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REVIEW

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What is the clinical significance of ventricular mural antagonism?

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Abstract

Recent morphological studies provide evidence that the ventricular walls are arranged as a 3D meshwork of aggregated cardiomyocyte chains, exhibiting marked local structural variations. In contrary to previous findings, up to two-fifths of the chains are found to have a partially transmural alignment, thus deviating from the prevailing tangential orientation. Upon contraction, they produce, in addition to a tangential force, a radial force component that counteracts ventricular constriction and aids widening of the ventricular cavity. In experimental studies, we have provided evidence for the existence of such forces, which are auxotonic in nature. This is in contrast to the tangentially aligned myocytes that produce constrictive forces, which are unloading in nature. The ventricular myocardium is, therefore, able to function in an antagonistic fashion, with the prevailing constrictive forces acting simultaneously with a dilatory force component. The ratio of constrictive to dilating force varies locally according to the specific mural architecture. Such antagonism acts according to local demands to preserve the ventricular shape, store the elastic energy that drives the fast late systolic dilation and apportion mural motion to facilitate the spiralling nature of intracavitary flow. Intracavitary pressure and flow dynamics are thus governed concurrently by ventricular constrictive and dilative force components. Antagonistic activity, however, increases deleteriously in states of cardiac disease, such as hypertrophy and fibrosis. ß-blockade at low dosage acts selectively to temper the auxotonic forces.

Keywords: 3D mural architecture • Contractility • Antagonism • ß-blockade

INTRODUCTION

The functional anatomy of the heart has stimulated the interest of researchers for centuries. Harvey's work from 1628, which established the combined circulatory character of the arterial and venous systems driven by a 4-chamber pump, was a seminal achievement. Harvey [1] postulated that ventricular emptying was driven by constrictive myocardial forces, whereas ventricular filling was considered to be exclusively dependent on the venous filling pressure. Centuries later, Brachet [2] conceived ventricular function as being based on active systolic ventricular emptying, followed by active diastolic ventricular dilation. He postulated the existence of cardiomyocytes aligned in a transmural fashion but provided no evidence for their existence. Pettigrew [3] demonstrated the complexity of ventricular mural architecture but again without observing components aligned in a radial fashion. Frank [4] subsequently presented the notion that ventricular forces were exclusively constrictive, arguing that such forces were generated by cardiomyocytes aggregated in strictly tangential fashion.

Although subsequent histological studies by Feneis [5] provided evidence to support the idea that some aggregates of cardiomyocytes extended in a transmural direction, the studies by Streeter *et al.* [6] have served to entrench the notion that, if any cardiomyocytes deviated from the tangential arrangement, they did so to a limited degree. Accordingly, Sonnenblick *et al.* [7] when formulating the concept of contractility suggested that the velocity of shortening of all myocardial contractile elements could be derived from the velocity of the rise in intracavitary pressures. Although subsequently shown to have limited validity, and to be in need of substantial revision, this concept has continued to underpin various mathematical models [8, 9]. Arts *et al.* [8], for example, in building their model, presumed the presence of homogeneous and equilibrated stresses throughout the ventricular walls. In contrast to this approach, Brutsaert *et al.* [10, 11] promoted the notion of a heterogeneous distribution of mural stress.

In the following manuscript, we summarize the structural and functional findings that permit a comprehensive description of myocardial functionality. In particular, we emphasize the findings with regard to the existence and significance of transmurally

