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Morphology and Electrophysiology of the Mammalian Atrioventricular Node

FRITS L. MEIJLER AND MICHIEL J. JANSE

Interuniversity Cardiology Institute of The Netherlands and Academisch Ziekenhuis, Utrecht; and Department of Clinical and Experimental Cardiology, University of Amsterdam, Academisch Medisch Centrum, Amsterdam, The Netherlands

I. INTRODUCTION

Tawara in 1906 (174) was the first to describe the morphological atrioventricular (AV) node in the hearts of several species. Rather than describing differences, he emphasized the similarities of this structure in various hearts to support his main hypothesis, that the AV node was the only electrical connection between atria and ventricles. Seven years later, Kent (83) wrote that the concept that "there is one, and only one muscular path capable of conveying impulses from auricle to ventricle" was "very generally held," but that the view that the "muscular path of communication may be multiple . . . has gradually been forced on some of those workers who have been brought into most intimate contact with experimental and clinical evidence." Although there is no doubt that accessory AV connections may occur in human and canine hearts, the view put forward by Tawara has stood the test of time

(9, 103). Apart from the fact that the AV node normally forms the only link between atria and the ventricular specialized conduction system, three different functional aspects may be distinguished. *1*) The AV node conducts the impulse slowly, thereby causing a delay between activation of atria and ventricles. Because of this so-called AV nodal delay, contraction of atria and ventricles are coordinated. *2*) The AV node is capable of blocking impulses on their way from atria to ventricles, when these occur prematurely or at a rapid rate, thus protecting the ventricles from too rapid rhythms and to a certain extent from irregularities in rhythm. *3*) The AV node may serve as a pacemaker to the ventricles when the sinoatrial pacemaker fails or when conduction block between atria and AV node develops.

The *British Medical Journal* of August 16, 1913, mentions that during a medical congress, "Prof Waller drew attention to the correlation of the size of an animal, its pulse-rate and the length of the auriculo-ventricular interval, instancing the horse, man and the dog." When AV conduction times in different animal species are studied, an intriguing issue becomes apparent, namely the mismatch between AV conduction time and heart weight. As Clark wrote in 1927, "The most striking thing is that the PR interval varies so little in different animals" (31). Thus the P-R interval of the elephant is only 10 times longer than the P-R interval of the rat, whereas the heart of the elephant may weigh 20,000 times as much as the rat heart. The P-R interval of the electrocardiogram consists of two components: the A-H interval (the time needed for the impulse to traverse the AV node) and the H-V interval (the time required for the impulse to travel from the atrioventricular bundle, or His bundle, to the first part of the ventricular myocardium to be activated). In Figure 1, P-R intervals for different animals are plotted against the third root of heart weight [data were obtained from Altman and Dittmer 1971 (6); it must be emphasized that the graph should be interpreted with caution because for most species the data for P-R interval and heart weight were derived from different sources]. When we compare P-R intervals with the size of the heart (roughly equivalent to the third root of heart weight), we cannot but come to the conclusion that in larger animals the relative value of AV nodal delay decreases (113, 114). It may be speculated that in very large mammals, such as the blue whale, the major part of the P-R interval is occupied by the time needed for the impulse to traverse the His bundle-Purkinje system and that AV nodal delay contributes but little. It is clear that in small mammals, where conduction time in the ventricular conduction system may take no more than 2–5 ms, an AV nodal delay is necessary to ensure that ventricular contraction does not begin before atrial contraction has ended. If in large animals the necessity for AV nodal delay diminishes, because activation of the His-Purkinje network consumes progressively more time, what then is the function of the AV node in these species?

It has been known for a long time that a minimal mass of cardiac tissue is required for fibrillation to occur (49) and that hearts of large animals fibrillate more easily than hearts of small animals (112). Atrial fibrillation is

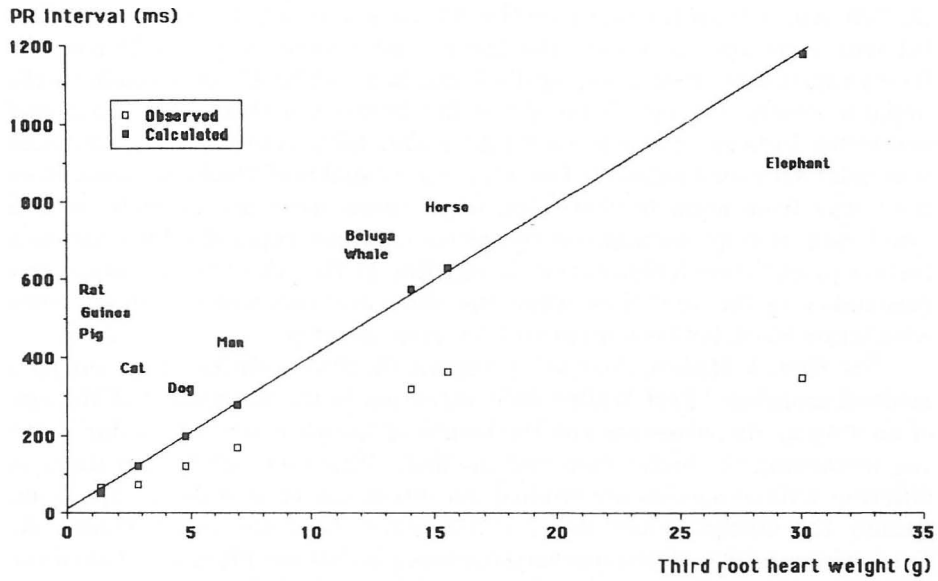

FIG. 1. Plot of P-R interval in the electrocardiogram versus the third root of heart weight in various animal species. Calculated values (■) assume a linear relationship between the 2 parameters. Observed values (□) were obtained from Altman and Dittmar (6) and show a mismatch between heart size and atrioventricular conduction time in large mammals.

