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Original Article

Tetralogy of Fallot: nosological, morphological, and morphogenetic considerations*

Robert H. Anderson,[1] Diane E. Spicer,[2] Jorge M. Giroud,[3] Timothy J. Mohun[4]

[1]*Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom;* [2]*All Children's Hospital, The Congenital Heart Institute of Florida, Saint Petersburg/Tampa and the University of Florida, Gainesville;* [3]*All Children's Hospital, The Congenital Heart Institute of Florida, Pediatric Cardiology Associates/ Pediatrix Medical Group, Saint Petersburg and Tampa, Florida, United States of America;* [4]*National Institute of Medical Research, London, United Kingdom*

Abstract It is timely, in the 125th anniversary of the initial description by Fallot of the hearts most frequently seen in patients presenting with "la maladie bleu", that we revisit his descriptions, and discuss his findings in the light of ongoing controversies. Fallot described three hearts in his initial publication, and pointed to the same tetralogy of morphological features that we recognise today, namely, an interventricular communication, biventricular connection of the aorta, subpulmonary stenosis, and right ventricular hypertrophy. In one of the hearts, he noted that the aorta arose exclusively from the right ventricle. In other words, one of his initial cases exhibited double-outlet right ventricle. When we now compare findings in hearts with the features of the tetralogy, we can observe significant variations in the nature of the borders of the plane of deficient ventricular septation when viewed from the aspect of the right ventricle. We also find that this plane, usually described as the ventricular septal defect, is not the same as the geometric plane separating the cavities of the right and left ventricles. This means that the latter plane, the interventricular communication, is not necessarily the same as the ventricular septal defect. We are now able to provide further insights into these features by examining hearts prepared from developing mice. Additional molecular investigations will be required, however, to uncover the mechanisms responsible for producing the morphological changes underscoring tetralogy of Fallot.

Keywords: Ventricular septal defect; interventricular communication; cardiac development; terminology

It is an appropriate time to revisit the anatomy of tetralogy of Fallot, as 2013 marks the 125th anniversary of Fallot's landmark publication.[1] Fallot was well aware that, before 1888, others had described the entity we now recognise in his name. It is Fallot, nonetheless, who deserves the credit for emphasising the frequent coexistense of four morphological features in the hearts of patients presenting with "la maladie bleu". It was he who first suggested that the features, when taken together, constituted a tetralogy. Maude Abbott subsequently promoted the notion that the tetralogy should be described in his name.[2] In the centenary year of his publication, translations appeared of both the complete initial paper, in which he described the first three of his overall series of patients,[3] and its abstract.[4] In the full translation, Allwork[3] was less than complimentary concerning Fallot's literary style. This was, perhaps, a harsh judgement. As we will discuss, there is much in the original that serves to arbitrate the multiple controversies that have arisen subsequent to his publication. Allwork's

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Correspondence to: Dr R. H. Anderson, BSc, MD, FRCPath, 60 Earlsfield Road, London SW18 3DN, United Kingdom. Tel: 00-44-20-8870-4368; E-mail: sejjran@ucl.ac.uk

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offering was also less than optimal as, for "purposes of clarity", she used "modern anatomical terms" when making her translation. This meant that she uniformly translated the interventricular communication as described by Fallot to represent a "ventricular septal defect". As we will emphasise in this review, the space that is equivalent to the plane of deficient ventricular septation does provide an interventricular communication. However, this plane, when considered in geometric terms, is not the one that separates the cavities of the right and left ventricles. In this review, therefore, we revisit the anatomy of tetralogy of Fallot, showing also how considerations of morphogenesis can cast significant light on the best way of describing its various morphological features.

The essence of the tetralogy

When describing the index case, the heart being obtained from a young man of 19 years, Fallot[1] reported a deficiency of the basal part of the ventricular septum. He noted that the aortic root overrode the crest of the ventricular septum, being equally supported by the two ventricles. He observed that the infundibulum was lengthened and flattened, being more to the left than normal. He also noted additional valvar stenosis, and commented, as translated by Allwork,[3] that "the concave edge of incomplete ventricular closure was visible posteriorly". He emphasised the presence of right ventricular hypertrophy. He noted similar features in the other two hearts described in his initial work, but pointed out that in the heart from his second patient the aortic root was supported exclusively by the right ventricle, whereas in the heart from the third patient it arose by two-thirds of its circumference from the right ventricle. In summarising the "true anatomopathological tetralogy", he emphasised the presence of narrowing of the pulmonary trunk, an interventricular communication, hypertrophy of the right ventricle, and rightward deviation of the aorta.

