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Guest-editorial

Structure conditions function and vice versa

The Alicante meeting was devoted to the proposition that "The structure of the heart determines its function and vice versa". This was not to indicate that we did not appreciate the astonishing progress in cardiology achieved by developments such as molecular biology, nor to re-run old controversies. It was rather to remind ourselves that new observations at the molecular level must ultimately be correlated with ventricular structure and mechanics; and furthermore that to concentrate research totally on the molecular level to the exclusion of morphology, pathomorphology and the cardiodynamics of normal and diseased hearts, with the mistaken idea that all is known about these aspects, would be short-sighted.

In cardiology morphology is held in low esteem. One main reason is the lack of preparation techniques to gain access to the intricate weave of the heart muscle. Tissue analysis has remained on a strictly cellular level. A common morphological substrate of myocardial failure has not been identified [70]. There is growing evidence in recent investigations [10,25,82,83] that morphology will not succeed in yielding a comprehensive understanding of the wide palette of adaptive heart diseases until tissue analysis engages also in the analysis of the heart's mesh texture. In fact, until recently there were no appropriate methods available to analyze spatial myocardial and connective tissue weave, neither post mortem, nor *in vivo*. However, recent advances in imaging techniques indicate that in the near future pathomorphology will be obliged to extend its analytical spectrum to keep abreast with clinical diagnostics.

1. The weight of morphology underrated by oversimplification: a ponderous conceptual heritage

Who dares to blame Frank for having misguided us about ventricular function, and for doing so in opposition to 18th and 19th century knowledge of the heart's structure [5,19,45,55,61,62]? For good reasons he simplified myocardial architecture by removing its subtleties to the extent that later decades saw no further need to investigate the matter [22]. With the following suggestion Frank shattered the results of more than a century of research [23] and discussion:

> "So little is known about the orientation of the myocardial fibres that any determination of tension in individual fibres seems to be impossible...
>
> The longitudinal direction of the myocardial fibres must generally be tangential with respect to the ventricular surface. If these fibres were in a normal direction to the wall surface, their shortening would induce ventricular dilatation rather than a reduction in ventricular volume..." (translated from the German).

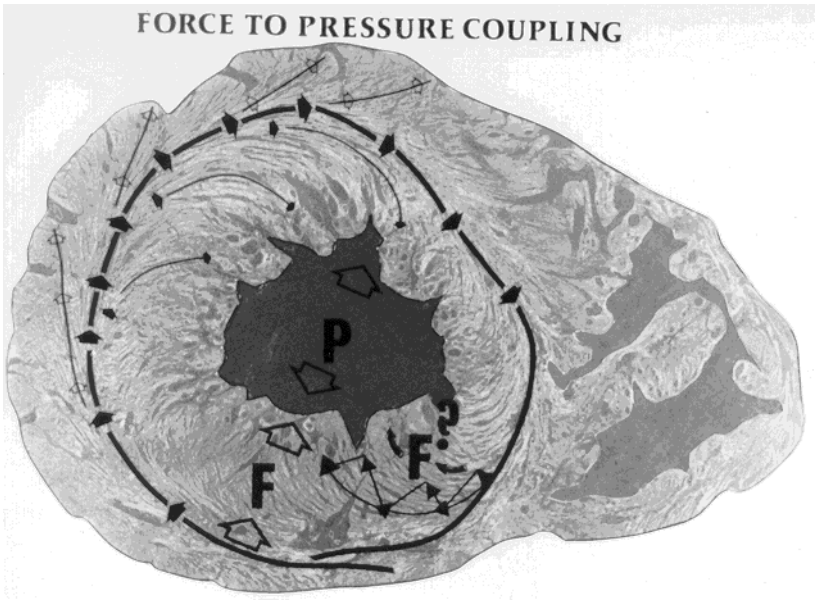

Fig. 1. The puzzle of the transmission of developed myocardial forces to intraventricular pressure: by what complex formula does Laplace's Law apply to the beating heart if ventricular structure and function are organized in a dualistic way?

More than two centuries prior to Frank's attempt, Lower [45] had delineated the helical continuum of a myocardial band that he supposed to be coiled around both ventricles. This concept implied oblique transmural trajectories. Lower's complex analysis of ventricular myoarchitecture could not, however, be demoted forever, even though Streeter's simple myoarchitecture [75–78] was accepted with alacrity when Sonnenblick [73,74] in the 1960s tried to transfer Hill's force velocity relation [30–32] to the function of the heart muscle. Even today non-invasive imaging methods tacitly assume that in any individual heart there is a geometrically unambiguously predictable transmission of myocardial force to ventricular pressure (Fig. 1). Points of concern are (1) that all myocardial fibres are assumed to be aligned in parallel to the epicardial and/or endocardial surfaces, and hence, it is taken for granted that all forces generated are acting in the direction of ventricular emptying and (2) histologically determined myocardial fibre alignment has been unconditionedly taken for the alignment of stress transmission pathways.