a common arrhythmia in humans, especially in the elderly, and also in large domestic animals that are allowed to reach an advanced age, such as dogs and horses (41, 116, 138). A second generally accepted aspect is that the main task of the AV node in large mammals is to protect the ventricles against atrial fibrillation. These comparative aspects of AV nodal function, speculative though they may be, prompted us to review the literature on AV nodal morphology and electrophysiology. In particular, we concentrated on the factors responsible for AV conduction delay and block and considered mainly those studies employing microelectrodes to study AV nodal function at the cellular level. As will become apparent, there are insufficient data to substantiate our views or to provide adequate explanations for the possibly different behavior of the AV node in large and small mammals. Previous reviews on functional and morphological aspects of the AV node during the past 30 years can be found in References 16, 30, 59, 77, 124, 162, and 177.

II. RELATIONSHIP BETWEEN MORPHOLOGY AND ELECTROPHYSIOLOGY

A. *Morphology*

1. Different cell types within the AV node

Tawara (174) examined the hearts of the dove, rat, guinea pig, rabbit, cat, dog, sheep, calf, and human and found in all these species essentially the same structure in the anterior part of the base of the interatrial septum. He

described a spindle-shaped compact network of small cells. These cells were connected via "Knotenpunkten" in which four to five fibers were often joined together. It was apparently this characteristic that prompted him "for simplicity's sake" to call this compact network "Knoten" ("node"). It must be emphasized that in addition to this compact node, Tawara also described what we now call "transitional cells." In this transitional zone, between atrial musculature and compact node, "the cells are very small. They do not form a complicated network, but course more or less parallel to the posterior part. They are joined into several small bundles, separated by strands of connective tissue, which in this area is abundant" (p. 136). "These bundles reach the floor of the coronary sinus" (p. 137). "These bundles are connected to ordinary atrial muscle . . . these connections are so gradual that no sharp boundary can be detected. . . . Either single cells become gradually larger and change inconspicuously into atrial fibers, or several small bundles gradually join into a broader bundle which then merges with atrial muscle" (p. 137). He also mentions that the change between "atrial and ventricular part" was gradual on the cellular level and stated, "I set the boundary at the site where this system penetrates into the membranous septum" (p. 127). Furthermore, he wrote that there is a large variability between individual hearts of the same species: "the network in the human is relatively small, but may in individual cases be very different" (p. 150; all quotations are in our translation). It is surprising that, despite Tawara's extensive and very accurate description, subsequently a great deal of confusion has arisen concerning the definition of the AV node as given by morphologists and electrophysiologists. The latter tend to define the AV node as the "area where the functional delay between atria and ventricles occurs" (58) and the former as the knot of densely packed small cells, described by Tawara as Knoten. Despite Tawara's often repeated statement that on the atrial side no sharp boundary between atrium and beginning of the AV nodal area can be given, a statement fully endorsed by later comparative studies (181), many subsequent morphological studies only considered the Knotenpunkten area, ignoring the zone of transitional cells. Some authors even denied the existence of the AV node (50). To confuse matters even further, Tawara found continuity between the AV node and the orifice of the coronary sinus. Specialized fibers were found in the coronary sinus by Koch (88) in 1907. The floor of the coronary sinus was described as a region with pacemaker activity and was even considered by Koch to be the normal pacemaker of the heart. Recent studies (206) have indeed confirmed that, especially in the presence of catecholamines, spontaneous and triggered activity can occur in fibers in the floor of the coronary sinus, well outside the area that is now defined as the AV node. As Cranefield (35) recently stated, "the confusion introduced by Tawara persisted so that we are never quite sure, when an author speaks of the coronary sinus as the origin of a rhythm, whether he did or did not mean to distinguish it from the AV node."

Rather than review all morphological studies performed in this century on the AV nodal area [the early literature has been excellently reviewed by

Scherf and Cohen (162)], we focus on recent studies, where, despite some differences in nomenclature, there is agreement about a subdivision of the AV nodal area into several regions (8, 10, 11, 16, 19, 42, 55, 99, 103, 139, 145, 177, 182, 191). It may be emphasized that only very time-consuming three-dimensional reconstructions based on serial sections give a complete picture of nodal architecture (11, 101, 171, 177).

2. Architecture of the AV node

The AV nodal area is located in a triangular region, the triangle of Koch (89), with the apex being the membranous septum, the inferior border the attachment of the septal tricuspid leaflet, and the superior border a strand of fibrous tissue extending from the central fibrous body to the sinus septum above the ostium of the coronary sinus, known as the tendon of Todaro. In the rabbit heart the AV nodal area can be divided into two regions: a posterior open node and an anterior closed node, surrounded by a collar of fibrous tissue formed by the fibrous annulus and an extension from the central fibrous body (8, 11, 19, 42, 177; Fig. 2). Fibers overlying this fibrous collar end in the base of the septal tricuspid valve leaflet and do not make contact with

