Myocardial perfusion in excessively trabeculated hearts: Insights from imaging and histological studies

Short title: Trabecular perfusion

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Summary

In gestation, the coronary circulation develops initially in the compact layer and it expands only in fetal development to the trabeculations. Conflicting data have been published as to whether the trabecular layer is hypoperfused relative to the compact wall after birth. If so, this could explain the poor pump function in patients with left ventricular excessive trabeculation, or so-called noncompaction. Here, we review direct and indirect assessments of myocardial perfusion in normal and excessively trabeculated hearts by in vivo imaging by magnetic resonance imaging (MRI), positron emission tomography (PET)/single photon emission computed tomography (SPECT), and echocardiography in addition to histology, injections of labelled microspheres in animals, and electrocardiography. In MRI, PET/SPECT, and echocardiography, flow of blood or myocardial uptake of blood-borne tracer molecules are measured. The imaged trabecular layer comprises trabeculations and blood-filled intertrabecular spaces whereas the compact layer comprises tissue only, and spatio-temporal resolution likely affects measurements of myocardial perfusion differently in the two layers. Overall, studies measuring myocardial uptake of tracers (PET/SPECT) suggest trabecular hypoperfusion. Studies measuring the quantity of blood (echocardiography and MRI) suggest trabecular hyperperfusion. These conflicting results are reconciled if the low uptake from intertrabecular spaces in PET/SPECT and the high signal from intertrabecular spaces in MRI and echocardiography are considered opposite biases. Histology on human hearts reveal a similar capillary density of trabecular and compact myocardium. Injections of labelled microspheres in animals reveal a similar perfusion of trabecular and compact myocardium. In conclusion, trabecular and compact muscle are likely equally perfused in normal hearts and most cases of excessive trabeculation.

Introduction

It is not clear what the 'true' prevalence is of left ventricular (LV) so-called noncompaction cardiomyopathy, which is a setting that is better termed excessive trabeculation [1,2]. The proportion of LV trabecular muscle is normally approximately 15% (and 85% compact), 25% can be used for diagnosing excessive trabeculation albeit a plethora of diagnostic criteria exists, and extreme cases can reach a proportion of 40% trabecular myocardium [3,4]. The extent and sizes of trabeculations varies considerably between animals [5] and it remains disputed whether a setting of excessive trabeculation is causally related to poor pump function and severe cardiovascular events [6,7]. What the mechanism or mechanisms would be that link excessive trabeculations to poor pump function is largely unexplored [8]. The identification of causative links may lead to improvement of the specificity of diagnosis, which in the case of excessive trabeculation is rather low [3,6,7]. Because the cost of health care is a growing challenge, false positive diagnosis is a burden of concern not only to the unduly diagnosed patient but also the budget. Under these circumstances, a reduction in false positive diagnoses is desirable and with regards to excessive trabeculation there is arguably a substantial scope for reduction of false positive diagnoses. Specifically, many clinicians face a challenge with how to deal with individuals who fulfill structural diagnostic criteria but who are otherwise asymptomatic and have a normal heart size, pump function, no personal or family history of major adverse cardiovascular events (these are so-called "benign" cases, [1,2]). Consequently, in the clinic the reduction of false positive diagnosis is as much a matter of concern as the identification of true cases [1].

Dysfunctional coronary micro-circulation as measured by positron emission tomography (PET)/single photon emission computed tomography (PET/SPECT) may affect the trabecular layer in particular and thus provide a cause for impaired contractility [9]. The timing of myocardial perfusion is mostly restricted to the diastolic interval [10,11]. In addition, systolic compression of the coronary vasculature is most pronounced on the endocardial side of the ventricular wall [10,11]. At high heart rates the time window for perfusion of the inner-most myocardium may become critically narrow [12]. The narrow time window may be particularly pertinent when the epicardial-endocardial distance is increased as it is in LV hypertrophy but also in excessive trabeculation. Ischemia as revealed by ST-segment elevation on the electrocardiogram has been found during exercise tests of athletes with physiological hypertrophy of the heart [13]. Myocardial perfusion in hypertrophic cardiomyopathy is negatively correlated with increasing end-diastolic wall thickness and especially so on the endocardial side [14]. In canine experiments, it has been shown that the residual oxygen concentration is lowest in venous blood of the endocardial side of the ventricular wall [15].

Nonetheless, the endocardial side of the left ventricular wall of healthy hearts may in fact be slightly more perfused than the epicardial side [10]. Also, the extent of trabecular muscle in humans is not correlated to ST-segment elevation when measured at rest [16,17]. Different lines of evidence therefore yield disparate conclusions regarding trabecular layer hypoperfusion and the functional consequences thereof.

The coronary vasculature develops differently in the trabecular and compact layers. In the embryo, coronary circulation is initially restricted to the outer and very thin compact layer [18]. Before that, a luminal trabecular layer has formed which comprises numerous avascular struts, or trabeculations, that are only a few cardiomyocytes wide and thus so small they cannot be seen with the naked eye. In the absence of coronary vasculature, such trabeculations are the only manner in which the myocardium can increase appreciably in mass without creating excessive diffusion distances and becoming ischemic [19]. A distinct molecular and metabolic identity set the avascular trabecular layer apart from the compact layer which has a developing coronary circulation [20-22]. There is consensus that trabeculations grow in the fetal period and acquire coronary vasculature [23], even if it is disputed whether the origin of the trabecular vasculature is endocardial, venous, or arterial tissue [24,25]. It is not clear whether the trabecular and compact layer of the adult heart have fully converged on the same phenotype or if remnants of the gestational differences persist [26,27].

Clinical assessments of myocardial perfusion are predominantly done by direct measurements of tissue blood flow by magnetic resonance imaging (MRI) or by measurements of myocardial uptake of radioactively labelled tracers by PET/SPECT [28]. Echocardiography with contrast has also been used [29]. On the electrocardiogram, ST-segment elevation indicates ischemia [30]. In addition, capillary density or vascularization is also informative because it is positively related to the metabolic rate and perfusion of the tissue [31,32]. In animal experiments, injections of radioactively labelled microspheres that get lodged in the micro-circulation have also been used to measure rate of perfusion [33]. These different methodologies to measure perfusion have strengths and weaknesses (Online Table 1; see Dewey et al. [12] for an in-depth discussion). They have all been applied to the heart, but not in a single study. The aim of this narrative review is to provide a synthesis of the insights gathered from these lines of evidence to assess whether the trabecular layer is hypoperfused relative to the compact layer.

Importance of spatial resolution in visualizations of trabeculation

In clinical settings, there are several types of measurement by which the extent of the trabecular layer can be assessed and it is found uniformly that the extent varies considerably between

individuals [34,35]. Also, in the adult heart the trabeculations can be so small and numerous that it is in effect impossible to count them [36]. If the spatial resolution of MRI is increased beyond the typical clinical resolution 1.8 × 1.8 × 10 mm [37], a greater number of trabeculations can be discriminated (Fig. 1) [4].

When the trabecular layer is visualized clinically, the signal of any voxel or pixel will likely be a composite value of signals from trabecular myocardium and intertrabecular space filled with LV cavity blood. When using PET to assess myocardial perfusion, for example, errors in measurements are greatest on the endocardial, or trabeculated, side of the ventricular wall and the signal intensifies gradually from lumen to mid-compact wall (Fig. 2) [38]. The compact wall on the other hand is often approximately 1 cm thick and its width is thus covered by several voxels or pixels [3, 39]. Consequently, a central notion of this review is that when the compact wall and central lumen exhibit different intensities of signal, the trabecular layer will have an intermediate value, either lower or greater relative to the compact wall. If the trabecular layer's fraction of trabeculation-to-lumen is known, the intermediate value of the trabecular layer can in principle be corrected by this fraction and a 'truer' value of the trabecular tissue can be obtained [38]. In the clinic setting, because of the limitations imposed by spatial resolution and image acquisition time, it is difficult to determine accurately the fraction of trabeculation-to-lumen of the trabecular layer.

