The advantages of naming rather than numbering the arteries of the pharyngeal arches

Robert H. Anderson[1] , Anthony Graham[2], Jill P.J.M. Hikspoors[3],
Wouter H. Lamers[3] and Simon D. Bamforth[1]

[1]Biosciences Institute, Newcastle University, Newcastle-upon-Tyne, UK; [2]Developmental Neurobiology, Guys Campus, Kings College, London, UK and [3]Department of Anatomy & Embryology, Maastricht University, Maastricht, The Netherlands

Abstract

Controversies continue as to how many pharyngeal arches, with their contained arteries, are to be found in the developing human. Resolving these controversies is of significance to paediatric cardiologists since many investigating abnormalities of the extrapericardial arterial pathways interpret their findings on the basis of persistence of a fifth set of such arteries within an overall complement of six sets. The evidence supporting such an interpretation is open to question. In this review, we present the history of the existence of six such arteries, emphasising that the initial accounts of human development had provided evidence for the existence of only five sets. We summarise the current evidence that substantiates these initial findings. We then show that the lesions interpreted on the basis of persistence of the non-existing fifth arch arteries are well described on the basis of the persistence of collateral channels, known to exist during normal development, or alternatively due to remodelling of the aortic sac.

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The naming of the pharyngeal arches to be found in mammals has long been controversial. The ancestral condition for jawed vertebrates is to have seven such arches, with five bearing the gills. Amphibians have six arches, with the number in amniotes reduced to five. The reduction in number is usually explained on the basis of the assumption of a terrestrial lifestyle. The numbering of the arches in amniotes, however, does not reflect the evolutionary trend. Thus, the arches are conventionally labelled one through four, with the ultimate arch then being nominated as the sixth. As we have recently suggested, there is neither logic nor evidence to support this approach.[1] The arches themselves are bounded by the pharyngeal pouches, of which there are but four. The ultimate arch, unlike the first four, is not bounded caudally by a pouch. Significant differences are to be found in the derivatives of the arches, with no skeletal muscles formed within the ultimate and penultimate arches. It is the arteries, therefore, that dominate the anatomical scene in these final two arches. And the arteries themselves are not always normally formed. There lies the rub since it still remains popular amongst several of those dealing with congenital cardiac malformations to interpret some of these anomalies on the basis of persistence of an artery of a presumed vestigial fifth arch.[2] We have recently summarised the lack of evidence supporting the notion that a fifth arch is to be found within a presumed complement of six.[1] Due to this fact, it would be logical simply to renumber the existing arches as one through five, as was initially the case.[3] Such an approach would result in the arterial duct being described, correctly, as the artery of the fifth pharyngeal arch.[4] This potential solution would then create great confusion with those who diagnose and treat congenital cardiac malformations. As discussed above, many such practitioners still accept the existence of presumed vestigial entities representing the alleged fifth arch arteries. A significant body of literature already exists in which various malformations of the extrapericardial arterial pathways are interpreted as persistent fifth arch arteries.[5–9] Our alternative solution to this potential conundrum was to argue in favour of naming the arches, rather than numbering them.[1] In this review, we emphasise the advantages of this approach for the understanding of those congenital malformations previously explained on the basis of persistence of the enigmatic fifth arch of six.

The historical background

Wilhelm His Senior, towards the end of the nineteenth century, produced a monumental textbook providing an account of human cardiac development.[10] In this book, he provided drawings of his investigations showing the formation of five pharyngeal arches, separated by four pharyngeal pouches. The scheme of developing arches he described was then shown in a classical textbook of physiology, which appeared in English under the editorship of Landois and Stirling.[11] The drawings used in Landois and Stirling were then adopted by Mills in his textbook.[12] Mills indicated that the model used by Landois and Stirling was based on the
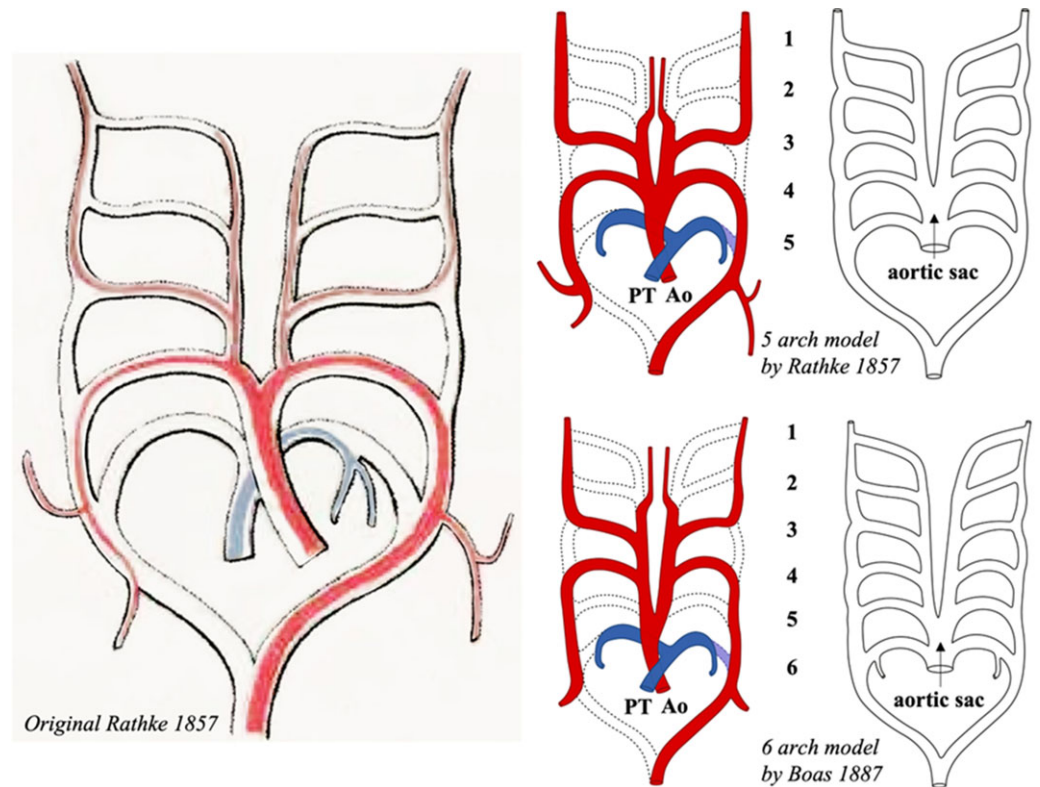
Figure 1. The images show the evolution in the information contained in the so-called Rathke diagram. The left-hand panel shows the original drawing of Rathke illustrating only five arches, but showing both pulmonary arteries taking origin from the ultimate left-sided arch. The right-hand upper panels show how the arches would now be illustrated had we retained Rathke's original prototype. The lower panels to the right-hand show the drawing popularised by Boas, who introduced an additional set of arteries on theoretical grounds, but provided no evidence for their existence.

