Heuristic Problems in Defining the Three-Dimensional Arrangement of the Ventricular Myocytes

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ABSTRACT

There is lack of consensus concerning the three-dimensional arrangement of the myocytes within the ventricular muscle masses. Bioengineers are seeking to model the structure of the heart. Although the success of such models depends on the accuracy of the anatomic evidence, most of them have been based on concepts that are far from anatomical reality, which ignore many significant previous accounts of anatomy presented over the past 400 years. During the 19th century, Pettigrew emphasized that the heart was built on the basis of a modified blood vessel rather than in the form of skeletal muscles. This fact was reemphasized by Lev and Simkins as well as Grant in the 20th century, but the caveats listed by these authors have been ignored by proponents of two current concepts, which state either that the myocardium is arranged in the form of a "unique myocardial band," or that the walls of the ventricles are sequestrated in uniform fashion by laminar sheets of fibrous tissue extending from epicardium to endocardium. These two concepts are themselves incompatible and are further at variance with the majority of anatomic studies, which have emphasized the regional heterogeneity to be found in the three-dimensional packing of the myocytes within a supporting matrix of fibrous tissue. We reemphasize the significance of this three-dimensional muscular mesh, showing how the presence of intruding aggregates of myocytes extending in oblique transmural fashion also contends against the notion that all myocytes are orientated with their long axes parallel to the epicardial and enodcardial surfaces. Anat Rec Part A, 288A:579–586, 2006.

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It is well recognized that, in terms of their histology, myocytes can be voluntary, involuntary, or cardiac. The different types of muscle differ not only in their microscopic appearances, but also in their function (Bozler, 1948; Burnstock, 1970; Williams et al., 1989). Cardiac muscle is intermediate in both structure and function between the striated and smooth variants. Initially thought also to be syncytial in nature (Williams et al., 1989), it is now accepted that the atrial and ventricular muscular masses are made up of millions of individual myocytes set in axially coupled endless chains embedded in a supporting matrix of fibrous tissue (Criscione et al., 2005). Each myocyte nonetheless is an entity in itself.

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Thus, each cardiac myocyte, about 80 micrometers long in man, and 15 micrometers in cross-section, divides at its ends, with each myocyte splitting further by giving rise to lateral offshoots (LeGrice et al., 1995; Costa et al., 1999). The multiple branches join with adjacent cells through the intercalated disks, thus producing a network of branching and anastomosing cylinders.

ACTIVATION OF VENTRICULAR MYOCARDIAL MASS

The mass of cardiac myocytes is activated through the so-called conduction system. The ventricular components of this system are significant because they remain insulated until they become the Purkinje fibers within the apical trabecular ventricular components (Anderson et al., 2005). When seeking to relate structure to function with regard to the ventricular myocardium, therefore, it is necessary to distinguish contraction, which describes mechanical activation subsequent to electrical activation, and which results in an increase of contractile tension within the cell, with or without shortening of its myofibrils, from shortening of the myocytes themselves. It is myocytic shortening that produces changes in the shape of the ventricles, with or without ventricular narrowing. Both these features must then be distinguished from ventricular constriction. It is this last mechanism that results in emptying of the ventricles.

Distinction between these terms is essential if we are to clarify ongoing controversies with regard to such purported structures as "the ascending limb of the apical loop" of a hypothesized unique myocardial band. These terms are derived from the work of Torrent-Guasp (1973), who suggested that the ventricular mass could be unraveled to reveal a solitary muscular tract, which could be traced from an origin at the aorta to an insertion at the pulmonary trunk, thus drawing an analogy between the anatomic structure of cardiac and skeletal musculature. As we will show, there is no supporting evidence in favor of this purported "unique band," which is hardly surprising, since as we will also show, the heart is arranged in the form of a modified blood vessel rather than skeletal muscles. Those who have accepted the concept of the "unique band" (Buckberg, 2005) nonetheless claimed to have used microsonometry to support the concept of a marked delay in onset of contraction of a particular part of the superior left ventricular wall, specifically, the part extending between the apex and the aortic root. Microsonometry measures distances and hence is capable of quantitating strain. But mechanical activation is triggered by the electrical activation, with the myocytes contracting to produce an instant rise in tension. Shortening, and hence the measured strain, starts later, when the resistance to shortening has been overcome by the necessary increase in tension. Microsonometry is insensitive to these initiating events. Only when the events have been initiated is it possible for shortening of one part of the aggregated myocytes to transform the ventricle into a sphere, and only when intraventricular pressure has overcome aortic pressure does the greatest part of the myocytes commence to shorten. A subpopulation of the myocytes nonetheless is refrained in its shortening, namely, the population that, because of its alignment, is able antagonistically to counteract systolic ventricular thickening (Lunkenheimer et al., 2004).

