Antagonism of contractile forces in left ventricular hypertrophy: a diagnostic challenge for better pathophysiological and clinical understanding

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ABSTRACT
Cardiac function is characterised by haemodynamic parameters in the clinical scenario. Due to recent development in imaging techniques, the clinicians focus on the quantitative assessment of left ventricular size, shape, and motion patterns mostly analysed by echocardiography and cardiac magnetic resonance. Because of the physiologically known antagonistic structure and function of the heart muscle, the effective performance of the heart remains hidden behind haemodynamic parameters. In fact, a smaller component of oblique transmural netting of cardiac muscle fibres simultaneously engages contracting and dilating force vectors, while the predominant mass of the tangentially aligned fibres only acts in one direction. In case of hypertrophy, an increased influence of the dilating transmural fibre component might counteract systolic wall thickening, thereby counteract cardiac output. A further important aspect is the response to inotropic stimulation that is different for the tangentially aligned fibre component in comparison to the transmural component. Both aspects highlight the importance to integrate the analysis of intramural fibre architecture into the clinical cardiac diagnostics.

INTRODUCTION
Almost all biological systems usually have an antagonistic principle of function since counteracting components enable finely graduated adjustments of function by action and counteraction. A separate measurement of the intramural deformation of individual cardiac muscle fibres and their force development is not yet possible. Otto Frank has described the pressure–volume relations of the frog ventricle mainly in relation to the ventricular filling conditions.12 Patterson and Starling showed the relation between ventricular filling pressure and cardiac output3 analysing the impact of contractile forces due to ventricular preload. The analysis of the myocardial ultrastructure by electron microscopy and the correlation between morphological alterations and function of the sarcomeres6-8 gave insights into the tension–length relationship of the myocardial fibres. Assuming a strictly tangential arrangement of the fibre architecture within the ventricular walls, the prevailing opinion was determined that the vectors of contractile forces are exclusively parallel to the ventricular surface contour assuming no antagonism of contractile forces within the myocardium, which was not considered in Frank’s model of ventricular function.4 Therefore, currently used terms like myocardial contractility, myocardial wall stress calculated according to the Laplace equation7 and left ventricular (LV) stiffness determined non-invasively8 are discussed with respect to external work of the heart muscle, and not considering myocardial metabolism with its dependency on heart rate,9 which is necessary for plausibility.

In clinical practice, cardiac function is characterised in haemodynamic terms of ventricular volumes—especially stroke volume—ejection fraction, heart rate, systemic and central venous blood pressure. Due to recent development in imaging techniques, the clinician focus on the quantitative assessment of ventricular size, shape and motion patterns mostly analysed by echocardiography and cardiac MRI (cMRI) targeting more insights into intramural dynamics.10-12 Using modern echocardiographic modalities, the analysis of different compounds of LV deformation including shear stress enables to elucidate intramural dynamics.13-15 Reflection patterns in echocardiography do not necessarily correspond to anatomical structures. However, these speckles are the basis for echocardiographic strain analyses. cMRI tagging and feature tracking can also visualise details of LV deformation without direct targeting of myocardial fibres. Preload, afterload and myocardial metabolism determine...
myocardial contractility and LV filling properties influenced by several parameters like LV wall thickness, LV wall stiffness and LV relaxation time. Nowadays, assessment of LV function is commonly performed by analysis of the load-dependent parameter LV ejection fraction and LV longitudinal strain. Myocardial work (MW) determined by non-invasive speckle tracking echocardiography combines LV contraction and afterload into a single parameter. Regional MW and regional glucose metabolism was shown to be correlated. Thus, this parameter might reflect the potential to characterise non-invasively regional myocardial energetics and enable new options to quantify LV energy waste. However, the analysis of MW is based on LV longitudinal strain as only one component of LV deformation. Thus, regional differences of MW allow conclusions about early subclinical abnormalities of myocardial function due to the main component of LV deformation, but it might be still uncertain to draw conclusions from regional MW about the functional state of myocardial fibres which are not contributing to longitudinal deformation. In this context, circumferential, radial and rotational strain analysis is an additional promising tool to analyse the underlying fibre architecture. The active myocardial performance is characterised by two components, constructive and wasted MW, which is strongly correlated to segmental cardiac glucose metabolism. In the clinical scenario, positron emission tomography (PET) with the radiotracer 18F-fluorodeoxyglucose (FDG) is possible in special centres for imaging glucose metabolism. However, FDG–PET is mostly used for the detection of viable myocardium in coronary heart disease to distinguish between hibernating, stunning and scar. This method is limited due to the non-ubiquitous availability, the high costs and the long investigation time required. The combination of FDG-PET and CMR is rarely described, and the potential clinical utility concerns the detection of myocardial viability, inflammation and specific diseases like sarcoidosis. Pathological patterns of MW as well as of reduced glucose metabolism again describe impaired regional myocardial function, which cannot be assigned to specific fibre strands of the myocardial architecture.

