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Title page:

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Abstract

Two of the leading concepts of mural ventricular architecture are the unique myocardial band and the myocardial mesh model. We have described, in an accompanying article published in this journal, how the anatomical, histological and high-resolution computed tomographic studies strongly favour the latter concept. We now extend the argument to describe the linkage between mural architecture and ventricular function in both health and disease. We show that clinical imaging by echocardiography and magnetic resonance imaging, and electrophysiological studies, all support the myocardial mesh model. We also provide evidence that the unique myocardial band model is not compatible with much of scientific research.

Key words: Helical ventricular myocardial band;Helical heart;Ventricular anatomy;Cardiac MRI;Echocardiography;Ventricular function;diastolic function;electrophysiology;contractile stress

Introduction

In our companion anatomical review,[1] we argued for a model in which the myocardium is represented as a continuous three-dimensional meshwork that has no large scale subdivision, and against the concept that the myocardium of the ventricular cone is formed of a counter-wound double loops of a single, "unique myocardial band". We showed that the leading alternative anatomical model, the unique myocardial band, reviewed recently in this *Journal*,[2, 3] has not been demonstrated by histological examination or high-resolution computed tomography and has little support from embryological studies, comparative anatomy or insight gained from congenital heart diseases. The differences between the two models are considerable. Understanding them is important not only to the continuing development of surgical repair but also in understanding normal physiology and disease processes.

Turning now to the ways in which these models relate anatomy to function, it is immediately apparent that the functional differences between the two models are not as

marked as their anatomical variation. This explains in why the differing concepts can continue to have their separate devotees. The generation of systemic pressure in the left ventricular cavity relates to the contractile stress generated in the ventricular wall in the tangential direction and oriented parallel to the surface. It follows that to be efficient in this task, the cardiomyocytes should be oriented mostly in the tangential direction. There are, however, important deviations from the strictly tangential direction towards or away from the epicardial and endocardial surfaces that are not considered in the concept of the unique myocardial band. The cells also lie at a variable angle to the long axial direction, the helical angle, and the models agree that the outer cells are in a "left handed" orientation, and the inner in a "right handed" orientation as outlined in Part 1.[1]. Where the models differ very considerably is in how the cell orientation makes the transition between the two directions.

Imaging perspectives

Echocardiography

Although there is a limited amount of detailed structural information that can be derived using cardiac ultrasound, some heterogeneity is seen within the left ventricular wall. Echocardiographic imaging of the left ventricle shows the presence of a hyper-echogenic zone in the midwall of the ventricular septum when imaged from the apex (Figure 1).[4] This zone had been considered as proof of the existence of a cleavage plane between the elements of the alleged unique band.[5] A recent study by our group, however, showed that the hyper-echogenic region is the consequence of reflected ultrasound from cardiomyocytes orientated in an orthogonal direction relative to the ultrasonic beam.[4] Careful analysis of this region in real time demonstrates that the echogenic zone is present in the septum and throughout much of the circumference of the left ventricle (Figure 1, also see video supplement by Agger and colleagues).[4] The video shows the presence of a contracting mid-mural zone reflecting circumferentially oriented cardiomyocytes. These findings are inconsistent with the notion of the unique myocardial band.

Magnetic resonance imaging

Diffusion tensor magnetic resonance imaging is a method that assesses the diffusion of

water-bound hydrogen in tissues. It is currently implemented in the clinical setting of neuroscience, but more recently has been used in assessing myocardial anatomy. Since diffusion of water mainly occurs along the length of the cardiomyocytes, its direction is a surrogate of the average alignment of the cardiomyocytes within the voxel of myocardium being interrogated. The presence of the three-dimensional mesh as described above has now received further endorsement by studies performed using diffusion tensor magnetic resonance imaging of porcine hearts obtained post-mortem.[6] Multiple studies using the technique [7-10] including our own,[4, 11, 12] demonstrate both the obvious helical arrangement of the cardiomyocytes (Figure 2), as well as the tendency of some of the chains of cardiomyocytes to deviate away from the surface parallel orientation (i.e. with an intrusional angle), as anticipated from the histological studies. As already discussed, they also confirm the presence of chains of cardiomyocytes aligned in circumferential fashion within the short axis of the left ventricle, in other words with zero helical angulation (Figure 2).[6, 13, 14] Helical angulation shows a smooth transmural progression from endocardium to epicardium, in contrast to the abrupt change that would be expected if the ventricular cone were to be formed on the basis of a wrapped unique myocardial band (Figure 3).[15-18]