THREE-DIMENSIONAL PACKING OF VENTRICULAR MYOCYTES: CELLS VERSUS FIBERS VERSUS AGGREGATES

In order to ensure harmonic atrial and ventricular activity, each myocyte within the heart must not only conduct the impulse, but also contract at the right moment, at the appropriate speed, and to the necessary extent. It is the fashion in which the ventricular myocytes are arranged to produce the coordinated systolic contraction that has long been understood to be synchronous and unidirectional (Frank, 1901). The precise arrangement has still to be determined, not least because of uncertainty with regard to the proportion of the overall population of myocytes that acts antagonistically to control rather than promote ventricular mural thickening (Lunkenheimer et al., 2004). In this review, we discuss the various problems that still remain in elucidating the intricate cellular architecture that permits such antagonistic function. Perhaps the biggest problem reflects one of the most intriguing features of cardiac muscle, namely that, although the myocardial cells form an anastomosing meshwork within their supporting fibrous matrix, the packing of the cells is such that, when the epicardium is stripped away to reveal the subepicardial surface of the myocardial mass, there is an obvious "grain" formed by the long axis of the aggregated myocytes (Fig. 1). When different layers of the wall are revealed by the technique of peeling (Fig. 1), then it can be seen that there is a ordered structure for the ventricular mass, albeit that the aggregated myocytes do not form clearly separable "fibers," nor are the layers isolated by supporting scaffolds of connective tissue. A model of the coherence of microscopic arrangement of the aggregation of the myocytes is shown in Figure 2. The evidence of such multitudes of spatial linkages is in conflict with the idea of sequences of axially coupled myocytes forming "fibers" that can be separated as a functional unit. Equally, it is simplistic to suggest that the myocardial walls are made up of layers, or lamellas, stacked in orderly fashion through the full thickness of the wall. This latter concept has attracted significant support since the initial suggestion of such an arrangement was made by LeGrice et al. (1995) in the mid-1990s. There is no evidence of which we are aware, however, to show shelves of fibrous tissue extending from the epicardium to the endocardium, as illustrated diagrammatically by Young et al. (1998), and sequestrating the ventricular wall into discrete myocardial lamellas. Instead, the myocardial mass is best considered as a meshwork of endless sequences of myocytes coupled axially in one preferential direction, this latter direction marking the "grain." Each chain of myocytes is also coupled to its neighbors by the variable numbers of lateral offshoots (Fig. 2) (Costa et al., 1999), while the "grain" changes markedly at different sites within the ventricular walls.

There is nonetheless some ordering of the overall pattern. When the superficial covering of myocytes is stripped away to reveal the middle and subendocardial portions (Fig. 1), it can be seen that, with slight variations between species, the superficial myocytes are oriented at angles of between 60 and 80° relative to the ventricular equator, with the myocytes occupying the middle portion of the left ventricle being circular, and the deeper portion returning to a still more longitudinal orientation than the subepicardial grain (Lower, 1669; Pettigrew, 1859, 1864; Robb