All of these features are readily seen in the hearts that we now recognise as satisfying his diagnostic criteria. It is salutary to compare the features of the normal heart (Fig 1a) with those seen in a typical case of the tetralogy (Fig 1b). The hole between the ventricles, when viewed from the right ventricle (Fig 1b), occupies the larger part of the space, which, in the normal heart, is filled by the supraventricular crest. In the setting of the tetralogy, it can also be seen that the "edge of incomplete ventricular closure", again as viewed from the right ventricle, is the leading edge of the muscular outlet septum; this structure is also known as the infundibular or conal septum (Fig 1b). In the normal heart, very little of the muscular septum interposes between the outflow tracts of the right and left ventricles. A small part of the musculature that interposes between the limbs of the septomarginal trabeculation, or septal band, can be removed so as to create a hole between the ventricles (Fig 1a). There is no way of knowing, however, where this component of right ventricular musculature stops, nor where it gives way to the inner heart curve, or ventriculo-infundibular fold. This latter structure separates the ventricular cavity from the extracardiac space formed by the rightward margin of the transverse sinus.[5] There is also no way of knowing, in the normal heart, where the ventriculo-infundibular fold becomes the free-standing muscular subpulmonary infundibulum, which lifts the leaflets of the pulmonary valve away from the base of the ventricular mass. It is the presence of the infundibular sleeve that permits the valve to be removed surgically, and used as an autograft in the Ross procedure (Fig 2).[6]

These building blocks of the right ventricular outflow tract come apart in the setting of the tetralogy. It is the interrelations of the blocks that then reflect the different morphologies of the plane of deficient ventricular septation. Thus, in the majority of hearts fulfilling the criteria for diagnosis, the caudal limb of the septomarginal trabeculation, or septal band, stops short of the ventriculo-infundibular fold. The inferior margin of the hole between the ventricles is then made up of fibrous continuity between the leaflets of the aortic and tricuspid valves (Fig 3a). This arrangement is found in around four-fifths of specimens obtained from patients of European ancestry.[7] In these hearts, the hole between the ventricles is perimembranous, as viewed from the right ventricle, as the atrioventricular component of the membranous septum is incorporated within the area of fibrous continuity. Oftentimes, a remnant of the interventricular component is also to be found reinforcing this corner of the defect, with this structure being known as the membranous flap.[8] In most of the remaining one-fifth of hearts obtained from patients of European ancestry, the posterocaudal margin of the hole between the ventricles, as seen from the right ventricle, is muscular, being formed by union between the caudal limb of the septomarginal trabeculation and the ventriculo-infundibular fold. The muscular structure produces discontinuity between the leaflets of the aortic and tricuspid valves. Its presence means that, when viewed from the right ventricle, the hole has exclusively muscular margins (Fig 3b). In a small number of hearts obtained from patients of European ancestry, but in a much larger number of hearts obtained from patients seen with East Asian ancestry, there is a further variation to be found. In these hearts, there is no formation of the

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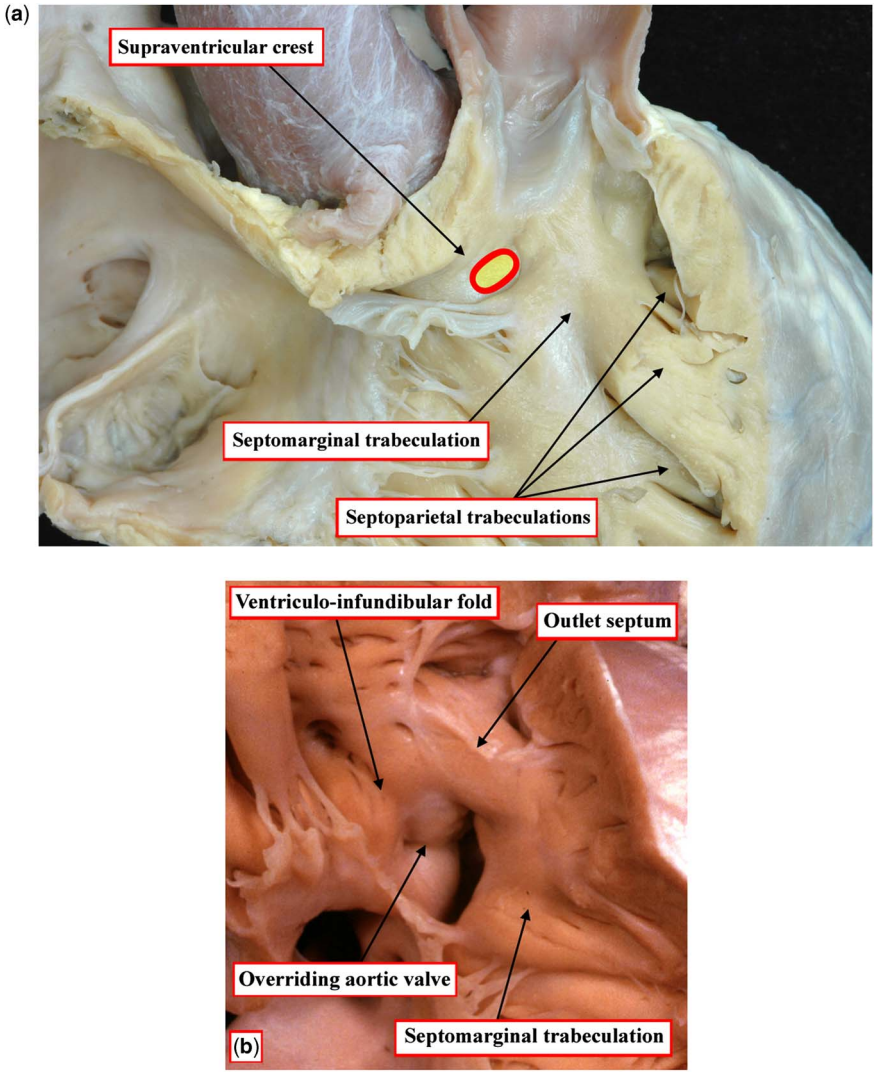


