Cardiology in the Young

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Reaching consensus as to how knowledge of development underscores our understanding of deficient ventricular septation

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Abstract

Some of us recently discussed the problems existing in describing the channels that permit interventricular shunting. We offered suggestions for improvement, particularly when assessing the channel that is found when both arterial trunks arise from the morphologically right ventricle. Our proposals engendered significant debate, with several criticisms appearing in an editorial commentary. The commentator now accepts that not all of the criticisms were justified. In an attempt to seek further consensus, we have now joined with additional colleagues so as to clarify the aspects of our initial work that created potential confusion. Having reviewed the aspects producing the misconceptions, we again provide an overview of the evidence relevant to deficient ventricular septation now provided by knowledge of cardiac development. We show how remodelling of the primary interventricular communication involves the provision of an inlet for the developing right ventricle and an outlet for the developing right ventricle. During this process, the secondary interventricular foramen, which is a subaortic-left ventricular communication when the outflow tract remains supported exclusively by the right ventricle, becomes the outflow tract for the left ventricle, with a subaortic-right ventricular communication then being closed to complete ventricular septation. We show how knowledge of these processes, coupled with an appreciation of the mechanism of formation of the muscular ventricular septum and the separate formation of an embryonic muscular outlet septum, which with normal development becomes the subpulmonary infundibulum, provides the basis for understanding the various phenotypic lesions that permit interventricular shunting in the postnatal heart.

Introduction

In a recent review published in the journal, a group of us posed the question as to how best to name the various channels that exist in the setting of deficient ventricular septation.[1] Our intention had been to concentrate on the arrangement found when both arterial trunks were supported by the morphologically right ventricle. The proposals attracted detailed criticism from an acknowledged expert, who now joins us in this subsequent attempt to resolve the problems as set out in the editorial commentary.[2] Those of us who produced the initial document accept the need for further debate, while our commentator has accepted that not all of her criticisms were entirely justified. As had been suggested in the editorial commentary,[2] the way forward is to engage in collegial debate as a group of informed individuals and to base any new interpretations on the current state of scientific morphological knowledge placed within a clinical context. It is with this approach in mind that we have now assessed carefully and jointly the aspects of the problems perceived in the initial review.[1] We have also been joined by additional colleagues, all of whom share our desire to produce a system that provides the means for describing all the salient features of the holes that permit ventricular shunting. Our aim is to recommend a system that is suitable not only in the setting of double outlet ventricles but in all those settings where the ventricular septum is deficient. Our hope is that the system now recommended is not only logical but is also one that is easy to understand and apply in clinical practice. To achieve this goal, we

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accept the need initially to clarify those concepts that were arguably not described in optimal fashion in the initial review.[1]

Agreements and misconceptions

From the outset, we should state unambiguously that all authors agree with the consensus document produced on behalf of the International Nomenclature Group.[3] This document highlighted the need, in clinical practice, to describe at least two features of any hole between the ventricles. These can be summarised as terms that account for the geography and borders of the defect, with the option for the user to start with either variable as the primary descriptor. When present, of course, it is also necessary to account for any malalignment of the septal components. We are able to see, with the aid of the retrospectroscope, that the problems created in our initial review largely reflected the fashion in which we presented our concepts. As emphasised, the review had been concerned primarily with hearts having a double outlet right ventricle. We had hoped to produce clarity.[1] We accept that, at least in the eyes of the editorial commentator,[2] we did no more than create a new level of confusion. As an example of such confusion, we had provided illustrations of perimembranous defects in the setting of hearts with concordant ventriculo-arterial connections. In using such hearts, our aim had been to avoid potential confusion with hearts having similar septal defects but with other forms of ventriculo-arterial connection. We recognise that our approach left open the interpretation that the ventriculo-arterial connections were not always concordant when an outlet defect was the consequence of malalignment of the outlet septum.[2] This was never our intention. We agree that the ventriculo-arterial connections remain concordant in most instances where the outlet septum is malaligned. The point made in the review,[1] which received endorsement in the editorial,[2] was that malalignment of the outlet septum is also a feature of hearts with double outlets from the right ventricle. In order to focus on this feature, we had made comparisons between the perimembranous defects found when the ventriculo-arterial connections are concordant with the situation found in tetralogy of Fallot. We then focused on the arrangement present when both arterial roots were supported by the right ventricle. In hearts with the ventriculo-arterial connection of double outlet, however, we had specifically addressed the variants in which the channel between the ventricles opened to the right ventricle adjacent to the aortic root. In concentrating on this variant, it had been our intention to show that the spectrum of lesions found in these settings was itself discrete from another spectrum. This second spectrum, found when the channel between the ventricles in the setting of double outlet opens to the right ventricle adjacent to the pulmonary root, is well described as the Taussig-Bing malformation.[4–6] This latter spectrum has, at its other endpoint, the hearts with discordant ventriculo-arterial connections or transposition. Hence, our need to illustrate the perimembranous defect that created problems for our editorialist.[2] The heart itself had concordant ventriculo-arterial connections. Malalignment of the outlet septum, of course, is also a feature of the Taussig-Bing spectrum. It is now known that yet another spectrum exists when there is a double outlet right ventricle and in which the outlet septum is malaligned relative to the apical muscular septum. This third spectrum is found when the channel between the ventricles opens directly beneath both arterial roots, with either a muscular or a fibrous outlet septum. It is increasingly recognised as representing a double outlet from both ventricles, with the endpoint of the spectrum being double outlet left ventricle.[7,8] It was the influence of all these spectrums on the morphology of the channel found between the ventricles that we had sought to emphasise in our initial review.[1]

Our purpose was to show that, within all these spectrums, depending on the extent of overriding of the arterial roots, there is a change in the ventriculo-arterial connections. Thus, in the spectrum where the septal defect is adjacent to the aorta, the ventriculo-arterial connection changes from being concordant to becoming a double outlet right ventricle. When the defect is adjacent to the pulmonary root, the change in the ventriculo-arterial connection is from being discordant to again becoming a double outlet right ventricle. When the septal defect is adjacent to both arterial roots, then the change is from a double outlet right to a double outlet left ventricle. In the past, many discussions have centred on where, within these spectrums, the change in description of the ventriculo-arterial connection should take place. For some time, it was considered that nine-tenths of an overriding arterial root should be supported by the right ventricle before permitting the diagnosis of double outlet. This was also a time when the presence of bilateral infundibulums, or conuses, was deemed necessary to make the diagnosis. More recently, however, it has been proposed that a double outlet right ventricle, representing a specific ventriculo-arterial connection, should be diagnosed when the greater part of both arterial roots are supported by the same ventricle.[9,10] Most, but not all, also now accept that a double outlet connection can be found when there is fibrous continuity between the leaflets of the overriding arterial valve and the mitral valve. Problems still exist, nonetheless, in determining precisely when both arterial trunks are supported predominantly by the right ventricle. For example, when using echocardiography as the diagnostic modality, it can be very difficult to determine the precise degree of overriding of an arterial root. In our initial review,[1] we re-emphasised the existence of a pragmatic means of making this decision.[11,12] As judged by the criticisms made in the editorial commentary,[2] we accept that the overall aims were insufficiently explained.

The problems relate to the difficulties that remain in accounting for the boundaries of the cavitary space subtended beneath an overriding arterial root.[13] The space in question is a complex three-dimensional area. It can be simplified into a two-dimensional section. Interpretation of such sectional images is the essence of echocardiographic investigation. Such sections can now be shown with greater resolution using computed tomography (Figure 1). This makes it possible to identify a triangular component of the area subtended beneath the overriding root. Of the sides of the triangles thus constructed, two represent communications between the subarterial area and the cavities of the right and left ventricles. In describing the communications in this fashion, we are not seeking to rename them. Rather, we are aiming to emphasise what they represent. It so happens that, by convention, in the example shown in Figure 1, the communication between the sub-aortic area and the cavity of the right ventricle is currently described as the "ventricular septal defect." The communication with the left ventricle is its outflow tract. The entirety of the area subtended beneath the root can arguably be considered to represent the interventricular communication.[13] We were not, therefore, in our initial review, seeking to change the names of the defects themselves, as had been suggested in the subsequent editorial.[2] We do accept that drawing attention to a need for change in interpretation was part of our purpose. Our major aim had been to focus on the lack of logic currently existing in the naming of the boundaries of the areas shown in Figure 1. We can now attempt jointly to rectify the initial failure to produce clarity.

