Left-ventricular non-compaction–comparison between different techniques of quantification of trabeculations: Should the diagnostic thresholds be modified?

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Left-ventricular non-compaction – comparison between different techniques of quantification of trabeculations: Should the diagnostic thresholds be modified?

Abbreviated title: Imaging left ventricular non-compaction

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Summary

Background. – Diagnosis of left ventricular non-compaction (LVNC) is challenging, and different imaging techniques propose different criteria.

Aims. – To compare the value of two-dimensional transthoracic echocardiography (2D-TTE) and cardiac magnetic resonance (CMR) criteria in diagnosing LVNC, and to test a new trabecular quantification method obtained by 2D-TTE, exploring its relationship with CMR non-compacted mass quantification.

Methods. – From a multicentre French study, we selected 48 patients with LVNC and 20 with dilated cardiomyopathy (DCM) who underwent 2D-TTE and CMR. Current 2D-TTE (Jenni et al.) and CMR criteria (Petersen et al., Jacquier et al.), were tested. A new 2D-TTE method of trabecular quantification (percentage of trabecular area) was also proposed, and compared with current criteria.

Results. – The best cut-off values for the diagnosis of LVNC were a non-compacted/compacted ratio ≥ 2.3 (Petersen et al.), a trabeculated left ventricular mass ≥ 20% (Jacquier et al.) and a non-compacted/compacted ratio ≥ 1.8 (Jenni et al.). Lowering the threshold for the criterion of Jenni et al. from > 2 to ≥ 1.8 improved its sensitivity from 69% to 98%. The 2D-TTE percentage of trabecular area was 25.9 ± 8% in the LVNC group vs 9.9 ± 4.4% in the DCM group ($P < 0.05$), and was well correlated with CMR non-compacted mass ($r = 0.65$; $P < 0.05$). A 15.8% threshold value for 2D-TTE percentage of trabecular area predicted LVNC diagnosis with a specificity of 95% and a sensitivity of 92%; its sensitivity was better than that for the criteria of Jenni et al. ($P < 0.01$) and Petersen et al. ($P = 0.03$).

Conclusions. – Revision of the current threshold for the criterion of Jenni et al. from > 2 to ≥ 1.8 is necessary to improve LVNC diagnosis in patients with left ventricular dysfunction. A new 2D-TTE trabecular quantification method improves TTE diagnosis of LVNC.

Résumé

Contexte. – Le diagnostic de non-compaction du ventricule gauche (NCVG) est difficile. Plusieurs critères diagnostiques ont été proposés.

Objectifs. – Comparer les critères échocardiographiques (ETT) aux critères IRM pour le diagnostic de NCVG, et tester une nouvelle méthode de quantification ETT des trabéculations en la comparant à la mesure IRM de la masse non-compactée.

Méthodes. – Dans une étude multicentrique française, 48 NCVG et 20 cardiomyopathies dilatées (CMD) ont bénéficié d'une étude ETT et IRM. Les critères ETT de Jenni et al. and IRM de Petersen et al. et Jacquier et al. ont été comparés. Une nouvelle méthode de quantification ETT des trabéculations (pourcentage de la surface trabéculée) a aussi été étudiée.
Résultats. – Le meilleur seuil pour le diagnostic de NCVG est un rapport NC/C ≥ 2.3 (Petersen et al.), une masse trabéculée ≥ 20 % (Jacquier et al.) et un rapport NC/C ≥ 1.8 (Jenni et al.). Pour ce dernier critère, la réduction du seuil de > 2 to ≥ 1,8 augmente sa sensibilité de 69 % à 98 %. La surface trabéculée ETT est de 25,9 ± 8 % dans le groupe NCVG vs 9,9 ± 4,4 % dans le groupe CMD ($P <$ 0,05) et est bien corrélée à la masse non-compactée IRM ($r = 0,65$; $P < 0,05$). Une surface trabéculée ETT ≥ 15,8 % a une spécificité de 95 % pour le diagnostic de NCVG, et une sensibilité de 92 %, meilleure que celle des critères de Jenni et al. ($P < 0,01$) et de Petersen et al. ($P = 0.03$).
Conclusions. – Une révision des seuils diagnostiques du critère de Jenni et al. de > 2 to ≥ 1,8 est proposée chez les patients présentant une dysfonction ventriculaire gauche. Une nouvelle méthode de quantification ETT (pourcentage de la surface trabéculée) améliore le diagnostic de NCVG.

KEYWORDS

Non-compaction;

Cardiomyopathy;

Echocardiography;

Cardiac magnetic resonance;

Imaging

Abbreviations: 2C, two-chamber view; 4C, four-chamber view; 2D, two-dimensional; CI, confidence interval; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ICC, intraclass correlation coefficient; LV, left ventricle/ventricular; LVNC, left ventricular non-compaction; ROC, receiver operating characteristic; TTE, transthoracic echocardiography.

Background

Left ventricular non-compaction (LVNC) is a recently recognized cardiomyopathy characterized by a distinct morphological appearance of the left ventricular (LV) myocardium, with prominent trabeculae, deep intertrabecular recesses and a thin compacted epicardial layer [1].

In 2008, the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases categorized LVNC as an "unclassified" cardiomyopathy [2]. The aetiological origin [3, 4] of this disease and the genetic pathways [5] involved in trabecular remodelling and the compaction process during embryogenesis [6] are still under debate, as is the best diagnostic method.

Although there is no gold standard, two-dimensional transthoracic echocardiography (2D-TTE) is the first-line imaging technique for diagnosis [7]. Three echocardiographic methods have been proposed [8-10], by Jenni et al. [11] (considering a non-compacted/compacted layers ratio > 2.0), Chin et al. [8] and Stollberger and Finsterer [9]. However, these methods do not quantify the global hypertrabeculation of the left ventricle (LV) [11], and very poor correlation between them has been demonstrated by Kohli et al. [12]. Another possible and useful echocardiography tool is speckle-tracking analysis [13, 14], but its potential diagnostic value is still challenging, and needs to be investigated further.

