Structural–functional correlates of the 3-dimensional arrangement of the myocytes making up the ventricular walls

Robert H. Anderson, BSc, MD, FRCPath,^a Damian Sanchez-Quintana, MD, PhD,^b Peter Niederer, PhD,^c and Paul P. Lunkenheimer, MD, PhD^d

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From the Cardiac Unit,^a Institute of Child Health, University College, London, United Kingdom; the Department of Anatomy,^b Universidad de Extremadura, Badajoz, Spain; the Institute of Biomedical Engineering,^c University and ETH Zürich, Zurich, Switzerland; and Experimental Thoraco-, Heart and Vascular Surgery,^d University Hospital, Munster, Germany.

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Address for reprints: Robert H. Anderson, BSc, MD, FRCPath, Cardiac Unit, Institute of Child Health, 30 Guilford St, London WC1N 1EH, United Kingdom (E-mail: r.anderson@ich.ucl.ac.uk).

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“There is always an easy solution to every human problem—neat, plausible and wrong.”

—Henry Louis Mencken. *New York Evening Mail*; November 16, 1917; later published in *Prejudices: Second Series* (1920), and *A Mencken Chrestomathy* (1949)

The aphorism from Mencken, which we have chosen as the header for our review, is particularly pertinent to the ongoing controversies regarding the anatomic arrangements of the myocytes that make up the ventricular mass. The 3-dimensional architecture of these cells has fascinated anatomists for centuries. Despite multiple investigations, it has proved difficult to relate the presumed anatomic arrangements to function so as to adequately explain the contractions that produce the forces driving the systemic and pulmonary circulations. In particular, it has been difficult to explain why, although the individual myocytes thicken by only one sixth as they shorten, the ventricular walls made up of the aggregated myocytes thicken by an appreciably greater proportion during systole. Most anatomic investigations, exemplified perhaps by the detailed study of Pettigrew,¹ have shown that the long axis of the aggregated myocytes changes in angulation relative to the ventricular equator at different depths within the ventricular walls. In recent years, at least 2 alternative concepts of myocytic aggregation have come to the fore, although neither has been substantiated by independent anatomic investigation. One of these concepts is based on the premise that radial fibrous lamellas interpose between ordered layers of myocytes, permitting them to slide between each other during the process of systolic thickening of the ventricular walls.^{2,3} A cartoon used to illustrate this concept, however, shows the lamellas extending uniformly from the epicardium to the endocardium.¹ Any examination of a histologic section across the thickness of the ventricular wall is sufficient to show that there is no support for this particular notion. Such examination also shows that there is no order in the arrangement of the supporting fibrous matrix sufficiently regular to segregate the walls into uniform myocardial sheets.

It is the other concept, equally spurious in our opinion, that has received greater attention in the surgical literature. Thus over the past few years, multiple articles have been published to support the notion that the ventricular myocardium is arranged in the form of a “unique myocardial band.”⁴⁻⁷ The concept itself stems from the work of Torrent-Guasp, who initially published his ideas in a book written in Spanish.⁸ To the best of our knowledge, the evidence supporting the notion has never subsequently been submitted to peer review, nor has the concept received support from any independent investigator. On the other hand, numerous groups, including ourselves,

have emphasized the anatomic findings that militate strongly against the hypothesis.⁹⁻¹³ Despite this strong body of evidence contradicting the notion of the unique band, it is perhaps surprising that those cardiac surgeons who now proselytize the notion have neglected to conduct their own histologic studies so as to validate the findings thus far obtained exclusively from dissection. As was pointed out long since by Grant,¹⁴ in a perceptive review of the problems facing those who seek to understand the structure of the ventricular mass, those dissecting the myocardium after denaturation with heat are able to produce precisely the patterns they wish to demonstrate simply because of the intricate 3-dimensional weave of the myocytes set in their supporting matrix of fibrous tissue. The process of dissection, however, destroys the initial 3-dimensional arrangement.

