A Reassessment of the anatomical features of multiple ventricular septal defects

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Abstract

Over the course of time, new developments associated with embryogenesis of the murine heart have served to clarify the developmental processes observed in the human heart. This evidence allows for creation of a developmental framework for many congenital cardiac defects. Here, we aim to solidify the framework related to the categorization of both solitary and multiple ventricular septal defects. Mice having genetic perturbation of the Furin enzyme have demonstrated perimembranous and juxta-arterial ventricular septal defects, permitting the inference to be made that these defects can co-exist with defects occurring within the apical muscular septum. Based on developmental evidence, furthermore, all interventricular communications can be placed into one of three groups, namely, those which are perimembranous, juxta-arterial, and muscular. All of the defects are described based on their borders as seen from the morphologically right ventricle. Our focus here will be on those defects within the muscular ventricular septum, recognizing that such defects can co-exist with those that are perimembranous. We discuss the differentiation of multiple discrete defects from those referred to as the 'Swiss cheese' variant. As we show, appropriate surgical management requires understanding of the specific terminology, as the surgical approach may differ depending on the combination of the individual defects. Data from the Society for Thoracic Surgeons revealed that both mortality and morbidity were increased in the setting of multiple as opposed to solitary ventricular septal defects.

A Reassessment of the anatomical features of multiple ventricular septal defects

Running title: Multiple ventricular septal defects

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Abstract

Over the course of time, new developments associated with embryogenesis of the murine heart have served to clarify the developmental processes observed in the human heart. This evidence allows for creation of a developmental framework for many congenital cardiac defects. Here, we aim to solidify the framework related to the categorization of both solitary and multiple ventricular septal defects. Mice having genetic perturbation of the Furin enzyme have demonstrated perimembranous and juxta-arterial ventricular septal defects, permitting the inference to be made that these defects can co-exist with defects occurring within the apical muscular septum. Based on developmental evidence, furthermore, all interventricular communications can be placed into one of three groups, namely, those which are perimembranous, juxta-arterial, and muscular. All of the defects are described based on their borders as seen from the morphologically right ventricle. Our focus here will be on those defects within the muscular ventricular septum, recognizing that such defects can co-exist with those that are perimembranous. We discuss the differentiation of multiple discrete defects from those referred to as the 'Swiss cheese' variant. As we show, appropriate surgical management requires understanding of the specific terminology, as the surgical approach may differ depending on the combination of the individual defects. Data from the Society for Thoracic Surgeons revealed that both mortality and morbidity were increased in the setting of multiple as opposed to solitary ventricular septal defects.

Keywords: Congenital heart disease, Muscular ventricular septal defects, Swiss-cheese ventricular septal defects

Introduction

Deficient ventricular septation is the commonest abnormality found when the heart is congenitally malformed. It can be found in isolation, or as an integral part of multiple lesions. When encountered as the major problem, the arrangement is appropriately described in terms of ventricular septal defects. When deficient septation is part of lesions such as double outlet right ventricle, or common arterial trunk, the channel between the ventricles is more accurately considered as an interventricular communication.[1] Such distinctions, however, are largely of semantic interest. The understanding of the differences in the terms, nonetheless, is key to appropriate surgical management. This is also the case when the defects are multiple. It is now agreed that, when considered as an overall group, and taking account of the fact that the communications can also be part of more complex lesions, the defects themselves, when assessed in isolation, exhibit one of three phenotypic patterns. There are the muscular, perimembranous, and juxta-arterial variants.[2] When approached on this basis, it should be no surprise that the perimembranous, or juxta-arterial, variants can co-exist with additional channels within the muscular ventricular septum. Several discrete channels can also be found within the confines of the muscular septum itself. On occasion, furthermore, the multi-fenestrated septum is justifiably compared to Swiss cheese. Yet another subtly different arrangement is found when a solitary channel within the apical part of the muscular septum is crossed, on the right ventricular side, by multiple trabeculations.[3] This gives the spurious impression of multiple defects.[4] The recent analysis of the trawl of surgical results made by the Society of Thoracic Surgeons revealed that both mortality and morbidity were increased in the setting of multiple as opposed to solitary ventricular septal defects.[5-9]The surgical approach in presence of multiple defects, however, is likely to be different depending on the combinations of individual defects. It is unlikely that the same operative intervention will be optimal for each of the different patterns. To the best of our knowledge, the significance of these different associations between multiple defects has yet to be explored in the context of therapeutic management. In this, the introduction to a review of such management, we have described the developmental background to the existence of multiple defects. We demonstrate the phenotypic combinations, and discuss their anatomical features. In our subsequent review, we will discuss the significance of the anatomical variations to diagnosis and options for treatment.