prototype established by Rathke.[3] It is, of course, the Rathke diagram that is now usually used to show the basic arrangement of the arteries of the pharyngeal arches. In its initial form, produced in the middle of the nineteenth century, Rathke had illustrated five sets of arch arteries, with the pulmonary arteries taking origin from the fifth set (Fig. 1, left-hand panel and upper right-hand panels). And as indicated, this was also the arrangement depicted by His.[10]

How, then, did the enigmatic fifth set come to intrude into the original pattern, extending it from five to six sets of arch arteries? Resolving this question is problematic. As far as we can establish, it was Boas who first put forward the possibility that a fifth set of arteries might exist in mammals (Fig. 1, right-hand lower panels).[13] He based his suggestion on deductions depending on the presence of six, or more, arches in other clades. Boas, however, produced no evidence to substantiate the existence, in mammals including man, of the presumed fifth set of arch arteries within a set of six. The possibility of their existence was then investigated by several investigators over the turn from the nineteenth to the twentieth century. Researchers such as van Bemmelen,[14] Locy,[15] and Reinke[16] argued in favour of the presence of the vestigial arch. Others, such as Lewis,[17] and Reagan,[18] were unable to find any supportive evidence. It was Tandler who produced perhaps the most significant evidence supporting the existence of the additional arches, illustrating the presence of collateral channels in 13 human embryos.[19] Surprisingly, although these findings were published in 1909, they received no attention in the account of Reagan,[18] published in 1912. Despite Tandler's descriptions, Congdon,[20] writing in 1922, expressed caution when accepting their presence as evidence of true arch arteries, and called for additional confirmatory proof. The developmental evidence that has subsequently emerged supports the original findings of His, and the initial diagram produced by Rathke, revealing the presence

of only five sets of arteries and pouches in both avian and mammalian species.[21,22]

Despite the lack of evidence in favour of the enigmatic fifth set of six arteries, paediatric cardiologists have continued to interpret anomalies as if the vestigial set does exist.[7,8] The anomalies in question certainly do exist. It follows, therefore, that if it is truly the case that there are only five sets of arteries formed during development, then an alternative explanation is required to account for the malformations.[3] Such explanations are readily forthcoming when the changes are reviewed that take place during the conversion of the initially bilaterally symmetrical pattern to the normal definitive arterial pathways.

