EMBRYOLOGY OF THE HEART

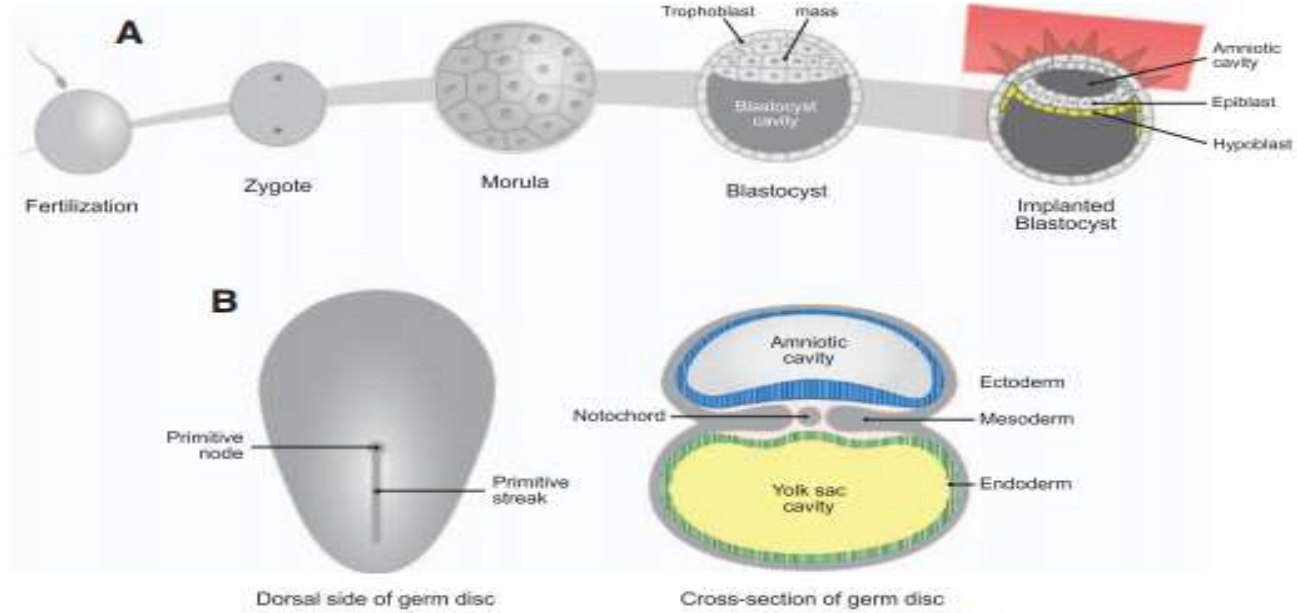


Figure 1. Overview of human embryogenesis. A, Stepwise progression from fertilization (fusion of sperm and oocyte to create a zygote) to morula and blastocyst with blastocyst implantation into uterus. B, Formation of the germ disk with 3 germ cell layers.

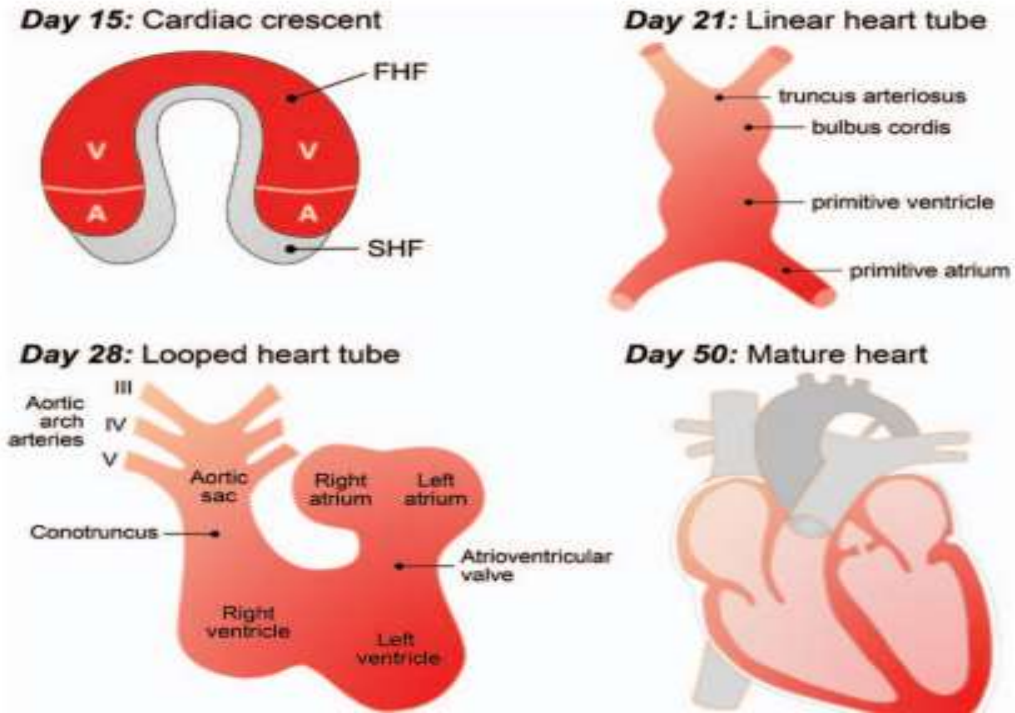
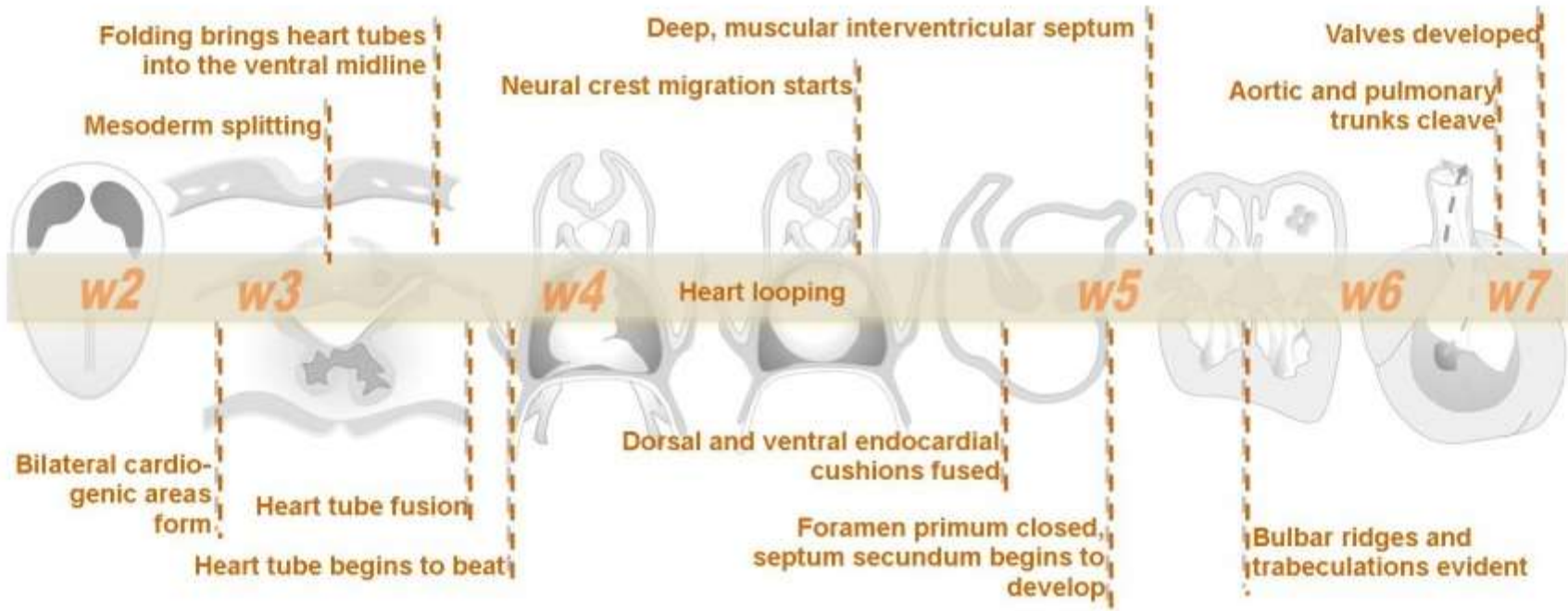


Figure 2. Schematic representation of cardiac embryology. A, Cardiac crescent at day 15. The first heart field is specified to form particular segments of the linear heart tube. The second heart field is located medial and caudal of the first heart field and will later contribute cells to the arterial and venous pole. B, By day 21, cephalocaudal and lateral folding of the embryo establishes the linear heart tube with its arterial (truncus arteriosus) and venous (primitive atrium) poles. C, By day 28, the linear heart tube loops to the right (D-loop) to establish the future position of the cardiac regions (atria [A], ventricles [V], outflow tract). D, By day 50, the mature heart has formed. The chambers and outflow tract of the heart are divided by the atrial septum, the interventricular septum, 2 atrioventricular valves (tricuspid valve, mitral valve) and 2 semilunar valves (aortic valve, pulmonary valve). FHF indicates first heart field; SHF, second heart field. Adapted in modified form from Lindsey SE, Butcher JT, Yalcin HC. Mechanical regulation of cardiac development. *Front Physiol*. 2014;5:318.

Intermediate - Primordial Heart Tube

Begin Intermediate: Primordial Heart Tube Heart Tube Looping Atrial Ventricular Septation Outflow Tract Heart Valves Cardiac Abnormalities Vascular Overview

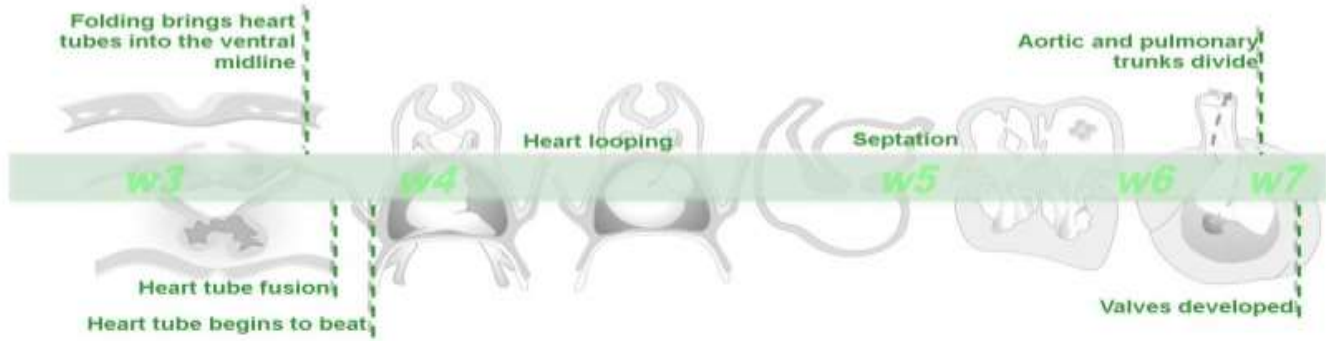
Cardiac Embryology Begin Basic Begin Intermediate Begin Advanced



The heart primordium arises predominantly from **splanchnic mesoderm** in the **cardiogenic region** of the trilaminar embryo. The cardiogenic region can be thought of as *bilateral fields that merge cranially* to form a horseshoe-shaped field. During the third week of development (approximately day 18) **angioblastic cords** develop in this cardiogenic mesoderm and canalise to form bilateral **endocardial heart tubes**.

Begin Basic Primitive Heart Tube Embryonic Heart Divisions Vascular Heart Connections

Cardiac Embryology | Begin Basic | Begin Intermediate | Begin Advanced

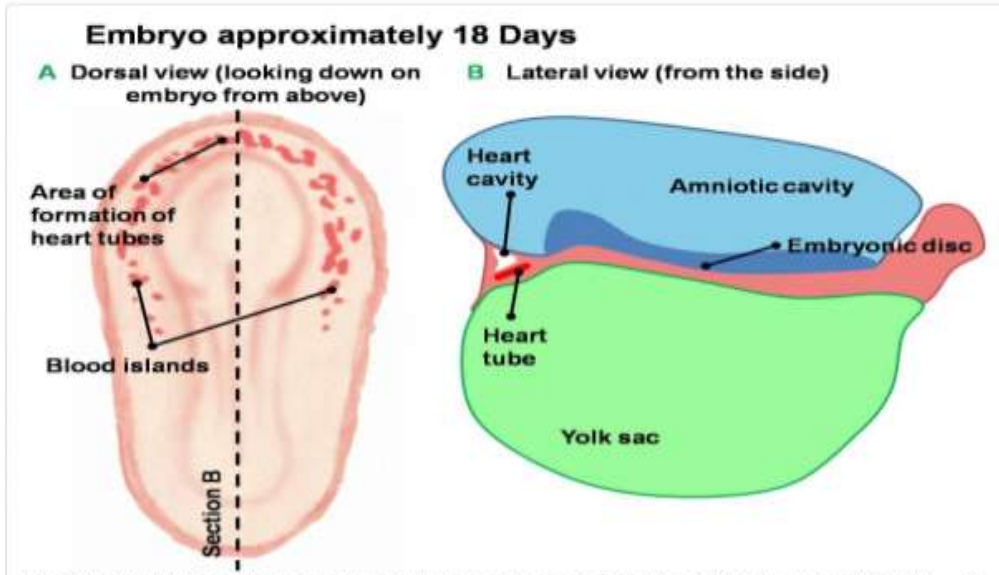


The heart is the first organ to function within an embryo. It starts to function at the beginning of the fourth week when the nutritional and oxygen requirements of the growing embryo can no longer be met by diffusion from the **placenta**. The heart initially forms from two tubes located bilaterally (on either side) of the **trilaminar embryo** in the **cranial** (head) region. The image on the right shows these primitive tubes developing in an embryo approximately 18 days after conception.

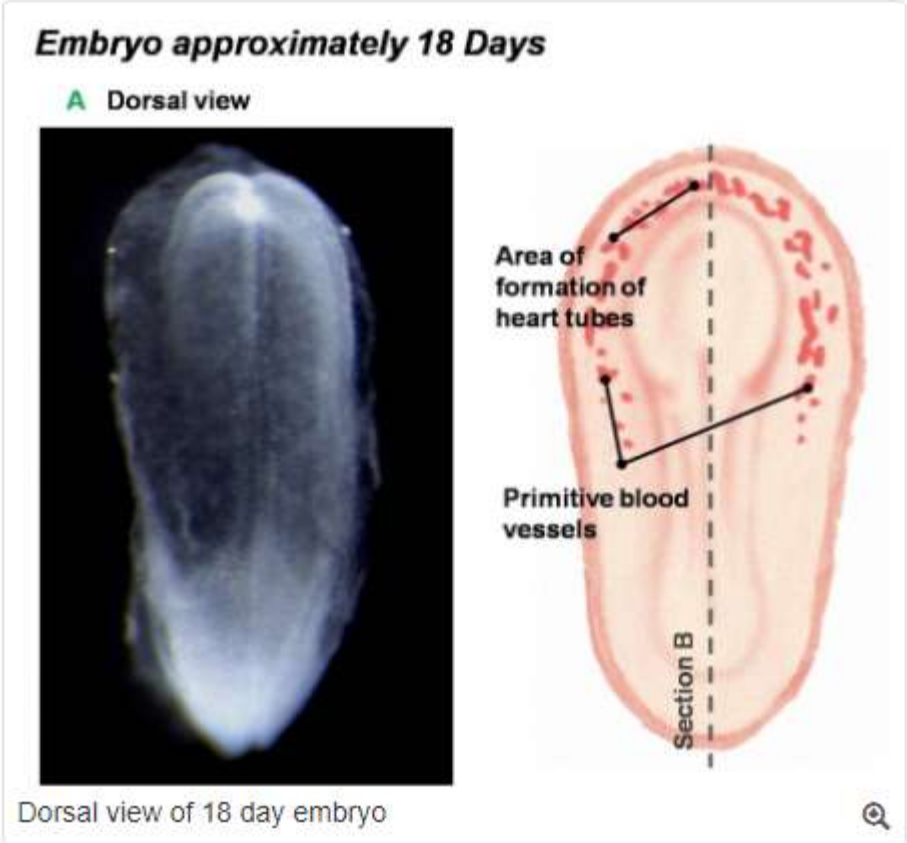
When looking down at this early embryo you can see multiple **blood islands** dispersed throughout the embryo. These will form the early blood vessels. At the most cranial end of the **embryonic disc** these blood islands are actually the **primitive heart tube**. From the side you can see one of the heart tubes and **heart cavity** developing in this position.