In this review we will recapitulate the evidence showing that the myocardium is arranged on the basis of a modified blood vessel rather than possessing components that have origins and insertions, as is the case for the skeletal musculature.¹⁵ We will then discuss how the 3-dimensional arrangement of the myocytes, with the majority oriented with their long axis tangential to the epicardial and endocardial surfaces but with some intruding so that their long axis is inclined more toward a radial orientation, is such as to explain the well-recognized dualistic function of the ventricular mass.¹⁶⁻¹⁸ In producing our review, we should also emphasize that we are combining the findings from investigators with diverse backgrounds. On the one hand, the anatomists (RHA and DSC) have spent a lifetime studying the structure of the heart. The anatomic investigations, however, are integrated with the physiologic observations of our other colleagues (PN, PPL), who has dedicated his career to the elucidation of cardiodynamics. Thus our review represents the synthesis of those who have studied personally both the structure and function of the myocytes making up the walls of the ventricular chambers of the heart.

Basic Structure of the Ventricular Mass

Histologic examination of the myocytes making up the bodily tissues shows that there are 3 specific types. The skeletal musculature is composed of striated syncytial cells that are under voluntary control. For the most part, these muscles have specific origins and insertions. In the case of the tongue, however, the myocytes intermingle within its substance, their long axes crossing each other to produce the obvious "grain" that becomes visible when the organ is prepared for human consumption.¹⁹ In contrast to the skeletal muscles, which contract in response to voluntary actions, the musculature of the bodily organs and the blood vessels is made up of multiple individual myocytes lacking obvious cross-striations. Within the walls of these organs and vessels, it remains possible to discern an overall alignment of the long axes of the smooth myocytes, with some oriented in a circular fashion and others having a longitudinal orientation. The cardiac

myocyte is intermediate between the extremes of the skeletal and smooth variants. Although possessing obvious cross-striations within each myocyte, the cells themselves being joined together at the ends and also through side linkages, the myocytes are not arranged in the form of a syncytium. Therefore each cardiac myocyte retains its individual function as a component of an endless and branching chain. Nor are the cardiac myocytes under voluntary control. Instead, the activation of the cardiac myocytes is governed by the so-called conduction tissues. Each cardiac myocyte is able to conduct and indeed must conduct by itself so as to produce synchronous cardiac activity. The cardiac impulse, or activation, nonetheless is generated by a specialized group of myocytes known as the sinus node and is delayed at the atrioventricular junctions by the second group of specialized myocytes, which forms the atrioventricular node. The cardiac impulse is then disseminated to the ventricular myocytes through the only system within the myocardium that is insulated from the neighboring areas, namely the atrioventricular conduction axis.²⁰ Unlike the cells of the conduction axis, which can be readily discerned as forming insulated tracts and which have an obvious beginning within the atrioventricular node and an end in the Purkinje network, the remainder of the ventricular walls is made up of an intricate 3-dimensional arrangement of myocytes set within a supporting fibrous matrix and fed by vessels, nerves, and lymphatics (Figure 1). Therefore the basic "building block" making up the ventricular walls is the myocyte. Significantly, there is no ordered packing of individual myocytes into recognizable anatomic units that could legitimately be described as secondary or tertiary arrays. Hence it is impossible to dissect fibers as functional entities from within the ventricular walls. It is nonetheless possible to recognize the overall orientation of the long axes of the myocytes because each individual myocyte is appreciably longer than it is wide (Figure 1). As we have already discussed, as each myocyte shortens during ventricular contraction, it does so in the mean by no more than 15% of its overall length. During ventricular systole, however, the walls increase by appreciably more than 15% of their thickness. Therefore the paradox for cardiodynamicists has been to explain how this limited shortening of the individual myocytes can adequately explain ventricular mural thickening.

Alignment of the Myocytes within the Ventricular Walls

The simple process of removal of the epicardial fat from the surface of the ventricular mass reveals an unequivocal "grain" to the myocardial architecture (Figure 2, A). When viewed from the aspect of the ventricular base, this process also reveals the helical arrangement of the myocytic arrays as they spiral into the atrioventricular valvar orifices (Figure 2, B). As already emphasized, the apparent units revealed in this fashion have no independent anatomic identity,

Figure 1. The histologic section (*left*) shows the overall structure of porcine ventricular myocardium. The wall is made of individual myocytes, each much longer than it is wide, set in a supporting matrix of fibrous tissue. It is not possible to recognize discrete anatomic units made up of given numbers of myocytes. The scanning electron micrograph (*right*) prepared from human myocardium shows the structure of the supporting collagenous matrix. There is no uniform repeating pattern of the thicker components within the matrix, so that the myocytes themselves are the only units that can be recognized as individual entities.