The formation of the pharyngeal arches and their contained arteries

The enigmatic fifth set of presumed six sets of arteries can only exist if there are six pharyngeal arches formed during normal development. The development of the arches depends on the formation of the pharyngeal pouches, which are out-pocketings of the pharyngeal endoderm. Formed at specific sites, they protrude to contact the ectoderm, with grooves or clefts becoming evident in the pharyngeal ectoderm.[23–25] The first arch artery develops concomitantly with the heart tube and the dorsal aortas at Carnegie stage 9, when around 26 days have passed since fertilisation. At that time, the buccopharyngeal membrane is still intact and a lateral bulge of the pharynx caudal to the single arch artery presages the development of the first pharyngeal pouch. It takes 3 more days to form the second bulge at Carnegie stage 11 (Fig. 2a), and another day to form the second arch artery at Carnegie stage 12 when approximately 30 days have passed since fertilisation (Fig. 2b). This sequence suggests that the arteries form inside a pre-existing arch,
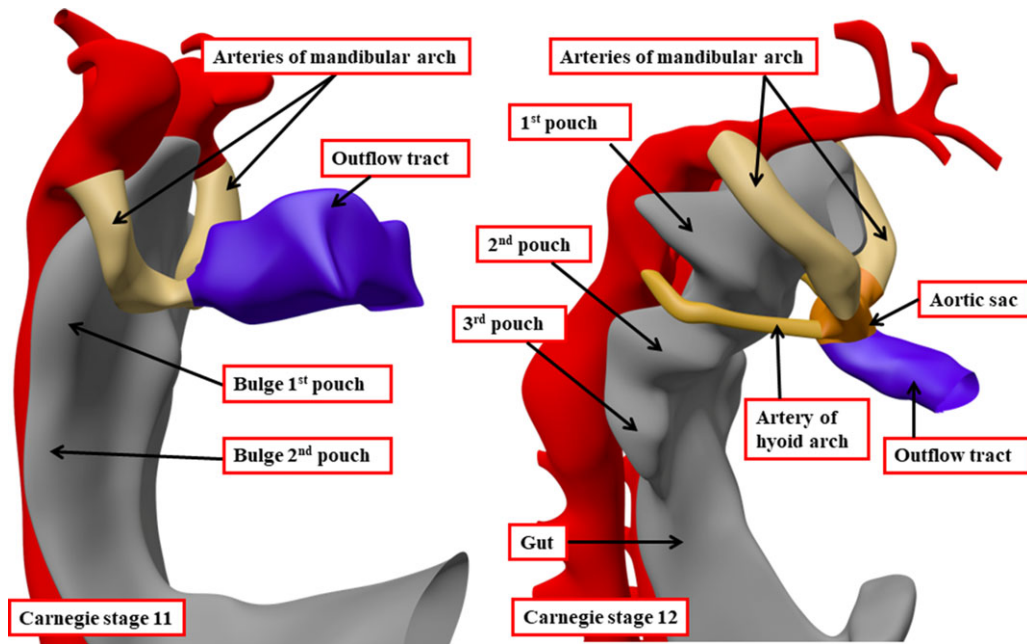
Figure 2. The images show three-dimensional reconstructions made at Carnegie stages 11 and 12 in human development. They reveal the formation of the arterial vessels that encircle the developing pharynx and unite dorsally to form the descending aorta.
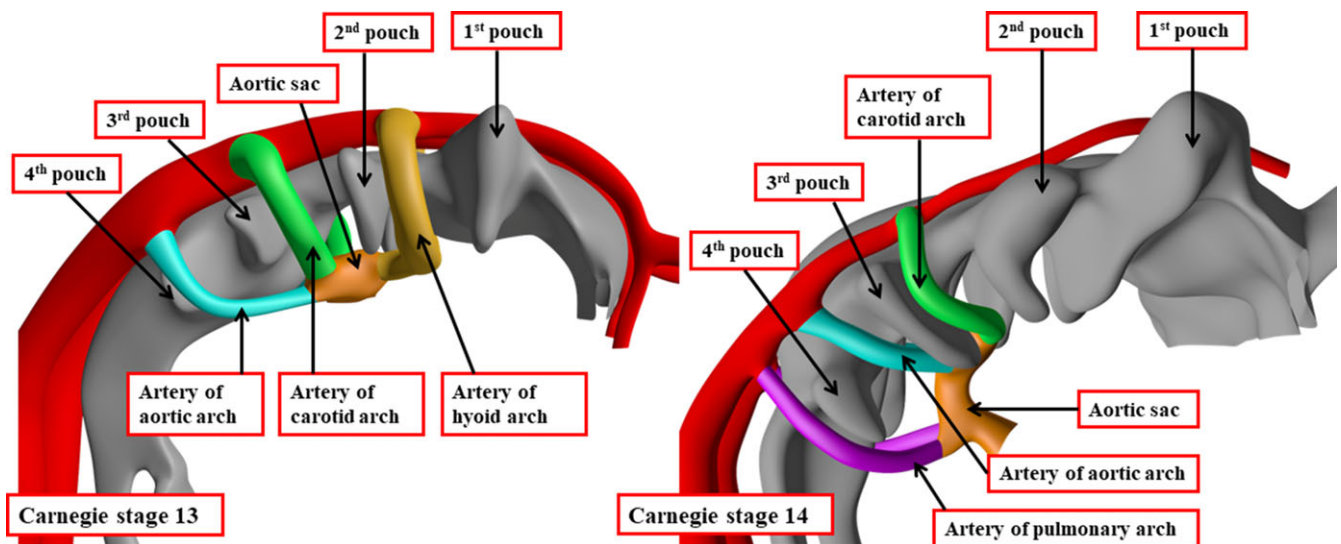

Figure 3. The image shows comparable reconstructions to those shown in Figure 2, but from human embryos at Carnegie stages 13 and 14. They show the diminution in significance, with ongoing development, of the arteries of the mandibular and hyoid arches. There are only four pharyngeal pouches.

rather than the arches forming around the arteries. The additional pouches then form rapidly. By Carnegie stage 14, representing around the end of the fifth week of development, the fourth pouch has formed, with the ultimate arch artery subsequently formed dorsal to it (Fig. 3). The arteries of the mandibular and hyoid arches have themselves regressed significantly at this stage. They persist as the mandibular and hyoid arteries.

Each arch, bounded by the endodermal and ectodermal layers (Fig. 4), contains cells derived from the neural crest surrounding a central mesodermal population. The derivatives of these tissues vary markedly. The first two arches, although eventually containing relatively insignificant arteries, give rise to multiple skeletal muscles, as well as forming important cartilaginous structures. The first forms the mandible, and associated muscles, as well as the malleus and incus of the middle ear. This arch receives its sensory and motor innervation from the trigeminal nerve. The second arch generates the stapes and part of the hyoid and muscles of the face and neck. This arch is innervated by the facial nerve.[1]