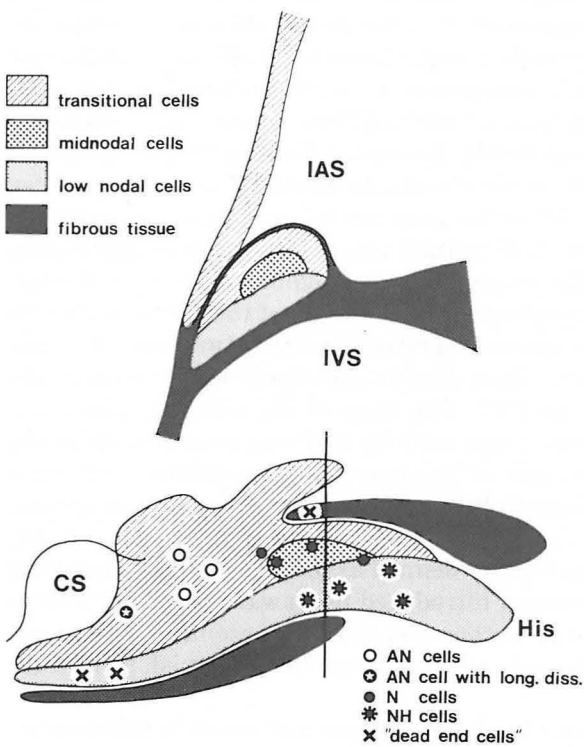

FIG. 2. Diagram showing distribution of morphologically different cell types in rabbit AV node. *Top*: transverse section showing trilaminar appearance of anterior part of the node. Level of sectioning is indicated by a bar in the bottom panel. *Bottom*: diagram of AV node indicating sites where typical transmembrane potentials were recorded (see sect. II*C*; AN cell with long diss, recording of an action potential with double components, indicative of longitudinal dissociation). CS, coronary sinus; IAS, interatrial septum; IVS, interventricular septum; His, His bundle. [From Janse et al. (76).]

the underlying cells of the AV node. The posterior, open node receives atrial inputs along its upper and posterior margins.

3. Histology of the AV node

In essence, the atrioventricular junction consists of five histologically different cell types: *1*) transitional cells between atrial myocardium and so-called midnodal cells, *2*) midnodal cells, *3*) lower nodal cells, *4*) cells of the penetrating AV bundle embedded within the central fibrous body (also called the bundle of His), and *5*) the cells of the ventricular bundle branches. We confine ourselves to the first four cell types.

Transitional cells are distinguished from atrial cells by their smaller size, their pale staining reaction, and by the fact that they are separated from each other by connective tissue septa. Three groups of transitional cells have been described in the rabbit heart (11): *1*) a posterior group merges with atrial myocardium beneath and behind the coronary sinus; *2*) a larger middle group, anterior to the ostium of the coronary sinus, is in contact with the atrial myocardium of the sinus septum and the deeper layers of the left side of the interatrial septum; and *3*) an anterior group merging with the atrial tissue at the junction with the closed node. There is a large variability in the extent of these three groups from heart to heart so that exact dimensions of these different groups of transitional cells cannot be given (177).

Midnodal cells are closely packed together with little intervening connective tissue. For this reason the zone of midnodal cells is also called "compact node." It corresponds to the Knoten of Tawara. Midnodal cells contain few myofibrils, which are randomly arranged (8, 42). As one approaches the compact node, nexuses become smaller in size and scarcer (42, 82).

Lower nodal cells form a bundle extending throughout the length of the AV node parallel to the AV ring. This bundle is very thin posteriorly. Within the region of the open node, no contacts between lower nodal cells and transitional cells are apparent (177). The bundle increases its diameter as it approaches the region of the closed node. In this region the bundle is in contact with both transitional and midnodal cells. Lower nodal cells are smaller than atrial cells and are elongated. Fibrous tissue septa separate individual cell groups into bundles (8). Anteriorly the lower nodal cells are continuous with the AV bundle. There is no sharp transition from lower nodal cells to AV bundle. At its beginning the AV bundle contains both cells with small diameter and cells with large diameter (9, 177). The cells with large diameter resemble ventricular Purkinje fibers and are connected by frequent and large areas of nexus formation (177).

Generally speaking, a similar arrangement also seems to be present in the AV nodal region of other species, including humans (9, 181, 182), although it has been stated that "the subdivisions employed in the rabbit heart could not be well differentiated in the cat heart" (169). In the ferret heart, a

division has been made in a transitional zone, a deep and superficial zone of "AV nodal cells," and the cells of the AV bundle (103, 180). While deep and superficial AV nodal cells are similar and may be compared with the midnodal cells described in the rabbit heart, the superficial cells have the smallest percentage of gap junctions, desmosomes, or fasciae adherentes, as well as the smallest fractions of cell membranes apposed to adjacent cells (103).

There is some degree of controversy regarding the following issues: the nature of atrial overlay fibers and bypass tracts, the nature of the inputs into the AV node, and the significance of so-called "P cells" and "intercalated clear cells."

4. Atrial overlay fibers and bypass tracts

In the rabbit heart, a superficial layer of atrial and transitional cells up to ~0.06 mm thick overlay the enclosed node, running perpendicularly to the fibrous annulus. De Felice and Challice (42) mention that occasionally these overlay fibers appear to make contact with atrial or nodal tissue beneath, but generally they are not in contact with underlying tissue (11, 42, 177). Atrial overlay fibers were found in the human AV nodal area (181, 182) near the orifice of the coronary sinus and above the annulus near the AV node and "have no consistent pattern or direct continuity with the AV node" (181). James described in the hearts of human, cow, dog, and rabbit (68, 70–72) a "bypass tract" consisting of atrial and Purkinje fibers descending from the right atrial endocardium, bypassing most of the node, and making contact with the inferior margin of the AV node. Rarely, these bypass fibers penetrated directly into the crest of the interventricular septum. Such bypass tracts, as a feature of the normal AV node, have not been found by others (9, 16, 126). Because of the functional implications of the term bypass tract, namely that impulses from the atrium can be transmitted without delay to the beginning of the atrioventricular bundle or the ventricular septum, it is useful to use a strict definition. As already said, it is difficult to define the beginning of the AV bundle on the basis of histological criteria alone, since both small nodal cells and larger cells are present (9, 174, 177). The beginning of the AV bundle has been defined as the point where the nodal-bundle axis becomes enveloped in the fibrous tissue of the central fibrous body (9, 174). Sometimes, this fibrous tissue is poorly formed in the human heart, but no contact is present at this point between atrial tissue and nodal or bundle tissue. A bypass tract, truly bypassing the AV node, should contact the nodal-bundle axis distal to this site. Such bypass tracts have been described in rare cases in humans (26). As suggested by Anderson et al. (9), the bypass fibers described by James could be the same as some of the transitional fibers that Anderson and colleagues found in the human heart. These transitional fibers make contact with the compact node posteriorly, superiorly, and deeply. As in the rabbit heart, transitional fibers were delineated in an