nor is it possible, simply by making gross dissections, to ascertain the arrangement of the individual myocytes. Histologic sectioning of strands pulled from the ventricular surface does reveal that the orientation of the myocytes, by and large, is parallel to the long axis of the removed strand.²¹ As demonstrated exquisitely by Pettigrew,¹ it has long been known that, as more and more of the ventricular walls are peeled away, the long axis of the units visible to the dissector change markedly in their orientation relative to the equator of the ventricular cone (Figure 3).^{22,23}

The potential significance of this change in angle relative to the ventricular equator, known as the helical angle, came to prominence with the investigations of Streeter and colleagues.^{22,23} Nonetheless, Streeter and colleagues were of the opinion that all of the myocytes, although changing their helical angle at different depths within the ventricular walls, were oriented in tangential fashion relative to the epicardial and endocardial ventricular surfaces. This presumption that all myocytes were aligned in tangential fashion stemmed from the work of Frank,²⁴ who, when discussing the inter-

relationship of structure and function stated, in our translation from the original German text: "The longitudinal direction of the myocardial fibers must generally be tangential with respect to the ventricular surface. If these fibers were in a normal direction to the wall surface, their shortening would induce ventricular dilation rather than a reduction in ventricular volume...." All of these studies are pertinent because even if note is taken only of those myocytes oriented with their long axis parallel to the ventricular surfaces, they provide sufficient evidence to dismiss immediately the notion of the "unique myocardial band." This is because within the left ventricle, the majority of the tangential myocytes are aggregated so as to encircle the ventricular cavity, producing the "triebwerkzeug," or "driving force," for ventricular contraction emphasized by von Krehl.²⁵ Therefore the larger part of the ventricular septum belongs to the left ventricle, as shown by the earlier dissections, validated by histology, carried out by Greenbaum and associates.¹⁰ It is hardly surprising that evidence emerges to support the existence of parts of the purported unique band. The hypothesis underlying the notion of

Figure 2. These dissections of human hearts have been made by removing the epicardial fat and dissecting along the long axis of the myocytes, so as to reveal the overall "grain" of the cells as they are aggregated together within the supporting fibrous matrix. The *left panel* shows a frontal view, whereas the *right panel* shows the helical arrangement of the aggregated myocytes at the base of the left ventricle.

Figure 3. The drawings are taken from the work of Pettigrew¹ and show his dissections of the sheep heart. The orientation of the long axis of the aggregated myocytes can be seen to change markedly at different depths within the ventricular wall, each drawing representing an increasing depth of dissection. It was this changing angle that Streeter and colleagues^{22,23} subsequently emphasized as the "helical angle."

the unique band, however, is that it exists as an entity. It cannot exist in part, and it does not exist as a continuous entity.

If we are properly to explain ventricular cardiodynamics, we must also question the assertion that all myocytes are oriented with their long axis tangential to the ventricular surfaces. As long ago as the beginning of the 19th century, Brachet²⁶ had suggested an ingenious mechanism to explain diastolic movement of the ventricular walls. He had argued that the larger part of the myocardium was arranged so as to promote ventricular ejection but that a separate component of ventricular myocytes, oriented in a radial direction, existed to sustain ventricular dilation. Because we now know that local measurements of force within the ventricular walls show that different parts of the heart respond in different fashions to inotropic interventions and to changes in preload and afterload,¹⁶⁻¹⁸ there is much to support the notion put forward by Brachet²⁶ for dualistic ventricular function. Against the concept is the fact that previous studies of myocardial architecture had signally failed to identify any collections of myocytes oriented with their long axis from the epicardium to the endocardium. In other words, they had failed to show any radial component of the ventricular mass. To a large extent, this was because, with the changing helical angle of the myocytes within the depth of the ventricular walls, it was difficult to measure the long axis over significant distances relative to the radial axis. We have now overcome this difficulty by cutting full-thickness sections of the ventricular walls with circular knives. When these sections are analyzed histologically, 2 important facts are revealed. First, although there is no anatomic layering within the walls, neither are there any ordered fibrous shelves that compartment the wall in radial fashion; the myocytes are packed together within the fibrous matrix such that they show a regular pattern (Figure 4). When

the long axis of the myocytes is measured relative to the plane from the epicardium to the endocardium, a proportion of the cells are found to be oriented with their long axis inclined at angles of up to 35° relative to the epicardial plane.²⁷ These patterns are reproduced throughout the ventricular walls, although there is no organization of the supporting fibrous matrix that permits the overall weave to be unraveled so as to produce an anatomically determined unique band.