Figure 1.
*The images compare the septal surface of the right ventricle in the normal heart (**a**) and the arrangement as seen in the setting of tetralogy of Fallot with a hole between the ventricles that is perimembranous (**b**). The hole in the malformed heart, which is overridden by the aortic root, opens into the right ventricle in the location of the normal supraventricular crest. A small part of the septal surface of the normal heart can be dissected so as to create an opening to the left ventricle (red oval). In the abnormal heart, this area is magnified to form the "edge of incomplete ventricular closure", or the muscular outlet septum.*

subpulmonary muscular infundibulum. Instead, the cranial margin of the hole between the ventricles is formed by fibrous continuity between the leaflets of the overriding aortic and the narrowed pulmonary valves, often reinforced by a fibrous raphe that hangs down into the ventricular cavities (Fig 3c). In hearts with such doubly committed defects, the caudal margin can either be perimembranous, as shown in Figure 3c, or formed by a muscular strap, the latter again produced by union of the caudal limb of the septomarginal trabeculation with the ventriculo-infundibular fold.

All hearts fulfilling the diagnosis of tetralogy have the hole between the ventricles in directly subaortic position, although its precise morphology can vary as described above. There is then further variability in the other two morphological components of the tetralogy, with the right ventricular hypertrophy being a haemodynamic consequence of the anatomic malformations. As was described by Fallot himself, there can also be marked variation in terms of the degree of aortic override. This feature is better accounted for by describing the extent of biventricular connection of the aortic root. "Aortic override" can be a potentially confusing term as, even in the normal heart, the right coronary aortic sinus overrides spatially the crest of the muscular ventricular septum. In the normal heart, however, the leaflets of the aortic valve are exclusively attached within the left ventricle. In any heart in

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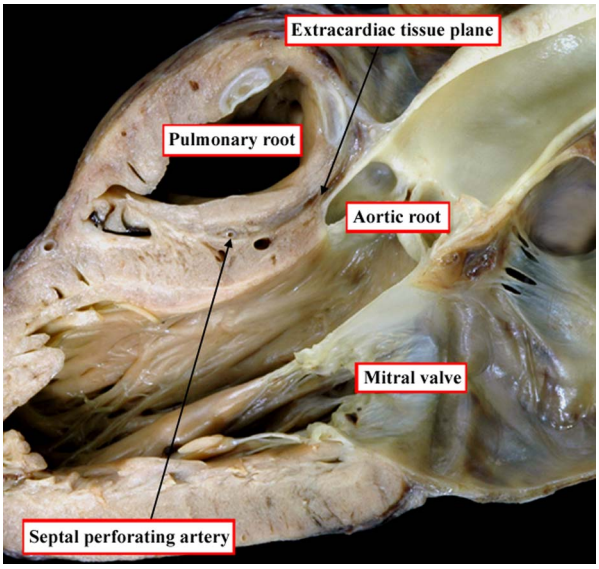


Figure 2.
The normal heart has been sectioned to replicate the parasternal long-axis echocardiographic section. The section has cut through the free-standing subpulmonary infundibulum, revealing the space that, in the normal heart, separates the pulmonary from the aortic root.

