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REVIEW

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

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Abstract

Stress echocardiography (SE) is based on the detection of regional wall motion abnormalities (RWMA) mirroring a physiologically critical epicardial artery stenosis which determines subendocardial underperfusion. Recently, the core protocol of SE has been enriched by the addition of left ventricular contractile reserve (LVCR) based on force. Changes in force can be caused by microvascular and/or epicardial coronary artery disease, but also by myocardial scar, necrosis, and/or sub-epicardial layer disease.

Left ventricular contractile reserve is calculated as the stress-to-rest ratio of force (systolic arterial pressure measured by cuff sphygmomanometer to end-systolic volume determined by two-dimensional echocardiography). In contrast to the ejection fraction, force is not dependent on changes in preload and afterload. Cut-off values for a preserved LVCR are > 2.0 for dobutamine or exercise stress and > 1.1 for vasodilators, which are weaker inotropic stimuli. Patients with a "strong" heart (normal LVCR values) have a better outcome than patients with a "weak" heart (reduced LVCR values), and this is the prognostic "bright side of the force," meaning that the prognostic value of force-based contractile reserve is higher than that of ejection fraction-based contractile reserve or RWMA.

The addition of force to standard SE based on RWMA detection increases the spectrum of risk stratification without any significant increase in imaging time and only a slight increase in analysis time. In both ischaemic (with RWMA) and non-ischaemic (without RWMA) hearts, the preserved force is associated with a more benign prognosis. The prospective multicentre international Stress Echo 2020 trial which started in September 2016 has already recruited > 5000 patients with dual RWMA-force imaging and will systematically test the impact of force on the prognosis 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

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ADDING FORCE TO STRESS ECHOCARDIOGRAPHY

Stress echocardiography (SE) based on regional wall motion abnormalities (RWMA) is a well-established technique 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 [6–9] was the main driver of the observed relative growth of SE over competing cardiac stress imaging techniques [10, 11]. As an example, in the Mayo Clinic of Rochester, NY, USA, the myocardial perfusion imaging/SE utilisation 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, this technique has limitations in contemporary populations. The positivity rate for SE decreased in the last decades, from 40% to less than 10% [13–15], mostly because of a reduction in

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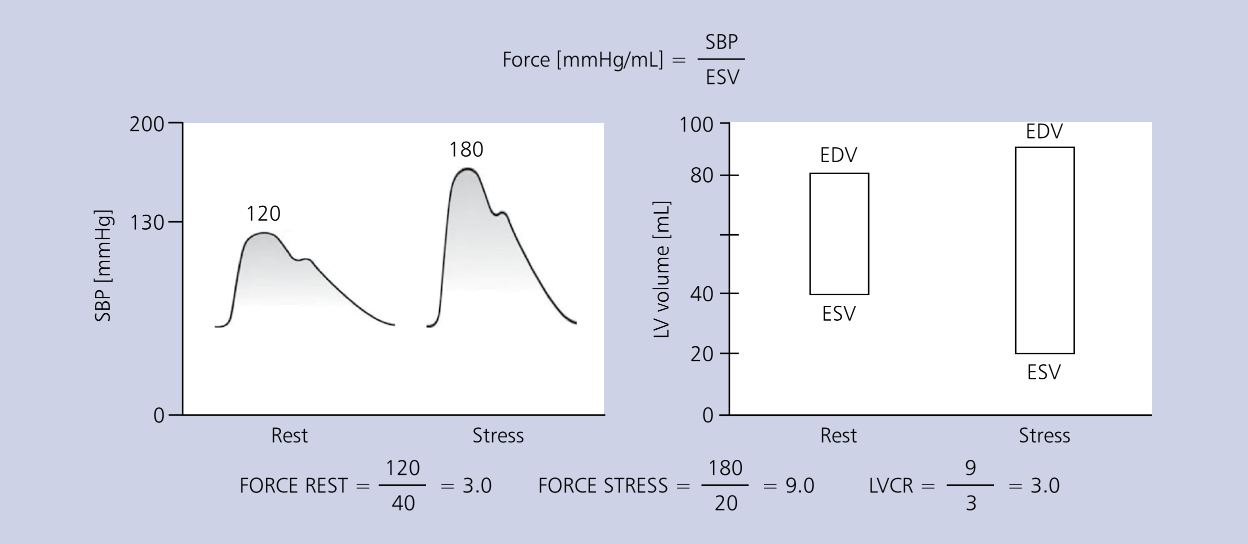