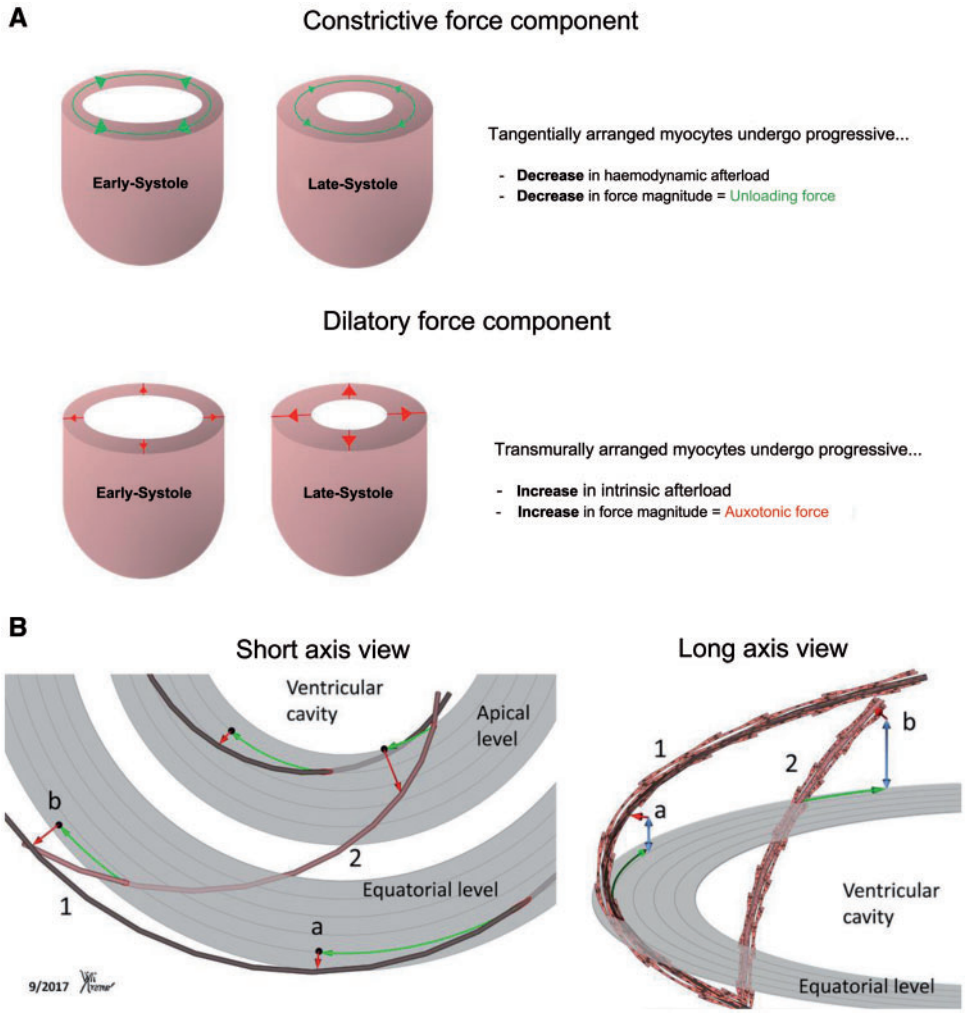

Figure 1: The relationship between myocyte orientation, loading conditions and force production. Chains of cardiomyocytes produce constrictive (green arrows), dilatory (red arrows) and longitudinal force (blue arrows). (**A**) Change in force magnitude of the constrictive and dilatory force components from early systole to late systole related to myocyte orientation and loading conditions is shown. (**B**) Transmurally arranged chains of myocytes produce predominantly constrictive forces (green and blue arrows) which are unloading in nature. To a lesser extent, they produce dilatory forces (red arrows) that are auxotonic in nature. The relationship between constrictive and dilative forces is the function of the angle of inclination of the chains 1 and 2.

oriented chains of cardiomyocytes within the ventricular walls [12–15]. Such entities have been shown to produce radially oriented force components, which act in an antagonistic fashion with respect to the dominating tangential constrictive forces (Fig. 1). We elaborate on the potential impact of these antagonistic forces on cardiodynamics, along with their potential clinical consequences. These forces are decisively smaller than the tangential constrictive forces. While opposing systolic mural thickening to a certain extent, they are auxotonic in nature, and last longer than the unloading forces.

TOWARDS ELUCIDATING THE STRUCTURE OF THE VENTRICULAR WALLS

The ventricular walls are composed of chains of cardiomyocytes connected together in an end-to-end fashion. In combination with the dense endomysium, myocytic branches serve to aggregate the individual cardiomyocytes into units described as lamellae or sheets [13, 16–27, 28]. These aggregated units of cardiomyocytes are markedly heterogeneous in dimension and shape [25–27] and are separated from one another by the loose perimysial spaces within the fibrous matrix [18–20]. It is the looseness of the perimysial packing that allows for rearrangement of the units during systolic mural thickening [5, 19]. Some of the units, however, deviate from the prevailing tangential orientation of the majority of the cardiomyocytes (Figs 1 and 2).

Histology

Streeter *et al.* [6], using histological techniques to investigate the orientation of the lamellar aggregates, cut the sections in tangential fashion. Deviations of the chains of myocytes in the transmural direction are thus obscured by the change in helical angulation. We reasoned that it would be possible to compensate for the change in helical angulation by cutting blocks from the ventricular walls using semicircular knives [12]. The use of this technique revealed the existence of chains of cardiomyocytes extending to varying degrees in a transmural fashion (Fig. 3). Such transmural chains were most abundantly found in the subendocardial component of the wall, with some of the chains

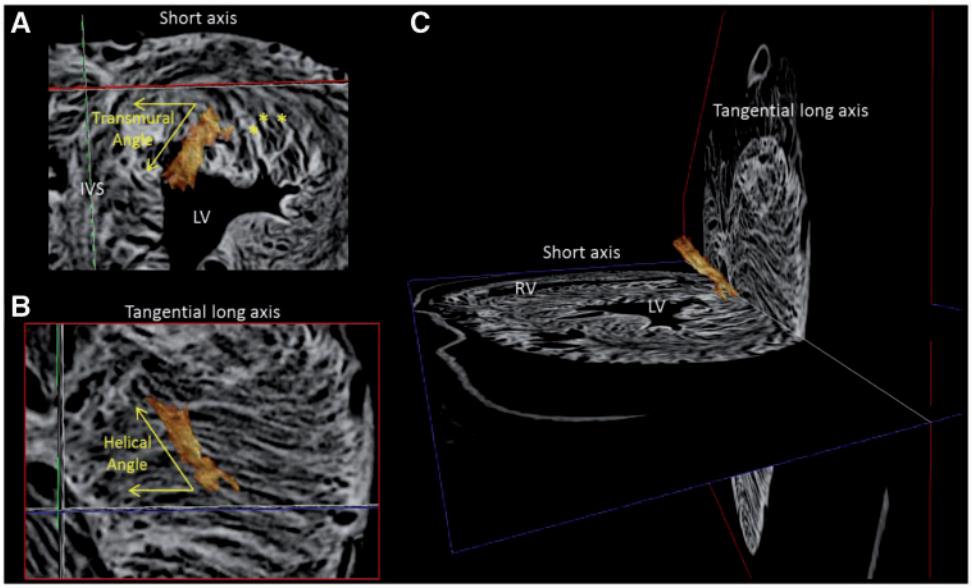

Figure 2: A 3D rendering of an aggregated unit of cardiomyocyte chains. (**A**–**C**) An aggregated unit (orange) segmented from computer tomography data of a pneumatically distended pig heart is shown [28]. The unit has a transmural angle; in other words, the angle between the myocyte chain long axis and tangential long axis plane was 24° (**A**) and the helical angle between the myocyte chain long axis and the short axis plane was 44° (**B**). (**A**) The asterisks indicate individual aggregated units as viewed in the short-axis plane. Whole heart dimensions ~6 cm × 6 cm. LV: left ventricle; RV: right ventricle.

