from 40 % to less than 10 % [13,14,15], mostly for a reduction in pre-test probability of disease at referral. The predictive value of a negative test for RWMA is low, but not so low as we would like and as other competing techniques: 1.7 % annual hard event rate [16,17], while it was < 1 % in the early series when SE was applied to more diseased populations evaluated off anti-anginal therapy [18,19,20].

The awareness of these limitations was a potent stimulus for the conceptual and methodological remodeling of the technique. SE underwent a conceptual and methodological mutation to create a new standard: the quadruple imaging SE [21]. In the new version, SE
simultaneously provides imaging of RWMA (a mirror of physiologically significant epicardial artery stenosis) [22, 23], extravascular lung water (with B-lines and lung ultrasound) [24-26], left ventricular contractile reserve based on Force [27], and coronary flow velocity reserve (CFVR, targeting coronary microcirculation) [28]. In the quadruple imaging ABCD protocol [29], A stands for the evergreen Asynergy in RWMA, B for B-lines, C for Contractile reserve of the left ventricle, and D for Doppler-based CFVR on left anterior descending artery [30].

The present review focuses on Force-based LVCR. It is well known since decades that contractile reserve of the left ventricle is an established prognostic predictor. In particular, Force is a new parameter but with old and deep roots in experimental physiology and cardiac imaging, with a variety of different approaches, from nuclear cardiology (myocardial perfusion imaging and radionuclide ventriculography) to echocardiography itself. Force is observed from different perspectives in the subspecialties of cardiology: it is a reduction of the slope in the pressure-volume loop for the cardiac physiologist and invasive cardiologist [31]; it is a LV transient ischemic dilation during stress for the cardiac imager [32]; it is systolic blood pressure (SBP) drop for the clinical cardiologist [33]. All three parameters have been independently associated to a poor outcome. Now the three parameters of reduced slope of end-systolic pressure/ESV curve, transient ischemic dilation of the LV and SBP drop during stress converge conceptually methodologically and clinically in the systematic use of Force-based LVCR during SE (Fig. 1).

THE PHYSIOLOGICAL BASIS OF FORCE

Ejection Fraction is notoriously dependent on heart rate, preload and afterload changes [34]. A good ejection fraction can be found in mitral regurgitation or aortic regurgitation for an increase in preload and decrease in afterload even after the point of no return of irreversible LV damage has been reached. It is also well established thanks to the pioneering work of Suga and Sagawa in the seventies that a conceptually immaculate insight into LV contractility can be gained with the pressure - volume loops. During a positive inotropic intervention, the pressure volume loop reflects a smaller ESV and a higher end-systolic pressure. In particular the slope of the pressure volume loop at end-systole after different loading manipulations and at increasing heart rates indentities the true elastance or contractility value of the individual patient [31]. An increased stimulation rate increases the force of contraction: the molecular explanation is that repetitive Ca++ influx with each depolarization, and hence an accumulation of cytosolic calcium responsible for Ca++-induced calcium release. As the heart fails, there is a change in the gene expression from the normal adult
pattern to that of fetal life with an inversion of the normal positive slope of the force-frequency relation: systolic calcium release and diastolic calcium reuptake process is lowered at the basal state, and instead of accelerating for increasing heart rates, slows down. The increased frequency accelerates Ca++ inflow in systole and reuptake from sarcoplasmatic reticulum in diastole and justifies the steep force-frequency relationship in healthy heart or the biphasic-flat relationship in failing hearts. However, this approach requires long, risky, costly and clinically unrealistic study in the cardiac catheterization laboratories. The technique remained strictly confined in the academic context for decades [35, 36, 37]. Nevertheless, in selected populations submitted to laborious studies, the Force evaluated with invasive methods clearly separated hypertrophic cardiomyopathy patients with steep Force Frequency relationship and good prognosis from those with flat or biphasic relationship and bad prognosis [38]. This elegant pathophysiological concept was never applied in a clinically realistic noninvasive environment.