Embryonic Folding

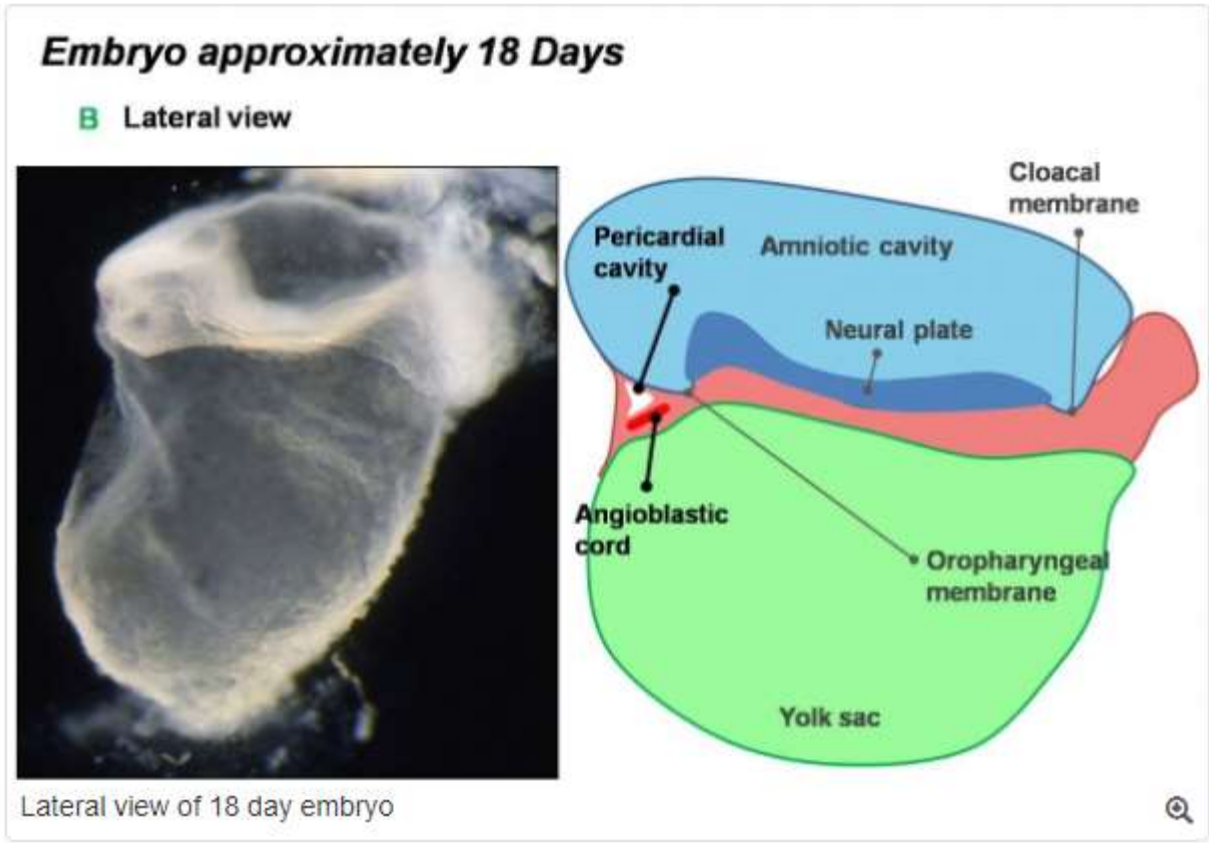
The disc-like embryo then undergoes a process of folding, in which both the *cranial* and *lateral* parts of the embryo fold ventrally (forwards). This brings the heart-forming region to a **ventral** (frontal) position. The following animation shows the development of the heart tubes and how embryonic folding brings them to fuse in the midline. (Click image to play on current page or Play video on new page)



The developing blood vessels and heart tube can be seen in an embryo at approximately 18 days



Dorsal view of 18 day embryo



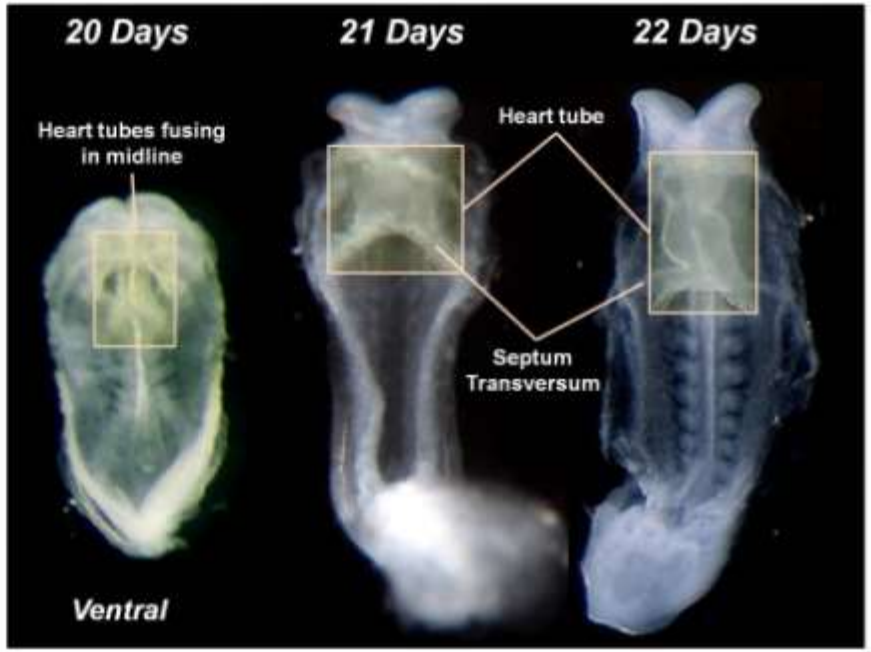
Lateral view of 18 day embryo

Lateral folding of the embryo brings the heart tubes into the ventral midline, allowing them to fuse to form a single primordial heart tube. Fusion of the heart tubes begins cranially and extends caudally and is facilitated by **apoptosis**. The animation below shows a cross section of the embryo and the development of the endocardial heart tubes as well as their migration and fusion in the midline.

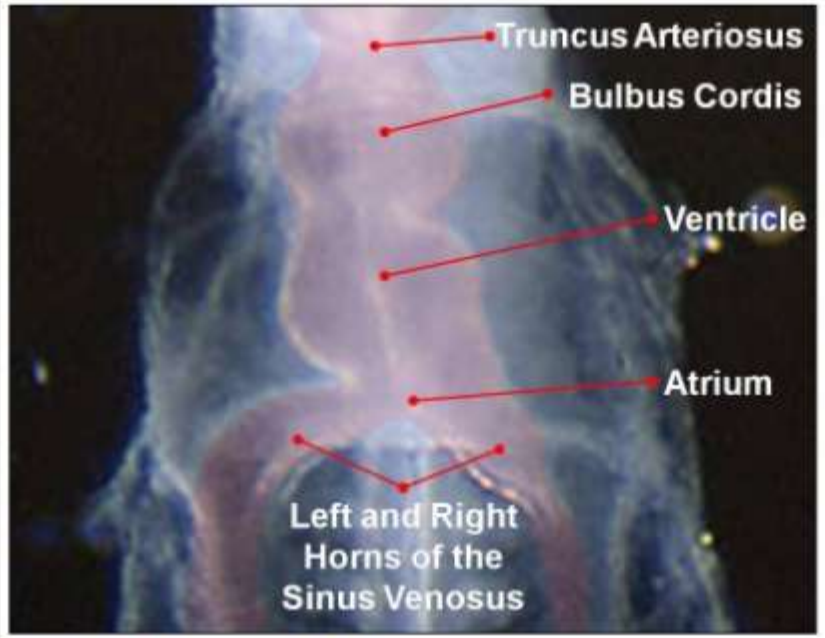
After fusion, *constrictions and dilations* appear in the heart tube, forming the following divisions (listed from cranial to caudal position):

- **Truncus arteriosus**
- **Bulbus cordis**
- **Primordial ventricle**
- **Primordial atrium**
- **Sinus venosus**

The sinus venosus is also divided into two parts: the right horn of the sinus venosus and the left horn of the sinus venosus.



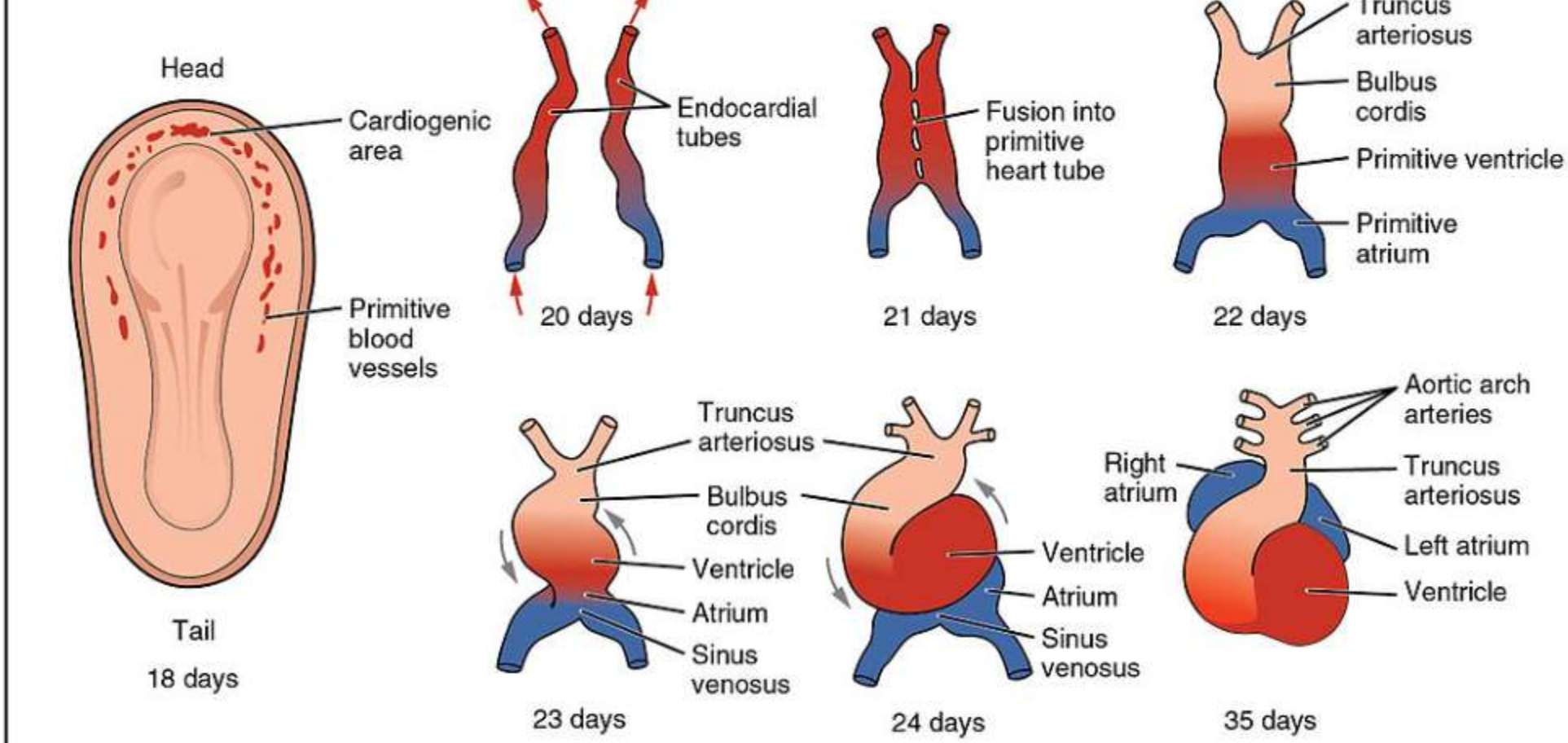
Brightfield images showing fusion of the heart tubes and the earliest appearance of segments of the fused heart tube



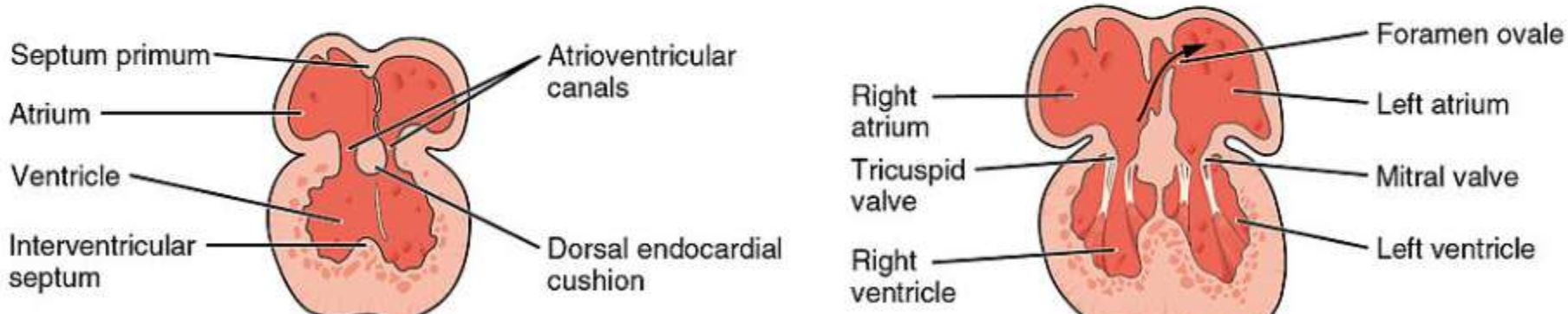
Early divisions of the heart tube

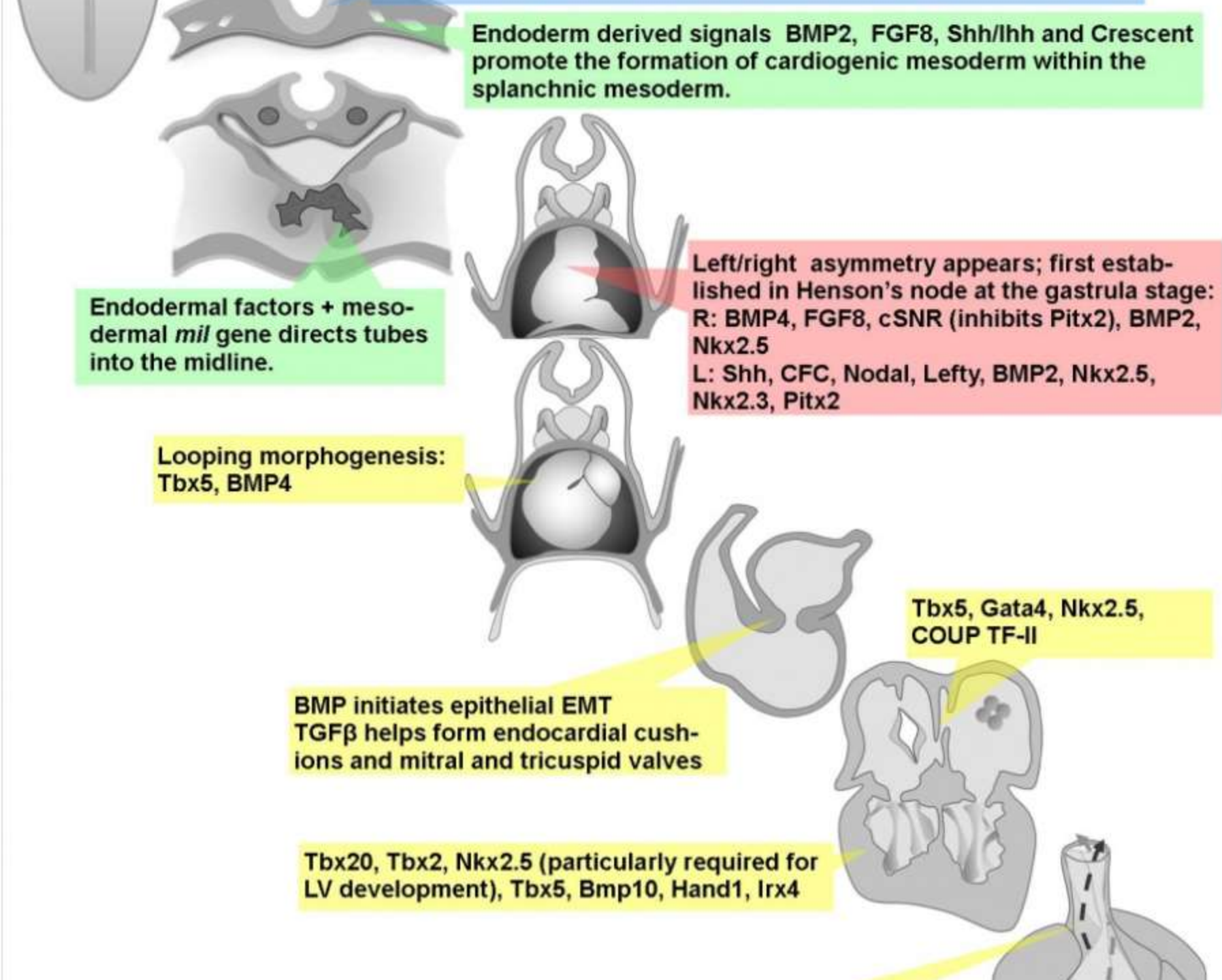
By day 22, coordinated contractions of the heart tube are present and push blood cranially from the sinus venosus.

In the previous animation you saw that the **dorsal aortae** develop concurrently with the endocardial heart tubes and form a cranial connection with the endocardial heart tubes prior to folding. As the embryo folds, the cranial ends of the dorsal aortae are pulled ventrally until they form a dorsoventral loop: the first **aortic arch arteries**. The embryonic vascular system is discussed in further detail here.



Partitioning of the heart into four chambers





Endoderm derived signals BMP2, FGF8, Shh/Ihh and Crescent promote the formation of cardiogenic mesoderm within the splanchnic mesoderm.

Endodermal factors + meso-dermal *mil* gene directs tubes into the midline.

Left/right asymmetry appears; first estab-lished in Henson's node at the gastrula stage:
R: BMP4, FGF8, cSNR (inhibits Pitx2), BMP2, Nkx2.5
L: Shh, CFC, Nodal, Lefty, BMP2, Nkx2.5, Nkx2.3, Pitx2

Looping morphogenesis: Tbx5, BMP4

Tbx5, Gata4, Nkx2.5, COUP TF-II

BMP initiates epithelial EMT
TGFβ helps form endocardial cush-ions and mitral and tricuspid valves

Tbx20, Tbx2, Nkx2.5 (particularly required for LV development), Tbx5, Bmp10, Hand1, Irx4