The most promising diagnostic technique is cardiac magnetic resonance (CMR) imaging, which combines anatomical and functional information about non-compacted and compacted myocardium [15]. CMR allows both diagnosis of LVNC according to definite CMR criteria, based on the non-compacted/compacted layers ratio [16], trabeculated mass quantification [17], fractal analysis of trabecular pattern [18], and fibrosis detection using the late gadolinium enhancement technique [19], which has shown an additional prognostic value [20, 21]. However, both echocardiographic and CMR criteria were validated in very small populations, and other studies are necessary to assess their respective values.

Our aims were: (1) to compare the respective diagnostic values of 2D-TTE and CMR current criteria in a large population with definite LVNC compared with DCM; and (2) to test a new trabecular quantification method, obtained by 2D-TTE.

Methods

Study population

From a prospective French multicentre study comparing patients with LVNC and DCM included from 2012 to 2016, we selected patients who underwent complete 2D-TTE and CMR studies.

The LVNC group was selected according to: (1) the presence of trabeculations (defined as localized protrusions of the ventricular wall > 3 mm in thickness associated with intertrabecular recesses filled with blood from the LV cavity, by colour Doppler) and identification of two myocardial layers (compacted and non-compacted); (2) at least one positive imaging quantification criterion from the echocardiographic criteria of Jenni et al. [11] (including non-compacted/compacted ratio > 2.0 in end-systole), the CMR criterion of Jacquier et al. [17] (LV non-compacted myocardial mass > 20% of the global mass) or the CMR criterion of Petersen et al. [16] (end-diastolic non-compacted/compacted ratio > 2.3 in at least one of the LV segments in long-axis CMR images); AND (3) the mandatory agreement of both two observers (gold standard) with extensive experience in diagnosing cardiomyopathies and LVNC, who independently reviewed the anonymized echocardiographic and CMR recordings.

The DCM group was selected based on current diagnostic criteria, including LV chamber dilatation, impaired global LV function and no other causes of LV dysfunction [2].

Exclusion criteria were: history of suspected or proved ischaemic heart disease; hypertrophic cardiomyopathy or significant (at least moderate) valve disease; a recent heart failure episode at the time of enrolment (within the previous month); age < 18 years; and poor image quality (defined as more than three myocardial segments not optimally visualized using conventional 2D echocardiography).

Among the patients included in the French Registry, 68 (48 with a definite diagnosis of LVNC and 20 with a definite diagnosis of DCM) underwent both echocardiographic and CMR studies, and met the selection criteria, constituting the final study population.

The study complied with the Declaration of Helsinki, and was approved by our institutional review board. Written informed consent was obtained from all patients.

Echocardiographic analysis

All patients underwent complete TTE, according to recommendations on quantification of cardiac chambers [22] and evaluation of systolic and diastolic function [23]. After standard echocardiography analysis, we focused on trabeculation quantifications, detecting the most trabeculated segment to

measure its non-compacted and compacted layer thickness in end-systole short-axis view, and to calculate the non-compacted/compacted layers ratio, following the criteria of Jenni et al. [11].

Trabeculated areas were derived from measurements made at end-diastole from the two-chamber view (2C) and the four-chamber view (4C), first tracing the outer endocardial border (defining the compacted myocardial layer) and then the inner border, excluding papillary muscles. Global outer/compacted and inner/non-compacted areas were obtained by summation of the 2C and 4C values, respectively (total outer compacted area = 2C compacted area + 4C compacted area; total inner area = 2C non-compacted area + 4C non-compacted area). LV trabecular quantification was then derived as the difference between the two measurements (outer – inner), in both 2C and 4C views. Finally, we obtained the percentage of trabecular area by comparing the trabecular area with the global compacted area, using the following equation: percentage of trabecular area = (trabecular area 2C + 4C)×100/(total compacted area 2C + 4C)

Fig. 1 shows an example of our trabecular quantification method, and Fig. 2 compares our method with those already validated, in a patient with LVNC.

2D speckle-tracking analysis was performed using EchoPAC advanced quantification software (EchoPAC PC, version BT 13; GE Healthcare, Horten, Norway). Automated point-and-click tracking of myocardial speckles on the endocardial surface was reviewed, and the endocardial border and myocardial thickness were adjusted manually, if necessary. We performed global and segmental measurements of longitudinal strain, in accordance with the most recent European Association of Cardiovascular Imaging/American Society of Echocardiography consensus document [24].

CMR analysis

CMR imaging

All patients underwent a CMR examination with different clinical scanners depending on the centre. We used a 1.5 T magnetic resonance scanner (Avanto or Aera [Siemens, Erlangen, Germany]; Achieva or Intera [Philips, Best, The Netherlands]) or a 3T magnetic resonance scanner (Trio Tim or Skyra or Verio [Siemens, Erlangen, Germany]), using a multichannel body array coil combined with a spine array coil. Conventional cine steady-state free precession sequences were acquired on three long-axis views and a full LV short-axis stack, with retrospective cardiac gating. To reflect clinical practice, each centre could use their own parameters. The following parameters were used: slice

thickness range, 5–7 mm; inter-slice gap range, 0–4 mm; repetition time range, 2.8–3.6 ms for the Siemens scanners, 3.2–3.3 ms for the Philips scanners; echocardiography time range, 1.2–1.6 ms; flip angle range, 38–80°; matrix resolution range, 192×150–256×173; field of view range, 262×350–399×399 mm.

CMR imaging analysis

All examinations were transferred to a dedicated workstation and analysed by a single observer, blinded to the clinical data. For all study participants, LV volume, LV mass and LV ejection fraction were determined using Argus postprocessing software (Siemens, Erlangen, Germany). Two methods for identifying LVNC by CMR were assessed in this study.

In the first method, for the percentage of trabecular mass assessment, we used in-house semiautomated software (non-compacted processing) as described previously [17]. This software identifies trabeculated contours and endocardial and epicardial borders on each end-diastolic frame using a region-growing algorithm. Blood was then removed from the trabeculae using a semi-automated thresholding tool based on the difference between bright blood and darker myocardial intensities. The papillary muscles were also segmented using this threshold tool, and added to the compacted mass. Finally, compacted mass, trabeculated mass and percentage of non-compacted mass were computed. Trabeculated and compacted masses were indexed to body surface area. The distribution of trabeculae was assessed according to the 17-segment model.