Is It Possible to Produce a "Unique Myocardial Band"?

The answer to the above question is an unequivocal yes. But by the same token, the ventricular mass, because of its composition of a 3-dimensional weave of myocytes set within a supporting fibrous matrix, can be unraveled to produce any band, as determined by the dissector. Thus Torrent-Guasp chose to unravel the ventricular mass so that the myocytes seemed to take their origin from the pulmonary trunk and ended at the aorta (Figure 5, A). It is equally possible to unravel the myocardial mass so that the band extends from the mitral orifice to the tricuspid orifice or from the apex of the right ventricle to the apex of the left ventricle. Therefore the question is not whether the ventricular mass can be unraveled but rather whether the band thus produced has any functional significance. Functional correlates can be examined by studying the overall orientation of the individual myocytes within the unwrapped band. If the array was truly of functional significance, then all the myocytes would follow the orientation of the band. When unraveled in the fashion suggested by Torrent-Guasp, it is certainly the case that, in different parts of the band thus produced, the myocytes are aligned parallel to the long axis of the band. When judged as an entirety, however, there is no overall consistency of

Figure 4. These full-thickness sections of porcine ventricular walls have been punched out with pairs of circular knives of varying diameter, stained histologically, and then marked with Indian ink to reveal all the myocytes sectioned specifically along the long axis. It can be seen that there is a reproducible pattern of alignment of the myocytes that changes its angulation, depending on the diameters of the knives used to punch out the sections. This pattern is reproduced to a varying extent throughout the ventricular walls.

packing (Figure 5, B). Furthermore, when we consider the pattern of ventricular activation, we know that the overall sequence is for each ventricle to contract sequentially and relatively synchronously from the apex to the base.

Figure 5. The preparation to the left has been made by unwrapping the freshly excised porcine ventricular mass so as to produce the "unique myocardial band," as described by Torrent-Guasp. Only then did we denature the band using heat and carried out blunt dissection to reveal the orientation of the long axes of the myocytes at various depths within the band. As can be seen by the cartoons to the right, showing the various depths, there is no uniformity of packing of the myocytes along their long axes, but rather the angulation of the aggregated myocytes changes at different depths within the ventricular walls.

The myocytes within the walls themselves show a temporal sequence of activation from endocardium to epicardium, with the initial activation being triggered by the ventricular conduction tissues. This sequence of activation obviously bears no resemblance to the structure of the purported unique band. If we then examine the contraction of the individual parts of the ventricular walls, we find that they also contract with relative synchronicity, although shortening of the myocytes and regional thickening of the wall has long been known to occur with some delay.²⁸ At all events, the observed sequence of mural thickening has no resemblance to contraction along a unique myocardial band. Thus it is certainly possible to produce multiple unique bands, but as yet, there is no evidence available to show that these configurations have any functional significance and much evidence to show that such arrangements would not have any mechanical value.

How Do We Account for Systolic Mural Thickening?

As we have stressed, it is well established that when the left ventricle contracts, its volume decreases by 50% or more. It is also known that when the individual myocytes shorten as they contract, they do so by no more than 15%. Therefore it follows that the extent of systolic mural thickening cannot be explained simply on the basis of thickening of the aggregated individual myocytes during their contraction. It has also been known that since the observations of Lower in 1669,²⁹ ventricular contraction could be compared with "the wringing of a linen cloth to squeeze out the water." These problems were elegantly discussed by Ingels.³⁰ He showed that models based on the varying helical angle, as described by Streeter and colleagues,^{22,23} combined with the "triebwerkzeug" of von Krehl²⁵ provided a working solution for ventricular dynamics. He also showed that to fully to account for the generated tensions, it was necessary to invoke coupling of the individual myocytes by the struts of the supporting collagenous network (Figure 3). As he stated,

Figure 6. Model showing a potential mechanism for the cyclic realignment of the myocytes stacked between the epicardium and endocardium. The *upper panel* shows the array of the myocytes, represented by matchsticks, during diastole (*D*). The *lower panel* shows the postulated arrangement in systole (*S*). There has been realignment of the myocytes, with concomitant thickening of the ventricular wall.

