What is the Clinical Significance of Ventricular Mural Antagonism?

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Summary

Recent morphological studies provide evidence that the ventricular walls are arranged as a three-dimensional meshwork of aggregated chains of cardiomyocytes, 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 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. Beta-blockade at low dosage acts selectively to temper the auxotonic forces.

Keywords: 3-dimensional mural architecture, Cardiodynamics, Contractility, Antagonism, Beta-blockade

I. Introduction

The intriguing functional anatomy of the heart has stimulated the interest of researchers for centuries. Harvey's classical work of 1628, which established the combined circulatory character of the arterial and venous systems driven by a four chamber pump, represented a seminal achievement. Harvey postulated ventricular emptying to be driven by constrictive myocardial forces, while ventricular filling was considered to be exclusively dependent on the venous filling pressure (1). Centuries later, Brachet conceived a ventricular function based on active systolic ventricular emptying, followed by active diastolic ventricular dilation (2). He postulated the existence of cardiomyocytes aligned in a transmural fashion without providing evidence of their existence. Pettigrew (3) elegantly demonstrated the complex ventricular mural architecture without confirming structural components aligned in 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 the subsequent histological studies of Feneis (5) provided evidence to support the idea that some aggregates of cardiomyocytes extended in a transmural direction, the studies of Streeter (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 and his associates (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 and his colleagues (8), for example, in building their model, presumed the presence of homogeneous and equilibrated stresses throughout the ventricular walls. In contrast to this approach, however, Brutsaert and his group (10, 11) promoted the notion of a heterogeneous distribution of mural stress.

In the following, we summarize structural and functional findings which permit a comprehensive description of myocardial functionality. In particular, we emphasize the findings in regard to the existence and significance of transmurally 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 (Figure 1). We then elaborate 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 to some extent systolic mural thickening, they are auxotonic in nature, and they outlast the unloading forces.

II.1Towards elucidating the structure of the ventricular walls

The ventricular walls are composed of chains of cardiomyocytes connected together in 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, 29]. These aggregated units of cardiomyocytes are markedly heterogeneous in dimensions and shape [25-27)], and are separated one from the other 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 lamellae during systolic mural thickening [5, 19]. In some instances, the aggregated units deviate from the prevailing tangential orientation exhibiting a transmural orientation [Figures 1 and 2].

II.2 Histology

Streeter using histological techniques to investigate the orientation of the lamellar aggregates, cut the sections in tangential fashion [6]. 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 transmural fashion [Figure 3]. Such transmural chains were found to be most abundant in the subendocardial component of the wall, with some of the chains showing

transmural angulations of between 30 and 40 degrees, and in hearts fixed in systole, angles in excess of 40 degrees were observed.

In contrast to our findings, some investigators have failed to find evidence for the existence of myocyte chains with significant transmural angulation [19, 20].Future studies will clarify to what extent different histological techniques are responsible for persisting different perceptions of the 3-dimensional alignment of the aggregates and the myocyte chains they house.

II.3 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 three-dimensional cardiac mesh [15], again revealing marked heterogeneity within the different parts of the ventricular cone (Figure 4).

II.4 Pneumatic distention of the heart

So as 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, and the short-axis slices (tomograms) viewed sequentially [28, 29], a complex structural pattern is observed. Ascending sub-epicardial and descending subendocardial aggregates are connected by a heterogeneously distributed circumferential zone in between. Their complex branching means the aggregates are inter-connected transmurally, the cardiac mesh thus forms a continuum which is seen to rotate in opposing directions about the ventricular long axis and which provides further confirmation that the aggregated units display a wide range of orientations, with the contained myocyte chains exhibiting not only helical but also transmural angulations [Figure 2 and 3] [13-15, 27]. The mean orientation of the individual cardiomyocytic chains follow the long axis of the aggregated unit in which they are housed, segmentation of a transmurally orientated aggregate is presented as a 3D rendering in Figure 2.

II.5. Local force measurements

Contractile forces generated by the prevailing number of tangentially orientated chains of myocytes have an almost exclusive constrictive effect. Those exhibiting a significant transmural orientation, be they intruding or extruding, have both a constrictive and radial effect. As they sustain mural thinning, they have a dilatory force component. Figure 1 shows the force vectors produced by tangentially and transmurally orientated myocyte chains respectively. The relative ratio of the dilating to constrictive force components locally varies with 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 two types of force signal [Figure 5], an 'unloading' signal which decreases during systole and which acts in constrictive direction, and an 'auxotonic' signal which increases during systole and which acts in dilatory direction [Figure 1]. These latter forces are auxotonic since the myocytes involved are confined in shortening or even become elongated during mural thickening. In contrast, the aggregated cardiomyocytes which are aligned tangential to the ventricular surface are free to shorten while 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 signal to be most prevalent in the deep sub-endocardial layers, while in the outer layers the unloading signal prevailed [30] [Figure 6]. This pattern is not altered in hypertrophic hearts. Furthermore, in normal control hearts we found a base to apex gradient in force maxima, with a maximum force observed in the base. We also observed a transmural force gradient, whereby force maxima were confined to the epicardial and endocardial layers with minimal force peaks in the mid-layers. The two gradients observed in the normal heart are absent in hypertrophic hearts [Figure 6].