which there is deficient ventricular septation, in contrast, a small part of the aortic root, of necessity, will be supported by the components of the right, rather than the left, ventricle. In the setting of tetralogy, this right ventricular support is sufficiently exaggerated that the override becomes obvious. In the initial hearts examined by Fallot himself, the override in the first was described as being equal. In another, Fallot noted that two-thirds of the aortic root was supported above the right ventricle, whereas in the third he noted exclusive origin from the right ventricle. In addition, in all of the cases described by Fallot, there was fibrous continuity between the leaflets of the aortic and mitral valves in the roof of the left ventricle. These observations are surely of significance to ongoing controversies as to whether double outlet from the right ventricle can coexist with tetralogy of Fallot. Using the notion that double-outlet ventriculoarterial connection exists when the greater part of both outlets are supported by the same ventricle, two of the original cases described by Fallot[1] would be diagnosed as having double outlet. The clear-cut description of Fallot's third case also shows that presence of bilateral infundibulums is not a prerequisite for both arterial trunks to arise exclusively from the right ventricle.

Fallot's initial description[1] also gives the lie to the claim that, in the tetralogy, the subpulmonary infundibulum is not only of reduced volume, but is also "too short".[9] As Fallot described, the narrowed infundibulum can be longer than usual, and is

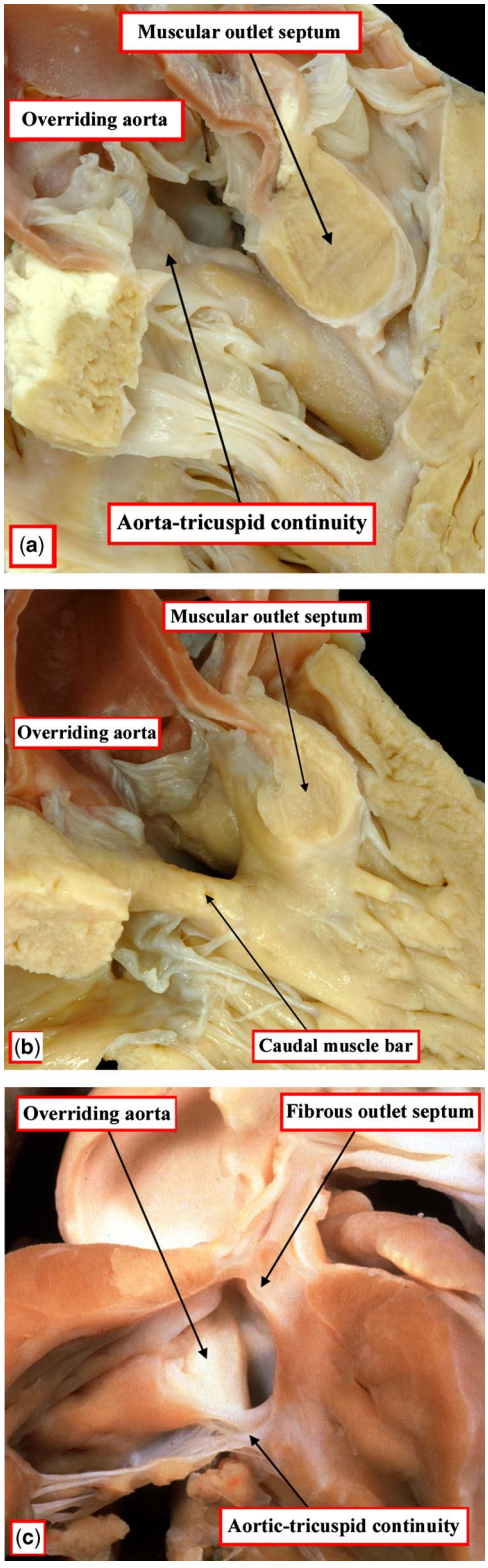


Figure 3.
*The photographs, all taken from the right ventricle, compare the morphology of the hole between the ventricles when the defect is perimembranous (**a**), has a muscular posterocaudal rim (**b**), or is doubly committed and directly juxta-arterial (**c**). The defect shown in (**c**) also extends to become perimembranous. Note that the outlet septum in this case is fibrous rather than muscular.*

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displaced to the left. It can also be short. Indeed, in the setting of the doubly committed defect, it can be totally lacking. In most instances, nonetheless, when compared with the normal heart, the subpulmonary infundibulum is longer than expected.[10,11]

It is not unsurprising that, when comparisons are made between the normal heart and the ones showing the features of the tetralogy, a search should be made for a solitary pathognomonic feature. For some time, one of us (R.H.A) promoted the notion that this feature was provided by antero-cephalad insertion of the muscular outlet septum relative to the limbs of the septomarginal trabeculation. This concept foundered when it was recognised that the so-called Eisenmenger variant of ventricular septal defect also satisfied this criterion. Antero-cephalad deviation of the muscular outlet septum, or its fibrous remnant, nonetheless, is certainly one of the features of the tetralogy. It is the combination of this feature with an abnormal arrangement of the septoparietal trabeculations that provides the pathognomonic feature of the lesion.[12] It is the squeeze between these two components that narrows the entrance to the subpulmonary infundibulum, or narrows the pulmonary valvar orifice when the subpulmonary infundibulum itself has failed to form.