Spirometry estimates global cardiac efficiency in the clinical setting and can distinguish between the causes of limited physical activity, which can be due to cardiac, pulmonary, cerebral or peripheral limitations. Even in normal or subclinical conditions, symptoms of exhaustion during stress are fatigue, pain in the peripheral muscles, angina and dyspnoea, which cannot be necessarily assigned to cardiac origin because no sensation subjectively indicates the limits of a healthy heart. Only stress-induced myocardial ischaemia can be detected with relative certainty by reduced regional perfusion with consecutive wall motion abnormalities.

In clinical settings, the quantification of regional LV deformation is currently possible (figure 1). However, technical improvements of modern cardiac imaging will certainly be able to determine the individual components of intramural geometry of the singular muscle fibres and their energetic state as special factors of intramural contractility in future. The assignment between increased LV wall thickness and cardiac diseases like hypertrophy, oedema, fibrosis and/or storage diseases will surely distinguish between pathological and normal conditions. Therefore, pathological LV hypertrophy and the athlete’s heart as a physiological enlargement of the cardiac cavities can serve as models to gain a better understanding of different mechanisms involved in cardiac deformation and LV remodelling under pathological conditions.

MYOCARDIAL MORPHOLOGY AND FUNCTIONAL ANATOMY

During the last 50 years, morphological research unanimously has shown that the parallel alignment of the myocardial fibres based on the understanding of planar fibres must be replaced by associations of sequentially splitted myocytes forming a continuous spatial network of endless chains of myocytes with no origin or insertion (figure 2). Less than a hundred chains are bundled and surrounded by connective tissue to form aggregates with muscle fibres of different orientation (figure 3). Smaller fibres of endless chains form the connection between respective aggregates as a strong network between two adjacent entities. Within an aggregate, each segment of an endless chain of myocytes contributes to the particular shaping.

Diffusion tension MRI analysis of mural architecture revealed that the orientation of typically 70% of the endless chains are essentially aligned parallel to the ventricular surface. However, the remaining 30% of the aggregates of muscle fibres significantly deviate from the tangential orientation ‘intruding’ towards the endocardium or ‘extruding’ towards the epicardium.

THE DISTRIBUTION OF LOCAL FORCES

Invasive multifocal measurement of local forces revealed a heterogeneous pattern of actively developed forces of aggregates depending on their spatial orientation within the myocardium. To elucidate the distribution of forces throughout the ventricular walls, needle force probes, 1.3mm thick and up to 15 mm long, have been implanted into the walls of beating hearts, each aligned in right angle to the striation of the layered order of myocardial aggregates (figure 4). With the experience of several thousand experiments on dogs, pigs and rabbits, we also did measurements on patients during cardiac surgery in agreement with ethical standards.

Recorded force signals mirror the different functions of the aggregates to which the force probe was coupled. An afterloaded (=auxotonic) signal, which rose during the entire ejection period and lasted the LV end-systolic pressure drop (figure 5), was measured when the force probe was coupled to oblique transmurally aligned aggregates. In contrast, the predominant mass of surface-parallel aggregates generated an ‘unloading signal’, which slightly dropped from the beginning of ejection. Its end-systolic decay run parallel to LV pressure drop.
The predominant tangentially aligned muscle aggregates generate the constrictive forces causing ventricular ejection and dominate wall deformation. Auxotonic dilatory forces impede ventricular constriction mitigating regional wall thickening during systole. The transmural deflection of non-tangential chains of muscle aggregates increases in line with wall thickening. This process reaches the maximum at end-systole. With further wall thickening in myocardial hypertrophy, transmural deviation of several subendocardial intruding aggregates exceeds 45°. Measured dilatory forces increase with rising intruding or extruding inclination of non-tangential aggregates. Therefore, the ratio of contracting to dilating forces increases within the complete heart cycle particularly in the subendocardial layers of spiralling chains of aggregates. This scenario is particularly pronounced in the hypertrophic heart.