II. Unloading and auxotonic forces complement each other sustaining Intrinsic Antagonism

The duration of active contraction of a cardiomyocyte is a direct function of its loading [11, 12]. 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 wall thickness, relax later than the tangential aggregates [Figure 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, which late in systole, supported by the persistent active radial force component, provides the impetus for the rapid late systolic ventricular dilation.

This fast dilation coincides with another independent phenomenon known in echocardiography as transient late systolic wall thickening. This phenomenon is likely caused by the hydraulic effect of coronary reperfusion [32], when the small transmural coronary branches are reopened when contractile activity in the prevailing tangentially aligned myocytes ceases. As one of the variables of end-systolic cardiodynamics, late systolic wall thickening is essentially determined by the degree of coronary reperfusion in any single patient.

III. Heterogeneities in mural structure and function are essential to global ventricular function

Upon turning our attention to functional aspects, it is important to note that the myocardium acts as a complex 3-dimensional continuum with significant local variations in its structural and functional characteristics. Our concept contrasts with the classical cardiodynamic notion of an uni-directionally acting heart muscle published by Frank [4]. It also contrasts with the mathematical concepts supported by Arts et al [8] and Hunter et al [9]. It likewise contrasts with the band-like model presented by Torrent-Guasp [33] suggesting the myocardial mass to be formed by a wrapped entity arranged like a

skeletal muscle [Figure 7B], which exclusively engenders equilibrated force trajectories parallel to the long axis of the band.

In our understanding the existence of the 3-dimensional meshwork implies that local functional demands dominate cardiodynamics, with the interplay between tangentially and transmurally orientated aggregates producing mural antagonism. We hypothesize such antagonism has the following 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 locally the velocity, termination, and 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.
- Third the antagonistic activity stores elastic forces generated during systole, thus enhancing late systolic dilation.
- Finally, 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]. Although 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, each region still reacts to hemodynamic working conditions as predicted by Frank [4]. This implies that their primary afterload is haemodynamic, and hence dependent on intracavitary pressure. However, the force component acting in a dilatory direction represents an intrinsic afterload, which will increase concomitant with

systolic increase in mural thickness hence with the increase in transmural angulation, as indicated by the auxotonic force signal. The three-dimensional meshwork of cardiomyocytes, therefore, must overcome a double afterload, haemodynamic and intrinsic. 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 which contain active elements producing different force components with varying directionality.

V.1. Derailment in intrinsic Antagonism

To appreciate the harmony of the interaction of auxotonic forces acting side-by-side with unloading forces, account must furthermore be taken of the influence of the supporting fibrous tissue matrix, which serves to maintain the long chains of aggregated cardiomyocytes in register [16-19]. In the healthy heart the endomysial matrix permits displacement of each myocyte and the transfer of contractile force to its surrounding myocytes 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 to fetter the cells within their housings, and to impede systolic rearrangement. It cannot be coincidental, therefore, that when making measurements with force probes in such fibrotic hearts, we detected an increase in the relative incidence of auxotonic forces [43, 44]. The measured forces, both the unloading as well as the auxotonic type, increased to three times the level measured in control settings. This finding underpins the critical impact of the connective tissue suspension of each myocyte. Shortening is not only hindered, but also diverted away from the physiological pathways of motion [36, 37]. That is what we call an “increase in structural afterload”.

V.2 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 intrinsic afterload, which in turn will promote still further global ventricular hypertrophy. So as to interrupt this vicious circle, and reduce intrinsic afterload, the ventricle will ultimately dilate (37). Such dilation, in turn, will reduce the mural thickness which geometrical alteration realigns 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 levels early in systole that exceed those generated by the constrictive forces. Such a situation would lead to a precipitous ceasing of ventricular constriction [10, 11], with an obvious reduced ejection fraction for some heart beats. In this setting, ventricular mean filling must increase hence within a short sequence of cycles, 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, however, such a mechanism of intrinsic rescue can only be achieved at the cost of an increased hemodynamic afterload [35]. Ventricular hypertrophy will thus reconvene.

VI.1. Intrinsic Antagonism requires beat-to-beat control of function of an Assist device

In 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 three 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 [45]. The output of the device, however, should be tuned beat-to-beat, to keep deviations in ventricular diameter and the amplitude of wall 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 anyway high intrinsic afterload and antagonism is enhanced. In this setting, hypertrophy and fibrotic fettering will progress, in the worst cases resulting in disruption of the woven in micro-vascular system and

intramural bleeding [46, 47]. By a beat-to-beat regime, controlled by measurements of the mean ventricular diameter and motion amplitude by a miniaturized echo-system, the stress acting on the myocardium and fibrous tissue can be reduced.