2. Pathomorphology underinterpreted

There is little interest in myoarchitecture in disease since it is thought to be trivial and to be untypically modified in myocardial disease. Exceptions such as fibre disarray in hypertrophic obstructive cardiomyopathy [59] and myofibrosis [11,82,83] remain functionally poorly interpreted. Clinicians are not used to examining the functional implications of structural myocardial remodelling. So pathomorphological diagnostics remained focused on myocellular or global ventricular observations, and alterations in fibre orientation did not share in diagnostic evaluations.

The recent arbitrary amalgamation of diverse pathomorphologies, subsumed under the term "cardiomyopathies", reflects the clinician's uncompromising preference for purely global haemodynamic descriptions rather than primary patho-morphological definitions.

3. Comprehension of ventricular function remains truncated until the gap in knowledge about ventricular structure is bridged

In the beginning of the 19th century Brachet [6] had a concept to explain indirectly the mechanisms by which myocardial scars are able to hamper systolic ventricular constriction and diastolic ventricular unfolding, respectively, or by which intramural performance continuously increases along with the development of myocardial hypertrophy, until the myocardium is ultimately exhausted by the increasing internal impediment of ventricular constriction. Brachet's intention was to explain diastolic ventricular unfolding. His morphological background was contestable, but his bioengineering concept was ingenious. It implied the interaction of tangential forces promoting ventricular ejection and radial forces mediating active wall thinning, and hence, sustaining ventricular dilatation.

Local force measurements within the ventricular wall [46,47,52] have demonstrated that the base, midportion and apex of the left ventricle do not respond in the same way and to the same degree of sensitivity to inotropic interventions and to changes in pre- and afterload. A function probably based on a structural compartmentation of the ventricular wall emerges, giving rise to the question: is this feature of the heart muscle a quirk of nature or essential for ventricular function? The rapid development of imaging methods enabled the clinicians to describe the motion pattern of the ventricles and that of separate layers in the free walls and the septum. However, it is fair to emphasize that data on global ventricular or segmental motion cannot be comprehensively interpreted in terms of myocardial function until wall stress also becomes measurable, directly or indirectly.

4. Indirect measurements

Enddiastolic ventricular volume is an ambiguous index: in the inhomogeneously damaged ventricle, the enddiastolic volume is essentially determined by the most damaged wall segment. Global ventricular performance, however, is generated mainly by the unimpaired part of the ventricle. The undamaged compartment determines the filling pressure. Enddiastolic volume measures the volume of both the impaired and the unimpaired compartments. However, visualization of changes in ventricular volume which also displays systolic bulging, thus indicating the actual state of deterioration or recovery of any diseased compartment, is of definite diagnostic value.

The rate of ventricular pressure increase during early systole is ambigious as it increases with inotropism *and* with augmenting preload [39,73,74]. This weakness in selectivity has ultimately led to the rejection of the *contractility concept* as a diagnostic tool in clinical cardiology.

In a recent paper Palladino et al. [60] have worked out the theoretical background of a clinically applicable procedure which allows one to measure the heart muscle's global contractile properties. Making use of a single isovolumetric contraction the heart muscle is kept in a functional position which is most comparable to the isometrically contracting papillary muscle. Under these conditions transients in intraventricular pressure give insight into the working conditions and capacity of the heart as a haemodynamic pump. However, inhomogeneities in ventricular wall function and any putative dualistic organization of functional anatomy remain hidden behind any contractility index derived from global ventricular pressure. This is a restrictive condition as there is growing evidence that inhomogeneities in wall motion and stress distribution increase in the diseased heart [66].

Recent endeavours have been focused on non-invasive measurements. What hinders the unqualified search for non-invasive diagnostics is the fact that "pressure work" definitely requires a higher rate of myocardial metabolic activity than "volume work" [29,44,69]. Though facing the problems inherent in

the measurement of wall stress, it is fair to stress the position that clinical diagnostics should measure what is *reliable* rather than what is accessible.

