

Comparative histological structure of the sinus node in mammals

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Abstract: The main function of the sinus node is to provide the electrical impulse responsible for normal cardiac rhythm. The rhythmic coordination depends on the passage of the excitation wave by the heart through its conductive system of impulse. There is considerable variability in the size and exact location of the sinus node of individual hearts even within the same species. Histological features of the sinus node including the cells, the nodal artery, the collagen framework, and the innervation, and also some physiological characteristics of the node, will be discussed.

Key words: Heart, sinus node, P cell, transitional cell, collagen framework, central artery

Introduction

Human circulation distributes oxygen to and removes metabolic waste from the tissues of our body. To keep all of our cells freshly oxygenated, our hearts pump about 350 L of blood each hour, over 8000 L every day or 3 million L in 1 year, enough to fill 4 Olympic-sized swimming pools. This is at rest. During exercise, e.g., race rowing, the young and healthy human left ventricle may deliver 25 L of blood per minute against a pressure of 100 mmHg on the average. The performance of the healthy human heart is prodigious, and it has to be. Cardiology is not about recognizing stamps in a collection; cardiology is the art of understanding the (patho)physiology of the heart and circulation (1).

The main function of the sinus node is to provide the electrical impulse responsible for normal cardiac rhythm (2) (Figure 1). Because of the tangible assets of the sinus node, it logically follows that scientists

should have more knowledge of the histological structure of the node and how the sinus node work. This review will therefore consider in sequence the normal histology of the sinus node and some observations on function of the node.

Embryology of the sinus node

By the sixth or eight week of fetal development, the human heart has attained most of its adult characteristics and the sinus node is readily discernible. The cells from which the sinus node is formed originate in the sinus venosus. At these early stages of development, the small dark cells of the sinus node are all similar. Present evidence indicates that these are specialized cells, and it is misleading to think of them as embryonal cells that failed to differentiate from their primitive form (3).

The human sinus node can be identified at 10 mm, but only at birth does it show the histological features

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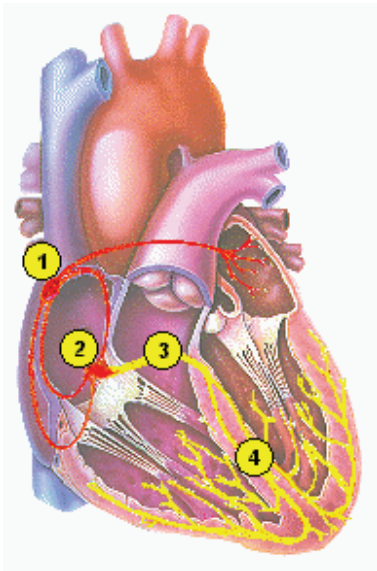


Figure 1. Showing impulse generation and cardiac conduction system of the human: 1) sinus node, 2) AV node, 3) bundle, 4) right and left bundle branches. Red lines are internodal pathways (<http://www.cardiocounsel.com/physiology>).

that characterize it in the adult (4). In house sparrow, the sinus node appears almost simultaneously at the 15-mm stage and the specialized conducting tissue develops earlier than the nervous elements. It is interesting to note that the sinus node appears near the cephalic portion of the interatrial septum, but as the development proceeds, it first shifts dorsally to the sinoatrial opening and then to the dorsocranial wall of the right atrium at the base of the right sinoatrial valve. Finally, in the adult, it is observed very close to and on the right of the cranial end of the interatrial septum. This shifting in the position of the sinus node has correlated with the appearance of the sinus venosus and then its gradual absorption into the right atrium (5).

Anatomical location and morphology of the sinus node

In the human heart, the sinus node lies just beneath the epicardium near the junction between the superior vena cava and right atrium (2) (Figure 1). This location is similar to that of cattle (6), horse (7), goat (8), dog (9), domestic cat (10), and camel (11), while in rabbit (12) and guinea pig (13), it lies beneath the epicardium at the more caudal part of terminal sulcus. In chicken, the sinus node lies near the base of

lower portion of the right sinoatrial valve (14). In fowl, the sinus node lies in the region between the orifices of the right cranial vena cava and of the caudal vena cava, and beneath the atrial epicardium at the base of the right sinoatrial valve (15). In house sparrow, due to the absence of the sinus venosus, the sinus node is situated at the cephalic end of the interatrial septum (5). In lizard, the sinus node lies in the invaginated portion of the wall of the sinus venosus and close to the right atrium (16). However, there is considerable variability in the size and location of the sinus node of any given heart, even within the same species (2).