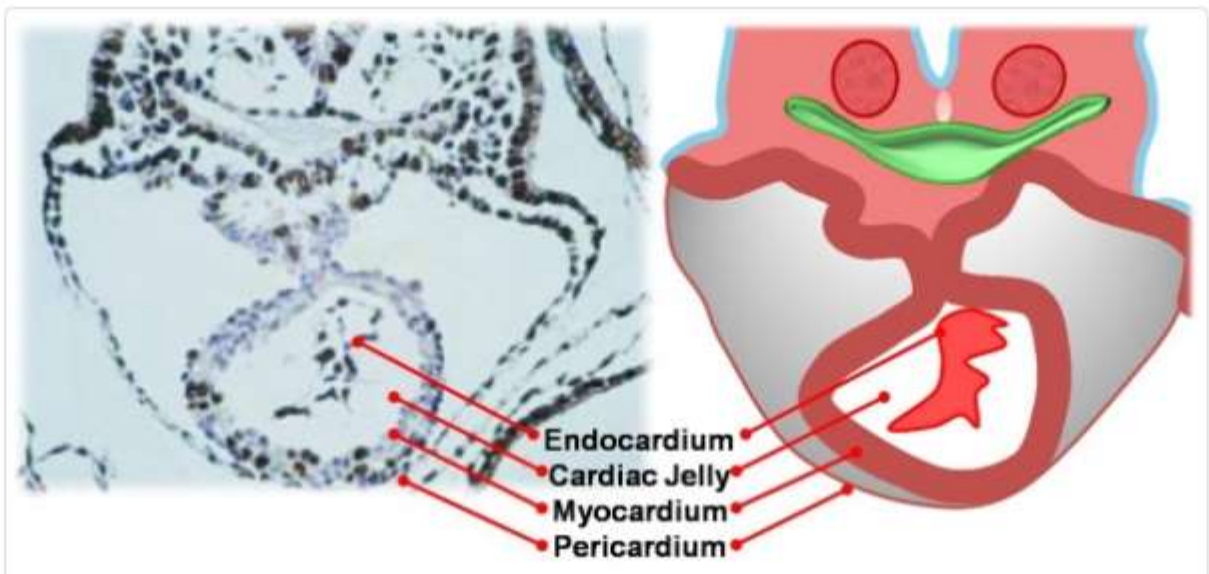
Heart Layers

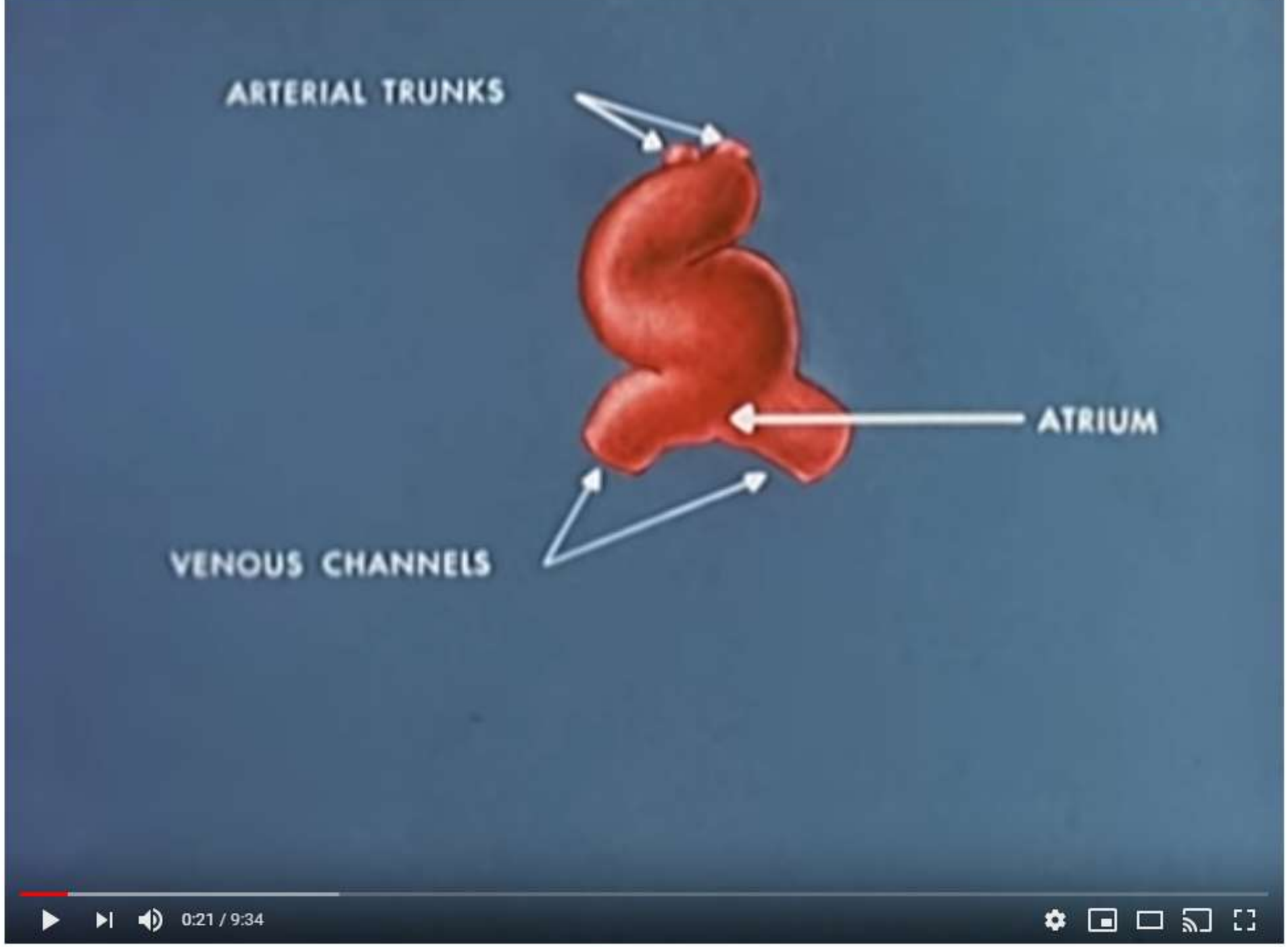
Myocardium: forms from splanchnic mesoderm surrounding the **pericardial coelom**. Additional myocardial cells are added to the outflow tract during heart looping.

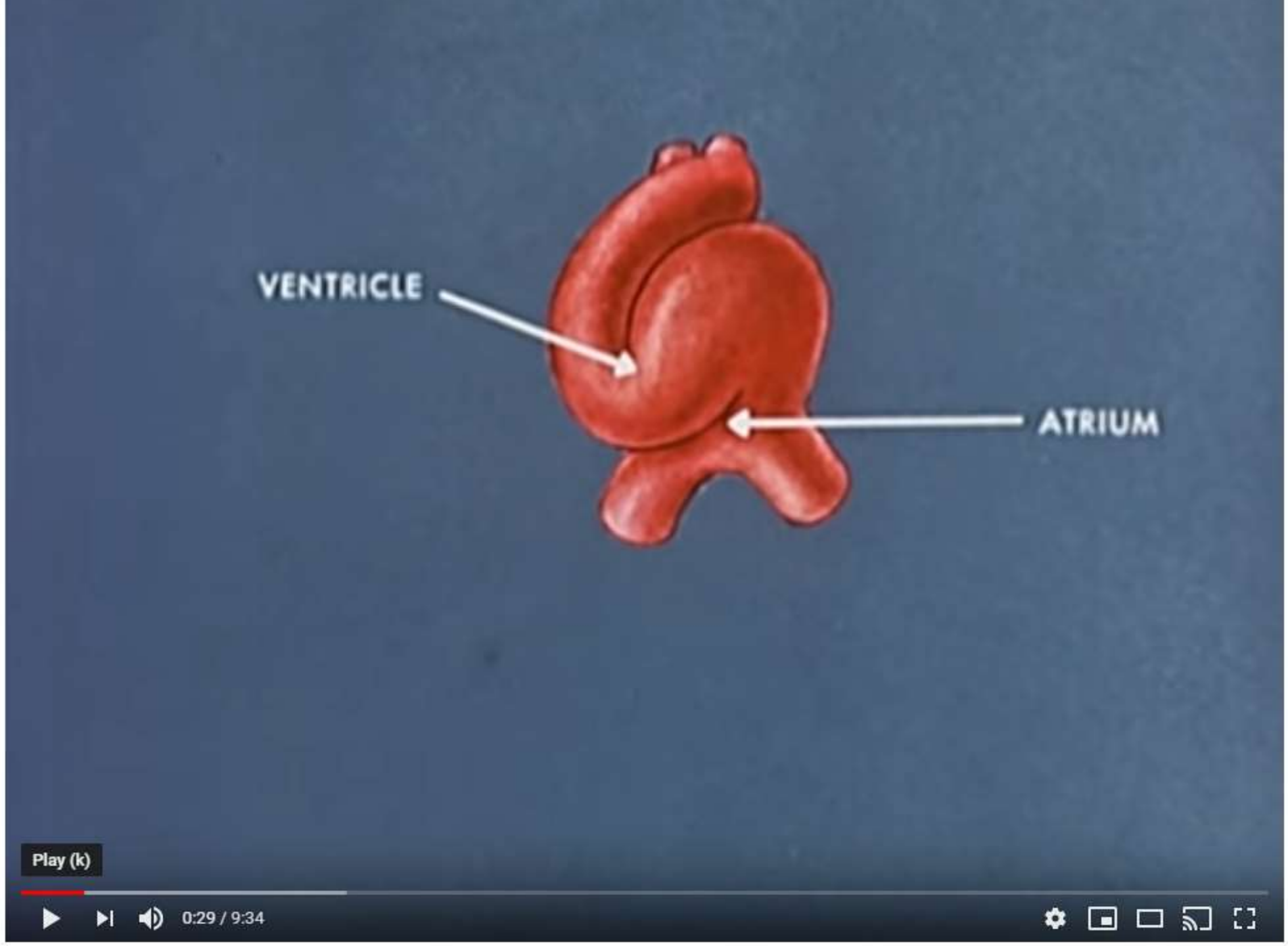
Cardiac Jelly: gelatinous **connective tissue** separating the myocardium and heart tube **endothelium**.

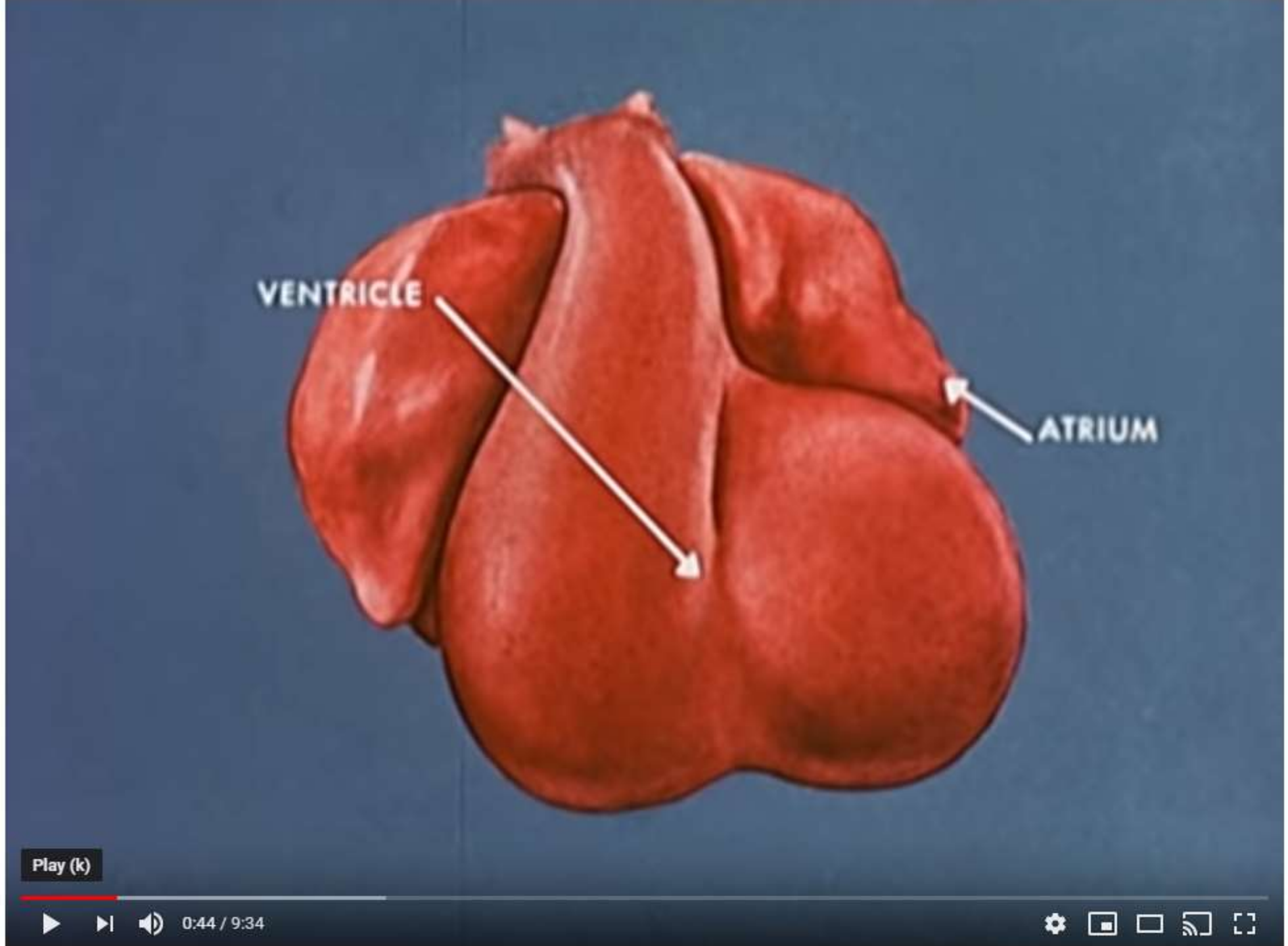
Endocardium: forms from the endothelium of the heart tube.

Epicardium: develops from mesothelial cells arising from the sinus venosus which spread cranially over the myocardium.