anterior and a posterior group, where the anterior group had a superficial and a deep portion. It was emphasized that the left atrial myocardium made contact with the compact node via the deep segment of these transitional fibers. It has been stressed that the AV node is an interatrial structure and not a right atrial structure (9, 162).

5. AV nodal inputs

When the input into the AV nodal area is considered, there is, on the one hand, the concept that it consists of the terminal portions of the three so-called internodal pathways described by James (69) and, on the other hand, that atrial and transitional fibers make contact over a broad area, even though a separation between a posterior and an anterior input region exists. Three-dimensional reconstructions of the human AV nodal area by several authors show a similar structure (9, 182) and can be diagramatically depicted as shown in Figure 2. As will be discussed in section II*B*, studies in which the activation pattern of the AV nodal area of the rabbit and the dog heart were described are in good agreement with this general scheme, although there are no studies in which the spread of activation from left-sided atrial myocardium into the node was examined.

6. P cells

Some confusion exists concerning the existence and role of P cells, Purkinje cells, and clear intercalated cells. On the one hand, P cells have been described as "a small round pale cell with randomly distributed sarcosomes and sparse myofibrils" (73), and it has been suggested that they are the pacemaker cells of the AV nodal-His bundle junction (73, 168). It is quite possible that they are the same as midnodal cells. On the other hand, large Purkinje-type cells have been described as being part of the internodal pathways converging onto the atrial margin of the AV node (69, 168), and it is not always clear whether P stands for pale, pacemaker, or Purkinje. Some authors failed to find either small P cells or larger Purkinje-like cells (9, 16, 182); others found intercalated clear cells, which, however, were not "preferentially located in so-called internodal tracts" (191). The morphological appearance of these cells (poor content of myofibrils, showing no organization, clear spaces, large nuclei, swollen mitochondria) could be the result of osmotic swelling and could have an artefactual origin (177).

7. Scarcity of intercellular contacts

One morphological feature, which may be important in explaining the nature of the AV nodal delay, namely the scarcity of nexuses, has been

observed in the AV node of the monkey (82, 191), guinea pig (84), cow (53), mouse (175), bat (82), and dog (54, 168). In the dog AV node, some cells were even said to have no nexuses at all (168). Classical intercalated disks were not observed in transitional cells, deep and superficial AV nodal cells, or in the beginning of the AV bundle (82, 103, 175). However, desmosomes, fasciae adherentes, and gap junctions often appear as a junctional complex (103, 175). The length and percentage of the plasma membrane occupied by these junctions decrease progressively from transitional cells to superficial cells of the midnodal area [in this study (103) the midnodal cells are called AV nodal cells] and then increase progressively from deep nodal cells to the AV bundle (103). The functional counterpart of the scarcity of junctional complexes, increased coupling resistance between AV nodal cells, is discussed in section v*B*.

B. Pattern of Excitation of the AV Node

There are only a few studies in which extracellular electrodes were used to record directly from the AV node (4, 5, 47, 150, 161, 170, 187). The interpretation of most extracellular waveforms recorded from the nodal area is very difficult. This is because the rate of change of the extracellular potentials is very slow (161) and activation of the AV node is a three-dimensional event, where at one location superficial cells may be excited much earlier than deeper ones (77). There is only one study in which intra-and extracellular recordings were made simultaneously from the AV node (170). In this study, extracellular electrodes with very fine tips (50-μm diam) were used, and it could be shown that "the time of the fast downstroke of the extracellular wave form was just as accurate as using the time of the upstroke of the intracellular waveform" (170). It must be said here that the time of activation is difficult to define, even when one uses intracellular recordings for cells with action potentials having very slow upstrokes. Some authors have chosen the moment when the action potential upstroke has reached the level of 50% of the total amplitude of the action potential (77, 186); others chose a level of 20% of the amplitude (18). These methodological differences may account for some of the discrepancies found in the different studies. In the study of Spach et al. (170), it was found that whenever extracellular waveforms with multiple deflections were recorded at the junction of atrium and AV node, the initial rapid deflection originated from superficial atrial tissue and the second, usually slower deflection was from underlying AV nodal cells. Activation maps were constructed from both the rabbit and the dog AV node (puppy and adult), and the maps agree well with activation maps based on microelectrode recordings in the rabbit AV node (18, 19, 77, 186). In both rabbit and dog hearts, there are two atrial inputs into the AV node, one posterior from the crista terminalis and one anterior from the anterior lower interatrial septum. (As mentioned earlier, all published studies utilizing extra- or intracellular electrodes approach the AV node from the endocardial side of the right atrium, and no studies are available in which connections

between left atrial tissue and AV node were investigated electrophysiologically.) The transition from atrial to AV nodal activation was smooth rather than abrupt, the terminal atrial tissue overlapping the beginning of AV nodal tissue. The input area (earliest AV nodal wavefront) had a width of 7 mm in the 6-day-old puppy, 18 mm in the adult dog, and 5 mm in the rabbit. This wave front was oriented parallel to the AV ring. In the upper region, extracellular activity showed components attributable to both atrial and nodal tissue, where the first diminished and the second increased as the electrode approached the AV ring. No detailed information about activity within the central (or compact) node can be obtained, however, from the extracellular recordings, and for this microelectrode studies have to be consulted. Excitation maps based on microelectrode recordings from the AV nodal area are only available for the rabbit heart (18, 19, 77, 145, 186, 196). Figure 3 shows a typical example of the activation of the AV nodal area of a rabbit heart during spontaneous sinus rhythm. Each circle indicates a site where a transmembrane potential was recorded. The activation sequence is depicted in 20-ms intervals, where *time zero* was the activation time of an extracellular electrode close to the sinus node. The main features of normal antegrade AV conduction are as follows.