An intriguing part of the analysis of diffusion tensor imaging data is tractography, whereby individual local orientation vectors are connected to form long tracks, which progress through the myocardium and delineate the preferential pathway of the long chains of cardiomyocytes. Such analyses are standard procedure in most contributions using diffusion tensor imaging [4, 6-8, 11, 13, 15, 19]. The findings need to be interpreted with care, since the cardiomyocytes are not organised like beads on a string. The myocardium is structured as a highly complicated three-dimensional branching meshwork, in which adjacent myocytes may be connected in many different directions. A recent paper by Knösche and colleagues investigated the reliability of tractography in the brain.[20] They concluded that with the current level of spatial resolution it is impossible to achieve both high specificity and high sensitivity at the same time when using tractography, especially in areas of high curvature and crossings of axons. Poveda and associates proposed that the unique band can be shown using this technique.[21] Most other studies, in contrast, fail to provide supporting evidence.[4, 6, 19] Poveda and co-workers based their conclusions on the images

produced when down-sampling their diffusion tensor imaging data. The result is a simplified structure, resembling the band. In our view, the resulting pattern does not reflect the unique myocardial band as described by Torrent-Guasp.[2] Examination of their figures 10 and 11, for example, shows part of the apical loop to be missing (between E and F), and the so-called basal loop is not always located in the base of the left ventricle. It is our opinion that the overwhelming evidence derived from most studies to date using magnetic resonance imaging does not support the concept of the unique myocardial band. With the conclusions of Knösche and colleagues in mind,[25] it is prudent to compare results of diffusion tensor imaging tractography with other three-dimensional methods such as those described in Part 1 using high-resolution computed tomography.[1]

Electrophysiology perspective

The proponents of the unique myocardial band describe sequential myocardial depolarisation starting in the right ventricular free wall, passing to the left ventricular free wall, followed by the descending and lastly ascending segments.[22] The authors further suggested that contraction of the ascending segment resulted in lengthening of the long axis of the ventricles in the fashion of a snake lengthening its body.[22]

Even though each cardiomyocyte is an individual anatomical entity, the walls of the cardiac chambers act as a functional syncytium, whereby there is coordinated contraction of all the cardiomyocytes. This is achieved through intercommunication between cells via gap junctions. The resulting coordinated activation wave spreads over the entire myocardial mass (Figure 4). Conduction velocity is the highest along the long axis of the myocyte, and slowest transversely across its short axis. Needle electrode recordings from isolated human hearts, have shown that ventricular depolarisation starts at the endocardium on the left side of the septum, and propagates toward the epicardium, apex, and the base of the heart, spreading outward in an uninterrupted, centrifugal manner.[23-25] The hypothesis of the unique band suggests two distinct components in the left ventricular wall, with different directions for the cardiomyocytes. Such an abrupt change in direction would reduce coupling, and thereby slow down conduction locally, leading to fractionation of local electrograms.[26] No such fractionation has been observed in the left ventricle of human, pig or dog hearts (Figure 4). High-resolution optical mapping of the cut surface of left

ventricular wedge preparations from human donor hearts has shown slower conduction velocity at the subepicardium compared to the subendocardium.[27] The change in conduction velocity was not abrupt, but decreased gradually from subendocardium to subepicardium. Stimulation at the apical side of the human left ventricular wedge preparation did not result in asymmetrical conduction at the subendocardium or subepicardium.[28] Sequential activation along the unique myocardial band would result in significant left ventricular dyssynchrony and a reduction in pumping efficiency. We conclude, that electrophysiological studies fail to support the concept of the "unique myocardial band".