Figure 1. An example of a calculation of force and left ventricular contractile reserve (LVCR). In simplified terms, force is calculated as the ratio of peak systolic blood pressure (SBP; obtained noninvasively with cuff sphygmomanometer) to end-systolic volume (ESV) of the left ventricle (LV). LVCR is calculated as the ratio of stress to rest force; EDV — end-diastolic volume

pre-test probability of disease at referral. The predictive value of a negative test for RWMA is low, but not as low as would be desired or as low as for other competing techniques: the annual hard event rate was 1.7% in the years 2000 to 2016 [16, 17], while in the early series published in the 1990s, when SE was applied to more diseased populations evaluated off anti-anginal therapy, this rate was < 1% [18–20].

The awareness of these limitations was a potent stimulus for a conceptual and methodological remodelling of the technique, which led to the creation of a new standard: 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 (LVCR) based on force [27], and coronary flow velocity reserve (CFVR, targeting coronary microcirculation) [28]. This new quadruple-imaging protocol of SE is referred to as the ABCD protocol [29], where *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 imaging of LVCR. It has been well known for decades that contractile reserve of the left ventricle (LV) is an established prognostic predictor. Force is a new parameter but it has 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 various subspecialties of cardiology: it is a reduction of the slope in the pressure-volume loop for the cardiac physiologist and invasive cardiologist [31]; a transient ischaemic LV dilation during stress for the cardiac imager [32]; and a drop in systolic blood pressure (SBP) for the clinical cardiologist [33]. All of the above have been independently associated with poor outcome. Nowadays, the parameters of reduced slope of end-systolic pressure (ESP) or end-systolic volume (ESV) curve, transient ischaemic 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 (EF) is notoriously dependent on heart rate, as well as on preload and afterload changes [34]. EF values can remain within reference range even after the point of irreversible LV damage has been reached in conditions reducing the LV afterload, such as mitral regurgitation. It is also well established, thanks to the pioneering work of Suga and Sagawa [31] published in the 1970s, 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 ESP. In particular, the slope of the pressure-volume loop at end-systole after different loading manipulations and at increasing heart rate identifies 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 there is a repetitive Ca^{++} influx with each depolarisation, which leads to 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 foetal life, with an inversion of the normal positive slope of the force-frequency relation:

the processes of systolic calcium release and diastolic calcium reuptake are slower at the basal state, and instead of accelerating with increasing heart rate, they slow down. The increased frequency accelerates Ca^{++} inflow in systole and reuptake from sarcoplasmic reticulum in diastole and justifies the steep force-frequency relationship in healthy hearts or the biphasic-flat relationship in failing hearts. However, this approach requires long, risky, costly, and clinically unrealistic study in the cardiac catheterisation laboratories. The technique remained strictly confined to the academic context for decades [35–37]. 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 non-invasive environment.

THE CLINICAL BASIS OF FORCE: LESSONS FROM CUFF SPHYGMOMANOMETERS

From the very same definition of force, any decrease in SBP during stress is accompanied by a decrease in 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 with hypotension or a lack of response to dynamic exercise. In fact, exercise-induced hypotension is an established marker of existing and probably 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 the reduced but also supernormal force values might be "too good to be normal," especially in view of the recognised 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 subsequent resting dysfunction [40].

The adverse prognostic meaning of stress-induced hypotension has also been shown for pharmacological stress, although the evidence is clearly much more limited than with regard to exercise. During dobutamine stress a substantial SBP drop (> 20 mmHg during stress compared to resting values) occurs in 15% of patients and carries an adverse prognostic meaning, as shown in 3381 patients with known or suspected CAD [41] and in 300 patients undergoing major vascular and thoracic non-cardiac surgery [42]. This prognostic value is additive to that of the RWMA presence. During dipyridamole imaging, profound hypotension (stress SBP < 90 mmHg) was reported in 2.5% of patients during oral (300 mg) dipyridamole stress and was associated with a fivefold increase in the frequency of severe resting LV dysfunction (19% vs. 4%) [43]. During adenosine or dipyridamole positron emission tomography perfusion imaging, patients with a higher drop in SBP during stress showed a higher risk of death, although the prognostic value did not add significantly to the information provided by resting SBP and inducible ischaemia [44, 45].