VI.2. The outcome of Partial Ventriculectomy is determined by the prevailing extent of intrinsic antagonistic activity

The second option, pioneered by Batista, was to reduce ventricular size by surgical means [Figure 7A]. The indications for such volume reduction surgery have proved controversial [48-52]. The results, nonetheless, have provided important insights into the basic function of the heart muscle. Using needle force probes we measured, subsequent to ventricular reduction, a significant reduction in mean mural stress, yet at the expense of marked diversity in distribution of contractile forces developed throughout the left ventricular walls [54]. In some patients, the remaining myocardium can perform in adequate fashion for years. Other patients, undergoing reduction surgery with hearts diseased by advanced fibrous fettering, in contrast, died after a period of weeks or months [50-53].The pivotal criterion to be proposed for appropriate selection of patients is the potential of the heart to increase systolic wall thickening upon volume reduction. In western countries, the frequent prevalence of myocardial fibrosis [50] excludes a great number of patients suffering from chronic dilated hypertrophy. In contrast, in the setting of acute development of dilated hypertrophy, as is often seen in Brazil and in eastern countries, volume reduction surgery, performed at a still low level of intrinsic afterload, can offer a most effective therapeutic option [48, 49].

Subsequent to excision of components of the ventricular walls, the remaining mural segments, although deprived of their interregional 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 [55]. Torrent-Guasp's myocardial band model [Figure 7B] suggests the myocardial vortex acts as a functional pivot, which during systole stores the elastic forces needed to drive ventricular diastolic dilation [33]. The Batista surgery, in contrast, reduces left ventricular length by excising the apex [Figure 7A]. Post-

surgery no disturbances in diastolic dilation were observed. Accordingly, these clinical experiences suggest the myocardium functions as a collection of locally controlled contractile units [10-13], which we term regional myocardial independence.

VI.3 Low-dose ß-blocker therapy directly acts on intrinsic antagonism

The third therapeutic option for the treatment of myocardial hypertrophy, investigated recently [30,56], is an extension of classical ß-receptor blockade (57). Reduction of global ventricular hypertrophy by ß-blockade had been described in patients suffering from hypertrophic obstructive cardiomyopathy [41,42]. Low dosages of ß-blockers had been shown to be remarkably effective. In an animal experimental study, we explored the negative inotropic action of rising doses of barbiturates, since 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 [Figure 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 on cardiac patients. If the ß-blocker esmolol was given intra-operatively at low dosage just after onset of extracorporeal circulation, the effect was to reduce dramatically auxotonic forces, while the unloading type of forces remained unaffected [figure: 8] Furthermore, in the non-fibrotic hearts of young volunteers, we found that this agent, when given at low doses, induced an enhanced ventricular constriction and a temporary reduction in ventricular size [58]. In contrast, in cardiac patients, if esmolol is given intra-operatively at low dosage, its effect on ventricular diameter was highly variable (Figure:8). We infer that, in fibrotic hearts, the potential to shrink is reduced by mural fettering. This finding suggests that esmolol might be of diagnostic value. It might help to evaluate the degree of myocardial fettering by fibrosis. Nonetheless, the mechanism underlying the selectivity of negative inotropes is still unknown, it does, however, present an intriguing future research area with potentially important clinical implications.

VII Conclusions

The ventricular walls are arranged as a three-dimensional meshwork, consisting of a continuum of aggregated chains of cardiomyocytes exhibiting marked local structural variations. Accordingly, there

is evidence that the cardiodynamic activity is governed by local demands. Up to two-fifths of the chains have a partially transmural alignment. By means of experiments using force probes, those cardiomyocytes aggregated together in transmural fashion were shown to 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 wall thickening to facilitate intracavitary flow and to render intracavitary flow spiralling. The presence of such intrinsic ventricular antagonism questions the existing conventional view that wall stress can be deduced from data derived from intracavitary pressure and ventricular size alone. In the settings of ventricular hypertrophy, furthermore, the antagonistic activity exaggerates the intrinsic afterload. Our study using beta-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 describes a synchronous constrictive and dilative activity of the ventricular walls.

Unloading contraction - The force magnitude **declines** as the cardiomyocyte shortens.

A**uxotonic 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. Obliquely orientated in epicardial to endocardial direction (i.e. **intruding**), or from endocardial to epicardial direction (i.e. **extruding**).

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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Figures