Right ventricular aspects

During embryonic development and early postnatal life, the wall of the right ventricle has a similar thickness to that of the left ventricle. Zhang and colleagues have shown that in the perinatal period around 50% of the interventricular septum is of right ventricular origin.[29] This proportion is reduced to 25% later in life, hence the interventricular septum must be considered a biventricular structure. Tractography originally published by Agger and associates confirms this finding (Figure 5) [11]. In this study, it is evident from the examination of several ovine hearts that the meshwork of cardiomyocytes in the interventricular septum originated from both ventricles. This sharing of the septum is reflected in the notions of interventricular interaction or interdependence, where a functional change on one side of the heart leads to functional changes in the other.[30] The ventricles share tracts of cardiomyocytes that encircle both ventricles (Figure 5) such that continuous chains of cardiomyocytes span the right to left ventricle.[6]. In the light of this, it makes little sense conceptually to disrupt the connection between the right and the left ventricle as proposed by Torrent-Guasp when unravelling the unique myocardial band.

Structure-function relationship in the left ventricle: the hydrostatic heart.

Shortening of individual cardiomyocytes is a consequence of contraction of their sarcomeres. Shortening of the cardiomyocytes reduces the external volume of the left ventricle. The forces engendered by contraction of the individual cells in a largely tangential direction produce hydrostatic forces which act in a radial direction to create a rise in luminal

pressure and drive the endocardium inward (Figure 6). No matter which model of architecture is espoused, this simple squeezing action is common to both but the coordinated contraction is not (see below).

Cell and mural shortening is nearly simultaneous despite activation by depolarisation taking a finite time to spread throughout the ventricular myocardium. When the S wave on the electrocardiogram returns to the isoelectric baseline, it marks the time at which mural depolarisation is complete: the aortic valve does not open until after this has happened, so it is a reasonable assumption that the entire myocardium is generating tension from the moment that ejection begins.

The fixed volume of the ventricular muscle enforces a relationship between the dimensional changes of the epicardium and the endocardium, and the mural thickness. In this respect, the ventricular mass acts as a muscular hydrostat, a mechanism which is common in the locomotion of creatures which have no rigid skeleton, as well as in tongues and tentacles, in which the action of a muscle is to change its own shape.[31] As exemplified in Figure 6, the consequences of this linkage can be summarized:

-in resting conditions, the cavity cannot eject a volume unless the outer shell (the epicardium and the mitral annular plane) moves inwards by the same volume. The total swept volume of the outer shell will equal the stroke volume.

-the degree of mural thickening will be a product of the inward movement of the outer shell and the diastolic volume of the wall: though cell thickening will contribute to overall thickening, it will not determine its magnitude.

-thus, there will be a gradient of circumferential strain, being least at the epicardium and greatest at the endocardium.

- in this way, a shortening of around 15 to 20% of the individual cardiomyocytes generates a radial strain (mural thickening) two to three times greater, thus producing an ejection fraction in the region of 60%.[32]

Again, these relationships are applicable to either model, as they share the same external

shape. Similarly, both models are bound by the limited range of cell shortening: the higher circumferential shortening at the endocardium usually exceeds the shortening ratio of the cell. The resulting endocardial fractional shortening of 35% must result in rearrangement of the subendocardial cardiomyocytes. A gradual change in the helical angle across the ventricular wall, combined with ventricular twist, is necessary to produce mural thickening whilst maintaining shortening of the cardiomyocytes within their physiological range.[33] There is no need to postulate that this configuration depends on the two directions comprising separate loops of a single band.