It is the arteries that are of greatest significance when assessing the derivatives of the caudal arches.[4] The vessels of the third arch contribute to the formation of the carotid arteries, so this arch is well described as the carotid arch. The skeletal derivative of this arch is a contribution to the hyoid bone, its muscular derivative is the stylopharyngeus, and its innervation is from the glossopharyngeal nerve. The dominant arteries of the postnatal extrapericardial pathways are derived from the final three arches. These arteries, all evident by Carnegie stage 14, representing the end of the fifth week of development in the human, arise from the cranial and caudal poles of the elongated aortic sac (Fig. 5). The sac itself is the extrapericardial manifold enclosed within the ventral pharyngeal
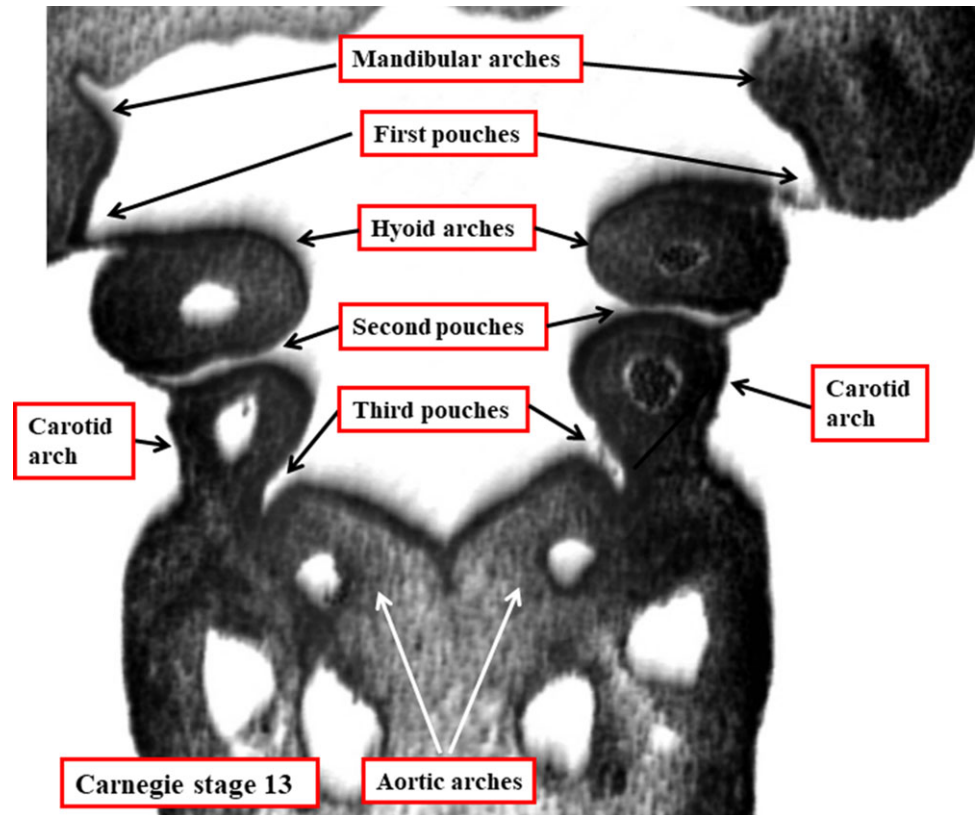
Figure 4. The image shows a frontal section taken from an episcopic dataset of a human embryo at Carnegie stage 13. It shows well the arches surrounding their contained arteries, and the pouches which separate them.
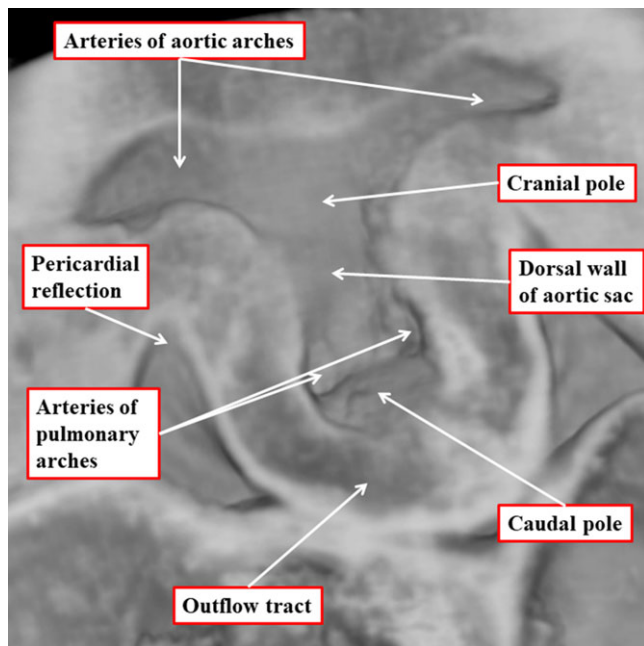

Figure 5. The image is a frontal section from an episcopic dataset made from a human embryo at Carnegie stage 14. It shows how the aortic sac, by this stage, has elongated to form cranial and caudal poles. The cranial pole gives rise to the arteries of the carotid and aortic arches, while the caudal pole supports the arteries of the pulmonary arches.

mesenchyme.[26,27] The dorsal wall of the sac will protrude in oblique fashion into the cavity of the distal intrapericardial outflow tract to become the aortopulmonary septum. This septum will itself separate

the non-myocardial distal part of the outflow tract into the intrapericardial aorta and pulmonary trunk, prior to losing its septal identity as the intrapericardial arterial trunks develop their own walls.

At the end of the fifth week of development, therefore, the developing extracardiac pathways are bilaterally symmetrical, with the now separated poles of the aortic sac giving rise only to the arteries of the final three arches (Fig. 6). The third arch, as already explained, will provide the basis for formation of the carotid arteries. They are well described as the carotid arches. Already, nonetheless, with remodelling of the aortic sac, the carotid arch arteries take their origin, along with the arteries of the fourth arch, from its cranial pole. It is the arteries of the fourth arch that, together with the horns of the cranial part of the aortic sac, form the basis of the aortic arch and its brachiocephalic branches. The fourth arch, therefore, is appropriately described as the aortic pharyngeal arch. This pharyngeal arch itself does not give rise to either muscular or cartilaginous elements. Its nerve is the pharyngeal branch of the vagus nerve.