1) There is a dual input into the AV node, a posterior input via the crista terminalis entering the node beneath the ostium of the coronary sinus and an anterior input entering the node as a broad wave front from the interatrial septum.

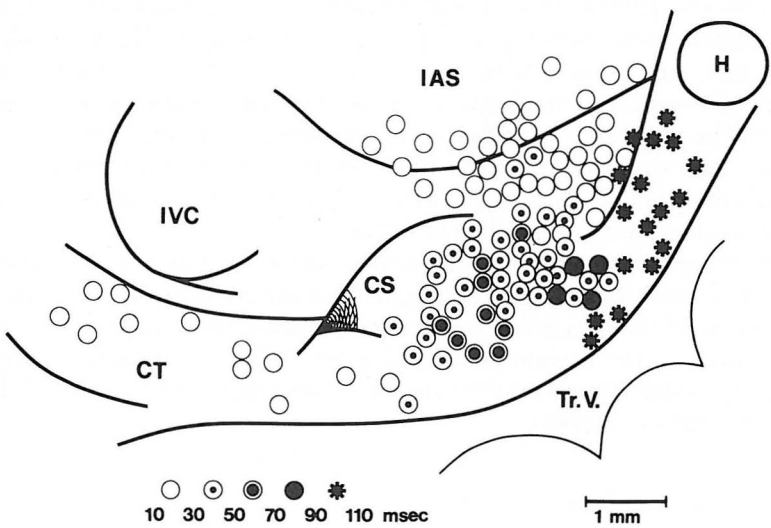

FIG. 3. Map showing sequence of normal antegrade activation of rabbit AV node. Symbols indicate position of AV nodal cells from which action potentials were recorded and also in which 20-ms interval these cells were activated. Note dual input into AV node. CT, crista terminalis; IAS, interatrial septum; CS, ostium of coronary sinus; Tr V, tricuspid valve; H, position of extracellular electrode on His bundle. [From Janse et al. (76).]

2) The activation pattern in the center of the node is difficult to follow, and isochronal lines cannot be drawn. This is partly because at one location superficial cells may be activated up to 40 ms earlier than deeper cells. The speed of propagation is slow; it takes some 60 ms to cover a distance of ~1 mm, which corresponds to a conduction velocity in the order of 1.7 cm/s.

3) In the last part to be activated (at 90–110 ms), activation is rapid and synchronous. There is a sharp division between cells activated early and cells activated late. The anterior input does not bypass the central node but curves in a posterior direction to merge with the posterior input.

One feature of AV nodal activation is not apparent from Figure 3, namely the existence of dead-end pathways (186). These consist of cells that, although excited, do not participate in transmitting the impulse from atria to ventricle and vice versa. They can be identified when the moment of excitation of a cell belonging to a dead-end pathway is expressed as a percentage of the atrium-His bundle and His bundle-atrium conduction time during antegrade and retrograde conduction, respectively. The sum of these times for a cell in the nodal mainstream is ~100%. For dead-end pathway cells this sum far exceeds 100%, indicating that they are activated "too late" in both modes of conduction. Two types of dead-end pathways have been identified in the rabbit AV node (11, 186), one consisting of anterior overlay fibers terminating in the base of the septal leaflet of the tricuspid valve, the other branching off from the central node and continuing in the posterior extension of the bundle of lower nodal cells. Cells in the posterior tract of lower nodal cells have been identified by the injection of cobalt ions through the recording microelectrode. They showed a fully developed action potential in the presence of conduction block in the distal, anterior AV node during a Wenckebach phenomenon, indicating that the excitatory wave within the posterior extension was of insufficient strength to excite the much larger anterior part of the tract. The functional significance of dead-end pathways is unclear, but it has been suggested that they can be expected to draw local circuit current during normal conduction and must therefore represent an additional reason for slow conduction through the node (199).

For retrograde conduction, the activation pattern of the AV node is in essence reversed. However, the retrograde activation pattern is not the exact mirror image of the antegrade conduction sequence (80) in the sense that the earliest "exit" to the atrium is located anteriorly to the ostium of the coronary sinus, so that the interatrial septum is activated much earlier than the crista terminalis (170, 186).

C. AN, N, and NH Zones

Paes de Carvalho and de Almeida (145) divided the AV nodal area into three zones, based on activation times and transmembrane potential characteristics, and since then, their terms AN (atrionodal), N (nodal), and NH