ARTERIAL TRUNKS
ATRIUM
VENOUS CHANNELS
0:21 / 9:34


VENTRICLE
ATRIUM
Play (k)
0:29 / 9:34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ATRIUM
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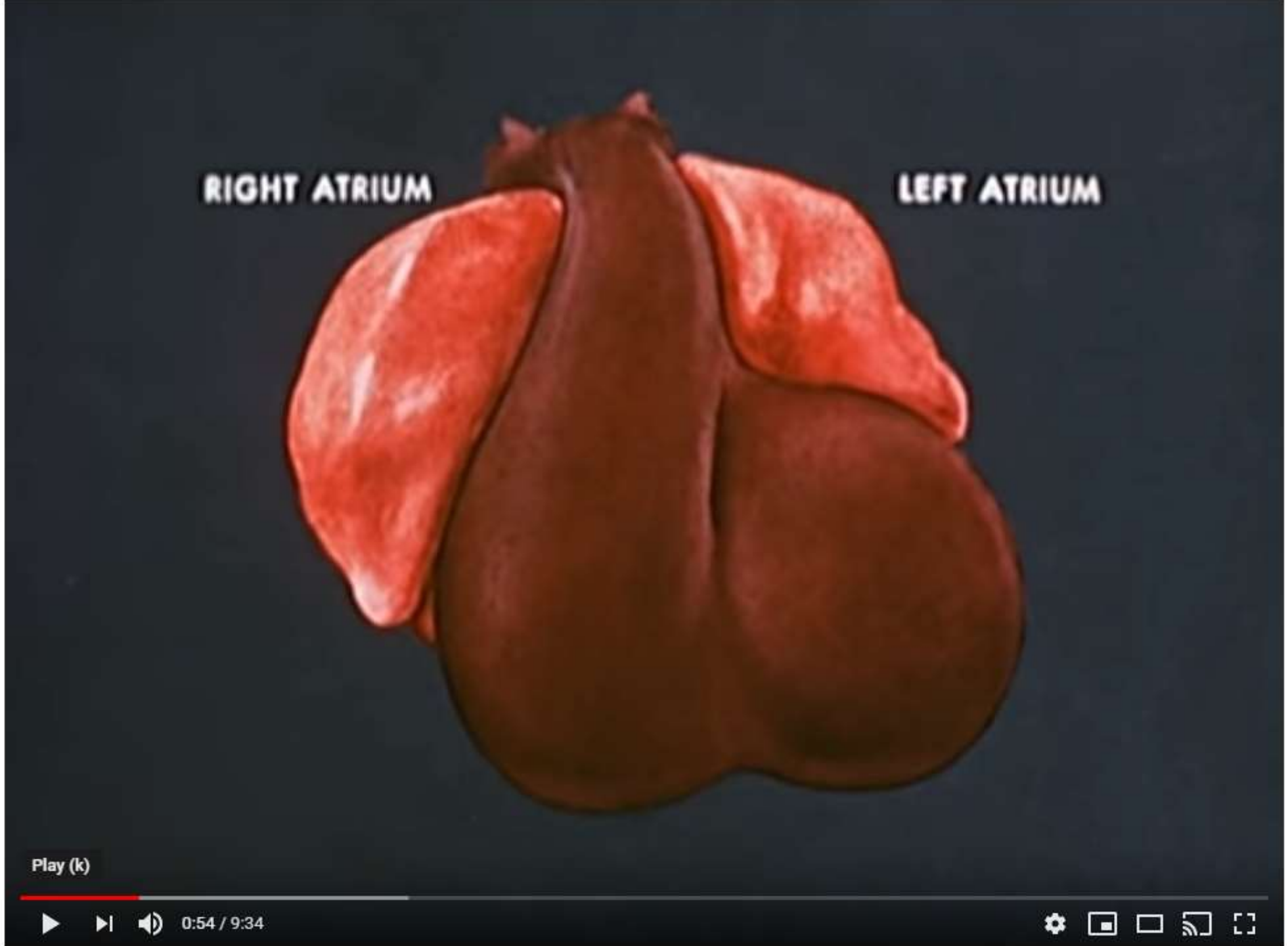
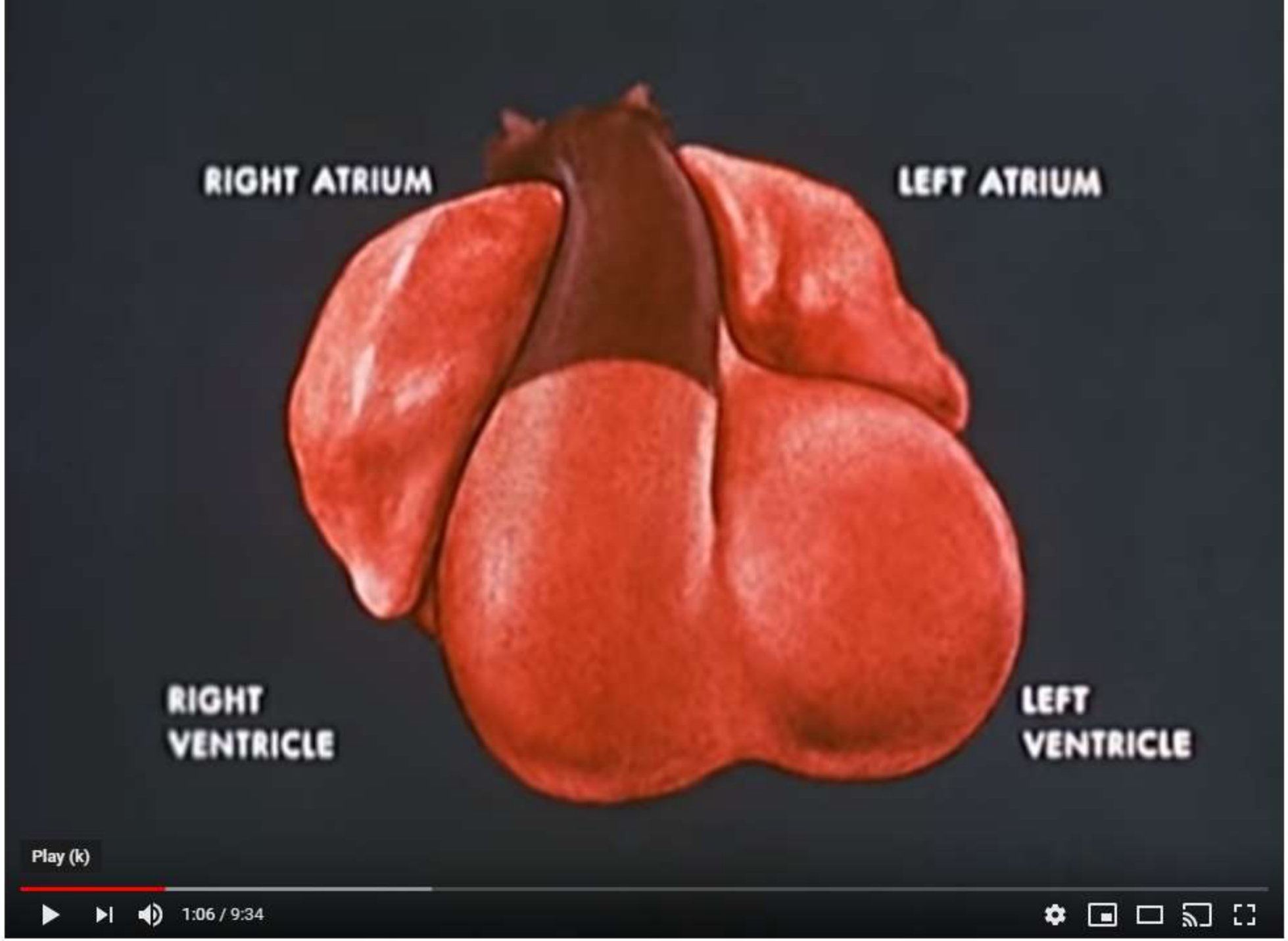
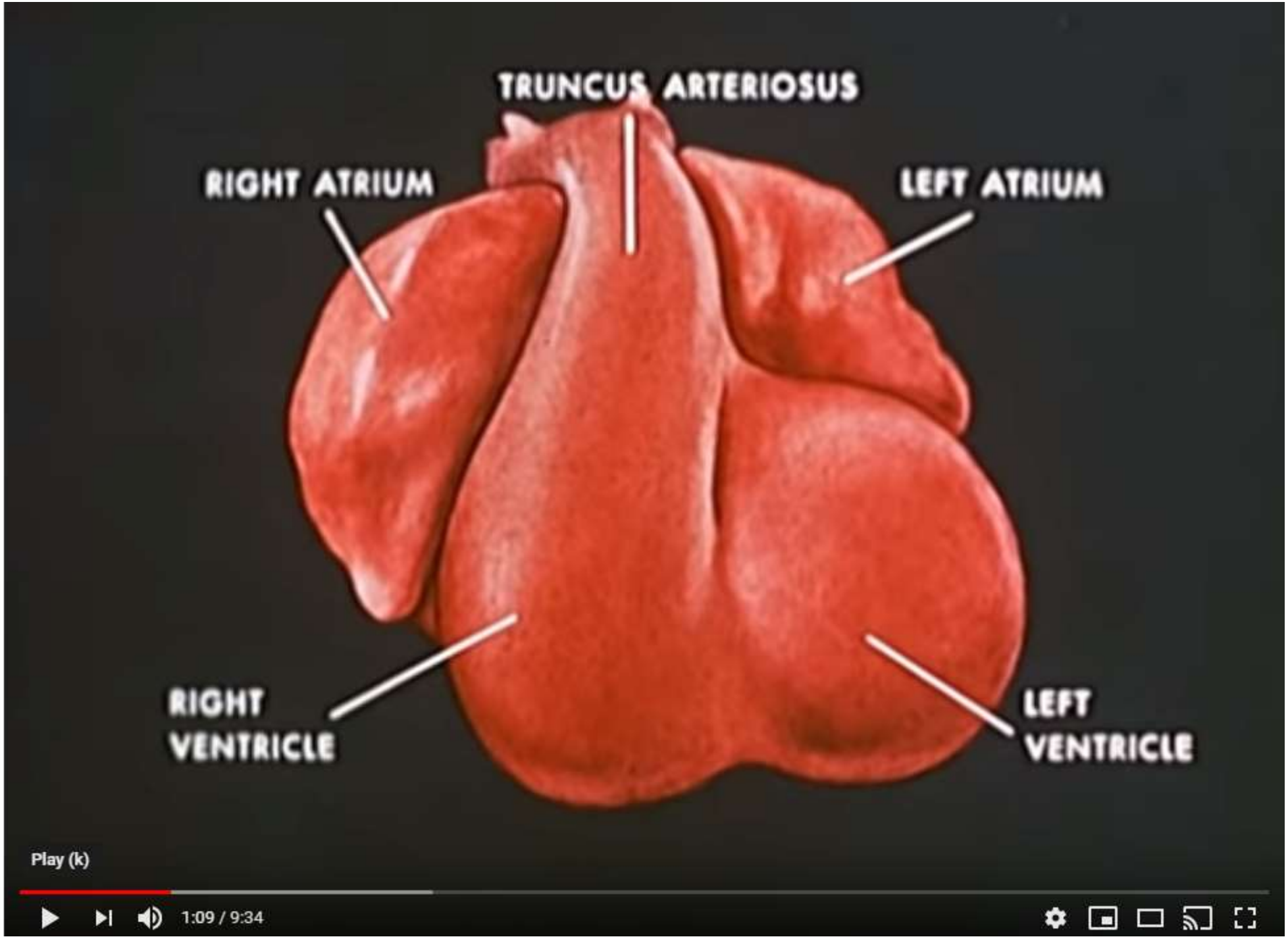
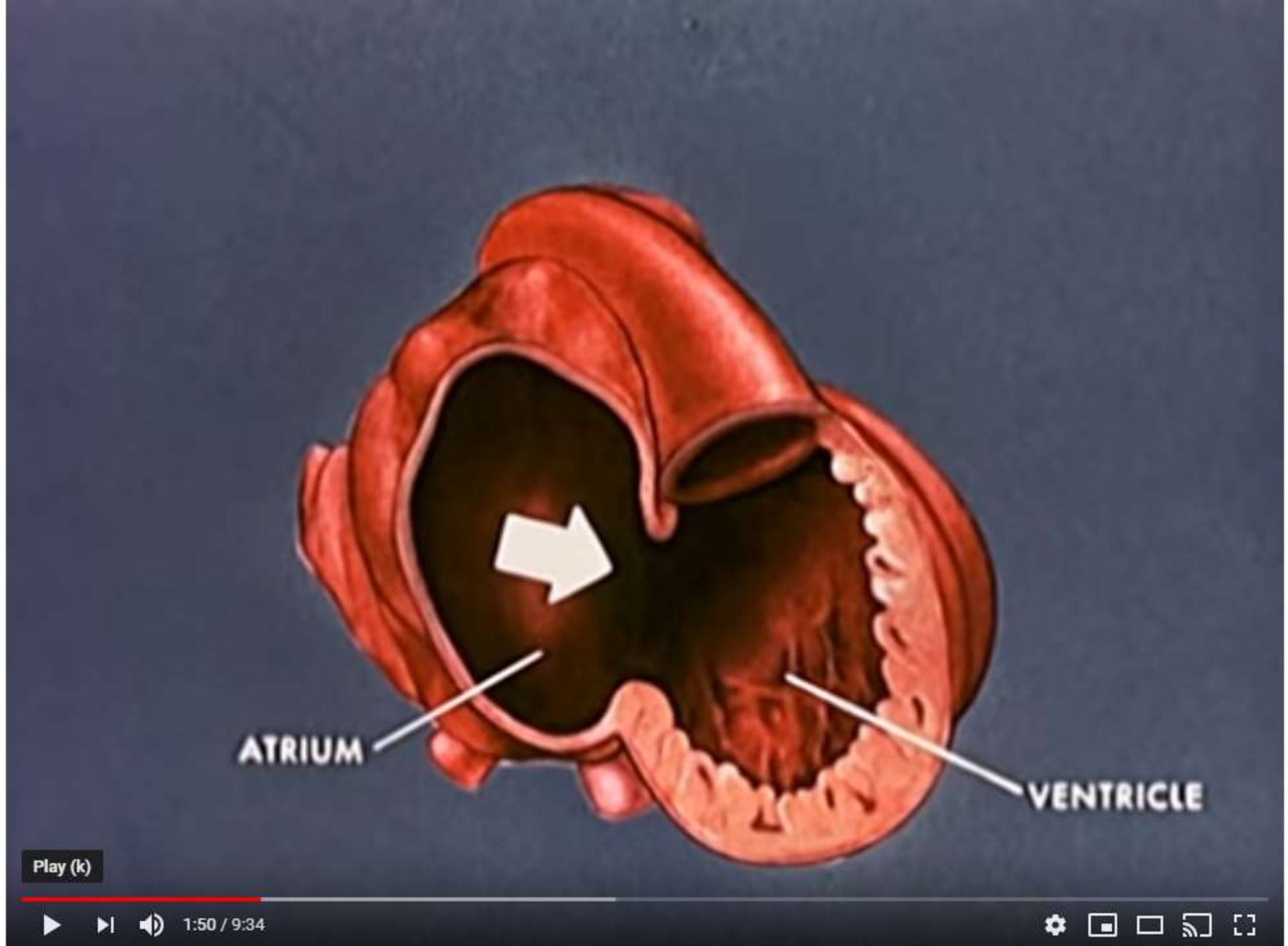
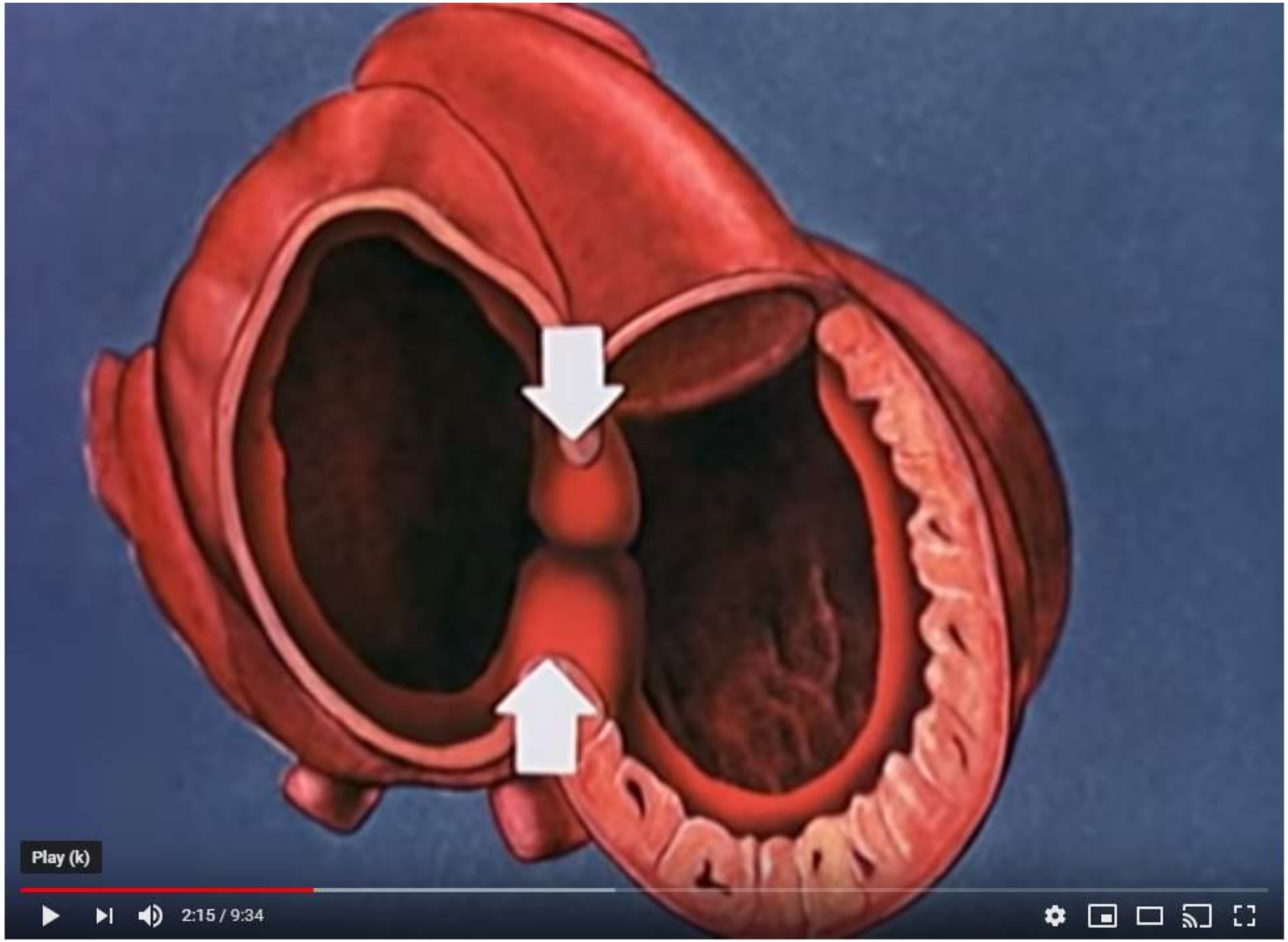
0:44 / 9:34