In the second method, for the non-compacted/compacted thickness ratio measurement according to Petersen et al. [16], the three long-axis cine acquisitions were assessed for the presence of a distinct two-layered appearance. The ratio was calculated at the end-diastolic phase on the most trabeculated segment of each axis. The maximal value was used for analysis. A cut-off > 2.3 was considered diagnostic for LVNC phenotype.

Statistical analysis

Clinical and biological patient characteristics, echocardiographic results and CMR results were described and compared according to the two groups of interest (patients with LVNC versus those with DCM). Quantitative variables are described using mean values ± standard deviations, and were compared using Student's *t* test, when valid, or the Mann-Whitney test otherwise. Qualitative variables

are described by numbers and percentages, and were compared using the χ^2 test, when valid, or Fisher's test otherwise.

For each diagnostic criterion, including validated criteria [11, 16, 17] and the candidates' criterion (percentage of trabecular area), the receiver operating characteristic (ROC) curve was plotted, the area under the curve and its 95% confidence interval (CI) were estimated and the optimal cut-off was defined according to the Youden's method, which maximizes sensitivity and specificity. Areas under curves, sensitivities and specificities were estimated and compared by pairs.

The correlation (and its 95% CI) between the candidate criterion and a validated criterion, such as that of Jacquier et al. [17], was estimated and tested using Pearson's correlation coefficient test.

To test intraobserver and interobserver variability, trabecular quantification using the method of Jenni et al. [11] and the calculated and derived parameters to obtain the new proposed criterion were performed by two blinded expert readers, randomly selecting 12 patients with LVNC and 10 with DCM. Interobserver and intraobserver reproducibility was assessed by estimating intraclass correlation coefficients (ICCs) and their 95% CIs.

All tests were performed bilaterally, and for all analyses a P value < 0.05 was considered statistically significant. All the analyses were carried out using R software, version 3.4.3 [25]. The R packages OptimalCutpoints, epiR and DTComPair were used.

Results

Baseline clinical and imaging features of the two groups

The study population was homogeneous in terms of general demographic characteristics, as shown in Table 1: the mean age was 45.0 ± 13.8 years in the LVNC group vs 45.6 ± 13.1 years in the DCM group (P = 0.96); there were 24 men (50%) in the LVNC group vs 13 (65%) in the DCM group (P = 0.26); and the mean body mass index was 24.1 ± 3.8 kg/m^2 in the LVNC group vs 24.9 ± 4.5 kg/m^2 in the DCM group (P = 0.53).

Echocardiographic features are presented in Table 2: the LVNC group had smaller LV volumes, a higher LV ejection fraction and a higher global longitudinal strain compared with the DCM group. Similar trends were observed by CMR analysis (Table 3).

Strain measurements could be performed in 38 (79%) patients with LVNC. No correlation was found between strain values and the extent of trabeculations by either echocardiography or CMR.

Trabecular quantification by 2D-TTE and CMR

The results of the different echocardiographic and CMR methods of quantification of trabeculations are presented in Table 4 (2D-TTE) and Table 5 (CMR).

Using 2D-TTE, the mean non-compacted/compacted layer ratio according to Jenni et al. [11] was 2.2 ± 0.3 in the LVNC group vs 0.6 ± 0.4 in the DCM group ($P < 0.0001$). As shown in Table 4, the compacted area was significantly lower in the LVNC group than in the DCM group. The mean global trabecular area and the percentage of trabecular area were higher in the LVNC group compared with the DCM group ($P < 0.0001$).

Table 5 summarizes the CMR variables in both groups. According to the definition of LVNC on CMR, the ratio between non-compacted and compacted layers measured in end-diastole long axis (criterion of Petersen et al. [16]) (mean non-compacted/compacted layer ratio = 2.6 ± 0.5 vs 1.6 ± 0.4; $P < 0.0001$) and the mean percentage of trabecular mass (criterion of Jacquier et al. [17]) (28.0 ± 5.6% vs 14.5 ± 2.9%) were higher in the LVNC group compared with the DCM group ($P < 0.0001$ for both).

Patient distribution according to the different trabecular quantification criteria is presented in Fig. 3. All four methods adequately separated patients with and without LVNC, with the CMR method of Jacquier et al. producing the best discrimination.

Finally, the percentage of trabecular area by TTE was well correlated with the percentage of non-compacted mass by CMR, as shown in Fig. 4.

Diagnostic value of conventional 2D-TTE and CMR criteria

Considering the existing cut-off values, and recalculating the sensitivity and specificity of each in our study population, we found that the criterion of Jacquier et al. [17] predicted LVNC diagnosis with a sensitivity of 98% and a specificity of 100%, the criterion of Petersen et al. [16] predicted LVNC diagnosis with a sensitivity of 75% and a specificity of 95% and the criterion of Jenni et al. [11] predicted LVNC diagnosis with a sensitivity of 69% and a specificity of 100%.

The best cut-off values for diagnosis of LVNC were a non-compacted/compacted ratio ≥ 2.3 for the criterion of Petersen et al., a trabeculated LV mass ≥ 20% for the criterion of Jacquier et al., as reported previously, but a non-compacted/compacted ratio ≥ 1.8 for the criterion of Jenni et al.

Lowering the threshold for the criterion of Jenni et al. from > 2 to ≥ 1.8 improved its sensitivity from 69% (95% CI 0.54–0.81) to 98% (95% CI 0.89–1.00) (*P* value for improvement 0.0002), without modifying its specificity (100%, 95% CI 0.83–1.00).

Diagnostic value of the new 2D-TTE method

ROC analysis showed that the percentage of trabecular area could predict LVNC diagnosis with a specificity of 95% (95% CI 0.75–1.00) and a sensitivity of 92% (95% CI 0.80–0.98), considering the threshold value of 15.8%. The sensitivity of this criterion was better than those for the current criteria of Jenni et al. (*P* = 0.0045) [11] and Petersen et al. (*P* = 0.0325) [16]. Moreover, the areas under the ROC curves showed that percentage of trabecular area performance was not inferior to the criteria of Jenni et al. [11] and Jacquier et al. [17] in predicting LVNC, as shown in Fig. 5.

