

## A CONCISE REVIEW ON THE MORPHOLOGICAL CHARACTERISTICS OF THE HIS BUNDLE IN ANIMALS

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### Summary

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The normal sequence of electrical activity in the heart is from the sinus node, where the pacemaking impulse originates to the atrioventricular (AV) node, where there is a slight delay in transmission, and thence to the atrioventricular fascicle (*fasciculus atrioventricularis*, His bundle) for rapid conduction into the branches distributing to the two ventricles. His bundle represents the most vulnerable part of the entire conduction system. A relatively small area of injury may completely block or seriously impair the transmission of impulse. The purpose of the present review is to summarize the information about the His bundle in animals, to compare its morphological features in different animal species and to discuss its embryology and blood supply.

**Key words:** bundle branches, cardiac conducting myocyte (Purkinje cell), heart, His bundle, myocardium

### INTRODUCTION

All the myocytes within the heart have the capacity to conduct the cardiac impulse. A population of myocytes is specialized so as to generate the cardiac impulse and then to conduct it from the atrial to the ventricular chambers. This population has become known as the conduction system (Anderson *et al.*, 2009). The conduction system extends from the AV node to the penetrating atrioventricular fascicle (*fasciculus atrioventricularis*; bundle of His) and then divides into the left and right bundle branches which descend through the interventricular septum (Sanchez-Quintana & Ho, 2003). Wilhelm His discovered the conducting pathway between the AV node and the bundle branches (Silverman *et al.*, 2006).

Cardiology is the art of understanding the (patho) physiology of the heart and circulation and, if possible, correcting abnormalities (Meijler & Strackee, 2006). Some of the cardiac arrhythmias are due to pathologic lesions and anatomical defects in the His bundle (atrioventricular bundle) or its blood supply. For example, an incessant junctional tachycardia originating from an automatic focus located in the His bundle was reported (Gonzalez-Torrecilla *et al.*, 2003).

In addition, exciting newer discoveries strongly implicate the His-Purkinje system as the cause of ventricular arrhythmias in patients with short-coupled premature ventricular complexes and in those with catecholaminergic polymorphous ventricular tachycardia. The role of the

His-Purkinje system in the genesis and maintenance of ventricular fibrillation is yet another frontier for fertile investigation (Scheinman, 2009). Also, pathological lesions in the conduction tissue may play a role in the occurrence of death attributed to intoxication consecutive to cocaine ingestion (Michaud *et al.*, 2007).

The purpose of the present review is to provide information about the His bundle in animals and to compare its morphological features in different animal species.

#### EMBRYOLOGY OF THE HIS BUNDLE

There are two main theories concerning the embryologic origin of the human His bundle with its proximal branches. One theory holds that the His bundle grows forward from the original AV node. Another suggests that the His bundle and its proximal branches originate *in situ* within primitive ventricular tissue and simply join the AV node (James, 1970). Walls (1947) mentioned the His bundle can be recognized in a human embryo of 8 mm crown-rump length and arises from the AV node by a process of rapid growth, whereas, a number of factors suggest that the His bundle and its branches originated separately. First, contrasting with the cellular heterogeneity of the AV node, the His bundle is composed almost exclusively of typical Purkinje cells, as are the bundle branches. This point itself supports the likelihood that the His bundle and its branches originated in a different way from the AV node. Second, when mesotheliomas have been found, they rarely extend into more than the proximal margin of the His bundle, being located predominantly proximal to and with the AV node. Third, the membrane action potentials of cells in the AV node and His

bundle are entirely different. Fourth, all cases of congenital AV block studied histologically have exhibited fundamentally the same lesion – a gap between the AV node and His bundle – although both structures have been present. Fifth, in a clinicopathologic study of AV block in a dog, the cells forming the AV node appeared to have failed to differentiate into their adult form, while the cells of the His bundle and its proximal branches were normal. Sixth, the area of junction between AV node and His bundle appears to be a *locus minoris resistentiae*, both electrophysiologically and by its tendency to undergo focal ischaemia degeneration in men and dogs (James & Drake, 1968; James, 1970).