In Figure 1, we have shown an example of the overriding aortic root as seen in a patient with tetralogy of Fallot. In the example

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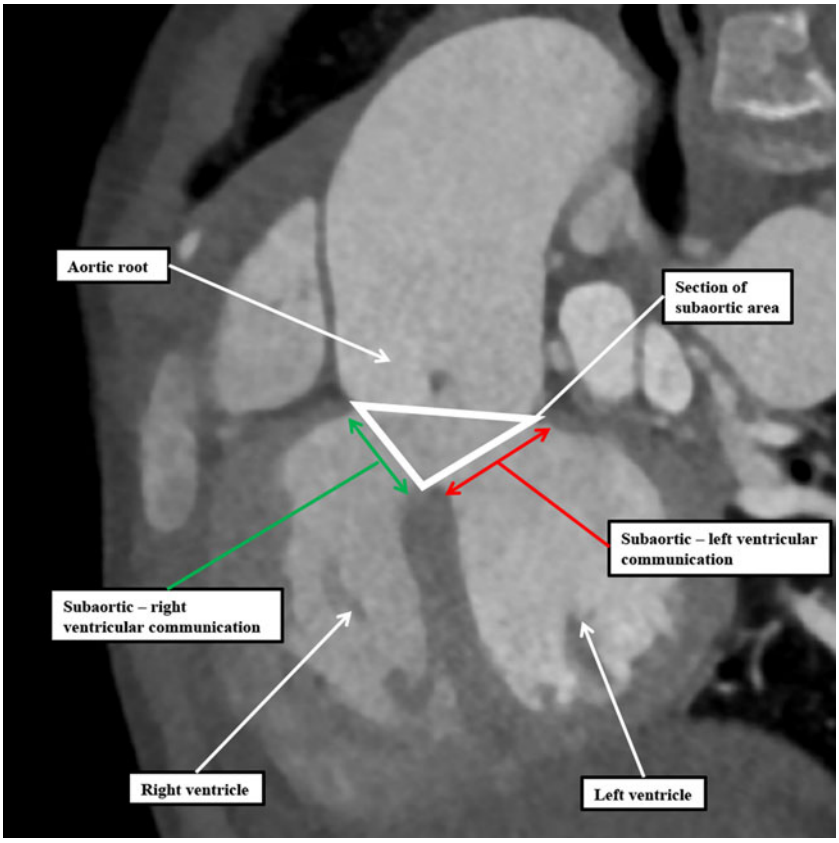

Figure 1. The figure shows a section from a computed tomographic dataset prepared from a patient having tetralogy of Fallot with concordant ventriculo-arterial connections. It is possible to construct a triangle within the area subtended beneath the overriding aortic root. The sides of that triangle represent communications between the area subtended beneath the root and the cavities of the right and left ventricles. It is currently the communication with the right ventricle, shown by the double-headed green arrow, that is named as the "ventricular septal defect." This space would be closed by the surgeon during operative repair.

shown, the aortic root is supported predominantly by the morphologically left ventricle, meaning that the ventriculo-arterial connections are concordant. But the aortic root in the setting of tetralogy is not always supported in its greater part by the left ventricle.[14,15] When more than half of the arterial root is supported by the morphologically right ventricle, then on the basis of current definitions,[9,10] the ventriculo-arterial connection should become one of double outlet. The relationship between tetralogy and double outlet right ventricle, however, continues to be contentious. This is surprising, since Fallot himself emphasised, taking as evidence one of his initial specimens, that the aortic root could be supported exclusively by the right ventricle in the patients who presented to him with "la maladie bleue."[16] In such cases, when the aorta arises in its greater part from the right ventricle, it remains possible to recognise the area of space subtended beneath the aortic root to the crest of the muscular ventricular septum (Figure 2). The triangular section that can be created within the area again has sides which represent communications with the cavities of both the right and left ventricles. The borders in question, therefore, can still appropriately be described as being related to the area beneath the aortic valve and then being either right ventricular or left ventricular (Figure 2). When the ventriculo-arterial connection is one of double outlet, it becomes problematic as to which border should be called the "ventricular septal defect." The communication with the left ventricle is obviously one of the borders of the septal defect. And currently, it is conventional wisdom to nominate this border as the "ventricular septal defect." This is the essence of the problem. In a recent review published from the Hospital for Sick Children in Toronto, it was emphasised that part of the surgical treatment of tetralogy involved closure of the "ventricular septal defect."[17] It would be less than optimal, in the example of tetralogy shown in Figure 2, if the surgeon chose to close the area representing the communication between the left ventricle and the sub-aortic area. But as stated above, in individuals with double outlet right ventricle, it is this deficiency of the ventricular septum, at least when the defect itself is adjacent to one or both of the arterial roots, which is usually described as the "ventricular septal defect." These septal defects, which are the outlet for the left ventricle, rather than being closed, are usually tunnelled to one or other of the arterial roots.

This operative approach, of course, must be considered in the context of the majority of instances in which patients are diagnosed with "ventricular septal defects." If such patients require treatment, then the optimal therapeutic option is usually to close the defect. Our intention in producing our initial review, therefore, had been to emphasise an obvious paradox. This was that, in patients with double outlet right ventricle, it is not advisable to "close the hole" currently described as the ventricular septal defect. We also wished to emphasise that the area closed by the surgeon in such patients during the process of tunnelling an arterial root to the left ventricle does not itself currently have a name. Its borders are unequivocally of surgical importance (Figure 3). When considered in terms of the area subtended beneath the arterial root, as shown in Figures 1 and 2 for patients with tetralogy of Fallot, the space is a communication between the sub-aortic area and the right ventricle (Figure 4). When seen in tetralogy of Fallot (Figure 2), at least in Toronto, we must presume that the area would itself be considered as the "ventricular septal defect."[17] This is because closure of the "septal defect," in that centre as in many other centres, is considered part and parcel of the surgical treatment for patients diagnosed as having tetralogy of Fallot. This fact suggests that, since it is now accepted by most that double outlet right ventricle can be defined on the basis of the greater part of both arterial roots arising from

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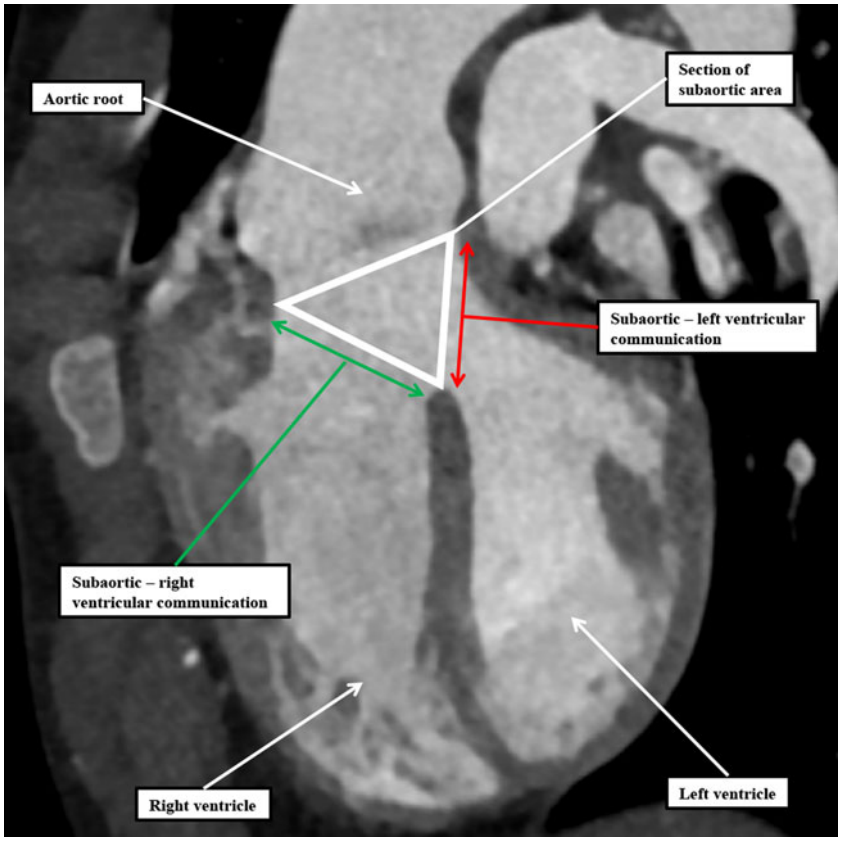

Figure 2. The image is taken from another patient with tetralogy of Fallot but with a double outlet ventriculo-arterial connection (compare with Figure 1). In this setting, it is the communication with the left ventricle, shown by the double-headed red arrow, that is conventionally named as the "ventricular septal defect." But in surgical repair of tetralogy, the surgeon is still asked to "close the ventricular septal defect." The space closed for this patient would have been the area shown by the double-headed green arrow. At present, however, this area is not considered to represent the "ventricular septal defect." In fact, it has no name, but it must still be closed surgically to restore septal integrity.

the right ventricle,[9,10] the implications of this definition have yet to be taken into account when naming the boundaries of the channel between the ventricles. It was this paradox that we sought to emphasise when publishing our initial review.[1]

What about the defects when the ventriculo-arterial connections are concordant?

Our emphasis in the initial review had been on the channels found in the setting of double outlet right ventricle (Figures 2 and 3).[1] Other areas for debate were then identified in the editorial commentary that required clarification.[2] One was the possibility that the central perimembranous defect could also be interpreted as a communication between the right ventricle and the area subtended beneath the aortic root. In the initial review, the area had been described as being "aortic-right ventricular." We now recognise it is better described as being "subaortic-right ventricular." The editorialist had suggested that, when a perimembranous defect is centrally located, the aortic root is "entirely above the left ventricle."[2] This statement is not always true. But even if it were true, the boundary in question would still be between the right ventricle and the area subtended beneath the aortic root (Figure 5). It is in determining the changes of this boundary during development that clarification is most needed. This is because our editorialist had suggested that "it is the fusion of the outlet cushions with the crest of the ventricular septum, between the two limbs of the septomarginal trabeculation, that closes the secondary interventricular communication." This was obviously a contradiction to our statement that the secondary communication could never be closed. Our statement is true because, throughout the period of normal development, it is the only outlet for the developing left ventricle. To clarify this issue, therefore, we have now revisited the datasets prepared from mouse embryos at the Francis Crick Institute by Dr Tim Mohun. These datasets are now housed within the archive of the Human Developmental Biology Resource and are available with open access for general study. Over 450 datasets have been prepared, covering the overall period of cardiac development. Additional datasets are also available from developing mice in which development had been disturbed on the dam by perturbation of the Furin enzyme. Some of these developing mice developed a double outlet right ventricle, with the septal defect adjacent to the aortic root, as shown in Figure 4. Other mouse embryos had persisting defects located centrally, as shown in Figure 5. In the editorial,[2] it had been suggested that we had considered such defects to represent the "real perimembranous examples." This term was not used in the initial review.[1] We acknowledge, nonetheless, its validity. It is, indeed, such central defects that most accurately reflect the failure, during development, of closure of the tertiary interventricular communication (Figure 6).