Reproducibility of measurements

Our new 2D-TTE trabecular quantification method showed a good degree of intraobserver and interobserver reproducibility: for interobserver reliability we found a minimum ICC for 2C compacted area equal to 0.99 (95% CI 0.94–1; per cent error –0.16); likewise, for intraobserver reliability, we found a minimum ICC equal to 0.99 (95% CI 0.96–1, per cent error 0.22) for 4C non-compacted area. Similarly, the criterion of Jenni et al. showed a high degree of intraobserver and interobserver reliability, with ICCs of 0.93 (95% CI 0.81–0.97, per cent error –0.15) and 0.93 (95% CI 0.84–0.97, per cent error –0.13), respectively.

Discussion

Study findings

The main findings of this study are: (1) that the measurement of LV trabeculation using 2D-TTE, expressed as a percentage of LV compacted area, is feasible and reproducible in patients with LVNC as well as in those with DCM; (2) that patients with a percentage of LV trabeculated area > 15.8% of the total LV compacted area should be considered as hypertrabeculated LV patients with a high probability of LVNC; and (3) that revision of current 2D-TTE and CMR diagnostic criteria thresholds should be considered in patients with LV dysfunction, to improve their diagnostic performance.

Quantification of LV trabeculation by conventional echocardiography and CMR criteria, and their limitations

Echocardiographic methods and their limitations

Several echocardiographic methods of quantification of trabeculations have been reported, but all have some limitations [26]. The criteria of Jenni et al. [11] are the most widely accepted, but were developed based upon pathological confirmation in only seven patients with LVNC, and the ratio between non-compacted and compacted layers in the most trabeculated area by definition cannot give a global view of the trabecular entity in all of the LV. In another small study, the criterion of maximal systolic compacta thickness of < 8.1 mm was found to be very specific for myocardial thickening in LVNC compared with normal controls or patients with aortic stenosis [27].

Similarly, the criterion of Chin et al. [8] was based upon observations from only eight patients, and is defined as the presence of $X/Y \leq 0.5$, where X is the distance from the epicardial surface to the trough of the trabecular recess and Y is the distance from the epicardial surface to the peak of trabeculation, at the LV apex on subxiphoid or apical 4C views at end-diastole. The criteria of Stollberger and Finsterer [9] emphasize hypertrabeculation, basing the LVNC definition on the presence of more than three trabeculations protruding from the LV wall in a single image plane, and intertrabecular spaces perfused from the ventricular cavity, visualized on colour Doppler imaging.

All these 2D-TTE criteria have several weak points – mainly their limited concordance and the lack of a gold standard to assess their accuracy. All of the echocardiographic methods detailed above have limited specificity when applied to other populations of patients and healthy controls, particularly black Africans. An “excessive” LV trabeculation at end-diastole may also be observed in normal athletes [3] or patients with hypertension [26]. As an example, lack of specificity of most of these echocardiographic LVNC criteria was noted in a retrospective study of 199 patients with systolic dysfunction referred to a heart failure clinic and 60 normal controls [12]. In this study, 24% of patients with systolic dysfunction and five of the 60 normal controls (including four black people) fulfilled one or more of the three sets of echocardiographic criteria for LVNC. Finally, despite considerable agreement, there remains substantial interobserver discrepancy in the diagnosis of LVNC by echocardiography in up to 35% of cases [28].

CMR methods and their limitations

Similarly, different CMR diagnostic methods have been proposed, given that CMR offers good spatial resolution of all LV segments, including the apex and lateral wall.

A maximum end-diastolic non-compacted to compacted myocardial thickness ratio of > 2.3 in long-axis views was the best criterion for LVNC in a study by Petersen et al. of seven patients with LVNC and 170 healthy volunteers, athletes and patients with dilated or hypertrophic cardiomyopathy, hypertensive heart disease or aortic stenosis [16].

Another method was defined by Jacquier et al. [17] in a study of 16 patients with LVNC, 16 patients with hypertrophic cardiomyopathy and 16 control subjects, namely trabeculated LV mass > 20% of global LV mass as a criterion for LVNC.

Finally, fractal dimension as a quantitative measure of trabeculation is high in LVNC, and may be very accurate and reproducible [18].

However, CMR evaluation also has some limitations. In a study assessing trabecular distribution in a population of selected healthy volunteers, Andre et al. [29] found that a considerable number of healthy subjects fulfilled the diagnostic criterion of Petersen et al., with female subjects showing a higher proportion of false-positive results than males, and with a progressive decrease in trabecular quantity with older age.

Revision of diagnostic thresholds

As discussed, all the LVNC diagnostic criteria derived from single studies were based on very limited populations; therefore, during the diagnostic assessment, we must consider carefully the cut-off values, which must be integrated with a global view of LV features and expert agreement.

For all these reasons, a review of the current threshold values, based on a larger number of subjects, may be appropriate. Based on matching at least one validated LVNC imaging criterion and expert consensus by two independent highly experienced observers as the gold standard, our study nearly confirmed the previously proposed diagnostic thresholds for the CMR methods, i.e. a non-compacted/compacted ratio of ≥ 2.3 for the criterion of Petersen et al. and a percentage of trabeculated LV mass ≥ 20% for the criterion of Jacquier et al. Conversely, the main finding was that the threshold for the criterion of Jenni et al. [11] should be reconsidered, and lowered to ≥ 1.8, to significantly improve its sensitivity in distinguishing between LVNC and DCM.

Value of our new 2D-TTE method of quantification

Considering all the limitations of current LVNC diagnostic criteria, we decided to test a new simple tool to quantify the trabeculation, which can be used routinely in clinical practice. This method has several advantages: first, using the global area obtained from the summation of 2C and 4C view values, and considering the percentage of trabecular entity, we minimized bias and measurement variability. Our quantification method has the potential to be particularly helpful in dilated LVs, to help to differentiate DCM hypertrabeculation from LVNC, because by considering the percentage and not the area values, we normalized the trabecular entity on the total area, which would be augmented in dilated hearts.

The percentage of trabecular area can be assessed during a simple routine bedside 2D-TTE, and hence is a low-cost diagnostic tool.

Finally, because of its good sensitivity and specificity, our method could be helpful when suspecting or confirming a diagnosis of LVNC if CMR is unavailable or contraindicated.

Study limitations

Our study had some limitations. First, the newly proposed diagnostic criterion was based on 2D-TTE, and thus has the same limitations as TTE (i.e. dependency on echogenicity and operator expertise), and may need a learning curve.