Developmental considerations

Towards the latter part of the twentieth century, one of us wrote an inflammatory chapter in which we suggested that knowledge of cardiac development was a hindrance rather than a help.[10] At the time, there was some justification for that statement, since the alleged knowledge of the developmental events was mostly speculative, and tended to be based on comparisons made between the anatomy of the malformations and the presumed fashion of development of the normal heart. All of that has now changed. We now have detailed knowledge of the stages of anatomical development of the murine heart, and we are able to compare those changes to abnormal arrangements found in mice with deficient ventricular septation.[11] Evidence is now also becoming available to show that the changes observed in the murine heart provide an accurate framework for understanding human cardiac development.[12] These changes now permit us to provide an equally solid framework to underpin the categorisation of both solitary and multiple ventricular septal defects.

In terms of cardiac development, the first evidence of ventricular septation is seen subsequent to so-called "looping" of the primary heart tube. This occurs on the tenth day of development in the mouse heart (Figure 1A). This is equivalent to around 5 weeks of development in the human, representing stage 13 in the system developed by the Carnegie Institute.[12] At this stage, the apical components of the developing ventricles are beginning to expand from the inlet and outlet parts of the heart tube by a process known as "ballooning".[13] As the apical components extend centrifugally, so the muscular part of the ventricular septum develops between them. Significantly, the septum first becomes evident when it is a meshwork of trabeculations. Such trabculations, at this early stage, form the greater part of the developing ventricular walls.[14] Another significant feature of this early stage of development is that, initially, the developing atrioventricular canal

is supported exclusively by the developing left ventricle, while the outflow tract arises entirely above the cavity of the developing right ventricle (Figure 1). The consequence of this arrangement is that, initially, all the blood entering the heart through the venous tributaries must pass through the interventricular communication so as to reach the outflow tract and the arterial pole. The channel between the ventricles as seen at this stage, therefore, can be described as the primary interventricular communication.

With ongoing development, there is significant remodelling of this initial interventricular communication.[11] This can be described in terms of two phases. In the first phase, there is expansion of the atrioventricular canal such that the cavity of the right ventricle achieves its own direct communication with the cavity of the right atrium. It is this expansion that produces the right atrioventricular junction. Once the right ventricle has its own connection with the right atrium, the communication between the ventricles can be considered to represent a secondary interventricular communication (Figure 2A). Subsequent to expansion of the atrioventricular canal, however, the entirety of the outflow tract remains supported above the cavity of the right ventricle, which now possesses its own inlet. This, of course, is comparable to the situation found in the setting of double outlet right ventricle.[1] The outflow tract, at this stage, is itself being divided into aortic and pulmonary channels by the formation and fusion of endothelial components described as cushions (Figure 2A). The role of these cushions is directly comparable to the steps taken by the cardiac surgeon in correcting double outlet right ventricle. The fusion of the cushions produces a shelf in the roof of the right ventricle, which tunnels the blood passing through the secondary interventricular communication into the aortic root (Figure 2B). During this process, additional endothelial cushions have been separating the atrioventricular canal into discrete tricuspid and mitral orifices. It is the formation of additional processes, known as tubercles, from the rightward margins of these cushions that eventually closes the remaining communication between the aortic root and the cavity of the right ventricle (Figure 2C).[11] The channel that is eventually closed, therefore, is a tertiary interventricular communication. This is because the process of completion of ventricular septation will have converted the secondary interventricular communication into the subaortic outflow tract. This tunnelling of the aortic root to the left ventricle is the second phase of remodelling of the initial primary communication. And, if development proceeds normally, the proximal outflow cushions, which themselves have formed the shelf in the roof of the right ventricle, become muscularised and remodelled, thus forming the free-standing subpulmonary infundibulum.[15] Only if development is incomplete, with the tertiary foramen persisting as a ventricular septal defect, do these myocardialised cushions persist as a muscular outlet septum.

Development relative to the variable patterns of multiple ventricular septal defects

It is the changes that take place during normal development that now underscore our understanding of the phenotypic variations to be found amongst isolated ventricular septal defects. The inferences made from normal development, furthermore, have now been validated by the finding of such defects in developing mice in which the Furin enzyme had been genetically perturbed. We are unsure precisely why perturbation of the Furin enzyme should interfere with ventricular septation, but the interrogation of three-dimensional datasets from developing fetuses sacrificed at the stage when, in normal development, the ventricular septum is intact, show the phenotypic features in different fetuses of the different types of ventricular septal defect. Analysis of normal development has also shown that the muscular ventricular septum is formed by the coalescence of the components of the initial trabecular meshwork. It is often presumed that these trabeculations come together to form the compact layer of the ventricular walls. This is not the case.[14] The trabeculations do coalesce, nonetheless, to form the papillary muscles of the atrioventricular valves, and also the muscular part of the ventricular septum. In the mice in which the Furin enzyme was perturbed, the process of septal coalescence was disturbed, producing the arrangement also known as the Swiss-cheese septum (Figure 3A). The inference can be made that failure of such coalescence might be less severe, leaving discrete but multiple defects with muscular borders at any site within the septum. In a proportion of the mice having undergone perturbation of the Furin enzyme, there was persistence of the tertiary embryonic interventricular communication. In these mice, there was fibrous continuity in the postero-inferior quadrants of the defects between the leaflets of the tricuspid and mitral valves. This, of course, is the phenotypic feature of the perimembranous defect.[16] In a small number of the mice with perturbation of the Furin enzyme, furthermore, there was evidence that the proximal outflow cushions had fused so as to separate the aortic and pulmonary roots, but had failed to