5. Prospect and aims

This author is on the horns of a dilemma: cardiology is an academic discipline and does not readily accept new concepts nor the resurrection of those that are assumed to have been overcome. It is our aim to view the structure and function of the heart muscle in synopsis because there are data supporting the concept that developed forces within the ventricular wall yield a comprehensive pattern of motion: ventricular constrictive forces should prevail, but, permanently active dilating forces are also supposed to exist, in addition to the intracavitary filling pressure [46,47].

In the case of myocardial fibre disarray, in fibre rearrangement related to ventricular hypertrophy, in myocardial fibrosis and in some storage diseases, we speculate that the equilibrium between the constricting and dilating forces becomes unbalanced. Intramural performance, i.e., hidden work, may be excessive, and hence, myocardial hypertrophy may occur without apparent haemodynamic stimulus. However, what are the primary mechanisms leading to myocardial fibre disarray or connective tissue ingrowth and what force determines its orientation? What is the "second" pre-and afterload in the "tethered", i.e., fibrotic heart?

6. The trouble with invasive methods

Methods, namely intramyocardial "pressure" measurements [1,3,17,18,27,38,64,65,67] and local "force" measurements [12,15,20,34,35,42,46,47,52,66,81], are available to measure local wall stress. Inhomogeneities in ventricular wall function suggest the need for functional investigations on a segmental level in addition to global measurements. However, the coupling geometry of any device introduced into the myocardial meshwork has been the subject of relentless controversies. One main point of concern is the general understanding of myocardial fibre alignment serving as stress transmission pathway. To stimulate the search for adequate diagnostics a more functional consideration of the heart muscle's weave is mandatory. The first step to be taken is to display and to interpret ventricular structure in the normal and diseased heart as a variably loaded spatial contractile net.

7. Point of departure

That was where we started when we summoned scientists from the various disciplines with the aim of reinvestigating potential new and practicable approaches to ventricular structure and performance. Admittedly, we felt under pressure, because any new idea had to be consistent, and near enough to clinical routine to turn the interest of cardiologists back to ventricular structure and performance.

Following the historical line [5,7,8,19,21,26,28,48,49,56,62,63] the ideas for the Alicante meeting were essentially linked to the search for the driving forces involved in ventricular diastolic unfolding: in 1965, the morphologists Puff and Feneis coined the expression "garden hose effect" [21,63]. In 1968, Lochner et al. [44] rediscovered the phenomenon and again called it "the garden hose phenomenon". In the American literature the impact of coronary perfusion on ventricular dimension had long been documented as "the Gregg-effect" [26]. Historically it is worth mentioning that the Austrian

physiologist Brücke (see Ebstein [19]) had described the ventricular dilating effect mediated by the coronary perfusion pressure as long ago as 1856. During the late 19th century and the beginning of the 20th century dilating forces affecting ventricular wall motion were widely discussed [19]. Between the early 1960s and the late 1980s the most extensively investigated approach to ventricular dilatation was the contribution of an intramural hydraulic driving mechanism [46].

In favour of a hydraulic mechanism involved in ventricular mechanics seemed to us to be the existence of wide intercapillary sinusoids which were supposed to serve as a compliant intramural blood reservoir [48,49]. However, the rare incidence of sinusoids in the human heart tempered belief in the importance of coronary perfusion dynamics on intramural hydraulics. Recently, Djavakhisvili presented data which demonstrated that in coronary heart disease there is an enormous proliferation of sinusoids [16], and hence, they are understood as an emergency blood supply system. In the search for mechanisms mediating ventricular diastolic unfolding, however, they seem to be of minor importance.

Harvey's [28] authoritarian opinion that the ventricular filling pressure alone was responsible for diastolic filling, was refuted by *subatmospheric* intraventricular pressure recordings [7,8,56] and by an *octopus-like* movement [62] of the freshly excised, still beating heart immersed in nutritive solution. In fact, during immersion the ventricular filling pressure and the coronary perfusion pressure are set to zero, but the ventricle still keeps rapidly dilating and refilling during diastole. So, coronary perfusion pressure probably has been overestimated as the main mechanism driving diastolic unfolding.

In the early 1970s we postulated an oblique transmural contractile element to be involved in actively reducing wall thickness and hence, supporting early diastolic ventricular unfolding [46,47]. The concept implied the interaction of (1) a fibre component more or less obliquely aligned in an endo-epicardial direction yielding a permanently active dilating force and (2) a hydraulic function of intramural fluids including blood, lymph and the myocardial mass itself. So a *dualistic organization* of the myocardial structure and function was conceived. Internal work remains, however, definitely hidden (blind performance) behind the global haemodynamic performance of the ventricle. This concept called for direct measurements of intramural mechanics, namely local pressures and fibre stress measurements.