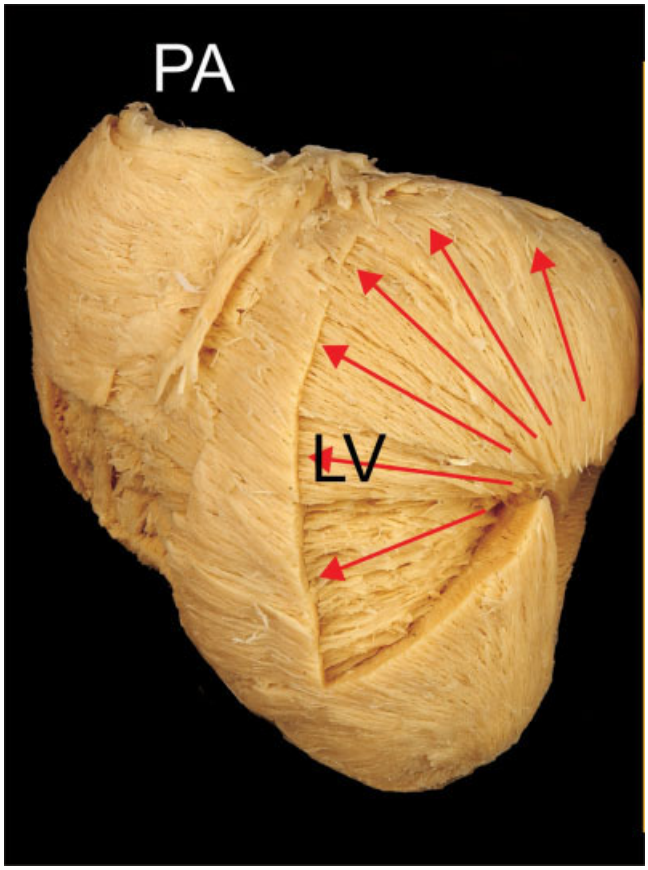

Fig. 1. The myocardial "grain" as seen at various depths through the left ventricular wall of the porcine heart, visualized by peeling aggregates of myocytes stepwise in planes intruding from the epicardium to the endocardium. Note the turn of the grain upon a radial axis (red arrows). PA shows the origin of the pulmonary trunk from the right ventricle. LV, left ventricle.

and Robb, 1942; Hort, 1960; Streeter and Bassett, 1966; Streeter et al., 1969; Streeter and Hanna, 1973). This angle relative to the ventricular equator is known as the helical angle (Fig. 3).

DO AGGREGATES FORM TERTIARY STRUCTURES?

Two main controversies still remain concerning the arrangements of these collections of myocytes. The first devolves on whether the aggregates, which can be considered as secondary structures, the myocytes themselves representing the primary components, are further grouped together to produce reproducible tertiary tracts or bands within the overall structure of the ventricular myocardial mass. The second potential disagreement concerns the arrangement of the supporting fibrous matrix, and whether this is arranged so as to produce lamellas that extend in orderly fashion from epicardium to endocardium (LeGrice et al., 1995), or if, instead, the lamellas throughout the ventricular walls constrain the myocytes into sheets of thickness of four to six cells (Hooks et al., 2002). It is of note that those proposing the concept of orderly myocardial sheets cite the work of Feneis (1944–1945) and Hort (1960) in support of their hypothesis. Our own reading of these extensive earlier works provides no evidence of such endorsement. It is also noteworthy that the proponents of the muscular tracts, and also those promoting the concepts of lamellar structures, pay scant regard to the multiple earlier investigations of the three-dimensional arrangement of the aggregations of ventricular myocytes. It is worthwhile, therefore, to review briefly these pertinent earlier studies and to discuss equally pertinent critical appraisals of the validity of the techniques used to reveal the three-dimensional patterns, criticisms that remain pertinent to the current accounts.

EARLIER ACCOUNTS OF VENTRICULAR MYOCARDIAL ARRANGEMENT

Senac had suggested, as long ago as 1749, that the inner and outer coats of the ventricular mass had a helical structure. Indeed, subsequent to the studies of Senac (1749) and similar investigations by Lower (1669) in the 17th and Ludwig (1849) in the mid-19th century, it became the norm to accept that, within the meshwork provided by the fibrous matrix, it was possible to discern discrete tracts of organized muscular fascicles (Pettigrew, 1859, 1864; MacCallum et al., 1900; Mall, 1911). All these early workers, however, had relied on gross dissections using the technique of peeling to show the purported tertiary packing of the myocytes. The problems inherent in such an approach were highlighted by Lev and Simkins (1956). In their critical review, having themselves also used the techniques of gross dissection, they explained how they were unable to distinguish either the "bulbospiral" or "sino-spiral" tracts, as had been described by Mall (1911), descriptions that, by then, had become accepted as conventional wisdom. They emphasized that the arrangement of the fibrous matrix was not such as to provide anatomical planes of cleavage between the superficial and deeper myocardial layers. Lev and Simkins (1956) agreed nonetheless that gross dissection unequivocally revealed the aggregates in the middle layer of the wall that encircled the base of the left ventricle. These important circular fibers of the left ventricle had previously been identified as the actuating fibers of systolic ventricular constriction, and christened the "triebwerkzeug" by Krehl (1891). They had also been recognized by Keith (1918) as providing the force for left ventricular emptying. The skepticism of Lev and Simkins (1956) regarding the presence of separate "muscles" existing as a tertiary arrangement within the ventricular mass was then wholeheartedly endorsed by Grant (1965). He reemphasized the fact that the myocardium was composed of strings of anastomosing myocytes, with no obvious beginning or end to the aggregated strings. In the opinion of Grant (1965), the distribution of tertiary muscle bundles was at the whim of the dissector, who could carve out of the myocardial mass various patterns depending on his or her subjective judgement. This, of course, remains pertinent to any description of gross anatomy, since the recognized arrangement of muscles within the limbs can be revealed by any dissector following the instructions of the dissecting manual. If comparable "muscles" existed within the heart, then they, too, would be displayed uniformly by techniques of gross dissection. Anyone who has tried to display such structures in the dissecting room will immediately become aware of the impossibility of the task.