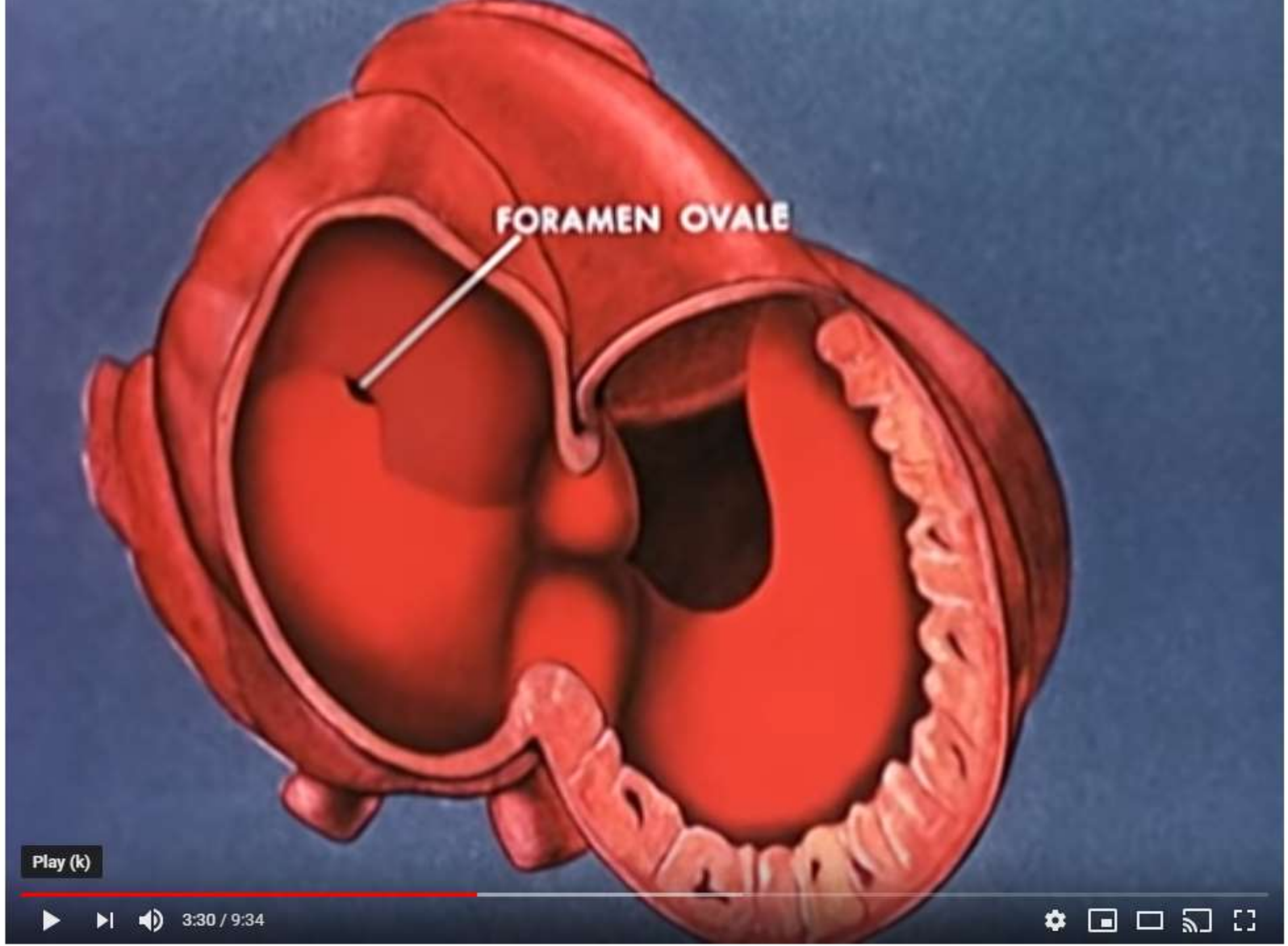

RIGHT ATRIUM
LEFT ATRIUM
Play (k)
0:54 / 9:34

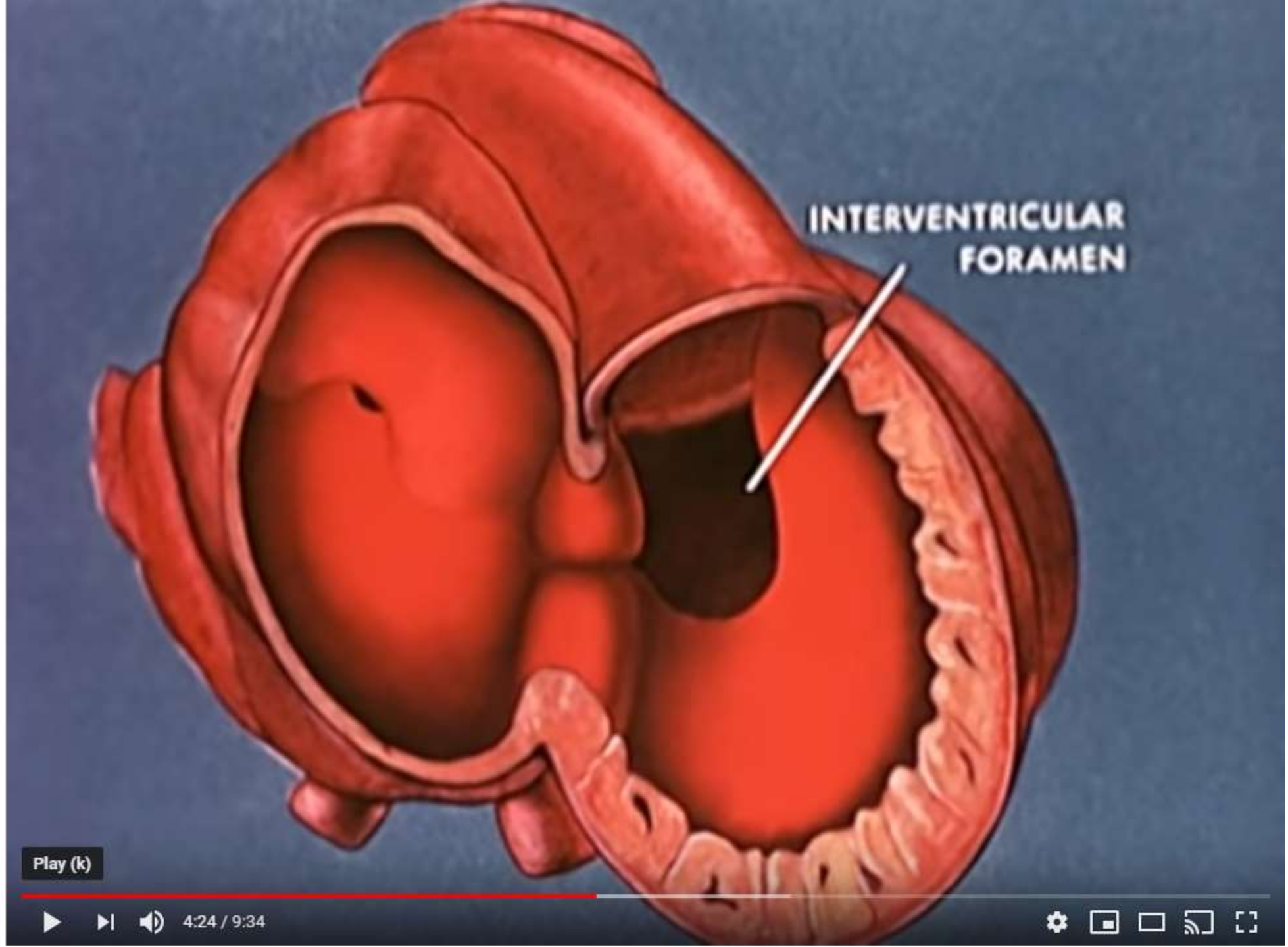

RIGHT ATRIUM
LEFT ATRIUM
RIGHT VENTRICLE
LEFT VENTRICLE
Play (k)
1:06 / 9:34

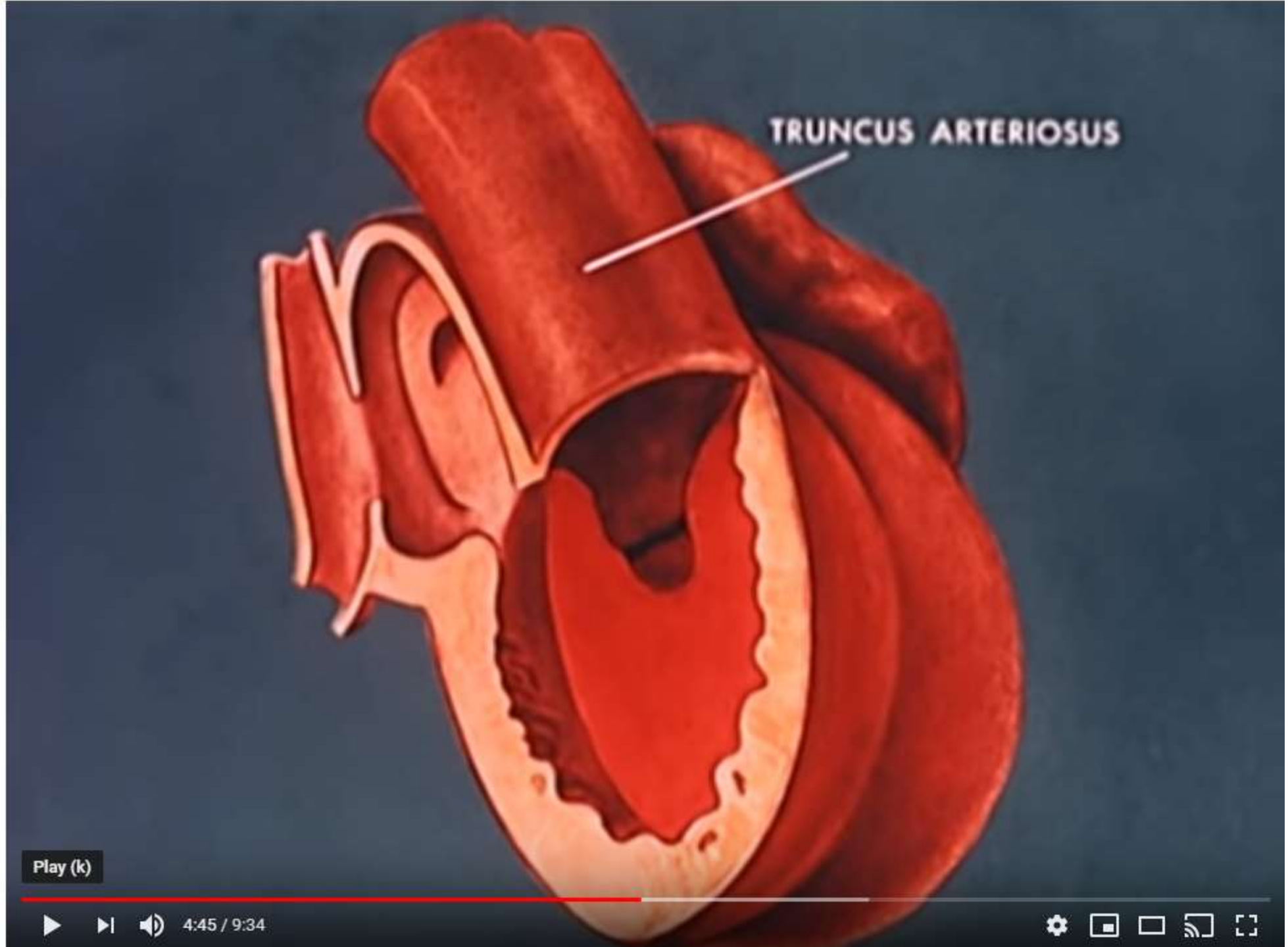

TRUNCUS ARTERIOSUS
RIGHT ATRIUM
LEFT ATRIUM
RIGHT VENTRICLE
LEFT VENTRICLE
Play (k)
1:09 / 9:34

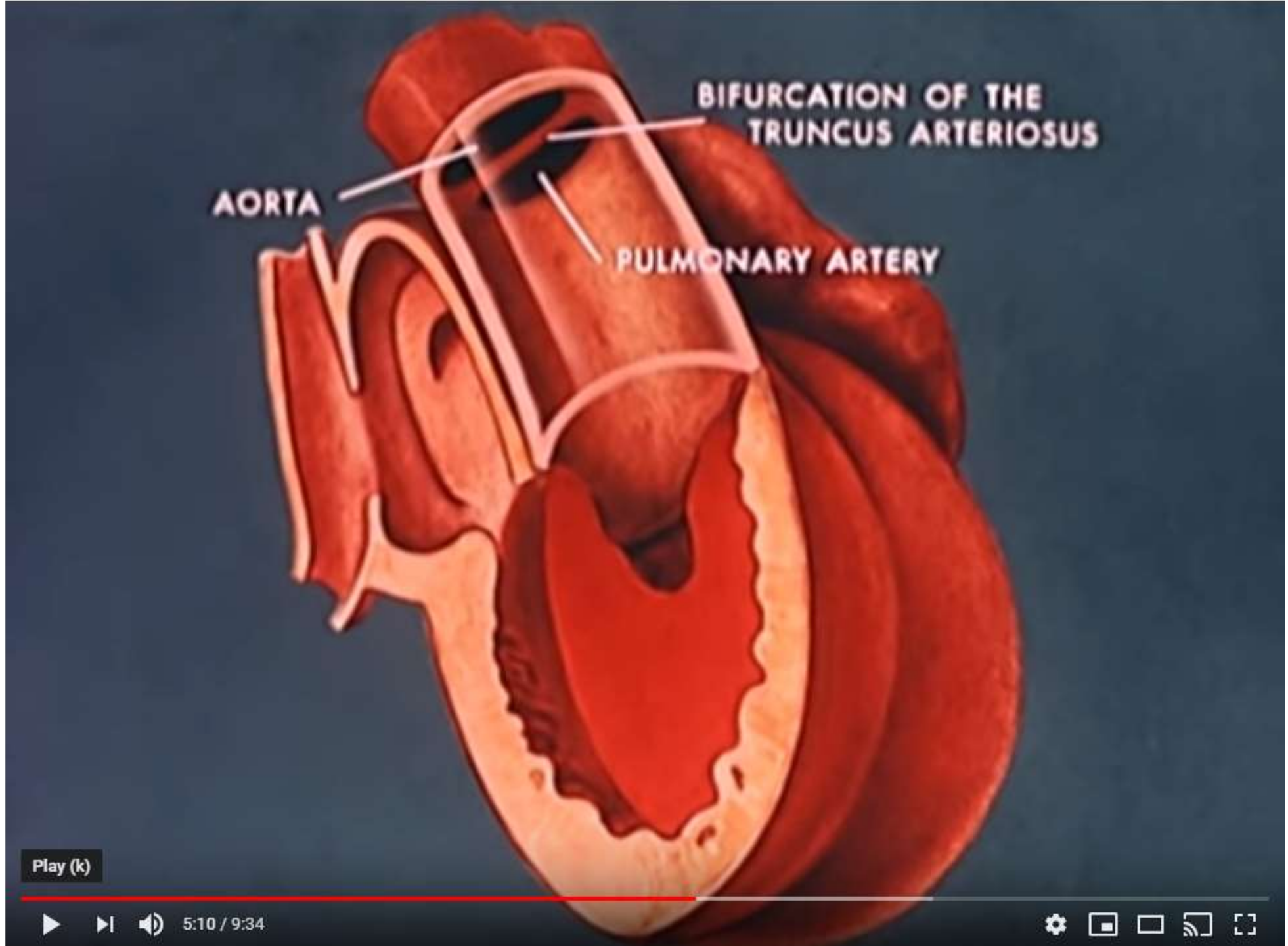

ATRIUM
VENTRICLE
Play (k)
1:50 / 9:34

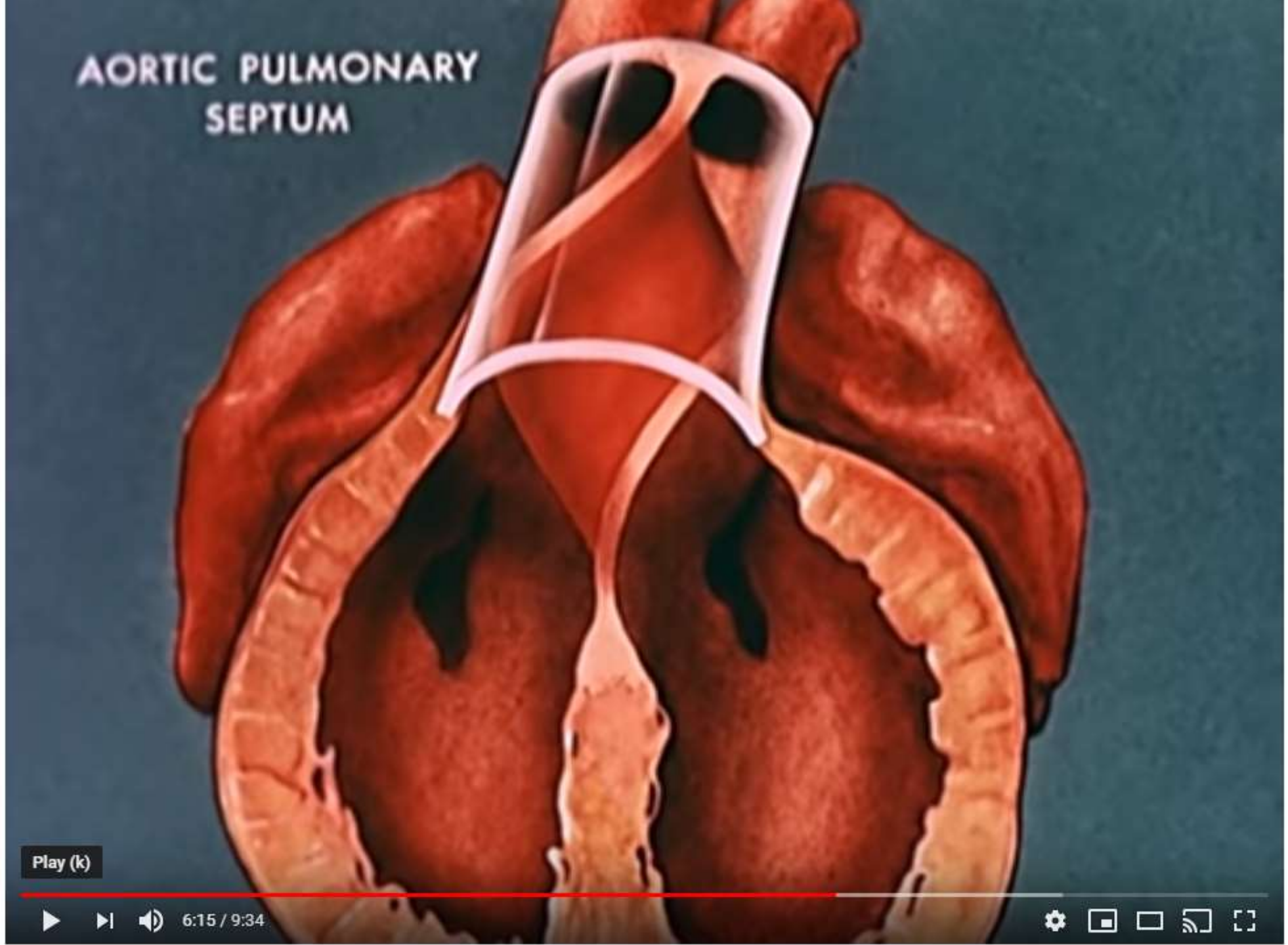

Play (k)
2:15 / 9:34

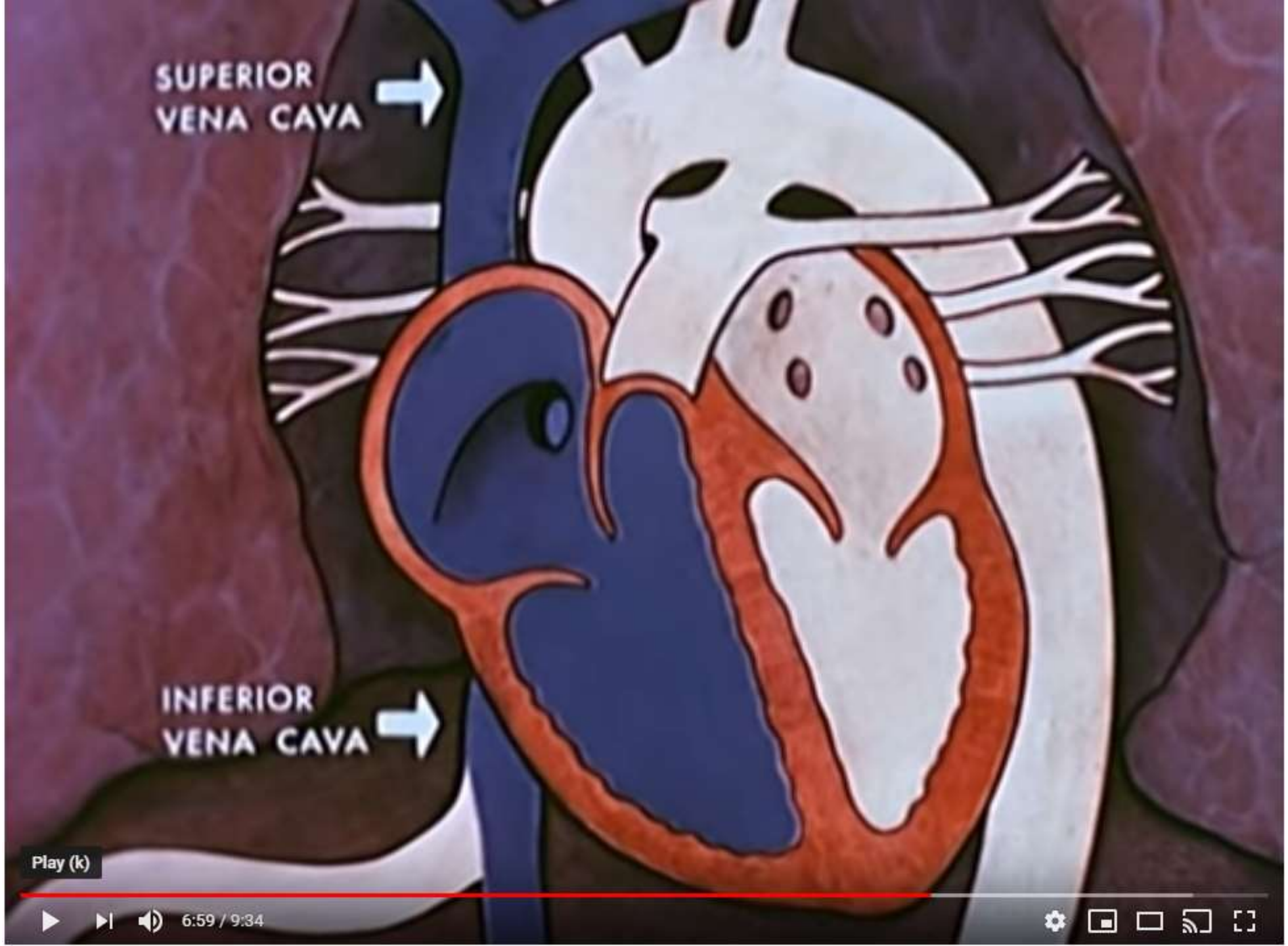

FORAMEN OVALE
Play (k)
3:30 / 9:34

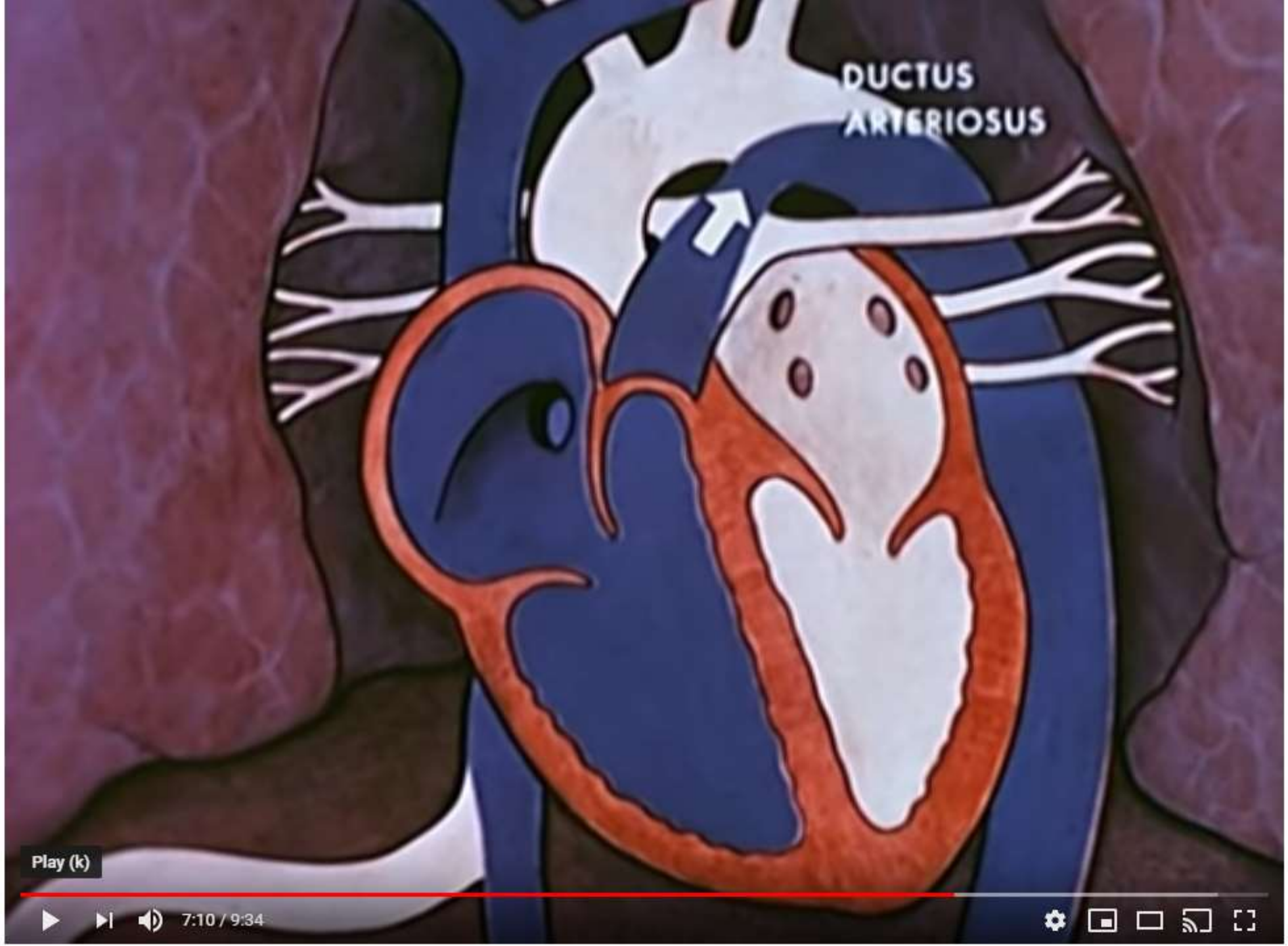

INTERVENTRICULAR
FORAMEN
Play (k)
4:24 / 9:34

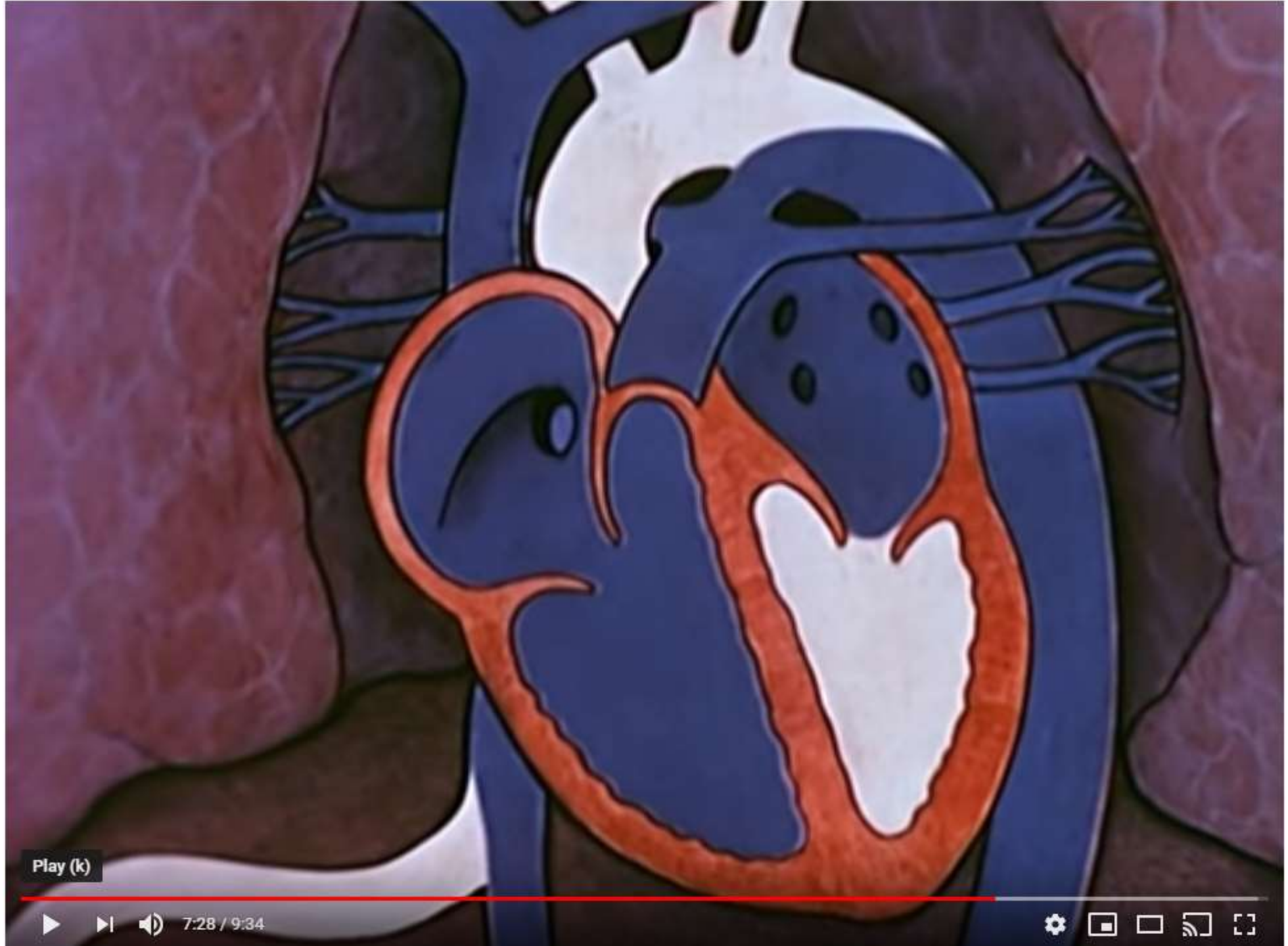

TRUNCUS ARTERIOSUS
Play (k)
4:45 / 9:34


BIFURCATION OF THE
TRUNCUS ARTERIOSUS
AORTA
PULMONARY ARTERY
Play (k)
5:10 / 9:34

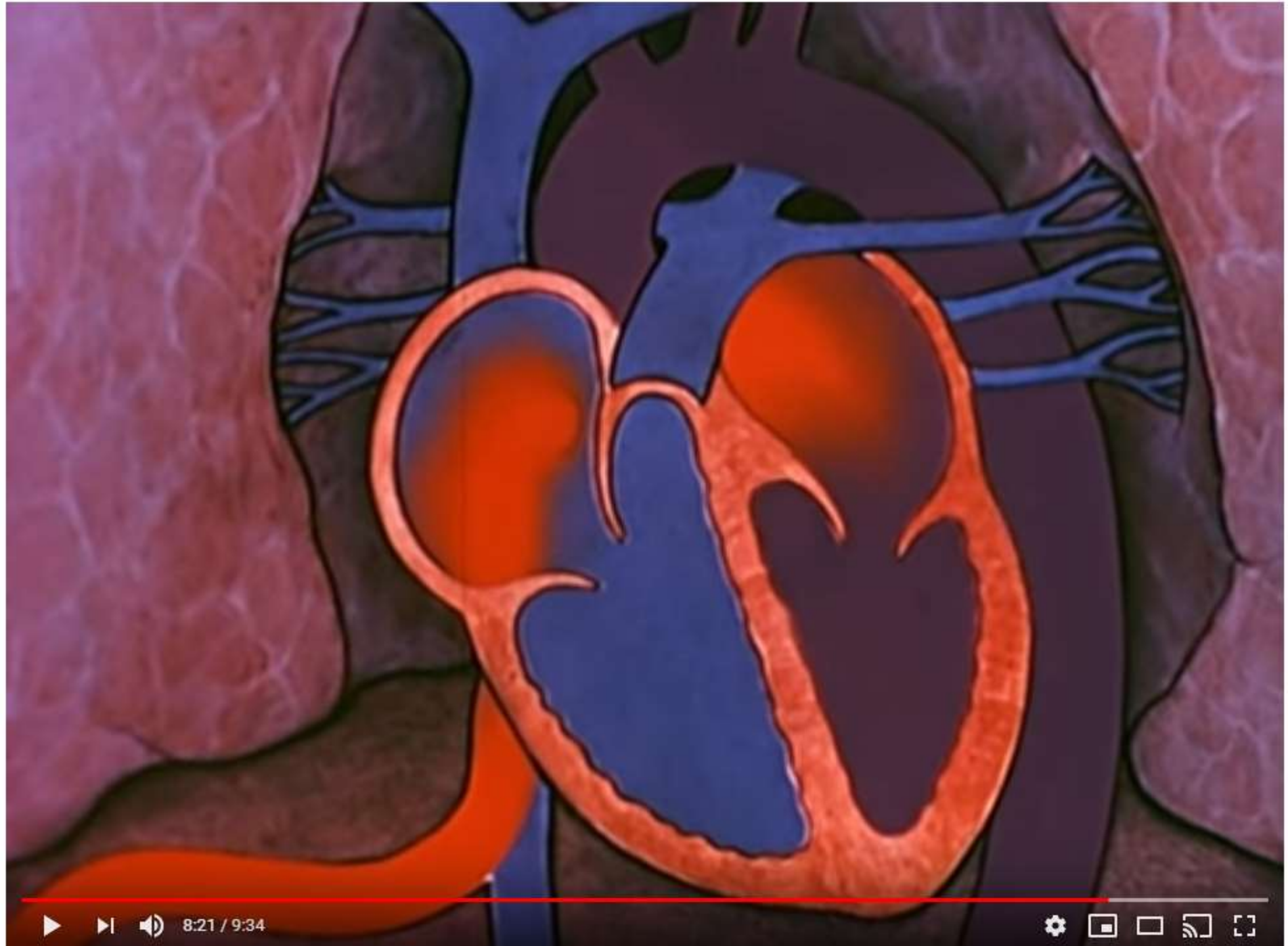

AORTIC PULMONARY
SEPTUM
Play (k)
6:15 / 9:34

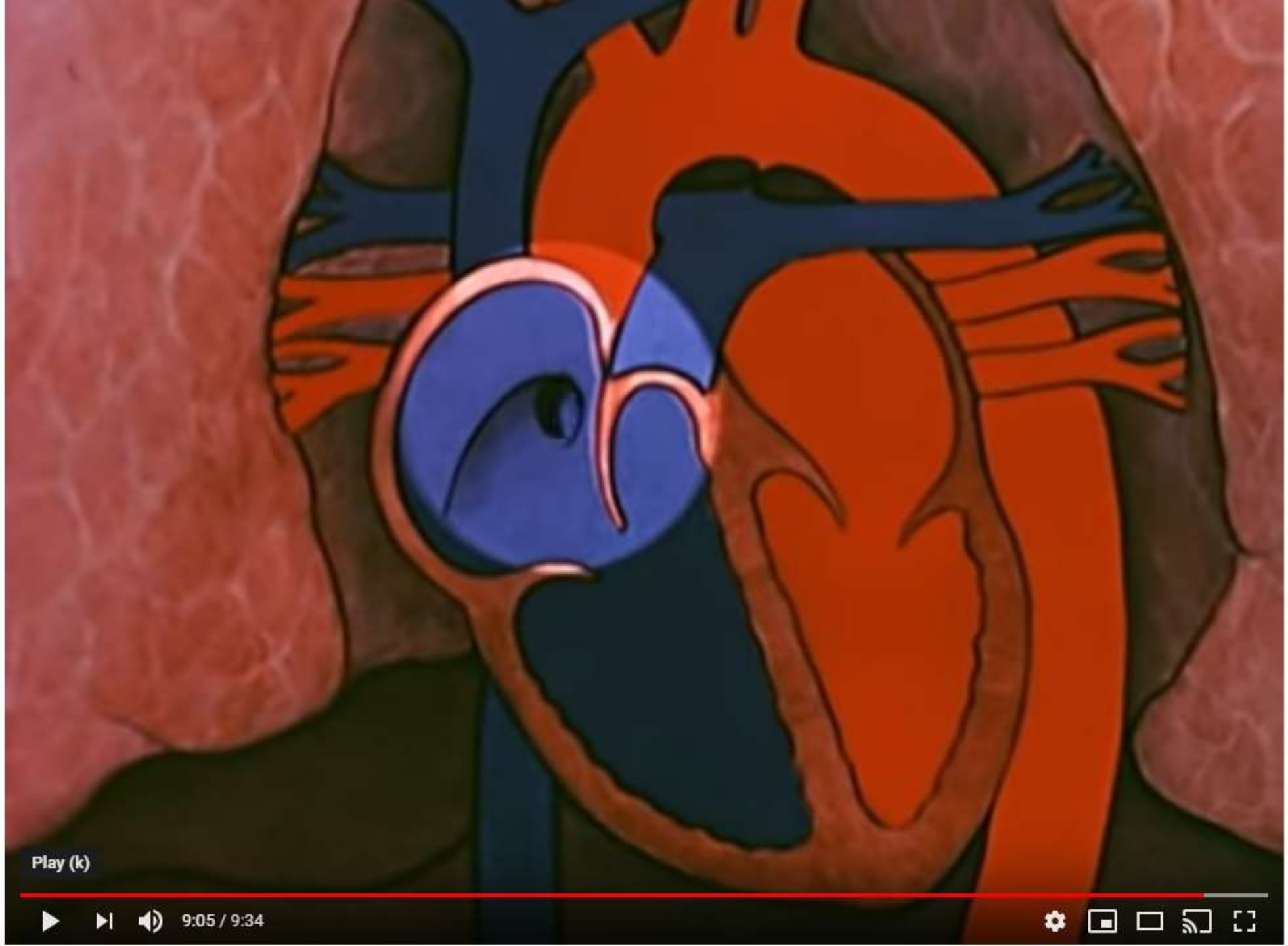

SUPERIOR
VENA CAVA
INFERIOR
VENA CAVA
Play (k)
6:59 / 9:34


DUCTUS
ARTERIOSUS
Play (k)
7:10 / 9:34


Play (k)
7:28 / 9:34

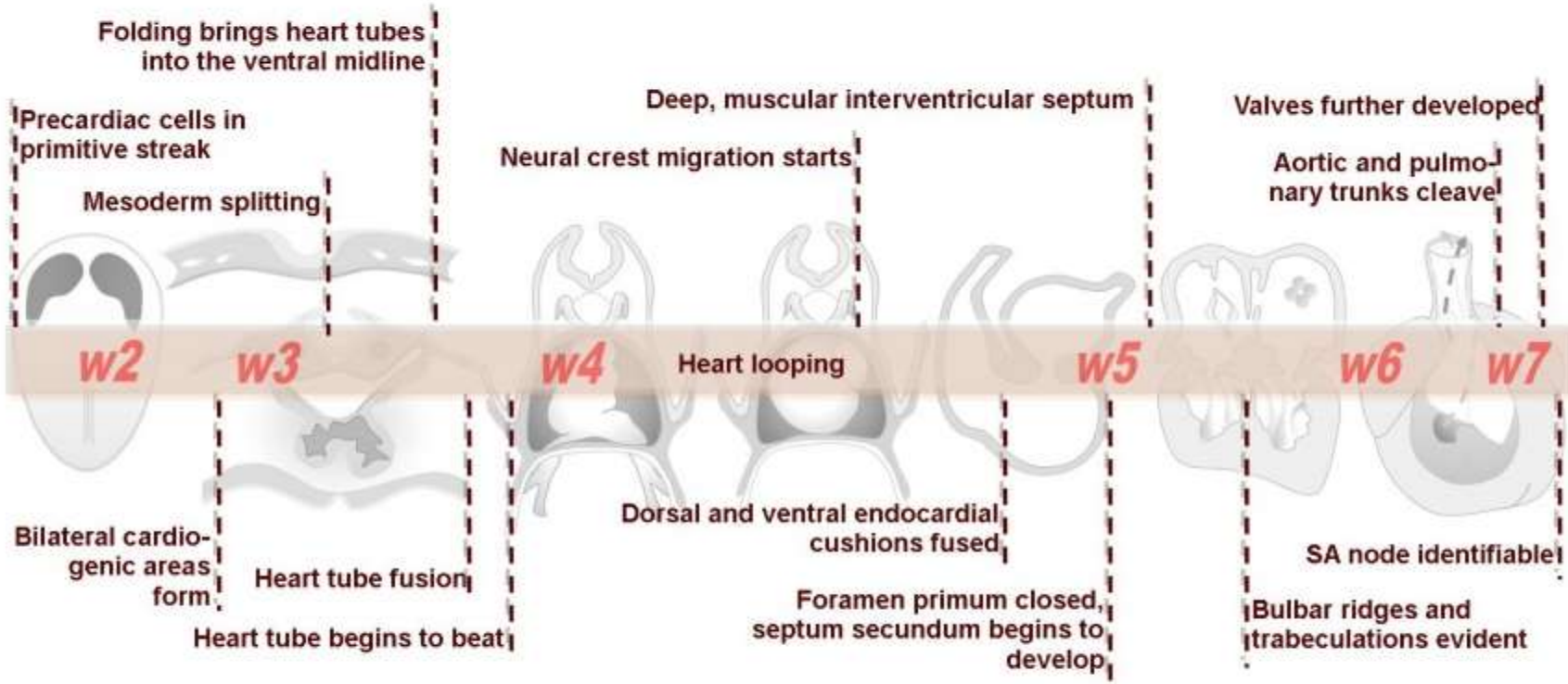

FROM THE PLACENTA
Play (k)
7:35 / 9:34


8:21 / 9:34


Play (k)
9:05 / 9:34

Cardiac Embryology

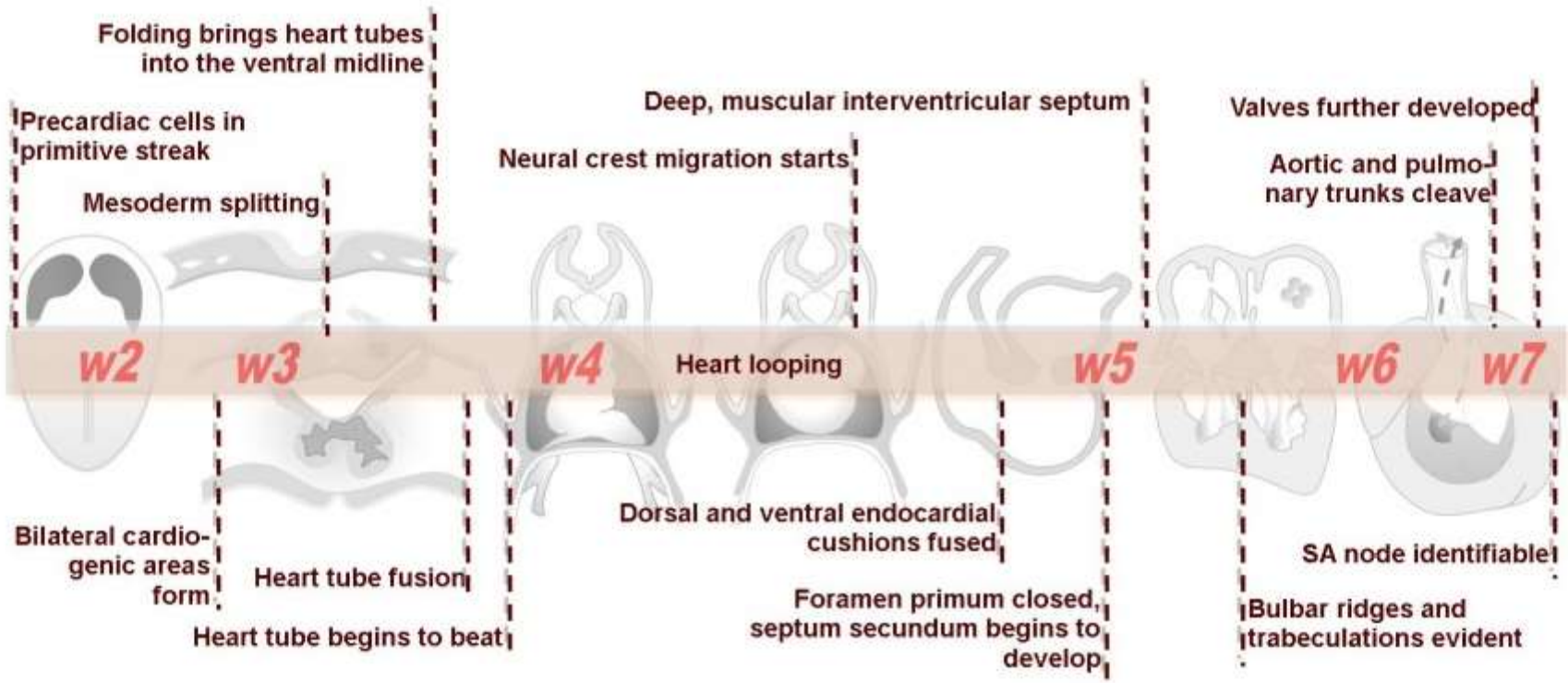
Begin Basic | Begin Intermediate | Begin Advanced