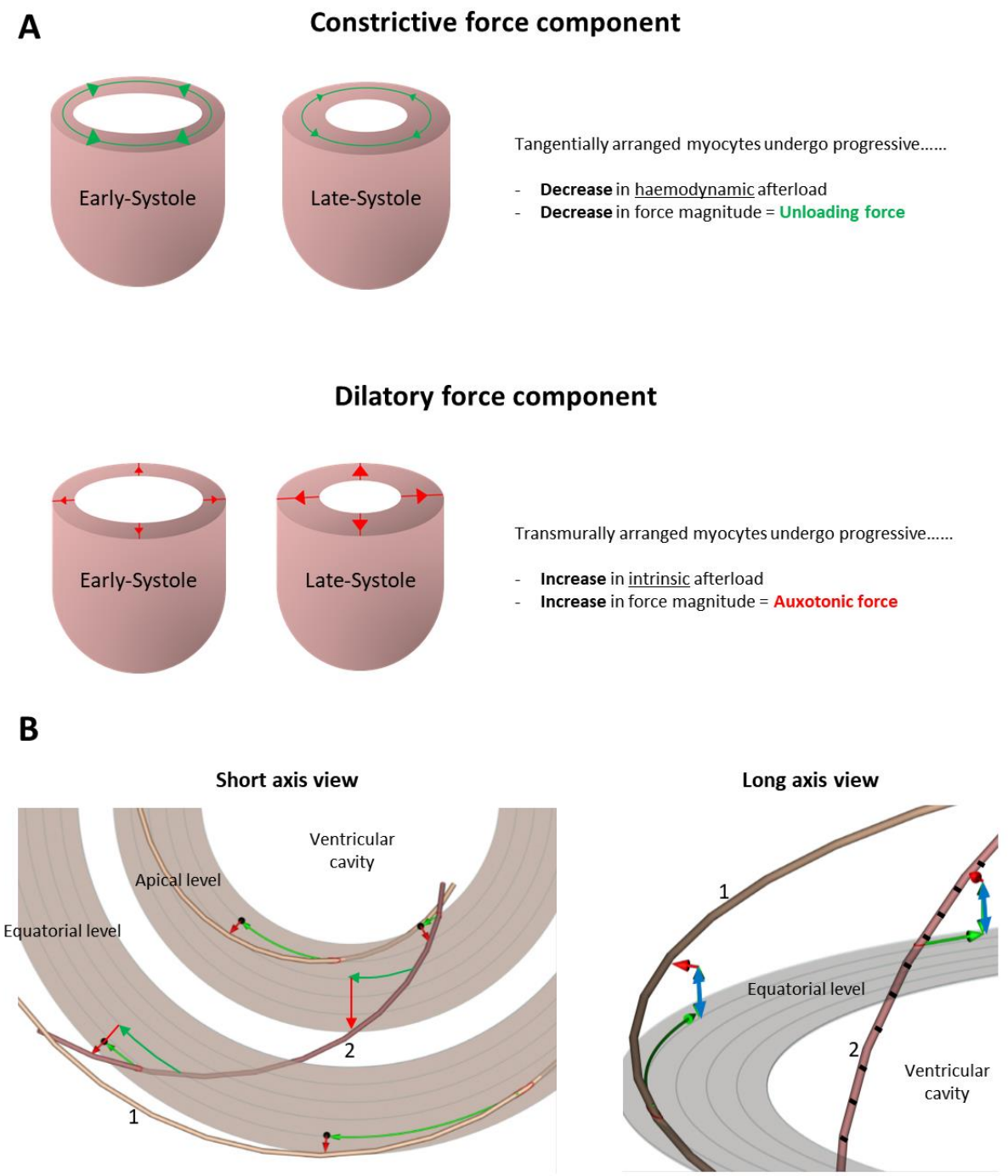

Figure 1. The relationship between myocyte orientation, loading conditions, and force production. Myocyte chains produce constrictive (green arrows), dilatory (red arrows), and longitudinal force (blue arrows). Panel A- shows change in force magnitude of the constrictive and dilatory force components from early-systole to late-systole related to myocyte orientation and loading conditions. Panel B- tangentially arranged myocytes (1) produce predominantly constrictive forces (green arrows) which are unloading in nature. Transmurally arranged myocytes (2) produce dilatory forces (red arrows) which are auxotonic in nature

