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Insights from examination of hearts from adults dying suddenly to the understanding of congenital cardiac malformations

Joseph D. Westabya, Susanna T. E. Coopera, Khari A. Edwardsa, Robert H. Andersonb and Mary N. Shepparda

aDepartment of Cardiovascular Pathology, Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St George’s University of London, London, SW17 0RE, United Kingdom

bInstitute of Genetic Medicine, Newcastle University, Newcastle-upon-Tyne, United Kingdom

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Corresponding author: Dr Joseph Westaby, Department of Cardiovascular Pathology, Cardiology Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St George’s University of London, London, SW17 0RE.

Tel: 0208725 5112; Fax: 020 8725 5139; Email: jwestaby@sgul.ac.uk

**Abstract**

Congenital heart disease is a rare but important finding in adults that experience sudden death. Examination of the congenitally malformed heart has historically been considered esoteric, and best left to those with expertise.

The Cardiac Risk in the Young cardiovascular pathology laboratory based at St George’s University of London has now received over 6000 cases. Of these, 21 congenitally malformed hearts were retained for research and educational purposes. Hearts were assessed using sequential segmental analysis, and causes of death were adjudicated based on thorough macroscopic examination and histology.

Congenital malformations that were encountered included atrial septal defects, ventricular septal defects, tetralogy of Fallot, and transposition of the great arteries in both its regular and congenitally corrected variants. Findings also included hearts with mirror-imaged and isomeric atrial appendages. Direct causes of death included myocardial fibrosis, pulmonary hypertension, and haemorrhage. A small but notable proportion did not reveal a substrate for arrhythmia, raising the question of whether the terminal event was due to the congenital heart disease itself, or an underlying channelopathy.

Here, we demonstrate the value of simple sequential segmental analysis in describing and categorising the cases, with the concept of the “morphological method” serving to identify the distinguishing features of the cardiac components.

1. **Introduction**

Much has been learned over recent decades regarding the substrates for sudden adult cardiac death. These advances themselves have been made possible, to no small extent, by the submission of hearts for autopsy examination to centres staffed by expert cardiac pathologists. One such centre is based at St George’s Hospital in London. Cases are referred by autopsy practitioners when there is an unexplained sudden cardiac death, an inherited cardiac condition is suspected or in complex cases such as grown up congenital heart disease. Since its establishment, over 6000 hearts have now been submitted for expert evaluation. Of these, a minor but significant proportion have come from patients known to have had congenital cardiac malformations. Examination of the hearts showed various probable causes of death, including myocardial fibrosis, pulmonary hypertension, and surgically related complications. Perhaps surprisingly, many of the individuals with quite complex combinations of lesions had not undergone surgical palliation or correction. The findings within the heart, however, revealed multiple features of interest with regard to their abnormal structure. In this regard, it remains a fact that many cardiac pathologists, used to dealing primarily with acquired disease, still consider difficult the interpretation of many of the nuances of the congenital anomalies. Recent approaches to the analysis of the congenitally malformed heart, however, suggest that such suspicion is unjustified. It can now be argued that all that is required to provide an expert description is the ability to distinguish the morphologically right from the left atrial appendage, the right from the left ventricle, and an aorta from a pulmonary as opposed to a common arterial trunk (Anderson and Ho, 1997). All that is required thereafter is a simple description and catalogue of the intracardiac features. Our analysis of the hearts from those dying suddenly bears out this prognostication. In this account, therefore, we outline the significant findings, showing how they demonstrate the value of sequential segmental analysis for description and categorisation of the lesions encountered.

1. **Materials and Methods**

Since the establishment, in 2013, of the centre at St George’s University of London Medical School for the evaluation of hearts from individuals dying suddenly, over 6,000 hearts have been submitted for expert analysis. Of these hearts, 21 congenitally malformed hearts were retained for research and educational purposes (Table 1). In all instances, the hearts were examined following the process known as sequential segmental analysis. Care was taken to exclude any obvious cause of the sudden death, such as anomalous origin of the coronary arteries, evidence of inappropriate surgical or interventional procedures, or acquired disease involving the surgical correction or percutaneous insertion of a device. The hearts were photographed, therefore, to show how it proved possible to provide an accurate account and description of the findings, despite the fact that most of the specimens were incomplete. Microscopic analysis was performed on selected sections including the atrial and ventricular walls, as well as the coronary arteries and the aorta. Demographics, circumstances of death, past medical history and pathological findings are prospectively entered into a database. All hearts were examined by two specialist cardiac pathologists (MNS and JDW) and a specialist cardiac morphologist (RHA).