**ANTAGONISTIC STRUCTURE AND FUNCTION OF THE HEART MUSCLE**

Tangential structures generate ventricular constrictive forces, while intruding and extruding network components simultaneously generate a constrictive and a dilatory force vector (figure 2). Therefore, the myocardial structure obviously sustains an antagonistic function. Dominant contracting forces are opposed to dilatory forces, both cooperating as a functional unit. In the normal heart, mutual interaction is an equilibrium, though it varies continuously during the cardiac cycle. This equilibrium persists during phasic myocardial realignment as a continuously repetition. However, it is prone to derail in the diseased heart.

Contractile function of each single myocyte is continuously controlled according to the Frank-Starling mechanism, which is partly linked to the intraventricular pressure, partly varies in local-specific dimensions by force of mutual interaction of tangential and non-tangential netting components. The van Anrep effect delivers additional energy when focal, late-systolic loading conditions exceed existing afterload. Thus, haemodynamic preload and afterload is supplemented by an intrinsic preload and afterload. This intrinsic preload and afterload are tuned by local specific antagonistic activity which varies with spatial alignment of chains of aggregates. The heterogeneous distribution of intrinsic ventricular loading cannot be analysed in the clinical scenario.

An active contractile limitation of wall thickening by oblique transmural netting is essential part of ventricular shaping. Though endless chains of myocytes connect aggregates with each other to form a continuum, they primarily contribute to the function of the respective host aggregate. Each segment of an endless chain of myocytes...
bundled within an aggregate, serves shaping it according to local geometry and coupling conditions. Therefore, the one aggregate generates an unloading force, the next an auxotonic force.

This kind of interaction also applies to the global heart muscle while actively contracting in longitudinal, circumferential and radial directions. Active shortening in longitudinal and circumferential direction necessarily causes a passive increase in wall thickness. Active wall thinning necessarily causes passive longitudinal and circumferential elongation. This spatial interaction mutually tunes the preload and afterload in neighbouring areas throughout the myocardial continuum.

**SELECTIVE SENSITIVITY TO POSITIVE AND NEGATIVE INOTROPES AT LOW DOSAGE**

A hitherto unknown feature of obliquely intruding and extruding aggregates is their statistically higher sensitivity to low-dosed positive and negative inotropic stimulation than that of tangential aggregates (figure 6). This asymmetric response to inotropes applies only to low-dose therapy with catecholamine and β-blockers. In contrast, oblique transmural and tangential aggregates show identical sensitivity to currently used high doses of positive and negative inotropes. Asymmetric sensitivity to low-dosed inotropic medication primarily enables to manipulate selectively the inotropic state of the intruding

*Figure 2* Cardiodynamic models: (A) Frank’s concentric stress model postulates unidirectional concentric forces and hence anticipates an exclusively tangential alignment of endless chains of myocytes. (B) The antagonistic stress model refers to the continuum of spatially netted myocardium. A segment of the ventricular wall has been divided into five layers to show the layered turn of endless chains of myocytes in helix angles. Superimposed layers are joined by dense transmural netting, which latter develops endo-epicardial, dilatory forces. (C) Histological cross-section through the free wall of the porcine heart in plane with the ventricular base. For better discrimination of the pattern of netting, the myocardium had previously been pneumatically distended by coronary perfusion with compressed air. The section shows (left) a thick subendocardial, densely netted myocardial network with a steep bending towards the endocardium, (mid) a thin layer of circular (vertical) endless chains of myocytes and (right) a small subepicardial layer of endless chains of myocytes which are moderately steep inclined towards the epicardium. (D) The tangential histological section through the left ventricular free wall of a porcine heart shows the prevailing striation, which, however, appears somewhat fuzzy because of the dense in-plane netting of the endless chains of myocytes.
and extruding aggregates.\textsuperscript{46,47} While interacting with the prevailing tangential netting global ventricular myocardium must be involved. This hypothesis is supported by observations regarding pathological hypertrophy in the state of unbalanced antagonism\textsuperscript{48,49}.