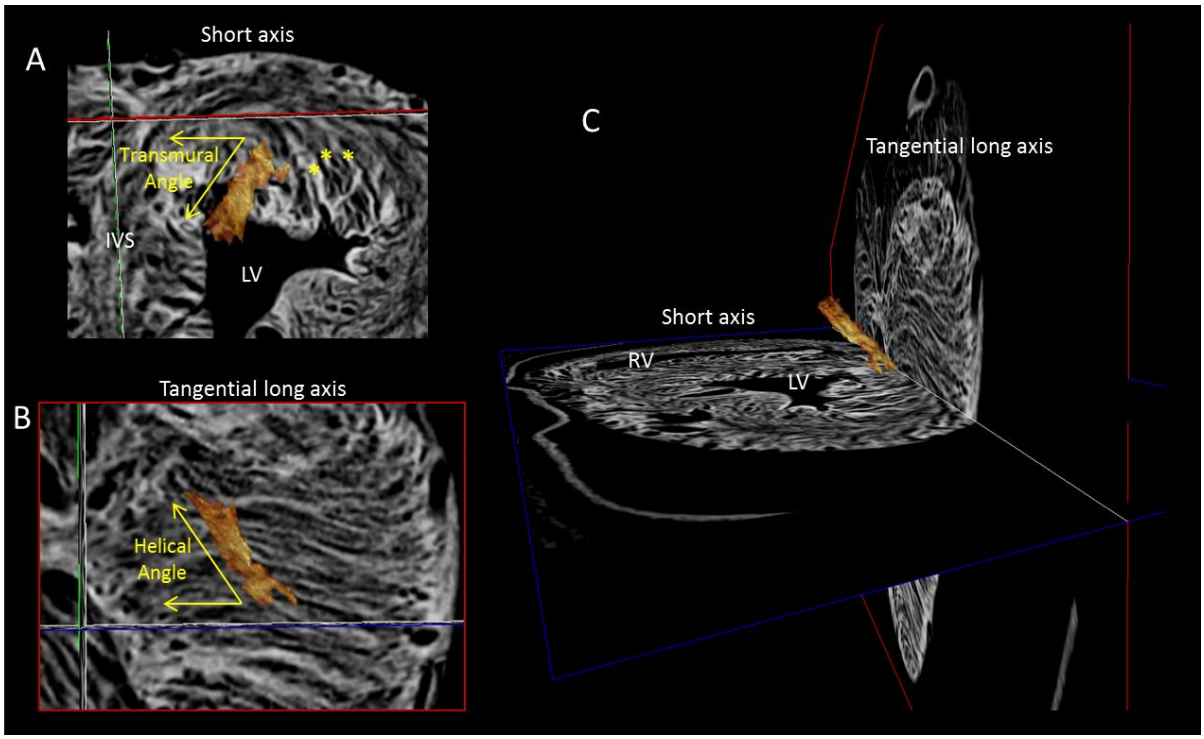

Figure 2. 3D rendering of an aggregated unit of cardiomyocyte chains. Panels A-C show an aggregated unit (orange) segmented from computer tomography data of a pneumatically distended pig heart [29]. The units has a transmural angle (angle between the myocyte chain long axis and tangential long axis plane) equal to 24 degrees (panel A), and a helical (angle between the myocyte chain long axis and the short axis plane) equal to 44 degrees (panel B). In panel A the asterisks indicate individual aggregated units as viewed in the short axis plane. Whole heart dimensions ~6 cm x 6 cm.

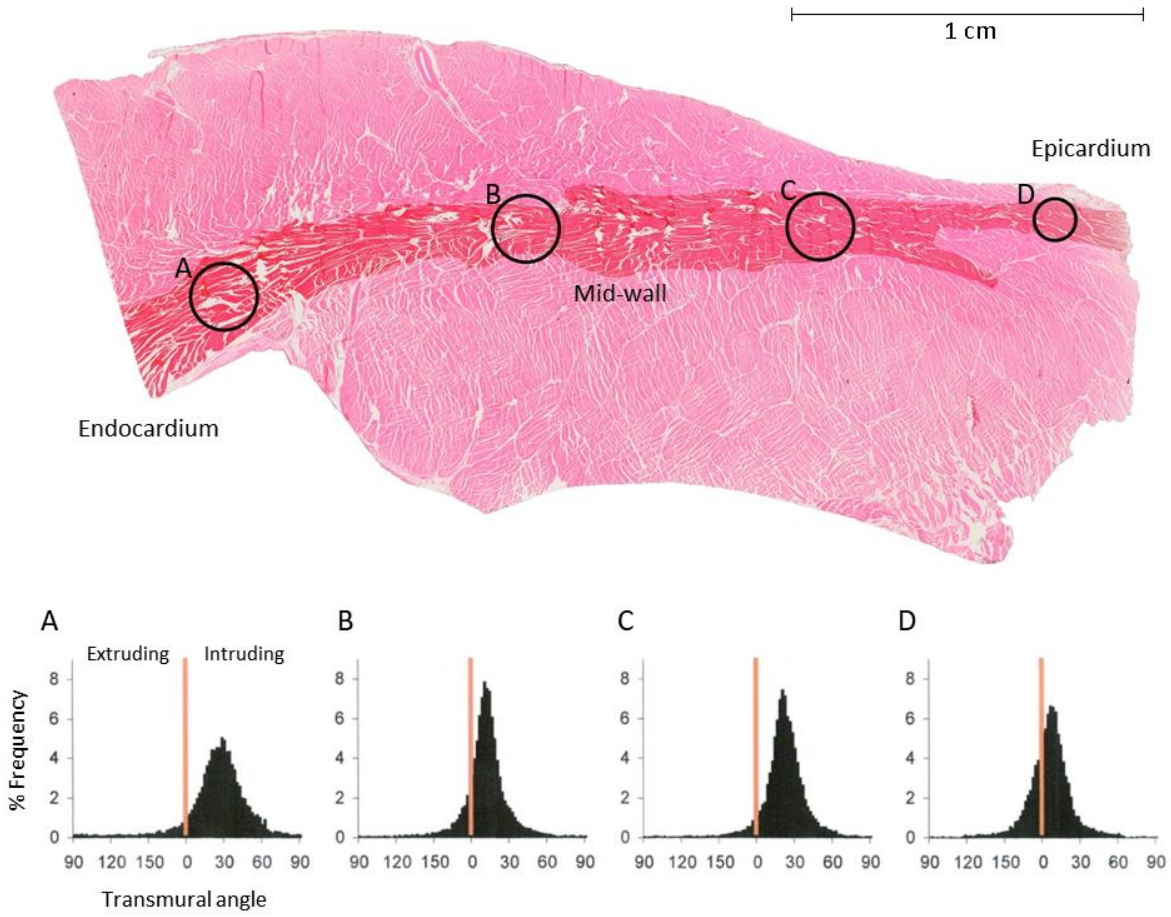

Figure 3. Myocyte orientation investigated using circular knives. The figure shows the percentage of distribution of angles of intrusion and extrusion of lamellar aggregates at four sites across the left ventricular wall (dark red marked) of a porcine heart in which long chains of myocytes are aligned 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.