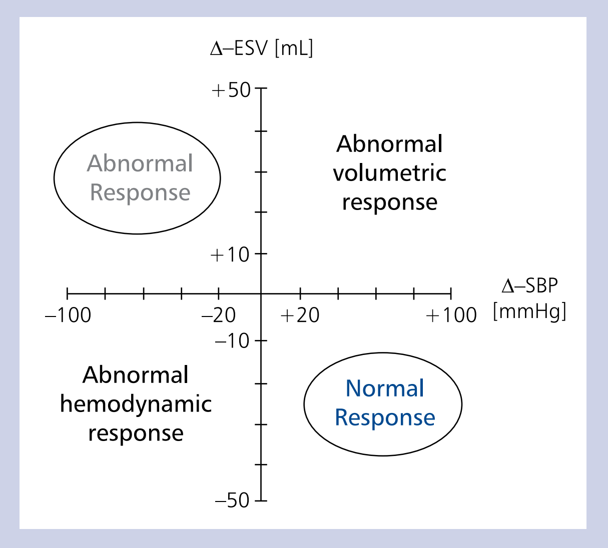

Figure 2. The relationship between force, systolic blood pressure (SBP), and end-systolic volume (ESV): the four quadrants of possible responses during stress. The x-axis shows stress-rest variations in SBP; the y-axis shows stress-rest variations in ESV

LEFT VENTRICULAR DILATION DURING STRESS: THE NUCLEAR CARDIOLOGY EXPERIENCE

The force is the ratio of SBP and LV ESV. LV dilation has been utilised for over 40 years in cardiac imaging, particularly in myocardial perfusion imaging, as an important variable associated with poor prognosis during physical and pharmacological stress [46]. Transient ischaemic dilation is reflected by an increase in cavity size on post-stress images compared to resting images. In fact, LV dilation is an old but still valid marker of coronary anatomic and prognostic severity, as recently reemphasised in a meta-analysis on 2037 patients from 13 studies ranging from the early 1970s to the present time [47]. Across studies, the annualised rate of cardiac death or myocardial infarction ranged from 0.2% to 1% in patients without dilation, from 2% to 5% in those with dilation and normal perfusion, and from 5% to 6% in those with LV dilation and ischaemia, CAD, or diabetes [47].

LEFT VENTRICULAR DILATION DURING STRESS: THE ECHOCARDIOGRAPHIC EXPERIENCE

On resting transthoracic echocardiography it is well established that regardless of the EF value, the larger the ESV, the poorer the prognosis, as shown with invasive ventriculographic and noninvasive echocardiographic techniques [48, 49]. The same pattern applies during stress. Thurakhia et al. [50] 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 (hazard ratio 2.1, 95% confidence interval 1.43, $p < 0.001$), even after adjustment for RWMA. ESV was measured with the biplane method of discs and the assessment 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 stress with dobutamine or dipyridamole [51–55]. These studies consistently showed that the prognostic value of LV dilation, assessed with EDV and/ or end-diastolic volume changes, increased the risk stratification value of RWMA and EF, and was associated with anatomically and functionally more severe forms of CAD.

SIMPLIFICATION OF THE CONCEPT OF FORCE

From a pragmatic point of view, it is necessary to have simple concepts and simple measurements before a successful dissemination of any method in daily practice. Very complex and expensive technologies tend to perform very well in initial efficacy studies but fail 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 the assessment of RWMA, several generations of quantitative methods have been proposed over the years, and although they were very successful in journals, they were never adopted in practice: they were too time consuming, poorly feasible in unselected patients, and dependent on expensive software. The diagnosis today lies — as it did 40 years ago — in careful evaluation by trained readers, because the capability of the human eye to integrate space and time is difficult to match, let alone to surpass.

With regard to B-lines, the most validated and exhaustive scan protocol was the 28-site scan of the antero-lateral chest, which can be performed in only 3 min and requires 1 min for reporting in pre-defined forms. The Stress Echo 2020 network accepted in principle the idea to include the assessment of B-lines in the core SE protocol, but only 5% of centres performed it in their initially recruited cases because it was deemed too time-consuming. Based on this feedback, different scanning protocols were tested and the four-site simplified scan was identified as a reasonable trade-off between accuracy and simplicity [57]. The acceptance rate of this method in the participating centres rose to 100%, and within a few months it was possible to collect stress lung ultrasound data from thousands of patients.