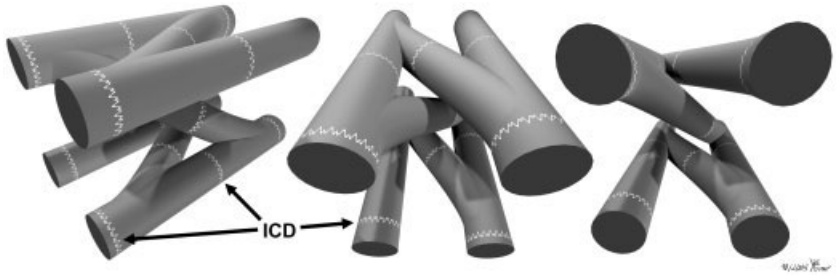

Fig. 2. The cartoon shows an aggregate of myocytes, as seen from various aspects, formed from chains of axially coupled myocytes, which are joined to their neighbors through their lateral offsprings. ICD, intercalated disks.

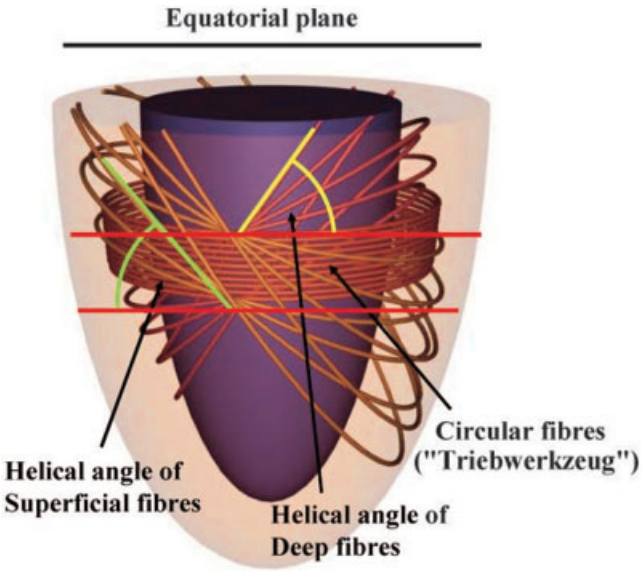

Fig. 3. The cartoon shows the variation in angle of the long axis of the myocytic aggregates when assessed relative to the ventricular equator. This is the so-called helical angle.

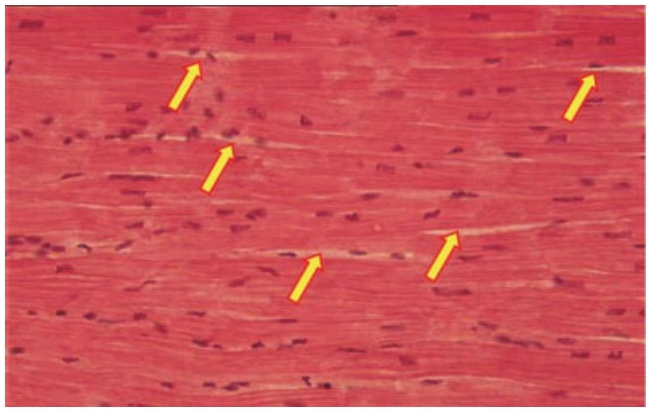

Fig. 4. This histological section is taken along the long axis of the myocytes. Note the irregular arrays of fibrous tissue interposing between the myocytes. There is no regular laminar arrangement to be seen.