The sinus node of human resembled and extended like a snail with its shell, and it is also subject to considerable variations (17). In dog, the shape is oblong or spindle-like, and its variations are even greater than in human (9). The feline sinus node is triangular (10). In horse, the tapering cranial and caudal crura of the node encircled the lateral half of the junction of the cranial vena cava with the right atrium (7). In rabbit, the shape is oblong, with its long axis parallel to the terminal crest (12). In guinea pig, the shape of the node is like a trapezoid with curved sides (13). In camel, it is elongated in shape and bent oblong (11). The porcine sinus node has a rather elongated shape and the longer part of its volume is taken up by collagen and fibroblasts. The impulse appears to emerge from a site where the percentage of myofilaments is relatively low (18).

Dimensions of the sinus node in human (17), dog (9), domestic cat (10), goat (8), rabbit (12), guinea pig (13), horse (7), and camel (6) are given in the Table.

The cells of the sinus node

In the adult human heart, there is no question that the sinus node and atrioventricular node act as the 2 most efficient pacemaking units, with the sinus node normally dominating. Although this dominance is in part due to an inherently faster pacemaking rate, the sinus node also has many other anatomic and physiologic advantages that enhance its dominance. These advantages include the optimal distribution routes for a pacemaking signal to go to the 2 atria and ventricles, abundant adrenergic and cholinergic nerves, and the consistent presence of a disproportionately large central artery about which the sinus node is normally organized in a dense collagen framework (3).

Table. Dimensions of the sinus node.

Animal	Dimensions
Human	15 mm × 5 mm × 1.5 mm
Dog	Total substance of the node is approximately 5 mm ³
Male domestic cats	2.78 mm × 2.80 mm × 0.54 mm
Female domestic cats	2.75 mm × 2.64 mm × 0.45 mm
Horse	Approximately 3.0 mm × 4.4 mm in cross-section
Goat	12.75 mm × 1.5 mm × 1.7 mm
Camel	28.25 mm × 5 mm × 5.38 mm
Rabbit	Total length varied from 0.5 mm to 0.8 mm
Guinea pig	0.14 mm × 0.03 mm × 0.55 mm

The sinus node contains at least 2 distinct cell groups. The first group includes the *perinuclear clear zone (P) cells*, which tend to occur in grape-like clusters with each cell shaped much like a grape. A P cell is small and round or ovoid; has an empty-appearing cytoplasm with what appears to be a disproportionately large central nucleus; contains only sparse myofibrils and small mitochondria, both of which are randomly oriented and distributed; and has very simple intercellular junctions. The P cell is probably the site of the origin of the sinus impulse (3). There are no intercalated disks and no tight junctions between these cells. The P cells tend to be centrally located. A second group of cells, named *transitional cells*, include all other myocardial cells found in the sinus node. These are slender, elongated cells that form the small nodal fibers seen with a light microscope (3) (Figure 2). Transitional cells are much smaller than ordinary myocardial cells (2) (Figure 3). They are distributed throughout the node but are the principal cell type in its outer half (3). Transitional cells act as routes for distribution for the sinus impulse that originates in the P

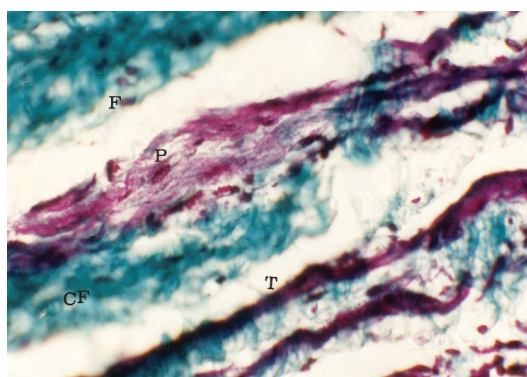


Figure 2. Microphotograph of the sinus node in the heart of goats showing perinuclear clear zone cells (P), transitional cells (T), collagen fibers (CF), and fibroblast (F) (640×, green Masson's trichrome staining).