At the earlier stages of development, whilst the aortic root continues to occupy its initial position above the cavity of the right ventricle, there is an extensive communication between the sub-aortic area and the remaining cavity of the right ventricle (Figure 7). At the stage of development shown, the communication, which represents the second stage of remodelling of the embryonic interventricular communication, is the outlet for the developing left ventricle. It remains the case that it is never closed during normal cardiac development. An inability to close a comparable defect also remains the situation when a double outlet right ventricle is found in postnatal life (Figure 2). The editorial was incorrect, therefore, when suggesting that fusion of the proximal outflow cushions with the crest of the ventricular septum "closes the secondary interventricular communication."[2]

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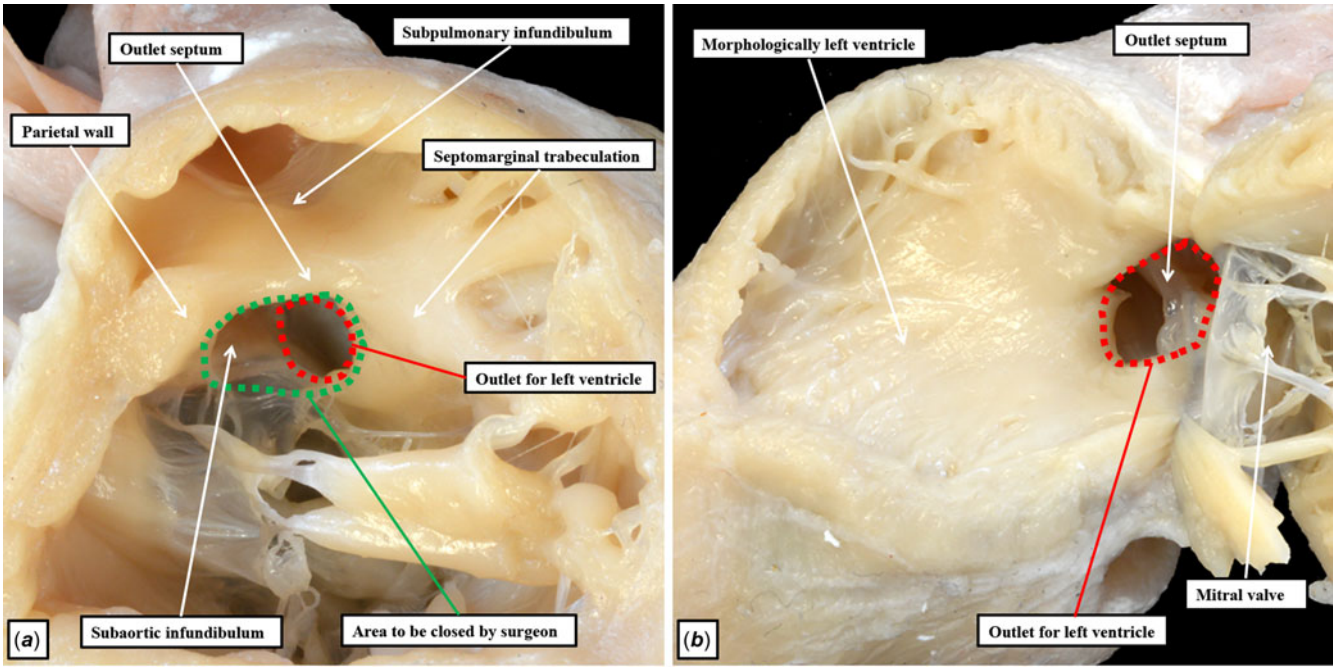

Figure 3. The images are taken from a heart in which the atrioventricular connections are concordant, but both arterial trunks are supported in their greater part by the morphologically right ventricle. Panel A shows the opened right ventricle. The ventricular septum is deficient. The area outlined by the red dotted line is the outlet for the left ventricle but is currently usually described as the "ventricular septal defect." It is an area of deficient ventricular septation but obviously cannot be closed during any attempted surgical repair. The green dashed line shows that area that would be closed by the surgeon to restore septal integrity. This area does not currently have a specific name. Panel B shows the view from the morphologically left ventricle, confirming that the area outlined by the red dotted line is its outlet.

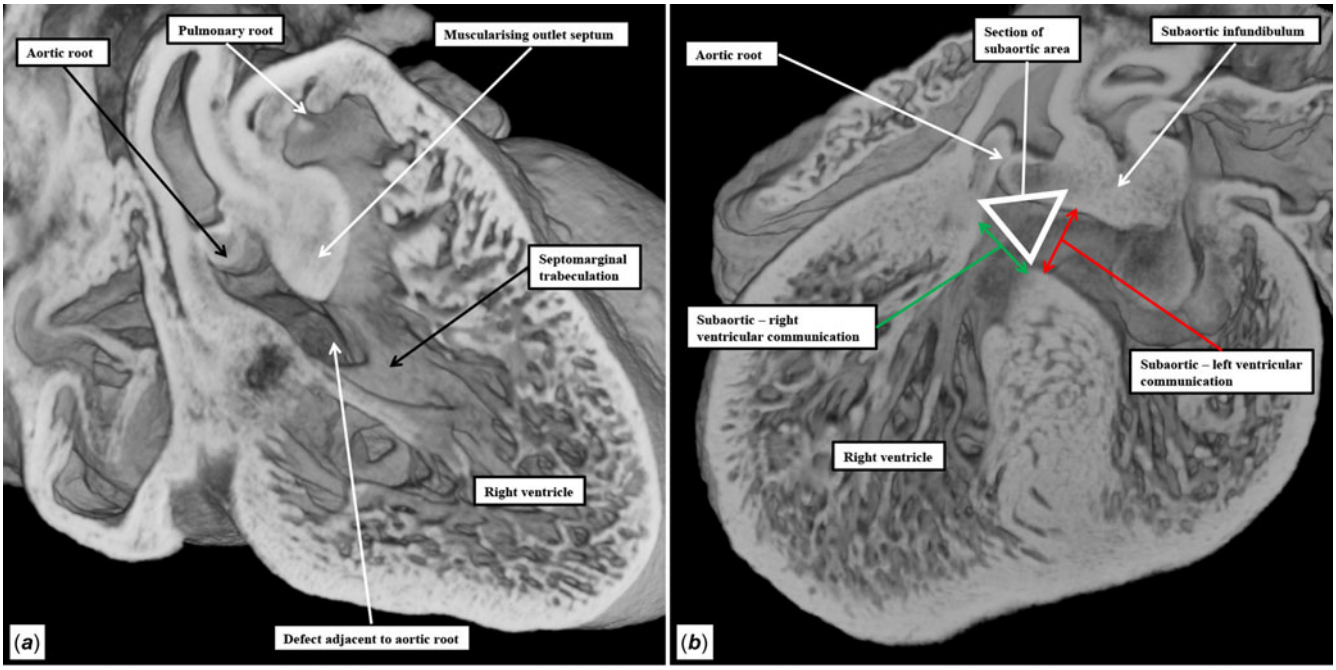

Figure 4. The images are taken from a mouse embryo in which the Furin enzyme was perturbed during development. The mouse was sacrificed at embryonic day 14.5, when the ventricular septum is normally intact. As shown in panel A, there is a double outlet right ventricle, with a septal defect directly adjacent to the aortic root. Panel B shows a section through the aortic root, illustrating the boundaries of the area beneath the root. It is the boundary with the left ventricle that provides the left ventricular outflow tract.

Our initial account, however, created further problems. The editorialist considered it an "embryological impossibility" that the superior margin of the central perimembranous defect could be formed by the developing outlet septum.[2] To check this suggestion, we have re-examined the appropriate three-dimensional datasets. The evidence confirms that fusion of the proximal outflow cushions does create a partition between the developing aortic root and the apical cavity of the right ventricle (Figure 7A).

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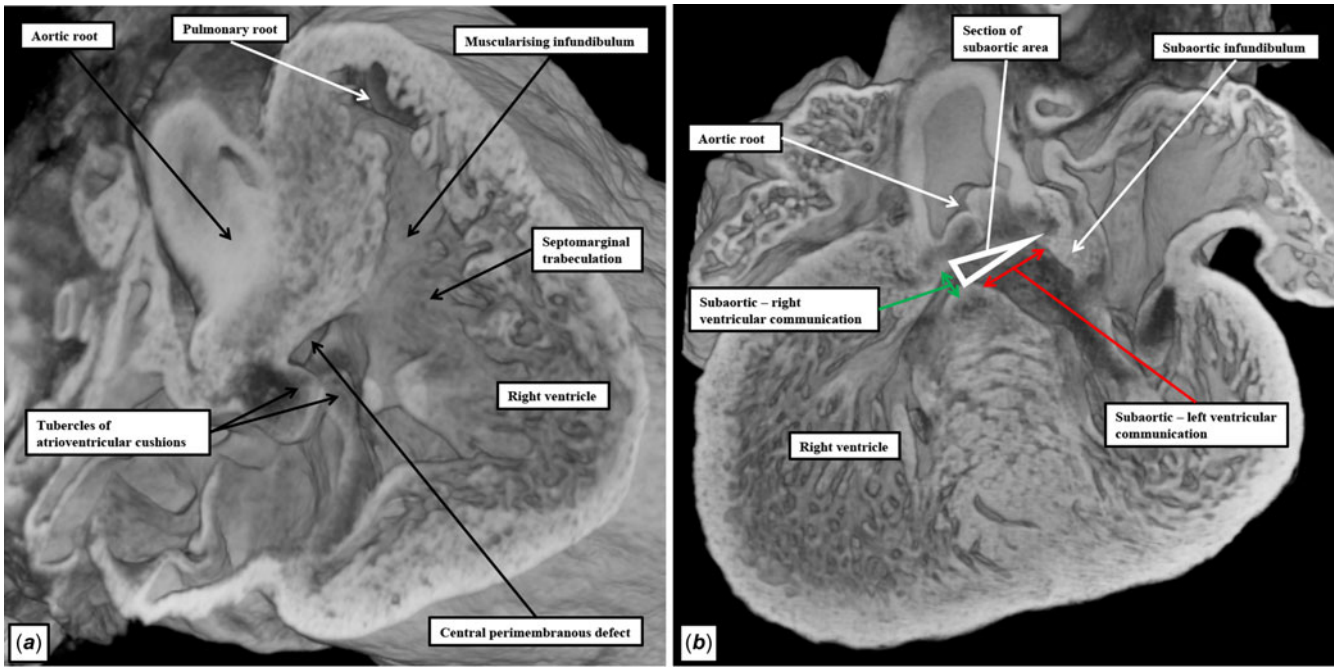