Various techniques for intramyocardial pressure measurements had been developed [3,17,18,38,64, 65]. Facing the difficult coupling conditions to myocardial interstitium Rabbany [65] outlined the various measuring approaches and the essentially different characteristics of the signals obtained by different methods. Following this line he further developed a bioengineering concept of the intramural distribution of regional wall stress ultimately assuming that cellular and subcellular components must be considered in order to understand the hydraulic properties of the ventricular wall.

Intramural hydraulics have been investigated extensively. Detailed concepts concerning the regulation of intramural fluids, in particular coronary blood apportionment, have been worked out [64]. The results obtained by animal experiments were particularly inhomogeneous with respect to the measuring site, the measuring depth, the functional state of the heart and coronary perfusion. Furthermore, as a feature of the methods used, the variably critical coupling conditions of the measuring system to the myocardial interstitium essentially determine the signal which is measured.

Another approach was to measure fibre stress [12,15,20,34,35,46,47,52,66,81]. We used needle force probes, small in dimension and shaped to be applicable to any measuring site within the beating heart *in situ* [47,52,66]. The existence of a dualistic basic organisation of ventricular function is supported by the finding of pronounced variations in the slope of the local force signal during ejection and during endsystolic inactivation, both in quantity and in time. What we found, by intermittent and long term measurements and by systematic mapping of the left ventricular free wall [66], is not

completely covered by Streeter's morphology [75–78] nor by Ingels' harmonic layered fibre activity, either in the normal or in the hypertrophied heart [36]. So we conclude that results obtained by intramyocardial measuring approaches, whether pressures, forces or shortening distances, emphasize that a renewed study of morphology is definitely mandatory.

8. Back to ventricular morphology

The study of left ventricular structure has a history stretching back to Vesalius (1514–1564). Lower's standard unwinding preparation [45], i.e., the blunt preparation technique of the heat denatured heart muscle (BUT), lent support to the idea that the ventricles were made up of discrete, overlapping muscle bands, each band being consistently identifiable. Torrent-Guasp [79,80] developed the idea of preferential pathways. He ultimately proposed a model in which a set of fibre pathways extended from the aorta to the pulmonary trunk, encircling the right and left ventricles as a figure of eight, and resembling a flattened rope.

The blunt preparation technique (BUT) quite generally opens the possibility of studying myocardial fibre alignment in all parts of both ventricles and in any layer, with the restriction that the heart muscle needs to be heat denatured.

One of the crucial questions not answered during our 1995 workshop was whether the inhomogeneities in ventricular motion pattern, segmental shortening distances, intramyocardial pressures and local forces are really the workings of an intricate – for instance band-like – secondary structure in the seemingly simply woven grid structure of Streeter's [75–78] myocardium? According to Ingels [36] the heart muscle is perfectly divided into spiraling muscles which promote ventricular emptying and circular fibres which overcome intraventricular pressure. A subendocardial spiraling muscle compartment complements a subepicardial one, and both together contribute to equilibrate transmural fibre work. Torrent-Guasp's rope model is understood to fit perfectly into Ingel's bioengineering model of ventricular wall dynamics. Furthermore, Ingels interprets collagen struts [11] to transmit forces from the earliest excited subendocardial to sequentially excited superjacent fibres and ultimately to the epicardium. Collagen is also seen as a possible site of systolic energy storage which might be expended during early diastole in favour of a rapid diastolic ventricular unfolding.

Torrent Guasp's band-like structure in particular includes the potential for:

- longitudinal stress transmission between remote segments belonging to both ventricles;
- an attenuation of and deviation from the primarily longitudinal stress transmission by large *areas* of *adhesion* between superjacent segments of the looping muscle band in both ventricles; and
- an endo-epicardial, i.e., oblique transmural, stress transmission pathway through the areas of intergrowth and along a rope-like twisting of the band-like muscle continuum.