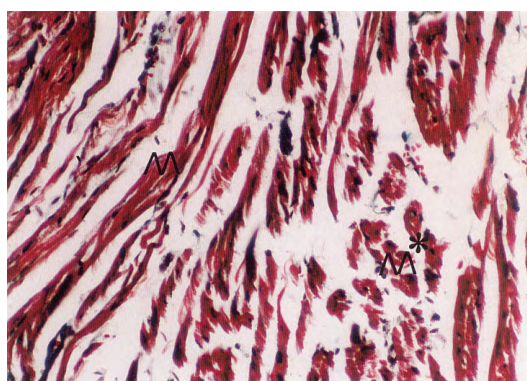


Figure 3. Showing atrial ordinary myocardial fibers of the heart of guinea pig. Longitudinal (M) and cross-sections (M*) of the ordinary myocardial fibers (640×, green Masson's trichrome staining).

cells (2). They may contain either a small or large number of myofibrils with the mitochondria arrayed between them, just as in ordinary myocardium. P cells contain conspicuously little glycogen, but transitional cells have a large amount. Transitional cells form the exclusive junction between the sinus node and the adjacent cells of the internodal and interatrial pathways. There are relatively fewer P cells in the adult sinus node than in that of the fetus or newborn. The slender, elongated transitional cells are more numerous in the adult sinus node, and the interweaving of these slender multicellular fibers is one of the more readily recognizable histologic features of the node (3). In the interstitium between the P cells and transitional cells, there are numerous fibroblasts, nerves, and capillaries, plus small arterial or venous branches (2).

In rabbit (12) and guinea pig (13), the proportion of P cells to transitional cells in the sinus node is exceptionally high (Figure 4). The primary pacemaker, i.e. the group of pacemaker cells discharging the sinus node, comprises less than 1000 cells in the guinea pig and about 5000 cells in the rabbit. The action potential of the leading cells has a higher upstroke velocity in the guinea pig than in the rabbit. Gap junctions have been observed even in the very center of the node in both species (19). According to transmission electron microscopic analyses, the nodal cells of the sinus node of sheep are small in size and contain few nexuses with poor sarcoplasmic reticulum and myofibrillar development. The nodal cells are spindle-shaped and their ends often show ramification (20). The directions of the cells of the sinus node of hamster are very irregular and are often found with many orientations. As a basic differential factor, cells of the sinus node, just like the Purkinje fibers themselves, show an eosinophilic aspect less reactive than that of the normal cardiac striated muscular cells (21). The nodal cells of fowl are smaller in size, and there is a fair amount of connective tissue interspersed between them (15). In house sparrow, the node is formed of Purkinje fibers, which are very prominent and well defined. These fibers show central nuclei with clear cytoplasmic spaces around them (5). The sinus node of lizard is composed of thick, elongated, closely interwoven fibers and large oval nuclei (16).

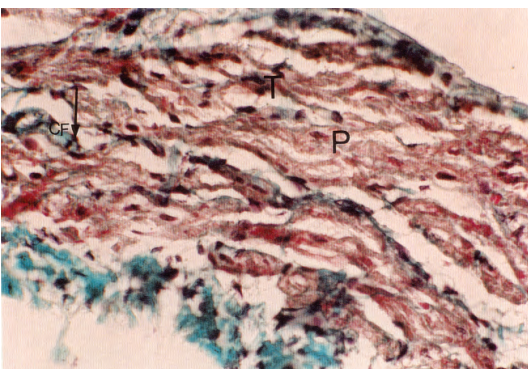


Figure 4. Microphotograph of the sinus node in the heart of guinea pig; note the high percentage of P cells in the node. Perinuclear clear zone cells (P), transitional cells (T), fibroblast (arrow), collagen fibers (CF) (640 \times , green Masson's trichrome staining).