Figure 5. The images are from another murine embryo, sacrificed at embryonic day 14.5 again subsequent to perturbation of the Furin enzyme. At this stage in normal development, the ventricular septum is intact subsequent to closure of the tertiary interventricular foramen. In this mouse, as shown in panel A, there is a centrally located septal defect. It is bordered postero-inferiorly by continuity between the developing leaflets of the mitral and tricuspid valves, themselves derived from the atrioventricular cushions, making the defect perimembranous. The tubercles of the cushions have failed to close the tertiary embryonic interventricular communication (see Figure 8). As shown in panel B, the defect is a communication between the subaortic area and the cavity of the right ventricle.

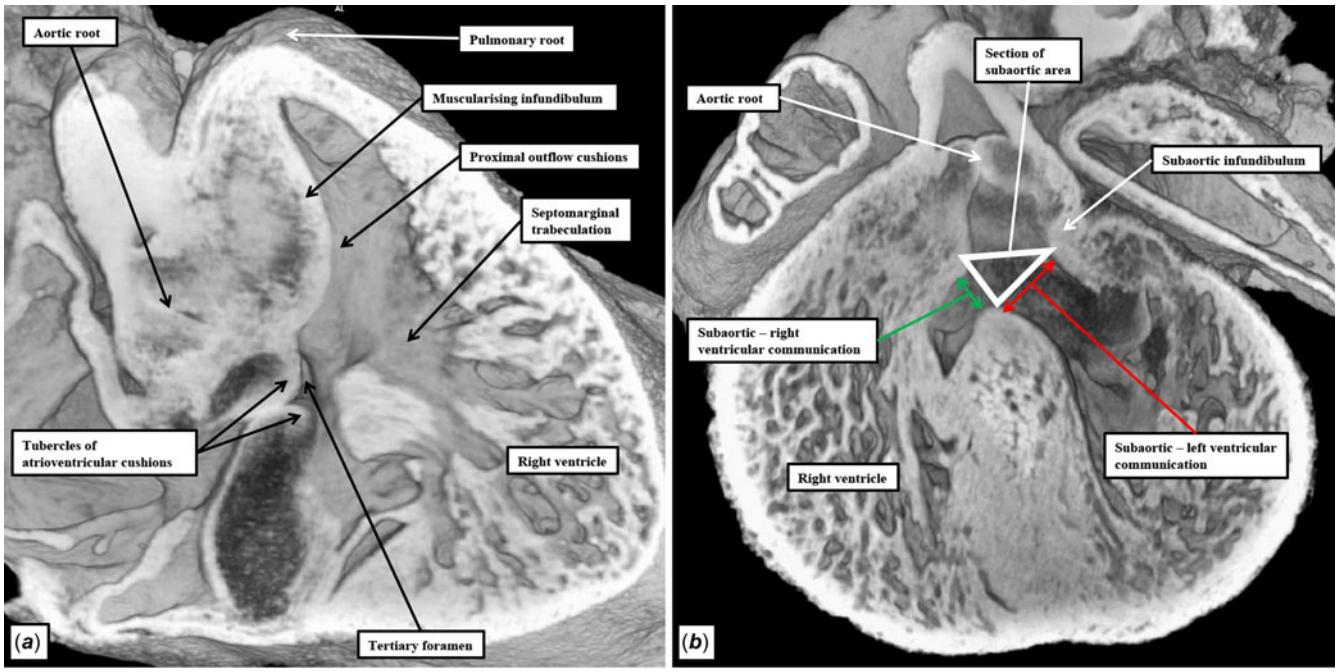

Figure 6. The images are taken from a murine embryo sacrificed at embryonic day 13.5. Panel A shows the small communication remaining between the aortic root and the cavity of the right ventricle. In terms of its evolution, it represents the tertiary embryonic interventricular communication. Panel B shows a section from the same embryo showing how, in terms of the area of space subtended beneath the aortic, the foramen is the boundary between the subaortic area and the right ventricle. The outflow tract from the left ventricle is the secondary embryonic interventricular foramen. At this stage of development, the developing aortic root is supported by a completely muscular infundibulum.

And, as was agreed by our editorialist,[2] this partition does, indeed, fuse with the crest of the muscular ventricular septum. The process, however, does not "close the secondary foramen." Instead, it serves to create a tertiary foramen. This space is initially a communication between the area beneath the aortic root and the cavity of the right ventricle (Figure 6B). The space is eventually closed to complete the process of ventricular septation. Closure is achieved by fusion of the tubercles of the atrioventricular cushions with each other and with

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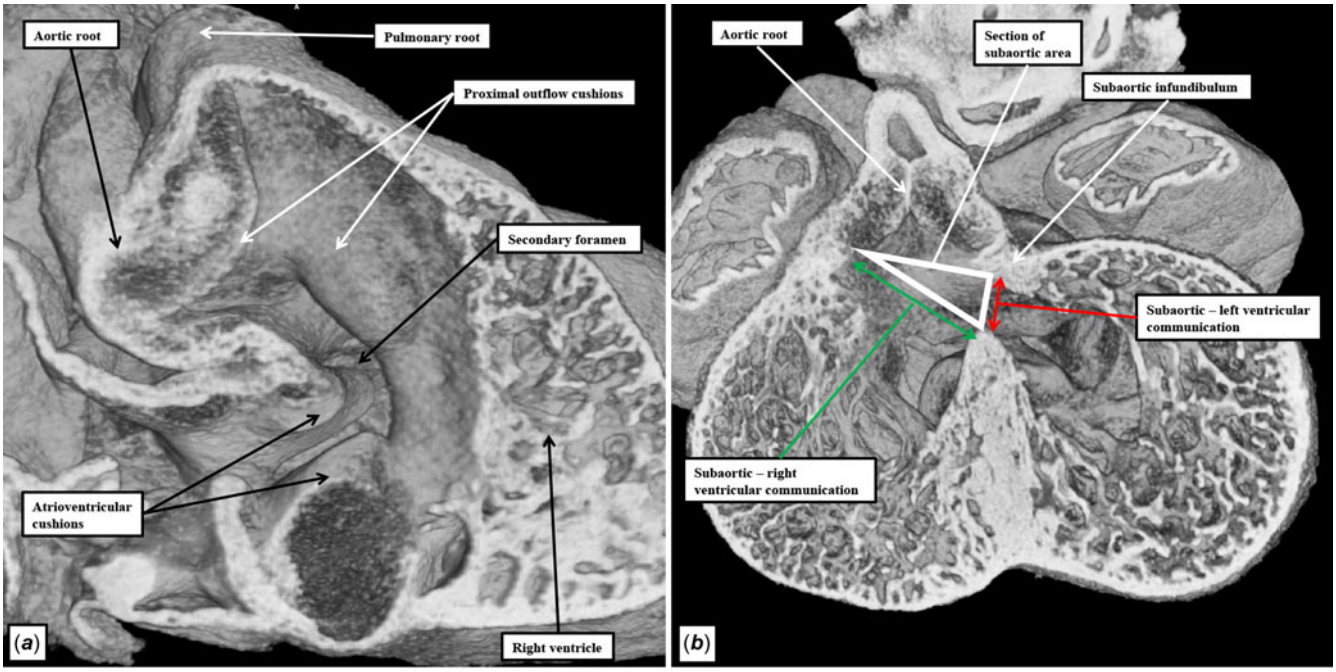

Figure 7. The images shown are from a mouse embryo sacrificed at embryonic day 12.5. At this stage, the proximal outflow cushions are beginning to fuse so as to create a shelf within the cavity of the right ventricle that will limit the extent of the communication between the ventricle and the aortic root. The extent of the space is shown by the green double-headed arrow in panel B, which is a section from the same embryo. The red double-headed arrow shows the secondary embryonic interventricular foramen, which is the outlet for the developing left ventricle.

the leading edge of the muscularised shelf formed from the proximal outflow cushions. The tubercles of the atrioventricular cushions themselves then remodel to produce the membranous part of the ventricular septum. As we showed in a recent account of the development of the ventricular outflow tracts,[18] at the stage when the space is closed during normal human development, the aortic root is positioned above the crest of the muscular ventricular septum (Figure 8). With closure of the tertiary communication, the tissues derived from the right ventricular component of the proximal outflow cushions (Figure 9A,B) become the sleeve of the subpulmonary infundibulum (Figure 9C). The tissues that muscularised and which supported the aortic root as it was transferred to the left ventricle are incorporated into the crest of the muscular ventricular septum. An extracavitary tissue area then develops to separate the right and left ventricular components of the newly formed outflow myocardium (Figure 9A,B).[19] Should the foramen not close, leaving a central perimembranous defect, then the majority of the tissues derived from the fused proximal cushions again become a subpulmonary infundibular sleeve. The leading edge of the mass, however, interposes between the subaortic area and the newly formed subpulmonary infundibulum. As such, it is separating the ventricular outflow tract and can be interpreted to represent a small muscular outlet septum.[19] The components producing the outlet septum, as opposed to the infundibular sleeve, are best recognised when the outlet septum is malaligned, as in tetralogy of Fallot (Figure 9D). A comparable muscular structure separating the subaortic area from the subpulmonary area can also be identified as forming part of the superior border of central perimembranous defects (Figure 10). This small outlet septum, which, as emphasised, is comparable to but also to be contrasted with the structure found in tetralogy of Fallot and the outlet perimembranous defect, is aligned with the apical septum but is hypoplastic. This accounts for the spectrum extending from the central defect to the outlet perimembranous defect as found in hearts with concordant ventriculo-arterial connections. That the outlet septum forms part of the superior border of central defects, therefore, is not necessarily an "embryological impossibility." The revisitation of the developmental evidence, nonetheless, does support the general concept put forward by our editorialist. This was that ventricular septal defects in general, according to their location as seen from the right ventricle, can only open centrally or to its inlet, outlet, or apical components.[3] In light of the criticisms made in the editorial, it is worthwhile to describe yet again the stages of normal development that validate this approach.