The ultimate pharyngeal arches are bounded cranially by the fourth pharyngeal pouches. They have no caudal endodermal boundary, nor do they give rise to muscular or cartilaginous derivatives. Their nerve is the laryngeal branch of the vagus. Their major components are the bilaterally symmetrical arteries arising from the caudal pole of the aortic sac, itself continuous with the intrapericardial pulmonary trunk (Fig. 6). The right and left pulmonary arteries, by the end of the fifth week of development, have canalised within the ventral pharyngeal mesenchyme. They extend caudally to feed the developing lungs (Fig. 6). They arise from the arteries of the ultimate arch shortly after the arteries themselves have branched from the aortic sac (Fig. 6). Hence, the
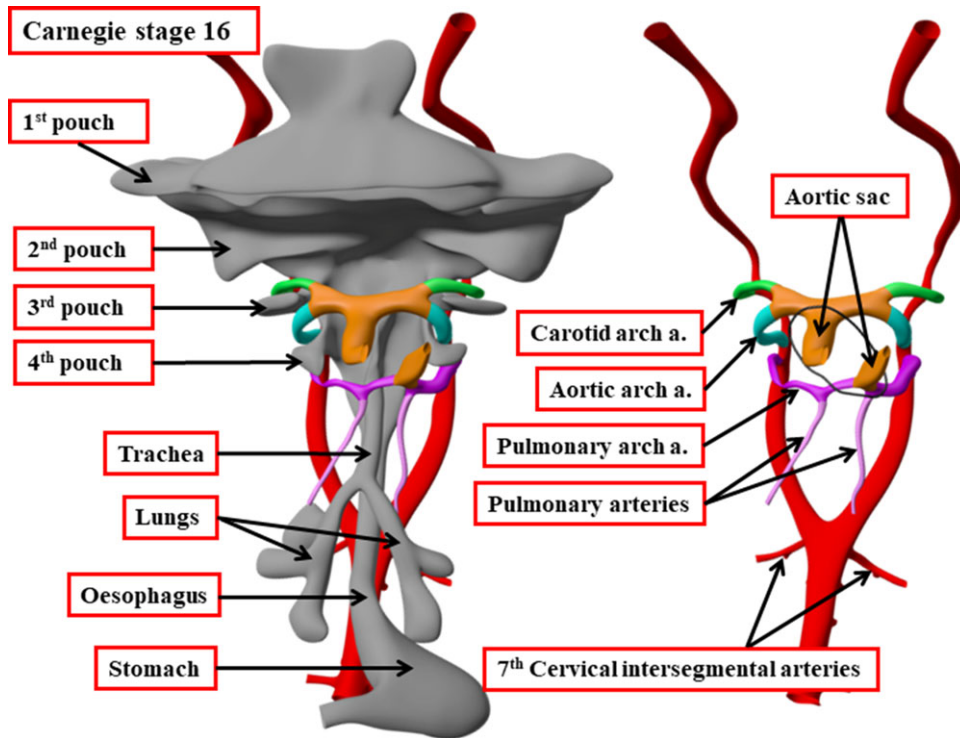
Figure 6. The images are reconstructions from a human embryo at Carnegie stage 16. The left-hand panel includes the gut, lungs, and the pharyngeal pouches (in grey), whereas the right-hand panel shows only the arterial components (the carotid arch arteries in green, the aortic arch arteries in blue, and the pulmonary arch arteries in purple). The aortic sac derivatives are coloured orange. The dark grey loop demarcates the pericardial boundary.
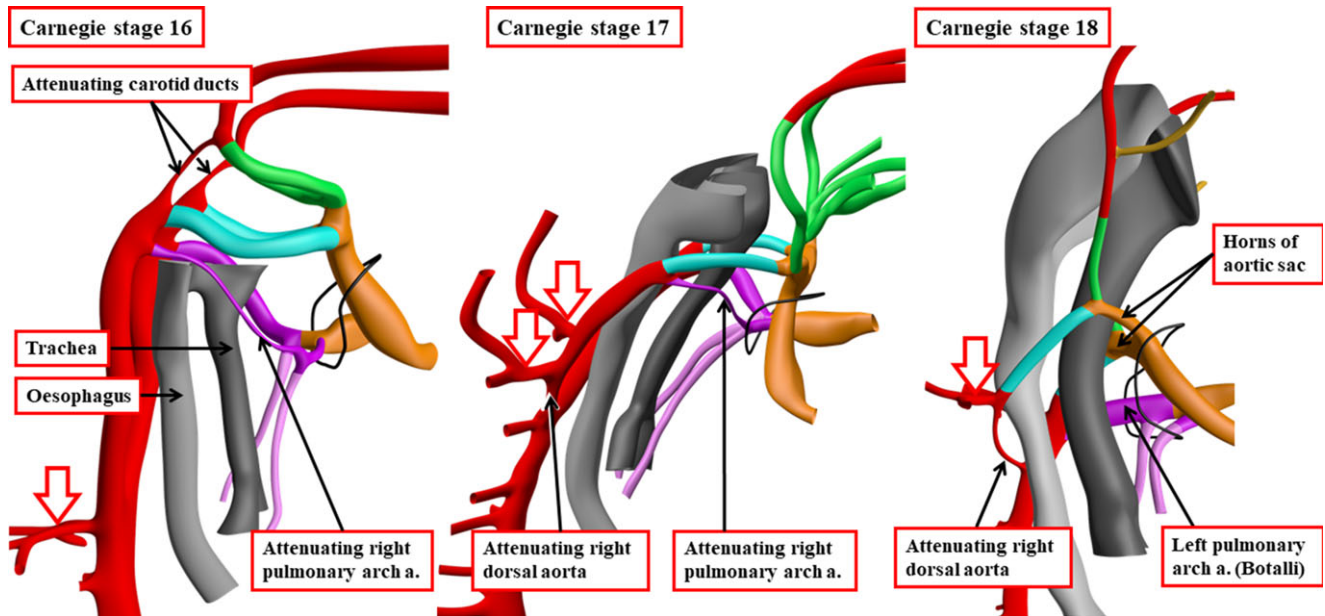

Figure 7. The reconstructions show the gradual regression of the right-sided components of the initially symmetrical arteries extending through the pharyngeal arches in human embryos. Whilst the dorsal right arch persists, it creates a ring around the trachea-oesophageal pedicle. The white arrows with red borders show the location of the seventh cervical intersegmental arteries, which become the definitive subclavian arteries. The trachea and lungs are coloured grey, and the carotid arch arteries in green, the aortic arch arteries in blue, and the pulmonary arch arteries in purple. The aortic sac derivatives are coloured orange. The dark grey loop demarcates the pericardial boundary.

ultimate set of arch arteries, which are the fifth in number, can be described as the arteries of the pulmonary arches.