1. **Results and Discussion**

We are limiting the descriptions of the features found within the specimens to those that are of particular relevance to the analysis and description of the congenital lesions encountered. The overall findings within the series are summarised in Table 1. There was little of particular interest in the 5 hearts obtained from patients who had undergone surgical correction of tetralogy of Fallot, with either pulmonary stenosis in 2 or pulmonary atresia in 3. Surgical correction had been performed in two patients with transposition, defined as the combination of concordant atrioventricular with discordant ventriculo-arterial connections. In these patients, correction had been achieved at atrial level, using the Mustard procedure in one, and the Senning procedure in the other. Evidence was found in the heart corrected using the Senning procedure of narrowing of the systemic venous pathways (Figure 1 – right hand panel). This was not considered sufficient to account for the sudden death. The findings in these hearts showed, nonetheless, that even though the venous channels were now connecting to morphologically inappropriate atrial chambers, it still proved possible to recognise the morphology on the basis of the features of the atrial appendages (Figure 1). This finding bears out the prognostication made by Van Praagh and his colleagues, and now known as the “morphological method” (Van Praagh et al, 1980). The principle states that cardiac structures should be identified on the basis of their most consistent features, and not according to other features that are themselves variable. The principle held its own in the subsequent analysis of all 3 of the hearts obtained from individuals in which discordant ventriculo-arterial connections were congenitally corrected by virtue of the additional presence of discordant atrioventricular connections (Figure 2).

In one of these hearts, the atrial chambers were themselves mirror-imaged, along with the remainder of the bodily organs. This arrangement is often described as “situs inversus”. In the hearts showing congenitally corrected transposition in this setting the morphologically left ventricle, connected to the left-sided morphologically right atrium, remains in left-sided position (Figure 3 – left hand panel). The right-sided morphologically right ventricle, which is connected to the right-sided morphologically left atrium, then shows right handed ventricular topology (Figure 3 – right hand panel). This topological arrangement of the ventricular mass is that anticipated for the normal heart, albeit that in the normal heart the ventricles support morphologically appropriate arterial trunks. The majority of patients with congenitally corrected transposition, nonetheless, are found with the atrial chambers in their anticipated usual position, often described as “situs solitus”. In this setting, it is the ventricular mass that is mirror-imaged, with left handed ventricular topology. This is believed to be the consequence of leftward looping of the ventricular mass during cardiac development, and hence is also known as “L-looping” (Van Praagh, 1972). In the past, this feature was often described in terms of “ventricular inversion”. Almost without exception, the apical component of the morphologically right ventricle is left-sided in comparison to that of the morphologically left ventricle. Following the principle of the “morphological method”, it is this morphology of the apical ventricular trabeculations (Figure 4 – lower panel) that serves best to distinguish between morphologically right and left ventricles, irrespective of their position in space.

In one of our specimens, the atrial arrangement was even more unusual. This heart was presumed to have been obtained from an individual initially thought to have had mirror-imaged atrial chambers. This was because all the pulmonary veins connected to the right-sided atrium, while all the systemic veins joined the left-sided atrium. The septal structures were intact, and there was left-handed ventricular topology. The ventriculo-arterial connections, furthermore, were concordant, and there was mirror-imaged spiralling of the arterial trunks, with the aortic root positioned posteriorly and to the left relative to the subpulmonary infundibulum. The individual, however, was also known to have had multiple spleens, along with interruption of the inferior caval vein. The venous return from the lower body reached the left-sided superior caval vein through the azygos venous system. These features were suggestive of left isomerism. Careful examination of the atrial appendages then showed that, despite the mirror-imaged venous returns, both appendages showed the features of the morphologically left appendage, with the pectinate muscles confined within the narrow opening of the appendage to the smooth walled atrial bodies (Figure 5).

The arrangement of quasi-mirror-imaged venous connections, along with isomeric left atrial appendages, left-handed ventricular topology with concordant ventriculo-arterial connections, and spiralling arterial trunks is exceedingly rare.

We also found another exceedingly rare combination of features in our relatively small number of hearts. In this specimen, which showed no evidence of prior surgical intervention, there was double outlet from a left-sided right ventricle, indicating the presence of left-handed ventricular topology. In this heart, however, the left atrioventricular valve was straddling and overriding the inferior aspect of the muscular ventricular septum. The orifice of the straddling valve was almost equally supported by the morphologically right and left ventricles. Careful assessment, nonetheless, showed that the major part was attached to the right-sided morphologically left ventricle, which also received the entirety of the orifice of the right atrioventricular valve. Both outflow tracts, arising from the right ventricle, were completely muscular. The sequential diagnosis, therefore, was double inlet to a dominant left ventricle, with double outlet from the left-sided right ventricle (Figure 6). The aorta, although arising anteriorly, was located rightward relative to the pulmonary trunk. The reason for the lack of any corrective surgery was the finding that the pulmonary vasculature was protected by dome-shaped pulmonary valvar stenosis.

Another of the hearts in our small cohort was also found to be associated with straddling and overriding of the tricuspid valve. In this heart, the straddling orifice of the tricuspid valve was predominantly connected to the morphologically right ventricle, meaning that the atrioventricular connections were essentially concordant, albeit that the ventriculo-arterial connections were discordant. As with the heart with dominant left ventricle, the orifice of the straddling valve was overriding the inferior aspect of a malaligned ventricular septum. The septum inserted inferiorly along the right atrioventricular junction, rather than being in line with the atrial septum at the crux. It is by virtue of the septal malalignment that the regular atrioventricular node, found within the atrial septum at the apex of the triangle of Koch, is unable to make contact with the ventricular conduction axis, which is carried on the crest of the malaligned ventricular septum (Milo et al, 1979). The large defect in this setting used to be considered to represent an “atrioventricular canal” type of defect (LaCorte et al, 1976). As is evident in the heart from the individual dying suddenly, however, there are well-formed and separate atrioventricular junctions, with the mitral valve guarding the left atrioventricular junction (Figure 7).