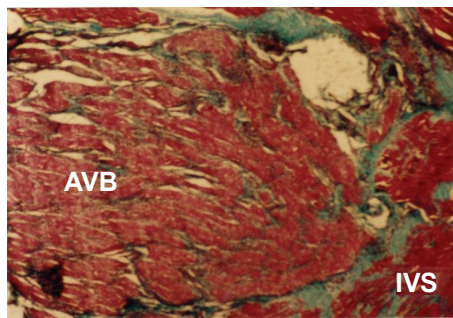
Cell birth dating in the chick embryo has revealed that inductive conscription of cells to central elements of the conduction system (e.g. the His bundle) precedes recruitment to the peripheral components of the network (i.e. subendocardial and periarterial Purkinje fibres). Birth dating studies in rodents suggest that an analogous recruitment process is occurring in this species (Gourdie *et al.*, 2003).

#### HISTOLOGICAL STRUCTURE OF THE HIS BUNDLE

The unbranched His bundle represents the most vulnerable part of the entire conduction system. All supraventricular impulses must funnel through this very small structure before proceeding to the ventricles. A relatively small area of injury may completely block or seriously impair the transmission of impulses (Frink & Merrick, 1974). The histological organization of the His bundle is not the same in all hearts, even in a single species. The histological structure of the His bundle is best considered under four headings (James & Sherf, 1971).

*General organization of the His bundle*

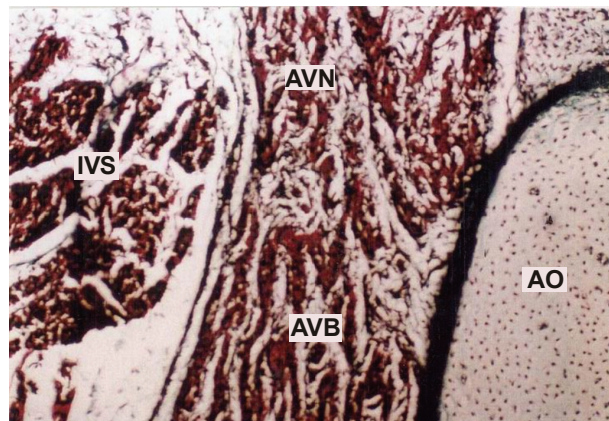
The bundle is composed predominantly of large Purkinje-type cells which are longitudinally oriented. The histologic boundary of AV node and His bundle is that point at which the cell type becomes predominantly large Purkinje-type and at which most of the cells become oriented parallelly in a longitudinal direction and cease interweaving (Fig. 1).



**Fig. 1.** Microphotograph showing the parallel fibres of the His bundle in the heart of goat. His bundle (AVB); interventricular septum (IVS). Green Masson's trichrome staining,  $\times 160$  (Picture reproduced by kind permission of the Journal of Applied Animal Research from Nabipour *et al.*, 2002).

This transition in intercellular geometry usually corresponds to the point at which the His bundle leaves the AV node and penetrates the central fibrous body, where it passes along the membranous interventricular septum to reach the muscular crest. In coursing through the central fibrous body, the His bundle is normally a smoothly outlined structure of ovoid or nearly triangular cross-sectional appearance. An important exception to this description occurs in the human foetal and newborn heart, where the His bundle has numerous outcroppings and loop connections which may be essential in the genesis of such electrocardiographic events as preexcitation or reentrant tachycardias (James & Sherf, 1971).

The bundle of rabbit (James, 1967), guinea pig (Nabipour, 2004), and four-month ovine fetus (Nabipour & Shahabodini, 2007) is displaced anteriorly near the root of the aorta (Fig. 2). It is relatively small in rabbit (James, 1967) and guinea pig (Nabipour, 2004). This is may be due to the foreshortening of the entire area produced by the presence of the large ostium of the coronary sinus, which drains not only the cardiac veins



**Fig. 2.** Showing more anteriorly the location of the His bundle of a four-month ovine foetus. It is displaced to near the root of the aorta. Atrioventricular node (AVN); His bundle (AVB); interventricular septum (IVS); aorta (AO). Green Masson's trichrome,  $\times 160$  (Picture reproduced by kind permission of the Iranian Journal of Veterinary Research from Nabipour & Shahabodini, 2007).