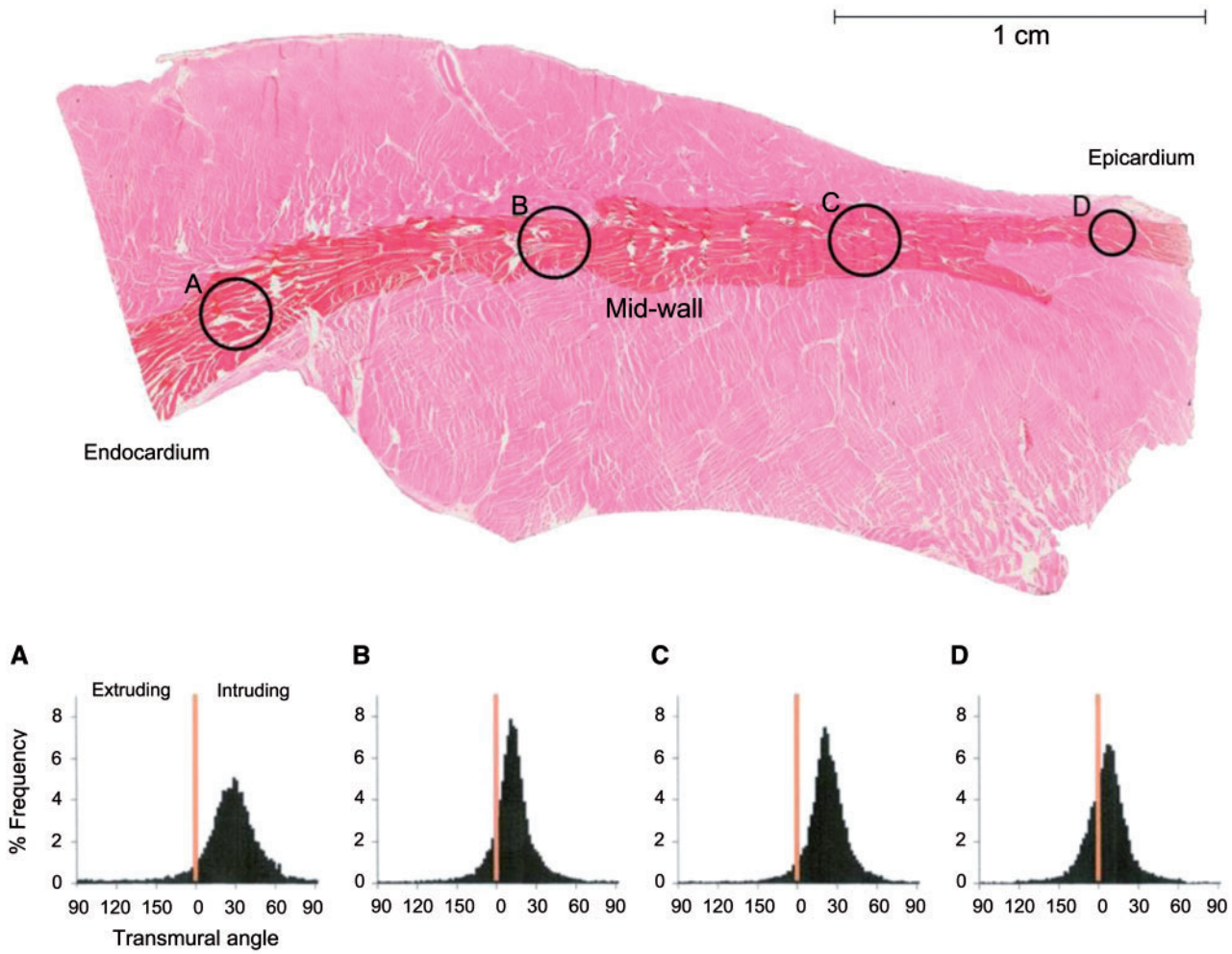

Figure 3: Myocyte orientation investigated using circular knives. The figure shows the percentage of distribution of angles of intrusion and extrusion of lamellar aggregates at 4 sites across the left ventricular wall (dark red marked) of a porcine heart in which the long chains of myocytes are aligned parallel to the circular knife section plane. The angles were measured by a computer-aided automatic system, as previously described [12] Here, the cardiomyocytes extending in transmural fashion accounted for two-fifths of the overall number, with the remaining three-fifths being aligned more or less tangential to the epicardial surface. **A**–**D**: sites of measurements between endocardium and epicardium.

