

Pharmadisclosure: much activity, but little progress, with the European Society of Cardiology ahead of many

While there is no doubt that the pharmaceutical industry and healthcare professionals need one another, it will probably be some time before there is universal agreement on the rules of the game, reports Barry Shurlock PhD

Few would disagree that, within the limits of commercial confidentiality, any payments or gifts in kind that doctors receive from companies should be declared by both the recipient and the company. The buzzwords are ‘transparency’ and ‘disclosure’. Stories of doctors receiving over-large payments for services rendered to companies keen to curry their favours—traditionally in cash in brown envelopes—are legend. The likelihood that most such stories are complete fiction does not, however, prevent them from undermining the confidence of many health care professionals (HCPs), patients, and law-abiding companies.

No one doubts that close interaction between HCPs and the pharmaceutical industry is essential. The fundamental point is whether these two halves of the healthcare world can ever reconcile the different philosophies under which they operate. Companies are in business to deliver profits to their stockholders. Doctors work to treat illness and disease. Companies want more success, more market share, and bigger prices than, respectively, science, sales, and governments can deliver. Have you ever met a pharmaceutical executive who wanted his company’s products to fail a clinical trial, who wanted a rival’s drug to be better valued, or argued that governments should reduce their healthcare expenditure?

A scenario which will be familiar to many doctors is that at a congress, or similar event, they meet a pharmaceutical executive who is interested in their field. They know that the treatment they give their patients on a daily basis has its limitations. They have ideas for improving it, perhaps based on existing drugs or procedures with some fresh insights from new scientific thinking. The executive is encouraging—he or she invites the doctor to a round table discussion held in a pleasant location. Later, if development of the drug or treatment in question is successful, there will be clinical trials, satellite meetings at congresses, and publications.

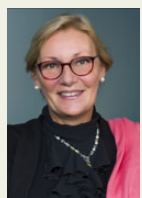
Almost certainly, the clinician will engage in a good deal of business entertainment and personal support (including nice hotels and generous expenses), and will no doubt welcome the frequent relief this brings from the daily load. Also he or she will get treated—and may even believe—that they are an ‘opinion leader’. All along, the doctor is likely to be involved in activities which will attract fees

and research costs. At a recent webinar arranged for the European Federation of Pharmaceutical Industries and Associations (EFPIA) by the Belgium-based communications company VitalTransformation, it was suggested by one participant that the normal fee for attendance at a round-table advisory group is between €800 and €2500. Unfortunately, it is not possible to verify or otherwise these sums, or determine what the participant has to do to earn the fee, as the information is not in the public domain.

To address this issue, a Europe-wide exercise by European national governments is underway, along the lines of the US Federal Physician Payments Act, a provision of the 2010 US Affordable Care Act. More immediately, industry is attempting to put its house in order, but there are problems. In the UK, a nascent body called the Ethical Standards in Health and Life Sciences Group—jointly convened by the Association of the British Pharmaceutical Industry, the Royal College of Physicians and other high-status partners—foundered very quickly when its intentions were perceived to be too biased towards industry. The EFPIA is trying to establish a disclosure code for its members, but has done so without consulting the healthcare profession. There is therefore a great deal of suspicion about its real objectives, with talk that it is really only a smokescreen for pulling out of funding for postgraduate education and congress attendance.

To further the EFPIA initiative, a ‘pharmadisclosure’ task force has been set up. One of its members is the European Society of Cardiology (ESC), which in fact has long had transparency and disclosure on its agenda. Anyone who has attended the ESC Congress knows that all speakers are required to start their presentation with a slide making a ‘declaration of interest (DOI)’. And, since 2011, anyone involved in any way with the ESC has had to submit a two-page DOI, which seeks detailed information on any relationships or financial arrangements with companies, including speaker’s fees, honoraria, consultancy and advisory board fees, receipts of royalties for intellectual property, and departmental and institutional funding of research. For each category, declarations of the amounts involved must be made, in the following tranches: <€10 000, €10–50 000, €50–100 000, and >€100 000.

'Positions of influence' must also be declared, defined as 'direct substantial shareholding or direct financial interest in healthcare, media and education companies', or other companies that supply, compete with, or contradict the ESC mission 'to reduce the burden of cardiovascular disease in Europe'. The ESC receives about 2000 DOIs a year, which are carefully scrutinized by the officers with whom the declarant may interact. In particular, vigorous scrutiny and publication of the DOI is required for anyone involved in drafting guidelines. The ESC is also considering making all DOIs public.



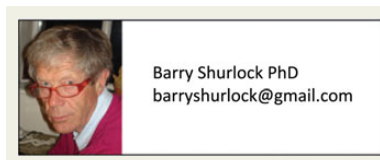
To outline the ESC's policy in this area, Chief Executive Officer, Isabel Bardinet, said: 'We are aiming to make DOIs public, if possible, but we also need to adhere to the requirements of data protection legislation. There are two big categories of concern. It is not the same to be employed by a company for research or for marketing.

Being a board member of a company is also different, since they have only limited influence in relation to other board members.

Holding shares in a company that operates in any area relevant to a guideline is a reason for exclusion from any involvement with those guidelines.

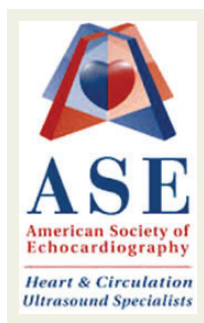
We also have to ask when a DOI becomes a conflict of interest [COI]. We need to consider whether the amounts declared are 'substantial or significant' in the context of a physicians' income and regard a sum of more than 10% of the annual salary as a COI.'

The reality is that exchanges between academia and industry cannot and should not be avoided, as they can result in some of the best and most innovative research ideas. What we must ensure is that the proper mechanisms are in place to promote transparency by enforcing disclosures of interest from all members, especially those involved in committees and task forces.



Cardiac imaging of adult cancer patients on chemotherapy

The ASE/EACVI expert consensus for multi-modality imaging of adult patients during and after cancer therapy



During the last years, novel adjuvant therapies have improved the survival of patients with cancer and, in some cases, turned cancer into a chronic cardiovascular (CV) disease. Nowadays, millions of cancer patients in the world are surviving long enough to develop adverse CV complications, which may become the cause of premature mortality.

Several highly effective chemotherapeutic agents may cause cancer therapeutic-related cardiac dysfunction (CTRCD). CTRCD has been classified as:

- (1) *CTRCD Type I*, typical of anthracyclines, is dose-dependent, leads to cell apoptosis, and is therefore irreversible at the cell level. Early detection and prompt treatment may prevent left ventricular (LV) remodelling and the progression to overt heart failure.
- (2) *CTRCD Type II*, typical of trastuzumab, is not dose-dependent, does not lead to apoptosis by itself, and is often reversible.

Of note, CTRCD types 1 and 2 can be associated sequentially in the same cancer patient (e.g. breast cancer).

Echocardiography and biomarkers such as brain natriuretic peptide (BNP) and cardiac troponins are current means for detecting pre-symptomatic cardiac damage and to evaluate cardioprotective treatments.

The joint Expert Consensus document of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) was planned to define CTRCD criteria and to fix cardiac imaging strategy to detect early CTRC in cancer patients.

The ASE/EACVI defined CTRCD as a decrease in the LV ejection fraction (LVEF) > 10 percentage-points, to a value <53% (normal reference value for 2D echocardiography). This decrease should be confirmed by repeat cardiac imaging. The repeated study should be performed 2–3 weeks following the baseline diagnostic study showing the initial decrease in LVEF.

The decrease in LVEF may be further categorized as symptomatic or asymptomatic, or with regard to reversibility, i.e. reversible (5 percentage-points increase in LVEF); partially reversible (improved by at least 10 percentage-points, but remaining more than 5 percentage-points below baseline); irreversible (remaining within 10 percentage-points of the nadir); or indeterminate (patient not available for re-evaluation).

Standard echocardiography is the method of choice for the evaluation of patients before, during, and after cancer therapy. Accurate calculation of LVEF should be done with the best ultrasound tool available in the echocardiography laboratory (ideally 3D

echocardiography). When using 2D echocardiography, the modified biplane Simpson's technique is the method of choice. Left ventricular ejection fraction should be combined with the calculation of wall motion score index (WMSI).

However, LVEF assessed by 2D echocardiography often fails to detect small changes in LV contractility. Myocardial deformation (strain), preferably performed by **speckle tracking echocardiography** (STE), represents the best technique to detect early, subclinical CTRCD, when LVEF is still normal.

Global longitudinal strain (GLS) is the best parameter, because of its very good feasibility and reproducibility. Ideally, GLS during chemotherapy should be compared with the baseline GLS. In patients with available baseline GLS measurements, a relative percentage reduction of GLS < 8% from baseline appears not to be meaningful, and those > 15% from baseline are very likely to be abnormal. Alternatively, if a baseline GLS measurement is not available, a GLS worse (less negative number) than -19% was shown to be predictive of later CTRCD. When applying STE for the longitudinal follow-up of cancer patients, the same vendor-specific ultrasound machine should be used. In the absence of GLS by STE, quantification of LV longitudinal function using mitral-annulus displacement by M-mode echocardiography, and/or peak systolic velocity (s') of the mitral annulus by pulsed-wave DTI is recommended.

A comprehensive assessment of LV diastolic function (including grading of LV diastolic function and a non-invasive estimate of LV filling pressures), RV function, heart valves and pericardium (pericarditis, pericardial effusion, and tamponade) is also recommended by the ASE/EACVI expert consensus.

Stress echocardiography should be performed in the evaluation of patients with intermediate to high pre-test probability for coronary artery disease (ECG uninterpretable or unable to exercise) who will receive regimens that may cause ischaemia (florouracil, bevacizumab, sorafenib, and sunitinib) and also in

the determination of contractile reserve of patients with evidence of CTRCD.

Cardiac magnetic resonance (CMR) shall be considered in situations where discontinuation of chemotherapy is being entertained, and/or when there is concern regarding echocardiographic calculation of LVEF. Cardiac magnetic resonance is also very useful in primary tumours of the heart with or without compromise of the pericardium, or, when the diagnosis of constrictive pericarditis remains uncertain after a careful echocardiographic evaluation.

Among **biomarkers**, the elevation of troponins (much more than BNP) may be a sensitive measurement for the early detection of CTRCD. Accordingly, the ASE/EACVI Expert Consensus also proposes the possibility of an integrated approach combining biomarkers and echocardiographic data. This approach can provide an incremental value in predicting subsequent CTRCD when used simultaneously. It may also provide a strategy for more aggressive surveillance if used in parallel, or reduction in the frequency of imaging when used in series (i.e. alternating imaging with biomarkers).

In clinical practice, it is recommended to evaluate LV function in high-risk patients before starting any anti-cancer drug therapy.

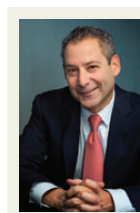


Drinking moderate amounts of alcohol is linked to reduced risk of heart failure

Heart failure is a major public health problem affecting over 23 million people worldwide

Evidence already exists for the beneficial effects of drinking moderate amounts of alcohol on the risk of developing a number of heart conditions; however, the role it plays in the risk of developing heart failure has been under-researched with conflicting results.

Now, a large study of nearly 15 000 men and women, recently published in the *European Heart Journal*,¹ shows that drinking up to seven drinks a week in early to middle age is associated with a 20% lower risk of men developing heart failure in the future when compared with people who did not drink at all, and a more modest 16% reduced risk for women.



Dr Scott Solomon



Dr Alexandra Gonçalves

Dr Scott Solomon, Professor of Medicine at Harvard Medical School and Senior Physician at Brigham and Women's Hospital,

Boston, USA, Dr Alexandra Gonçalves, a research fellow at Brigham and Women's Hospital, and colleagues analysed data from 14 629 people aged between 45 and 64 years who had been recruited to the Atherosclerosis Risk in Communities Study between 1987 and 1989 in four communities in the USA. They followed up the participants for 24–25 years to the end of 2011, and they questioned them about their alcohol consumption at the start and at each of the three subsequent visits made at three-yearly intervals.

They defined a drink as one that contains 14 g of alcohol. The study participants were divided into six categories: abstainers (people who recorded having drunk no alcohol at every visit by the researchers), former drinkers, people who drank up to seven drinks a week, or 7–14 drinks, 14–21 drinks, or 21 or more drinks a week.

During the follow-up period, 1271 men and 1237 women developed heart failure. The lowest rate of heart failures occurred in those drinking up to 7 drinks per week and the highest rate was seen among former drinkers.

After taking account of various factors that could affect the results such as age, diabetes, high blood pressure, heart disease or heart attacks, body mass index, cholesterol levels, physical activity, education and smoking, men who consumed up to seven drinks a week had a 20% reduced risk of developing heart failure compared with abstainers, while the risk was reduced by 16% in women consuming the same amount. Former drinkers had the highest risk of developing heart failure—a 19 and 17% increased risk among men and women, respectively, compared with abstainers. Interestingly, among both men and women consuming the most amount of

alcohol (14 or more drinks a week), the risk of heart failure was not significantly different compared with the risk for abstainers.

However, when the researchers looked at death from any cause, there was an increased risk of death of 47% for men and 89% of women who reported consuming 21 or more drinks a week at the start of the study.

Professor Solomon said: 'These findings suggest that drinking alcohol in moderation does not contribute to an increased risk of heart failure and may even be protective. No level of alcohol intake was associated with a higher risk of heart failure. However, heavy alcohol use is certainly a risk factor for deaths from any cause'.

The protective effect of moderate drinking was more marginal in women than in men and the authors think this may be due to the fact that women metabolize alcohol in a different way to men and it can affect them differently.

'It is important to bear in mind that our study shows there is an association between drinking moderate amounts of alcohol and a lower risk of heart failure but this does not necessarily mean that moderate alcohol consumption causes the lowered risk, although we did adjust our results to take account, as far as possible, for a variety of other lifestyle factors that could affect a person's risk', concluded Professor Solomon.

Reference

1. Gonçalves A, Claggett B, Jhund PS, Rosamond W, Deswal A, Aguilar D, Shah AM, Cheng S, Solomon SD. Alcohol consumption and risk of heart failure: the Atherosclerosis Risk in Communities Study. *Eur Heart J* 2015;**36**:939–945.

The dilemmas in diagnosing left ventricular non-compaction in athletes

Left ventricular non-compaction (LVNC) is an intriguing novel cardiomyopathy characterized by prominent myocardial trabeculations and deep recesses.^{1–4} The precise stage of development and the natural history of the disorder are not fully understood; however, preliminary data suggest that it is a morphologically and clinically heterogeneous disorder. Whereas some individuals present with overt heart failure and potentially fatal arrhythmias, others may remain asymptomatic.³ The clinical diagnosis is predominantly reliant on three proposed echocardiographic criteria and based on an increased ratio of a non-compacted inner layer to a compacted outer layer of the LV myocardium (*Figure 1*).³

The past two decades has witnessed significant advances in tissue harmonics and image resolution in echocardiography, which have enabled a detailed assessment of the ventricular myocardium. Unsurprisingly, such advances in echocardiography have coincided with increased reports of features consistent with LVNC in patients with heart failure⁴ and low-risk cohorts, including patients with sickle cell anaemia⁵ and athletes,^{6–9} particularly those of African/Afro-Caribbean origin. Data from a dedicated heart failure clinic in the UK revealed that nearly 25% patients showed features consistent with LVNC irrespective of the criterion used.⁴ Almost 10% of patients with sickle cell anaemia

fulfil echocardiographic criteria for LVNC⁵ and a study of over 1000 asymptomatic athletes demonstrated that 8% revealed criteria for LVNC and this phenomenon was more common in black athletes.⁶

Most athletes fulfilling echocardiographic criteria for LV non-compaction exhibited recognized manifestations of the athlete's ECG such as voltage criterion for left ventricular hypertrophy and normal LV function. However, a minority (0.9%) demonstrated concomitant T-wave inversion and reduced indices of systolic function that may be considered diagnostic of LVNC. Conversely, these manifestations may represent atypical features of cardiac adaptation. The distinction between cardiac remodelling from athletic training ('athlete's heart') and LVNC is important when one considers that primary cardiomyopathies are the most commonly implicated cause of exercise-related sudden cardiac death in young athletes.¹⁰

The dilemma in differentiating benign myocardial trabeculations from a primary cardiomyopathy arise because the current echocardiographic and more recently proposed cardiac MRI diagnostic criteria for LVNC^{1,2,11–13} are derived from small cohorts and lack specificity, particularly in asymptomatic low-risk populations. The most widely used criteria in common practice are the echocardiography based Jenni,

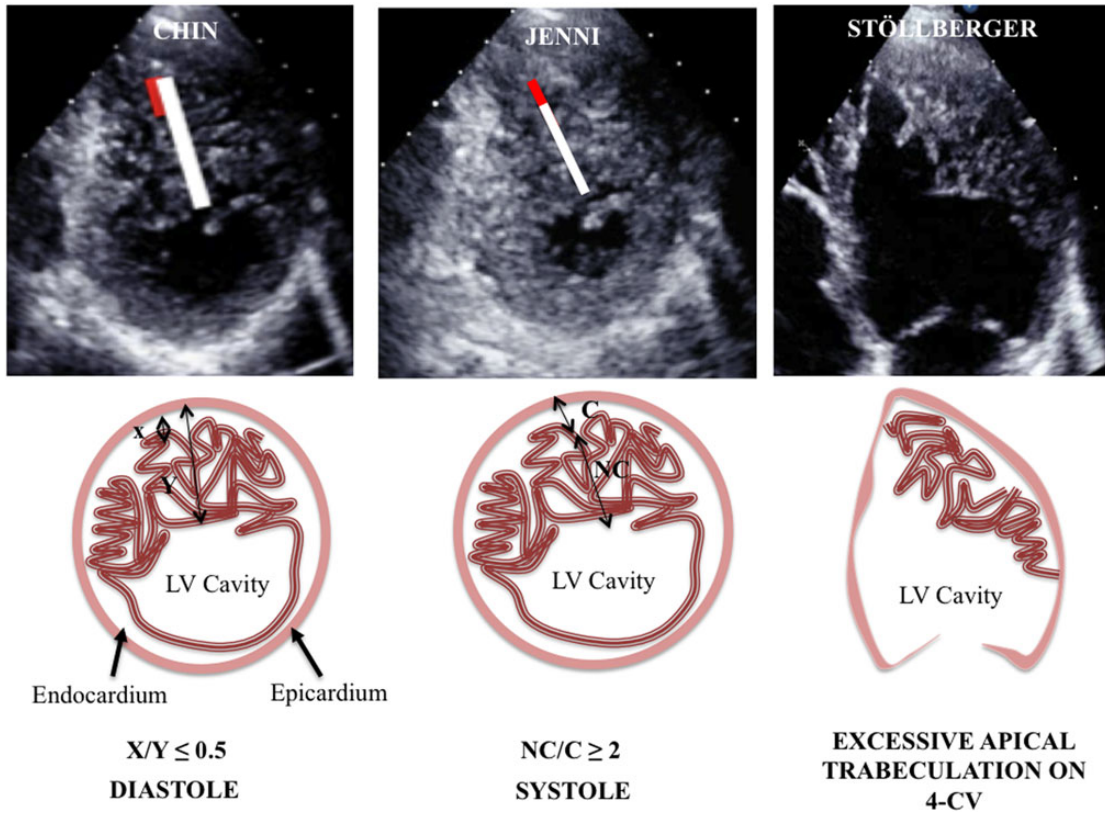


Figure 1 Echocardiographic criteria for left ventricular non-compaction.