but normally present left cranial vena cava. The length of the His bundle is short in goats (Nabipour *et al.*, 2002), cattle and horses (Meyling & Terborg, 1957) and four-month ovine foetus (Nabipour & Shahabodini, 2007). In above mentioned animals, due to the absence of the membranous part of the interventricular septum, the His bundle extends to a shorter distance. However, in cats (Ghazi *et al.*, 1998), the His bundle extends longer. In sheep (Frink & Merrick, 1974), the size and staining characteristics of the initial Purkinje cells of the His bundle allow easy identification in contrast to human hearts in which the actual transition between AV node and His bundle is very difficult, if not impossible, to identify (James, 1970). The junction between AV node and His bundle in the sheep heart is characterized by finger-like projections in which the two types of tissue overlap (Frink & Merrick, 1974). The presence of an os cordis in the heart of sheep blocks the usual route of the His bundle to the crest of the ventricular septum. As a consequence, the unbranched His bundle must sweep beneath the *os cordis* to reach the right side of the ventricular septum where it remains relatively deep within the ventricular myocardium. This is in contrast to the human His bundle which lies just beneath the membranous septum at the crest of the interventricular septum. In addition, the unbranched His bundle in humans is usually 2–3 mm in length, while it is 4–6 mm in sheep. The location of the His bundle in sheep hearts would seem to be more protected one than in human, less prone to stress and potential trauma of the left ventricular outflow tract (Frink & Merrick, 1974).

The His bundle of chickens descends from the anterior and inferior margin of the AV node into interventricular septum

(Lu *et al.*, 1993). Through the fibrous tissue of the right dorsal part of the right fibrous trigone, the His bundle of fowl runs ventrally to the left into the interventricular septum as a thin rounded bundle (Kim & Yasuda, 1979). In hens, pigeons and quails, the proximal portion of the His bundle is located on the right dorso-lateral side of the interatrial and interventricular septa, the main bundle runs laterally to become deeply embedded into the myocardium of the interventricular septum (Szabo *et al.*, 1986). The His bundle of lizards is an oval body of specialized tissue located near the junction of the left atrium and the ventricle. The fibres and nuclei of this bundle have the same histological structure as described for the His bundle in birds and mammals (Prakash, 1960).

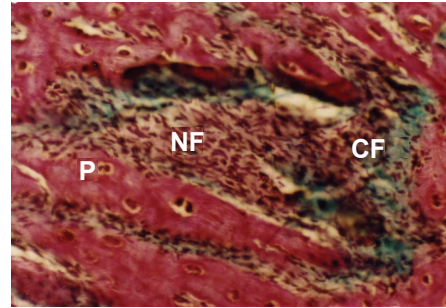
Fast pathway-His bundle connections were present in 13 of 102 rabbit hearts, providing an anatomic and physiologic basis for rapid retrograde AV conduction and a possible retrograde pathway for sustained AV nodal reentrant tachycardia (Patterson & Scherlag, 2004).

#### *Types of cells in the His bundle*

The principal type of cell in the human and canine His bundle is Purkinje cell. This cell is broader and shorter than ordinary myocardial cells, contains relatively few myofibrils, has a large perinuclear clear zone (which means that the myofibrils are peripherally located near the sarcolemma), has comparatively less scalloping and exhibits typical intercalated discs only rarely (James & Sherf, 1971). In longitudinal sections, characteristic cross-striations and intercalated discs typical of cardiac muscle cells are visible (Eurell & Frappier, 2006). Other features of these prominent Purkinje-type cells include presence and abundance of mitochondria in the perinuclear zone and oc-

casional presence of two separate nuclei. The typical Purkinje cells (Copenhaver & Truex, 1952), as seen in the His bundle of ungulates (James & Sherf, 1971), have a distinct light zone and a much greater diameter than the cardiac cells (Fig. 3). Purkinje cells are almost spherical or polyhedral and make contact with other cells at virtually their entire periphery, whereas the cells in the canine and human His bundles are elongated and oblong in shape, making contact to some extent along their lateral margins but more often at their terminal ends (James & Sherf, 1971). The cells of the His bundle of goats are almost exclusively of typical Purkinje cells (Nabipour, 2002). In sheep, the cells of the His bundle have abundant nexuses but exhibit poor sarcoplasmic reticulum and myofibrillar development (Shimada *et al.*, 1986). The compact His bundle of the cat is composed of the parallel fibres of the Purkinje cells (Ghazi *et al.*, 1998). There are two types of cells in the His bundle of guinea pigs (Nabipour, 2004) and four-month ovine foetus (Nabipour & Shahabodini, 2007): Purkinje cells and the cells that do not represent typical characteristics of the Purkinje cells. The fibres of the His bundle of house sparrows are so closely interlaced with each other that they appear like cells having central nuclei, each with clear perinuclear space (Yousuf, 1965). The His bundle of hens, pigeons and quails is composed of Purkinje-type fibres (Szabo *et al.*, 1986). The His bundle of fowl consists of bundle cells that are larger in size, contains a fair amount of connective tissue interspersed between them (Kim & Yasuda, 1979).