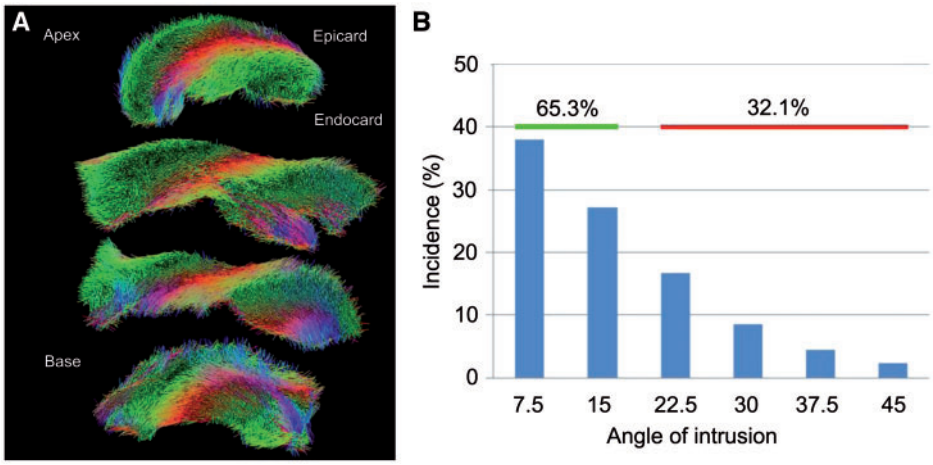

Figure 4: Myocyte orientation investigated by diffusion tensor magnetic resonance imaging. The figure shows the relative number of transmurally orientated lamellar aggregates (*Y*-axis) and their respective angulation (*X*-axis) as measured in 10 porcine hearts. Four transmural myocardial slices were harvested using circular knives from the basal (lower image), upper equatorial, lower equatorial and near apical (upper image) level of a porcine ventricle. Slices were embedded in agar–agar and imaged using diffusion tensor magnetic resonance imaging (**A**) [14]. The red marked zones indicate the long chains of myocytes that have been sectioned longitudinally using this technique. In these regions, the cardiomyocytes extending in transmural fashion (red bar) accounted for one-third of the overall number, with the remaining two-thirds being aligned more or less tangential (green bar) to the epicardial surface (**B**).

showing transmural angulations of between 30° and 40°. In hearts fixed in the systole, angles in excess of 40° were observed. Nonetheless, other investigators have failed to find evidence for the existence of myocytic chains with significant transmural angulation [19, 20]. Future studies will clarify the extent to which different histological techniques are responsible for these persistently different perceptions of the 3D alignment of the aggregates and the cardiomyocytes they house.

Diffusion tensor imaging

We subsequently used diffusion tensor magnetic resonance imaging to visualize the orientation of the chains as revealed in the blocks cut with circular knives [14]. These studies confirmed our initial histological findings [12, 13]. Further studies using diffusion tensor imaging then endorsed the model based on a 3D cardiac mesh [15], again revealing marked heterogeneity within the different parts of the ventricular cone (Fig. 4).

Pneumatic distension of the heart

To further assess the global nature of this variability, we injected compressed air through the coronary arteries of porcine and bovine hearts, thus pneumatically distending the loose perimysial spaces and making the aggregated units and their associated myocytic connecting branches clearly discernible. When imaged using computed tomography, sequential viewing of the short-axis tomograms revealed a complex structural pattern [28, 29]. Ascending subepicardial and descending subendocardial aggregates are connected by a heterogeneously distributed mid-mural circumferential zone. The complexity of branching means the aggregates are interconnected transmurally. The resulting cardiac mesh forms a continuum, which is seen to rotate in the opposing direction about the ventricular long axis. The aggregated units, therefore, display a wide range of orientations, with the contained cardiomyocytes exhibiting not only helical but also transmural angulations (Figs 2 and 3) [13–15, 27]. The mean orientation of the chains of individual cardiomyocytes follows the long axis of the aggregated unit in which they are housed. Segmentation of a transmurally orientated aggregate is presented in a 3D form in Fig. 2.

Local force measurements

Contractile forces generated by the prevailing number of tangentially orientated chains of myocytes have an almost exclusively constrictive effect. Those exhibiting a significant transmural orientation, be it intruding or extruding, have both a constrictive and a radial effect. As they sustain mural thinning, they produce a dilatory force component. Figure 1A and B shows the force vectors produced by tangentially and transmurally orientated myocyte chains, respectively. The relative ratio of dilating to constrictive force components varies locally according to the topical prevalence of angles of intrusion or extrusion. By making direct measurements using needle force transducers in animal experiments [30], as well as in human patients during cardiac surgery, we confirmed the presence of 2 types of force signals (Fig. 5). The 'unloading' signal decreases during systole, acting in a constrictive direction. In contrast, the 'auxotonic' signal increases during systole and acts in a dilatory direction (Fig. 1). We described these latter forces as auxotonic because the myocytes producing them are confined in shortening or even become elongated during mural thickening. The aggregated cardiomyocytes that are aligned tangential to the ventricular surface are free to shorten when the ventricle empties and hence generate an unloading signal.

In accordance with the increased concentration of intruding myocardial aggregates towards the endocardium [12–15, 23, 24], we found the auxotonic signals to be most prevalent in the deep subendocardial layers. The unloading signals prevailed in the epicardial layers [30] (Fig. 6). This pattern is not altered in hypertrophic hearts. In normal control hearts, furthermore, we found a gradient in maximal force from base to apex, with maximal force observed at the base. We also observed a transmural gradient, with maximal forces confined to the epicardial and endocardial layers and minimal forces peaking mid-murally. The gradients

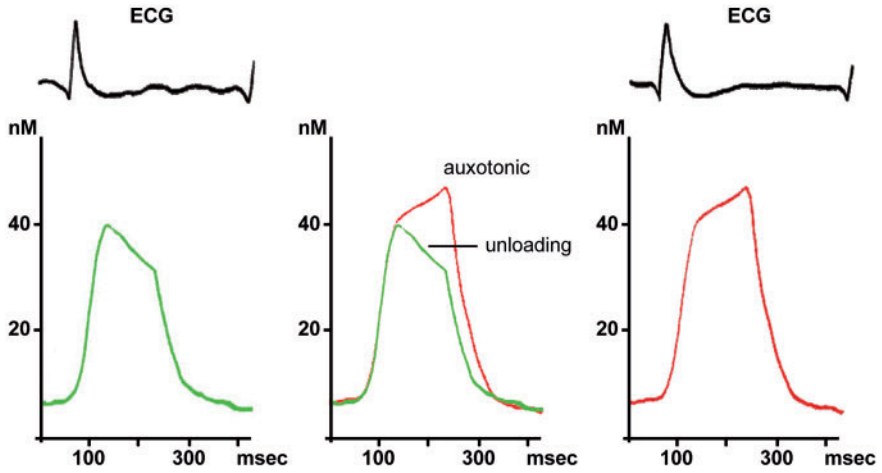

Figure 5: The force signal characteristics of unloading and auxotonic forces. The left-hand panel shows an unloading type signal (green) recorded using a needle force probe [30] from cardiomyocytes aggregated together with a tangential alignment. The right-hand panel shows an auxotonic signal (red) recorded when the probe is coupled to cardiomyocytes aggregated together with either intruding or extruding transmural alignment. The 2 signals are superimposed in the middle panel showing the delay in endsystolic decay of the auxotonic signal. This is illustrated further by presenting the force signals with their corresponding ECG. ECG: electrocardiogram.