(nodal-His) cells, or zones, have been widely used. The definitions are not always very strict. In the original report, the N zone was the area where slowing of conduction velocity and of action potential upstroke velocity was maximal, accounting for a 25- to 30-ms delay (corresponding to a conduction velocity of 2 cm/s). The AN zone was a transitional region between fast conducting atrial muscle (70 cm/s) and the N zone. Within the AN zone, changes in conduction velocity and maximal upstroke velocity were gradual. The NH zone was a transitional zone between N zone and His bundle, where changes were again smooth. Several attempts have been made to arrive at a more precise classification. One such classification was based on the response of the AV node during a 3:2 Wenckebach-type block, evoked by rapid stimulation of the atrium or His bundle (retrograde Wenckebach) (11, 77). Atrionodal cells during an antegrade Wenckebach were proximal to the zone of block, and, regardless of conduction delay or block further downstream, the interval between atrial activity and action potential upstroke was constant. The action potential upstroke of N cells, which always is slow, changed with each beat of the Wenckebach cycle: the upstroke became slower, showed notches or double components, and the action potential became smaller until finally a low-amplitude nonpropagated local response was present. Nodal-His cells were distal to the zone of block. Their upstrokes were faster than those of N cells. The most complete classification to date is given by Billette (18). This author based his division of AV nodal cells on action potential configuration, activation time, and changes during premature atrial stimulation. He distinguished between AN, ANCO (AN cells with an action potential upstroke that has two components), ANL (late AN), N, NH, and H (His bundle) cells. Action potentials of AN cells had a phase 1 and a plateau. Their timing with respect to an atrial reference was constant during premature stimulation. The ANCO cells had a similar timing but a lower amplitude and a notch on the upstroke. Late AN cells had a lower upstroke velocity, no phase 1, and were intermediate between AN and N cells. The lowest upstroke velocities were found in N cells, which also had a more positive resting membrane potential and a greater prematurity-dependent increase in action potential duration. During premature atrial stimulation, action potential amplitude of N cells decreased, and the response dissociated into two components. Activation times of N cells were linked to those of AN, ANCO, and ANL cells, all of which increased only slightly with premature stimulation. Activation times of NH cells increased markedly with prematurity, and the second component of the N cell action potential was linked to the upstroke of NH action potentials. Similar double components, attributed to electrotonic interaction with adjacent tissue, have been recorded by a number of authors (3, 63, 74, 105, 106, 122, 123, 139, 145, 159, 193, 195). Action potentials from H cells had a long duration and a temporal proximity to the His bundle potential recorded with an extracellular electrode. It was emphasized that the distribution of these cell types varied considerably from one preparation to another. Examples of these different AV nodal action potentials are shown in Figure 4; the distri-

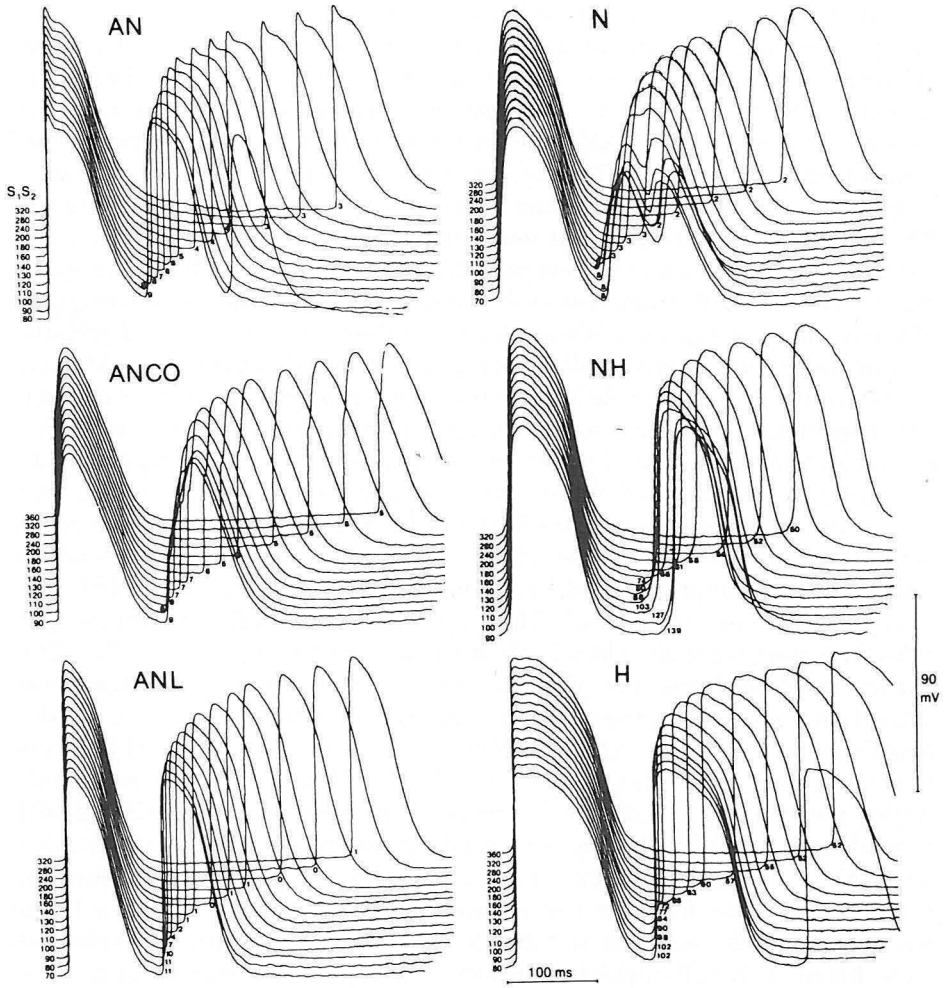

FIG. 4. Action potentials of 6 types of AV nodal cells during periodic premature stimulation of the right atrium. Each section was obtained by superimposing [in decreasing order of coupling stimulation intervals (numbers at left in ms)] tracings corresponding to last basic and premature beat. Base line of each subsequent tracing was shifted downward to help distinguish potentials. Numbers associated with premature action potentials indicate activation times in ms with reference to interatrial septum. Action potential after premature potential in lower trace in AN (atrionodal) and H (His) was caused by an atrial reentrant beat. Note double components in N (nodal) cell of early premature responses. ANL, late AN cells; ANCO, AN cells with action potential upstroke with 2 components. [From Billette (18).]