In terms of CFVR assessment, there was a discussion as to whether dual or even triple imaging of the coronary arteries had to be included in the protocol. There is no doubt that double imaging is feasible and informative [58], but once again the issues were time and feasibility. The acceptance rates for imaging of particular arteries were 95% for the left anterior descending artery (LAD) (duration < 3 min), 58% for the right coronary artery (duration < 5 min), and 65% for the left circumflex artery (duration < 10 min). Consequently, only LAD flow imaging was incorporated in the quadruple ABCD protocol, with an extraordinary success rate, and in two years over 4000 patients could be recruited with dual imaging (RWMA and CFVR of LAD).

Also for LVCR the inclusion of the parameter in the dissemination study led to a necessary simplification of its math and semantics. A first attempt to incorporate the assessment of LVCR in the SE protocol was made in 1984 by Ginzton et al. [59], who suggested using cuff sphygmomanometer data as a proxy for ESP and performing echocardiography to assess LV volumes. This innovative approach remained, however, isolated in the literature, apparently abandoned even by those who had originally proposed it. The ESP/ESV ratio was initially called elastance, which was the name used by Suga and Sagawa [31] in their pioneering experimental work. The term force is now preferred, as it is much more familiar to clinical cardiologists, who are inclined to think that a better heart is also a stronger heart. In most studies force is calculated using ESP, which means that peak systolic pressure is multiplied by a correction coefficient of 0.9. It is common knowledge that peak systolic pressure is higher than ESP, but this correction factor was not introduced in the Stress Echo 2020 study. 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 the results. We therefore deleted the correction factor of 0.9 adopted in previous studies, and we included the raw cuff sphygmomanometer data of SBP in the calculation of force (Table 1).

Further simplification consisted in excluding normalisation for body mass index (BMI) from the formula. In other studies, BMI was included in the assessment of LVCR, but the same values appeared in the numerator (force at peak stress) and in the denominator (force at rest). In the effectiveness studies, 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 and does not need to be expressed in a complex unit of measurement, in contrast to elastance ($mmHg/mL/m^2$). It takes a range of values very familiar to the cardiologist because normal values for exercise and dobutamine stress are > 2.0 (as in the case of CFVR), with a titration of abnormal values also mirroring those of CFVR, indicating mild (1.7–2.0), moderate (1.4–1.7) and severe (< 1.4) abnormalities.

The issue of feasibility was also important. The assessment of ESV with the method of discs 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 for the evaluation of relative changes, and therefore — when the Simpson method is not feasible — an apical single-plane or even the linear Teichholz method can

Table 1. Force measurement in efficacy vs. effectiveness studies

	Standard	**Simplified**
Name	Elastance	Force
Units	mmHg/mL/m^2	None (dimensionless)
End-systolic pressure	Peak SBP × 0.9	SBP
End-systolic volume	Simpson biplane method	Area-length or linear method
Measurements	All stress steps	Rest and peak stress
Analysis time	Minutes	Seconds

SBP — systolic blood pressure

be employed. This increases the feasibility to almost 100% and allows dual imaging (RWMA and LVCR) in virtually all patients [60].

Originally, the evaluation of elastance in the SE lab included measurement in all steps of stress. This was the best way to assess the upsloping vs. flat vs. biphasic response. However, from the prognostic viewpoint the flat and the biphasic patterns have the same meaning; they both generate blunted values of peak force and, therefore, reduced LVCR value. This method was, however, further simplified, so that only rest and peak stress measurements were performed.

Thanks to all these simplifications and reasonable approximations, force and LVCR could be measured in all patients during all types of stress, without an increase in the dedicated imaging time.