The process of ventricular septation

During normal development, the channel between the developing ventricles undergoes significant remodelling.[20] When the channel is first seen, subsequent to the formation of the ventricular loop, the atrioventricular canal opens exclusively to the developing left ventricle, while the outflow tract is supported in its entirety above the cavity of the developing right ventricle (Figure 11A). The channel, which is the initial, or primary, embryonic interventricular communication, serves as both the outlet for the developing left ventricle and the inlet for the developing right ventricle. Both developing ventricles at this stage, furthermore, are incomplete. The left ventricle is incomplete because it lacks its own outlet, while the right ventricle lacks a direct inlet (Figure 11B). A comparable situation can be seen in congenitally malformed hearts with dominant left ventricles, such as classical tricuspid atresia (Figure 11C). In most of the hearts of this kind found in postnatal life, the outlets have usually been divided and shared between the ventricles. In the heart shown in Figure 11C, in which the ventriculo-arterial connections are concordant, the ventricular septal defect has exclusively muscular borders. Its cranial border is formed by the muscular outlet septum, and the caudal border is the crest of the muscular ventricular septum. Similar arrangements are to be found in hearts with a double inlet left ventricle, when the ventriculo-arterial connections are usually

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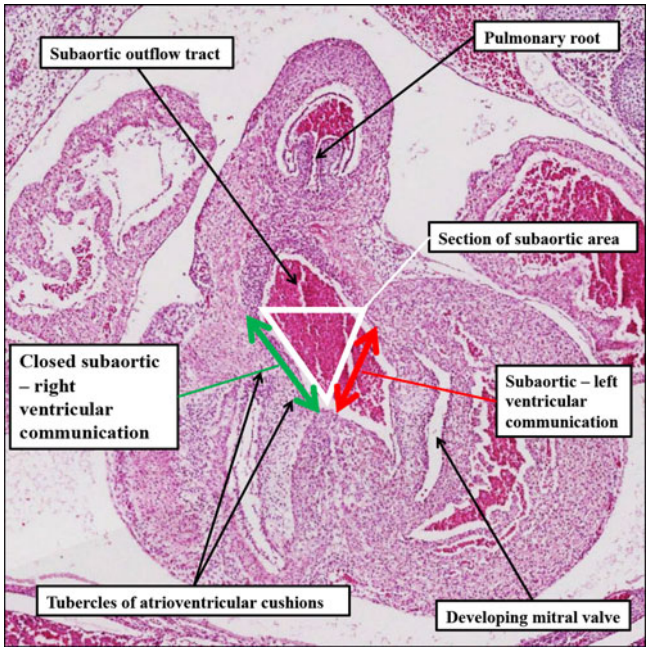

Figure 8. The histological section, available for general interrogation via the Human Developmental Biology Resource, is from a human embryo at Carnegie stage 20. The tubercles of the atrioventricular cushions have closed the tertiary interventricular communication. As can be seen, nonetheless, the area closed was initially a communication between the cavity of the right ventricle and the area beneath the aortic root. With closure of the tertiary foramen, the secondary communication becomes the outflow tract of the left ventricle.

discordant. For quite some time, it was suggested that the anterior chamber in such settings was no more than an infundibulum. In reality, the chamber is the incomplete right ventricle, possessing apical trabecular and outlet components. The communication between the ventricles is a muscular ventricular septal defect (Figure 11C).

The muscular part of the ventricular septum is formed concomitant with the development of the ventricular apical components by the process of ballooning.[21] It is often presumed that the ventricular walls are formed by a process of "compaction" of pre-existing trabecular myocardium. This is not true.[22] The muscular part of the ventricular septum is formed by coalescence of trabeculations, as are the tension apparatus of the atrioventricular valves and the ventricular ramifications of the atrioventricular conduction axis. Should the coalescence of the septal trabeculations be incomplete, defects can persist anywhere within the muscular ventricular septum. They can be located very close to the central part of the septum. They can never be directly central, however, since in such defects an intact membranous septum can still be identified in the central location. Defects with exclusively muscular borders as viewed from the right ventricle can also open to the outlet of the right ventricle. The latter defects are different from the ones that reflect abnormal coalescence of the septal trabeculations. When muscular defects open to the right ventricular outlet, they are the consequence of divorce between the developing outlet septum, derived from the proximal outflow cushions, and the crest of the muscular ventricular septum (Figure 12A). The postero-inferior rim of such defects is also muscular. This again means that the defects are not directly central. The myocardial nature of the postero-inferior rim reflects fusion between the caudal limb of the septomarginal trabeculation and the ventriculo-infundibular fold, with the latter component representing the initial inner curvature of the heart tube. A similar arrangement, producing a muscular postero-inferior rim to an outlet defect, can also be seen when the defect itself extends cranially to be bordered by an area of fibrous continuity between the leaflets of the aortic and pulmonary valves, often in the presence of a fibrous outlet septum (Figure 12B). The latter defect, therefore, is juxta-arterial. A similar juxta-arterial defect is found in the setting of a common arterial trunk, itself known to be due to failure of fusion of the outlet cushions.[23] We now have evidence confirming the role of hypoplasia of the proximal outflow cushions in producing the defects that open to the outlet of the right ventricle. Such defects, not only with hypoplasia of the proximal outflow cushions but also with evidence of failure of their muscularisation, have been found in some of the murine embryos suffering from perturbation in the dam of the Furin enzyme (Figure 13).

Defects opening to the outlet of the right ventricle, therefore, can have exclusively muscular rims or can extend to become juxta-arterial. There is then a third type of defect that opens to the outlet of the right ventricle (Figure 14A). This third variant is found when the defect extends postero-inferiorly to reach the area of fibrous continuity between the leaflets of the mitral and tricuspid valves (Figure 14B). It is this feature of fibrous continuity between the leaflets of the atrioventricular valves that makes the defect perimembranous.[24] The area of fibrous continuity occupies the region between the caudal limb of the septomarginal trabeculation and the ventriculo-infundibular fold. When found with an outlet defect, this is usually because the outlet septum is malaligned such that it no longer inserts between the limbs of the septomarginal trabeculation (Figure 14A). A perimembranous defect can also open to the outlet; however, when the outlet septum itself is hypoplastic, it is still normally aligned with the apical part of the ventricular septum. As was emphasised in our introduction, therefore, malalignment of the septal structures, if present, is an additional feature that must be considered when describing any type of septal defect.[3]

As with the perimembranous defect opening to the outlet of the right ventricle, so can defects be found opening to the inlet of the right ventricle (Figure 14C) when their postero-inferior border is formed by fibrous continuity between the leaflets of the mitral and tricuspid valves (Figure 14D). We agree, therefore, that all septal defects can be described as opening into the right ventricle centrally or to its inlet or outlet components or as opening through the muscular part of the ventricular septum.[3] The central defect is always perimembranous. The criterion for recognition of this defect is the fibrous continuity between the leaflets of the mitral and tricuspid valves, reflecting the derivation of these leaflets from the major atrioventricular cushions. Inlet defects are typically perimembranous but, in some instances, can be muscular. These variants should be distinguished because the atrioventricular conduction axis takes a superior course relative to the muscular defect but is directly related to the postero-inferior margin of the perimembranous defect (Figure 14 C&D).[25] When the defect is perimembranous, it is also necessary to recognise that malalignment can involve not only the outlet septum, producing an outlet defect, but also the atrial septum. The presence of atrioventricular septal malalignment heralds yet another important crucial feature. This is the origin of the conduction axis from an anomalous postero-inferior atrioventricular node (Figure 15).[25,26]

Discussion

In reality, there was not so much disagreement to be found between the content of the initial review offered by some of us[1] and the

