

## Inter-ventricular septum: New observations on the structure and function coupling

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### Abstract

Histological relationships and the distribution of junctions between myocardial cells and connective tissue were investigated in the inter-ventricular septum. Pig hearts were studied using 2 techniques: Picro-Sirius red-collagen-staining of frozen sections for connective tissue septa, and immune-staining with antibodies against Desmoplakins for intercalated discs. By overlaying serial sections 10 microns apart, the distribution of 1,010 intercalated discs in 11 base-to-apex fields was counted and scored in relation to connective tissue septa. The orientation of connective tissue structures was also observed in rat and rabbit hearts. The inter-ventricular septum is not separated into gross anatomical parts by connective tissue septa. Perimysial connective tissue septa run base-to-apex within the inter-ventricular septum following spiral patterns. Gap junctions are absent from connective tissue septa larger than twice the myocyte diameter. Only 8.36% of the total number of intercalated discs were co-localised with in the connective tissue using an overlay technique of immunocytochemical and connective tissue stains. Co-localisation was only 3.00% when the counts were made in the immune-stained sections, guided for connective tissue localisation by serial sections stained with Sirius red. Histology confirms the spiral pattern of ventricular myocardial structures. The reported ultrasound septal reflection is caused by changes in the direction of myocytes rather than the presence of connective tissue sheets. The near absence of intercalated discs in perimysial connective tissue tracts in the inter-ventricular septum confirms the myocardial predisposition for longitudinal propagation of electrical excitation along the sheets of myocardium defined by the perimysial septa. These septa, not directly involved in impulse transmission between myocardial cells, modulate the propagation of electrical excitation. These aspects of structure and electrophysiological relationship within the inter-ventricular septum have important consequences for understanding ventricular function and dysfunction, and for choosing anisotropy factors to be used in mathematical models of impulse propagation in the heart.

**Key Words:** electrical excitation, electrophysiology, histology, inter-ventricular septum, myocardium, myocardial structure, propagation, ventricular function

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**A**dequate understanding of the myocardial structure and function is indispensable for the management of patients with congenital and acquired heart diseases. In an attempt to improve understanding, the late Francesco Torrent-Guasp published his first observations on cardiac anatomy and physiology and in particular his discovery of the helical ventricular myocardial band 50 years ago in the Spanish language [72-75]. He eventually managed to disseminate his observations to the international scientific community only in the last few years before his untimely death on 25th of February 2005 [76-79]. Although the helical arrangement of the

cardiac muscle fibers had been known for more than 500 years [60], the anatomic concepts proposed by Torrent-Guasp were challenging: he proposed that the ventricles consist of a single myocardial band extending from the right ventricular outflow tract just below the pulmonary valve to the left ventricular outflow tract reaching the aortic valve. The band becomes twisted and wrapped into a triple helical coil during embryological development, and is capable of the sequential contraction responsible for ventricular ejection and filling [72-79]. Since the anatomical and functional observations made by Torrent-Guasp were in

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contrast with the prevailing understanding of ventricular function established over centuries, an ongoing debate appeared in the international literature from supporters on one side and from strong critics on the other [2-6,9-17,21,22,25-29,46,47,49-51,65,66,80,81].

Within the last few years, in addition to several studies on the developing heart [10,19,20,30,43-45,54,55,57,58,67,68,70,82,83], modern technologies, supported by powerful computing hardware and algorithms, have provided astonishing advances in analysis and understanding of the information available from experimental and imaging studies of cardiac structure and function [8,15-17,23,33,35,36,40,42,48,59,61,69]. The common structural spiral feature is only one of the elements responsible for the functional interaction of right and left ventricles [5,6,9,12-14,16,21,22,25,26,46,72-79,81]. Pressure and/or volume overload of either ventricle influences the performance of the other ventricle. Ventricular interdependence is particularly evident in the neonatal myocardium [37]. In adult clinical practice the aphorism “left heart failure begets right heart failure” [1,62,63] is also well known. Right ventricular pressure and/or volume overload stretches the right ventricular free wall, increasing the size of the right ventricle, which causes the inter-ventricular septum to bow towards the left side thereby reducing left ventricular filling and therefore left ventricular stroke volume. The first recognition of this process in congenital heart defects was reported 50 years ago by Dexter, who described the “reverse Bernheim [7] effect”: after surgical closure of a large atrial septal defect causing right ventricular volume overload, the left ventricular function improved because the previously bowed inter-ventricular septum became a functional midline structure [32]. The role of the inter-ventricular septum is even more important in congenital heart defects with complex intra-cardiac anatomy, the best demonstration of which is in children with a single ventricle. The absence of part of the septal structure implies the absence of the myocardial segment responsible for the oblique orientation of the fibers generating the twisting action of the septum and free wall. This results in a ventricular chamber with a spherical shape because of transverse fibre orientation, and therefore a reduced functional performance [27]. The importance of the inter-ventricular septum is also evident in acquired heart disease, such as in patients with inferior myocardial infarction who sustain septal damage resulting in right ventricular failure with consequent mortality exceeding 40% [18]. The septal role in defining cardiac function was initially described in 1865, when the anatomist Hegar indicated that “cardiac anatomy and function will be uncertain until the structure and function of the crossed angles of fibers in the septum are defined” [53]. Both conventional echocardiography [34] and Doppler tissue imaging [8] demonstrate the morphological and functional bi-