At approximately day 19 the lateral plate mesoderm divides into dorsal (somatic) and ventral (splanchnic) layers, forming the pericardial coelom between them. Angioblastic cords develop in the splanchnic mesoderm and canalise to form bilateral heart tubes. Following lateral folding of the embryo, fusion of the heart tubes occurs, beginning cranially and extending caudally. Folding of the heart of the embryo during the fourth week brings the heart tube dorsal to the pericardial cavity. The precardiomyocytes differentiate to form the myocardial sleeve of the heart tube, allowing the heart tube to begin beating. By the end of the fourth week (day 22) coordinated contractions of the heart tube, which push blood cranially, are present. This function initiates as nutritional and oxygen embryologic demands can no longer be met by passive diffusion from the placenta.

The primordial myocardium forms from splanchnic mesoderm surrounding the pericardial coelom. It is separated from the endothelial heart tube by cardiac jelly (gelatinous connective tissue). The endothelium of the heart tube forms the internal endocardium, while the epicardium develops from mesothelial cells arising from the sinus venosus,

Advanced - Cardiac Septation



All of the partitioning of the primitive heart occurs between the middle of the fourth week and the end of the fifth week. Division of the atrioventricular canal is described below while **septation of the atria and ventricles** is described here.

Division of the AV Canal

Two endocardial cushions form on the dorsal and ventral surfaces of the AV canal. Following expansion of the cardiac jelly, epithelial to mesenchymal transformation (EMT) of the endocardial cells in the canal occurs forming the cushions. Synergistic signalling between BMP and TGFβ facilitates EMT. The cushions grow as they are invaded by mesenchymal cells from the endocardium during the fifth week, eventually fusing to create the right and left AV canals, hence partially separating the primitive atrium and ventricle (Click image to play on current page or Play video on new page).

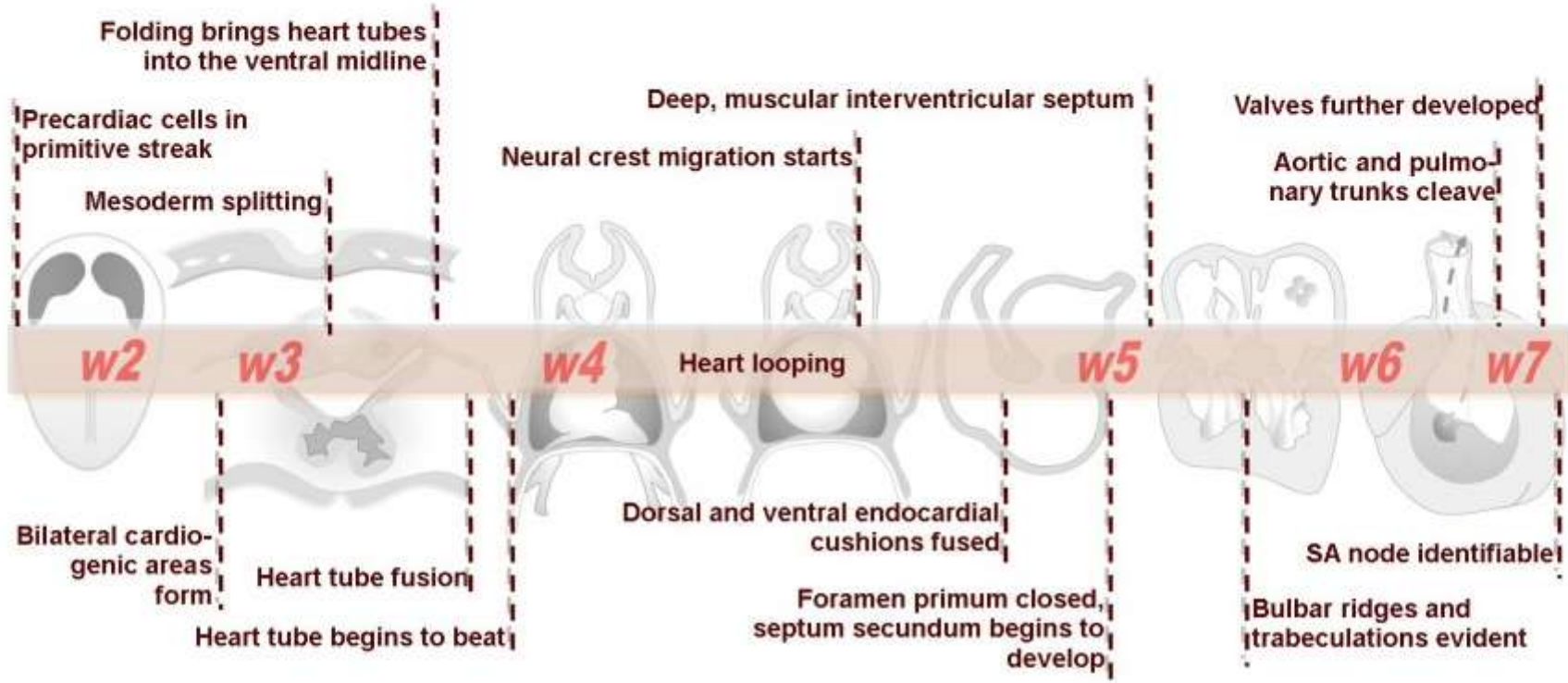
Advanced - Cardiac Septation 2

To return to the first page describing cardiac septation click here.

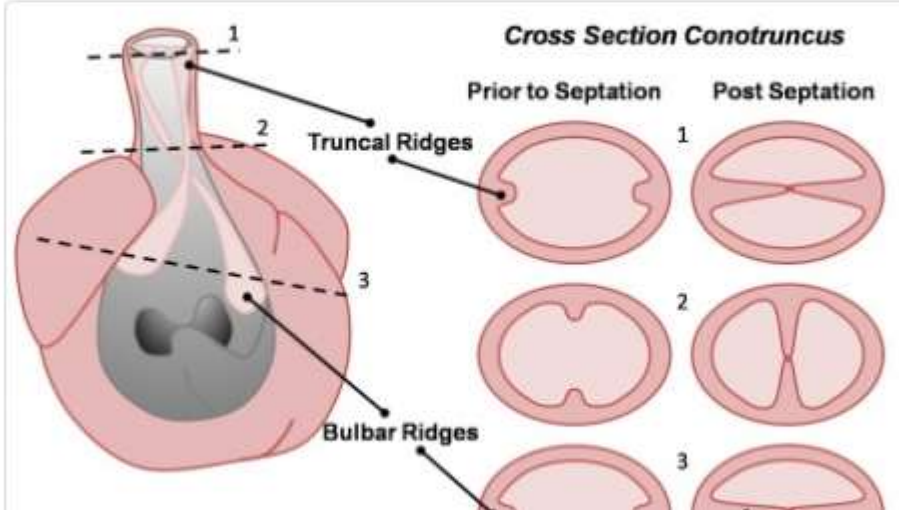
Development of the Atria

Membranous tissue forming the septum primum grows from the roof of the atrium, dividing it into left and right halves. The septum primum originates from myocardium that differentiates from splanchnic mesoderm near the venous pole and approaches the endocardial cushions. The foramen primum refers to the decreasing communication between the septum primum and endocardial cushions. The junction of the septum primum and endocardial cushions becomes myocardialised by ingrowth of myocardial cells, although the centre is maintained as dense connective tissue and is referred to as Todaro's tendon. Apoptosis-induced perforations appear in the centre of the septum primum to produce the foramen secundum. At this time, the strong, muscular septum secundum grows immediately to the right of the septum primum and gradually overlaps the foramen secundum during the fifth and sixth weeks of development. Part of the atrial septum and dorsal right atrium, as well as the septum secundum develop from left-sided mesenchyme. The incomplete partition of the atrium by the septum secundum forms the foramen ovale. Blood flows through the foramen ovale and foramen secundum to the left atrium. The remaining portion of the septum primum acts as the valve of the foramen ovale. Blood cannot flow in the opposite direction as the muscular strength of the septum secundum prevents prolapse of the septum primum.

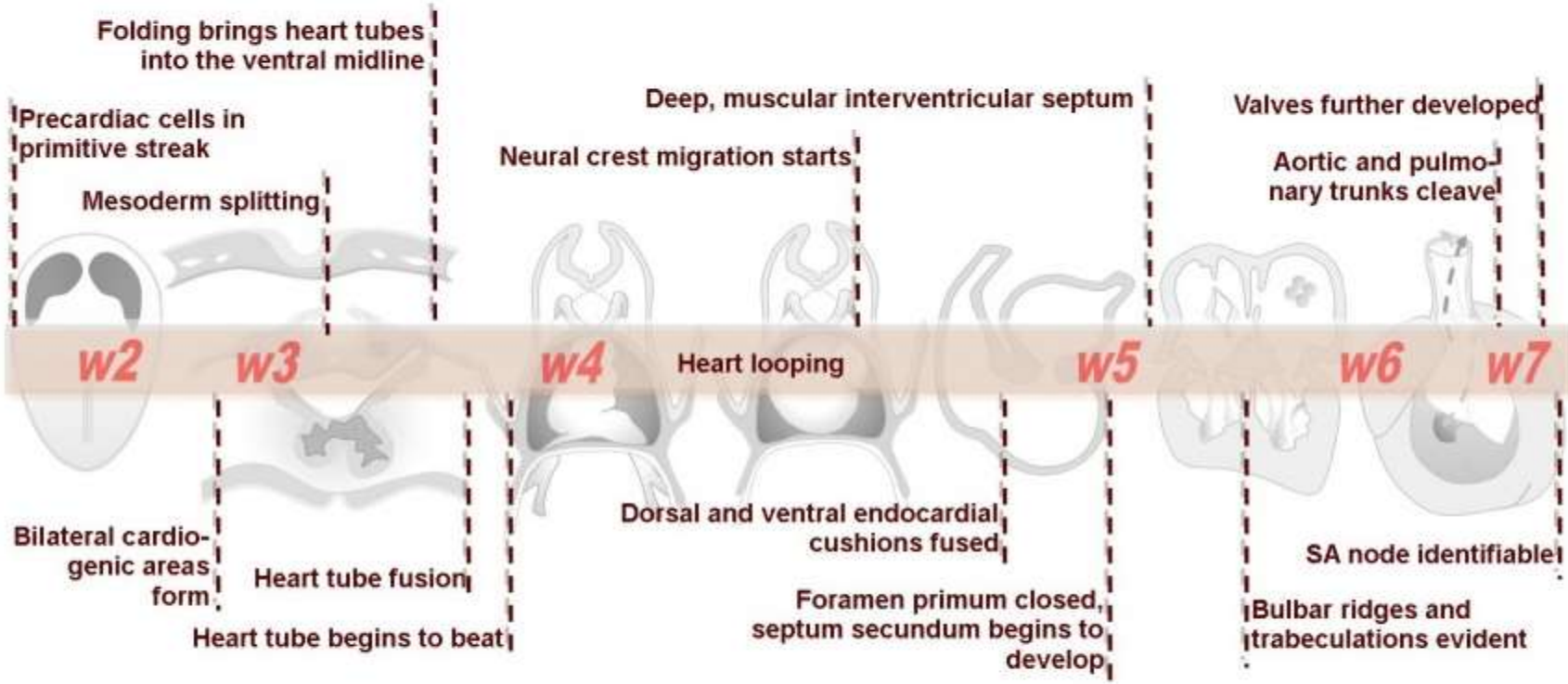
Remodelling of the venous pole, including the further induction of myocardial cells, contributes to the development of the atria. In the mouse, myocardial differentiation occurs in the dorsal mesocardium and cells are then recruited to the venous pole. The development of two left to right shunts in the venous system leads to an increase in the right horn of the sinus venosus and consequentially a decrease in left horn by the end of the fourth week. The sinuatrial orifice correspondingly shifts to the right thus becomes located in the right atrium. Hence the right atrium receives the superior vena cava (SVC) and inferior vena cava (IVC) in the adult. In mice and chicks the left sinus horn develops as the left SVC, however this regresses to form the coronary sinus in humans. Thus the sinus venosus gradually becomes incorporated into the right atrium. It contributes to the smooth walled part of the adult right atrium, referred to as the sinus venarum. The trabeculated right atrium corresponds to the primordial atrium; the division between these structures is indicated by the inner crista terminalis and outer sulcus terminalis. The primordial pulmonary vein develops in the dorsal wall of the left atrium. As the atrium increases in size it incorporates more of the branches of the pulmonary vein, culminating in its receiving the four pulmonary veins. The smooth wall of the adult left atrium originated from the primordial pulmonary vein, while the trabeculated wall represents the primordial atrium. (Click image to play on current page or Play video on new page).



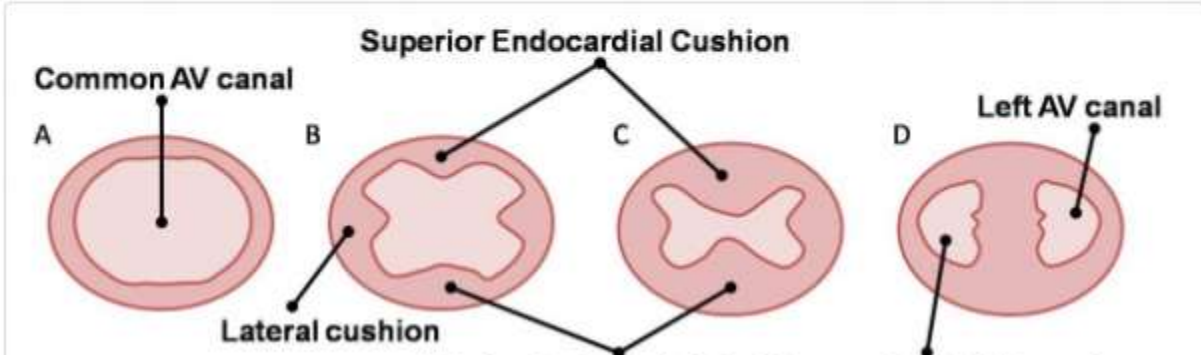
Cardiac neural crest originates between somites 1 and 3 of the neural tube and migrates through the pharyngeal arches to contribute to the conotruncal septum. Active proliferation of pharyngeal mesenchymal cells in the bulbus cordis during the fifth week creates bulbar ridges which are continuous in the truncus arteriosus (see image to the right). The cardiac neural crest migrates into these ridges, condensing as cellular columns to support the outflow tract septum. The ridges form a 180° spiral to create the helical aorticopulmonary septum. Myocardialisation of the ridges gives a zippering effect resulting in fusion. Fusion occurs in a distal to proximal direction during the sixth week, allowing for cleavage of the aorta and pulmonary trunk. The spiralling nature of the ridges causes the pulmonary trunk to twist around the aorta. The bulbus cordis accounts for the smooth conus arteriosus (or infundibulum) in the right ventricle and the aortic vestibule in the left ventricle. The animation below depicts the septation of the outflow tract. (Click image to play on current page or Play video on new page).