“Elastic energy is stored in the collagen struts and weaves ... to aid in filling the next beat.”³⁰ Fully to explain the thickening of the ventricular walls, it is also necessary to postulate rearrangements of the individual myocytes relative to each other within the thickness of the walls. Thus as has been shown by Hort³¹ and Spotnitz and coworkers,³² the myocytes realign themselves within the thickness of the wall during systole such that up to 40% more are packed between the endocardium and the epicardium than is the case during diastole (Figure 6). This mechanism is also that postulated by the Auckland school in their various publications.^{2,3} We endorse their notion of repacking of the myocytes, but we cannot support their claim that this is achieved on the basis of uniform radial fibrous shelves extending from the epicardium to the endocardium, as shown in their simplified cartoon.² As we have already emphasized, the overall arrangement of the collagenous matrix is far from orderly and certainly not arranged, at least in the human heart, so as to produce uniform radial sheets of comparable thickness extending from the epicardium to the endocardium. The so-called

“feathering” of the ventricular walls, as seen in short-axis sections and described by Feneis³³ and readily evident in the illustrations of Greenbaum and colleagues,¹⁰ is also incompatible with the concept of continuous clefts existing between myocardial sheets and extending from the epicardium to the endocardium. Additional evidence is now emerging from so-called tracking of the myocardial aggregates with diffusion tensor magnetic resonance imaging. This technique validates the concept of a 3-dimensional myocardial mesh but produces images that are exceedingly difficult to explain on the basis either that the myocardium is arranged either in the form of a unique myocardial band or orderly sheets stacked in a radial fashion (Figure 7).

Dualistic Function of the 3-Dimensional Myocardial Weave

The presence of a 3-dimensional netting of the ventricular myocardial mass that gives rise to tangential, as well as radial, forces seems paradoxical in an organ that is assumed to be designed so as to eject blood during systole and then to be filled passively by virtue of the filling pressure of the vascular bed. It is well established in basic physiology, however, that biphasic ventricular motion comprises a balanced, low-resistance systolic constriction of ventricular cavity, followed by an early diastolic fast dilation, thus preserving ventricular size and shape through the normal lifespan. Our researches¹⁷ show that this intricate pattern of motion requires the action of 2 opposing forces. The first is sustained by a population of myocytes with prevailing tangential alignment relative to the walls, which uniquely constricts the cavity. The second smaller force is produced by a population of myocytes oriented obliquely from the epicardium to the endocardium, which act in concert with the supporting matrix of connective tissue. The force vector produced by this second population supports ventricular constriction while also acting to support ventricular dilation. The pivotal mechanism necessary to sustain such antagonism is the heterogeneous presence of auxotonic contractions, which we have correlated with the similarly heterogeneously distributed population of myocytes oriented obliquely from the epicardium to the endocardium.¹⁷

Auxotonic contraction accounts for the force produced by the myocardium as it contracts against an increasing afterload, with the oblique transmural population of myocytes supplying these forces as it contracts against the systolic increment in mural thickness.¹⁷ The larger proportion of myocytes within the ventricular mass is aligned more or less parallel to the epicardial surface, and they produce the unloading forces. These myocytes, although contracting, obey the law of Laplace, so that their loading decreases while the mural radius decreases, the mural thickness increases, and the left ventricular pressure achieves a plateau. This decrease in developed forces has been confirmed by means of direct measurements performed both in various laboratory

Figure 7. The images are produced by tracking the myocardial aggregates in the ventricular mass of the pig by means of diffusion tensor magnetic resonance imaging. Starting from a seeded area, segments of aggregated myocytes are concatenated voxel by voxel while observing a defined set of algorithmic rules of continuation. Similar pictures are obtained when other areas are chosen for seeding. The findings are entirely compatible with the notion that the myocytes are aggregated together in the form of a 3-dimensional mesh in that it is possible to trace a continuous and uninterrupted trajectory between pairs of points selected arbitrarily within the myocardial mass. This property cannot be explained either on the basis of a "unique myocardial band" or sheets stacked in radial fashion within the ventricular wall.