layered structure of the inter-ventricular septum. One of the principles that Torrent-Guasp proposed was that cardiac excitation was constrained by the hypothetical borders of the helical ventricular myocardial band. The structure of the inter-ventricular septum, rightly considered the fulcrum of the myocardial mechanical contraction, has been previously investigated [11,17,22,39,41,49,62,63].

In the current study, in order to investigate the coupling of structure and function relationships in the inter-ventricular septum we analyzed: a) the histological relationship between myocardial fibers and connective tissue; b) the distribution of cardiac intercalated discs defined by anti-desmoplakin immunoreactivity within the inter-ventricular septum

### Materials and Methods

Fresh heart material was prepared from pig, rabbit and rat. The hearts from the smaller animals were mounted apex upwards using tissue-tek mounting medium on to cork discs (Speci-Microsystems, Carshalton, UK) and immersed in isopentane (VWR, Lutterworth, UK) suspended over liquid nitrogen. The pig hearts were first sectioned into 6 slices (Figure 1), and then the inter-ventricular septum was further divided into manageable blocks for cryostat sectioning. The quantitative analysis was performed in the sections from one pig heart. From each block ten serial sections of 10 microns thickness were taken. Adjacent (serial) sections were then stained with one of the three following techniques:

- a) Picro-Sirius red-collagen-staining (sirius red in aqueous picric acid) for connective tissue [52]
- b) Immunoperoxidase staining (DAB technique) with antibodies selective against Desmoplakins (Chemicon, Hampshire, UK)
- c) Immunofluorescent stain using fluorescent avidin conjugate with the same primary antibody as in b) [38]

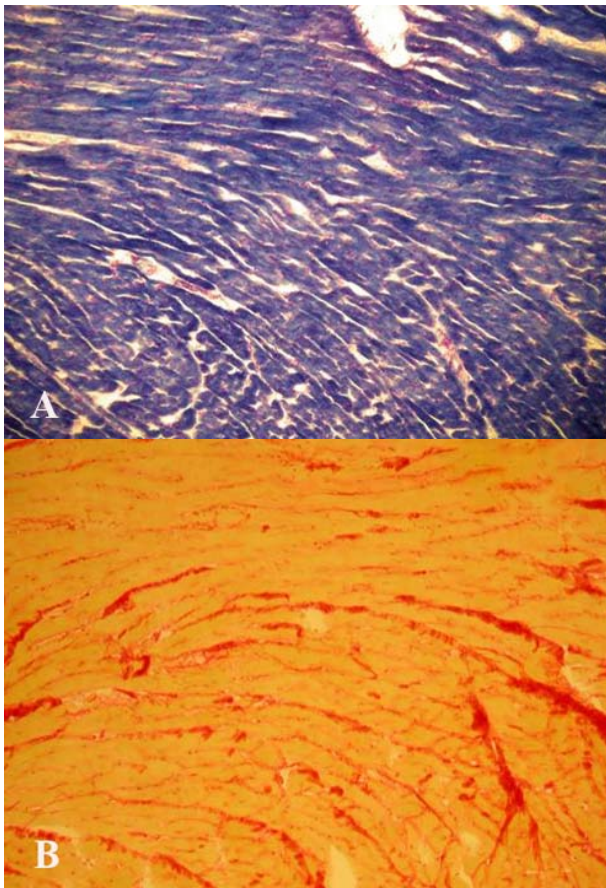
Photographs were taken through the microscope of the various stained sections for analysis.