Contraction of most of the cardiomyocytes results in a combination of both long axis and circumferential shortening, since their vectors are not exactly aligned in either direction. For example, a tangentially orientated cardiomyocyte with a helical angle of 45° will have an equal force component and contractile stress in both the long axis and circumferential directions (Figure 7).[34] Shortening of the individual cardiomyocytes results in thickening without a change in their volume. A combination of overall shortening in the long axis of the left ventricle, as revealed by mitral annular displacement, combined with the shortening of the entire myocardial mesh, results in a reduction in the total external volume of the left ventricle (Figure 6). This change in the shape of the ventricle, in turn, results in a greater proportional reduction of the smaller luminal volume because the absolute reduction in volume is the same.

Both longitudinal and midwall circumferential myocardial strain are directly related to radial thickening.[35] Mural thickening, in turn, is an important determinant of endocardial displacement, the volume of blood ejected, and hence the ejection fraction.[36] Increasing left ventricular mural thickness results in a greater left ventricular ejection fraction for a given myocardial strain.[37] A thick-walled ventricle due to hypertension must have a reduced myocardial strain when the left ventricular ejection fraction is normal.[36] Similar findings of augmentation of the ejection fraction by mural 'hypertrophy' have been demonstrated in hypertrophic cardiomyopathy[38, 39] and heart failure with a normal ejection fraction.[40] A mathematical relationship is found between myocardial shortening, end-diastolic mural thickness and ejection fraction (i.e. ejection fraction $==e^{0.14Ln\varepsilon+).058)\omega+0.9ln\varepsilon+1.2}$ where ε is myocardial strain and ω is diastolic wall thickness

).[32, 33, 41]

During systolic contraction of the left ventricle myocardial mesh, the groups of aggregations of cardiomyocytes, often referred to as sheets,[42] that change their orientation to facilitate the transmural thickening of the left ventricle [43]. In the two-dimensional short axis view of this results in flattening the chevron-like patterns (Figure 8). Slippage between the aggregations presumably along the perimysial planes between cardiomyocytes and between bundles of cardiomyocytes reduces the passive shear stresses that might otherwise inhibit mural thickening.

Left ventricular twist can be observed using speckle tracking during echocardiography. Twist is a measure of motion, or shear, and should not be confused with a direct measure of function. It is a relatively minor motion compared with myocardial longitudinal shortening and midwall circumferential strain. A ventricular twist of 12°is only about 3% (i.e. 12° of 360°), while mid-mural circumferential strain is of the order of -20%, suggesting that twist is a relatively minor contributor to the stroke volume. Based on the findings we have cited to show the three-dimensional aggregation of the cardiomyocytes, we suggest that twist is the consequence of shear strain, the latter brought about by the contraction of helically arranged cardiomyocytes. As such, it reflects no more than the consequences of cardiomyocytic contraction. The mechanisms can be deduced by the differences in moment of the arms of the right and left-handed helixes. Hence, the twist of the left ventricle, well recognised during cardiac surgical procedures, is readily explained by the anatomical arrangements of cardiomyocytes, a feature known since the seventeenth century in studies by Richard Lower.[44] It is unnecessary to invoke the concept of a unique myocardial band to account for this observation.[41] All aspects of myocardial function as currently understood are readily explained based on the anatomy as demonstrated within our reviews. The myocardial mesh model, however, would provide more uniform cardiomyocyte stresses and strains when compared with the concept of unique myocardial band.

Additional problems with the concept of the unique myocardial band

We have listed many histological, developmental and imaging studies that demonstrate a lack of evidence for the alleged band. We also suggest that the dissection of the heart as

performed by Torrent-Guasp [2] conjures a band of myocardium tissue that is not a physical anatomical entity. The physiological descriptions based on the concept of the band, despite its potential attraction, must be considered invalid given the lack of any supporting anatomic evidence. Analogies between skeletal muscle and the unique myocardial band are often made. The unfolded band, however, becomes thinner in its middle region, near the ventricular apex, whereas most skeletal muscles, such as the biceps muscle, are much thicker at the centre of their length. Physiologically, it is hard to see how such morphology would permit sufficient force generation, were the contraction indeed to follow the length of the band. The concept that contraction of an ascending segment results in lengthening of the ventricular long axis to produce diastolic filling[22, 45], for example, is also difficult to understand. When considering the analogy of a snake uncoiling, we should remember that it is the presence of the spine which gives the muscles an anchor that enables the animal to straighten. When any muscle contracts, furthermore, it shortens rather than lengthens. The illustrations of the dissected and unrolled band from Torrent-Guasp[22, 46, 47] shows that the grain of the bovine myocardial tissues does not follow the longitudinal orientation along its complete length.[48]