bution of these cells is shown in Figure 5. Several studies have been performed on single cells isolated from the AV node (79, 140, 141, 173). It is, however, impossible to make correlations between the action potential recorded from single cells and the configuration of AN, N, and NH action

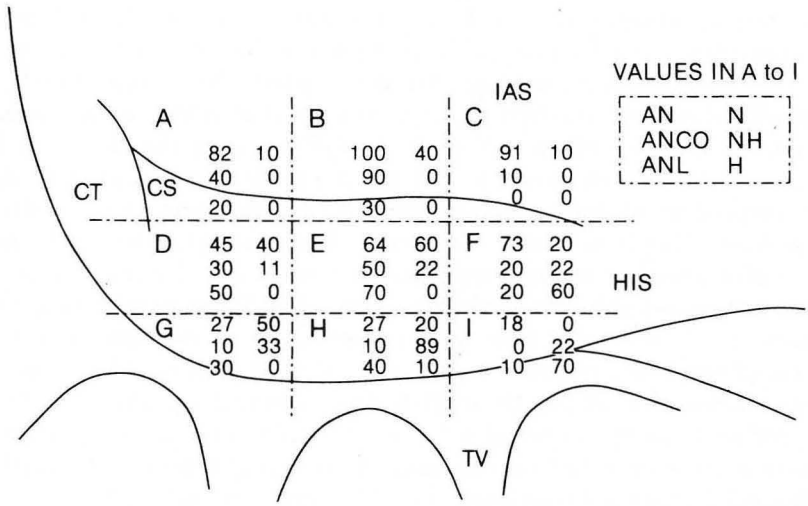

FIG. 5. Topographical distribution of various functionally defined cells in rabbit atrioventricular node. Node is subdivided into 9 sections, A–I, by broken lines. In each section, the percentage of preparations in which each cell type (listed in inset) was present appears in same order. Note overlap in cell distribution. CT, crista terminalis; IAS, interatrial septum; His, His bundle; TV, tricuspid valve. [From Billette (18).]

potentials in intact preparations because it cannot be determined from which zone of the AV node the isolated cells were obtained.

When the characteristics of transmembrane potentials recorded from the AV node are considered, it should be realized that almost without exception, studies employing microelectrodes used isolated preparations that were superfused with oxygenated solutions in a tissue bath. These preparations have the disadvantage that, especially when they have been superfused for several hours, hypoxic cell damage may be present at depths >100–150 μm below the surface of the preparation (76). The possibility exists that even when microelectrode recordings are made from superficial well-oxygenated cells, their action potential configuration may be influenced by electrotonic interaction with deeper hypoxic cells (178).

D. Anatomic and Electrophysiological Correlations

When comparative studies of the AV node are considered in an effort to understand why there is so little variation in P-R interval between very small and very large animals, two considerations must be made. The first one regards the dimensions of the AV node, and we quote Truex and Smythe (181), who in their comparative study confirmed in essence what Tawara had also observed, "The atrial margins of the AV node are not sharply defined macroscopically and one would have considerable difficulty stating precisely

where the node stopped and the AV bundle began. It is our opinion that gross measurements of the AV node, or the length and diameter of the AV bundle, mean very little." The second consideration regards the concept (hardly ever specifically stated but implicit in most reports) that cells with a specialized function (in the case of the AV node slow conduction, the ability to block impulses at short cycle lengths, and the property of automaticity) should have morphological characteristics distinguishing them from "ordinary" myocardium. This is not necessarily true. For example, cells in the mitral valve leaflet showing automaticity and triggered activity are morphologically undistinguishable from ordinary atrial fibers (208). In very early stages of embryonic development a delay in the activation of atria and ventricles is present, of the order of 100 ms (127, 146). Recent studies (14) of the chick embryo showed that at the 45- to 47-h stage, conduction velocity in the AV canal region is in the order of 0.7 cm/s, whereas in ventricle and atrium conduction velocity is 10 times greater. At this stage there is no particular histological feature distinguishing the AV canal region, which is a circular band of 75–100 μm, from neighboring cardiac regions. Transmembrane potentials from the AV canal zone have smaller amplitudes, lower upstroke velocities, and longer durations than action potentials from atrial or ventricular cells. In later stages, conduction velocity in the AV canal region increases somewhat (to 1.5 cm/s), while the increase in atrium (15.8 cm/s) and ventricle (12.8 cm/s) is more marked. Morphologically, the AV canal begins to show some changes after 96 h, the most conspicuous change being enlargement of intercellular spaces. These findings should make it clear that the differentiation into cells with small action potentials with slow upstrokes that conduct the impulse slowly occurs at a time when no histological identifiable features distinguish them from their neighbors with fast action potential upstrokes. There is therefore no compelling reason why, in the adult heart, the region between atria and ventricles where the impulse conducts slowly should consist entirely of cells that are morphologically distinct from atrial or ventricular cells. Despite these considerations, it must be said that in the few adult hearts studied, there seems to be a fairly good correlation between the morphological and the electrophysiological AV node.