High resolution ex vivo assessments of vascularization

Ex vivo studies including histology may only measure correlates of perfusion such as capillary density while they have the advantage of greater spatial resolution than in the clinical setting. Estes and colleagues studied cadaver human hearts to give a qualitative description of the vasculature of the LV papillary muscles and its relation to the LV free wall [40]. Their illustrations, and subsequent ones (e.g. [41]), document a substantial vascularization of both the trabecular and compact layer (Fig. 3). Studies on dog and pig hearts show similar illustrations [42,43] and the distribution of capillaries is highly regular and dense throughout the LV wall [44]. Dye was injected in the coronary circulation by Wearn [45] who counted in four human hearts the number of capillaries per cardiomyocyte in the LV, right ventricle, and LV papillary muscle and found 1.08, 1.03, and 1.06 respectively. Such evidence for equal vascularization was also found in hearts of cat and rabbit and it was later replicated in a series of domestic mammals [46]. In dogs, the coronary arterial lumen may take up a greater part of the subendocardial wall than the subepicardial wall [47]. In rats, the same capillary-cardiomyocyte ratio is approximately 1 for compact myocardium, 0.5 for trabecular myocardium, and the smallest trabeculations may be avascular [48]. A high density of capillaries was found in both the trabecular and compact layers in cases of human fetal excessive trabeculation [49].

When assessing capillary density as above, the advantage is that there is no signal from the cavity blood to interfere with the measurements. Generally, trabecular and compact myocardium have the same capillary density. In rats, the trabecular layer may have relatively few capillaries, perhaps because the rat heart is so small that a fraction of the trabecular layer can rely on cavity blood for homeostasis.

Microspheres, the gold standard of perfusion measurement

Microspheres labelled radioactively or fluorescently can be used experimentally to assess blood flow between and within organs [32, 50,51]. After injection into the left side of the heart (or a major systemic artery), the microspheres will be trapped in pre-capillary vessels. In harvested tissue, the concentration of the microspheres per gram is then a measure of perfusion. A relatively high spatial resolution can be achieved, especially when fluorescent labels and microtome sectioning are combined [32]. When only myocardium is harvested or the cavities are cleaned, there is no signal from the LV cavity to obscure the signal from the trabecular myocardium. As long as the assessed tissue samples are not very small, microsphere density can be considered the gold standard of perfusion measurements [12] while it is applied in animal experiments only.

LV myocardial blood flow was measured in dogs at rest and at three different levels of exercise [52]. There was no difference in blood flow between the subendocardial layers, which must contain trabeculations, and the subepicardium layers at any level of exercise. In arrested dog hearts with pharmacologically induced vasodilation, arterial lumen per area and perfusion was greatest subendocardially [47]. Ball and colleagues [52] also compared perfusion of the apical region, which is the most trabeculated, and the base, which is the least trabeculated, and no difference was found per gram tissue. Similar findings were reported later in dogs with induced myocardial infarction, only the infarcted regions of course had abnormally low perfusion [53]. In dogs with LV hypertrophy induced by aortic banding, the subendocardium and subepicardium were not different in flow reserve during exercise, albeit the flow reserve was lower than that of the two mid-wall layers [54]. In aggregate, the dog trabecular myocardium does not appear to be hypoperfused relative to the compact myocardium. In one study on pigs with induced heart failure, however, hypoperfusion was more severe in the endocardial part of the LV [55].

PET and SPECT

PET and SPECT rely on positron and gamma radiation respectively. Both modalities aim to detect tissue enrichment of radioactive tracers that are transported intracellularly by membrane transporters and which are delivered in a very dilute concentration in the blood. That is, blood has a

very low signal intensity. Interest and awareness of excessive trabeculation began at the turn of the last millennium [8] and highly influential papers from this period utilized PET and SPECT [9, 56]. Compared to other non-invasive modalities and to ex vivo assessments in particular, detection of radioactive tracers with PET and SPECT have a low spatial resolution due to poor temporal resolution and large voxel size [12].

Spurred by the hypothesis that excessive trabeculation may associate with subendocardial ischemia [57] a subsequent study [9] investigated myocardial perfusion in five adolescents with isolated LV excessive trabeculation. Electrocardiograms were recorded and during exercise one individual showed ST-segment depression to suggest ischemia. An additional three individuals also showed ST-segment depression under vasodilator (dipyridamole) stress test [9]. When assessing the tissue uptake of ammonia N-13 with a field-of-view of 35 x 4.25 mm, it was consistently found that perfusion was greater in the segments that were not excessively trabeculated. The illustrations of Junga and colleagues [9] clearly show excessive trabeculation (Fig. 4A). They also show hypoperfusion of the parts of the LV wall with excessive trabeculation (Fig. 4B), where, presumably, the compact wall is also the thinnest. In addition, the trabecular layer exhibits an intermediate value between the low signal of the central cavity and the high signal of the compact wall that is not excessively trabeculated (Fig. 4B). This suggests that the detection of tracer-uptake could be biased towards low values in the trabecular layer and perhaps even in the thinnest parts of the compact wall. Later case reports also reported relatively poor perfusion of the segments with much trabeculation [58-60].

Jenni and colleagues [56] studied 12 cases of isolated LV excessive trabeculation of which four had an angiogram and which revealed normal coronary vasculature. Ultimately, nine individuals were included to quantify myocardial perfusion during rest and adenosine-induced vasodilation. The study design was not set up to directly compare perfusion of the trabecular and compact layers, but to compare LV segments with or without excessive trabeculation. As in [9], perfusion was assessed as tissue uptake of ammonia N-13 with a field-of-view of 35 x 4.25 mm, but in addition Jenni and colleagues [56] attempted a correction for amount of myocardium per region of interest, following the principles of Hutchins and colleagues [38, 61]. It remains unclear to what extent this correction worked. Normal perfusion was found in 76 out of 84 of segments without excessive trabeculation, whereas only 10 out of 24 excessively trabeculated segments showed normal perfusion. Similarly, Hamamichi and colleagues [62] used SPECT with thallium-201 in six teenagers in resting conditions and found several segments with perfusion defect and excessive trabeculation in five individuals, whereas case 4 had normal perfusion.

The initial findings [9, 56, 62] were not fully replicated in later studies. Gao and colleagues [63] studied in resting conditions 17 cases of isolated excessive trabeculation of which 15 had conditions that fit New York Heart Association functional classes III or IV. Myocardial perfusion was measured by 18F-fluorodeoxyglucose (FDG) PET/CT and 99mTc-sestamibi SPECT and analyzed in the 17-segment model while analysts remained blinded to which segments were excessively trabeculated. Although hypoperfusion was detected, its prevalence was not greater in the excessively trabeculated segments and the number of excessively trabeculated segments did not correlate with ejection fraction [63]. Myocardial perfusion was also measured by 18F-FDG PET/CT and 99mTc-sestamibi SPECT in a study of 30 patients with excessive trabeculation during rest and adenosine-induced vasodilation [64]. Perfusion was reduced in excessive trabeculation compared to eight healthy controls. The apical-lateral segments that typically are the most excessively trabeculated were not more severely hypoperfused, however, than the basal segments that are typically the least trabeculated. Cerar and colleagues [65] enrolled 41 individuals with excessive trabeculation and measured perfusion during rest and vasodilation induced with an adenosine receptor agonist (regadenoson). Of these, 11 exhibited reversible ischemia but it was not tested whether micro-circulatory dysfunction was related to the extent of trabeculation or if it affected the excessively trabeculated segments in particular.