A clinical perspective

The clinical implications of the unique myocardial band have been discussed previously in this *Journal*.[2] We would concur that linking ventricular structure to function in both health and disease is extremely important. We argue that the myocardial mesh model provides a better explanation for both normal and diseased ventricles. We have explained above how twisting and torsion can be readily explained. We have also shown how the individual cardiomyocyte shortening of around 15-20% can translate into an ejection fraction of 60%, and how a global reduction in contractile strain results in reduced ejection fraction when the wall thickness is normal, and a normal ejection fraction when wall thickness is increased.[32, 36, 37, 41, 49]

Left ventricular diastolic dysfunction is also an area under intense investigation. Various mechanisms for diastolic dysfunction have been proposed that include increased interstitial collagen, abnormal collagen type, abnormal titin, greater diastolic pressure requirements of

thick-walled ventricles and higher levels of intracellular calcium during diastole.[40] We have also described how hypertrophic cardiomyopathy and its various phenotypes might be better explained by an abnormality of contractile stress produced by the mesh, rather than diastolic dysfunction, where the wall thickens to normalise myocardial forces.[38, 39]

Acute heart failure consists of two distinct syndromes a) acute pulmonary oedema and b) hypotension or cardiogenic shock.[50] The former is brought about by an imbalance between the right and left ventricular stroke volumes,[51] and the latter due to a reduction in cardiac output. A higher pulmonary artery pressure is a consequence of increased right ventricular contraction and results in a higher pulmonary capillary pressure resulting in interstitial and alveolar oedema.[52] Similar mechanisms appear to be present in immersion pulmonary oedema.[53] In hypertensive left ventricular disease there is parallel hypertrophy with left ventricular wall thickening secondary to increasing contractile force requirements. Chronic heart failure with a low ejection fraction, on the other hand, is seen as a condition where the left end diastolic volume is regulated, via increased filling pressure resulting in series hypertrophy, and a normalization of stroke volume.[54, 55] The chronic heart failure syndrome can be described as a condition whereby the resting stroke volume is partly or fully normalised by eccentric or concentric remodelling and where there is a failure to increase stroke volume and cardiac output with effort often due to a myocardial disease.[55, 56]

Conclusions

The dissections performed by Torrent-Guasp involve destruction of the continuum of cardiomyocytes. Any model of myocardial architecture must allow both sharing and maintenance of the widespread interconnections between the aggregated cardiomyocytes. Internal consistency between myocardial function and anatomy is important. Given the lack of anatomical support, any functional consequence of the unique myocardial band has shaky foundations. It follows that attempts to use these presumed functional consequences to support the initial concept are no more than circular argumentation. We provide evidence that the myocardial mesh model best describes the clinical and functional findings. In our opinion, the multiple experiments described in these two reviews provide strong evidence that the unique myocardial band not exist and we suggest the Torrent-Guasp

model of ventricular structure should be replaced by the myocardial mesh model.

Figure 1. Echocardiography

Images showing 3D reconstruction in short axis derived from the apical view. Note the midwall echogenic zone representing the circumferentially orientated cardiomyocytes. The contracting midwall cardiomyocytes are best clearly shown in real-time.[4]

Figure 2. Eigen analysis of Diffusion tensor imaging

Eigen analysis of diffusion tensor imaging (3D) from our group. Note the circumferentially orientated cardiomyocytes have a zero-helical angle in the human foetus (blue) and adolescent (20 kg) pig (blue). Colour bars indicate absolute helical angle.