Is the interventricular communication different from the ventricular septal defect?

We have already commented that, when making the translation of the first description, Allwork rendered Fallot's "communication interventriculaire" as the "ventricular septal defect".[3] Is this justified? Is the interventricular communication necessarily the same as the ventricular septal defect? This potential difference is of great significance to the optimal naming, and differentiation, of holes between the ventricles, as we have emphasised in a recent commentary published in "Congenital Cardiology Today".[13] It remains a fact that, in most circumstances, those working in countries that communicate using Romance languages continue to describe holes between the ventricles as interventricular communications. Those using Germanic languages, in contrast, use the notation of ventricular septal defect. If we examine a long-axis cut through the overriding aortic root in a heart obtained from a patient with tetralogy of Fallot, we see that these holes are not necessarily identical. Any hole between the ventricles obviously provides a communication between the ventricular cavities. Whenever the aortic root is overriding the crest of the ventricular septum, or when the pulmonary root is overriding, it is a cone of space, rather than a specific hole, that provides the communication between the chambers.[14] Within this cone of space, there are then multiple planes that can be defined as providing interventricular communications. Only one of these planes, however, represents the true geometric line of division between the two cavities (Fig 4).

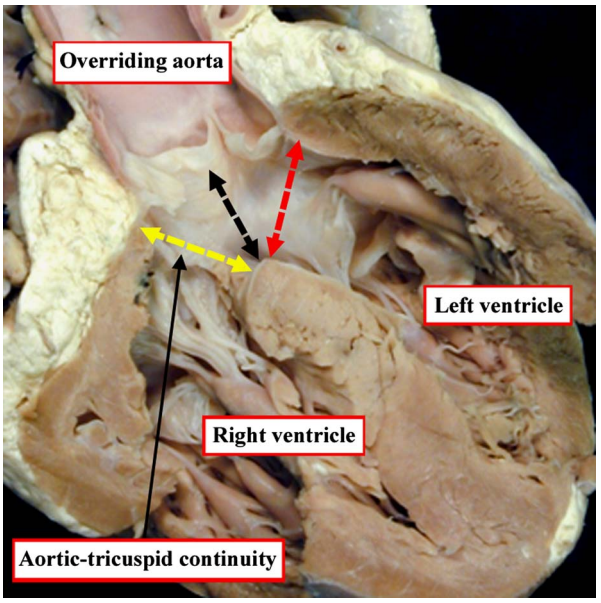


Figure 4.
The section is taken through the long axis of the overriding aortic root in the heart from a patient with tetralogy of Fallot. It shows the significant planes of space that can be recognised with the cone subtended from the leaflets of the overriding aortic valve to the crest of the apical muscular septum. The true interventricular communication is the cranial continuation of the plane of the muscular septum itself shown by the dashed double-headed black arrow. The red double-headed arrow shows the exit from the left ventricle to the cone of space. The yellow double-headed arrow shows the caudal margin of the right ventricular exit from the cone of space. It is this latter plane that represents the zone of deficient ventricular septation, and it is this plane that is usually defined as representing the ventricular septal defect. It is subtly different from the true interventricular communication.

This plane, the geometric interventricular communication, represented by the black double-headed arrow in Figure 4, is the cranial continuation of the long axis of the apical muscular septum. This is the plane that Fallot noted to be deficient at the basal component of the septum when describing his first case. The plane of deficient ventricular septation, in contrast, is the one extending between the leading edge of the muscular outlet septum and the "concave edge of incomplete ventricular closure" as noted by Fallot. Its caudal extent is shown by the double-headed yellow arrow in Figure 4. In the heart illustrated in Figure 4, and in the one shown in Figure 3a, this plane of space has a fibrous

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posterocaudal rim. In contrast, the caudal margin of the plane of space in the heart shown in Figure 3b is muscular. If this plane is taken to represent the ventricular septal defect, and it is the plane that is closed by the surgeon so as to reconnect the aorta with the left ventricle, then it is perimembranous in Figure 3a, and muscular in Figure 3b. In both of these hearts, however, the defect would be considered to be of conoventricular variety.[12] This shows that if defects are categorised as being conoventricular, it is also necessary to indicate whether they are perimembranous or muscular. It is this latter designation that provides the necessary information regarding the surgical vulnerability of the atrioventricular conduction axis.[15] It is also then the case that, should the patient with tetralogy have the aorta arising exclusively from the right ventricle, as was the case with the second patient described by Fallot, the left ventricular margin of the plane of space would represent the geometric interventricular communication. This space, however, does not represent the plane of deficient ventricular septation. Considerations of morphogenesis can cast further light on this potential conundrum.