Remodelling of the arch arteries

By the end of the fifth week of development, the ultimate three sets of arteries encircle the developing trachea-oesophageal pedicle in bilaterally symmetrical fashion (Fig. 6). Significant remodelling, therefore, is needed to produce the definitive patterns. The remodelling takes place with remarkable rapidity (Fig. 7). It involves not only the arch arteries themselves, and the aortic sac, but also the seventh cervical intersegmental artery. At Carnegie stage 16, these segmental arteries, which retain their position during development, are seemingly located well caudal to the heart
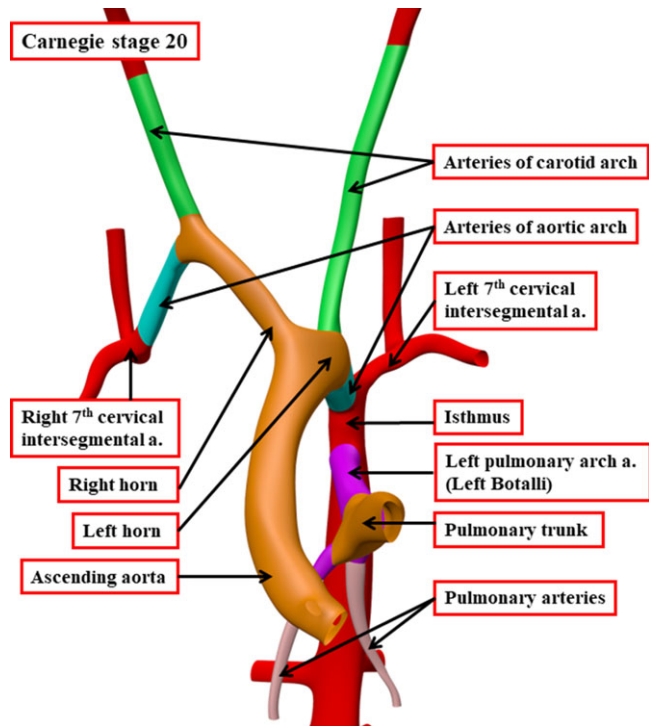
Figure 8. The image is from a human embryo at Carnegie stage 20. Comparison with Figure 6 reveals the results of remarkable remodelling shown in Figure 7, which in just over one week have transformed the initial bilaterally symmetrical arrangement into the definitive postnatal situation. The carotid arch arteries are coloured green, the aortic arch arteries in blue and the pulmonary arch arteries in purple. The aortic sac derivatives are coloured orange.

itself (Fig. 6). Because the segmental arteries are fixed, with the heart being located cranially at this time, the extensive remodelling requires a caudal shift of the heart. There is also rapid diminution in the size and calibre of the right-sided channels. Eventually, the cranial pole of the aortic sac will form the extrapericardial component of the ascending aorta. Its right horn will then become the brachiocephalic trunk, with its left horn forming the transverse aortic arch (Fig. 8). The descent of the heart, relative to the fixed seventh cervical intersegmental arteries, then underscores the formation of the subclavian arteries.[28] The developing left artery crosses the junction of the left pulmonary arch artery with the descending aorta as part of this process (Fig. 8). It is this crossing of the left subclavian artery that has been likened to the castling movement in chess, with this having significance for the understanding of the variants of aortic coarctation. The arteries of the carotid arches then persist as the carotid arteries themselves, with the arteries arising from the remodelled horns of the aortic sac (Fig. 8). The loss of the dorsal connections of the arteries of the right arches is also of obvious significance. With regard to the ultimate arch, it is the loss of the right-sided arch artery that leaves the right and left pulmonary arteries taking their origin extrapericardially from the proximal parts of the arch arteries at their union with the caudal pole of the aortic sac. The artery of the left pulmonary arch then persists as the arterial duct (Fig. 8).

When considering the extent of remodelling that takes place between Stage 16 (Fig 6), when around 38 days have elapsed subsequent to fertilisation, and Stage 20 (Fig. 8), which is

reached at the end of the seventh week of development, it is remarkable that there are not fewer congenital abnormalities involving the extrapericardial arterial pathways. All the known lesions that do ensue are well explained on the basis of the so-called hypothetical double aortic arch, as proposed by Edwards and his colleagues.[29] In the hypothetical model, an arterial duct arises from the caudal aspect of an arch artery that encircles the trachea-oesophageal pedicle on both sides, with common carotid and subclavian arteries arising from the cranial aspect (Fig. 9). It is also known that collateral channels are found in around half of all developing murine embryos between the dorsal extents of the arch arteries and their junctions with the descending aorta on both sides (Fig. 10).[30] When these collateral channels are taken into consideration, then it is an easy matter, on the basis of remodelling, not only to explain the multiple lesions grouped together as vascular rings but also to account for the various lesions that previously had been interpreted on the basis of persistence of the arteries of the non-existent fifth arches of the presumed set of six.

### Previous interpretations of "fifth arch arteries"

It was Van Praagh, as long ago as 1969, who first invoked the potential presence of a persistent "fifth arch artery" to explain the so-called double-barrelled aorta.[4] Persistence of the collateral channels found during normal development of both human and murine embryos provides a plausible explanation for these lesions.[3] The duplicated collateral channels themselves can be extensive. We had initially interpreted such an extensive channel as a potential "fifth arch artery" (Fig. 11).[30] Since we now know that the fifth arch of six does not exist, we now consider the channel to be a collateral vessel.[3] We had also interpreted the proximal origin of a channel feeding the pulmonary arteries in the setting of tetralogy with pulmonary atresia as another presumed artery of the "fifth arch" (Fig. 12). In the light of the extent of remodelling required to take the seventh left intersegmental artery to its definitive position, it is just as easy to interpret the location of the channel seen feeding the pulmonary arteries as a malpositioned arterial duct. Similar changes in remodelling can then offer plausible explanations for the various entities previously interpreted widely as the non-existent arteries of the alleged fifth pharyngeal arches. As we explained from the outset, however, since we now know that there are only five sets of pharyngeal arches, it is unacceptable to seek to rename the arterial duct as the artery of the fifth arch, although this, in reality, is what it is.[3] It is much better to opt for names rather than numbers and to consider the arterial duct as the artery of the left pulmonary arch.[1]