To summarize, in symptomatic patients with excessive trabeculation, micro-circulatory dysfunction is often found when the hearts are assessed with PET and SPECT. While early studies reported a high prevalence of dysfunction in the excessively trabeculated segments, later studies suggested the dysfunction had similar prevalences in segments with or without excessive trabeculation. No study appears to have been designed to directly compare perfusion of the trabecular and compact layers per segment, possibly because of the limitations imposed by large voxel size and long image acquisition time. There is limited insight to what constitutes an accurate correction for the unusual anatomy in excessive trabeculation. Assessments of perfusion by PET and SPECT will likely be biased towards low values in wall segments with a thin compact wall [66] and, or, with much trabeculation.

MRI

MRI achieves greater spatial resolution than SPECT by the combination of better in plane resolution and shorter acquisition time [12]. The spatial resolution of MRI in the clinic is typically 1.8 × 1.8 × 10 mm [37]. Perfusion as measured by the first pass of gadolinium-based contrast agents (GBCA) is becoming more frequently used, but analyses are typically restricted to the compact wall and the trabecular layer is omitted (Fig. 5) [12, 67-69].

In the context of excessive trabeculation of the LV, case reports analyzed perfusion of the compact as well as the trabecular layer. Borges and colleagues [70] reported on a 52-year-old woman with severe LV dilatation, ejection fraction of 20%, and substantial excessive trabeculation (Fig. 6A). When analyzing first pass of GBCA at rest, relatively low perfusion was detected in the lateral wall and similar findings were made with contrast echocardiography. The perfusion defects appeared to be the most severe in the compact layer whereas perfusion of the trabecular layer was comparable to that of the relatively well-perfused septum (Fig. 6B). In an asymptomatic 21-year-old man with an ejection fraction of 62%, first pass of GBCA at rest revealed hypoperfusion around a deep recess but the trabecular layer at large was not obviously hypoperfused [71]. Similarly, local hypoperfusion was found using first pass of GBCA at rest in a 39-year-old woman with severe hypokinesis in the lateral and inferior segments of the LV, but the trabecular layer at large was not obviously hypoperfused [59].

Few studies have attempted to assess myocardial perfusion of the trabecular layer on the basis of injections of GBCA and detected by MRI. Perfusion defects are reported, but these do not appear to be restricted to the trabecular layer. The intense signal from the LV cavity (partial volume) may obscure much of the signal from the inner-most tissue and it is not clear how this intense signal has been and can be corrected for (Fig. 7).

Echocardiography

The study of Bodiwala and colleagues [29] employed myocardial contrast echocardiography using perflutren lipid microspheres on one adult at resting condition with bi-ventricular excessive trabeculation and found myocardial hypoperfusion in the LV apex. While the regional hypoperfusion is clearly illustrated, the compact and trabecular layer appear equally affected. Much of the trabecular layer is not visible when there is intense signal from the lumen. This suggests that it is hypoperfusion of the compact layer that is most readily illustrated (Fig. 8). In addition, such illustrations are consistent with hyperperfusion of the trabecular layer, although it seems more likely that the signal from the cavity blood obscures the trabeculations. In assessing a single case of isolated LV noncompaction, Borges and colleagues [70] injected 3 ml of the contrast agent Optison (GE Healthcare, Chicago, IL, USA) over four minutes at resting conditions and found no difference in perfusion of the trabecular and compact layer.

Echocardiography guidelines recommend using contrast to achieve better discrimination of the lumen-compact wall boundary [72] which also attests that the trabeculations are obscured by the signal of the contrast agent of the LV cavity blood. Generally, there is no recommendation for the use of contrast echocardiography to assess perfusion of the trabecular myocardium [72]. In dogs with

experimentally induced transmural myocardial infarctions, large differences in perfusion were found between infarcted and non-infarcted areas while the trabecular and compact muscle of the non-infarcted areas appeared equally perfused [73].

Concerning assessments of perfusion of the trabecular layer, a limiting factor in contrast echocardiography may be the obscuring of trabeculations by the high intensity signal from the cavity. Experiments in dogs do not support pronounced differences in perfusion of the trabecular and compact layers.

Electrocardiogram

On the 12-lead electrocardiogram a shift from the isoelectric line in the ST-segment is a sensitive marker for the identification of ischemia [30]. Dabrowska and colleagues [74] studied autopsy cases with signs of acute myocardial infarction of LV papillary muscles and conducted a retrospective study of associated 12-lead electrocardiograms. Most cases associated with a >1 mm ST-segment depression in precordial leads V_3 and V_4, while many infarcts to the anterolateral papillary muscles could be detected in lead I and many infarcts to the posteromedial papillary muscles could be detected in lead II-III. This suggests that electrocardiography can be used to detect at least substantial hypoperfusion of the trabecular layer. The extent of trabecular muscle in humans, however, is not correlated to ST-segment elevation [16,17] nor is it a frequent finding in excessive trabeculation [75]. Electrocardiograms have been recorded from a great number of people and they do not support hypoperfusion of the trabecular layer, with the caveat that the electrocardiogram, especially when recorded in resting conditions, likely has inferior spatial resolution and sensitivity to assess myocardial perfusion compared to in vivo imaging.

Synthesis

When reviewing the literature on symptomatic individuals with excessive trabeculation, a clear picture emerges that micro-circulatory dysfunction is a common finding. Perfusion defects, however, are often found in a setting of cardiomyopathy and not only in excessive trabeculation [67, 76]. Studies that can be considered foundational to the identification and understanding of excessive trabeculation suggested that perfusion defects could causally explain the poor pump function [9, 56, 62]. Here, we reviewed multiple lines of evidence to assess whether the trabecular and compact layers are differentially perfused. The perfusion of the trabecular layer is not a major concern when cardiomyopathies are evaluated clinically [77] and this review provides a factual basis to support that practice.

If the trabecular layer is poorly perfused relative to the compact layer, it could suggest a causal link between excessive trabeculations and poor pump function. Most measurements done on patients, healthy controls, and animals have not been set up to directly compare the trabecular layer to its neighboring compact wall. Based on PET/SPECT measurements during rest and while affected by vasodilators, the case has been made for hypoperfusion of segments with excessive trabeculations. These imaging modalities, however, also have relatively poor spatio-temporal resolution [12]. Imaging with better spatio-temporal resolution such as contrast echocardiography and MRI do not support hypoperfusion of the trabecular layer and neither do measurements of capillary density nor most measurements based on animal experiments.

Myocardial perfusion of the inner-most myocardium is particularly vulnerable to the short diastolic interval at high heart rates [13]. On the basis of the reviewed literature, we cannot assess whether excessive trabeculations are overly prone to develop ischemia at high heart rates.

If perfusion defects occurred more frequently in segments that fulfill criteria for excessive trabeculation, it could suggest a causal link between excessive trabeculations and poor pump function. Perfusion defects do occur in some hearts that fulfill criteria for excessive trabeculation. While early studies suggested that perfusion defects occur more frequently in LV segments that fulfill criteria for excessive trabeculations [9, 56, 62], this was not replicated in later studies [63,64]. In so far as micro-circulatory dysfunction is causative of poor pump function, part of the pathology is likely micro-circulatory dysfunction of the compact wall. In this way, symptomatic excessive trabeculation may be similar to dilated and hypertrophic cardiomyopathy [67, 76].