THE CLINICAL BASIS OF FORCE: LESSONS FROM CUFF SPHYGMOMANOMETER

From the very same definition of Force, any decrease in SBP during stress is accompanied by a decrease of Force reserve (Fig. 2). The normal response to graded exercise is a progressive increase in SBP with no change in diastolic blood pressure. In patients with known or suspected CAD, an increase in SBP is associated with a better prognosis compared to that of a hypotensive or no response to dynamic exercise. In fact, exercise-induced hypotension is an established marker of existing and likely severe cardiovascular disease with associated poor prognosis [33,39]. A reduced SBP is a co-determinant of a decreased value of Force. In theory, not only reduced Force values but also supernormal Force values might be "too good to be normal" especially in view of the recognized fact that some diseases (such as hypertrophic cardiomyopathy) may have a transient phase of abnormal compensatory hyperfunction before entering the clinical phase of overt reduction of LVCR and later resting dysfunction [40].

The adverse prognostic meaning of stress-induced hypotension has also been shown for pharmacological stresses, although the evidence base is clearly much more limited than with exercise. During dobutamine stress a profound SBP drop (> 20 mmHg during stress compared to resting values) occurs in 15 % of patients and carries an adverse prognostic meaning, incremental over RWMA, as shown in 3,381 patients with known or suspected CAD [41] and in 300 patients undergoing major vascular and thoracic non-cardiac surgery [42]. During dipyridamole imaging, profound hypotension (stress SBP < 90 mmHg) has been reported in 2.5 % of patients during oral (300 mg) dipyridamole stress and is associated to 5-fold higher frequency of severe resting LV
dysfunction (19% vs 4%) [43]. During adenosine or dipyridamole PET perfusion imaging, patients with higher drop in SBP during stress showed a higher risk of death, although the prognostic value was not additive over resting SBP and inducible ischemia [44, 45].

**LV DILATION DURING STRESS: THE NUCLEAR CARDIOLOGY EXPERIENCE**

The Force is the ratio of SBP and LV ESV. LV dilation has been utilized for over 40 years in cardiac imaging during myocardial perfusion imaging as an important variable associated with poor prognosis during physical and pharmacological stress [46]. Transient ischemic dilation describes an increase in cavity size on post-stress images compared to resting images. In fact, LV dilation is an old but still not obsolete marker of coronary anatomic and prognostic severity, as recently reemphasized by a meta-analysis on 2,037 patients from 13 studies ranging from early seventies to nowadays [47]. Across studies, annualized rate of cardiac death or myocardial infarction ranged from approximately 0.2 to 1 % in patients without dilation, 2 to 5 % in those with dilation and normal perfusion, and 5 to 6 % in those with LV dilation and ischemia, CAD or diabetes [47].

**LV DILATION DURING STRESS: THE ECHOCARDIOGRAPHIC EXPERIENCE**

At resting TTE, it is well established that for any given level of EF the larger the ESV and the poorer the prognosis, as shown with invasive ventriculographic and noninvasive echocardiographic techniques [48,49]. This same pattern applies during stress. Thurakhia et al. evaluated 1024 patients enrolled in the prospective Heart and Soul study with treadmill SE and found that ESV dilation (stress> rest) was the only significant predictor of mortality (HR 2.1, 95 % CI 1.43, p< 0.001) even when adjusted for RWMA. ESV was measured with the biplane method of discs and could be completed in all patients. Patients with ESV dilation also showed lower peak values of SBP [50]. Similar findings on the prognostic impact of LV dilation were obtained in other studies with exercise or pharmacological stresses with dobutamine or dipyridamole [51-55]. These studies consistently show the prognostic value of LV dilation, assessed with EDV and/or ESV changes, additive over RWMA and EF, and associated to anatomically and functionally more severe forms of CAD.

**THE SIMPLIFICATION OF THE CONCEPT OF FORCE**
From the pragmatic point of view, it is necessary to have simple concepts and simple measurements before the successful dissemination of any method in daily practice. Very complex and expensive technologies performed often very well in initial efficacy studies but failed to gain prime time in the real world populated by real patients, real doctors and real problems [56]. SE makes no exception to this "simplify for success" rule.

For RWMA, several generations of quantitative methods have been proposed over the years, and they were very successful in journals but never adopted in practice: too time consuming, poorly feasible in unselected patients, depending on expensive software. The diagnosis is today - as it was 40 years ago - by eyeballing of trained readers, since the capability of the human eye to integrate space and time is difficult to match, not to say to surpass.

For B-lines, the most validated and exhaustive scan protocol was the 28-site scan of the antero-lateral chest, which requires only 3 minutes to be performed and 1 minute for reporting in pre-defined forms. The SE2020 network accepted in principle the idea to include B-lines in the core SE protocol, but only 5 % of centers included it in their initially recruited cases. The reason? Too much time required. Based on this feedback, we had to test different scanning protocols and found the 4-site simplified scan as the reasonable trade-off between accuracy and simplicity [57]. Acceptance rate of the centers rose to 100 %, and in a few months we could collect thousands of patients with stress lung ultrasound.

For CFVR, there was a discussion as to whether dual or even triple imaging of the coronary arteries had to be included. No doubt that double imaging is feasible and informative [58] but once again the problem is time and feasibility. The success rate of imaging LAD is 95 % with < 3 minutes, the success rate of RCA is 58% with < 5 minutes, and the success rate of LCX is 65 % with < 10 min. As a result, only LAD flow imaging was incorporated in quadruple ABCD protocol, with extraordinary success rate and - in 2 years- over 4,000 patients could be recruited with dual imaging (RWMA and CFVR of LAD).

Also for LVCR, the transfusion of the parameter in the dissemination study led to a necessary simplification of the math and semantics of the parameter. A first attempt by Ginzton et al. in 1984 proposed the technique in the stress echo lab, using cuff sphygmomanometer as a proxy for end-systolic pressure and echocardiography to assess LV volumes [59]. This innovative approach remained however isolated in the literature, apparently abandoned even by those who originally proposed it. It was initially called elastance, which is the name preferred by Suga and Sagawa in their pioneering experimental work. We now use the synonymous of Force, much more familiar to
clinical cardiologists, who are inclined to think that a better heart is also a stronger heart. End-systolic pressure is peak systolic pressure multiplied by a correction coefficient of 0.9. We all know that peak systolic pressure is higher than end-systolic pressure, but in this case we preferred not to introduce this correction factor. In the clinical arena, every avoidable computational step is a source of error. We are interested in the relative (stress compared to rest) variation, and therefore any error averages out. We therefore deleted the correction factor 0.9 adopted in previous studies and we included the raw cuff sphygmomanometer data of SBP in the calculation of force.

We might index the value for body mass index as done in the past, but again the same index appears in the numerator (Force at peak stress) and in the denominator (Force at rest) and therefore a further simplification is possible ignoring normalization for body mass index. Values are expressed as raw Force (SBP/ESV).

The focus of LVCR is the ratio of peak stress/rest values, and therefore the resulting parameter has several advantages. It is dimensionless, with no need for the complex unit of measurement of the elastance (mmHg/mL/m²). It takes a range of values very familiar to the cardiologist, since normal values for exercise and dobutamine stress are > 2.0 (as happens with CFVR), with a titration of abnormal values also mirroring the CFVR values: mild (1.7-2.0), moderate (1.4-17) and severe (<1.4) abnormalities.

The feasibility problem was also important. The method of disks requires biplane views, which are of good quality in most but not all patients. Simpler methods are less accurate for absolute measurements but equally accurate to assess relative changes, and therefore - when Simpson is not feasible - apical single plane or even the linear Teichholz method can be employed. This increases the feasibility near 100 %, and allows dual imaging (RWMA and LVCR) in virtually all patients [60].

Originally, the measurement of elastance in the SE lab included measurement in all steps of stress. This was the best way to assess the upsloping versus flat versus biphasic response. However, for the prognostic viewpoint the flat and the biphasic pattern have the same meaning and both produce blunted values of peak Force, and therefore reduced LVCR. The method is however further simplified, since only rest and peak stress measurements are needed. In the end, with these simplifications and reasonable approximations Force and LVCR can be measured in all patients, with all stresses, and the dedicated additional imaging time is zero and the extra analysis time (offline calculation of volumes) is < 1 minute.
FORCE IN STRESS ECHO LAB: HOW TO DO IT

The force is measured as the ratio of end-systolic pressure (by cuff sphygmomanometer)/ESV (by 2D echocardiography). ESV is calculated from apical biplane views, and - when 2 views are not of good quality - with apical single plane view. When the apical views are not of sufficient quality, the linear measurement from parasternal view is accurate in assessing the relative (rest-stress) changes, with accuracy comparable to apical biplane method- and higher feasibility with shorter analysis time [60]. The calculation of ESV by 2D echocardiography is a relatively precise measurement, with > 90 % measurements within 10 % difference, and a substantially lower inter-observer variability of ESV than end-diastolic volume [61]. LVCR is the peak stress/rest ratio of left ventricular force. LVCR values during dobutamine or exercise stress may range from normal (> 2.0) to mild (1.5-2.0), moderate (1.01-1.49), and severe (≤1.0) dysfunction. Values are shifted towards lower values (abnormal <1.1) for vasodilators [59].