9. Are there active dilating forces?

Torrent-Guasp interprets his band-like heart muscle structure as a spring which is charged during systole by winding it up like an elastic spring [79]. He believes that the stored elastic energy contributes to late systolic or early diastolic ventricular unfolding. However, Gibbons-Kroeker et al. [24] and Shapiro and Rademakers [72] have shown, using MR-tagging, that the unwinding of intramural myocardial spiralling happens exclusively during the isovolumic relaxation period, and hence, according to our understanding, it has no direct volume effect in the sense that it does not directly promote

ventricular filling. In consequence, we doubt Torrent-Guasp's suggestion that this intramural restoring activity engenders elastic forces, whether they are temporarily stored to enhance ventricular unfolding later (but still during early diastole), because in that case a further elastic structure – other than the then quickly unloading muscle itself – must be postulated to serve as temporary storage. A sequential energy transfer between potentially elastic structures would result in an inefficient driving mechanism. So, in due appreciation of Shapiro's and Rademakers' results we are inclined not to attribute an important direct or indirect part of the heart muscle's wringing activity to diastolic ventricular unfolding.

Schmid et al. [71] referring to human NMR-data succeeded in simulating in a computer animation the unwinding and rewrapping of the myocardial band as it is arranged, according to Torrent-Guasp, around the ventricular lumina. Starting from the inner and outer biventricular boundaries they manage to associate each band segment to its unique locus within the natural spatial coordinates and then to continuously reassemble the sequence of segments within a sliding, changing system of coordinates in order to cleave the muscle body and hence unwind it to a stretched out band.

Coiling is an important feature of heart structure both on the myocardial [36] and the connective tissue level [50]. However, the average bend radius essentially varies in the different compartments of the left ventricle [80] and it may further essentially vary in the diseased heart. So, the prospective benefit of the new software could be that it might help to detect coiling disorders, for instance as part of developmental diseases in newborn hearts. A main prerequisite for this type of investigation to become clinically feasible is the non-invasive recognition of the exact coiling direction on the beating heart *in situ*. NMR-tagging displays the apical twisting during the ejection period and untwisting during late systole [24,72]. Supposing that the apical twisting mirrors the main alignment of the contractile pathways, dynamic analysis may reveal the heart's intricate spatial composition in health and disease.

By extending the preparation technique and overcoming Torrent-Guasp's restricted view of the cleavage plane, the fibre *strand peel off technique* (SPOT), which is visualised by digitizing the contractile pathways as they are displayed, definitely confirms the existence of an obliquely orientated endo-epicardial fibre netting component [13,51]. If the oblique transmural structure corresponds to an equidirectional force transmission pathway, according to our understanding it carries an *internal load*. It yields an *endo-epicardial force vector* which opposes systolic ventricular wall thickening and summons up an amount of energy stored in the elastic properties of the myocardium itself. Measured meshtension qualifies this opposing myocardial activity by a characteristic force recording displaying a continuous increase during the ejection period (auxotonic contraction = afterloaded type of local force signal) and a definitely delayed decay [64]. This load is primarily independent of haemodynamic pressure afterload. It is a function of *ventricular size* and *motion amplitude*. The forces thus during systole stored and longer persisting [9,37] are, we believe, released at end systole to give the first kick of ventricular unfolding. Late systolic active wall thinning is thus taken for one mechanism which initiates ventricular unfolding [47].

The digitized heart muscle [13,14,51] confirms Streeter's morphology in so far as it displays layered fibre rotation upon a transmural axis, erected in a normal direction to the epicardium. Yet, it supplements Streeter's morphology since the whole heart is analyzed including the septum and the right ventricle. Finally, it overcomes Streeter's, Torrent-Guasp's and Sanchez-Quintana's [68] recent morphology because it introduces an oblique transmurally arranged netting component as being essential to the heart muscle structure. A new dimension of myocardial anisotropy has thus been quantified.

10. Other putative functions of the three-dimensional weave

The promotion of dilating forces is one potential function of an oblique transmural netting component. Another function could be its involvement in the *regulation* of ventricular function. Kresh and Amour [40] postulate a "homeodynamic" mechanism designed to act as a self-regulation system. For this system to adapt ventricular function to global haemodynamics an afferent monitoring system is required. As has been shown by Lakatta [41] the Frank Starling mechanism is indeed utilized to augment stroke volume in order to meet the need for increased cardiac output during exercise. During strenuous exercise there is an increased reliance on the mechanism, especially in elderly subjects in whom the effectiveness of catecholamine modulation of myocardial performance and stroke volume is diminished. An intracardiac self-regulating system, namely the Frank Starling mechanism, acts from and on a cellular level. Its interplay with an extracardiac, i.e., a central nervous or humoral, control system however, needs instantaneous information about ventricular size and wall stress (sensing intracavitary pressure) which might be monitored as an afferent signal.