animals^{16,17} and more recently in patients undergoing cardiac surgery.¹⁸

Therefore it is surely significant that when measured specifically in their long axis, it has been shown that about one third of the myocytes within the left ventricular myocardium intrude within the left ventricular wall at various angles from the epicardium toward the endocardium, some achieving angulations of up to 40°. ³⁴ The forces engendered by those myocytes are able, with one vector, to sustain tangential ventricular constriction, while with a smaller vector, they oppose systolic mural thickening. Clinical data³⁵ suggest that the supporting fibrous matrix, particularly when the myocardium is abnormally fibrotic, assists in deviating the generated forces from a tangential to an oblique direction. We also have confirmed through direct measurements¹⁷ the resulting increase in developed forces during ventricular ejection in the population of myocytes intruding obliquely from the epicardium toward the endocardium. The resulting auxotonic, or augmenting, forces become more pronounced the more the local myocardial weave is inclined toward the endocardium. The most outstanding feature of such myocytes contracting auxotonically is that they maintain their actions for longer periods than do those myocytes that are unloaded during contraction. This prolongation of contractile activity can extend by more than 100 ms when compared with the contractions of the myocytes producing unloading forces, depending on the degree of their intrusion, and hence the amount of augmentation of contractile force.¹⁷ With perfection of ventricular emptying, mural thickening has reached its regional maximum. Constricting forces then decrease, whereas auxotonic

forces are on the verge of reaching their maximum. Only at this stage does the population of intruding myocytes within the 3-dimensional myocardial mesh become able to shorten to its maximum. This shortening is then directed more-or-less toward active thinning of the wall and hence toward early diastolic ventricular dilation, which sustains the first impetus of ventricular filling.¹⁷

On the basis of our proposed concept, both ventricular structure and function are organized in an antagonistic fashion. Myocardial activation is ubiquitous and almost synchronous, with a maximal delay of 60 ms within the ventricular mass.³⁶ The prevailing mass of myocytes oriented tangentially to the ventricular wall is able to shorten instantly after opening of the aortic valve, acting against a decremental load. Hence the myocytes arranged tangentially within the ventricular walls shorten early and extensively but have only a short period of activity, during which they bring about ventricular emptying. The population of myocytes oriented obliquely from the epicardium to the endocardium is activated synchronously, yet as mural thickness increases during ejection, the myocytes are hindered in their shortening while developing continuously incrementing forces. By their activity during ventricular ejection, they temper the thickening of the wall according to their angulation relative to the epicardium. In this way the population of intruding myocytes is able to control regional mural thickening. The narrower the ventricular cavity and the more pronounced the regional thickening, the more effective becomes the intruding population, supported and enhanced by its anchorage within the matrix of connective tissue. In this setting the action of the

augmenting auxotonic forces will be greater. Concomitantly, their effect of tempering systolic mural thickening grows more pronounced. Although controlling mural thickening, the population of intruding myocytes also slows down tangential shortening.

Such holosystolic antagonism is a function of ventricular size. The smaller the ventricular cavity, the greater will be the tempering of systolic mural thickening required to preserve an unimpeded flow from the ventricular inflow to the outflow. This intramural antagonism is far from uniform throughout the left ventricular walls. Thus the motion is known to be delayed in a major fashion in the superior ventricular wall immediately above the ventricular apex.²⁸ This local phenomenon was misinterpreted by Torrent-Guasp⁸ to be the effect of late excitation, whereas Hammermeister and co-workers²⁸ rightly indicated that this region is subject to inter-regional contractile interaction, which leads in itself to delayed freedom of shortening.