**Fig. 1** Pig heart cut into different levels (from bottom right to top left): apex, level 1, level 2, level 3, level 4, level 5, and plane of the atrio-ventricular valve.

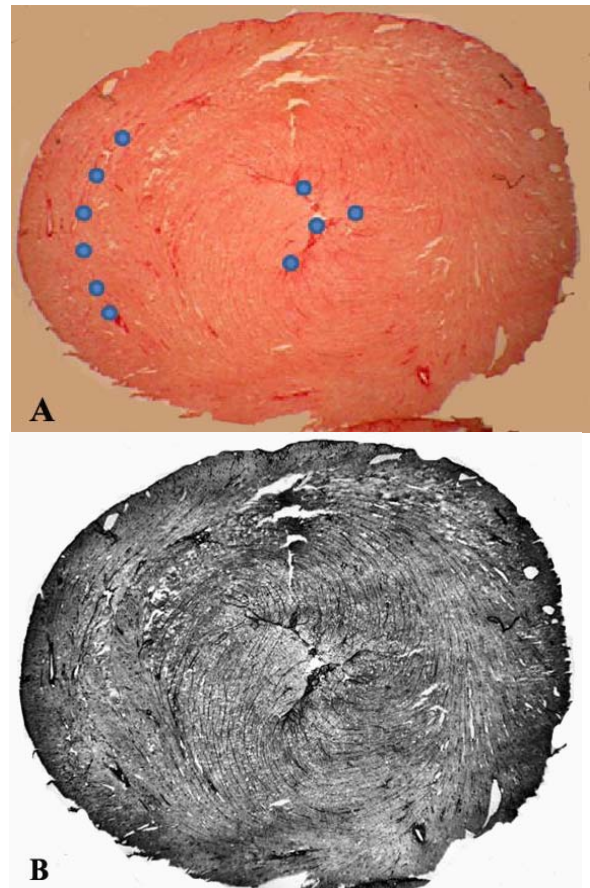
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**Fig. 2** A, Section from the centre of the inter-ventricular septum of a rabbit heart, showing the change of fibre direction. Section stained with Massons trichrome. Connective tissue appears white. B, Section from the centre of the inter-ventricular septum of a rat heart, showing the change of fibre direction. Section stained with picro-sirius red. Connective tissue stains red.

The distribution of intercalated discs, stained by antibodies against desmoplakins, was measured in two ways. First, we marked the antibody staining in fluorescent micrographs on a transparent overlay. We chose areas of the section that had landmarks such as blood vessels that could be used to position the overlay on a photomicrograph of a serial section with connective tissue stained with picro-Sirius red. The gap junctions were then scored as coincident or non-coincident with the red stained connective tissue. However, even within ten micron section, there is a degree of smearing of endo- and perimysial connective tissue during the cutting of the sections so that the degree of overlap of antibody and connective tissue staining can be overestimated. We performed a second analysis using only the immunoperoxidase stained sections in which connective tissue is not so clearly delineated.



**Fig. 3** Whole rat heart stained with picro-Sirius red to demonstrate connective tissue structures. In b), the stain has been enhanced to demonstrate the spiral arrangement of connective tissue septa, particularly in the left ventricle. The luminal spaces, indicated by series of dots are almost obliterated. The right ventricular lumen is crescent shaped, and situated to the left of the figures.

In cases where it was not certain whether a particular intercalated disc co-localised with connective tissue, comparison was made with a serial Sirius-red stained section to confirm the distribution of connective tissue in that location.

### Results

a) Picro-Sirius red-collagen-staining for connective tissue septa

Particularly in the pig samples it was possible to observe a distinction between the gross appearance of the left and the right sides of the inter-ventricular septum. Microscopically, however, this distinction is not easy to demonstrate. There was certainly no clear anatomical separation by a tract of connective tissue into right and left parts. Rather it was possible to visualise a general change of direction of the minor connective tissue septa and the fibres contained within them (Figure 2). The connective tissue septa in the right