FORCE IN STRESS ECHO LAB: HOW TO DO IT

The force is measured as the ratio of ESP (by cuff sphygmomanometer) to ESV (by two-dimensional [2D] echocardiography). ESV is calculated from apical biplane views or — if one of the views is of poor 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 that of apical biplane method and higher feasibility with shorter analysis time [60]. 2D echocardiography is a relatively precise tool in the evaluation of ESV, with $>$ 90% of measurements remaining within 10% difference, and the inter-observer variability of ESV is substantially lower than that of end-diastolic volume [61]. LVCR is the peak stress/rest ratio of left ventricular force. LVCR values during dobutamine or exercise stress may range to indicate normal ($>$ 2.0), mild (1.5–2.0), moderate (1.01–1.49), or severe ($\leq$ 1.0) dysfunction. For vasodilators, normal values are lower (abnormal $<$ 1.1) [59].

From the technical viewpoint, force can be assessed and analysed in almost all patients. Image acquisition involves the same 2D views necessary for the evaluation of RWMA, without additional dedicated imaging. Volume measurement requires around 60 s (and even less in the case of linear measurements using Teichholz formula). The simple combination of LVCR and RWMA evaluation allows to identify four distinct response patterns: non-ischaemic and strong, non-ischaemic and weak, ischaemic and strong, as well as ischaemic and weak (Fig. 3).

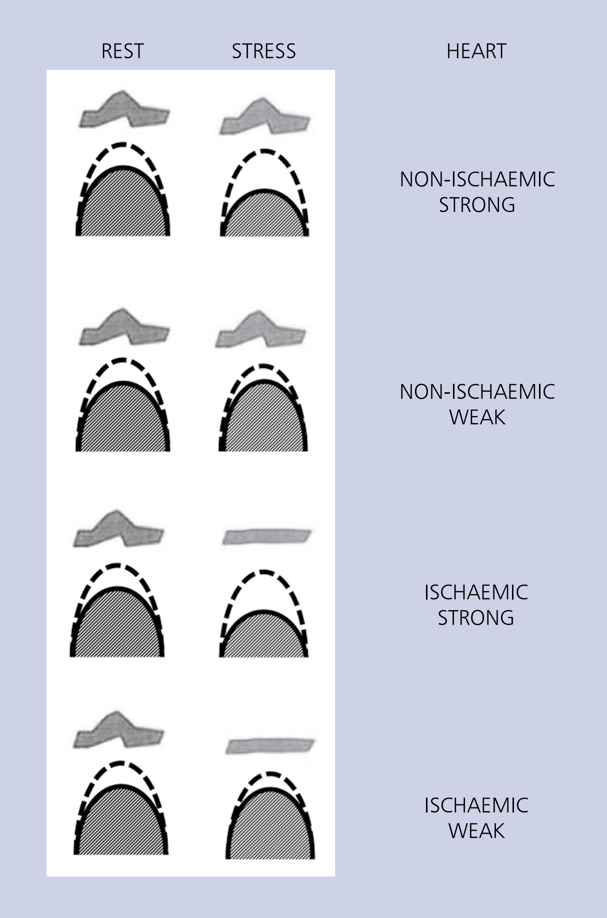

Figure 3. The force and regional wall motion response during stress

CLINICAL AND PROGNOSTIC VALUE OF FORCE

Left ventricular contractile reserve 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 86% sensitivity and 87%