Conclusions

The evidence now available from detailed reconstructions of human and murine embryos, combined with previous studies of avian and murine embryos concentrating specifically on the arch arteries, shows that, during development, there is formation of only five sets of pharyngeal arches.[1,27] These arches are separated by four pharyngeal pouches. They can sensibly be named as being, from cranial to caudal, mandibular, hyoid, carotid, aortic, and pulmonary. The lesions previously interpreted on the basis of persistence of a non-existent fifth set of arch arteries in a model containing six arches can readily be explained either because of
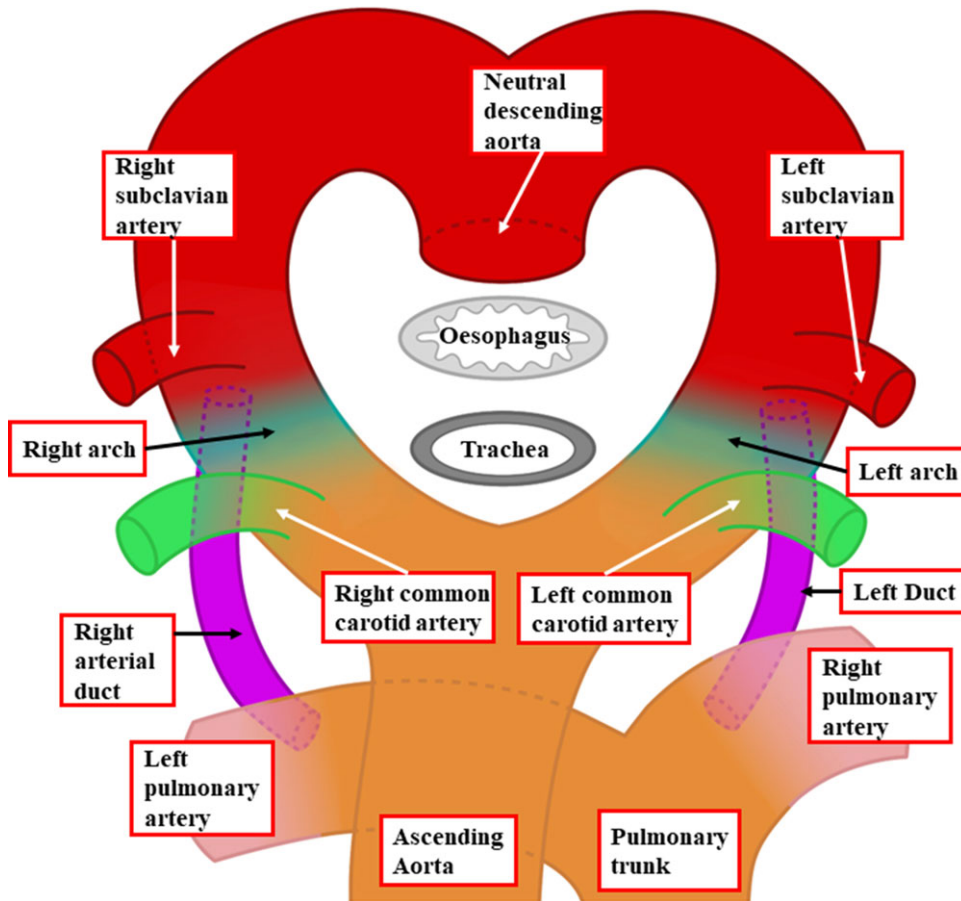
Figure 9. The drawing shows the hypothetical perfect double aortic arch as proposed by Edwards and his colleagues to explain the various malformations known as vascular rings or interruptions. The colour coding matches that is used in the previous figures.
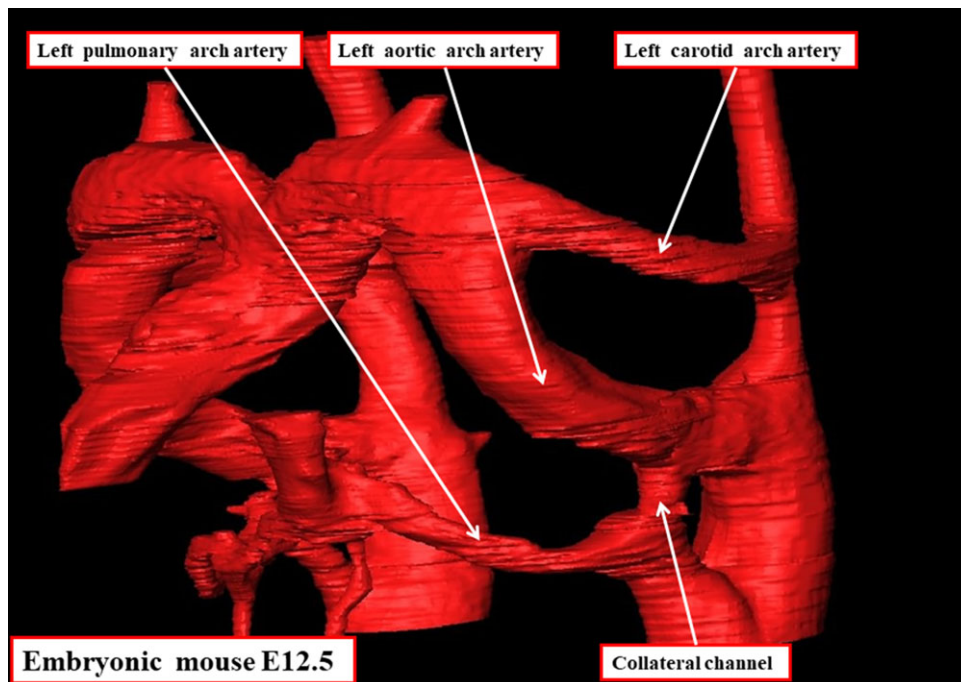
Figure 10. The image shows a reconstruction of the remodelling of left-sided arteries of the pharyngeal arches in a mouse embryo at embryonic day 12.5. There is a collateral channel present between the dorsal ends of the arteries of the left aortic and pulmonary arches. Such collateral channels were found in around half of all murine embryos.