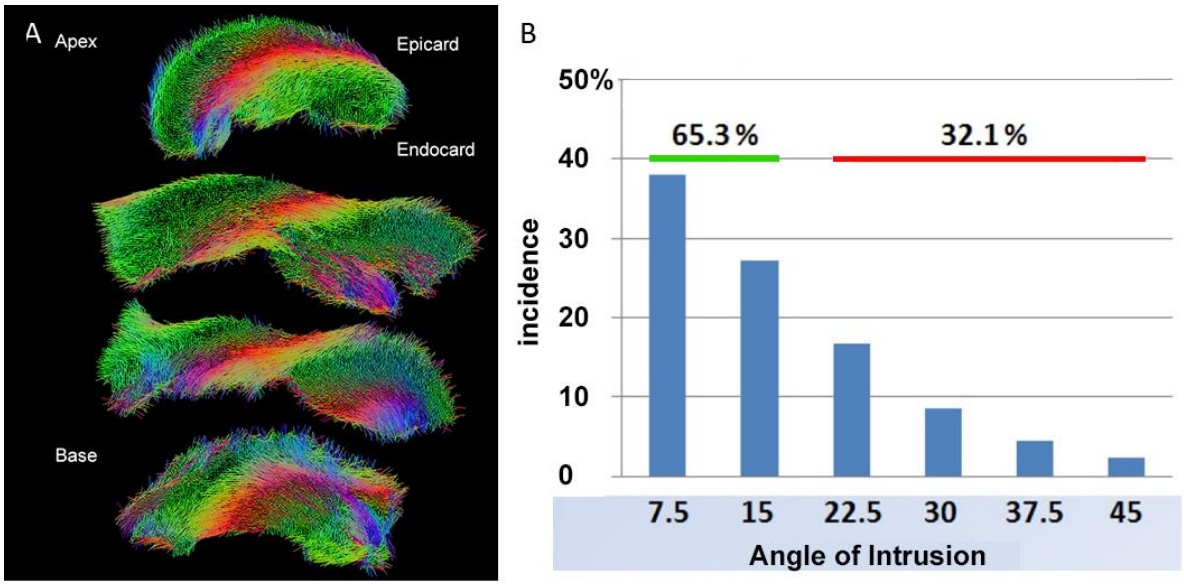

Figure 4. Myocyte orientation investigated by diffusion tensor magnetic resonance imaging. The figure shows the relative number of transmurally orientated lamellar aggregates (Y-axis) and their respective angulation (X-axis) as measured in 10 porcine hearts. 4 transmural myocardial slices were harvested 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 (panel A)[14]. The red marked zones indicate the long chains of myocytes which 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 (panel B).