REMEMBERING THE IMPORTANCE OF THESE EARLIER STUDIES

It is clear that the criteria suggested for description of "bundles," or "tracts," and the basic rules of the dissecting room were ignored totally by Torrent-Guasp (1973). As we have already discussed, Torrent-Guasp (1973) originated the concept of the "unique myocardial band." This investigator, undaunted by the possible subjective nature of his dissections, claimed to be able to follow "principal fiber pathways" through the substance of the myocardium. Indeed, as we have already discussed, he concluded that such a set of pathways extended from the aorta to the pulmonary trunk, encircling the right ventricle through one loop and the left ventricle by two loops. Within the left ventricle, he also argued that the purported principal pathways formed a nested set of conical spiral sheets, this being in keeping with the findings of a group of investigators who had used techniques of serial sectioning to revive the long-held notion of continuous variation in the helical angle of aggregated myocytes across the ventricular wall (Hort, 1960; Streeter and Bassett, 1966; Streeter et al., 1969; Streeter and Hanna, 1973). More recently, it has been surgeons seeking to explain the "forced reciprocal twisting" of the ventricles observed during cardiac surgery who have provided further support for the concept of the "unique myocardial band," again apparently unaware of its anatomic shortcomings. The surgical supporters have adopted the concept with enthusiasm not only to explain the purported arrangement of the ventricular myocardial mass, but also to produce a revisionist account of cardiac development and to provide a springboard for various surgical procedures (Buckberg et al., 2001). It is understandable that cardiac surgeons should seek to understand the detailed structure of the organ on which they operate (von Segesser, 2005). At the same time, it is axiomatic that such understanding must be established within the basic rules of anatomy, since it is the morphology of the organ that is under consideration, rather than its surgical treatment.

The importance of noting the earlier anatomic investigations is also relevant to consideration of the "lamellar" hypothesis, which currently attracts favor among physiologists and bioengineers. These investigators, also focusing on the arrangement of the supporting fibrous matrix, have suggested that, rather than existing as a unique band, the myocardium is compartmented by a particular laminar structure that extends across the full thickness of the ventricular walls (LeGrice et al., 1995). Supporters of this

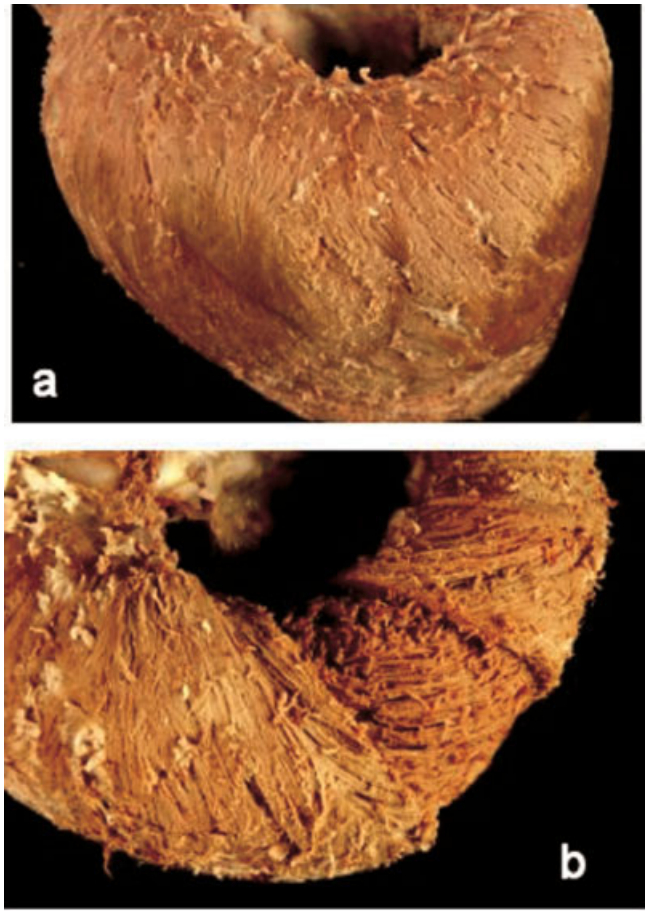

Fig. 5. The left ventricular base of the porcine heart is shown (**a**) as seen from the atrium having removed the atrial wall. Note the almost radial course of the myocardial grain from the epicardial surface toward the endocardium. When the superficial fibers are peeled away (**b**), the grain begins to achieve a circumferential orientation. This is the margin of the "triebwerkzeug."