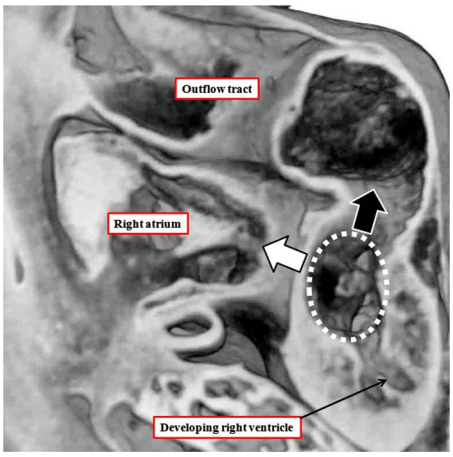


Figure 5.
The section is from a human embryonic heart at Carnegie stage 14 prepared using high-resolution episcopic microscopy. The cut shows the embryonic interventricular communication (dotted oval) viewed from its right side. The entirety of the cardiac output, at this stage, passes through the interventricular communication. Already, however, the rightward margin of the foramen – white arrow with black borders – provides continuity between the developing walls of the right atrium and the right ventricle, while the cranial margin – black arrow with white borders – provides continuity between the roof of the left ventricle and the dorsal wall of the outflow tract, which will become the aortic vestibule.

Developmental considerations

Maude Abbott, who popularised the notion that it was Fallot who first recognised the importance of the tetralogy, was herself convinced that knowledge of cardiac development would enhance the understanding of the structure of the congenitally malformed heart.[16] Until recently, however, the knowledge of the anatomic changes occurring during cardiac development has rarely been sufficiently advanced to permit the making of worthwhile inferences. All of that has changed with the emergence of the technique of high-resolution episcopic microscopy.[17] Using this technique, it is now possible to analyse the developing heart in all its orthogonal planes, varying the axis of the planes to match that of the heart itself. In addition, by examining large series of murine hearts, it is possible to compensate for the subtly different changes occurring within a given day of developmental time. Using this approach, we are now able to offer insights directly relevant to the morphology of tetralogy of Fallot.

Subsequent to the initial formation of the atrial appendages, and growth of the apical ventricular components, the embryonic atrioventricular canal is supported exclusively by the developing left ventricle, whereas the outflow tract arises exclusively above the developing right ventricle. The rightward margin of the interventricular communication, nonetheless, already provides continuity between the developing walls of the right atrium and right ventricle, while the cranial margin of the dorsal component of the outflow tract is in continuity with the roof of the developing left ventricle (Fig 5).

All the blood flowing from the atrial chambers to the outflow tract at this early stage, of necessity, has to pass through the embryonic interventricular communication. Owing to the fact that the heart develops its separate systemic and pulmonary circulations, this embryonic communication is never closed, but rather is remodelled so as to provide the inlet from the right atrium to the right ventricle, and the outlet from the left ventricle to the aorta. Only subsequent to this process of remodelling is it possible to close the final remnant of the communication between the right ventricle and the aortic root. It is incomplete remodelling of the latter part of this process that provides the understanding of the anatomy of tetralogy.

The process that brings the cavity of the right atrium into direct continuity with that of the right ventricle is rightward expansion of the atrioventricular canal. Subsequent to this process, the entirety of the outflow tract remains supported by the cavity of the right ventricle. This is akin to the postnatal situation of double-outlet right ventricle. As can be seen in a mouse heart at embryonic day

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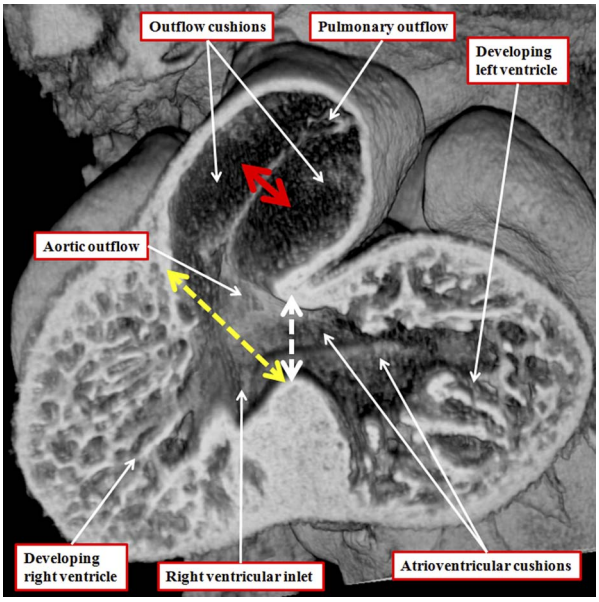