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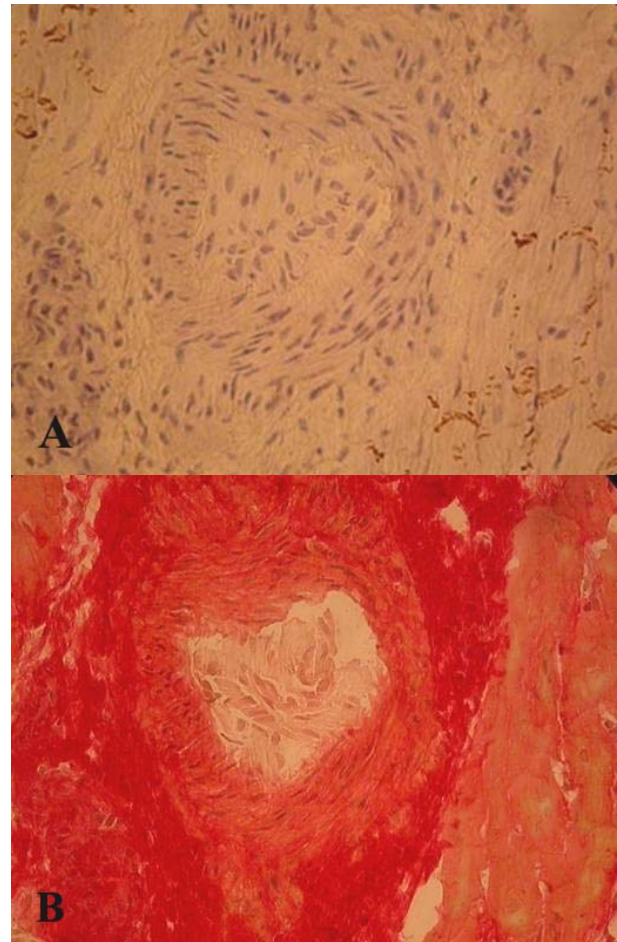
sided component were oriented in an antero-posterior (or tangential) direction and in the left component in an oblique (or more nearly radial) direction (Figure 3). Thin connective tissue septa, clearly visible, separated the fibers into bundles or sheets of muscle fibers approximately five cells thick, with a consistent number of fibers at any level in both right and left components.

b) Immune-stains against Desmoplakins for intercalated disks

The number of gap junctions and their percentage distribution, guided for connective tissue localisation in Picro-Sirius red-collagen-stained sections is reported in Table 1. Desmoplakin-rich junctions were absent from connective tissue septa larger than twice the myocyte diameter (Figure 4). Only 8.36% of the total number of these junctions were co-localised with connective tissue using the overlay technique. The percentage reduced to just 3.00% when the counts were made in the Immunoperoxidase (DAB) sections.

**TABLE 1.** Spread sheet representing the distribution of intercalated discs (IDs) and connective tissue (CT) by two methods: columns 2-5 show results using an overlay generated from immunofluorescent desmoplakin staining on a serial picro-Sirius red section, and scoring co-localisation. Columns 6 and 7 show results obtained by examination of immunoperoxidase stained sections, guided for connective tissue localization by serial picro-Sirius red stained sections.

| septum level | IDs in CT | IDs in non CT | total IDs | % IDs in CT | IDs in CT by DAB | % IDs in CT by DAB |
|--------------|-----------|---------------|-----------|-------------|------------------|--------------------|
| L1 sup       | 6         | 59            | 65        | 9.2         | 3                | 4.62               |
| L1 inf       | 7         | 107           | 114       | 6.1         | 1                | 0.88               |
| L2 ant       | 11        | 94            | 105       | 10.5        | 5                | 4.76               |
| L2 post      | 2         | 41            | 43        | 4.7         | 0                | 0.00               |
| L3 ant       | 5         | 48            | 53        | 9.4         | 2                | 3.77               |
| L3 post      | 6         | 81            | 87        | 6.9         | 2                | 2.30               |
| L4 ant       | 6         | 89            | 95        | 6.3         | 3                | 3.16               |
| L4 post      | 19        | 82            | 101       | 18.8        | 6                | 5.94               |
| L5 ant       | 7         | 52            | 59        | 11.9        | 2                | 3.39               |
| L5 mid       | 2         | 88            | 90        | 2.2         | 0                | 0.00               |
| L5 post      | 7         | 113           | 120       | 5.8         | 4                | 3.33               |
| <b>means</b> |           |               |           | <b>8.4</b>  |                  | <b>3.00</b>        |



**Fig. 4** Serial sections stained with anti-Desmoplakin using the immunoperoxidase method (a) and with Sirius red and haematoxylin (b) showing the gap junctions (intercalated disks) stained brown in a) and the absence of intercalated discs in connective tissue septa. The field chosen includes an intra-myocardial blood vessel to illustrate the staining pattern in gross tracts of connective tissue as well as in the sheets of cardiomyocytes that can be seen towards the periphery of the figures.