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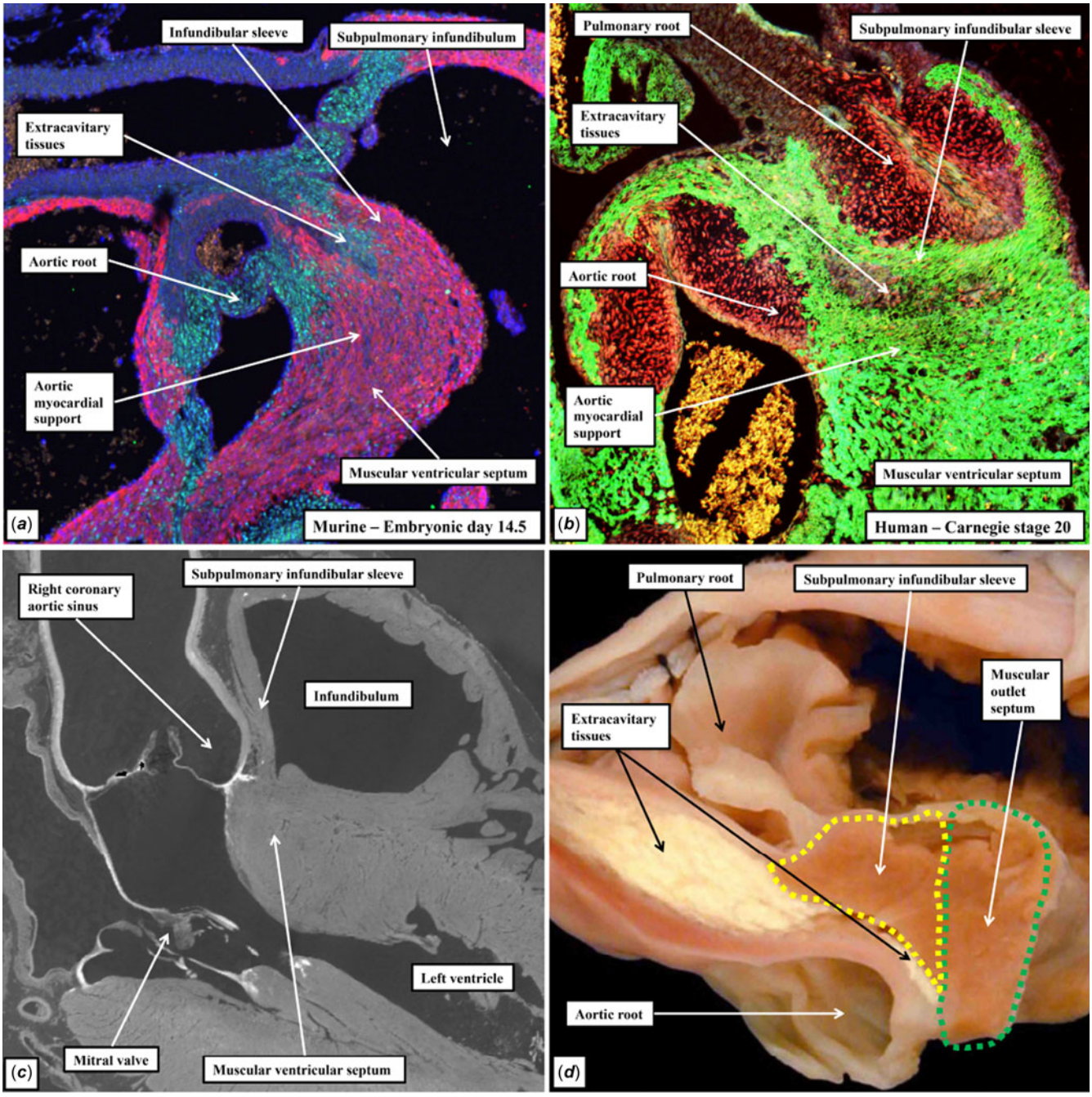

Figure 9. Panel A is from a murine embryo sacrificed at embryonic day 14.5, which is after the completion of ventricular septation. Panel B is a comparable section taken from a human embryo at Carnegie stage 20, again subsequent to the completion of ventricular septation. The section shown in panel A has been stained to show myocardium in reddish-purple and mesenchymal tissues in green. In the section shown in panel B, myocardium has been stained green. On both sections, it can be seen that the right ventricular component of the fused proximal cushion mass becomes the part of the infundibular sleeve adjacent to the aortic root, with the outflow myocardium supporting the aortic root incorporated into the crest of the muscular ventricular septum. There is an area of extracavitary tissue separating the two such that it is not possible to identify an "outlet septum" in the normal heart. Panel C is a section from a dataset of an adult human heart prepared using hierarchical phase contrast computed tomography. It shows how the subpulmonary infundibular sleeve, derived from the right ventricular components of the fused proximal cushions, separates the cavity of the right ventricle from the wall of the right coronary aortic sinus. The left ventricular component of the muscularised proximal cushions is fully integrated within the crest of the muscular ventricular septum. Panel D shows the removed pulmonary root from a patient who sadly died after surgical correction of tetralogy of Fallot. This section shows how, when septation is incomplete, it is possible to recognise how the leading edge of the fused proximal cushions can be recognised as a muscular outlet septum, which supports the infundibular sleeve separating the cavity of the right ventricle from the wall of the right coronary aortic valvar sinus.

editorial offered by another of the current authors.[2] It had not been the intention in the initial review, furthermore, to suggest that a major change was needed in the document published on behalf of the International Nomenclature Society.[3] The purpose of our own initial review[1] had been to concentrate on the channels to be found when both arterial trunks were arising in their greater part from the morphologically right ventricle. We had aimed to focus the attention of the imager and surgeon on identifying and distinguishing the

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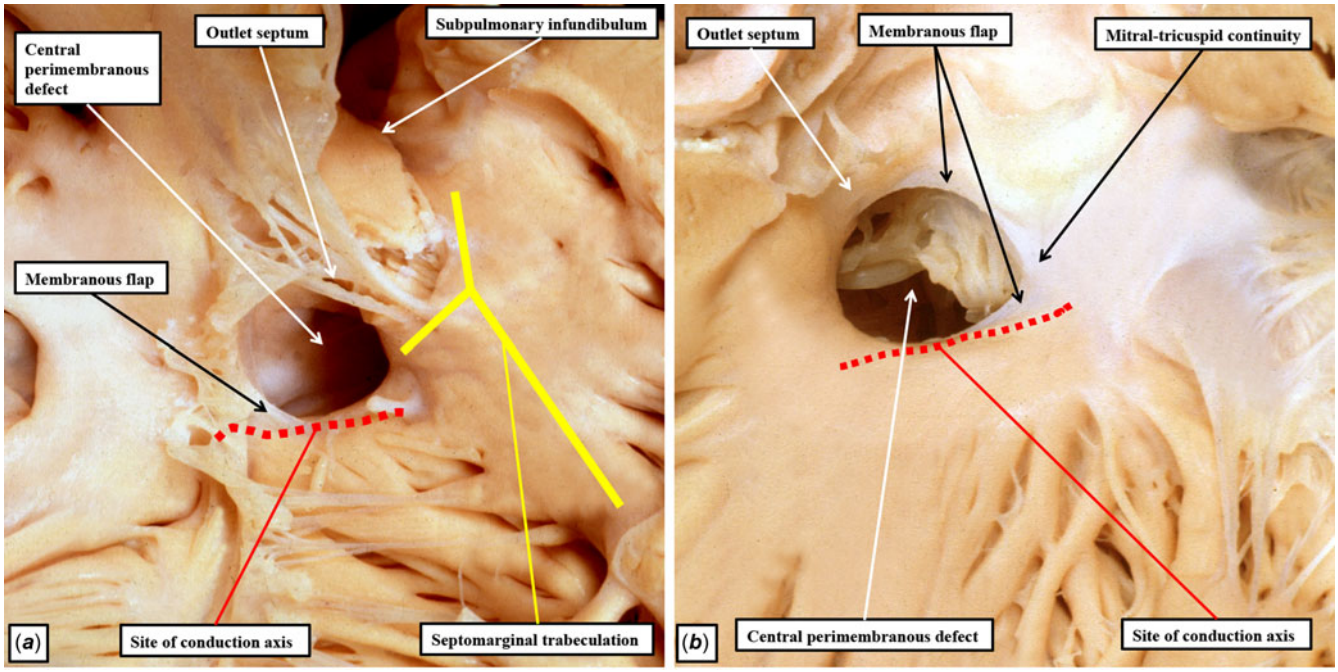

Figure 10. These images from a central perimembranous ventricular septal defect show that, as was the case for tetralogy of Fallot when the outlet septum was malaligned, a muscular outlet septum, shown by the green dashed lines, can still be recognised, in this case forming the superior margin of the defect. The red dashed line shows the location of the atrioventricular conduction axis.

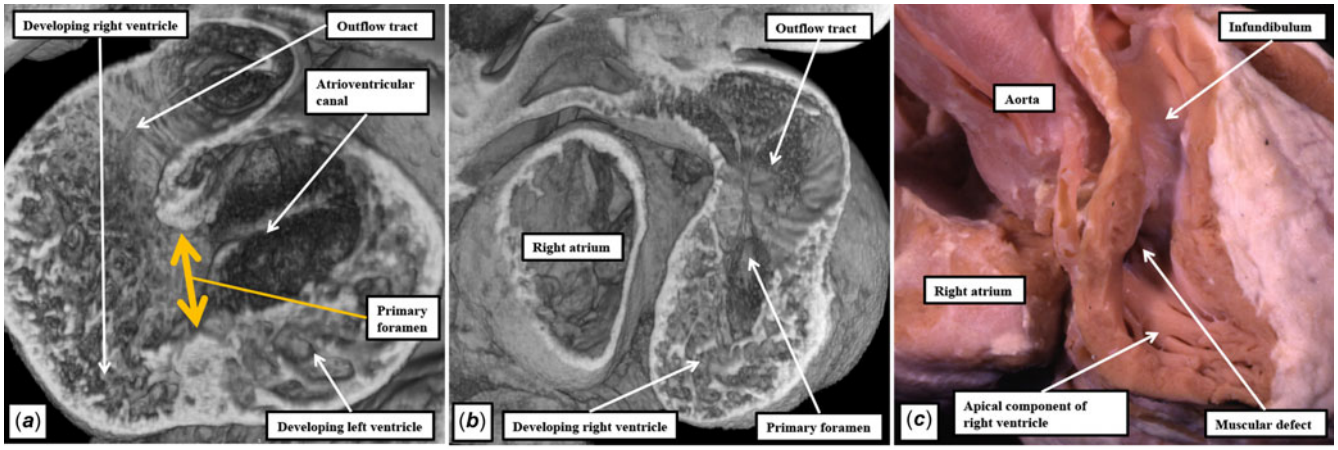

Figure 11. Panels A and B are taken from an episcopic dataset prepared from a mouse embryo sacrificed at embryonic day 10.5. At this stage, the atrioventricular canal is supported exclusively by the developing left ventricle, while the outflow tract arises in its entirety above the cavity of the developing right ventricle. As shown in panel A, all the blood entering the left ventricle must pass through the primary interventricular foramen to reach the developing right ventricle. Panel B shows that the right ventricle has already acquired its apical component. The chamber can be compared to the incomplete right ventricle shown in panel C, which is from an individual with classical tricuspid atresia. The chamber is incomplete because it lacks any direct inlet from the morphologically right atrium.