Second, we did not include a healthy control group in our analysis. However, we decided to compare our LVNC population with a DCM group without remarkable hypertrabeculation to really identify a cut-off value that is able to distinguish between significant and non-significant trabeculation entity.

The main limitation of our study was the absence of a true gold standard for the diagnosis of LVNC, which is why we decided to combine the main current imaging criteria with expert consensus to select our LVNC population.

In addition, as no patient without cardiomyopathy was included, the proposed criterion revision should not apply to the global population, but only to patients with LV dysfunction.

Finally, future genetic definition of this cardiomyopathy could provide a more powerful means of validating our method and the diagnostic tools already in existence.

Conclusions

A revision of the current thresholds for LVNC diagnostic criteria is necessary to improve the diagnosis of this cardiomyopathy in patients with LV dysfunction, mainly reducing the cut-off for the criterion of Jenni et al. [11] from > 2 to ≥ 1.8, with a consequent increase in sensitivity.

A new and simple 2D-TTE trabecular quantification method, based on compacted and non-compacted area measurements, could increase the value of 2D-TTE for the diagnosis of LVNC.

Of course, the current imaging criteria are still weak and, in the future, the LVNC diagnosis might be enhanced by defining a multiparametric score, including imaging, clinical and genetic data.

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Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Figure legends

Figure 1. Example of the proposed trabecular quantification method in a patient with left ventricular non-compaction: first calculating outer and inner global areas, then deriving the trabecular area and, finally, obtaining the percentage of trabecular area. 2C: two-chamber view; 4C: four-chamber view; trab: trabecular.

Figure 2. Example of trabecular quantification in a patient with left ventricular non-compaction: (A) using our two-dimensional transthoracic echocardiography method; (B) using the method of Jenni et al.; (C) using the CMR criterion of Petersen et al.; (D) using the CMR criterion of Jacquier et al. A. The described method for measuring the total/outer (blue trace) and inner/trabeculated (green trace) left ventricular areas using two-chamber (above) and four-chamber (below) end-diastolic views. D. Short-axis end-diastolic images used for mass measurement in the method of Jacquier et al.: in the top image, inclusion of papillary muscles and trabeculation for the measurement of global left ventricular mass; in the bottom image, inclusion of papillary muscles and exclusion of left ventricular trabeculation for the measurement of compacted left ventricular mass.

Figure 3. Graphs showing the distribution of patients with left ventricular non-compaction (red) versus patients with dilated cardiomyopathy (blue), considering the current criteria of Jacquier et al., Petersen et al. and Jenni et al., and our newly proposed quantification technique (percentage of trabecular area). 2D: two-dimensional; C: compacted; CMR: cardiac magnetic resonance; NC: non-compacted; trab: trabecular; TTE: transthoracic echocardiography.

Figure 4. Correlation between percentage of trabecular area obtained by our proposed two-dimensional transthoracic echocardiography method and percentage of trabecular mass obtained by cardiac magnetic resonance (technique of Jacquier et al.). The left ventricular non-compaction and dilated cardiomyopathy groups are marked with red and blue circles, respectively. trab: trabecular

Figure 5. Receiver operating characteristic curve describing the performance of our proposed percentage of trabecular (trab) area, compared with the criteria of Jenni et al. (on the left) and

Jacquier et al. (on the right). AUC: area under the curve; C: compacted; CMR: cardiac magnetic resonance; NC: non-compacted; trab: trabecular; TTE: transthoracic echocardiography.

Table 1 Baseline clinical characteristics in patients with left ventricular non-compaction versus dilated cardiomyopathy.

	LVNC group (n = 48)	DCM group (n = 20)	*P*
Age (years)	45.0 ± 13.8	45.6 ± 13.1	0.96
Body mass index (kg/m^2)	24.1 ± 3.8	24.9 ± 4.5	0.53
Male sex	24 (50.0)	13 (65.0)	0.26
Hypertension	11 (26.2)[a]	4 (20.0)	0.75
Diabetes	1 (2.4)[a]	3 (15.0)	0.09
Obesity	3 (7.1)[a]	2 (10.0)	0.65
Dyspnoea	19 (45.2)[a]	12 (60.0)	0.28
Syncope	5 (11.9)[a]	0 (0)	0.17
Angina	2 (4.8)[a]	0 (0)	1
Palpitations	12 (28.6)[a]	5 (25.0)	0.77
NYHA functional class			0.14
I	25 (59.5)[a]	7 (35.0)	
II	15 (35.7)[a]	12 (60.0)	
III	2 (4.8)[a]	1 (5.0)	
IV	0 (0)	0 (0)	
BNP (ng/L)	59.0 ± 102.3	118.4 ± 180.6	0.16

Data are expressed as mean ± standard deviation or number (%). BNP: B-type natriuretic peptide; DCM: dilated cardiomyopathy; LVNC: left ventricular non-compaction; NYHA: New York Heart Association.

Table 2 Two-dimensional transthoracic echocardiography results in patients with left ventricular non-compaction versus dilated cardiomyopathy.

	LVNC group (n = 48)	DCM group (n = 20)	P
LV end-diastolic volume index (mL/m^2)	77.1 ± 30.1	95.4 ± 30.8	0.01
LV end-systolic volume index (mL/m^2)	43.7 ± 28.0	60.7 ± 28.5	0.002
LVEF (%)	47.2 ± 14.5	39.4 ± 10.3	0.03
2D global longitudinal strain (%)	–14.0 ± 4.5 (n = 38)	–10.0 ± 4.3 (n = 16)	0.03
Left atrial volume index (mL/m^2)	38.3 ± 19.3	31.4 ± 14.1	0.13
E/A ratio	1.4 ± 0.9 (n = 45)	1.4 ± 1.3 (n = 18)	0.98
E/e' ratio	9.0 ± 5.9 (n = 44)	9.3 ± 3.6 (n = 15)	0.80
Systolic PAP (mmHg)	28.2 ± 10.1 (n = 32)	27.6 ± 9.1 (n = 15)	0.85

Data are expressed as mean ± standard deviation. 2D: two-dimensional; DCM: dilated cardiomyopathy; LV: left ventricular; LVEF: left ventricular ejection fraction; LVNC: left ventricular non-compaction; PAP: pulmonary artery pressure.