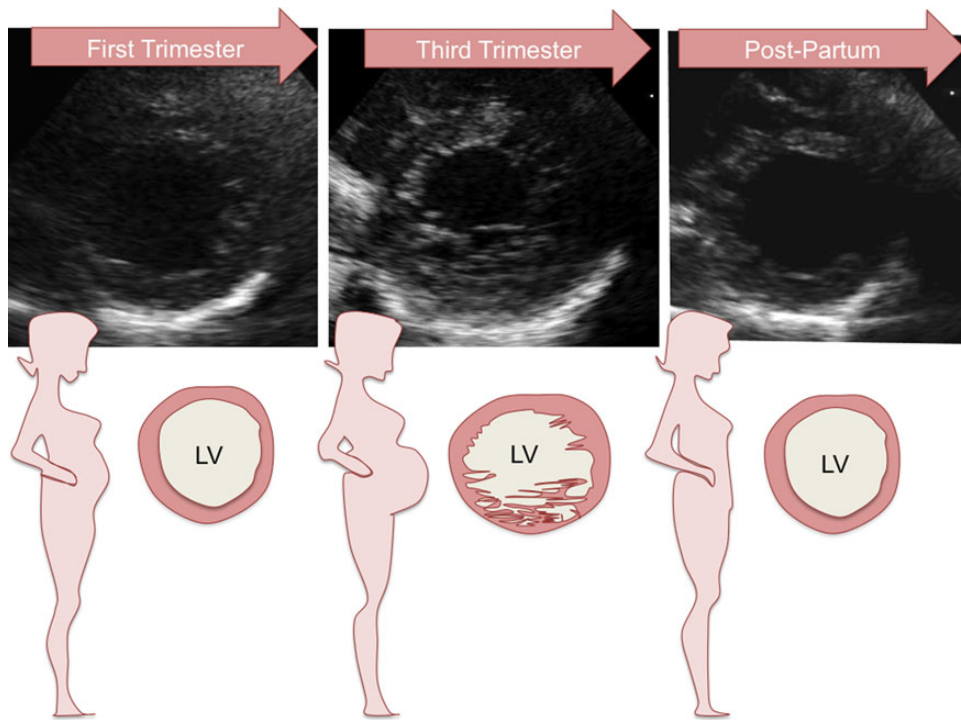
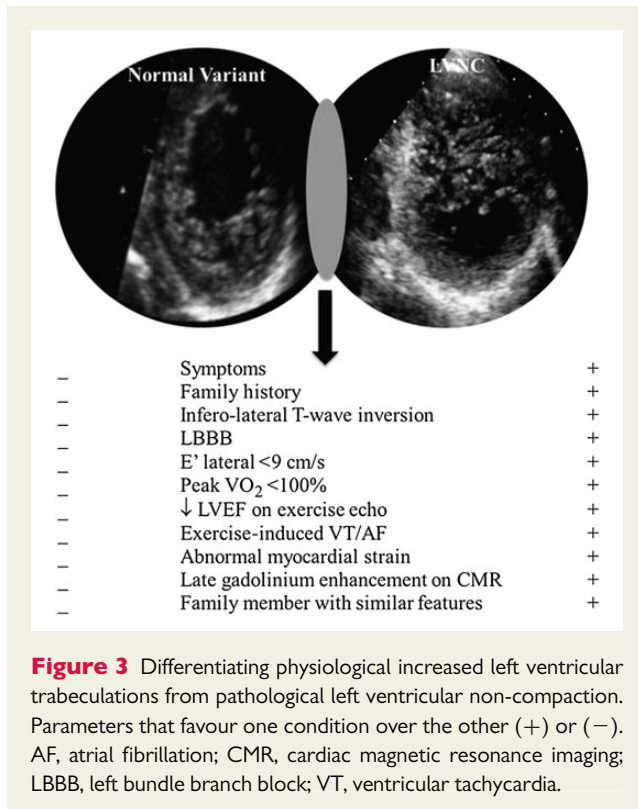