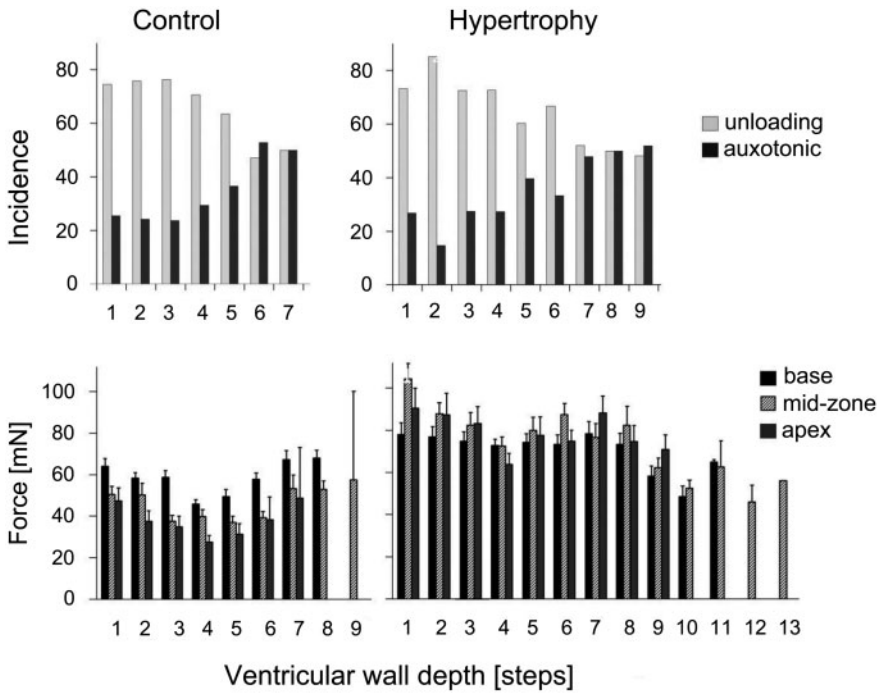

Figure 6: Remodelling of force distribution in myocardial hypertrophy. Unloading and auxotonic forces were measured using force probes in steps from epicardium [1] to endocardium [2, 30]. The upper panels show auxotonic versus unloading forces in control hearts (left) and hypertrophied (right) hearts. The lower panels show the maximal systolic forces recorded at the basal, equatorial and apical level of the left ventricular cone, again comparing control (left) measurements to those found in the setting of hypertrophy (right). The results were obtained from 10 dogs assessed in the control state and after 6 weeks of hypertrophy induced by aortic banding.

observed in the normal heart, however, were absent in hypertrophic hearts (Fig. 6).

UNLOADING AND AUXOTONIC FORCES COMPLEMENT EACH OTHER, THUS SUSTAINING INTRINSIC ANTAGONISM

The duration of active contraction of a cardiomyocyte is a direct function of its loading [11, 12]. The forces produced by the prevailing population of cardiomyocytes aligned tangentially progressively drop during systole to a level where contractile activity eventually ceases. The transmurally inclined aggregates, while contracting in auxotonic fashion against the increasing afterload due to growing mural thickness, relax later than the tangential aggregates (Fig. 5). During systole, most of the energy expended by the cardiac muscle is translated to cardiac output. Another part of the energy is dissipated as intrinsic afterload and, hence, constitutes idle power. A third part is stored in elastic proteins [31]. This elastic energy causes a recoil. This recoil, supported by the persistent active radial force component, provides the impetus for the rapid late systolic ventricular dilation. This rapid dilation coincides with another

independent phenomenon, known in echocardiography as transient late systolic/early diastolic mural thickening. This phenomenon is likely caused by the hydraulic effect of coronary reperfusion [32], when the small transmural coronary arterial branches are reopened with cessation of the contractile activity in the prevailing tangentially aligned cardiomyocytes. As one of the variables of end-systolic cardiodynamics, late systolic/early diastolic mural thickening is essentially determined by the degree of coronary arterial reperfusion in any single patient.

HETEROGENEITIES IN MURAL STRUCTURE AND FUNCTION ARE ESSENTIAL TO GLOBAL VENTRICULAR FUNCTION

When considering function, we argue that the myocardium acts as a complex 3D continuum, with significant local variations in its structural and functional characteristics. This contrasts with the classical cardiodynamic notion of a unidirectionally acting myocardium, as envisaged by Frank [4]. It also contrasts with the mathematical concepts supported by Arts *et al.* [8] and Hunter *et al.* [9]. It is incompatible with the band-like model presented by Torrent-Guasp *et al.* [33] who considered the myocardial mass to be formed by a wrapped entity arranged in the skeletal muscle fashion (Fig. 7B). In our understanding, the existence of the 3D meshwork implies that cardiodynamics are dominated by local functional demands. The observed interplay between tangentially and transmurally orientated aggregates produces mural antagonism. We hypothesize that such antagonism has several functional consequences:

- By sustaining mural stiffness, we presume that the intrinsic antagonism is able to stabilize the shape and size of the ventricles.
- Second, by controlling the velocity locally, termination and the amount of inward motion, the auxotonic forces are able to decelerate ventricular constriction, thus minimizing the resistance to flow in the already narrow left ventricular cavity.
- The antagonistic activity stores elastic forces generated during systole, thus enhancing late systolic dilation.
- Finally, by making use of the marked heterogeneity in regional mural architecture, the antagonism promotes the known intracavitary spiralling pattern of flow [34].