From the technical viewpoint, force can be acquired and analyzed in almost all patients. Image acquisition involves the same 2D view necessary for RWMA without dedicated imaging. Volume measurement requires around 60 sec (and even less with linear measurements from teichholz formula). All in all, integrating the required training for image acquisition and analysis, B-lines can be considered the kindergarten, LVCR the primary (for acquisition) or secondary (for analysis) school, RWMA the university, and CFVR the PhD course of the SE cursus studiorum.

CLINICAL AND PROGNOSTIC VALUE OF FORCE

LVCR is highly feasible during all forms of stress: exercise [62], pacing [63], dobutamine [64] and dipyridamole [65]. In patients with stable angina and normal resting left ventricular function, LVCR reduction during dipyridamole stress showed a 86% sensitivity and 87 % specificity for the detection of angiographically assessed CAD [66]. In absence of RWMA, an impaired LVCR is more often present with underlying critical CAD and/ or myocardial scar in brain-dead marginal heart donors who underwent autopsy verification after stress [65]. When outcome is the gold standard, LVCR reduction outperforms RWMA, Δ-WMSI and Δ-EF in predicting adverse events including death [67,68]. In diabetic patients with no RWMA, the annual hard event rate is three-fold higher in patients with abnormal compared to those with normal LVCR [69].

THE FUTURE OF FORCE
Force as it stands nowadays is simple, not time-consuming, accurate and informative. Yet, force can become even simpler, faster, more accurate and more informative. Innovations in progress target the measurement of SBP, ESV and the extension of the concept of force to the right ventricle.

At present, we measure SBP each minute by cuff sphygmomanometer. Peak and true end-systolic pressures can be continuously evaluated with finger tonometer or applanation tonometry on the carotid or the brachial artery, and the signal easily fed into the echocardiographic machine for real time, continuous, operator-independent assessment of SBP. A tonometric pulse wave recording is well tolerated, reproducible, fast and noninvasive. The main limitation is the inability to provide absolute values of arterial blood pressure, therefore a calibration with brachial artery pressure is always required [70].

At present, we efficiently measure ESV with 2-D, but RT3D is obviously more accurate and less time consuming in the acquisition phase [71]. The volumes can be combined with pressure signal, and a second-generation, operator independent Force is obtained and possibly displayed in real time on the echo monitor.

At present, force is systematically measured for the LVCR. However, the same rationale of using Force in LV applies to the right ventricle. Also for right ventricle, we have indices of performance that have served us well for the last 4 decades. They are linear and based on M-mode (TAPSE), based on 2-D (fractional area change in %) or 3D (ejection fraction). All these indices have limitations, since they are heavily load-dependent. Experimentally, the concept of Force has been successfully applied to the right ventricle [72], but non invasive clinical applications have met limited success, mainly because TRV jet necessary to derive SPAP has a low feasibility at rest and even lower during stress, especially in patients with normal pulmonary hemodynamics (without TRV signal) even after saline echo-contrast injection. However, recently the feasibility problems were circumvented with the TRACT protocol: when TRV is absent or unreadable, the systolic pulmonary flow acceleration time is an excellent surrogate with close to 100% success rate [73]. In this way the RV Force (SPAP/ ESV) can be obtained in all patients. ESV is usually obtained from the monoplane Simpson method applied to the right ventricle imaged from the apical 4-chamber view. As with the LV, the estimation of ESV is more reliable and faster with the RT3D approach, which in recent years has gained clinical plausibility thanks to highly improved spatial and temporal resolution and a more ergonomic, relatively small transducer size and footprint [74].