Advanced - Valve Development



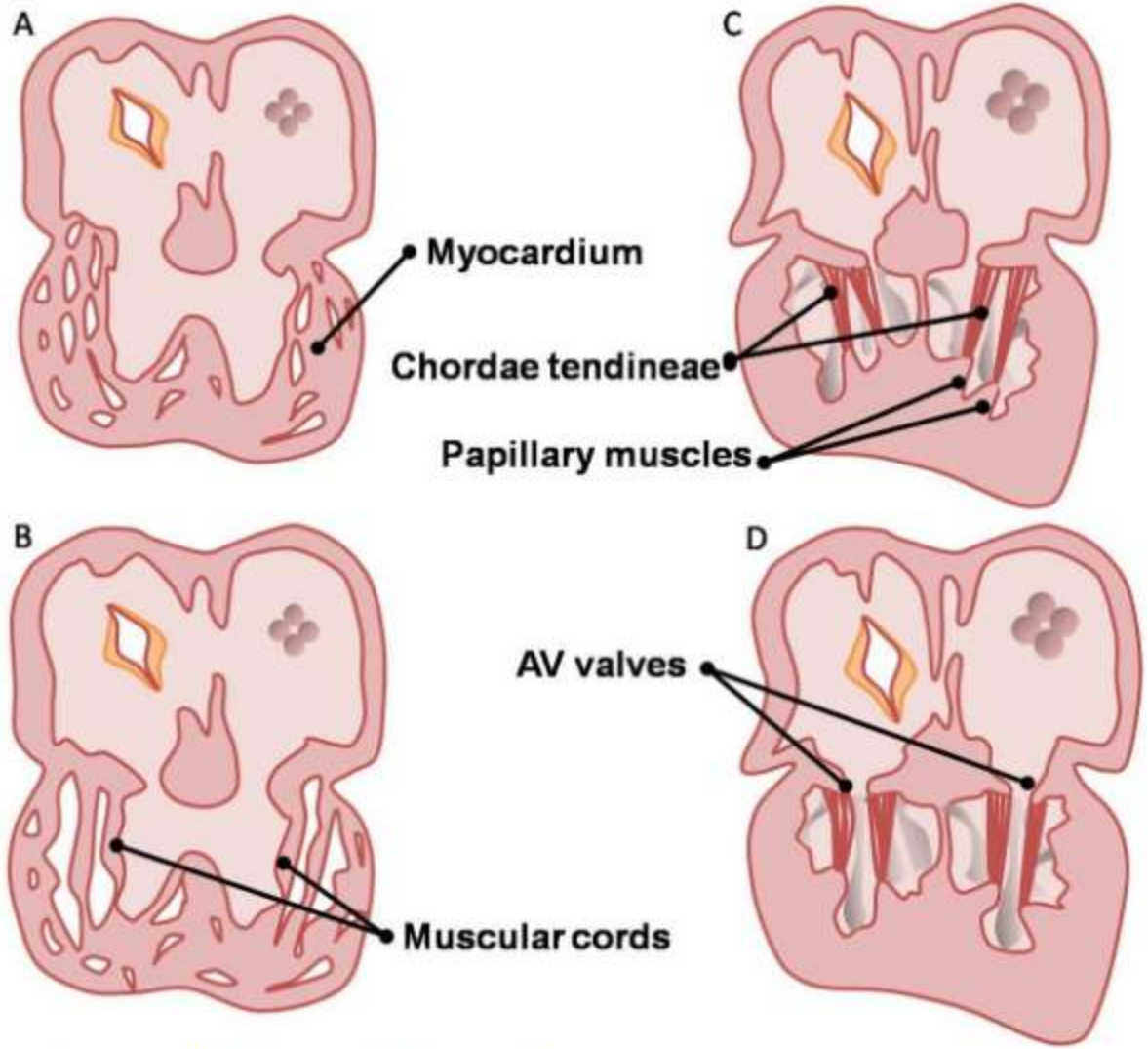
Many of the mechanisms involved in the development of cardiac valves, particularly the process of epithelial to mesenchymal transformation (EMT), are poorly understood. Much of valve formation revolves around expansion of endocardial cushion tissue, yet limitation of cell proliferation is vital in ensuring the cushion swellings can be remodelled to form thin sheets. EMT, which allows for cushion proliferation, is limited by neurofibromin acting through the inhibition of Ras signalling as well as Smad6 which interferes with TGFβ signalling.



The AV valves begin to form between the fifth and eighth weeks of development. The valve leaflets are attached to the ventricular walls by thin fibrous chords: the chordae tendineae, which insert into small muscles attached to the ventricle wall: the papillary muscles. These structures are sculpted from the ventricular wall. The left AV valve has anterior and posterior leaflets and is termed the bicuspid or mitral valve. The right AV valve has a third, small septal cusp and thus is called the tricuspid valve. These concepts are depicted on the right.

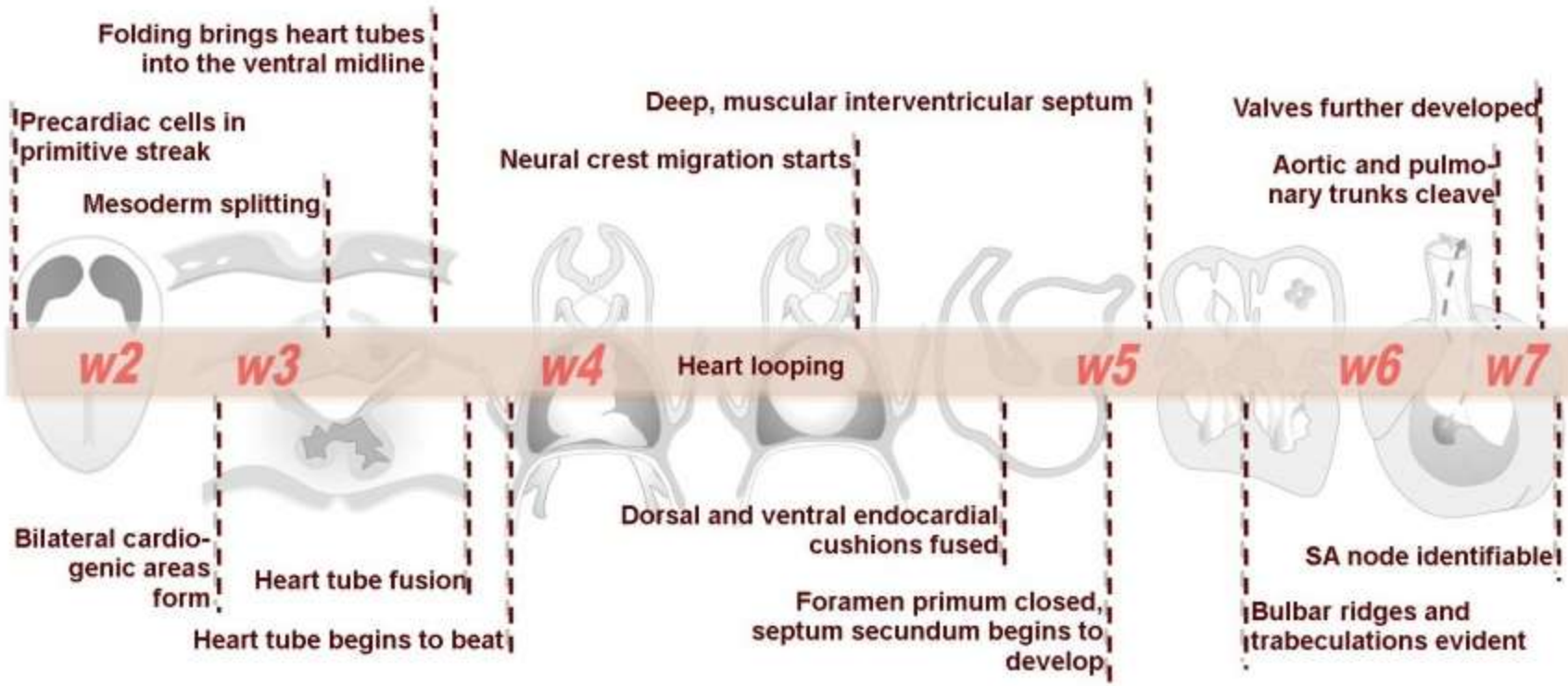
The aortic and pulmonary valves, termed the semilunar valves, are formed from the bulbar ridges and subendocardial valve tissue. The primordial semilunar valve consists of a mesenchymal core covered by endocardium. Excavation occurs, thinning the valve tissue thus creating its final shape (see left). These valves form the four valves of the adult heart depicted below. The mechanisms of valve remodelling in these final steps in both the AV and semilunar valves are not fully understood yet are thought to involve apoptotic pathways.

Inferior Endocardial Cushion **Right AV canal**



Development of the mitral and tricuspid valves

Advanced - Cardiac Conduction



Cardiac conduction in the adult heart begins in the sinoatrial (SA) node which is located at the junction between the SVC and the right atrium. The impulses generated here spread through the atria, initiating contraction. The impulses travel to the atrioventricular (AV) node which acts to slow the transmission of an impulse between the atria and ventricles. After this time lag, impulses travel to the ventricles via the common atrioventricular bundle (bundle of His) to the bundle branches in the IV septum. The branches split and terminate throughout the myocardium in a network of Purkinje fibres. The adult conduction system is shown below.

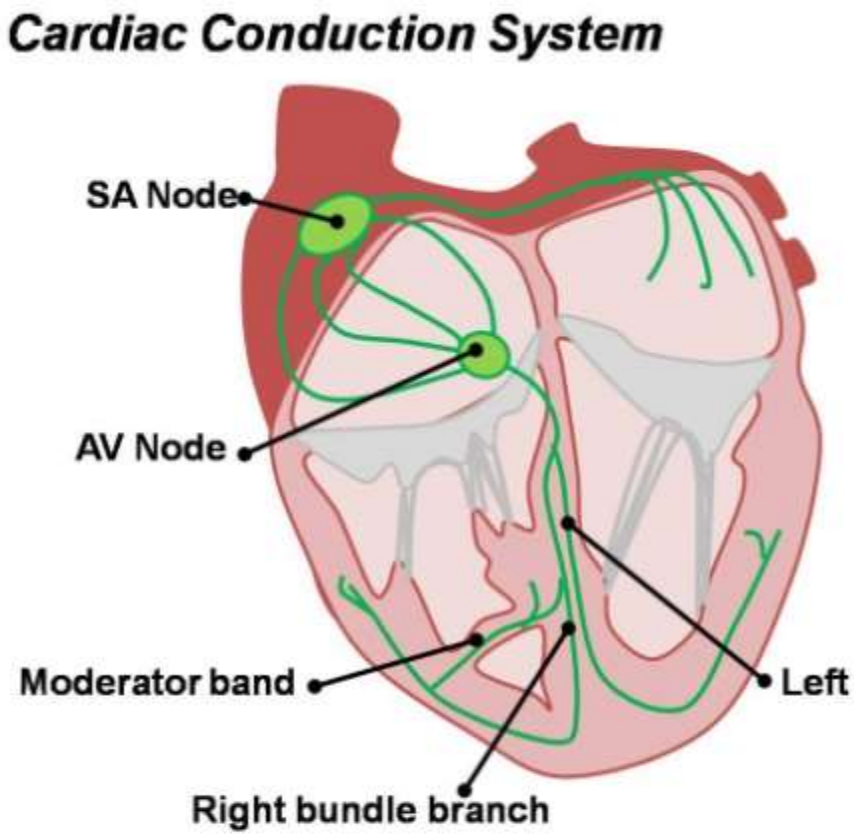
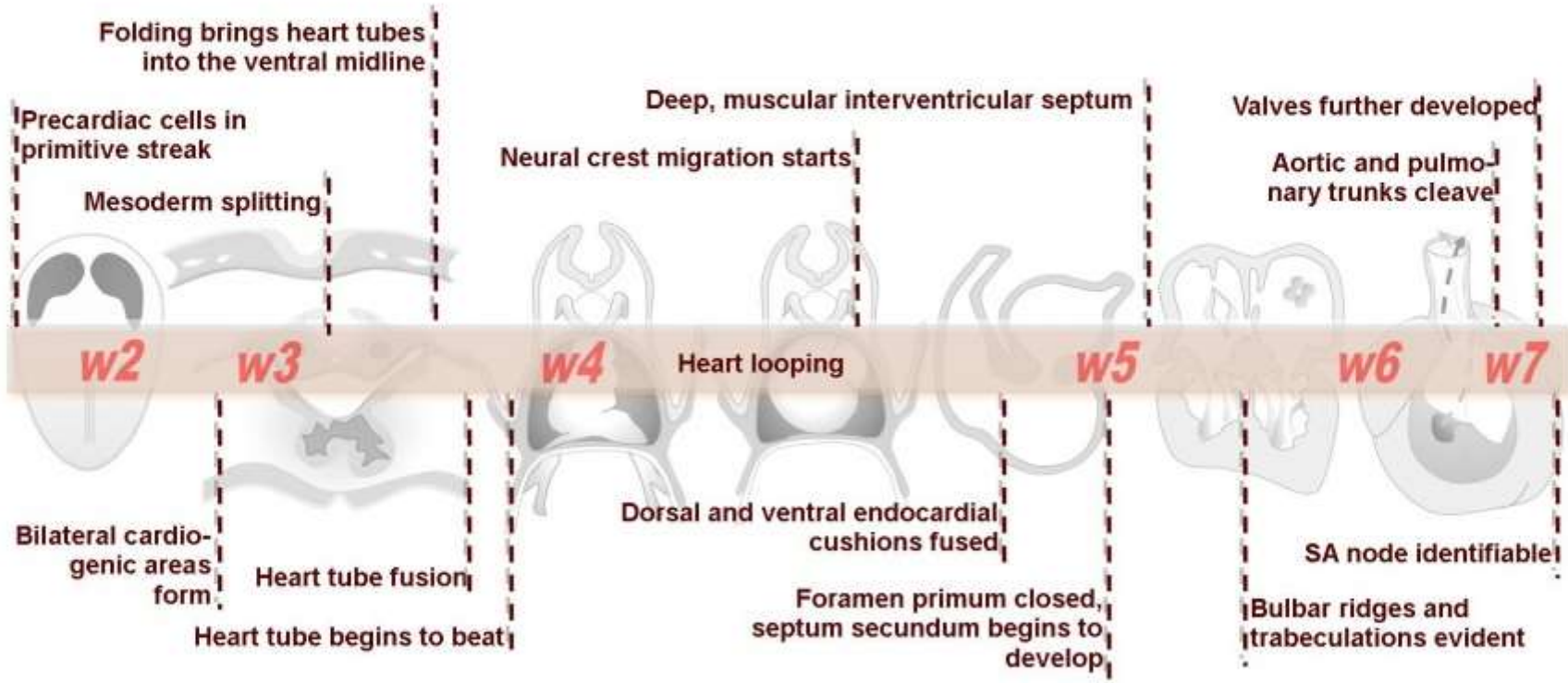


Diagram of the adult cardiac conduction system

Development of the conduction system

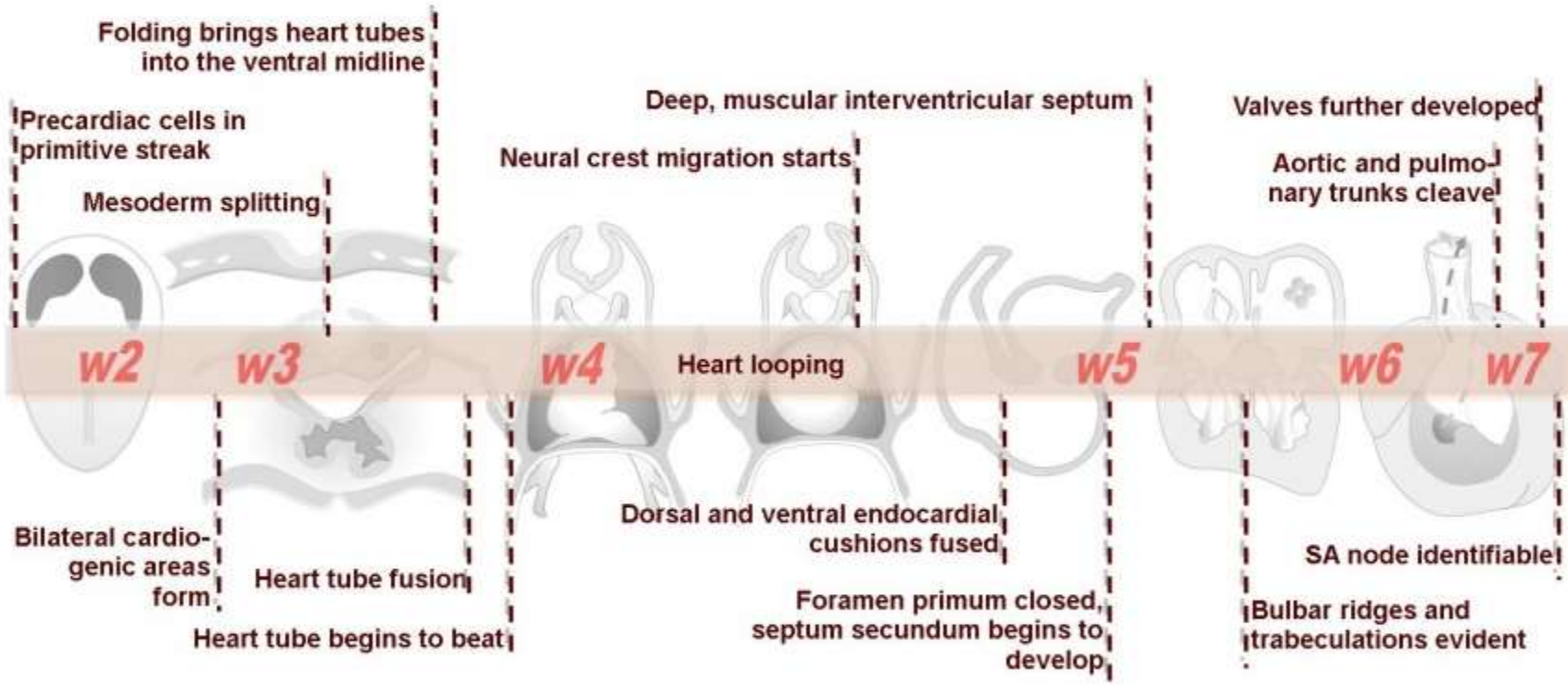
Cardiomyocytes in the caudal heart tube are the first to become electrically active and become the “pacemaker”. The SA node, which develops during the fifth week, initially develops in the sinus venosus and then is incorporated into the RA. The AV node arises slightly superior to the endocardial cushions. Fibres forming the bundle of His develop from fast-conducting ventricular myocardium while the SA and AV nodes are formed from the slow-conducting myocardium of the inflow tract and AV canal. Connective tissue grows in from the epicardium, forming the cardiac skeleton that separates conduction in the atria and ventricles.

Advanced - Abnormalities



Congenital Heart Disease (CHD) is a broad term for a variety of cardiac and vasculature pre-natal defects. They affect about 8-10 of every 1,000 births in the United States. This increases considerably to 75 in 1,000 births if trivial lesions are included and even more so in those stillborn or spontaneously aborted. Cardiovascular abnormalities are the most common form of birth defect, comprising around 20% of all congenital malformations. In addition, given the increasing survival of patients with CHD, treated or untreated, it is expected that large numbers of adults will maintain CHD in the future. Hence CHD becomes a significant part of the clinical environment. The table below outlines some of the common obstructive, septal and hypoplastic defects in order of their incidence.

Advanced - Molecular Development



In attempts to determine the molecular mechanisms controlling heart development, scientists have focussed on early cardiomyocyte development including the cellular movement of cardiomyocyte progenitors and the signaling mechanisms that regulate cardiomyogenesis from the blastula to gastrula stages as well as the morphological changes that occur later in development such as looping and septation. Some of the molecular and genetic factors regulating cardiac development have been previously described in this module in the aspect of development they pertain to. The following diagram provides an overview to the steps in cardiac development and the important associated genes, transcription factors and signalling molecules. Underneath this is a list of some of the predominant molecular pathways contributing to cardiac development.