The spatial netting feature of the heart muscle displays the potential to measure (1) intraventricular pressure by sensing tangential stress in the prevailing surface parallel netting component. (2) Wall-thickness, and hence, ventricular diameter, could be measured by sensing stress in the oblique transmurally aligned netting component. Likewise, stress in spatial directions could be measured by receptors coupled to the connective tissue. However, to our knowledge, the morphological substrate of stress receptors has not been identified in either coupling position.

Furthermore, in the interventricular septum the myocardial fibre arrangement is different from that in the free walls of the left ventricle in so far as the turning in some layers of the fibre alignment upon a transmural axis is more abrupt between layers. Considering that superimposed layers in the septum are densely netted we infer that shear stress must be high in the septum. This assumption is in keeping with our measurements. Microergometry has confirmed a particularly high level of meshtension in some measuring sites of the septum, namely higher than in any measuring site in the free walls. High shear stress would explain the relative lack of motion of the septum as compared to that in the heart's free walls, as documented by various imaging methods [2,4,10,71].

Thus, the septum is likely to be a main site of action of internal, i.e., blind performance, resulting in septal (self)stiffening. The mechanism may be an important element of ventricular shaping just like the sepia shell acts in the cuttle fish.

11. Myocardial weave versus the connective tissue network

The evidence compiled by Caulfield and Janicki [11] concerning the impact of connective tissue on the heart's shape, size and dynamics opens quite another page in the story of ventricular structure and function. Here collagen in all its different expressions, rather than the contractile tissue element, is a most important variable in the determination of ventricular remodelling in disease. Clinical evidence seems to confirm what has been suggested by the authors [11], namely that the polymorphous aspects of cardiomyopathies are mainly determined by the collagen turnover. The lack of understanding and methods of investigation of the spatial orientation of connective tissue, however, remains a point of restriction.

12. The mathematical approach

Calculated wall stress has been used as a reference value for intramural force and pressure measurements [35,36] and for far reaching therapeutic extrapolations which suggested that in chronic arterial hypertension single fibre stress in the hypertrophied myocardium is the same as in the normally loaded ventricle [43,58].

Mathematical approximations of ventricular wall stress start principally from two different visions: ventricular wall structure can easily be modelled when the goal is to yield physiological intracavitary pressures [57,84]. However, when the simulation of intramural mechanics and dynamics is the goal, using the results of intramyocardial pressure, fibre stress and shortening distance measurements, then the mathematical model becomes rather complex because any, for instance band-like, secondary structure of the heart muscle imposes important inhomogeneities in fibre direction and in wall thickness, and hence, in segmental wall stress. Referring to that latter morphology, a mathematical model should include the existence of segmental adhesions which attenuate and bias wall stress transmission between remote segments. From our recent studies [13,14,51,53,54,66] we infer that for modelling a reliably comprehensive ventricular function an oblique transmural weave component has also to be taken into consideration.

13. Pathomorphology

Models also become of clinical interest when referring to tissue alterations. For instance, when areas of adhesion are transformed into transmural scars after infarction, there is a dramatic increase in tissue stiffness which converts the zone of smooth adhesion into a rigid *pathological fixed point*. Myocardial fibres attached to these rigidly fixed points hypertrophy as a result of their quasi isometric mode of contraction on the rigid scar [33,46].

Methods in pathomorphology are not adapted to analyzing the diseased heart muscle in terms of aberrations from the “normal” three-dimensional structure. Histological examination of specimens taken at post mortem has so far been unable to demonstrate the three-dimensional gross fibre alignment. Combining, however, the fibre Strand Peel Off Technique (SPOT) on the heat denatured heart muscle with digitizing techniques promises to become a simple way of assessing fibre alignment in the normal heart and fibre disarray in [53].

14. Myocardial imaging and cardiac surgery

Imaging techniques are ahead of the clinicians mental pictures of the functional anatomy of the heart [2,4,71]. Imaging methods are able to discriminate details in the pattern of the heart’s motion, the structural and functional base of which is not incorporated in routine concepts of clinical cardiology. For instance, layered wall motion in the normal and the diseased heart is not within the scope of clinical diagnostics. The effects of pathological fixed points, i.e., concretion of layers by scars, have not been investigated.

The cardiac surgeon, during four decades of breathtaking development, has nevertheless virtually failed to become interested in the structure of the ventricular wall to an extent that even the most invasive interventions on the ventricular myocardium itself, such as aneurysm surgery, are performed on a strictly empirical base rather than on the basis of a structural concept.

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