margins of the communication found between the cavity of the right ventricle and the area beneath one of the arterial roots. It is this area which is closed by the surgeon to restore septal integrity, as opposed to the communication from the left to the right ventricle. The latter channel, subsequent to the surgical closure of the communication of the arterial root with the right ventricle, will subsequently serve as the outflow tract of the left ventricle. These distinctions are increasing in their importance with the growing applications of advanced cardiac imaging for quantitative assessment of these complex three-dimensional communications, thus providing a personalised approach to improve outcomes.[27]

The definition of the entity loosely described as a double outlet right ventricle continues to be contentious. There are some who continue to maintain the presence of a "fundamental anomaly," arguing that this is found when the aortic root arises exclusively from the right ventricle and is supported by a completely muscular infundibulum.[27] Such an arrangement can be found during normal embryological development. It was this feature that had served as a point of emphasis in the initial review.[1] As was pointed out in the editorial, nonetheless, definitions have now been created to indicate that a double outlet from the right ventricle is a ventriculo-arterial connection, rather than a specific phenotype.[2] Such definitions were

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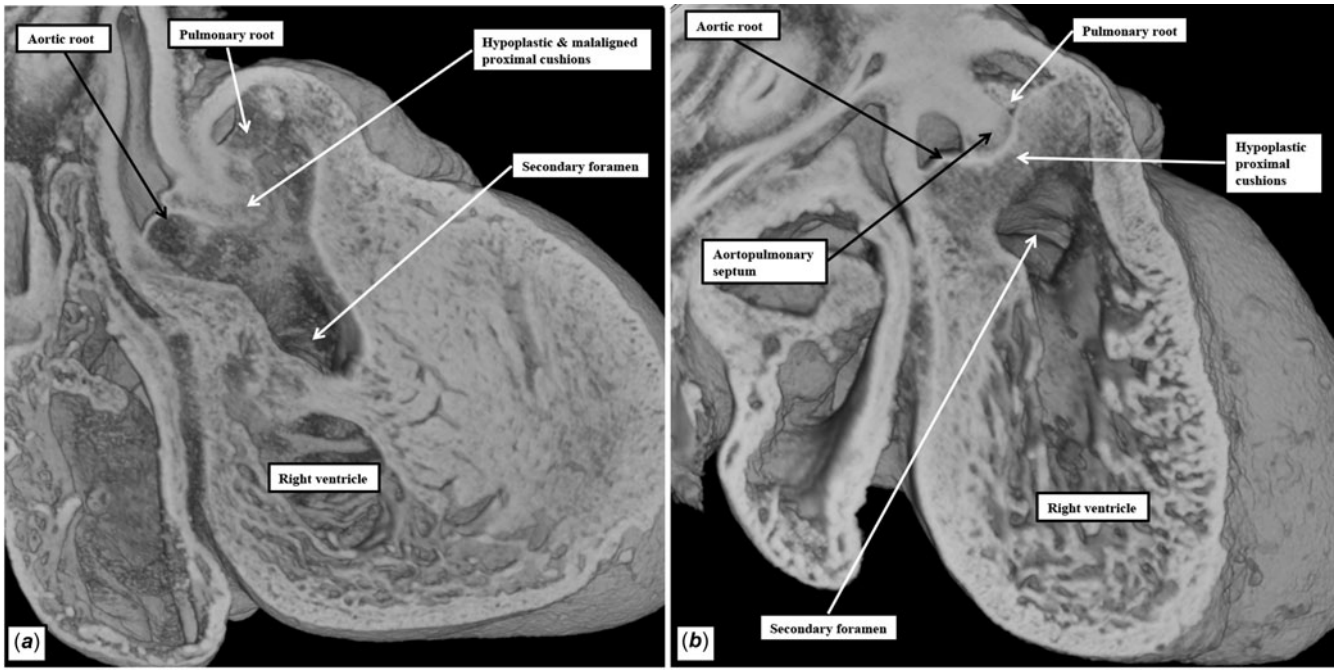

Figure 12. The images are taken from mouse embryos undergoing perturbation of the Furin enzyme and sacrificed at embryonic day 14.5. In both embryos, the proximal outflow cushions are hypoplastic and have failed to muscularise. In panel A, the cushions are attached to the cephalad limb of the septomarginal trabeculation so that the septal defect, which represents the secondary interventricular communication, opens into the right ventricle beneath the aortic root. In panel B, the defect opens to the right ventricle beneath both arterial roots and is doubly committed.

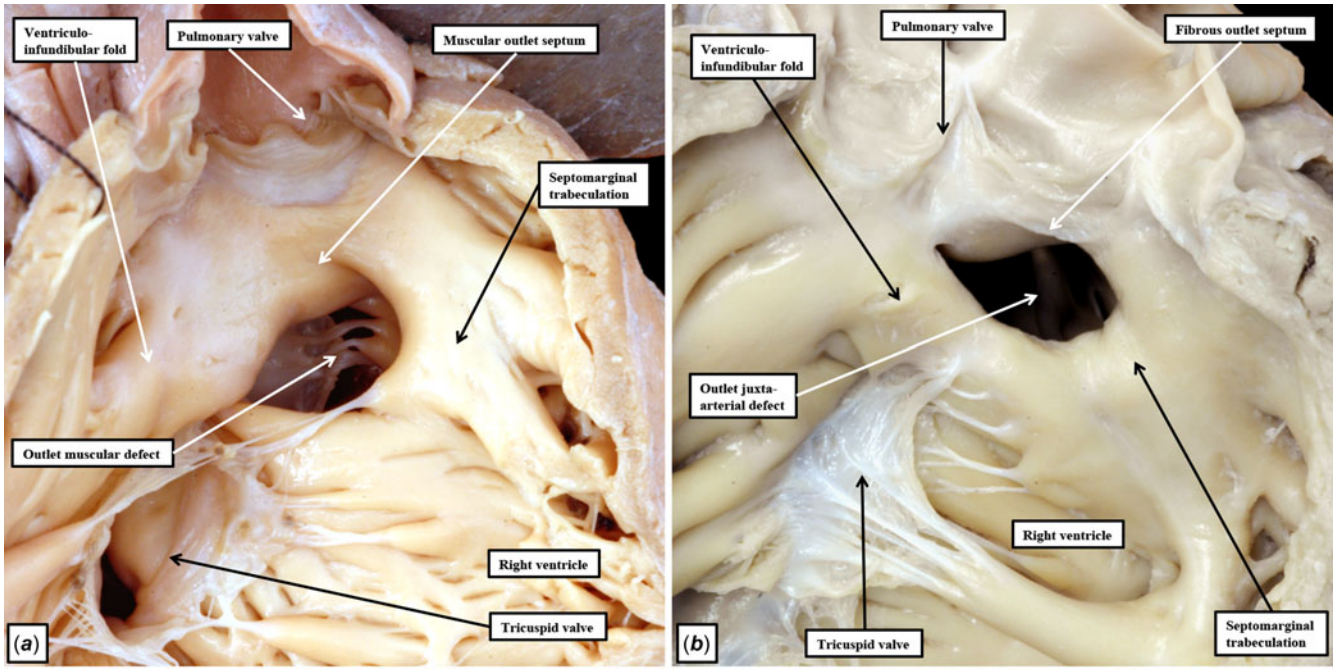

Figure 13. The images are taken from hearts with defects opening to the outlet of the right ventricle. In the heart shown in panel A, the defect, as viewed from the right ventricle, has exclusively muscular borders. It is an outlet muscular defect. In panel B, in contrast, the cranial margin of the defect is formed by fibrous continuity between the leaflets of the aortic and pulmonary valves, with a small fibrous outlet septum present. The defect is juxta-arterial, but with a muscular postero-inferior rim because the caudal limb of the septomarginal trabeculation has fused with the ventriculo-infundibular fold. The muscular rim, also present in the heart shown in panel A, protects the atrioventricular conduction axis.

provided both by the International Society[10] and by the group of surgeons addressing the overall group of congenital cardiac malformations.[9] The lead author promoting the concept of a "fundamental lesion,"[28] furthermore, was himself a co-author of the review defining the term on the basis of the ventriculo-arterial connection.[9] Again, therefore, there is a greater extent of agreement as opposed to disagreement when considering the definition of double outlet, although it may well be that the definitions have yet to