The transmurally orientated aggregates are densely interwoven within the larger population of aggregates orientated in near tangential fashion [12–15], with one modulating the function of the other in a locally specific fashion. Such regional heterogeneities dictate that each short segment of aggregated cardiomyocytes contracts against locally specific, and sometimes rapidly changing, loading conditions. Measurements made locally have shown that the amplitudes of the contractile forces vary widely over time [30]. Local function is determined by the specific alignment of the units of aggregated cardiomyocytes, the extent of their suspension within the fibrous matrix, their connections to adjacent units and their location within the depth of the ventricular walls. Nonetheless, each region still reacts to haemodynamic working conditions as predicted by Frank [4]. This implies that their primary afterload is haemodynamic and, hence, is dependent on intracavitary pressure. The force component acting in a dilatory direction, however, represents an intrinsic afterload. This will increase concomitant with the systolic increase in mural thickness and, hence, with the increase in transmural angulation, as indicated by the auxotonic nature of the force signal. The 3D meshwork of cardiomyocytes, therefore, must overcome the double haemodynamic and intrinsic afterloads. This fact calls into question the notion that global mural stress can be quantitated according to the law of Laplace [35]. Strictly speaking, this formula is not suited for thick-walled objects that contain active elements producing different force components with varying directionality.

DERAILMENT IN INTRINSIC ANTAGONISM

To appreciate the harmony of the interaction of auxotonic forces acting side by side with unloading forces, the influence of the supporting fibrous tissue matrix, which serves to maintain the long chains of aggregated cardiomyocytes in register, must be taken into consideration [16–19]. In a healthy heart, the endomysial matrix permits the transfer of contractile force between the cardiomyocytes within an aggregate [19, 36]. Such an arrangement, however, can be predicted to be particularly prone to malfunction in the setting of myocardial hypertrophy, which is generally complicated by fibrosis [36–41]. Fusion of the endomysial and perimysial matrix by scar tissue can be predicted further to fetter the cells within their housings and to impede systolic rearrangement. It cannot be coincidental, therefore, that when taking measurements with force probes in such fibrotic hearts, we detected an increase in the relative incidence of auxotonic forces [42, 43]. The measured forces, both the unloading and the auxotonic types, increased to 3 times the level measured in the control settings. This finding underpins the critical impact of the suspension of each cardiomyocyte within the supporting matrix. Shortening is not only hindered but also diverted away from the physiological pathways of motion [36, 37], thus producing an increase in structural afterload.

Acute ventricular dilation as observed in the setting of concentric hypertrophy denotes a process of intrinsic rescue

As part of the derailment of intrinsic antagonism in the setting of global ventricular hypertrophy, the angle of intrusion will increase concomitant with mural thickening [15]. In terms of function, this means that antagonistic forces must perforce increase, producing a progressive increase in the intrinsic afterload, which, in turn, will promote further global ventricular hypertrophy. To interrupt this vicious circle, and thus reduce the intrinsic afterload, the ventricle will ultimately dilate [37]. Such dilation, in turn, will reduce the mural thickness and realign the transmural chains towards the prevailing tangential alignment. The result, therefore, will be some lessening of intrinsic antagonism. It is tempting, therefore, to suggest that, in a critical state of concentric hypertrophy, antagonistic auxotonic forces will reach the levels early in systole that exceed those generated by the constrictive forces. Such a situation would lead to a precipitous cessation of ventricular constriction [10, 11], with an obvious reduced ejection fraction for some heartbeats. In this setting, ventricular mean filling must increase. Within a short sequence of cycles, therefore, the ventricular mass will achieve a new dilated geometric configuration, with reduced mural thickness along with a reduction in the angulation of the transmurally orientated chains. The effect will be a tempering of intramural antagonism. Because the ventricular diameter has increased,

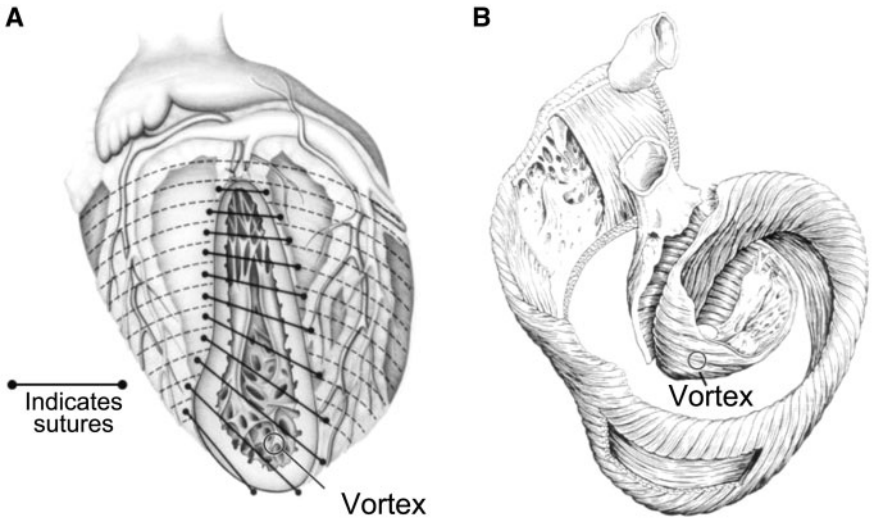

Figure 7: The myocardium functions as a collection of locally controlled contractile units. (**A**) A schematic of the ventricular reduction surgery technique as performed by Batista and colleagues [42, 43] is shown. Note that the removed segment of left ventricular myocardium includes a portion of the ventricular apical 'vortex'. (**B**) The notion of the 'unique myocardial band' as proposed by Torrent-Guasp is shown. The myocardial band model suggests the myocardial vortex plays a key functional role, acting as a functional pivot and suggesting that the left ventricle would be incapable of continuing to function subsequent to removal of the vortex [54]. The success of ventricular reduction surgery as achieved by Batista invalidates the concept.

however, such a mechanism of intrinsic rescue can only be achieved at the cost of an increased haemodynamic afterload [35]. Ventricular hypertrophy will thus reconvene.