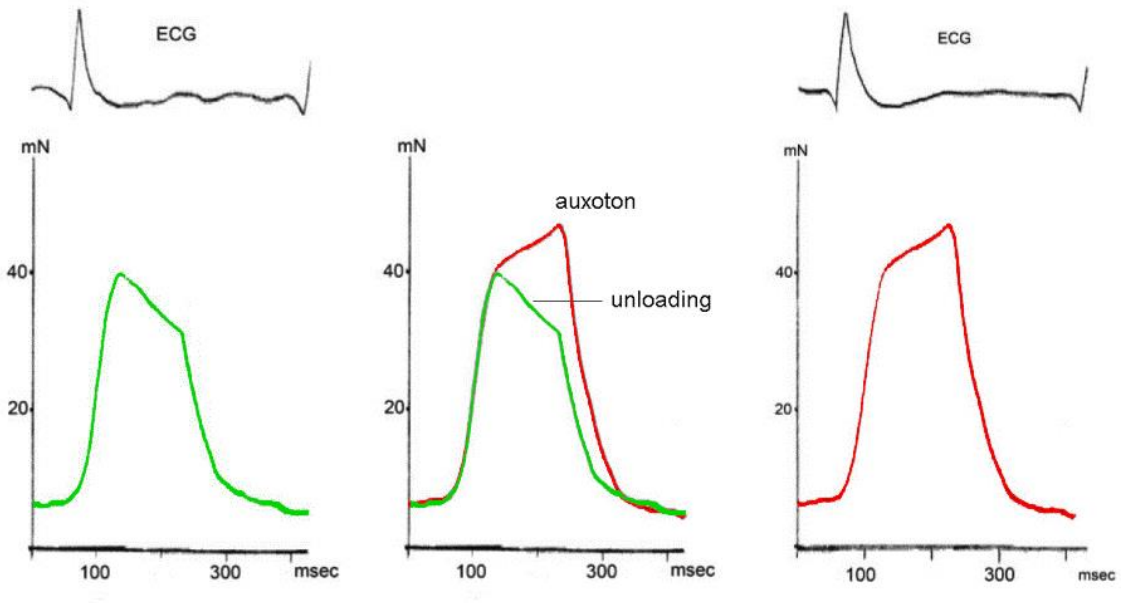

Figure 5. The force signal characteristics of unloading and auxotonic forces. The left hand panel shows an unloading type signal (green) recorded using a needle force probe [30] from cardiomyocytes aggregated together with a tangential alignment. The right hand panel shows an auxotonic signal (red) recorded when the probe is coupled to cardiomyocytes aggregated together with either intruding or extruding transmural alignment. The two 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

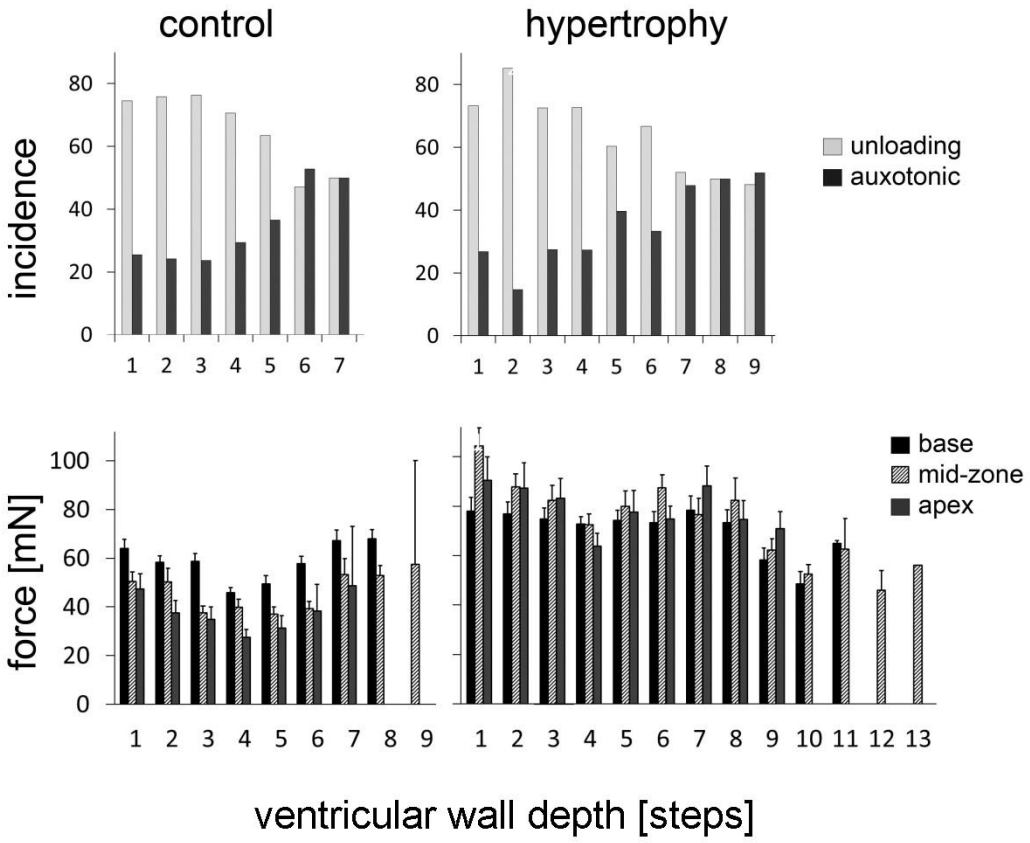

Figure 6. Remodeling of force distribution in myocardial hypertrophy. Unloading and auxotonic forces were measured using force probes in steps from epicardium (1) to endocardium (2)[30]. The upper panels show auxotonic versus unloading forces in control hearts (left) and hypertrophied (right) hearts. 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.