**Figure 3** Electron-microscopic cross-section through three neighbouring flat aggregates joined by fine connective tissue which allows gliding of the aggregates against one another. The shape of cross-sections of single myocytes within the aggregates varies depending on how the angle of the section plane is oriented to the aggregate section plane.

**Figure 4** Miniaturised needle force probe; 15 mm long, 1.3 mm thick, (1) strain gauge, (2) bending beam, (3) temperature sensor, (4) pointed end of the needle probe, (5) side window serving as escape-fluid, (6) outer tube and (7) support of the bending beam.

**PATHOPHYSIOLOGICAL POTENTIAL OF SELECTIVE SENSITIVITY TO INOTROPES**

The hypertrophied heart muscle is the result of an adaptive primarily physiological process in the presence of increased pressure or volume condition like in pregnancy or in response to continuous physical exertion. Clinical observations confirm that this adaptation is reversible. The process of pathological myocardial hypertrophy presumably cause an antagonistic imbalance with respect to contractile and dilatory forces of the muscle aggregates.

In the scenario of permanently elevated level of positive inotropes triggering of selective hypertrophy of the dilatory active oblique transmural netting occurs.\textsuperscript{50,51} Further impeding of wall thickening and an enhanced interaction within the netted continuum cause an increase in tangential forces. The consecutive hypertrophy of the tangential structures causes an increase of wall thickness.\textsuperscript{42,46} In consequence, transmural straightening of non-tangential netting increases and causes more antagonistic transmural dilatory forces. A self-enhancing process continues causing an imbalance of antagonistic forces and structures. This process probably finds its limitation by limited oxygen transport to tissue. In this context, the distribution of developed forces measured in hypertrophied porcine hearts is important.\textsuperscript{52} Contrary to the Laplace’s
law, the forces are highest in the subendocardial layers of the spiral aggregates. The resulting compression and strangulation of myocardial microcirculation primarily occurs in the layers, in which coronary supply is limited anyway.

The asymmetrical sensitivity to low dosed negative inotropes (figure 6) presumably provide a therapeutic approach. The effect of selective sensitivity of non-tangential netting components to low-dosed negative inotropes was described in the literature. In a case report, Emeis et al successfully treated a baby born with right ventricular hypertrophy. Under low-dosed β-blockade, there was complete remission of hypertrophy. Obviously, the self-reinforcing process of myocardial hypertrophy has been interrupted by low dose β-blockade.

In the presence of increased LV wall thickness, it is a diagnostic challenge to distinguish between LV hypertrophy due to the physiological response to chronic physical stress or due to a pathological self-enhanced formation. Timely limited therapy with low dosed β-blockers might be a tool of distinction.

**SUMMARY AND CONCLUSION**

The presence of myocardial intrinsic antagonism limits a simplified view to regional myocardial deformation. LV ejection fraction solely does not provide sufficient information about global and regional LV contractility. Stroke volumes, intracavitary pressures and ventricular...
motion are not suitable to reflect intramural energetics or dynamics in detail. An increase of intramural performance relative to haemodynamic performance correlates with evolving LV hypertrophy. Stress-related LV performance is probably tuned by initially enhanced dilatory performance. Physiological and reversible LV hypertrophy presumably might be distinguished from pathological and irreversible LV hypertrophy as well as pathological LV wall thickness by modern diagnostic tools. The assessment of the spatial coordinates of single fibre strand seems to be helpful to understand the individual importance of myocardial architecture for the disease process in specific cardiac diseases, in which ventricular geometry is pathologically changed, for example, ischaemic heart disease, dilative and hypertrophic cardiomyopathy, as well as takotsubo cardiomyopathy. Because non-tangential parts of fibre strands increase LV dilatation with increasing wall thickness, specific pharmacological interventions can address selected compounds of myocardial fibres to optimise muscle contractility. The predominant effect of low-dose beta-blockade on circumferential and radial shortening was documented with 3D tagging by CMR, which can be explained by the different compounds of the myocardial fibre architecture. New sophisticated modalities of deformation imaging and CMR tagging might be able to detect better pathological inhomogeneities in the architecture of the ventricular musculature in the future.

Cardiac imaging diagnostic will certainly be improved considering the antagonism of contractile forces within the heart muscle.

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