INTRINSIC ANTAGONISM REQUIRES BEAT-TO-BEAT CONTROL OF FUNCTION OF ANY ASSIST DEVICES

In the Western countries, it is the progression of fibrosis that has become the prevailing mechanism behind the development of cardiac failure. Over the past 4 decades, at least 3 therapeutic concepts have been developed to counter this progression. The first, the implantation of an assist device, is designed to unload the fettered myocardium by minimizing the amplitude of ventricular mural motion [44]. The output of any such device, however, should be tuned beat to beat, so as to keep deviations in ventricular diameter, and the amplitude of mural motion, as small as possible. If the heart is allowed to deform at highly variable amplitudes, cardiomyocytes within the walls are compelled to fight against the high intrinsic afterload, and thus, antagonism is enhanced. In this setting, hypertrophy and fibrotic fettering will progress, in the worst cases resulting in the disruption of the microvascular system and intramural bleeding [45, 46]. A beat-to-beat regime, controlled by measurements of the mean ventricular diameter and motion amplitude by a miniaturized implantable echo system, can reduce the stress acting on the ventricular walls.

THE OUTCOME OF PARTIAL VENTRICULECTOMY IS DETERMINED BY THE PREVAILING EXTENT OF INTRINSIC ANTAGONISTIC ACTIVITY

The second option, pioneered by Batista, was to reduce the ventricular size by surgical means (Fig. 7A). The indications for such volume reduction surgery have proved controversial [47–51]. The results, nonetheless, have provided important insights into the basic function of the heart muscle. Using needle force probes subsequent to ventricular reduction, we measured a significant reduction in mean mural stress, yet at the expense of marked diversity in the distribution of contractile forces developed throughout the left ventricular walls [52]. In some patients, the remaining myocardium can perform in an adequate fashion for years. Other patients, with hearts diseased by advanced fibrous fettering, died after a period of weeks or months [49–53]. The pivotal criterion for appropriate selection of patients is the potential of the heart to increase systolic mural thickening subsequent to volume reduction. In the Western countries, the frequent prevalence of myocardial fibrosis [49] excludes a great number of patients who suffer from chronic dilated hypertrophy. In contrast, in the setting of acute development of dilated hypertrophy, as often seen in Brazil and in Eastern countries, volume reduction surgery, performed at a still low level of intrinsic afterload, can offer the most effective therapeutic option [47, 48]. Subsequent to excision of components of the ventricular walls, the remaining mural segments, although deprived of their inter-regional functional connection, and although electrically isolated from one another by extended scars, are able to function adequately for years. These observations challenge the notion that the left ventricular apex must be excluded from surgical intervention [54]. The myocardial band model (Fig. 7B) suggested the myocardial vortex, which is the myocardial whirl formation in the ventricular apex, to act as a functional pivot, which during systole stores the elastic forces needed to drive ventricular diastolic dilation [33]. Volume reduction surgery, in contrast, reduces the left ventricular length by excising the apex (Fig. 7A). No disturbances in diastolic dilation were observed subsequent to such surgery. These clinical experiences, therefore, suggest that the myocardium functions as a collection of locally controlled contractile units [10–13], thus providing regional myocardial independence.

LOW-DOSE ß-BLOCKER THERAPY DIRECTLY ACTS ON INTRINSIC ANTAGONISM

We have recently investigated [55] ß-receptor blockade [56] as a third therapeutic option for the treatment of myocardial hypertrophy.