We speculate that in the diseased heart with increased fibrosis, this primarily balanced intrinsic antagonism is likely to degenerate, eventually entering into a critical state of impediment of systolic mural thickening. The effect of fibrosis on cardiodynamics, however, is still fragmentary. We were able to show through direct measurements in patients that those forces produced by myocytes that antagonize systolic mural thickening are more sensitive, by a factor of two fifths, to β -receptor blockade than are the prevailing constrictive forces.³⁵ We suggest that this finding is of direct clinical relevance because it explains the basic mechanism of action of β -receptor-blocking agents on the failing heart and opens new pathways of understanding the state of hypocontractility. The hypocontractile ventricle, in particular cases, might be the consequence of extreme intrinsic antagonistic activity. Patients with such problems might profit from the asymmetric negative inotropism mediated by β -blockade, which tempers predominantly the antagonistic dilating forces.

Conclusions

Although there have been suggestions made recently that the ventricular myocardium is arranged either in the form of a unique myocardial band or else is organized as radial sheets, neither of these hypotheses has been validated by histologic studies nor is supported by the wealth of existing anatomic studies devoted to the architecture of the ventricular mass. Rather than showing the postulated secondary or tertiary patterns, histologic studies show that the ventricular walls are composed of an intricate 3-dimensional meshwork of myocytes set within a supporting matrix of fibrous tissue. Our own measurements of forces within the ventricular walls, validated themselves by detailed histologic studies, now show that there are 2 populations of myocytes within the 3-dimensional mesh. The prevailing population is oriented with the long axis of the myocytes aligned in tangential fashion

relative to the ventricular walls. This population produces the unloading forces responsible for ventricular emptying. Equally important, nonetheless, is the second population of myocytes oriented with the long axis at varying intruding angles from the epicardium toward the endocardium. This second population, ignored by most cardiodynamicists, produces auxotonic forces. It is the antagonism between the 2 sets of forces, in our opinion, which best explains the complex actions of the ventricular mass during ventricular systole and diastole.

References

1. Pettigrew JB. On the arrangement of the muscular fibres in the ventricles of the vertebrate heart, with physiological remarks. *Philos Trans.* 1864; 154:445-500.
2. Nielsen PMF, LeGrice IJ, Smaill GH, Hunter PJ. Mathematical model of geometry and fibrous structure of the heart. *Am J Physiol Heart Circ Physiol.* 1991;260:H1365-78.
3. LeGrice IJ, Smaill BH, Chai LZ, Edgar SG, Gavin JB, Hunter PJ. Laminar structure of the heart: ventricular myocyte arrangement and connective tissue architecture in the dog. *Am J Physiol Heart Circ Physiol.* 1995;269:H571-82.
4. Buckberg GD, Clemente C, Cox JL, et al. The structure and function of the helical heart and its buttress wrapping. IV. Concepts of dynamic function from the normal macroscopic helical structure. *Semin Thorac Cardiovasc Surg.* 2001;13:342-57.
5. Buckberg GD. Basic science review: the helix and the heart. *J Thorac Cardiovasc Surg.* 2002;124:863-83.
6. Buckberg GD. Architecture must document functional evidence to explain the living rhythm. *Eur J Cardiothorac Surg.* 2005;27:202-9.
7. Buckberg GD. Rethinking the cardiac helix—a structure/function journey: overview. *Eur J Cardiothorac Surg.* 2006;29(suppl):S2-3.
8. Torrent-Guasp F. Anatomía funcional del Corazón. Madrid: Paz Montalvo; 1957. p. 62-8.
9. Lev M, Simkins CS. Architecture of the human ventricular myocardium, technique for study using a modification of the Mall-MacCallum method. *Lab Invest.* 1995;8:306-409.
10. Greenbaum R, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J.* 1981;45:248-63.
11. Fernandez-Teran MA, Hurler JM. Myocardial fiber architecture of the human heart ventricles. *Anat Rec.* 1982;204:137-47.
12. Sanchez-Quintana D, Garcia-Martinez V, Hurler JM. Myocardial fiber architecture in the human heart. Anatomical demonstration of modifications in the normal pattern of ventricular fiber architecture in a malformed adult specimen. *Acta Anat.* 1990;138:352-8.
13. Sanchez-Quintana D, Anderson RH, Ho SY. Ventricular myoarchitecture in tetralogy of Fallot. *Heart.* 1996;76:280-7.
14. Grant RP. Notes on the muscular architecture of the left ventricle. *Circulation.* 1995;32:301-8.
15. Anderson RH, Ho SY, Sanchez-Quintana D, Redmann K, Lunkenheimer PP. Heuristic problems in defining the three-dimensional arrangement of the ventricular myocytes. *Anat Rec.* 2005;288A:579-86.
16. Lunkenheimer PP, Redmann K, Dietl KH, et al. The assessment of intramural stress alignment on the beating heart in situ using micro-ergometry: functional implications. *Technol Health Care.* 1997;5:115-22.
17. Lunkenheimer PP, Redmann K, Florek J, et al. The forces generated within the musculature of the left ventricular wall. *Heart.* 2004;90: 200-7.
18. Lunkenheimer PP, Redmann K, Kim Aun D, et al. A critical evaluation of results of partial left ventriculectomy. *J Card Surg.* 2003;18:225-35.
19. Gilbert RJ, Wedeen VJ, Magnusson LH, et al. Three-dimensional myoarchitecture of the bovine tongue demonstrated by diffusion spectrum magnetic resonance imaging with tractography. *Anat Rec.* 2006;288A: 1173-82.
20. Anderson RH, Christoffels VM, Moorman AFM. Controversies concerning the anatomical definition of the conduction tissues. *Anat Rec.* 2004;280B:8-14.