CONCLUSIONS
With the Force added to RWMA, SE separates strong hearts with normal LVCR from weak hearts with blunted LVCR. The new Force-based parameter needs minimal extra-imaging and extra-analysis time but yields multiple potential benefits, since SE gains versatility and objectivity, increases the positivity rate, broadens the domain of application from CAD to HF patients, and improves the risk stratification potential. The information provided by RWMA and Force can be also combined with the B-lines and CFVR in the full quadruple imaging with omnivorous ABCD core protocol.

Large scale effectiveness studies with IQ-SE are now under way with the Stress Echo 2020 project, and will hopefully provide the evidence needed for inclusion of the Force into the recommended standard of SE [75]. In the next years the use of Force may become simpler, faster and more accurate, with radial or carotid applanation tonometry for SBP and RT3D for ESV. Force could be adapted to assess also RV performance, with SPAP measured with tricuspid regurgitant jet velocity or acceleration time of systolic forward pulmonary flow velocity. Cardiologists and echocardiographers becoming increasingly familiar with the concept of Force may repeat the mantra of Star Wars saga: Let the Force be with you!

**Acknowledgements**

The technical assistance of Michele De Nes, informatics technician of Pisa Institute of Clinical Physiology of National Research Council, was highly appreciated.

**Availability of data and materials:** Data will be made available by Authors upon reasonable request.

**Funding:** The study was made possible by The Ageing project funding of the Italian national Research Council (P001328)

**Conflict of interest:** none declared
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Table 1. Force measurement in efficacy vs effectiveness studies

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<th>Standard</th>
<th>Simplified</th>
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<tr>
<td>Name</td>
<td>Elastance</td>
<td>Force</td>
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<tr>
<td>Units</td>
<td>mmHg/mL/m²</td>
<td>None (dimensionless)</td>
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<tr>
<td>End-Systolic pressure</td>
<td>Peak SBP x 0.9</td>
<td>SBP</td>
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<tr>
<td>ESV</td>
<td>Simpson biplane</td>
<td>Area-length or linear</td>
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<td>Measurements</td>
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<td>Rest and peak stress</td>
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<td>Analysis time</td>
<td>Minutes</td>
<td>Seconds</td>
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FIGURES

**Figure 1. The definition of Force.** Force is the ratio of end-systolic BP/ESV of the LV. In more pragmatic terms, since only peak systolic pressure is obtained noninvasively with cuff sphygmomanometer, and end-systolic blood pressure = peak-systolic pressure x 0.9, we measure with SBP a good surrogate of end-systolic blood pressure.

**Figure 2. The relationship between Force, SBP and end-systolic volume.** The 4 quadrants of possible response during stress. On the x-axis, the stress-rest variations in SBP, on the y-axis, the stress-rest variations in ESV. The four quadrants in clockwise rotation starting from the left upper quadrant are: normal response; abnormal hemodynamic response; abnormal hemodynamic and volumetric responses; abnormal volumetric response.

**Figure 3. The Force and regional wall motion response during stress.** The normal Force response of a non-ischemic and strong heart (*first row*), non-ischemic and weak (*second row*), ischemic and strong (*third row*); ischemic and weak (*fourth row*) heart.

**Figure 4. The risk stratification with quadruple imaging.** The risk stratification with SE, from binary (black or white) response based only to RWMA endorsed by current guidelines (*upper row*) to the spectrum of responses (from green of lowest to red of highest risk) obtained by dual imaging based on RWMA supplemented with LVCR. The dynamic range of risk stratification can be further expanded by adding B-lines and CFVR.
Force (mmHg/mL) = \frac{SBP}{ESV}

FORCE REST = \frac{120}{40} = 3.0
FORCE STRESS = \frac{180}{20} = 9.0
LVCR = \frac{9}{3} = 3.0
REST

STRESS

HEART

NON-ISCHEMIC STRONG

NON-ISCHEMIC WEAK

ISCHEMIC STRONG

ISCHEMIC WEAK
Risk stratification beyond regional wall motion abnormalities

- Ø
- 1 – 2 segments
- ≥ 3 segments

<1%
>3%

Hard event rate/year

(ESC guidelines 2013)

LVCR > 2.0 (>1.1 for vasodilator stress)
LVCR ≤ 2.0 (<1.1 for vasodilator stress)

Non-ischemic-Strong-Heart
Non-ischemic-Weak
Ischemic-Strong
Ischemic-Weak-Heart