muscularise. This had left an interventricular communication between the outflow tracts that was bordered cranially by the fused proximal outflow cushions. It is this feature that is diagnostic for the ventricular septal defects that are juxta-arterial.[15] The inference can also be made, on the basis of the development observed in the normal mice, and those suffering perturbation of the Furin enzyme, that either the perimembranous or juxta-arterial defects could co-exist with defects in the apical muscular part of the septum. It also follows that multiple individual defects might be anticipated to exist within the muscular septum, or that failure of coalescence could hav been sufficiently severe to produce the Swiss-cheese arrangement. All of these possibilities are borne out by examination of hearts with ventricular septal defects as found in archival collections.

The Phenotypic Features of Multiple Ventricular Septal Defects

When taking note of our current knowledge of cardiac development, we can now argue that all interventricular communications, depending on their borders, can be placed into one of three groups.[11,15]The significant feature of the first group is that the defects are within the substance of the ventricular septum. These are the so-called muscular defects (Figure 4A). As can also be inferred from the developmental evidence, they can be found anywhere within the muscular septum. Multiple muscular defects, therefore, can be found when opening through different parts of the septum. The most obvious multiple muscular defects, nonetheless, are found when the septum has not properly coalesced during development. Our analysis of the hearts contained within historical archives shows that this problem can manifest as two patterns, which we interpret as representing a spectrum of incomplete coalescence. At the milder end of the spectrum, the apical part of the septum is itself intact, but multiple discrete defects, of variable size, are found at the borders of the apical ventricular components with the ventricular inlets and outlets (Figure 5). In the heart shown in Figure 5, two of the defects are large, and are well seen from both the right and left side of the septum. The severe end of the spectrum is shown in Figure 6. In this heart, there is persisting excessive trabeculation at the apex of the left ventricle (Figure 6B). The entire apical part of the septum, furthermore, shows evidence of inappropriate coalescence of the muscular septum. As such, it is exceedingly difficult to recognise the multiple individual defects that percolate through the substance of the septum. This feature is even worse to recognise when assessed from the right ventricular aspect (Figure 6A). This arrangement is the so-called "Swiss cheese" variant. As is shown, it is impossible, on the basis of direct examination, to establish the precise number of fenestrations within such a septum. This is not the case when the spectrum of coalescence is less severe (Figure 5). As we will discuss in the our surgical review, this means that the "Swiss-cheese" variant can be difficult to repair, the more so since it is usually the most apical part of the septum that has failed to coalesce.

The group of defects reflect failure of closure of the tertiary interventricular communication.[15] Its phenotypic feature is fibrous continuity between the leaflets of the mitral and tricuspid valves (Figure 4B).[16] The defect incorporates within its borders the atrioventricular component of the membranous septum. It often additionally has a flap in its postero-inferior border formed by the interventricular part of the membranous septum. It is because the myocardial margins of the defect extend around these components of the membranous septum that the defect is designated as being perimembranous.[17] The defect, which opens directly beneath the aortic root, can co-exist with muscular defects existing anywhere within the muscular part of the septum. The combination of particular importance is that which exists with a muscular inlet defect (Figure 7A). This is because, in this setting, the atrioventricular conduction axis extends through the myocardial bar which separates the two individual defects (Figure 7B). Should the heart be very small, as is the case in neonates and infants, the bar separating the defects may be of insufficient size to permit sutures to be placed so as to close each defect individually.[18]In this setting, therefore, it may be judicious to place a single patch covering the right ventricular exits of both defects. The alternative is to temporise until it is judged that the muscular bar is of sufficient size to permit sutures to be placed so as to close each defect without jeopardising the conduction axis.

The third group of defects is characterised by failure of formation of the muscular subpulmonary infundibulum (Figure 3C).[15]The phenotypic feature is fibrous continuity between the leaflets of the arterial valves (Figure

4C). This is the rarest type to be found in the setting of multiple defects, but must be anticipated to co-exist with muscular defects opening either to the apex or inlet of the right ventricle.