Even when dysfunctional coronary circulation occurs in hearts with excessive trabeculation, it is not clear whether the setting of excessive trabeculation is secondary to dysfunctional coronary circulation. That many cases of excessive trabeculation exhibit perfusion defects in LV segments without excessive trabeculation would be consistent with a primary (coronary) vasculopathy. At least in the embryo, new trabeculations form when the coronary circulation has not yet developed [19]. It is not unequivocally demonstrated that perturbed coronary angiogenesis can cause excessive growth of trabeculations, but mice without the expression of Ino80 in endothelium, for example, develop a spectacularly excessively trabeculated ventricular wall [78].

Conclusion

When the general population is surveyed, most individuals who fulfill a criterion for excessive trabeculation will have normal pump function [16,17, 33, 79,80]. The trabecular layer is then unlikely to be substantially weaker than the compact wall per gram tissue and recent experimental data

support an equal force generation potential of trabecular and compact wall cardiomyocytes [81]. In our assessment, the trabecular layer in asymptomatic cases is not likely to be perfused less than the compact layer. Most of the clinical cases we have reviewed here concern the trabecular layer in individuals with poor pump function. Such individuals have a much greater pre-test probability for cardiomyopathy than the general population and micro-circulatory dysfunction is a common finding in cardiomyopathy [67, 76]. If there is symptomatic cardiomyopathy, perfusion defects are likely to be present but their prevalence may not be higher in the trabecular layer than the compact layer. Because of the small size of each strut of the trabecular layer and the spatio-temporal resolution of most clinical imaging modalities, technical limitations may bias measurements towards underestimations (PET/SPECT) or overestimation (MRI, echocardiography) of myocardial blood perfusion of the trabecular layer unless careful corrections are made.

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Figure legends

Figure 1 Spatial resolution and detection of trabeculations. Individual trabeculations are better recognized on histology (**A**) than on high resolution *ex vivo* MRI (**B**) and with greater spatial resolution, more trabeculations can be counted (**C**). Adapted with permission from Riekerk et al. [4].

LV, left ventricle; MRI, magnetic resonance imaging.

Figure 2 Tracer uptake in the LV wall as measured by PET. The signal gradually intensifies from the subendocardium to the mid-compact wall. Consequently, myocardial perfusion as measured by PET is likely to be underestimated in the trabecular layer and very thin compact wall. Adapted with permission from Hutchins et al. [38].

LV, left ventricular; PET, positron emission tomography; RV, right ventricle.

Figure 3 Equal vascularization of the human left ventricular trabecular and compact layer. The white dashed line indicates approximately the boundary between the compact and trabecular layer, with the white arrow indicating the anterolateral papillary muscle and grey arrows indicate additional trabeculations. From the heart of a 52-year-old man with no cardiac abnormalities. Adapted with permission from Estes et al. [40].

Figure 4 Case 5 of Junga and colleagues (1999) [9]. (**A)** Short-axis magnetic resonance imaging showing excessive trabeculation (black arrowheads, original) in the LV wall. (**B)** Positron emission tomography four-chamber view of the same heart as in **A**, showing the greatest signal intensity in the basal parts of the LV, which were not excessively trabeculated. With less myocardium comes lower signal intensities, from the thinned compact wall (white arrowhead, original), to the trabecular layer (light blue), to the central cavity (purple/dark). Adapted with permission from Junga et al. [9].

LV, left ventricle.

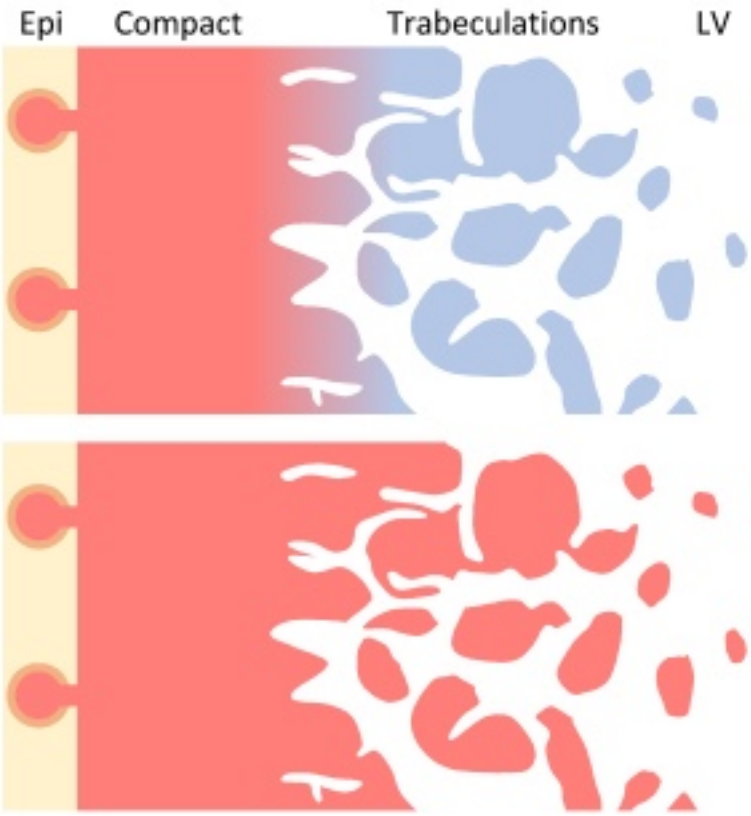
Figure 5 Myocardial perfusion assessed by magnetic resonance imaging in three patients with heart failure. Notice only the compact layer of the left ventricular wall is analyzed and trabeculations are omitted (a few trabeculations are indicated with red arrows). Adapted with permission from Sammut et al. [67].

Figure 6 Myocardial perfusion assessed by magnetic resonance imaging (MRI) in excessive trabeculation. (**A)** MRI short-axis view at mid-left ventricle (LV) height showing excessive trabeculation. (**B)** Relative perfusion rate assessed from first-pass gadolinium-based contrast agents in a slice from approximately the same position as in A. Notice hypoperfusion is mostly restricted to the compact layer. Adapted with permission from Borges et al. [70].

Figure 7 Trabecular perfusion can be obscured by signal from left ventricular (LV) cavity. Perfusion in the trabecular layer as determined from gadolinium-based contrast agent signal can be obscured by the intense signal from the LV cavity (compare the trabeculations indicated by white and red arrows). Adapted with permission from Hsu et al. [68].

Figure 8 Hypoperfusion revealed by contrast echocardiography. (**A)** Case 1 of Bodiwala and colleagues [29], adapted with permission, showing prominent apical trabeculations (example indicated with red arrow). (**B)** Same case, notice the apical hypoperfusion (red arrow) and that the trabecular layer has been obscured by the intense signal of the contrast agent of the LV cavity.

LV, left ventricular; RV, right ventricle; VS, ventricular septum.