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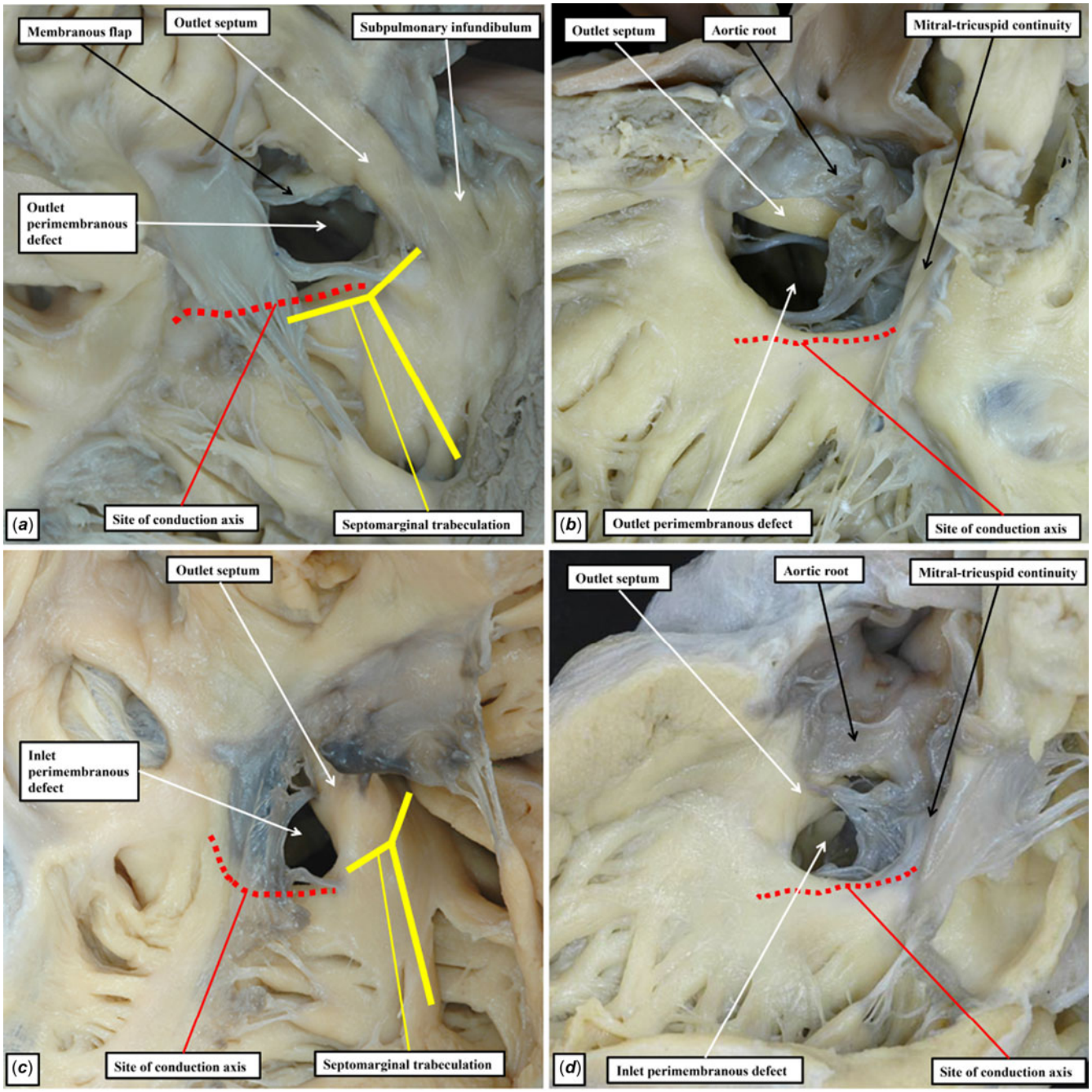

Figure 14. The images compare the features of defects that are perimembranous, being bordered by fibrous continuity between the leaflets of the atrioventricular valves, but opening either to the outlet of the right ventricle (panels A and B) or to the ventricular inlet (panels C and D). The red dotted line shows the anticipated location of the atrioventricular conduction axis. Panels A and C are shown from the right ventricle, and B and D from the left ventricle.

achieve universal acceptance. But the question as posed in the initial review[1] remains unanswered. This suggests, as we have already acknowledged, that the question itself was not obvious. So, let us again reiterate the perceived problem. In the majority of patients having deficient ventricular septation, the optimal treatment is to restore septal integrity. This is done by closing the "ventricular septal defect." In a minority of patients, specifically those in whom both arterial trunks arise exclusively from the right ventricle, with this variant representing the "fundamental anomaly" identified by the multi-centre group of authors,[28] the immediate defect between the ventricles serves as the outlet for the morphologically left ventricle. During surgical treatment of such patients, the defect is not closed. Instead, it is ideally tunnelled to the aortic root. Despite the fact that the defect cannot be closed, it is still conventionally described by those using Germanic languages as the "ventricular septal defect." The point of the initial review was to do no more than question the use of the same term to account for a channel that, in most circumstances, is closed as the optimal therapeutic option, yet in other circumstances cannot be closed without disastrous consequences.[1] This lack of logic remains problematic.

The other point made in the initial review, having recognised that some channels named as "ventricular septal defects" could not be closed, was that this fact could itself be used as a means of arbitrating yet another contentious issue. This is the best means of

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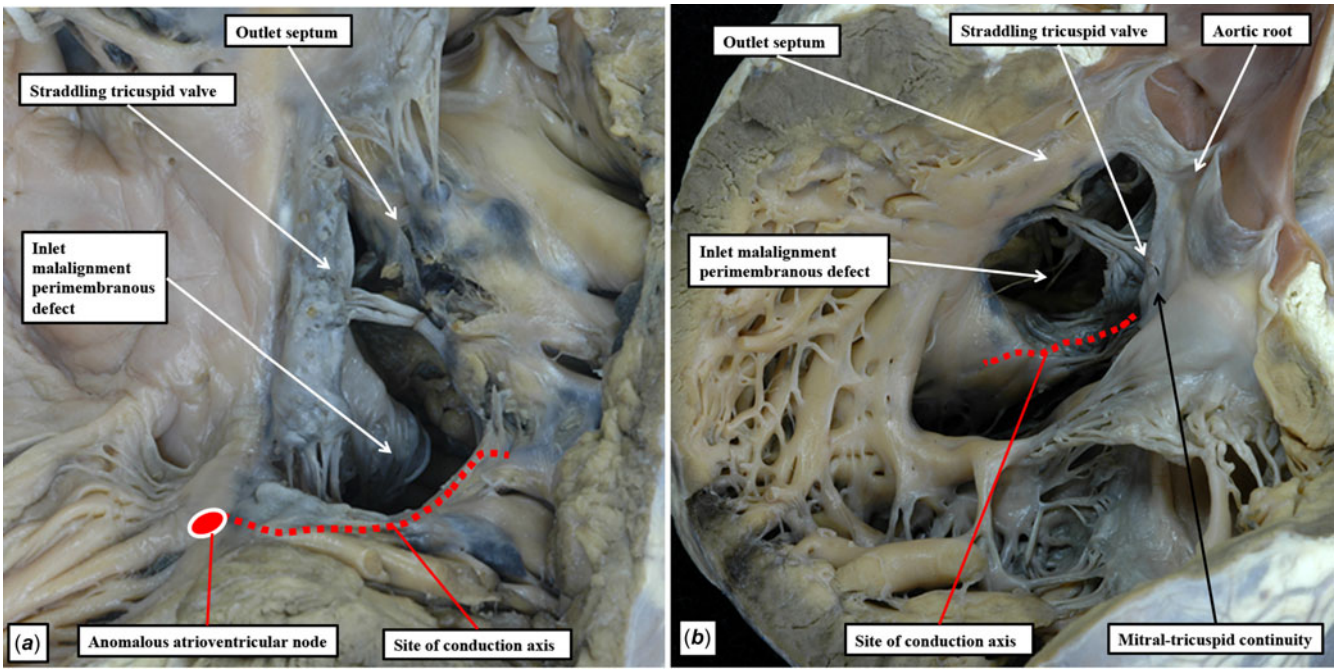

Figure 15. The images show the features of a perimembranous defect opening to the inlet of the right ventricle, but with malalignment between the atrial septum and the muscular ventricular septum. Panel A shows the view from the right ventricle, and panel B from the left ventricle. As can be seen, because of the septal malalignment, the conduction axis arises from an anomalous postero-inferior atrioventricular node.

diagnosing the presence of a double outlet right ventricle.[1] It is obvious that surgeons throughout the world, although calling the exit from the left ventricle the "ventricular septal defect," are well aware that, when performing their surgical repairs, the channel cannot be closed. The same surgeons also recognise that, when the ventriculo-arterial connections are concordant or discordant, it is standard procedure to "close the holes." Such recognition provides a pragmatic definition for the diagnosis of double outlet right ventricle.[11,12] Thus, when seeking to arbitrate the ventriculo-arterial connections in this situation, the connection of double outlet will be present when the clinician recognises that the immediate channel between the ventricles cannot be closed but instead must be tunnelled to one or other of the arterial roots. If tunnelled to the pulmonary root, then nowadays it is also necessary to perform an arterial switch.

With regard to channels between the ventricles as found in the setting of concordant or discordant ventriculo-arterial connections, we all agree that such holes can be central, can open to the inlet or outlet of the right ventricle, or can open more towards the right ventricular apex.[2] Provision of such "geographic" information is obviously of great importance. But we all also agree that a simple description of the geography is insufficient to distinguish the various phenotypes, although the developmental evidence shows that the central defect must also be perimembranous. So, as always, to define the phenotypic variation, it is essential also to take note of the borders of the defects.[24] It is the latter information, furthermore, that then provides the crucial information regarding the likely location of the atrioventricular conduction axis.[25] Of late, there has been a resurgence of interest in using electrophysiological mapping of the atrioventricular conduction axis.[29] Those promoting the value of mapping argue that a simple description of the defects is insufficient to permit them to know the likely location of the conduction axis. What is more likely is that the system they use to describe the different defects lacks sufficient granularity to provide a specific phenotypic definition. Both borders and geography, therefore, are important, although it is primarily knowledge of the borders of the defect which helps to identify the relationship of the defect to the atrioventricular conduction axis. In our consensus thinking,[3] providing that both are applied to daily clinical practice, the order in which the features are listed does not matter. Thus, to all of us, it is immaterial whether a defect is described as being outlet perimembranous or perimembranous outlet. What matters is to include both terms, taking care to add details of septal malalignment when this is pertinent.

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