The findings in our second heart with straddling tricuspid valve, nonetheless, do serve to demonstrate the features of the three hearts obtained from individuals who did, indeed, have “atrioventricular canal defects”. This lesion is now accepted as being due to deficient atrioventricular septation in the setting of a common atrioventricular junction (Becker and Anderson, 1982). The first two hearts exhibited the so-called “ostium primum” variant of the lesion. In these specimens, shunting through the atrioventricular septal defect was possible only at atrial level. This is because the essence of this variant is the finding of dual orifices within the common atrioventricular junction. The tongue of valvar tissue that joins together the superior and inferior leaflets of the common atrioventricular valve is firmly bound down to the crest of the scooped-out ventricular septum. This feature then confines shunting across the defect at atrial level (Figure 8). The images also show well that, in this setting, the left atrioventricular valve is a trifoliate structure. The space between the leaflets that bridge the ventricular septum is a zone of apposition between them, rather than representing a “cleft” in an otherwise normally formed mitral valve (Figure 8 – right hand panel).

The final heart with common atrioventricular junction, when first assessed, was diagnosed as demonstrating the so-called “Gerbode” defect (Gerbode et al, 1958). When first described, this lesion was recognised as having direct and indirect variants. The direct variant is an atrioventricular septal defect, but with separate atrioventricular junctions. The essence of the lesion, which again is very rare, is a deficiency of the atrioventricular component of the membranous septum (Gerbode et al, 1958). Analysis of the location of the left ventricular outflow tract in our specimen, however, showed that the ventricular septum was “scooped out”, as was the case in our “ostium primum” defects. It was also possible to recognise a zone of apposition between the left ventricular components of two leaflets that bridged the ventricular septum (Figure 9).

Re-evaluation of the septal defect then showed that it was located on the ventricular aspect of the atrioventricular junctions (Figure 10 – left hand panel). There was a tongue of valvar tissue joining together the bridging leaflets, but in this heart the tongue was attached to the leading edge of the atrial septum, thus confining shunting through the atrioventricular septal defect at ventricular level. There was also fusion of the leaflets at the apex of the zone of apposition between them, at the point where the leaflets crossed the crest of the ventricular septum (Figure 10 – right hand panel). The defect, therefore, was a small atrioventricular septal defect, but one which permitted only ventricular shunting. It is an example of the true “ventricular septal defect of atrioventricular canal type”.

1. **Conclusions**

Our analysis of our small cohort of hearts obtained from adults dying suddenly showed that myocardial fibrosis appears to act as a substrate for terminal arrhythmia in a majority of those with grown-up congenital heart disease. Myocardial fibrosis occurs as a result of an insult to the cardiomyocytes caused by ischaemia or abnormal loading, resulting in increased deposition of collagen in the extracellular matrix in the setting of congenital heart disease (Rathod et al, 2016). In cases such as these, it is important for pathologists to look for complications related to surgery, or consequential pulmonary hypertension. Sections should be taken from the ventricles to allow assessment for fibrosis, and from the lungs to assess for pulmonary hypertension. One should have a low threshold for specialist referral.

In those cases where a substrate was not identified, one may postulate that the death may be due to the congenital heart disease itself, or to an underlying channelopathy. The channelopathies consist of Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and the long, and short QT syndromes. These conditions do not reveal themselves on pathological analysis, requiring both genetic analyses and familial screening for identification. A recent study has shown that nearly two-fifths of those experiencing sudden cardiac death with a morphologically normal heart can be diagnosed with a channelopathy (Lahrouchi et al, 2017).

Pulmonary hypertension is a well-recognised complication of congenital heart disease which can lead to sudden death. Additionally, those with tetralogy of Fallot or pulmonary atresia may develop significant acquired aortopulmonary collateral arteries, which can result in haemorrhage. Over and above these issues, our analysis demonstrates the ease with which it is now possible to describe and categorise the findings using the system of sequential segmental analysis (Anderson and Ho, 1997), with the concept of the “morphological method”(Van Praagh et al, 1980) serving to identify the distinguishing features of the cardiac components.

**4.1 Limitations**

We acknowledge that we will not receive all the hearts from adults dying suddenly with congenital heart disease from around the United Kingdom. This is primarily because some may not be autopsied, as the cause of death is simply designated as “congenital heart disease”. Despite this, our analysis highlights that a specific cause of death may be identified through autopsy, helping the families, as well as, the cardiologists and surgeons who manage the increasing population of adults with congenitally malformed hearts (Brida and Gatzoulis, 2019).

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