The final combination to be considered is not truly an example of multiple defects. This is when there is a large defect in the apical part of the muscular septum (Figure 8A). When viewed from the right ventricle, however, the defect is seen to be crossed by apical trabeculations, giving the impression of multiple defects (Figure 8B).[4] The understanding of this defect has been obfuscated by suggestions that it extends into the infundibulum of the right ventricle.[3] It represents a defect within the apical part of the muscular septum. As is now evident from development, formation of the infundibulum is a late event. It cannot be completed until the secondary interventricular communication is tunnelled into the aortic root. These processes, in themselves, show that an outlet defect could not open into the apical part of the right ventricle. It is also clear from the anatomical arrangement that the infundibular part of the right ventricle is found cranial to the limbs of the septomarginal trabeculation, or septal band.[16]

Discussion

As we have shown, multiple, or seemingly multiple, ventricular septal defects can be found in three discrete patterns. In the first arrangement, separate and discrete defects co-exist within different parts of the ventricular septum. Most usually this is because of a combination of perimembranous and muscular defects. This variant is of particular surgical significance when the muscular defect opens to the inlet of the right ventricle. This is because the atrioventricular conduction axis is particularly vulnerable in this setting (Figure 7). The second arrangement is found when the muscular ventricular septum has failed properly to coalesce during cardiac development. This then produces two variants according to the extent of coalescence. When less severe, multiple discrete holes can be observed within the muscular septum, usually at the borders between the right ventricular inlet and outlet and the apical part of the septum. It is the more severe end of the spectrum of failure of coalescence that manifests as the so-called Swiss-cheese septum. This variant poses perhaps the greatest challenge for surgical correction. The final arrangement is not truly an example of multiple defects. It is found when a large, but solitary, defect in the apical part of the muscular septum is crossed in the right ventricle by trabeculations, giving the spurious impression of multiple defects.[4] The surgical approach to each of these variants will itself vary, although several options have been proposed for each specific sub-set. It is those options that we will discuss in the our surgical review.

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Author's contribution

Author's name	Concept/ design	Data analysis/ interpretation	Drafting article	Critical revisi
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Robert H. Anderson	?	?	?	?
Ujjwal Kumar Chowdhury	?	?	?	?
Lakshmi Kumari Sankhyan	-	?	?	?
Niwin George	-	?	?	?
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Figure Legends

Figure 1. The images show the arrangement of the developing heart at the stage of the beginning of formation

of the muscular ventricular septum. The left hand panel shows a section from a murine embryo sacrificed on embryonic day 10, while the right hand panel shows a reconstruction of the cavities of the developing human heart at around 5 weeks of development, which is graded as Carnegie stage 13. The star shows the site of formation of the apical muscular septum, separating the ballooning apical ventricular components.

Figure 2. The images show the stages of remodelling of the primary interventricular communication to form the secondary and tertiary communications in the developing murine heart. Panel A shows the stage subsequent to expansion of the atrioventricular canal. Panel B, at a later stage, shows how the proximal outflow cushions have fused (dotted line) to form a shelf in the roof of the right ventricle. Panel C, from the same heart, shows the persisting tertiary interventricular communication between the aortic root and the cavity of the right ventricle.

Figure 3. The images show the different types of defects produced in developing mice in which the Furin enzyme has been perturbed. Panel A shows the non-compacted apical muscular septum in a heart which also shows an ostium primum defect. Panel B shows a perimembranous defect, while panel C shows an outlet defect that is juxta-arterial because of failure of formation of the subpulmonary infundibulum.

Figure 4. The images show the features of the different types of ventricular septal defects as determined on the basis of their borders. Panel A shows the features of a muscular inlet defect, with panel B showing a perimembranous defect, both in cuts replicating the echocardiographic four-chamber plane. Panel C shows a juxta-arterial defect in a cut simulating the parasternal long axis plane.

Figure 5. The images show multiple muscular defects found at the border between the inlet of the right ventricle and its apical component when there has been a degree of inappropriate coalescence of the septum during development. Panel A shows the view from the right ventricular aspect. As can be seen when assessing the situation from the left ventricular apex (Figure 5B). the most apical part of the septum is intact.

Figure 6. The images show the situation produced when there has been severe lack of coalescence of the muscular ventricular septum during cardiac development. Panel A shows the right ventricular aspect, with Panel B showing the view from the left side. Although the entire apical part of the septum has failed to coalesce, it is difficult to identify individual defects. Note also the excessive apical trabeculation in the left ventricle.

Figure 7. The images show multiple defects produced by the combination of perimembranous and muscular inlet defects. The red dashed line shows the location of the atrioventricular conduction axis, which runs through the myocardial bar separating the defects. The defects are shown from the right (panel A) and left (panel B) ventricular aspects.

Figure 8. The images show how a solitary defect when viewed from the left ventricle (panel A) can seem to represent multiple defects when viewed from the right ventricle (panel B).