Table 3 Cardiac magnetic resonance results in patients with left ventricular non-compaction versus dilated cardiomyopathy.

	LVNC group (n = 48)	DCM group (n = 20)	P
LV end-diastolic volume index (mL/m^2)	105.1 ± 35.1	134.1 ± 48.2	0.018
LV end-systolic volume index (mL/m^2)	61.1 ± 36.3	90.1 ± 50.9	0.016
LVEF (%)	45.2 ± 15.9	36.0 ± 16.2	0.046
LV mass index (g/m^2)	66.5 ± 19.9	84.4 ± 27.0	0.0037

Data are expressed as mean ± standard deviation. DCM: dilated cardiomyopathy; LV: left ventricular; LVEF: left ventricular ejection fraction; LVNC: left ventricular non-compaction.

Table 4 Two-dimensional transthoracic echocardiography trabecular quantification in patients with left ventricular non-compaction versus dilated cardiomyopathy.

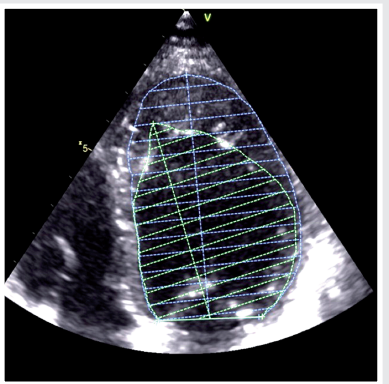
	LVNC group (n = 48)	DCM group (n = 20)	P
Compacted area 4C + 2C (cm^2)	78.2 ± 16.0	99.9 ± 21.0	0.0001
Trabecular area 4C + 2C (cm^2)	20.0 ± 6.7	10.0 ± 5.5	< 0.0001
Trabecular area (%)	25.9 ± 8.1	9.9 ± 4.4	< 0.0001
Non-compacted/compacted ratio (Jenni et al.)	2.2 ± 0.3	0.6 ± 0.4	< 0.0001

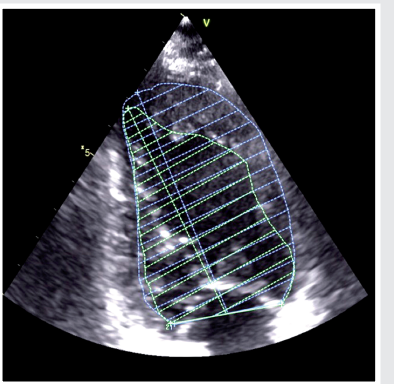
Data are expressed as mean ± standard deviation. 2C: two-chamber view; 4C: four-chamber view; DCM: dilated cardiomyopathy; LVNC: left ventricular non-compaction.

Table 5 Cardiac magnetic resonance trabecular quantification in patients with left ventricular non-compaction versus dilated cardiomyopathy.

	LVNC group (n = 48)	DCM group (n = 20)	P
Non-compacted/compacted layers ratio (Petersen et al.)	2.6 ± 0.5	1.6 ± 0.4	< 0.0001
Non-compacted/compacted mass (%) (Jacquier et al.)	28.0 ± 5.6	14.5 ± 2.9	< 0.0001
Number of segments (n)	6.6 ± 2.2	1.9 ± 1.6	< 0.0001

Data are expressed as mean ± standard deviation. DCM: dilated cardiomyopathy; LVNC: left ventricular non-compaction.