In humans and dogs, in addition to the predominant cell type there are others cells that are found in the His bundle. The slender transitional cells are most numerous at the AV nodal end of the His bun-



**Fig. 3.** Microphotograph of the His bundle in the heart of goat. Purkinje cells (P); collagen fibers (CF); nerve fibers (NF). Green Masson's trichrome,  $\times 640$  (Picture reproduced by kind permission of the Journal of Applied Animal Research from Nabipour *et al.*, 2002).

dle but may course much further (James & Sherf, 1971). The transitional cells lack intercalated discs and in turn connect with ordinary myocardial cells (Eurell & Frappier, 2006). A second cell type has features intermediate between those of the Purkinje cell and working myocardium. These may be called broad transitional cells (James & Sherf, 1971). Immunohistochemical techniques have now been developed that better demonstrate the distinction between the cells specialized to conduct from working myocytes (Anderson *et al.*, 2009).

Blood vessels and nerve fibres exit within around the His bundle and bundle branches, but no ganglia have been seen in humans and other species (James & Sherf, 1971). Unlike most of other animals, the His bundle and its branches are weakly innervated in guinea pigs (Nabipour, 2004).

#### *Collagen partitioning of the His bundle*

One of the more striking histological features of the His bundle is its intricately patterned partitioning by collagen. In fact, the loss of interweaving sheets and septa

of collagen and the appearance of longitudinally oriented ones is another useful characteristic for defining histologically the junction of the AV node and His bundle. By contrast, at the other end of the His bundle the separation by collagen continues unaltered from the main body of the His bundle directly into the bundle branches. The density of the collagen septa varies from one heart to another, but in general the sheet of collagen is more prominent in dog than in the human heart (James & Sherf, 1971). Also, collagen is much more prominent in camels (Ghazi & Tadjalli, 1993) than in the heart of cats (Ghazi *et al.*, 1998).

The growth of collagen partitions in various components of the conduction system of the heart is a normal postnatal developmental activity which undoubtedly plays an important role in the normal maturation of function in those special structures. The paucity of collagen there may introduce a significant limitation in interpreting findings relative to function in the mature or adult heart. This point is emphasized here because one of the histologic differences between the His bundle of newborn babies or puppies and that of their adult counterparts is the development of collagen partitioning in a longitudinal direction. The collagen would at least minimize and actually prevent lateral spread of the propagated impulse (James & Sherf, 1971).

#### *Intercellular junctions in the His bundle*

Purkinje cells of the His bundle have much thicker interdigitations between cells than the myocardium, and consequently fewer of them in number across the cell. The terminal intercellular junctions of Purkinje cells are not in a line perpendicular to the cell's long axis, as in working myocardium, but are obliquely oriented. Furthermore, there are fewer

and less dense desmosomes. Another contrast to working myocardial cells, where lateral junctions between such cells are rare, are the more abundant lateral connections between the Purkinje cells of any given strand in the His bundle. Finally, and perhaps most important of all, the nexuses (gap junctions), which are seen as small or short sites of very close apposition between membranes in intercalated discs of working myocardium, are much longer and relatively more frequent in junctions of Purkinje cells in the His bundle. One maturational change that may influence the function of His bundle cells is the specialization of intercellular connections. Thus, the simple intercellular junctions seen in embryonal myocardial cells may not permit the rapidity of conduction observed between cells with numerous nexuses such as are present in the adult His bundle. The abundance of specialized intercellular connections within the His bundle cells facilitate rapid longitudinal spread of the impulse (James & Sherf, 1971).

Gap junctions are present at appositions between Purkinje fibres and could provide a mechanism for propagating impulses between these cells. Studies of the expression of connexins – the family of proteins from which gap junctions are formed – reveal that connexin 40 is prominent in the conduction system (Simon *et al.*, 1998). The gap junctional proteins connexin 40 and connexin 45 have overlapping and partially compensatory functions with regard to heart morphogenesis and cardiac conduction (Kruger *et al.*, 2006).