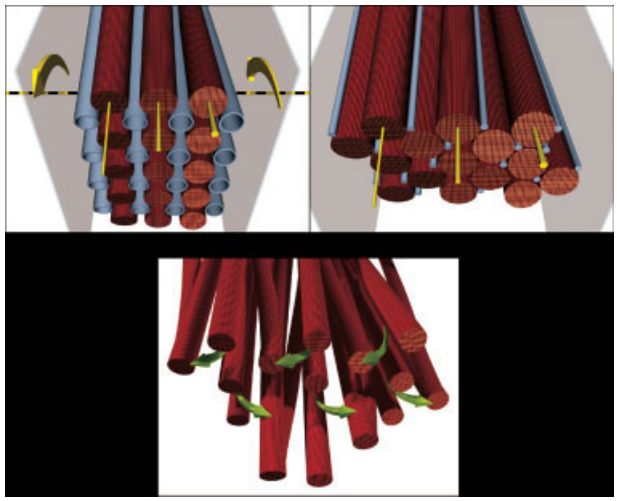

Fig. 6. Realignment of an aggregate of myocytes and their accompanying capillaries from diastole (upper left) to systole (upper right), with the epicardium paralleling the aggregates on their left and the endocardium on their right hand. In the lower panel, we display the potential interference of lateral offshoots, which have the capacity to temper, and hence control, both the alternate systolic interleaving and diastolic rearrangement of the myocytes. This basic mechanism is able to enhance systolic mural thickening independent of whether the myocytes are aligned parallel to the epicardium, or whether they intrude in the wall at variable angles to the epicardium.

notion now argue for a fully radial arrangement of the organized myocytic sheets within the ventricular walls (Hooks et al., 2002). In our own earlier review, which combined investigations using gross dissection and serial histological sectioning, we cautioned regarding the potential dangers of imposing oversimplified ideas on a complex biological structure (Greenbaum et al., 1981). It is not only those promoting the concept of the "unique myocardial band" (Torrent-Guasp, 1973), but also those promoting the existence of radial myocardial sheets (LeGrice et al., 1995; Karlon et al., 1998), who take no heed of these potential heuristic problems. Elsewhere in this issue of the journal, we have described our most recent study using histology, carried out in an attempt to provide the precision needed to understand the mechanics of ventricular contraction (Lunkenheimer et al., this issue). So as to place the controversies discussed above in context, and hoping to emphasize the morphologic approach required to resolve them, we now summarize our current understanding of the overall three-dimensional arrangement of the packing of the myocytes within the ventricular mass, showing how the architecture is arranged to permit the heart to function as a pump, but permitting the generation of antagonistic forces within the myocardial walls (Lunkenheimer et al., this issue).

BASIC STRUCTURE OF VENTRICULAR MYOCARDIAL MASS

When histological sections are cut across blocks of myocardial tissue removed from the ventricular mass (Fig. 4), it is immediately evident whether the sections have been taken in the plane of the long or short axes of the myocytes. Like the technique of peeling (Fig. 1), histologic sections reveal the obvious "grain" produced by the long axis of the myocytic aggregates. Care must be taken, however, when extrapolating between sections of the ventricular mass viewed using the microscope and those seen with the naked eye. Thus, the dissection shown in Figure 5, when viewed grossly, gives an unmistakable section of a radial rather than a tangential orientation of many of the myocytes. When studied more carefully using histologic sections, the greatest number of myocytes within the aggregates are still found to be running more or less in the tangential plane. There is potential danger of misinterpretation, therefore, if presumptions of global ventricular structure are based on examination of gross dissections, or of isolated microscopic sections removed from the ventricular wall (Feneis, 1944–1945).

When correlations are made between the gross and microscopic findings, no evidence emerges to support the notion that the fibrous matrix of the myocardium is arranged so as to produce reproducible secondary or tertiary patterns. Instead, each myocyte is wrapped within an endomysial weave, with adjacent myocytes joined together by endomysial struts. Small collections of myocytes are

then unified within a perimysial weave, with the entirety of the myocardial mass enclosed within the epimysium (Borg and Caulfield, 1981). There is marked variation nonetheless with regard to the degree of perimysial packing produced in different parts of the ventricular mass. The only recognized orderly arrangement of discrete isolation of collections of myocytes within the remainder of the ventricular walls is found subendocardially, where serial sections reveal the sheaths of fibrous tissue that ensure the continuity and discreteness of the right and left bundle branches of the ventricular conduction system.

When taking into account of the caveats expressed by Lev and Simkins (1956) as well as Grant (1965), therefore, we can see that the purported "unique myocardial band" (Torrent-Guasp, 1973) exists not because of a reproducible organized structure of the myocytes within a supporting fibrous matrix, but because of the skill of the dissector, who is able to sculpt from the myriad myocytes the pattern he wishes to display. Furthermore, histological sections taken to show the full thickness of the ventricular walls in man fail to demonstrate lamellar fibrous shelves extending from epicardium to endocardium, as was suggested by LeGrice et al. (1995). Yet, despite the lack of muscular tracts within the ventricular walls, and in spite of the relatively uniform nature of the fibrous matrix supporting the myocardial cells, it cannot be denied that there is some order in the arrangement of the myocytes (Pettigrew et al., 1864; Greenbaum et al., 1981). It is an appropriate understanding of this three-dimensional structure that is now needed to underpin the science of cardiodynamics (Criscione et al., 2005).