### Discussion

In 1991 Dell'Italia [31] observed that the inter-ventricular septum is the central theme to both ventricles, since it binds them together with spiral muscle bundles that encircles both ventricles in a complex interlacing fashion to form a highly interdependent functional unit that exists despite their markedly different muscle mass and chamber geometry.

The importance of the septum versus the free wall was defined by several studies showing that right ventricular performance was not impaired despite either cauterizing the entire right ventricular free wall [71] or replacing the free wall with prosthetic patch material [64],

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provided that the septum remained intact. In contrast, right ventricular failure became evident if the septum was cauterized, or made ischemic by embolic occlusion of the right coronary artery, or exposed to pulmonary hypertension [11].

The most important consequence of the morphological and functional observations of Torrent-Guasp is that the inter-ventricular septum does not have a predominant right or left ventricular side, but rather that it is the central structure between right and left-sided cavities and is composed of the same fiber elements that form the free left ventricular wall.

The increased knowledge of the mechanisms responsible for the ventricular function according to the concepts of Torrent-Guasp [76-79] were not universally accepted and agreed because it was assumed that the right and left components of the inter-ventricular septum should be separated by a distinct layer of connective tissue [2,50,51,65]. In the absence of connective tissue between the right and left components of the inter-ventricular septum, it was difficult to explain and justify the differences in timing and direction of contractility between right and left inter-ventricular septum components (corresponding to the descending and ascending segments of the ventricular myocardial band of Torrent-Guasp), observed by different researchers with different methods: echocardiography [21], Doppler tissue imaging [8], sonomicrometer crystals [15,17,22,41,62], electrophysiology [23,59], SPECT imaging [36] and Magnetic Resonance Imaging [5,6,16,35,40,61].

To better understand the coupling of structure and function, this study was designed to investigate: a) the histological structure of the inter-ventricular septum; b) the distribution of intercalated discs.

### a) Histological structure of the inter-ventricular septum

In order to better visualize the histology of the inter-ventricular septum, we decided not to use electron microscopic analysis, which requires chemical fixation that tends to cause some distortion of the tissues. As already observed by other investigators [2,50,51], because of the changes induced by chemical fixation the tissue planes in cardiac muscle tend to separate, so that what we observed as minor septa with the picro-sirius red stain, appear as cleavage planes in electron micrographs. In our study only freshly frozen tissues were investigated, avoiding any fixation, so that the connective tissue proteins were not denatured and the native tissues remained in place, avoiding any shrinking. The stain was able to show the tissues in their natural position and relationship.

The results of our observations confirmed previous reports on the absence of an anatomical separation between the right and left components of the inter-ventricular septum. The right (descending) and left (ascending) segments have exactly the same characteristics regarding the connective tissue septa and

the constant number of fibers. They are separated and distinguishable because of the difference in fiber direction within their boundaries as demonstrated by the several non-invasive studies. They are not defined by major connective tissue sheets.

### b) Distribution of intercalated discs

Gap junctions are necessary for cell-to-cell communication, as they guide the electrical excitation that stimulates contraction through the cardiac muscle cells. In cardiac muscle cell-to-cell communication is also dependent on desmosomes, associated with transmembrane proteins like Desmoplakins. With regard to the functional consequences of the structural observations, in the absence of a major connective tissue tract separating right and left components of the inter-ventricular septum, the number and distribution of intercalated discs was investigated to identify the structural basis for longitudinal versus transverse conduction of electrical excitation. The presence of only few desmoplakin-positive sites in the perimysial connective tissue septa of the inter-ventricular septum confirmed the preferential propagation of the electrical excitation in the direction defined by the minor connective tissue septa, longitudinal and not transverse. These findings again are in agreement with the observations of Torrent-Guasp and the subsequent experimental and clinical studies with echocardiography [21], Doppler tissue imaging [8], sonomicrometer crystals [15,17,22,41,62], electrophysiology [23,59], SPECT imaging [36] and Magnetic Resonance Imaging [5,6,16,35,40,61].

In conclusion we can confirm the layered structure of the inter-ventricular septum. The two major segments, right (descending) and left (ascending), are not separated by major connective tissue sheets. Perimysial connective tissue septa, not directly involved in impulse transmission between myocardial cells, modulate the propagation of electrical excitation.

These structure/electrophysiological relationships within the inter-ventricular septum have important implications in understanding of ventricular function and dysfunction.

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