#### *His bundle block*

In patients with narrow QRS complexes, atrioventricular block is usually localized to the AV node, and it is frequently benign. The more distal intra-His bundle

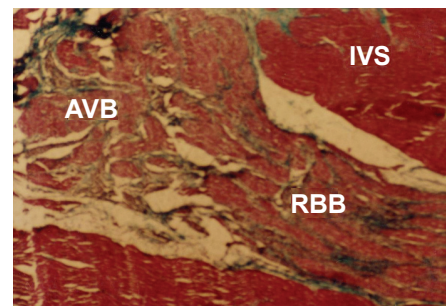
blocks are rare, potentially malignant, and difficult to recognize. The bundle block can be diagnosed by analyzing the effects of certain manoeuvres on the heart rate. Paradoxically, exercise and atropine tend to provoke His bundle block, whereas carotid massage may release it. Implantation of a permanent pacemaker is generally indicated (Jain *et al.*, 2005).

In congenital atrioventricular block, it is known that maternal immunological factors such as systemic disease are involved in the genesis of cardiac conduction problems in the foetus. Histological examination of the foetal heart showed an altered atrioventricular node and bundle of His with fibrosis, calcifications, endocardial fibroelastosis and mononucleated inflammatory cells. The search of these specific lesions can be determinant in establishing the disease pathogenesis; also, it is important to eliminate this diagnosis in an unexplained foetal death (Piercecchi-Marti *et al.*, 2003).

#### BUNDLE BRANCHES

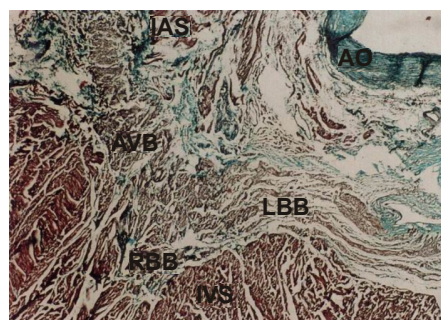
In humans and dogs, at the septal crest the His bundle promptly begins to provide branches to the left ventricular endocardium, and at a slightly more distance and variably placed point provides a single slender right bundle branch. The right branch usually plunges directly into the septal myocardium, although sometimes it passes along the right endocardium. In humans, it then becomes a thin cord that penetrates deep into the septomarginal trabeculation or moderator band connecting the medial and anterior papillary muscles. The origin of the left branch lies below the commissure between the right and non-coronary cusps of the aortic valve (Sanchez-Quintana & Ho, 2003). Its branches virtually always distribute di-

rectly beneath the left ventricular endocardium rather than plunge into the myocardium (James & Sherf, 1971; Netter, 1981). The proximal part of the left branch is much longer than the right. Occasionally a third branch called "dead-end tract" is seen in foetal or infant hearts, and this continues the bundle of His in an antero-superior direction toward the root of the aorta (Sanchez-Quintana & Ho, 2003). In the heart of the goat, the His bundle fibres continue under the *os cordis* and pass through the fibrous atrioventricular ring and at the muscular ventricular septum, the right bundle branch (RBB) is given off as a compact structure and plunges into the interventricular septum (Fig. 4). The histological structure of the RBB is similar to that of His bundle (Nabipour *et al.*, 2002). Calf hearts are more similar to human hearts in that the fascicles of the left bundle branch are usually three in number and originate in the upper part of the interventricular septum. However, sheep hearts show only two fascicles (Sanchez-Quintana & Ho, 2003). The His bundle of cats at the



**Fig. 4.** Microphotograph showing branching of the RBB from the His bundle of goat. His bundle (AVB); right bundle branch (RBB); interventricular septum (IVS). Green Masson's trichrome,  $\times 64$  (Picture reproduced by kind permission of the Journal of Applied Animal Research from Nabipour *et al.*, 2002).