21. Lunkenheimer PP, Redmann K, Dietl KH, et al. The heart's fibre alignment assessed by comparing two digitizing systems. Methodological investigation into the inclination angle towards wall thickness. *Technol Health Care*. 1997;5:65-77.
22. Streeter DD Jr, Bassett DL. An engineering analysis of myocardial fiber orientation in pig's left ventricle in systole. *Anat Rec*. 1966;155:503-11.
23. Streeter DD Jr, Sponitz HM, Patel DJ, Ross J Jr, Sonnenblick EH. Fiber orientation in the canine left ventricle during diastole and systole. *Circ Res*. 1969;24:339-47.
24. Frank O. Isometrie und isotonie des Herzmuskels. *Z Biol*. 1901;41:14-34.
25. von Krehl L. Beiträge zur Kenntnis der Füllung und Entleerung des Herzens. *Abhandlungen der Mathematisch-Physischen Classe der Königlich Sächsischen Gesellschaft der Wissenschaften*. 1891;17:340-83.
26. Brachet JL. Sur la cause du mouvement de dilatation du Cœur [dissertation]. Paris: Imprimerie de Didot Jeune; 1813.
27. Lunkenheimer PP, Redmann K, Kling N, et al. Three-dimensional architecture of the left ventricular myocardium. *Anat Rec*. 2006;288A:565-78.
28. Hammermeister KE, Gibson DG, Huges D. Regional variation on the timing and extent of left ventricular wall motion in normal subjects. *Br Heart J*. 1986;56:226-35.
29. Lower R. Tractus de Corde. In: Gunther RT, ed. Early science in Oxford, vol. 9. Oxford (UK): Sawsons; 1968:1669.
30. Ingels NB. Myocardial fiber architecture and left ventricular function. *Technol Health Care*. 1997;5:45-52.
31. Hort W. Untersuchungen zur funktionellen Morphologie des Bindegewebsgerüsts und der Blutgefäße der linken Herzkammerwand. *Virchows Arch*. 1960;33:565-81.
32. Spotnitz HM, Sonnenblick EH, Spiro D. Relation of ultrastructure to function in the intact heart: sarcomere structure relative to pressure volume curves of intact left ventricles of dog and cat. *Circ Res*. 1966;18:49-66.
33. Feneis H. Das Gefüge des Herzmuskels bei Systole und Diastole. *Gegenbauers morphol Jb*. 1944/45;69:371-406.
34. Schmid P, Lunkenheimer PP, Redman K, et al. Statistical analysis of the obliquely intruding myocardial aggregates within the mammalian ventricular mass using magnetic resonance diffusion tensor imaging. *Anat Rec*. 2007;290:1413-23.
35. Lunkenheimer PP, Redmann K, Cryer CW, et al. Beta-blockade at low doses restoring the physiological balance in myocytic antagonism. *Eur J Cardiothorac Surg*. 2007;32:225-30.
36. Durrer D, van Dam RTh, Freud GE, Janse MJ, Meijler FL, Arzbaeher RC. Total excitation of the isolated human heart. *Circulation*. 1970;41:899-912.