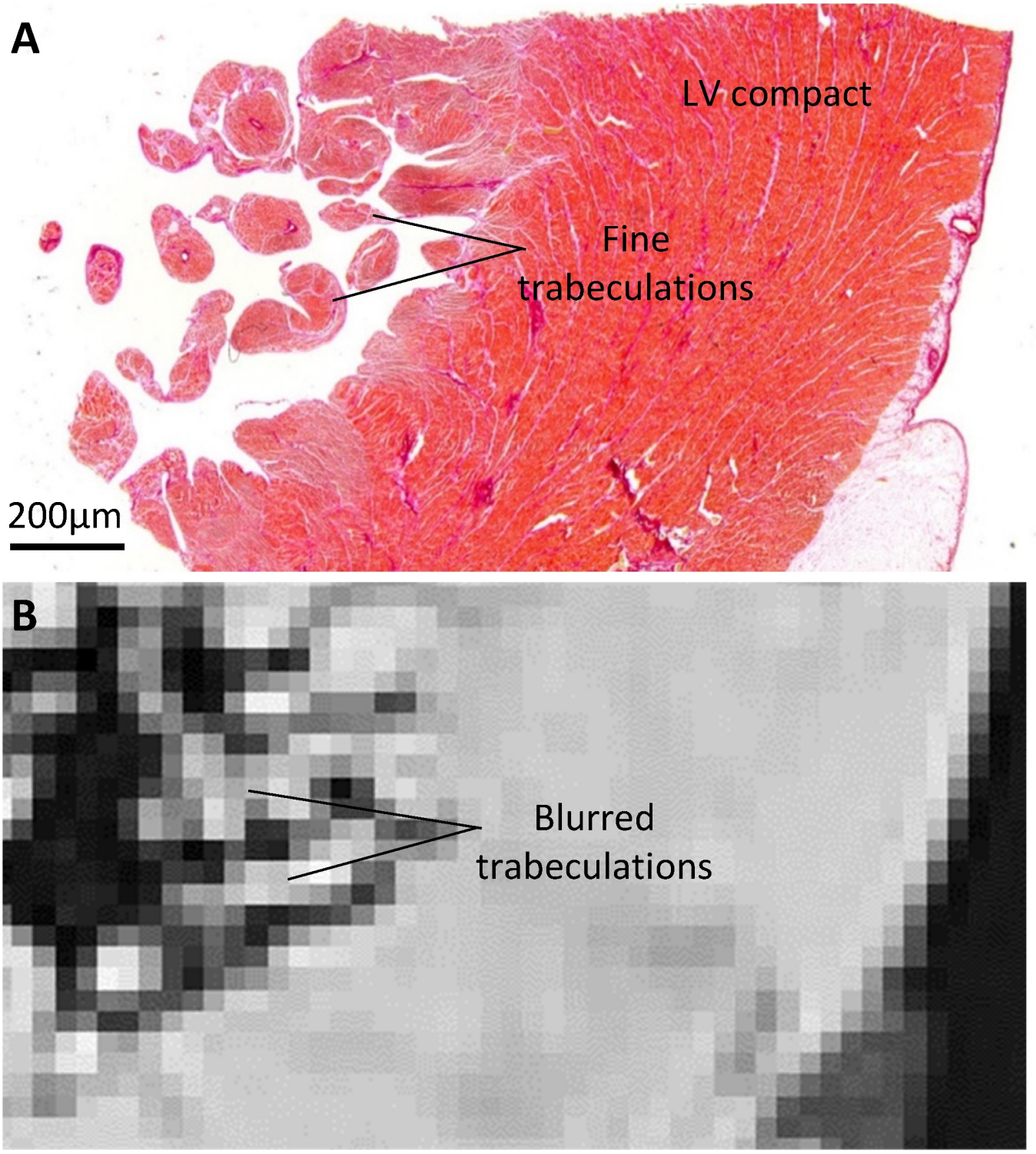


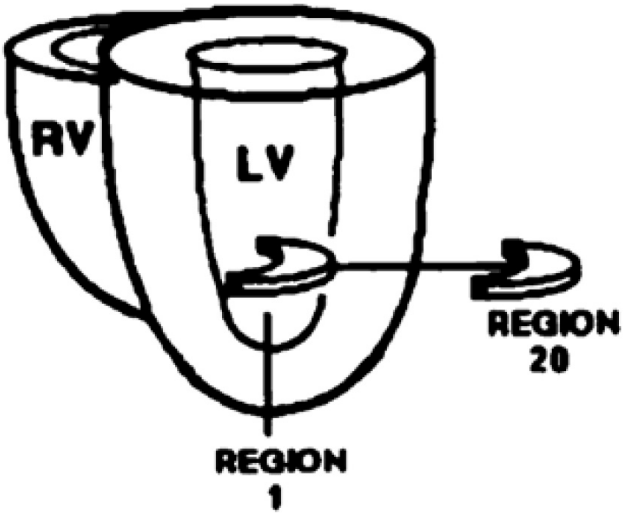
PROPOSED DISEASE MECHANISM

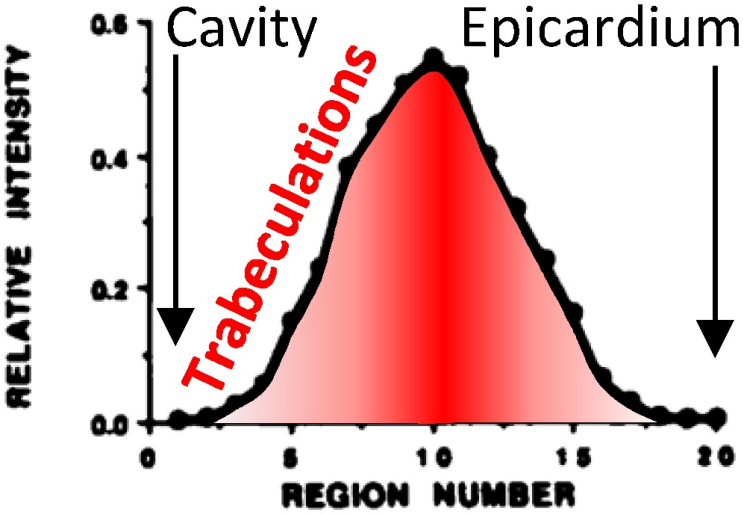
The cause of poor pump function in excessive trabeculation, or so-called noncompaction, is **hypoperfusion** of the trabecular layer

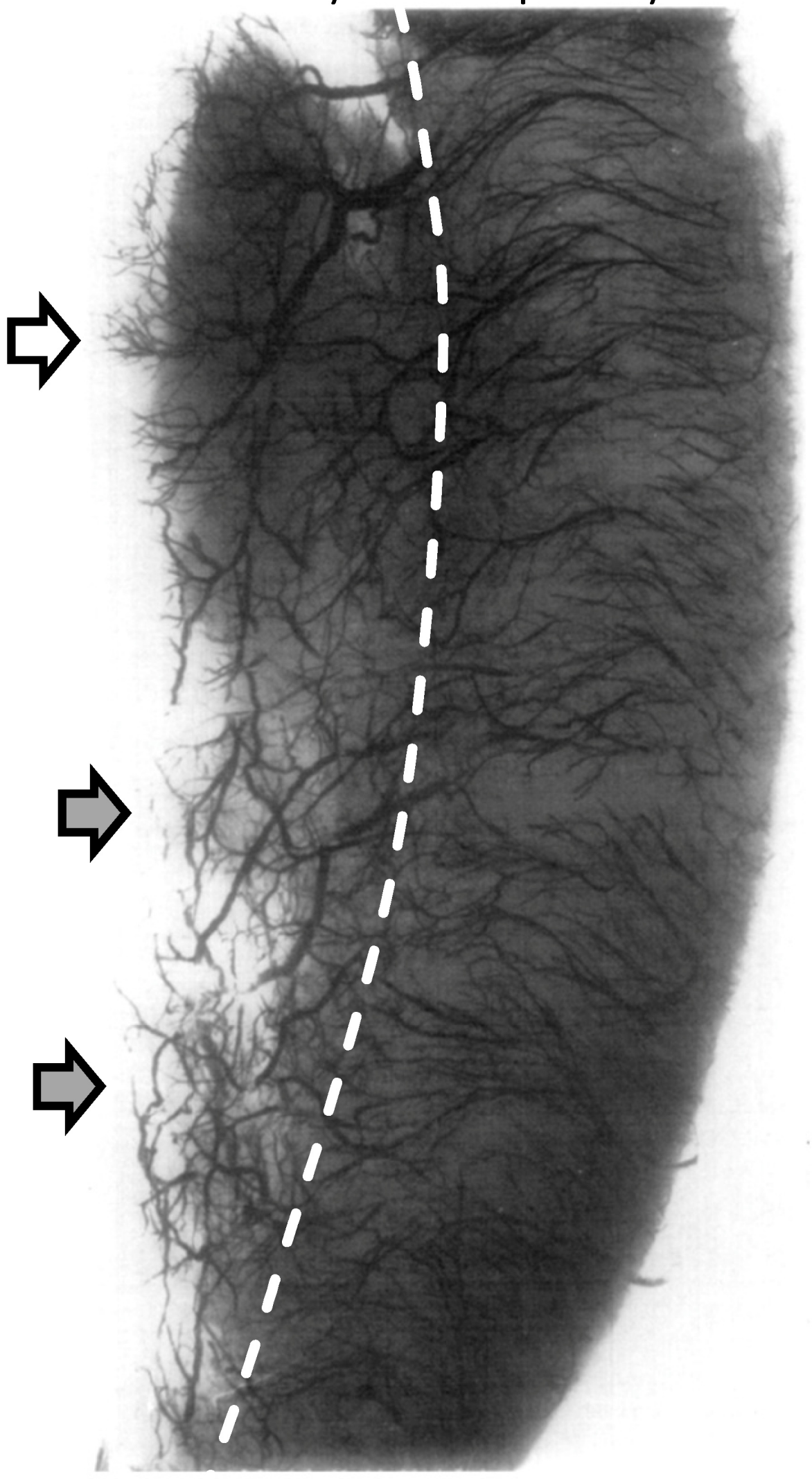
REVIEW

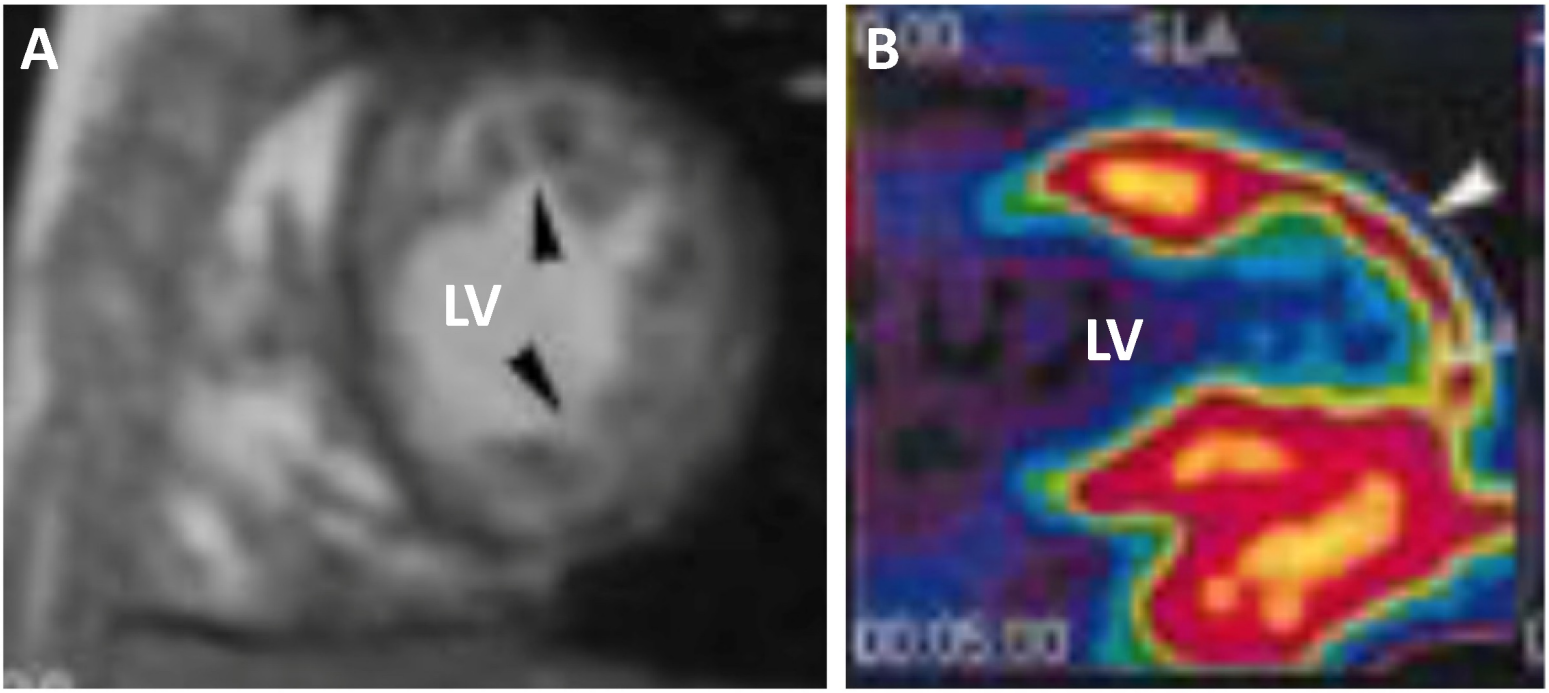
In aggregate, data (SPECT/PET, MRI, Echo, Histology, ECG) suggest the trabecular and compact layer are **equally perfused**

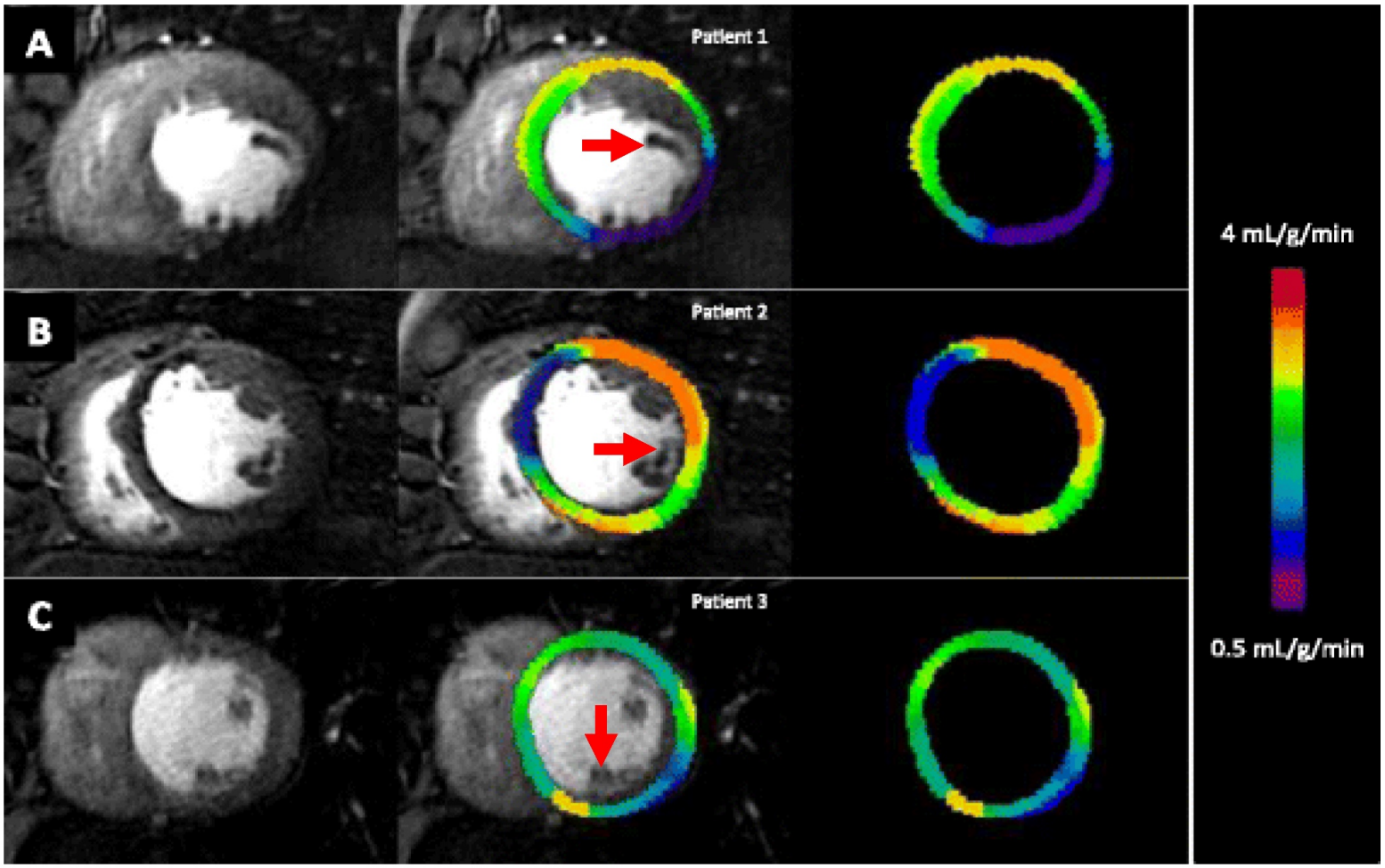

A
LV compact
Fine
trabeculations
200µm
B
Blurred
trabeculations
C
Number of trabeculations
10
8
6
4
2
0
P<0.001
MRI Low Res
MRI High Res
Histology

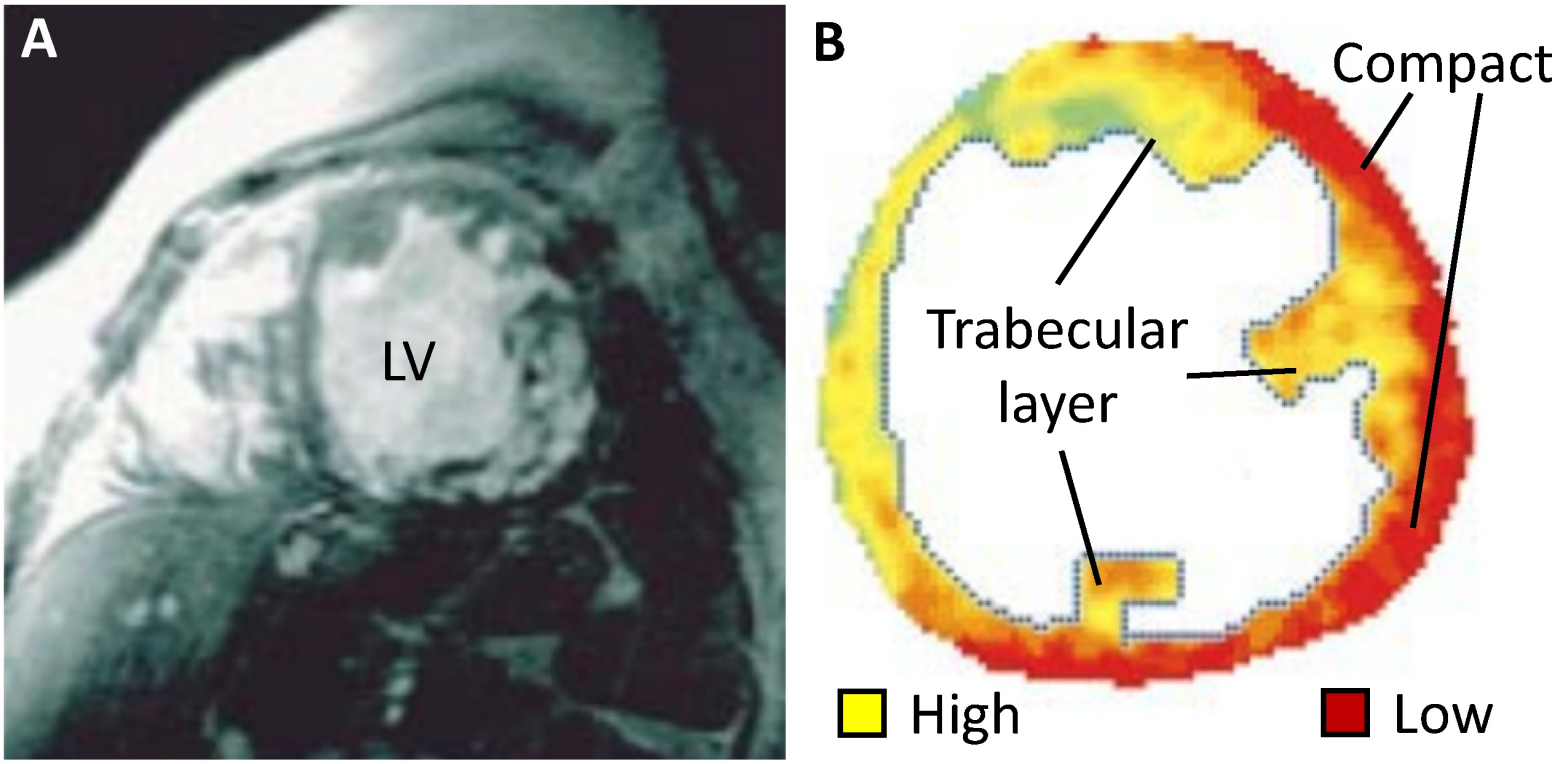

RV
LV
REGION
20
REGION
1

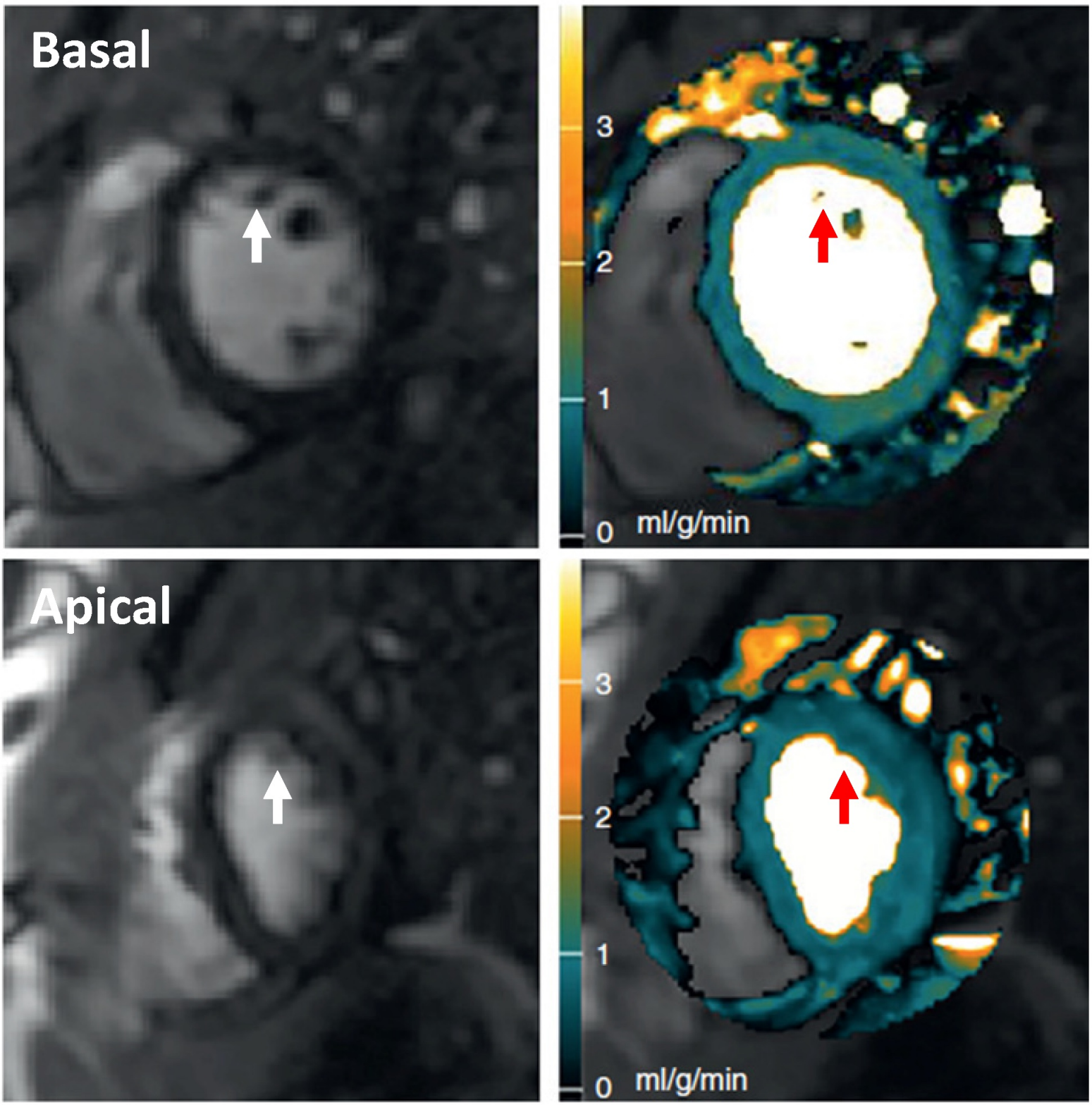

Cavity
Epicardium
Trabeculations
RELATIVE INTENSITY
0.6
0.4
0.2
0.0
0
5
10
15
20
REGION NUMBER

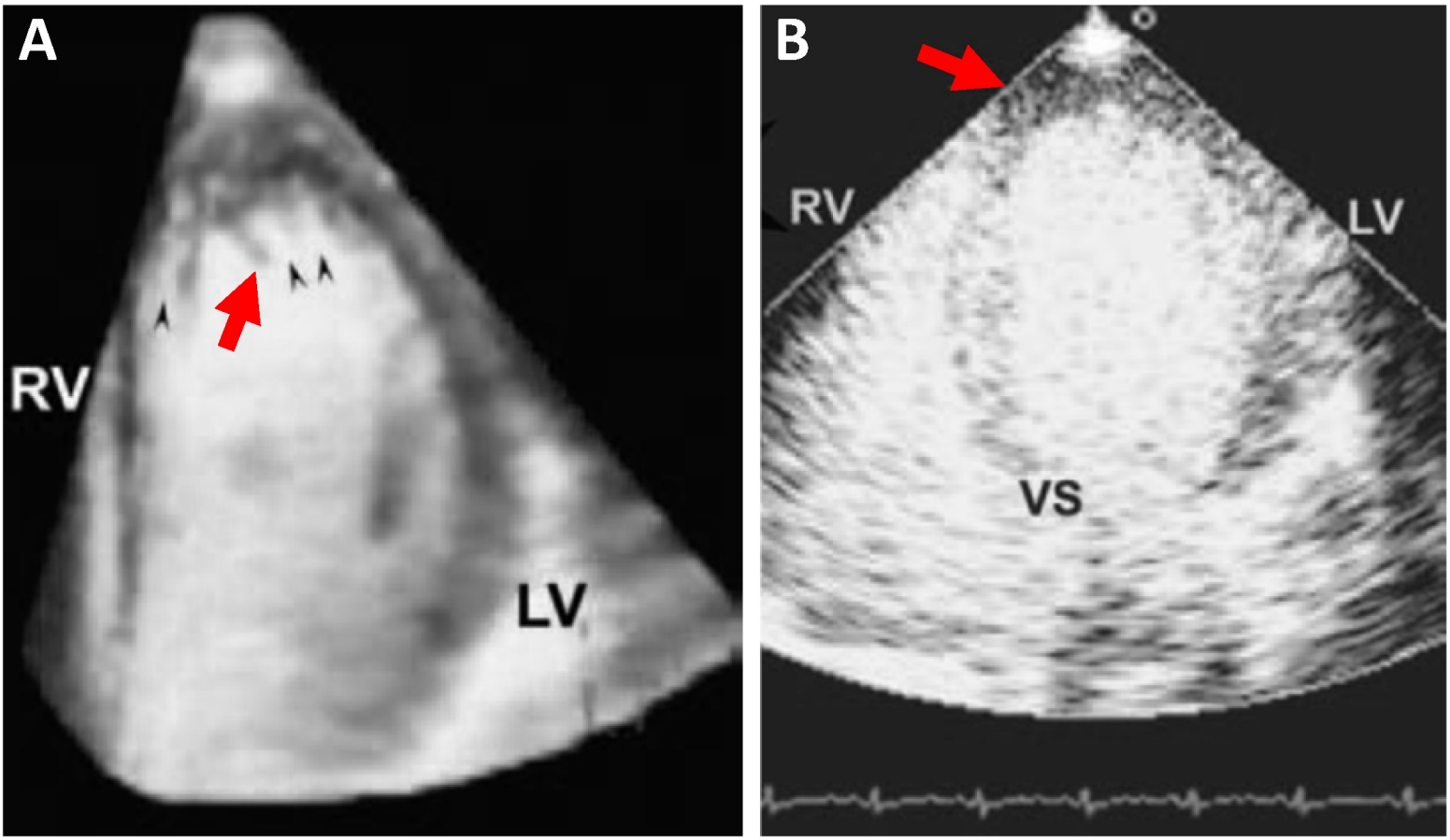

Trabecular layer
Compact layer


A
LV
B
LA
LV


A
Patient 1
B
Patient 2
C
Patient 3
4 mL/g/min
0.5 mL/g/min


A
LV
B
Compact
Trabecular
layer
High
Low


Basal
3
2
1
0
ml/g/min
Apical
3
2
1
0
ml/g/min


A
RV
LV
B
RV
LV
VS

Online Table 1 Modalities to investigate vascularization and perfusion of myocardium.

Modality	*In vivo* / *Ex vivo*	Spatial resolution	Temporal resolution	Measurement of perfusion	Detection of metabolic substrate	Detection of hypoxia
Histology	*Ex vivo*	Very high	NA	No	Possible[#]	Possible[#]
Microspheres	*In vivo**	High	Low	Yes	No	No
PET/SPECT	*In vivo*	Low	Low	Yes	Possible	No
MRI	*In vivo*	Medium	Medium	Yes	Possible	Possible
Contrast echo	*In vivo*	Medium	High	Yes	No	No
ECG	*In vivo*	Low	High	No	No	Yes

*The microspheres are injected and lodge in the tissues *in vivo*, but their concentration is analyzed *ex vivo*.
[#]With immunohistochemistry.
NA, not applicable.