THREE-DIMENSIONAL PACKING OF MYOCYTES

In their attempts to provide a blueprint of a consistently simple basic ventricular structure, which can then be modeled in mathematical terms, Streeter and his colleagues focused their attention on restricted areas of the left ventricular free wall (Streeter and Bassett, 1966; Streeter et al., 1969; Streeter and Hanna, 1973). Having concentrated on those segments of the ventricular wall situated between the bases of the papillary muscles, they then presumed that their findings were equally applicable to the remainder of the ventricular mass. They paid scant attention to the papillary muscles themselves, or to the junction of the parietal walls with the septum. Much of current mathematical modeling of myocardial structure, based on the investigations of Streeter and his colleagues (Streeter and Bassett, 1966; Streeter et al., 1969; Streeter and Hanna, 1973), is based on data derived from histological investigations on perhaps 1/10 of the left ventricular myocardial mass. Even these data, as we have shown (Lunkenheimer et al., this issue), is further divorced from reality because, as a feature of their histological methods, these investigators underestimated the three-dimensional nature of the aggregated myocytes, failing to take note of myocytes orientated away from the planes parallel to the epicardial and endocardial surfaces. It is paradoxical in this respect that Streeter and colleagues emphasized the tangential orientation of myocytes, following the "conventional wisdom" as established by Frank (1901), namely, that all myocytes were orientated with their long axis parallel to the ventricular endocardial and epicardial surfaces. The more recent cadre of bioengineers, in contrast, promotes the concept that laminar fibrous sheets divide the ventricular walls in radial fashion.

In reality, any description of the architecture of the myocardium must address its most prominent feature, namely, the specific three-dimensionality to be discerned throughout the ventricular mass, but which can only be appreciated at gross rather than microscopic level. This requires detailed knowledge about disparities in segmental spatial meshing throughout the ventricular walls. At the macroscopic level, the question to be answered is whether the three-dimensional meshing itself merges to form reproducible and recognizable tertiary patterns within the ventricular walls. There is no convincing evidence to support this notion (Anderson et al., 2005). At the microscopic level, the question devolves on whether the perimysial sheaths extend in radial fashion from epicardium to endocardium. Once more, the evidence is unequivocal. There are no such continuous fibrous sheets compartmenting the ventricular walls into regularly arranged layers. The matter remains nonetheless as to how the ventricular walls thicken during systole.

ENIGMA OF SYSTOLIC VENTRICULAR MURAL THICKENING

In classical physiology, systolic mural thickening was deemed the main mechanism underscoring ventricular ejection (Spotnitz et al., 1974). Shortening of the ventricular cone from apex to base had been measured in the range of 10% or less (Rushmer, 1955). Only recently have Rademakers et al. (1992), using magnetic resonance tagging, called into question this perceived role of systolic mural thickening. Any mechanism invoked to explain such thickening must obey the laws of geometry. Any constriction of a thick-walled and hollow muscular cone, provided the volume of the ventricular wall remains constant over the cardiac cycle, must be associated with an increase in the thickness of its wall. This assumption is likely to apply, within narrow limits, to the heart (Guyton, 1963). The amount of mural thickening depends on the relationship between stroke volume and end-diastolic volume, and to the mural thickness at end-diastole. The thicker the wall becomes in the setting of ventricular hypertrophy, the more it thickens for any given end-diastolic filling, and for any increase in stroke volume. The larger the end-diastolic radius of the ventricle, the smaller the increase in mural thickness for any stroke volume and end-diastolic control thickness of the wall. The myocardial mass, however, as we have explained, is organized as a mesh of myocytes embedded in a scaffold of connective tissue. Mural thickening is part of an active process brought about by contraction, shortening, and thickening of the mesh. Myocytes in the middle part of the left ventricular wall have been calculated to shorten by just over 1/10 of their end-diastolic length at rest, this deformation being associated with a similar increase in their cross-sectional area, and half such increase in thickness (Spotnitz et al., 1974). Systolic thickening of the ventricular walls of between one- and three-fifths, therefore, cannot be achieved on the basis of summation of thickening of the overall number of myocytes aggregated together between the epicardium and the endocardium. Instead, changes in mural thickness are more likely to be related to the number of myocytes aligned across the wall, rather than to changes in their individual dimensions. Chains of axially coupled myocytes aligned side-by-side and parallel to the

ventricular surface must move in radial direction, with two adjacent rows of myocytes becoming three or four by alternate interleaving (Fig. 6). Such an arrangement is obviously facilitated by the perimysial packing of the myocytes, but it is simplistic to imagine that the perimysial fibrous strands are stacked in orderly fashion throughout the ventricular walls. Examination of sections taken through the full thickness of the ventricular wall reveals the marked anatomic heterogeneity.