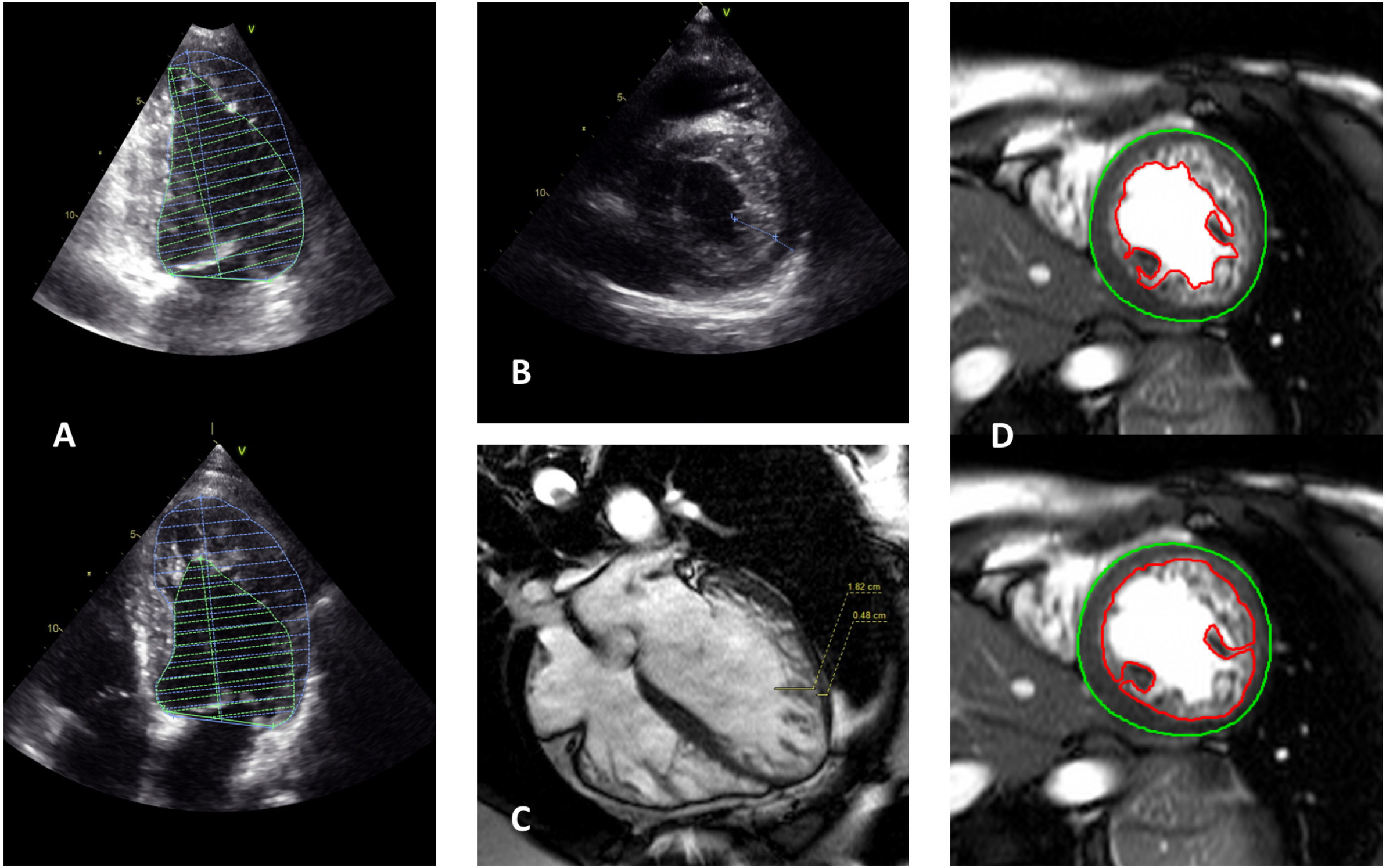


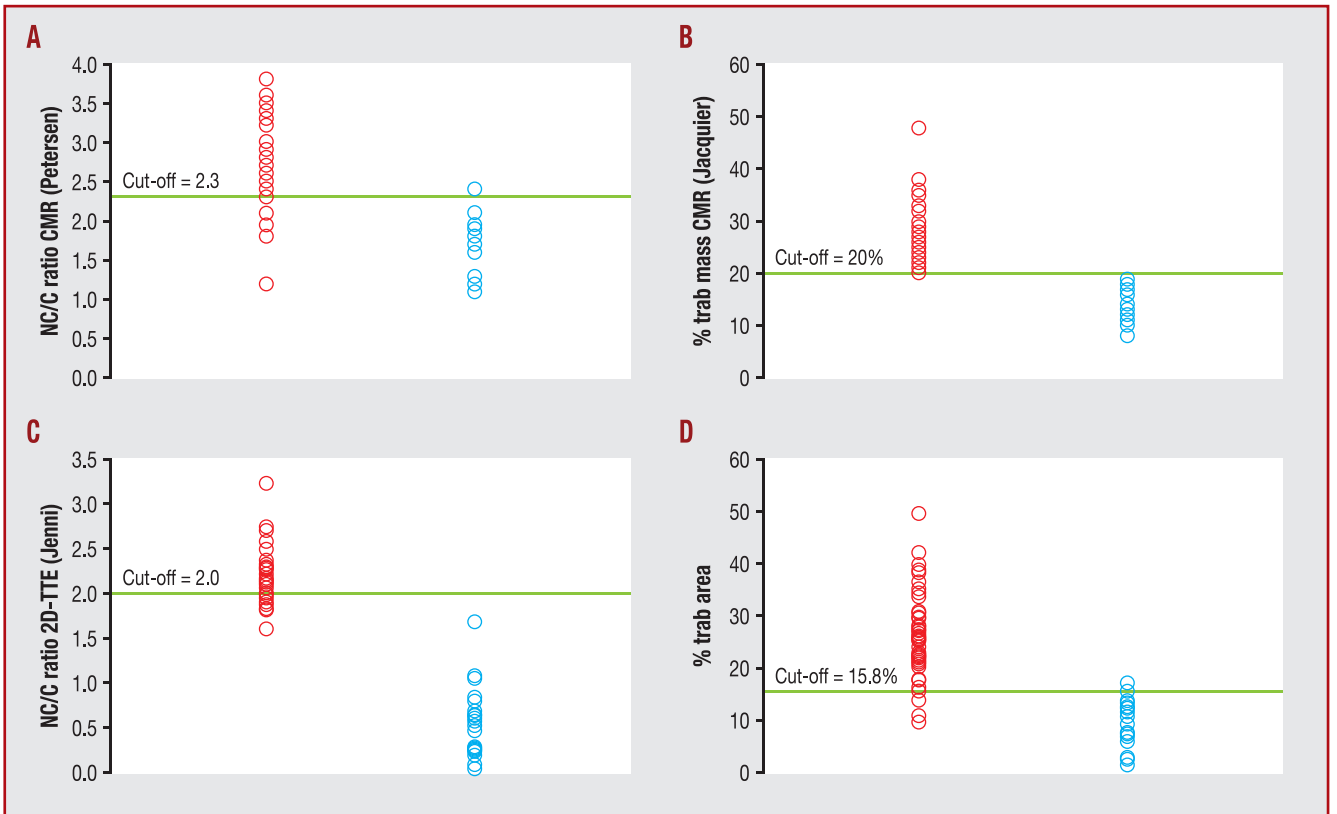
A = Outer compacted area (4C + 2C)