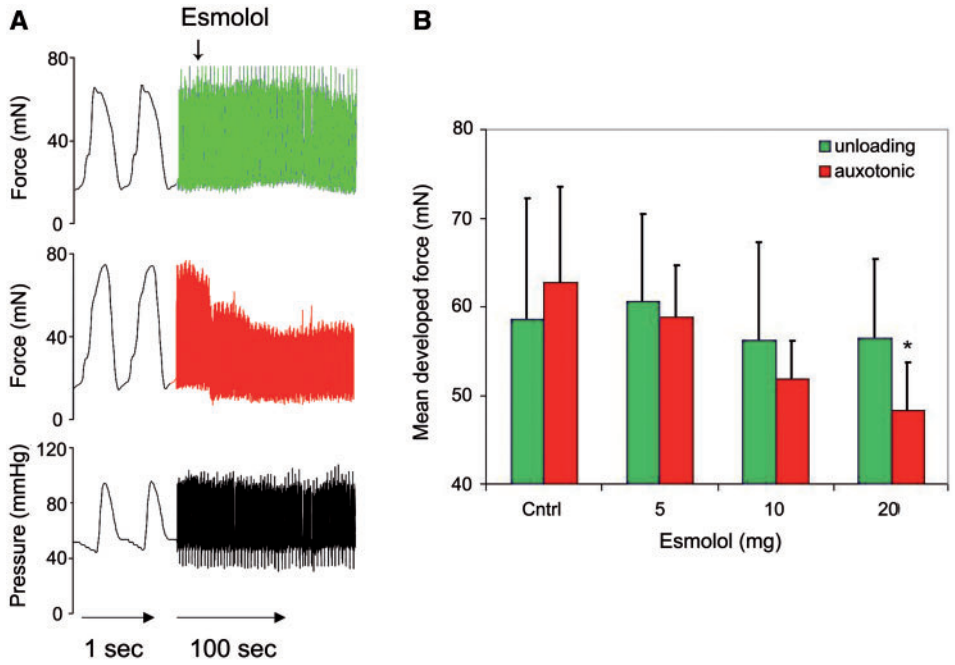

Figure 8: Auxotonic forces are selectively reduced by negative inotropes. (**A**) Force plots from human left ventricle showing how administration of esmolol at low dosage induces an acute and dramatic drop in the generation of auxotonic force (red box), while the development of the unloading type of force remains unaltered [55]. The lower panel shows the corresponding aortic pressure signal. (**B**) Mean force production as obtained in 10 patients when esmolol was administered at increasing dosages. At a 20 μg/kg of bodyweight, a significant drop in auxotonic forces is reached while the unloading forces remaining unaltered. *indicate statistical significant.

Reduction of global ventricular hypertrophy by ß-blockade is well described in patients suffering from hypertrophic obstructive cardiomyopathy [41, 57], with low dosages of ß-blockers shown to be remarkably effective. In an animal experimental study, we explored the negative inotropic action of rising doses of barbiturates, because the hearts of our breeding swine had proved insensitive to ß-blockers [30]. We showed that the cardiomyocytes contracting in auxotonic fashion were more sensitive to negative inotropic medication than those providing unloading forces (Fig. 8). At low dosage, the effect on auxotonic forces was selective, having little impact on the cardiomyocytes producing unloading forces. Based on these experimental findings, we extended our measurements to patients. If the ß-blocker esmolol was given intraoperatively at low dosage just after the onset of extracorporeal circulation, the effect was to reduce the auxotonic forces dramatically, with the unloading type of forces remaining unaffected (Fig. 8). In the non-fibrotic hearts of young volunteers, this agent, when given at low doses, induced an enhanced ventricular constriction and a temporary reduction in ventricular size [58]. In contrast, esmolol given intraoperatively at low dosage in patients produced a highly variable effect on ventricular diameter (Fig. 8). We infer that, in fibrotic hearts, the potential to shrink is reduced by mural fettering. Esmolol, therefore, might prove to be of diagnostic value. It might help to evaluate the degree of myocardial fettering by fibrosis. Although the mechanism underlying the selectivity of negative inotropes remains unknown, their use presents an intriguing area for future research, with potentially important clinical implications.

CONCLUSIONS

The ventricular walls are arranged as a 3D meshwork, consisting of a continuum of aggregated cardiomyocyte chains exhibiting marked local structural variations. This implies that cardiodynamic activity will be governed by local demands. Up to two-fifths of the chains have a partially transmural alignment. By means of experiments using force probes, we have shown that the cardiomyocytes aggregated together in a transmural fashion generate an auxotonic component of force that acts so as to produce ventricular dilation. Such dilatory forces act in harmony with the forces produced by the majority of cardiomyocytes, which are aggregated tangentially, and which generate an unloading signal. The end result is to produce an antagonistic system that serves to stabilize ventricular shape and size, to sustain late systolic dilation, to confine the amplitude of ventricular mural thickening and to facilitate and enhance the spiralling intracavitary flow. The presence of such intrinsic ventricular antagonism questions the existing conventional view that mural stress can be deduced from data derived exclusively from intracavitary pressure and ventricular size. In the settings of ventricular hypertrophy, furthermore, the antagonistic activity exaggerates the intrinsic afterload. Our study using ß-blockade supports the concept that, because of the specific sensitivity to the auxotonically contracting cardiomyocytes, negative inotropic medication could serve to mitigate the progression of ventricular hypertrophy.

GLOSSARY

Cardiac antagonism: A synchronous constrictive and dilative activity of the ventricular walls.

Unloading contraction: The force magnitude 'declines' as the cardiomyocyte shortens.

Auxotonic contraction: The force magnitude 'increases' as the cardiomyocyte shortens.

Afterload: Resistance against which the cardiomyocyte shortens. During unloading contraction, afterload decreases, during auxotonic contraction afterload increases.

1. Haemodynamic afterload is intracavitary pressure.

2. Intrinsic afterload is the resistance of intruding cardiomyocytes to mural thickening.

3. Structural afterload results from fettering of cardiomyocytes by fibrosis.

Laplace's Law: It states that the tension in the wall of a sphere is the product of the pressure times the radius of the chamber, with the tension inversely related to wall thickness.

Contractility: A putative indicator of global ventricular function derived from the velocity of intracavitary pressure rise. It is assumed to reflect the velocity of shortening of all the cardiomyocytes.

Cardiomyocyte chain: Formed by many individual cardiomyocytes connected end to end.

Aggregated unit: A collection of 'cardiomyocyte chains' bound together by endomysial connective tissue.

Cardiac mesh: The complex heterogeneous cardiomyocytic netting, formed by a continuum of interconnected aggregates of cardiomyocytes bound within a fibrous matrix.

Tangential: Parallel to the epicardial surface plane.

Transmural: Meaning across the wall. If obliquely orientated in epicardial to endocardial direction, the chains are 'intruding' or 'extruding' when running in endocardial to epicardial direction.

Endomysium: A component of the fibrous matrix which houses the individual chains of cardiomyocytes, and bundles multiple chains together into 'aggregated units'.

Perimysium: A broader loose component of the fibrous matrix located in the space between the 'aggregated units'.

Myocardial fettering: The pathological lacing together of chains of cardiomyocytes to one another by endomysial and perimysial scar tissue.

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