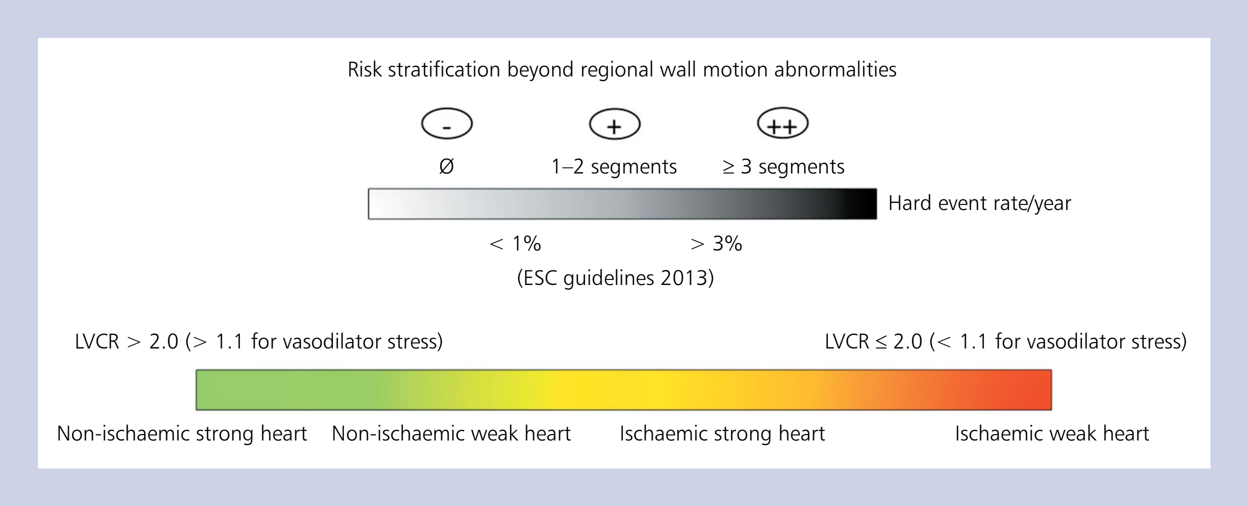

Figure 4. Risk stratification with stress echocardiography. Upper row: stratification based only on the presence of regional wall motion abnormalities (RWMA), endorsed by current guidelines of the European Society of Cardiology (ESC) [3]. Lower row: stratification obtained by dual-imaging, based on the presence of RWMA supplemented with measurement of left ventricular contractile reserve (LVCR); from green for lowest to red for highest risk. The dynamic range of risk stratification can be further expanded by adding B-lines and coronary flow velocity reserve (quadruple imaging)

specificity for the detection of angiographically assessed CAD [66]. In the 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]. In terms of the prognostic strength, LVCR reduction outperforms the presence of RWMA as well as stress-rest variations in wall motion score index and EF, in predicting adverse events including death [67, 68]. In diabetic patients with no RWMA, the annual hard event rate is threefold higher in persons with abnormal compared to those with normal LVCR [69]. The risk stratification capability of RWMA increases when it is supplemented by an evaluation of LVCR, because an ischaemic response is less malignant in the presence of a strong heart with a preserved global LVCR, and a non-ischaemic response is less benign in the presence of a weak heart with reduced global LVCR (Fig. 4).

THE FUTURE OF FORCE

Force, as it stands now, is a simple, time-efficient, accurate, and informative parameter. However, all those characteristics can be further improved. Innovations are helping to target the measurement of SBP and ESV and the extension of the concept of force to the right ventricle (RV).

At present, SBP is measured every minute by cuff sphygmomanometer. Peak and true ESPs can be continuously evaluated with a finger tonometer or applanation tonometry on the carotid or brachial artery, and the signal can be 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 non-invasive. Its main limitation is the inability to provide absolute values of arterial blood pressure; therefore, a calibration with brachial artery pressure is always required [70].

End-systolic volume is currently efficiently measured by 2D echocardiography, but real-time three-dimensional (RT3D) echocardiography 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 evaluation of LVCR. However, the same rationale of using force applies to the RV. Well-established indices of RV performance that have been used for the last four decades. These include linear indices based on M-mode (tricuspid annular plane systolic excursion), or those based on 2D (fractional area change in %) or 3D echocardiography (EF). All of them have limitations because they are heavily load-dependent. Experimentally, the concept of force has been successfully applied to the RV [72], but non-invasive clinical applications have had limited success, mainly because the tricuspid regurgitant velocity (TRV) jet necessary to derive systolic pulmonary artery pressure (SPAP) has a low feasibility at rest and even lower during stress, especially in patients with normal pulmonary haemodynamics (without TRV signal), even after saline echo-contrast injection. However, the feasibility problems have recently been circumvented with the TRACT (Tricuspid Regurgitant velocity + ACceleration Time) protocol: when TRV is absent or unreadable, the systolic pulmonary flow acceleration time is an excellent surrogate with a success rate close to 100% [73]. 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 RV imaged from the apical four-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 addition of force to RWMA, SE separates strong hearts with normal LVCR from weak hearts with blunted LVCR. The new force-based parameter needs minimal extra time for imaging and analysis but yields multiple potential benefits. It increases SE versatility and objectivity as well as the positivity rate, broadens the domain of application from CAD to heart failure patients, and improves the risk-stratification potential. The assessment of force and RWMA presence can be also combined with the evaluation of B-lines and CFVR in the full, quadruple-imaging ABCD core protocol.

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

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