summit of interventricular septum divides into the RBB and left bundle branch (LBB). The RBB is given off as a compact structure that entered into the interventricular septum. After the emergence of the RBB, the continuation of the His bundle is termed the LBB. The proximal part of this branch is a compact structure consisting of a mixture of transitional and Purkinje cells but the rate of transitional cells is gradually increased. The LBB after a short course terminates to a brush-like structure consisting of transitional cells. The His bundle of cats is composed almost exclusively of typical Purkinje cells, while the RBB and LBB are composed of both Purkinje and transitional cells though the ratio of transitional cells is increased as more distal ramifications are occurring (Ghazi *et al.*, 1998). This is different from camels (Ghazi & Tadjalli, 1993), and humans (James, 1970) in which the RBB and LBB are composed only of Purkinje cells. The RBB of the four-month ovine foetus consists almost entirely of Purkinje cells and the percentage of Purkinje cells is remarkably higher than in the His bundle (Nabipour & Shahabodini, 2007). Beginning with left bundle branches, the length of the His bundle of rabbits is 100 to 200  $\mu\text{m}$ , and in this course, the RBB originates at variable points of departure (James, 1967). In the heart of adult sheep (Frink & Merrick, 1974), dogs (James, 1964), cats (Ghazi *et al.*, 1998), goat (Nabipour *et al.*, 2002), guinea pigs (Nabipour, 2004) (Fig. 5) and four-month ovine foetus (Nabipour & Shahabodini, 2007), RBB is the first branch, whereas, in the heart of humans (Titus *et al.*, 1963), horses (Bishop & Cole, 1967) and camels (Ghazi & Tadjalli, 1993) the first branch is LBB. In the heart of humans (Titus *et al.*, 1963), rabbits (James, 1967), cat (Ghazi *et al.*, 1998), goats (Nabipour *et al.*, 2002), dogs



**Fig. 5.** His bundle and bundle branches in the heart of guinea pig. His bundle (AVB); right bundle branch (RBB); left bundle branch (LBB); interatrial septum (IAS); interventricular septum (IVS); aorta (AO). Green Masson's trichrome,  $\times 64$  (Picture reproduced by kind permission of the Iranian Journal of Veterinary Research from Nabipour, 2004).

(James, 1964) and guinea pigs (Nabipour, 2004) the RBB is more compact and narrower than the LBB. In hens, pigeons, quails (Szabo *et al.*, 1986), fowl (Kim & Yasuda, 1979) and chickens (Lu *et al.*, 1993) the His bundle divides into right, left and medial (recurrent) branches at the level of the upper and middle third of the interventricular septum. The medial branch is also observed in the heart of turkeys (Nabipour & Safaei, 2008). In house sparrows, the right and left bundle branches extend through the AV valves of their sides and reach the other wall of the ventricular cavities. This feature enables the His bundle to quickly distribute the contraction impulse well over the surface of the ventricles. There is also a branch from the right limb of the His bundle to pass directly into the right atrioventricular valve. This special branch is necessary so that the valve may contract at the onset of ventricular septum (Yousuf, 1965).

#### *Bundle branch block*

Interest in bundle-branch block (BBB)



has focused primarily on its role as a predictor of mortality and co-existing cardiovascular disease. Several studies have found an increased mortality among patients with BBB and concomitant cardiovascular disease. The presence of BBB was strongly associated with future high-degree atrioventricular block that was more pronounced for left BBB. An unexpectedly high prevalence of BBB was found in patients who survive ventricular fibrillation. In patients with acute myocardial infarction, the presence of BBB is a marker of worst outcome, which persists in the modern era of thrombolytic therapy (Eriksson *et al.*, 2005).

Bundle branch re-entrant ventricular tachycardia (VT) is most often encountered in dilated cardiomyopathy, but can cause VT in patients with coronary heart disease and other structural heart disease (Irtel & Delacretaz, 2006).

#### *Blood supply of the His bundle and bundle branches*

In general terms there are two primary sources of blood supply to the human His bundle and the proximal portion of its two branches; the AV node artery and the first septal branch of the left anterior descending coronary artery. The blood supply to most of the human His bundle and its proximal branches is dual in origin. The dual blood supply to the His bundle helps explain certain events seen in posterior myocardial infarction complicated by heart block (Frink & Merrick, 1974). In dogs, branches from the septal artery form the primary supply to the His bundle and proximal branches (James, 1964). For the His bundle of rabbit, the only arterial circulation available is that of the septal artery (a branch of left coronary artery) (James, 1967). In the sheep heart, the His bundle receives a dual blood supply from both the anterior septal branches and the

AV node artery. The proximal part of the left and right bundle branches is supplied by the anterior septal branches in the majority of hearts (Frink & Merrick, 1974).

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