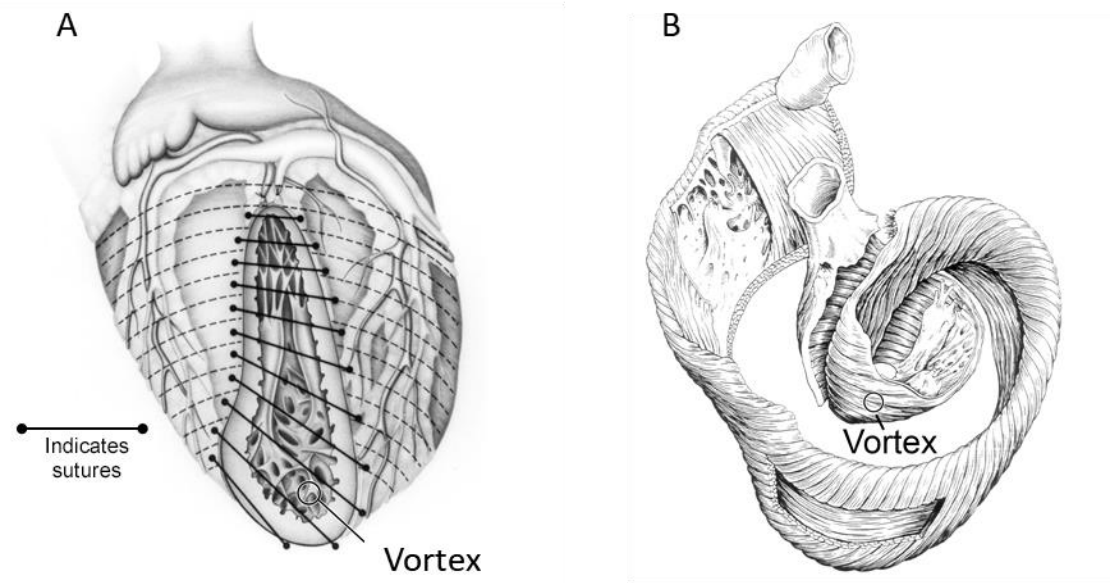

Figure 7. The myocardium functions as a collection of locally controlled contractile units. Panel A shows a schematic of the ventricular reduction surgery technique as performed by Batista [43,44]. Note that the removed segment of left ventricular myocardium includes a portion of the ventricular apical 'vortex'. Panel B shows the notion of the 'unique myocardial band' as proposed by Torrent-Guasp. The myocardial band model suggests the myocardial vortex plays a key functional role, acting as a functional pivot, claiming the left ventricle would be incapable of continuing function subsequent to removal of the vortex [55]. The success of ventricular reduction surgery achieved by Batista contradicts the concept.

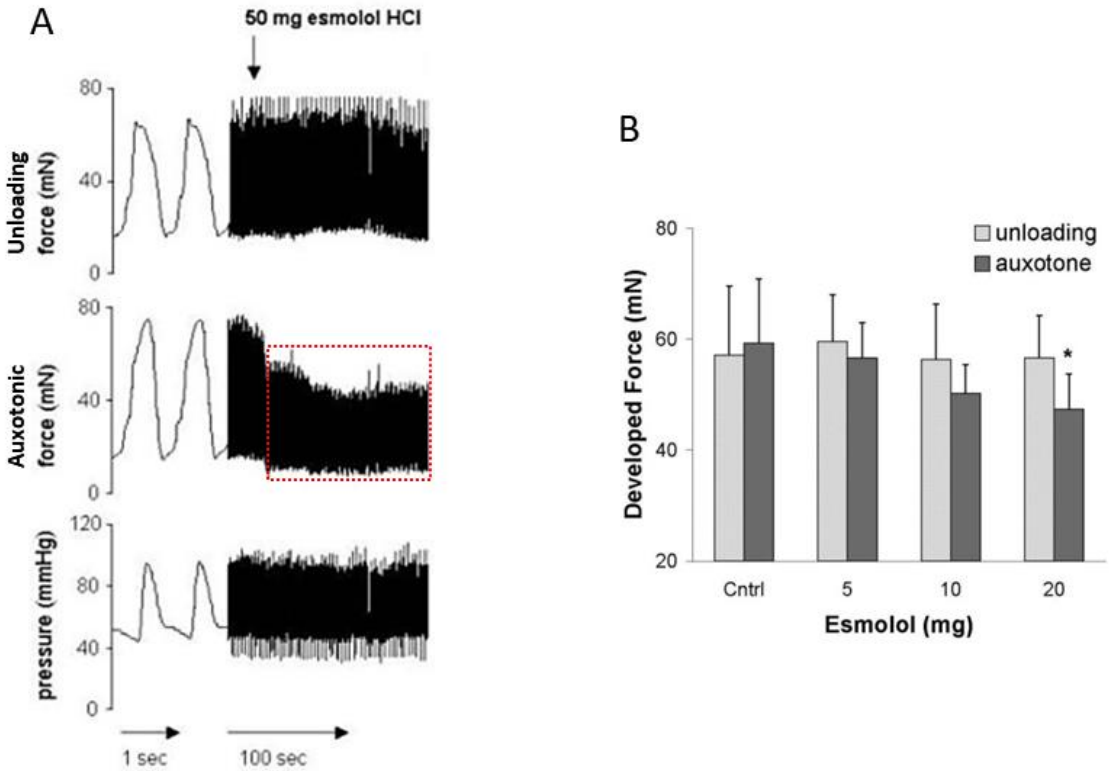

Figure 8. Auxotonic forces are selectively reduced by negative inotropes. (A) Force plots from human left ventricle showing how administration of Esmolol at low dosage induces an acute and dramatic drop in the generation of auxotonic force (red box), while the development of the unloading type of force remains unaltered [56]. The lower panel shows the corresponding aortic pressure signal. (B) Mean force production as obtained in 10 patients when Esmolol was administered at rising dosages. At a 20 microgram per kilogram of bodyweight, a significant drop in auxotonic forces is reached while the unloading forces remaining unaltered.