It is essential to visualize these 2 principal myocardial cell types of the sinus node, but it is equally important to understand the mature sinus node functions as a complex biological unit that has 3 other fundamentally important anatomic features: the central artery, the collagen framework, and the innervation.

Sinus node artery

One distinguishing feature of the sinus node of human (2), dog (9), horse (7), and camel (11) is the characteristic presence of a *centrally located artery*. In fact, the entire node appears to be organized about its central artery, a feature that prompted Söderström (22) aptly to describe the node of man as resembling an enormous adventitia of its artery. Because this artery is subject to thrombotic or dysplastic proliferative occlusion and to many arteritic processes, many diseases of the sinus node originate within its artery (2). The consistent central location of the sinus nodal artery within the node and the proximity of the artery's origin to the aorta make the periarterial node an ideal sensing device for monitoring central aortic pressure and pulse. The validity of this teleological reasoning is supported by the observations that experimentally controlled changes in pressure or pulse in the sinus node artery have a significant effect on the sinus pacemaking rate. The concept that pulse and impulse in the sinus node are functionally related as a stabilizing servomechanism is further supported by the finding that arrhythmias and sudden death occur in subjects with grossly abnormal thickening or obliteration of the sinus node artery, making its pulsatile activity either much less or totally absent. The sinus rate of the fetus and newborn child is rapid and relatively unstable, while that of the adult is slower and far more stable. A number of developmental changes are possible explanations for this age-dependent difference, but the maturation of the size and internodal relation of the sinus node artery must be included as one of these possibilities (3).

Histologically, the sinus nodes of cattle (6), rabbit (12), domestic cat (10), guinea pig (13), and house sparrow (5) have no central artery. The sinus nodes of sheep (23) and goat (8) contain a distinct arteriole near the central section of the node and the nodal cells

are not organized around it (Figure 5). It seems likely that, in many forms, the pulse normally delivered into the sinus node artery with every cardiac cycle acts as a modulating influence in animals without a central artery in their sinus node. It synchronizes otherwise relatively random pacemaking cellular activity and thereby serves to stabilize the node's pacemaking activity and make it less easily disrupted by extranodal influence (3).

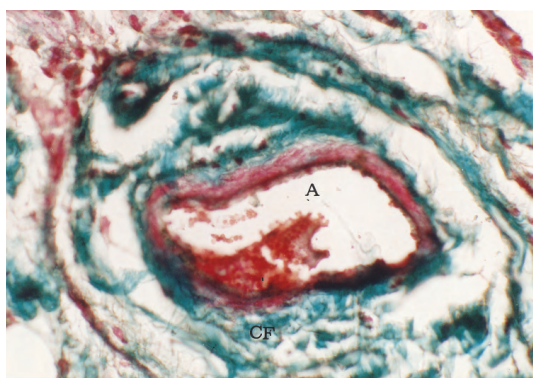


Figure 5. The sinus artery of the sinus node in the heart of goats: arteriole (A), collagen fibers (CF) (640 \times , green Masson's trichrome staining).

The sinus node artery has many intercoronary and intracoronary anastomoses, which comprise an important anastomosing net between the right coronary and left circumflex arteries. These findings suggest that the sinus node artery plays a major role in the blood supply of the atrial myocardium apart from the sinus node (24).

Collagen framework of the sinus node

In human, there is very little collagen within the sinus node of the fetus or newborn heart, but with increasing age, the collagen frame becomes increasingly dense up to about early adulthood. The speed of this change and its ultimate normal extent vary from one heart to another (2). The collagen within the sinus node is intricately woven among groups of P cells and transitional cells to form a regularly patterned framework. In serving as a periarterial framework for the sinus node, the collagen also separates small groups of cells from each other and thus limits the extent of intercellular contact. This limitation of intercellular contact may be an important factor relative to the maturation of nodal cells, and also

for the ultimate pacemaking activity of the node. Diseases in which the collagen framework is damaged are associated with arrhythmias that may in part be due to essential features for optimal stability of the normal cardiac pacemaker (3).