Figure 6.
The image shows a four-chamber section from an episcopic data set prepared from a mouse at embryonic day 11.5. The atrioventricular canal has already expanded rightward, remodelling the original interventricular communication so as to provide the right ventricular inlet. The outflow tract, however, remains exclusively supported by the developing right ventricle. Blood entering the left ventricle, therefore, must pass to the developing aortic root by traversing the persisting embryonic interventricular communication, shown by the double-headed white arrow. The aortic root is the dorsal part of the outflow tract, and is being divided from the pulmonary root by the fusing outflow cushions – double-headed red arrow. The double-headed yellow arrow shows the extensive communication present at this stage from the right ventricle to the developing aortic root.

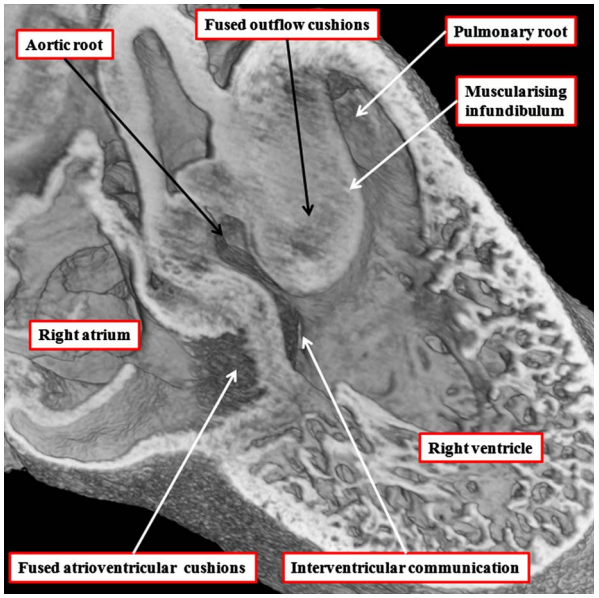


Figure 7.
The image shows an oblique section paralleling the subcostal echocardiographic plane, and revealing the transfer of the aortic root during embryonic day 13.5 in the mouse to the developing left ventricle. At this stage, however, the root remains largely supported by the developing right ventricle. The pulmonary outflow tract is now separated from the aortic root, and the comparable situation with tetralogy of Fallot, should the outflow tract be restrictive, is obvious – compare with Figure 3.

11.5, it is the interventricular communication that then provides the egress from the left ventricle to the developing aortic root (Fig 6). So as to complete the septation of the normal heart, the developing dorsal component of the outflow tract expands leftwards, thus shifting the aortic root to a position more directly above the left ventricle. At the same time, the proximal outflow cushions fuse to separate the aortic from the pulmonary root, with their surface muscularising to form the subpulmonary infundibulum (Fig 7).

In normal development, the process of transfer of the aorta continues. As it takes place, the muscularising outflow septum is brought into line with the crest of the apical trabecular septum. It is this process that commits the aortic root to the left ventricle (Fig 8a), with the eventual formation of the membranous part of the septum from the rightward margin of the atrioventricular cushions serving to close the right ventricular margin of the initial embryonic interventricular communication (Fig 8b). The remainder of the embryonic interventricular communication remains patent, providing the outflow from the apical part of the left ventricle to the aortic root (Fig 8).

Comment

The changes observed during normal cardiac development now permit several inferences to be made concerning the morphology of tetralogy of Fallot. First, the rightward margin of the cone of space subtended by the overriding leaflets of the aortic valve to the crest of the muscular ventricular septum (Fig 4) is the plane that is closed during normal development by the membranous part of the ventricular septum (Fig 8). This is the plane identified by Fallot as representing "incomplete ventricular closure". It is also the plane of space that is closed by the surgeon so as to reconnect the aorta with the left ventricle. Most clinicians identify the space as the ventricular septal defect. It is different, however, from the geometric plane of space that separates the cavities of the right from the left ventricle. This second plane is the cranial continuation of the long axis of the apical muscular ventricular septum (Fig 4). The plane of space closed by the surgeon is also different from the component of the initial embryonic interventricular