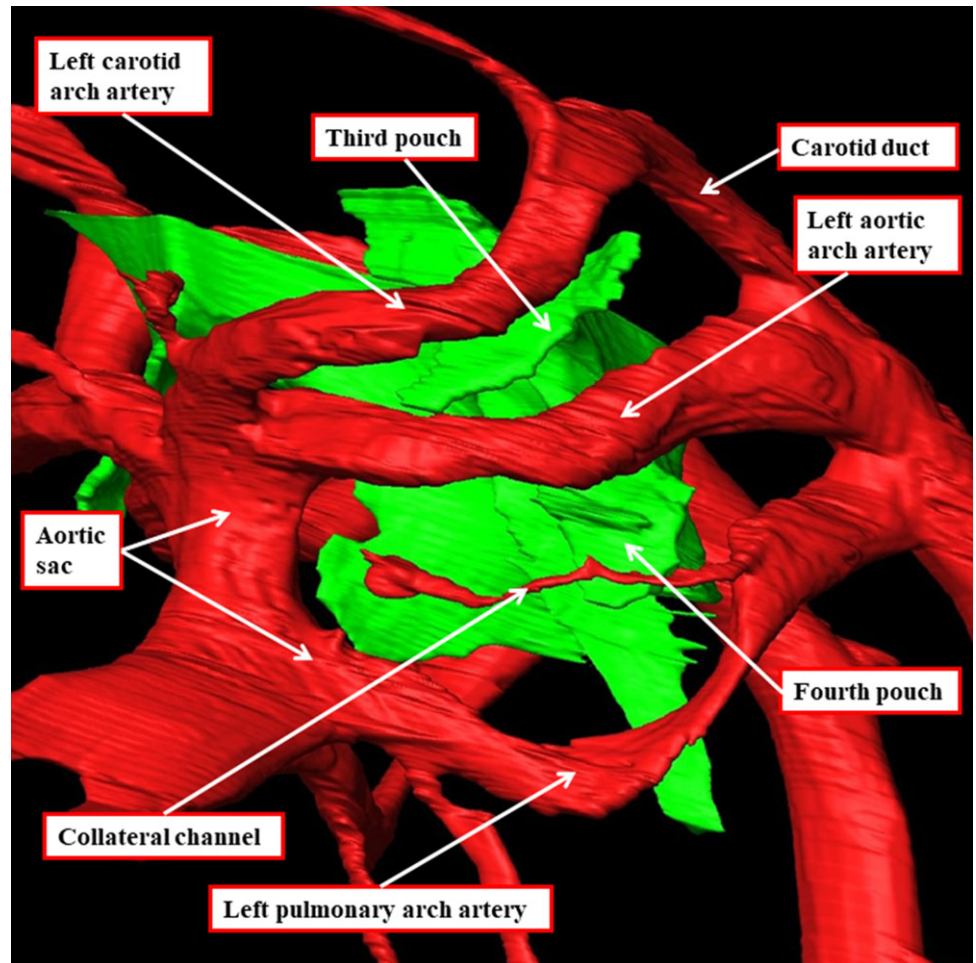
Figure 11. The image shows a reconstruction of the remodelling arteries of the left-sided pharyngeal arches in a human embryo at Carnegie stage 14. We initially identified this channel as an artery of the fifth arch. Since there is no evidence supporting the existence of such a pharyngeal arch, we now consider it to be an extensive collateral structure.
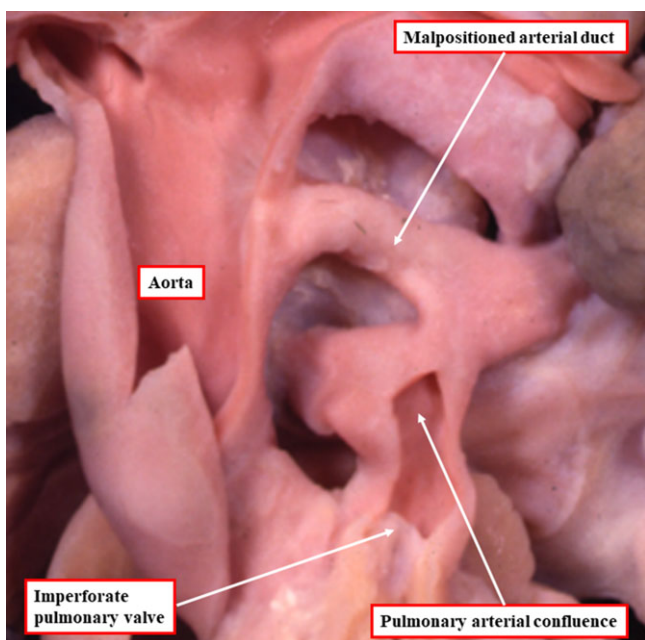
Figure 12. The image shows a vessel feeding confluent pulmonary arteries in the setting of tetralogy of Fallot with pulmonary atresia. Prior to the realisation that there is never a fifth pharyngeal arch formed during human development, we had interpreted the channel as representing an "artery of the fifth arch." We now consider the vessel to be an abnormally positioned arterial duct, taking a cranial origin from the underside of the aortic arch.

persistence of collateral channels or because of abnormal remodelling of the aortic sac and its branches.

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