Figure 3. The transmural change in helical angle

The hypothetical septal myocyte angulation plot if the so-called unique myocardial band existed with a demarcation between the ascending and descending segments of the band (A) and the actual results of experimental investigation using diffusion tensor magnetic resonance imaging (B) are shown. Myocardial level indicates the position in the wall with 0% at the endocardium and 100% at the epicardium.

Figure 4. Electrophysiological findings in the ventricles.

Figure A shows transmurally recorded local electrograms from the left ventricular wall from human, dog and pig. The electrograms were recorded with plunge needle electrodes from the left ventricle of Langedorff-perfused human, dog and pig hearts a pacing interval of 700 ms, 800 ms and 450 ms respectively. Note the lack of fractionation and only a minimal delay between the subendocardial, mid and subepicardial regions. The presence of distinct layers, such as the ascending and descending segments of the proposed unique myocardial band, would be expected to produce both fractionation and a stepwise delay. Figure B demonstrates the activation pattern measured and isolated human heart measured during Langendorff-perfusion using needle electrodes. Activation starts at the endocardium and follows an endocardial–epicardial sequence in the left ventricle (LV) and a sequence toward the base (courtesy of Tobias Opthof, Amsterdam, Netherlands).[25]

Figure 5. Diffusion tensor imaging tractography in ventricular septum

Diffusion tensor magnetic resonance imaging showing the tractographies of the cardiomyocytes originating from the septum progressing into both ventricles in control ovine hearts (top panel, a to d). These findings are more prominent in pulmonary hypertension (lower panel, e to h).[11] Whilst aware that tractography should be interpreted with caution, this data suggests that the interventricular septum is not a strictly left ventricular structure. Disrupting the connections between the right ventricle and the rest of the heart, as performed by Torrent-Guasp when producing his preparations of the unique myocardial band, interrupts both anatomical and functional connections.

Figure 6. Magnetic resonance images showing the shape change during contraction of the left ventricle

Panel 1 is an end-diastolic two chamber view of the left ventricle. The outer shell (the epicardium and mitral plane) have been outlined and the long axis drawn. The hatch across the long axis marks the geometric centre. Panel two has the same for an end-systolic image, with the outer shell superimposed with respect to an external static frame of reference (the chest wall). The apex is nearly immobile, and the mitral plane shows the greatest excursion. Some of the more apical epicardial surfaces seem to move only slightly. The total excursion of the outer shell (the red stippled area) equals the stroke volume. However, it must be noted that the ventricle has moved apically, as the shift in the centre attests. In panel 3, the centres have been overlain, giving a truer impression of the outer shell excursion and showing that all areas make a similar contribution to overall volume change. Panel 4 is in the transverse plane, when the centre does not move. Any diameter in any direction in either view will show systolic shortening, so mural tension must be generated in all directions (see text).

Figure 7. Contractile stress and forces

The contractile stress expected from the helical angle (A) and mural depth (B) in the circumferential and longitudinal directions and assuming a cardiomyocyte generates stress of 20 kPa and using values derived from figure 3B. Note when the helical angle is 45° the

contractile stresses and forces are the same (red arrows). Figure C shows the accumulative forces across the ventricular wall (derived using numerical integration).

Figure 8. Schematic showing the simplified arrangement of the cardiomyocyte aggregates within the ventricular cone.

The figure shows the average change in transmural helical angle and the alterations during systole with opening of the aggregated units (dot dash lines) as wall of the ventricle thickens. It should be emphasised that the “lamellar sheets” consist of multiple interdigitating units of cardiomyocyte aggregates rather than a single defined structure forming a chevron shape. The apex of the chevrons consists of the midwall circumferential cardiomyocytes. It is these cells that are disrupted by Torrent-Guasp’s blunt dissection (black arrow) into the apex of the chevron. (A) Coloured lines indicate the mean direction of cardiomyocyte chains (B and C) the blue and green arrows indicate direction of shear stresses and resulting twisting. Note the opening of the chevrons, and consequent change in sheet angle, during systole to allow for shear strain thus minimising shear stresses.

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