The sinus nodes of horse (7), dog (9), pig (25), domestic cat (10), and camel (11) consist of a large amount of a dense collagen frame, which is similar to that of human. Meanwhile, in cattle (6), rabbit (12), and guinea pig (13), there are relatively fewer collagen fibers.

This is, however, no consequence for the sinoatrial conduction time and the regularity of the beat-to-beat cycle length in the different species, because the rabbit and cat have comparable sinoatrial conduction times, although their nodal collagen content is very different and the beat-to-beat cycle length showed a comparable variability in the different species (25).

Innervation of the sinus node

In addition to the functional stabilizing influence of pulse and impulse in the sinus node, a second form of modulation is provided by the adrenergic and cholinergic nerves of the node (3). Cholinergic nerve endings stained the most heavily of all tissues studied and are numerous in the sinus node. Stellate-shaped cells previously suggested to be pacemaking sites in the sinus node are found to contain abundant cholinesterase. Within individual cells of the sinus node, cholinesterase could be identified within the myofibrils (26). The pulse and impulse servomechanism provides an intrinsic regulatory feedback and functions beat-to-beat or over the sequence of a short period of beats. The autonomic innervation influences the sinus node over longer periods of time and also serves as the principal link between the normal pacemaker of the heart and extracardiac regulatory centers, such as the brain and carotid sinus. As balanced autonomic innervation develops in the postnatal sinus node, the node becomes an intrinsically more stable performer as the pacemaker of the heart. Ultimately it is the loss of these same normally developing stabilizing mechanisms (the pulse and impulse servomechanism and balanced autonomic neural control) that accounts for the ready disorganization of sinus rhythm in many cardiac diseases (3).

There are abundant nerve fibers at the periphery and also within the sinus node of human (17), horse (7), goat (8), dog (9), and domestic cat (10). Furthermore, in the mentioned animals, ganglions are present at the periphery of the sinus node (Figure 6). In the heart of guinea pig, there is a very small amount of nerve fibers. There are also no ganglions at the periphery or within the sinus node of guinea pig (13). In lizard, nerve fibers and a few ganglia have been seen in the region of sinus node (16).

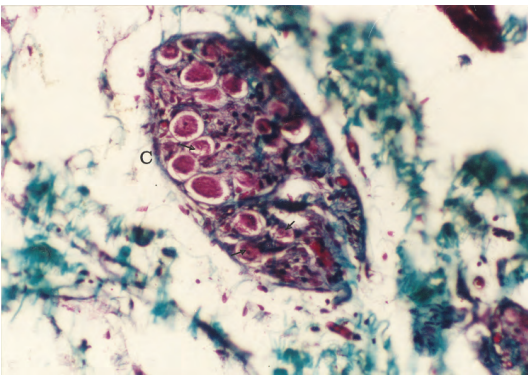


Figure 6. A ganglion of the sinus node in the heart of goats. Nucleus and nucleolus in the perikaryon (arrows); capsule (C) (320×, green Masson's trichrome staining).

Blood supply to the sinus node

In human, blood supply to the sinus node comes from a single stout atrial artery (the largest in atrial circulation), which originates from the first or second proximal centimeter of the right coronary artery in about 55% of hearts and from the first or second proximal millimeter of the left circumflex branch in about 45%. In rare instances, the sinus node artery may originate more distally, from the aorta directly, or from the main left coronary artery, or there may be a dual arterial supply to the sinus node; however, all of these variations cumulatively comprise no more than a small percentage of normal human hearts (2). In dog, the sinus node artery arises from the right coronary artery in over 90% of canine hearts. In dog, the anastomoses with neighboring arteries are particularly rich, and causing the canine sinus node to malfunction experimentally by ligating its nutrient arteries is difficult (9). The sinus node artery originated from the right coronary artery in sheep heart (27) and from the left circumflex coronary artery in cattle (6), horse (7), and camel (28). In the rabbit, the blood supply of the sinus node is from terminal small branches of both the right and left coronary arteries (12). The sinus node artery of hamster is in the junction of the node with the myocardial wall. It is a branch of the right coronary artery (21).

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