STRUCTURAL HETEROGENEITIES

Contrary to the accounts given by Streeter and colleagues (Streeter and Bassett, 1966; Streeter et al., 1969) and LeGrice et al. (1995), myocardial architecture is far from homogeneous. In reality, marked heterogeneity is found in terms of angulation of the myocytes relative both to the equator of the left ventricle and to the epicardial surface lining. The most prominent aberration is seen at the apical vortex (Pettigrew, 1864). Further obvious deviations from the purported tangential alignment of the myocytes are seen at the basal margins of both ventricles (Greenbaum et al., 1981). The deviation becomes more pronounced deeper within the ventricular wall, as aggregations of myocytes can be traced in orderly fashion from subepicardium to subendocardium, while their long axes turn in opposite radial directions (Lunkenheimer et al., this issue). Extended areas of muscular heterogeneity are found at the bases of the papillary muscles, where the parallel fibers within the bodies of the papillary muscles coalesce with the spiraling musculature at the apex. In similar fashion, the sites of insertion of the right ventricular walls on the superior and inferior walls of the left ventricle and the septum show marked interdigitation of their myocytes. Little attention has been paid to the structure of the right ventricular wall, since physiologists have relegated right ventricular function to a secondary role (Gauer and Thron, 1965). Right ventricular structure is also far less regular when compared to its left ventricular partner. Only recently have pathomorphologists begun to investigate the structure of the right ventricular wall (Sanchez-Quintana et al., 1996).

FUNCTIONAL IMPLICATIONS OF STRUCTURAL HETEROGENEITIES

A contractile pathway that consists of aggregated myocytes generates a constant force all along its length, unless some of the forces are intercepted by offshoots aligned away from the long axis of the chain. The amount of contractile force engendered by a sequence of axially coupled myocytes is independent of the number of myocytes thus coupled in series. Yet, in an array of myocytes, the amount of maximally developed force increases proportionally to the number of myocytes acting in parallel. Strain, in contrast, in particular the maximal possible distance over which the chain can shorten, increases proportionally to the number of myocytes coupled in series.

Histology confirms that the "grain" made visible by gross dissection reflects the prevailing aggregation of myocytes. Although single myocytes are rarely aligned strictly parallel to the epicardial surface, their predominant orientation within the myocardium is more parallel to the epicardial lining, rather than being aligned in radial direction. Hence, the myocardium shortens most efficiently in the direction that parallels the epicardial surface, thus supporting ventricular ejection. While the myocytes shorten, the ventricle empties, its radius gets smaller, and the thickness of its wall increases. By direct measurements using needle force probes, we have shown that the afterload of the greatest population of myocytes decreases to produce an "unloading" type of force signal (Lunkenheimer et al., 2004). Myriads of short branches nonetheless cross between adjacent myocytes, with the obvious potential of linking them together. In so doing, these branches intrude in a direction from the epicardium toward the endocardium. The contractile force engendered by these short contractile bridges fuses to provide a measurable force directed in more or less radial orientation. Our investigations using force probes have revealed that those myocytes contract concomitantly with an augmentation of their developed force.

Thus, because the force generated by these myocytes increases while they contract, we describe it as being auxotonic, differentiating it in this way from the unloading forces, which are found in the setting of a decrementing afterload during contraction of the greatest population of myocytes aligned more parallel to the epicardium. The intruding population of cells needs much more investigation, with respect to both their structure and function.

Because the maximal deviation of these aggregates is not more than 45°, we believe that they need to work in concert with the supporting fibrous matrix so as to achieve the oblique deviation of forces required to control the amount and timing of regional mural thickening that is known to take place during systole. It is this control that determines the inner shaping of the ventricle, and hence the intracavitary resistance to flow. Furthermore, we opine that these myocytes constitute the major determinant of the cyclical realignment of the three-dimensional arrangement of cells, thus being involved in diastolic reopening of the ventricle, and in regional stabilization of ventricular shape. It is the existence of these intruding populations of myocytes that is in need of the attention of bioengineers, rather than the nonexistent laminar fibrous sheets that are purported to extend in continuous fashion from the epicardium to the endocardium (LeGrice et al., 1995; Hooks et al., 2002).

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