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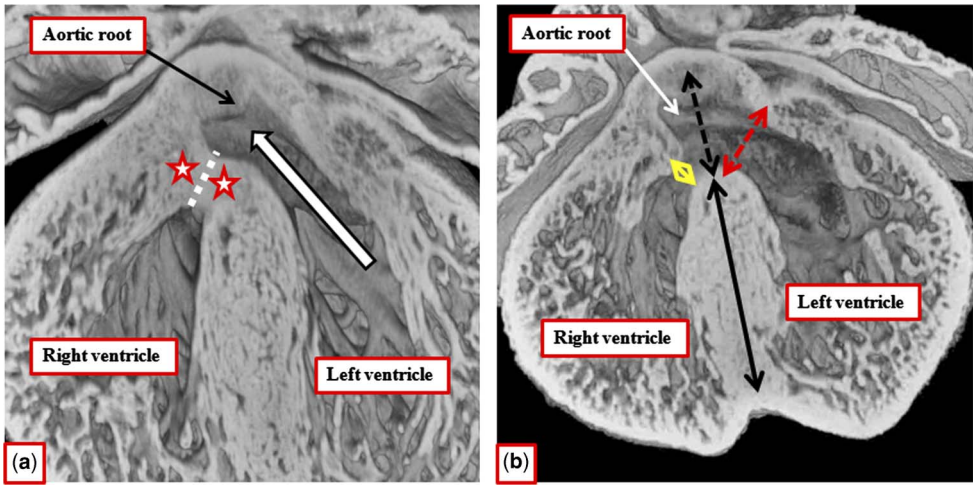


Figure 8.
*The two images are from episcopic data sets prepared from different developing mice at embryonic days 12.5 and 13.5. (**a**) Day 13.5, shows how the proximal outflow cushions (stars) have fused with each other (white dotted line), and also with the crest of the apical muscular septum so as to commit the aortic root to the left ventricle – white arrow with black borders. (**b**) A similar plane but taken more dorsally, at day 12.5, shows how the rightward margin of the initial interventricular communication – yellow double-headed arrow – has yet to close. This will be achieved by formation of the membranous septum, derived from the rightward margins of the atrioventricular cushions. The plane of the true interventricular communication (dashed double-headed black arrow) is now the cranial continuation of the long axis of the apical muscular septum (solid double-headed black arrow). The remaining patent component of the embryonic interventricular communication provides the connection between the left ventricle and the aortic root – red double-headed arrow. This situation should be compared with the arrangement seen in tetralogy of Fallot (Fig 4).*

communication that remains after the aorta is committed to the left ventricle. This latter space then provides the channel from the body of the left ventricle to the aortic root. When both arterial trunks arise from the right ventricle, however, the comparable space is usually described as the "ventricular septal defect". It is fundamentally different from the plane of space usually described as the ventricular septal defect in the setting of tetralogy. Surgeons are well aware that the hole between the ventricles cannot be closed when both arterial trunks arise from the right ventricle. In the setting of double-outlet right ventricle, therefore, it is better to describe the hole as the interventricular communication, rather than as a ventricular septal defect. This then implies that an interventricular communication is not necessarily the same thing as a ventricular septal defect. This latter fact could pose problems for those who, when describing lesions in the Romance languages, conventionally describe the hole between the ventricles as the interventricular communication, but not necessarily considering the communication as representing the geometric plane that is the basal continuation of the apical muscular ventricular septum.

The second important inference regards the formation of the muscular outlet septum. During normal development, the outflow cushions fuse with each other, and also with the crest of the apical muscular septum. Their surfaces then muscularise to form the subpulmonary infundibulum, with the core of the cushions effectively disappearing as an extracardiac tissue plane is formed between the infundibulum and the aortic root. As the aortic root is transferred to the left ventricle, so the leading edge of the newly formed infundibulum is brought into line with the crest of the apical muscular ventricular septum. The membranous septum is then formed from the rightward margins of the fused atrioventricular cushions. This explains why, in the normal heart, there is so little of the muscular septum positioned directly between the subpulmonary and subaortic outlets. Should the aortic root not be fully transferred to the left ventricle, however, as occurs in the Eisenmenger defect, and in the setting of tetralogy, then part of the muscularising outflow cushions will form a muscular outlet septum, which will remain a right ventricular structure. When we examine postnatal hearts, we find that the mere presence of the muscular outlet septum in the right ventricle in association with aortic overriding is insufficient to serve as a diagnostic marker for tetralogy. Something additional is likewise needed during the developmental process to produce tetralogy rather than the Eisenmenger defect. The morphological observations suggest that this will be related to formation of the septoparietal trabeculations, but increasing experience with molecular biological

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techniques will hopefully pinpoint the morphogenetic mechanisms. The availability of the episcopic technique for examination of the developing hearts will certainly facilitate the understanding of the morphological changes.

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