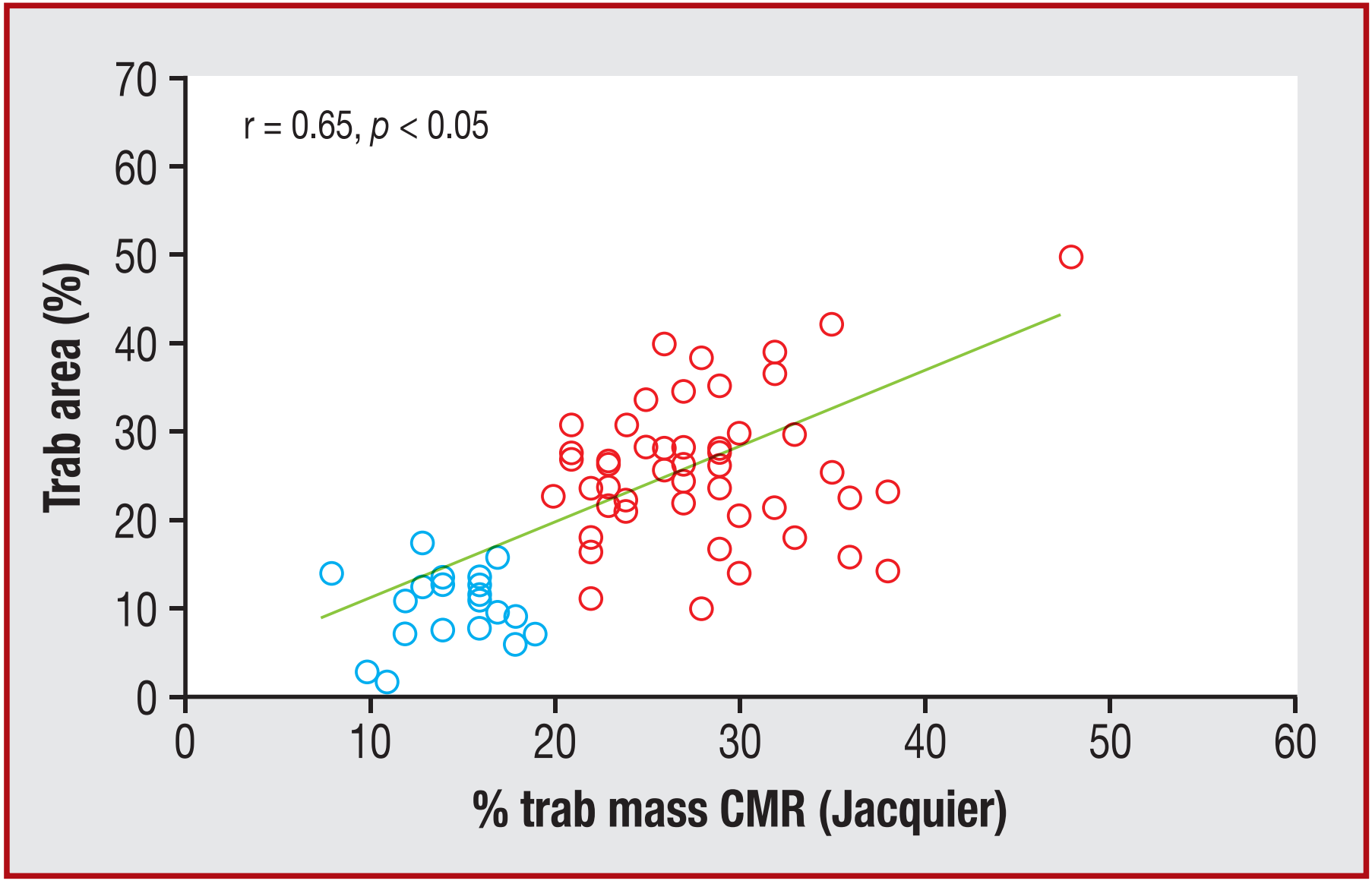
B = Inner area with trabecular exclusion (4C + 2C)

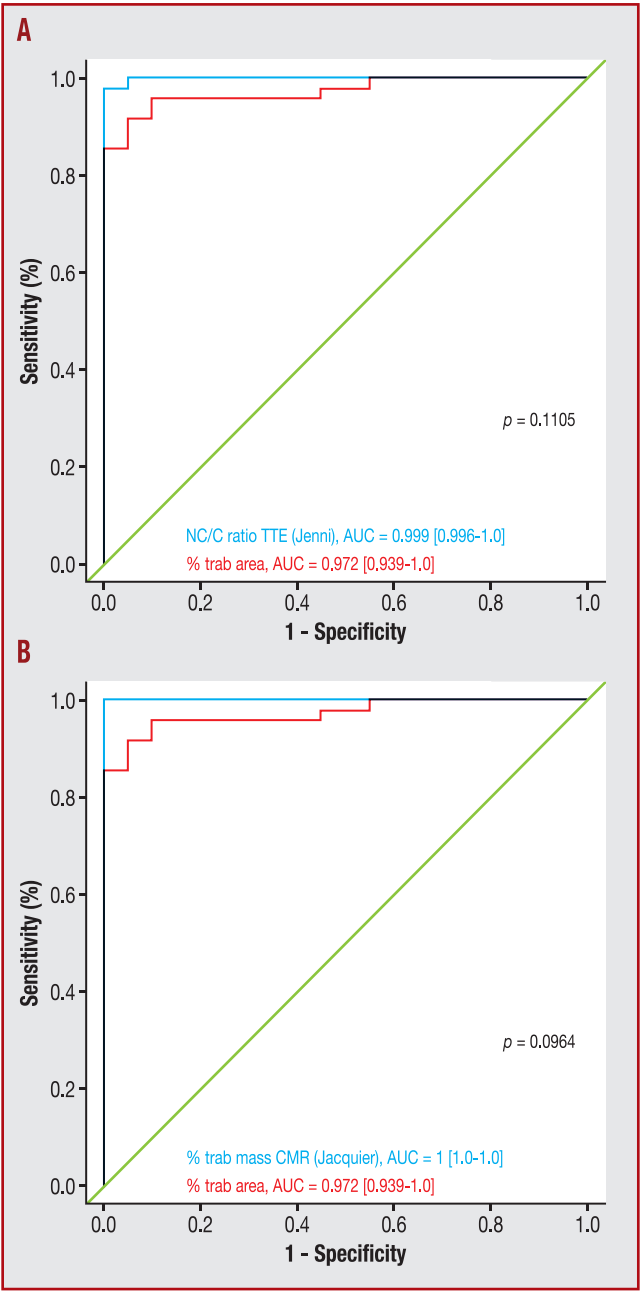
Trabecular area (4C + 2C) = A - B

$$\textbf{\% trab area} = \frac{\text{(trabecular area 4 chamber + 2 chamber) X 100}}{\text{(compacted area 4 chamber + 2 chamber)}}$$


A
B
C
D
1.82 cm
0.48 cm


A
NC/C ratio CMR (Petersen)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Cut-off = 2.3
B
% trab mass CMR (Jacquier)
60
50
40
30
20
10
0
Cut-off = 20%
C
NC/C ratio 2D-TTE (Jenni)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Cut-off = 2.0
D
% trab area
60
50
40
30
20
10
0
Cut-off = 15.8%


r = 0.65, p < 0.05
Trab area (%)
% trab mass CMR (Jacquier)
0
10
20
30
40
50
60
70


A
1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity (%)
p = 0.1105
NC/C ratio TTE (Jenni), AUC = 0.999 [0.996-1.0]
% trab area, AUC = 0.972 [0.939-1.0]
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
B
1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity (%)
p = 0.0964
% trab mass CMR (Jacquier), AUC = 1 [1.0-1.0]
% trab area, AUC = 0.972 [0.939-1.0]
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity