Full title: Relationship between the left ventricular size and the amount of trabeculations

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ABSTRACT

Contemporary imaging modalities offer non-invasive quantification of myocardial deformation; however, they make gross assumptions about internal structure of the cardiac walls. Our aim is to study the possible impact of the trabeculations on the stroke volume, strain and capacity of differently sized ventricles. The cardiac left ventricle is represented by an ellipsoid and the trabeculations by a tissue occupying a fixed volume. The ventricular contraction is modelled by scaling the ellipsoid whereupon the measurements of longitudinal strain, end-diastolic, end-systolic and stroke volume are derived and compared. When the trabeculated and non-trabeculated ventricles, having the same geometry and deformation pattern, contain the same amount of blood and contract with the same strain, we observed an increased stroke volume in our model of the trabeculated ventricle. When these ventricles contain and eject the same amount of blood, we observed a reduced strain in the trabeculated case. We identified that a trade-off between the strain and the amount of trabeculations could be reached with a 0.35-0.41 cm dense trabeculated layer, without blood filled recesses (for a ventricle with end-diastolic volume of about 150 ml). A trabeculated ventricle can work at lower strains compared to a non-trabeculated ventricle to produce the same stroke volume, which could be a possible explanation why athletes and pregnant women develop reversible signs of left ventricular non-compaction, since the trabeculations could help generating extra cardiac output. This knowledge might help to assess heart failure patients with dilated cardiomyopathies who often show signs of non-compaction.

Keywords: trabeculations, LVNC, NCC, non-compaction, hypertrabeculation

1. Introduction

One of the hypotheses of trabecular development suggests that the formation of trabeculae is an initial step of myocardium formation that allows accumulating large amount of tissue temporarily perfused by the surrounding blood. Subsequently the trabeculae undergo a process of compaction, transforming the intertrabecular spaces into capillaries, and accompanied by the appearance of the coronary artery tree (Agmon et al., 1999; Bernanke & Velkey, 2002; Freedom et al., 2005). More recent studies on myocardial cell growth suggest that after the trabeculations are formed, the cell proliferation concentrates only in the outer myocardial wall, forming the compact layer (Boer et al., 2012). Once the heart has developed, the trabeculations do not disappear from the ventricles and the reason is not completely clear. The excess of trabeculations, often attributed to genetic cardiomyopathies, can lead to heart failure, atrial and ventricular arrhythmias, and thromboembolic events (stroke) (Ritter et al., 1997; Oechslin et al., 2000; Panela et al. 2013).

There is an important lack of clinical knowledge about the interior structure of the cardiac chambers. The increasing awareness of non-compaction cardiomyopathy (NCC) or left ventricular non-compaction cardiomyopathy (LVNC) has awakened the need to know how the ventricular wall is organized and understand the role of the trabeculated myocardium, which can be seen in normal hearts. The trabeculations are more frequently seen at younger ages, with gender differences and were found to diminish with ageing (Dawson et al., 2011). Young athletes display a higher prevalence of increased left ventricular (LV) trabeculation compared to the controls (Gati et al., 2013, reported 18.3% of such cases among the athletes aged 20.9±6.0 years, while 8.1% of the whole population exhibited conventional criteria for LVNC), which highlights the non-specific nature of current diagnostic criteria if applied to elite athletic populations. LV hypertrabeculation was also more common in athletes of African/Afro-Caribbean origin.

In the last years, studies started to appear analysing cardiac morphogenesis in zebrafish, showing how the myocytes form protrusions and interconnect to become trabeculations and demonstrating the important role of the blood flow in the formation of the latter (Peshkovsky et al., 2011; Staudt et al., 2014). The weak atrium mutant embryos (Peshkovsky et al., 2011) with non-contractile atrium exhibited substantially inhibited blood flow through the ventricle, in which case the initial protrusions did not progress toward creating myocardial ridges (trabeculations). Similarly, disrupting flow into the left ventricle of embryonic chick hearts by left atrial ligation decreased left ventricular trabecular volume (Sedmera et al., 1999). Finally, mice that do not have primary cilia in their endothelial cells showed decreased cardiac trabeculations and abnormal outflow tract development, suggesting a role of shear stress sensing in chamber maturation (Captur et al., 2015; Samsa et al., 2013).

In this paper, we focus on the relation between the trabeculations and the cardiac performance. Ashikaga et al. (2008) demonstrated that myocardial volume decreases in end-systole (ES) more than accounted for by the vasculature inside the myocardium. The authors argued that the myocardial volume change during the cardiac cycle in the LV anterior wall of normal canine heart *in vivo*, using transmurally implanted markers and biplane cineradiography, is due to existence of additional mechanisms besides coronary blood volume movement that regulates myocardial volume. One of the anatomical structures that would potentially give rise to the blood-filled spaces within the myocardium is the ventricular trabecular tissue. Peshkovsky et al. (2011) argue that trabeculae increase the amount of myocardial mass in the chamber and also create elaborate lacunae through which blood flows, which is also supported by Sedmera et al. (2000). Trabeculated myocardium has markedly different viscoelastic behaviour than the compact myocardium, influencing the rate and magnitude of contraction and relaxation (Miller & Wong, 2000). The abundance of observational papers point to the fact that the trabeculations could be serving as a mechanism

for efficient filling and emptying of the chambers. Recently, Bijnens et al. (2012) and Gabrielli et al. (2014) discussed the cardiac pump function in different cardiomyopathies from the engineering point of view, working out the relationship between the dimensions, output, and forces required to produce that output and how these factors could provoke cardiac remodelling. Although their model shed some light on the underlying mechanics of cardiac response to different conditions, the analysis assumes that the cavities are smooth, ignoring the effect that cardiac trabeculations may have, even though they are present in every heart. In this paper, we have developed a geometrical model of a trabeculated left ventricle and analysed its performance in the presence and absence of trabeculae.

2. Materials and Methods

2.1. 2D Visual Calculations

The effect of the trabeculations on the ventricular performance can be shown using a simple theoretical model. We represent a ventricle by a 2D rectangle on a grid (Fig. 1), where we can easily measure enclosed area, relative displacement (surrogate of strain), and easily model contraction. We consider 2 cases: smooth ventricle (the blue "U" shape) and a ventricle with trabeculations ("U" shape with squares in the interior). The top row shows the ventricle at end-diastole (ED) and the bottom row – the same ventricle at end-systole (ES), overlaid over the ED shape (shaded).

2.2. Ellipsoidal Model of the Left Ventricle

To quantify the relationship of the LV size and performance, the LV endocardium was modelled as a half of a prolate spheroid with a fixed ratio between the minor R_s and major R_l radii: $R_l = kR_s$, the major axis representing the ventricular long axis. The trabeculations are modelled as a certain volume inside of the ventricle (not occupied by the blood), that does not

change during the cardiac cycle (non-contracting tissue, see Fig. 2). Let V_c^{ED} represent the volume enclosed within the compact myocardium of a trabeculated ventricle and V_t the volume occupied by the trabeculations, then according to our definition of the trabeculations $V_c^{ED} = EDV + V_t$. In the following, EDV, ESV, SV will represent the end-diastolic, end-systolic and stroke volumes of the modelled left ventricle; $\varepsilon, \varepsilon_t$ represent the longitudinal strain for a non-trabeculated and trabeculated left ventricles respectively. The ventricular contraction from ED to ES was modelled by scaling the radii, with the scaling factor estimated from the required volume. The relationship between the minor (short) axis radius R_s and the half-ellipsoid volume V is given by: $R_s = (3V/2k\pi)^{1/3}$. V is equal to EDV or ESV for non-trabeculated ventricle and V_c^{ED} or V_c^{ES} for the trabeculated one. To measure the longitudinal strain, the ellipsoid was cut by a plane passing through the major axis (long axis of the ventricle and passing through the apex) to obtain an ellipse and the relative change of its circumference from ED to ES was taken as strain (for convenience the absolute value of the strains is reported), which with the above assumptions can be reduced to: $\varepsilon_t = \left(\frac{V_c^{ES}}{V_c^{ED}}\right)^{1/3} - 1$ and $\varepsilon = \varepsilon_t(V_t = 0)$. In this paper, we used $k = 1.3$, as in Bijnens et al. (2012), nevertheless, the plotted relationships are independent of any particular choice of k, as can be seen from the formulas. The detailed description of the model can be found in the supplementary material.

3. Results

3.1. 2D Visual Calculations

The ventricle ejects a certain amount of blood with each heartbeat by an overall contraction of the cavity. In terms of geometrical measurements, the stroke volume (SV) is affected by both the amount of contraction and the size of the ventricle with the relationships shown by

Bijnens et al. (2012), which allows the ventricle to adapt to changing conditions. In particular, the authors demonstrated, that if more SV is required (e.g. with valve regurgitation or shunts), a dilatation of the ventricle will provide a way to increase the SV (keeping the strain constant). In the case of decreased contractility (e.g. with ischemia or genetic alterations), dilatation provides a way to generate the same amount of SV with less deformation. This can be seen in Fig. 4, first row second column, fixing the stroke volume to, for example, 60 ml (red dot), if we move along the x axis to the right (increase EDV), from the strain isocontours we can see that we are effectively moving towards the areas of lower strains.

There is one more mechanism, however, that allows the ventricle to adapt to the changing conditions – the trabeculations. Fig. 1a shows the initial configuration with trabeculations (dark blue represents compact myocardium, light blue – trabeculations) with interior area of 18 squares at ED. The ES in Fig. 1a-b was obtained by fixing the strain: contraction by 1 square radially and 2 squares longitudinally. The resulting "SV" (change in cavity areas) is 16 squares for the trabeculated ventricle and 13 squares for the smooth ventricle. If SV is fixed instead of the strain, Fig. 1c shows the contraction that preserves the SV (18 squares), then the radial contraction increases to 1.5 squares and the longitudinal to 2.5 squares with respect to the trabeculated ventricle. This model shows how trabeculations can contribute to ejecting more blood out of the ventricle.

3.2. Relationship Between EDV, SV and Strain Using the Ellipsoidal Model

Fig. 3-4 illustrate the relationship between EDV, SV and strain for smooth and trabeculated ventricle. The amount of trabeculations was chosen as to occupy 60 ml (approximately 8 mm thick trabeculated layer in ES) for the ventricle with ESV of about 50 ml (the blue interior in

Fig. 2). Fig. 3 shows the relationships as two surfaces, one for the trabeculated, and one for the non-trabeculated ventricle, while Fig. 4 shows the same surfaces by projecting them onto the coordinate planes defined by all the pairs of EDV, SV and strain. Note that EDV and SV represent the amount of blood in both the trabeculated and non-trabeculated ventricles. However, to estimate the strain of the trabeculated ventricle, V_c^{ED} and V_c^{ES} are used. Two dots (red and blue) are shown on the plots to help compare the ventricles with and without the trabeculations, with a table in Fig. 4 summarizing the measurements. From the plot, we can observe:

- The blue point corresponds to the condition when two cardiac chambers (trabeculated and non-trabeculated) contain the same amount of blood (125 ml) and contract with the same strain (10%). In this case one can see the increased SV (about 47% more) in the trabeculated ventricle.
- The red dot on the other hand represents two cardiac chambers (trabeculated and non-trabeculated) that contain (100 ml) and eject (20 ml) the same amount of blood. One can see that the trabeculated chamber requires less strain (about 40% less) to perform the ejection.

The surfaces in Fig. 3 show a strong increase in strain required to generate high stroke volume in smooth-walled LV. In order to completely empty the cardiac chamber, in the absence of trabeculations, the required strain increases exponentially, while with trabeculations it is possible to completely empty the chamber using much lower strains.

We can conclude therefore that an increase in the amount of trabeculations can lead to reduced strains if SV and EDV are maintained constant. However, to accommodate the same volume of blood with an increased amount of tissue within the ventricle (trabeculations), the cavity has to dilate, effectively reducing the strain required to generate the same SV, but with

a possibly higher wall stress. This dilatation leads to the observations similar to Bijnens et al. (2012):

- If an increased SV is required (e.g., during exercise), it can be generated by adding more trabeculations while simultaneously dilating the ventricle.
- If the volume of circulating blood increases (e.g., increased preload), but there is no requirement for higher SV (ventricular dilatation with constant strain will naturally lead to an increased SV), additional trabeculations in the ventricle would keep the SV at the required level while reducing the overall strain.

3.3. Relationship Between Strain and the Amount of Trabeculations

By expressing the amount of trabeculations and SV as a percentage of EDV ($V_t = F_t \cdot EDV$), in Fig. 5a, we illustrate how the trabeculations affect the longitudinal strain for different SVs. The SV is taken as a percentage of the EDV (equivalent to ejection fraction, EF), with values ranging from 0 to 100%. Although physiologically it is not possible to completely empty the chamber, ejection fractions above 90% have been observed in athletes (Klabunde 2005) or hypertrophic hearts. One can see that in the scenarios of high SV demand, low amounts of trabeculations lead to large strains, which tend to increase exponentially. For each of the isolines of the Fig. 5a, we can define a strain-trabeculation trade-off point at the location where the curve bends (we define this point as the point furthest away from the line connecting the curve's ends, see Supplementary Materials). Plotting these trade-off points for the isolines, we can see in Fig. 5a how these points shape a curve with trabeculation values ranging from 33% to 41% of EDV (if we limit maximum EF to 90%). The Fig. 5b shows an approximate thickness of the dense trabeculated layer (without recesses) for the different

cavity volumes V_c^{ED} and the percentage of trabeculations F_t. Comparing this plot to Fig. 5a, we can see that the 33-41% band corresponds to a trabeculated layer of about 0.35-0.41 cm (for V_c^{ED} of about 150 ml, within a normal EDV range) or 0.7-0.8 cm, if one could assume (for example) that about 50% of the trabeculation volume are blood filled recesses. The latter correlates with the measurements of the typical thickness of the trabeculated layer of Dawson et al. (2011), where its thickness in ED was reported to vary from 0.3 to 0.8 cm.

From the above arguments, one can see that adding trabeculations reduces the strain, but at the cost of dilating the ventricle. If the cavity does not dilate, however, the trabeculations will tend to occupy space and with too many trabeculations the capacity of generating SV by the ventricle will rapidly decrease.

4. Discussion

In this paper, we presented an analysis of the relation of ventricular size, trabeculations, deformation and the resulting SV. We found that

- trabeculations allow increasing SV with less strain for a given ventricle
- from the idealized geometrical point of view, it is possible to find a trade-off between the amount of trabeculations and the strain, where, with less trabeculations, the cavity might be subject to unnecessarily large strains, while, with more trabeculations, there is no more considerable gain in the strain reduction, but the excessive trabeculations might start hampering the normal cardiac filling and emptying. The identified range of trabeculation thickness appears to be within the range of a normal ventricle.

We believe that in the cardiac development there is a search for an optimum. Nature tries to reduce both stress (related to ventricular size, shape, pressure, among others) and strain (related to energy consumption) while adapting the SV to the necessities of the body. The

strain can be reduced by adding trabeculations. However, adding too many trabeculations requires dilation to accommodate a certain volume of blood. The literature seems to point out that the trabeculations were most often observed in the subjects with increased preload, where the significant amount of trabeculations seem to be easily identified even in echocardiography. In particular, in chick embryos, experimental changes in loading conditions have been shown to lead to changes in ventricular myoarchitecture: increased pressure load resulted in an accelerated development of the compact layer with thicker, coarser trabeculae and diminished intertrabecular spaces. On the other hand, volume loading resulted in an increased number of thinner trabeculae (Sedmera et al., 1999). Patients with heart failure and chronic anaemia frequently demonstrate increased LV trabeculations, which may be compatible with the diagnosis of LVNC. Due to reduced ability of the heart to contract, the heart could be trying to produce additional SV by adding trabeculations. A similar effect was noticed in pregnant women where, due to increased requirement on cardiac output and increased preload (Melchiorre et al., 2012), the heart seems to develop more trabeculations to cope with the new requirements, which disappear in approximately 2 years post-partum (Gati et al., 2014).

Intense and regular physical exercise is responsible for various cardiac changes, some associated to enlargement of the cardiac chambers and an increased amount of trabeculae, sometimes meeting the criteria for the LVNC (Dores et al., 2015). For instance, Gati et al. (2013) showed a higher prevalence of LV trabeculation in athletes compared to controls (18.3% vs. 7.0%), with 8.1% fulfilling criteria for LVNC. In this particular population, the increased level of trabeculations would allow for increased rates of ventricular emptying and ventricular filling of the trained subjects (about 20% and 71% greater) (Gledhill et al., 1994).

The amount of trabeculations is also directly related to the cardiac output (CO), the latter being a product of heart rate (HR) and SV. The CO of trained endurance athletes may

increase from 5-6 L/min at rest to up to 40 L/min during maximal exercise (Ekblom & Hermansen, 1968) with the HR between 160 and 220 bpm. In pregnancy, the CO increases by about 1 L/min (Sanghavi & Rutherford, 2014) with HR increasing to about 85-90 bpm. An increase of CO can be achieved either by increasing HR, EDV or SV. An HR and EDV increase provides an acute increase of CO, while SV increase is predominantly due to chronic cardiac remodelling. From the graphs presented in this paper, it can be seen that to reach a certain CO in a non-trabeculated ventricle one would require either stronger contraction (higher strain) than in the trabeculated one, or higher HR (or both). Given a fixed EDV, higher strain would provide an additional SV, but in order to generate more strain chronic beta-adrenergic stimulation or hypertrophy of the myocardium might be required. On the other hand, increasing trabeculation together with dilatation of the ventricle (to accommodate the same amount of blood) would lead to either: a) maintenance of normal strain and an increase in SV, or b) smaller strains to output the same SV.

Fig. 5 suggests that mild trabeculations, as long as they are not interfering with the blood flow, can help reducing the ventricular strain, while providing the same amount of blood to the body. However, the excessive trabeculations bring a risk of cardiac insufficiency by either hampering the development of the necessary strain or simply by reducing the space occupied by the blood, possibly leading to higher blood pressures. In both scenarios, the ventricle may be forced to dilate, if possible.

While NCC has been related to genetic mutations and similarities have been found with hypertrophic cardiomyopathy (HCM) (Arbustini et al., 2014), from our analysis, the hypertrabeculation in HCM might find their origin in an adaptive mechanism to optimize cardiac performance in the presence of altered tissue micro-structure or cellular contractility. This would partially explain the wide variety of phenotypes of NCC seen in different genotypes.

5. Conclusions

In this paper we presented a theoretical analysis of how cardiac trabeculations relate to the SV and strain for the chamber of different sizes. The main conclusion that we can draw is that the trabeculations can serve to aid the heart in increasing its SV without increasing the strain. The analysis has been carried out on an ellipsoidal representation of a left ventricle. In this paper we proposed a model that did not assume any specific shape or localization of the trabeculations. For our analysis and derivations, we considered the trabeculations as a piece of tissue that occupies some volume in the interior of the chamber. Nevertheless, in reality, the shape and the distribution of the trabeculations are important as well, having considerable impact on haemodynamics of the blood. For instance, the left ventricle tends to have all the trabeculations accumulated towards the apex and mostly on the lateral walls, having most of the cavity clean so that the blood can efficiently circulate from the inlet to the outlet.

Limitations

The 2D visual model, presented at the beginning, offers a limited view on a realistic ventricle and is used simply to illustrate how, from a geometrical point of view, the trabeculations can help generate additional SV and can thus help to intuitively understand the results shown by the ellipsoidal model. The ellipsoidal model, presented in the paper, does not reflect the true geometry of the left ventricle. Wall thickness, fluid and tissue properties were not considered as well. The analysed contraction was also simplified to represent a global deformation. In pathologies, the deformation might be larger or smaller and may vary across myocardial regions, but our conclusion can be extrapolated to these regional scenarios. The rate of deformation due to pathologies is not taken into account in our simulations, and the main focus is on a normal ventricle with and without trabeculations. The shape and placement of the trabeculations, although not considered by our model, is also a very important factor

influencing the filling and emptying of the ventricles, especially combined with anisotropic regional wall strains. In this paper, we considered them shapeless without any specific location.

While the specified simplifications and limitations do not allow to determine patient specific values, or patient population specific values, for the cardiac trabeculations, the derived model is realistic enough to show important and relevant trends in cardiac remodelling due to changing conditions, which would lead to a better understanding of the role of the trabeculations.

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Additional Information

Competing interests

The authors have no competing interests.

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Author contributions

All the authors contributed to the paper in the following: C. Butakoff - conception, design, analysis and interpretation of the results, drafting of the manuscript, B. Paun - drafting of the manuscript, analysis and interpretation of the results, B. Bijnens – conception, analysis and interpretation of the results, critical revision. All the authors approved the final version of the manuscript, agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

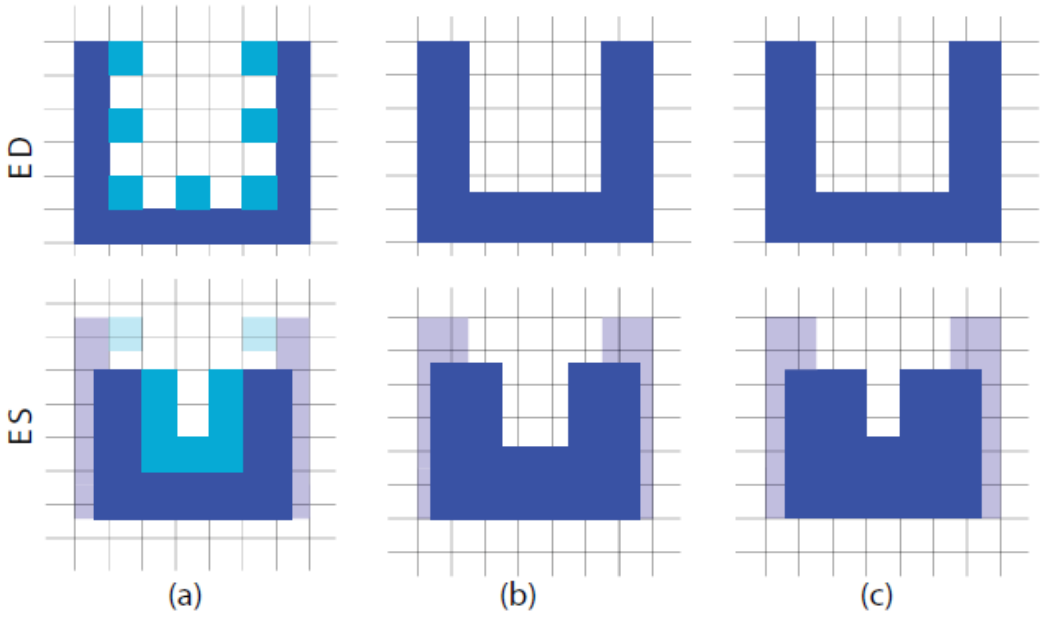


Fig. 1: The illustration of the impact of the trabeculations on the SV and strain for constant myocardial mass. The ventricle is represented by a rectangular 2D cavity overlaid over a grid to allow for visual calculations. Fig. (a) shows the initial configuration with trabeculations (dark blue represents compact myocardium, light blue – trabeculations) the interior area is 18 squares at ED, at ES the compact endocardium is contracted by 1 square radially and 2 squares longitudinally, the resulting "SV" (change in areas) is 16 squares. Fig. (b, c) show the contraction of the cavity that only has compact myocardium. Fig. (b) shows the same contraction as (a) but without the trabeculations, as the result the SV is 13 squares. Fig. (c) shows the contraction that preserves the SV (18 squares), however then the radial contraction is 1.5 squares and the longitudinal is 2.5 squares. The grid in every sub-figure is positioned independently to simplify strain and area calculations. The apex is fixed and the base is moving towards the apex.

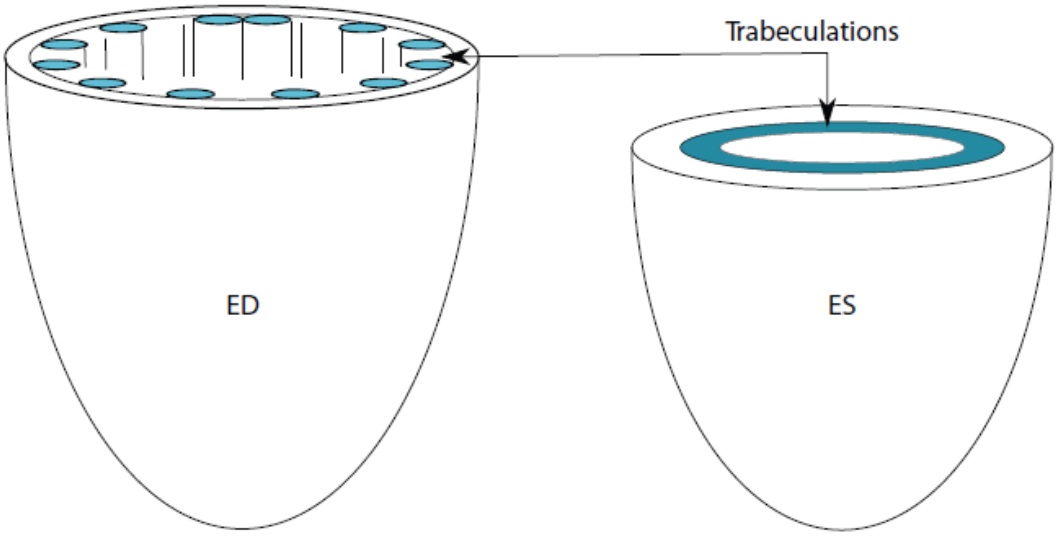


Fig. 2: Schematic representation of the geometrical LV model used to study the relationship between EDV, SV and strain in trabeculated ventricle. Assumptions: wall mass conserved, trabeculations do not thicken.

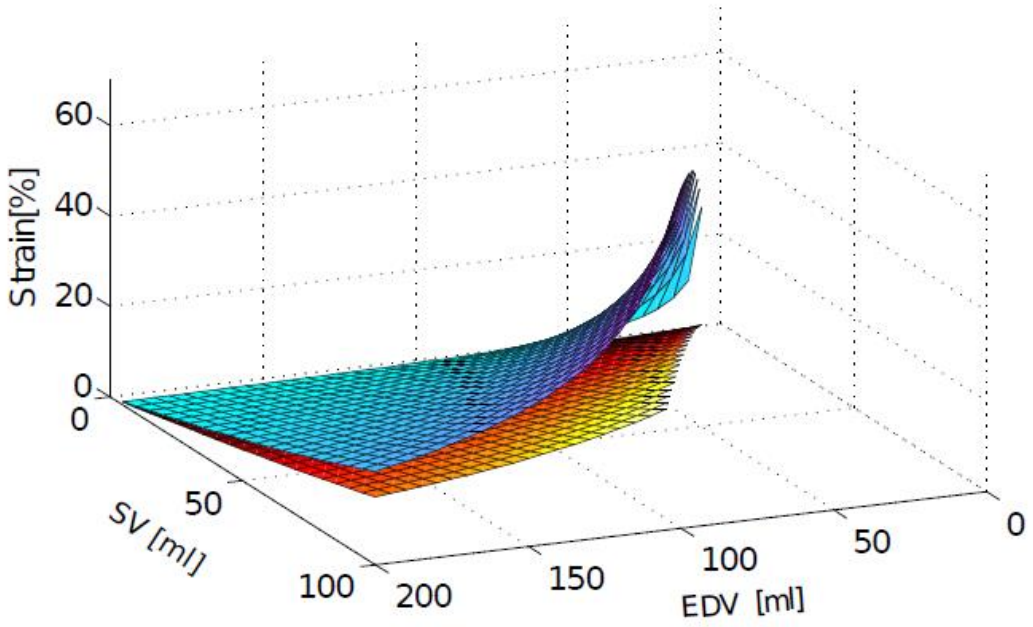
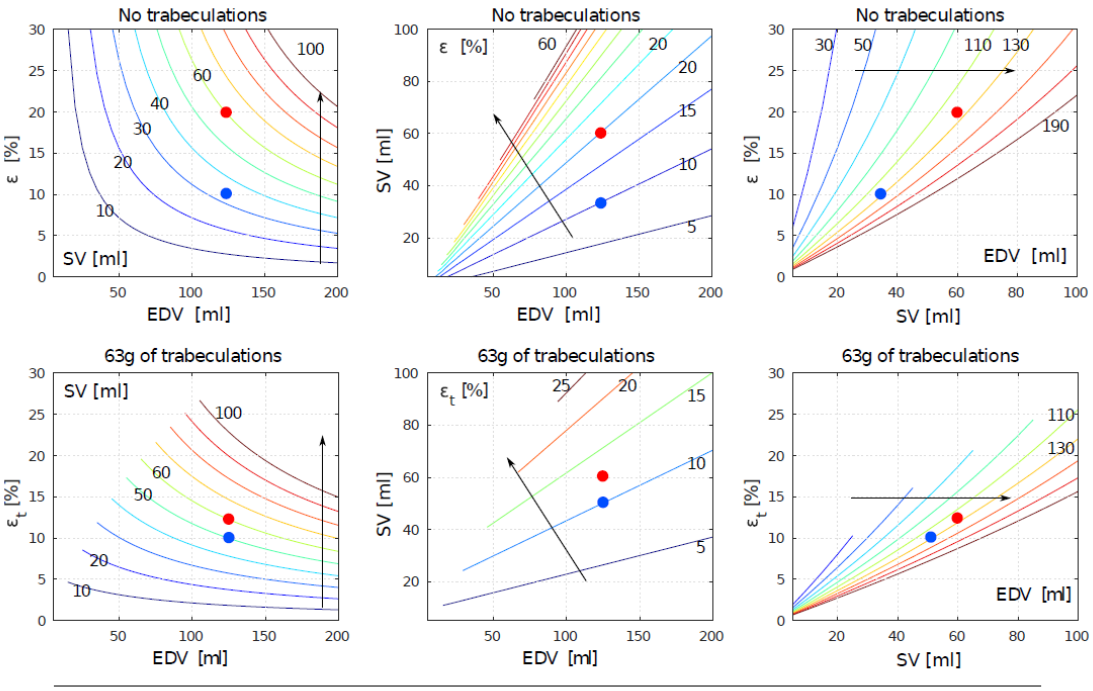


Fig. 3: Results of simulating the ventricular contraction for the ventricle with (red surface) and without trabeculations (blue surface), showing the relationship between the EDV, SV and strain.



Ventricle	Fixed EDV & Strain			Fixed EDV & SV		
	EDV[ml]	Strain[%]	SV[ml]	EDV[ml]	Strain[%]	SV[ml]
Trabeculated	125	10	50	125	12	60
Nontrabeculated	125	10	34	125	20	60

Fig. 4: The relationship between the EDV, SV and strain for a trabeculated and non-trabeculated ventricles. The plots show the projections of the 3D plot of Fig. 3 to the three different coordinate planes. The first column shows the relationship between EDV and strain for different SV (as isolines); the second – between the EDV and SV for different strains (as isolines); the third – between SV and strain for different EDV (as isolines). One can see that the trabeculated ventricle can generate more SV (50 ml vs. 34 ml) than non-trabeculated one given constant EDV and strain (blue dot), and on the other hand the trabeculated ventricle needs less strain (12% vs. 20%) to generate the same SV as the non-trabeculated, given constant EDV (red dot). The arrows indicate the direction of the increase of the isoline values.

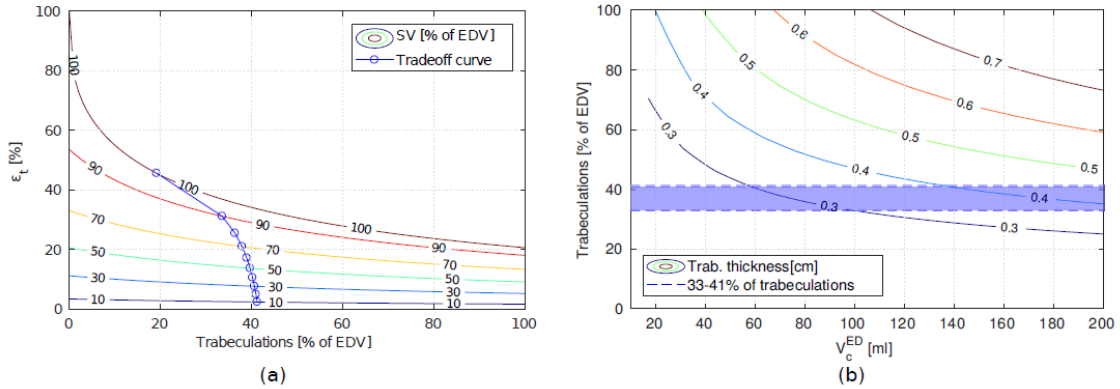


Fig. 5: The relationship between the amount of trabeculations and the strain for different SV expressed as a percentage of EDV. Fig. (a) shows the trade-off points between the strain and the amount of trabeculations for different SV, distributed between 33% and 41% of trabeculations. Fig. (b) shows the thickness of the trabeculated layer for any percentage of trabeculations and the size of the trabeculated ventricle V_c^{ED}, with a blue band showing 33-41% range. V_c^{ED} is the total volume occupied by both blood (EDV) and trabeculations ($F_t \cdot EDV$). The thickness of the trabeculated layer is calculated assuming that the trabeculations do not have recesses (form a dense layer).

Relationship between the left ventricular size and the amount of trabeculations

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Using a geometrical model of the left ventricle we show that: a trabeculated ventricle can work at lower strains compared to a nontrabeculated one to produce the same stroke volume; the trabeculations can help increasing stroke volume with less strain; it is possible to find an optimal amount of trabeculations, where SV is optimized while LV size remains within physiological ranges; the trabeculations are necessary for a more efficient cardiac function, even a small amount of them can be beneficial.