Figure 2 2-D echocardiographic example of a pregnant woman that developed LV trabeculations in the third trimester, which regressed in the post-partum period.



Chin or Stollberger criteria (Figure 1). All three rely on the presence of increased LV trabeculations and the presence of a double myocardial layer; an outer compacted area and an inner non-compacted layer, however, they differ from each other with respect to the precise area and the timing in the cardiac cycle for the measurement of the compacted and non-compacted layers. The mechanism for the development of increased LV trabeculations in low risk cohorts is unclear; however, the common factor appears to be an increased preload that may lead to an exaggeration in myocardial trabeculations in response to increased wall stress (an epiphenomenon) rather than LVNC cardiomyopathy.

We recently performed a longitudinal study assessing the impact of a physiological increase in cardiac loading conditions on left ventricular trabeculations.¹⁴ We used a pregnancy model which is associated with a 50% increase in blood volume (preload) by the 24th week and demonstrated that of 102 women with a completely normal left ventricle initially, 25% developed *de novo* trabeculations as pregnancy progressed (Figure 2). The data support the theory that most athletes fulfilling criteria for LVNC are unlikely to have a cardiomyopathy.

We propose the following guidance, utilizing several diagnostic modalities, for the assessment of athletes presenting with increased LV trabeculations consistent with LVNC, impaired resting LV function, and T-wave inversion on the ECG (Figure 3). The proposal is based on our own experience of comparing athletes with features of LVNC and actual patients diagnosed with the condition.⁶

Patients with LVNC frequently (75%) express symptoms of left ventricular dysfunction whereas athletes are asymptomatic. These individuals also frequently (66%) demonstrate an LV cavity of >64 mm, an ejection fraction <45%, suppressed longitudinal LV function ($S_a < 9$ cm/s) and impaired LV filling. In contrast, athletes with increased LV trabeculations and reduced EF usually show an EF range of 45–50% and normal indices of longitudinal LV function and normal diastolic function.

The pattern of T-wave inversion is different between the two groups; patients with non-compaction show T-wave inversion in the inferior–lateral leads whereas majority of athletes showed T-wave inversion in V1–V3. Left bundle branch block is most unusual in athletes but is common in patients with LVNC.

In our experience, a cardiopulmonary exercise stress test followed by a peak exercise echo is useful in the differentiation between the two groups. Athletes reveal a high peak VO₂ (>120% predicted for age and size) and dynamic LV contraction whereas patients with LVNC show low peak VO₂ and exercise echo reveals persistently reduced LV function.

The identification of non-sustained ventricular tachycardia or paroxysms of atrial fibrillation during exercise in athletes with criteria for LVNC would favour pathology. Abnormal myocardial strain patterns are in the experimental phase for this condition but an abnormal parameter may imply disease. The presence of late gadolinium enhancement at cardiac MRI would also suggest a cardiomyopathy process.

A family history of premature sudden cardiac death and heart failure in such athletes are an indication for long-term follow-up. In such circumstance we recommend screening of first-degree relatives for features of LVNC; the detection of another member with a similar phenotype would favour a diagnosis of LVNC.

Conclusion

Current imaging criteria for LVNC are non-specific in low risk populations and prone to an erroneous diagnosis. Increased cardiac preload is the most probable mechanism for increased trabeculations in athletes.



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References

References are available as supplementary material at *European Heart Journal* online.