Several attempts have been made to correlate AV nodal architecture and electrophysiology (11, 19, 39, 42, 139, 145, 160, 168, 172, 178). As indicators of microelectrode position, the glass left behind in the preparation (42) and the mark produced on the endocardial surface (39) have been used. These are not very accurate markers of the microelectrode tip position, since there may be large discrepancies between the actual tip position and the endocardial entrance site (178). Sano et al. (160) injected ferricyanide solution via the recording microelectrode and visualized it with ferrous chloride applied endocardially. A blue ring formed at the boundary between the two solutions. The authors stated that the typical nodal action potential (slow upstroke, low amplitude, "step" on the upstroke) originated from "the atrioventricular node or at least from the special junctional tissue adjacent to it." They

examined 23 AV nodal preparations from the dog heart and never found these potentials to originate from ordinary atrial muscle fibers, "although it was fairly difficult to make such a negative statement because of the infrequent formation of the blue ring." Three studies report on marking the microelectrode tip position by filling the microelectrodes with a cobalt-containing solution and by electrophoretically injecting cobalt after recording an AV nodal transmembrane potential from an isolated, superfused rabbit heart preparation (11, 139, 172). The cobalt was subsequently identified histologically, at best in 20-μm cryostat serial sections (11). Although this method allows action potentials of different configurations to be correlated to nodal architecture, identification at the cellular level was not possible. In one study, action potentials were recorded from a coronary-perfused rabbit heart preparation. After the recording, the preparation was immediately fixed by perfusion of the coronary arteries with glutaraldehyde while the microelectrodes remained in place. After withdrawal of the microelectrode, the track of the electrode could be followed in 4-μm serial sections, and the very cell recorded from could be identified (178). Although this method would seem to be the ideal one for correlating cellular electrophysiology to cellular morphology, it is a very time-consuming one, and a complete inventory of the AV node seems a herculean task. The results of these studies may be summarized as follows. AN potentials were recorded from transitional cells and NH potentials from the anterior portion of the tract of lower nodal cells. Dead-end pathway cells were identified in the anterior overlay cells and in the posterior extension of the lower nodal cells. Nodal potentials were recorded from the central AV node, where open and closed node meet; they could be recorded from transitional cells (11) and also from cells in the beginning of the atrioventricular bundle (178). Thus far, it has not been demonstrated unequivocally that N potentials originate from midnodal cells, and we are faced with the paradoxical situation that the most "typical" nodal action potential has not yet been linked to the most "typical" nodal cell.

III. WHERE IS THE SITE OF CONDUCTION DELAY AND BLOCK?

There is some disagreement about the contribution of the different zones of the AV node to the conduction delay of a normally propagating impulse from the atrium. Some studies indicate that a large fraction of the basic delay takes place in the AN zone (19, 77). During the first beat of a 3:2 Wenckebach type of conduction block, produced by rapid pacing of the atrium in an isolated rabbit heart preparation, atrial activation occupied the first 20% of the total atrium-His bundle interval, activation of the AN zone was from 20 to 80%, activation of the N zone was from 70 to 98%, and activation of the NH zone was from 93 to 100% (77). In a later study on the isolated rabbit heart, excitation of the proximal node (AN, ANCO, and ANL cells) accounted for ~25% of the basic delay, whereas the central node (N cells)

was the main source of the conduction delay (18). Possibly these different results are related to differences in definition of "moment of activation" of an AV nodal cell.

There is less conflicting evidence regarding the site of cycle length-dependent AV nodal delay. Studies in which activation patterns were recorded during the Wenckebach phenomenon elicited by rapid pacing of atrium or His bundle (retrograde Wenckebach block) or in which during regular atrial pacing a train of five premature stimuli was delivered (18, 19, 77) all point to the N zone as the area where cycle length-dependent delay is produced.

Analysis of clinical electrocardiograms of complex arrhythmias had long ago provided evidence that conduction block could occur at different levels of the AV node (81). This was also suggested by microelectrode studies showing that during rapid atrial stimulation successively blocked impulses could give rise to local responses within the AV node of varying amplitude and configuration (134, 194). Later, the spread of activity within the AV nodal area was mapped when, during regular atrial pacing, atrial premature beats with three different coupling intervals were introduced after every 10th regular beat (77, 176). All three premature beats failed to reach the His bundle. The "late" premature beat was blocked in the N zone, the earlier premature beats in the AN zone.

IV. WHAT IS THE MECHANISM OF AV NODAL DELAY?

A. Decremental Conduction Versus Electrotonic Transmission

Hoffman and Cranefield (59) introduced the concept that the normal delay in the AV node is due to slow conduction that could be decremental. "By decremental conduction we may understand a type of conduction in which the properties of the fiber change along its length in such a manner that the action potential becomes progressively less effective as a stimulus to the unexcited portion of the fiber ahead of it. . . . Since the efficiency of the action potential as a stimulus depends on its amplitude, upon its rate of depolarization, upon the extent to which the depolarization it causes reaches ahead, and upon the threshold of the fiber, a progressive change in any of these factors might cause decremental conduction. The propagation of an impulse decrementally differs from the electrotonic spread of an impulse into an inexcitable fiber, in that, in decremental conduction, at the point at which block occurs, the fiber is excitable but the action potential is unable to excite it" (59). They quoted a number of findings that support this concept, but stated, "there is no demonstrative evidence to support the interpretation that conduction in the atrial portion of the atrioventricular node is in fact decremental." A key observation was that during application of acetylcholine in a dosage that blocked antegrade AV conduction and caused very small ampli-

tude responses in the N zone, retrograde excitation produced by stimulation of the His bundle produced a normal action potential in the N zone. Later studies by West and Toda (201) failed to confirm this (see sect. v*D*).

Studies by Billette and co-workers (18, 19) in which extensive mapping with multiple microelectrodes was performed during regular driving of the atrium and during application of a train of five successive premature stimuli suggested another mechanism for cycle length-dependent conduction delay. The key observation in these experiments was that, with shortening of cycle length, action potentials in the N zone dissociated progressively into two components that were synchronous with late AN and early NH activity, respectively. No action potential upstrokes were found occurring during the interval between these two components. The increase in AV nodal transmission time with shortening of cycle length was due to "stagnation" between N and NH zone. This stagnation was likened to the mechanism of electrotonic transmission described for other cardiac tissues, where an inexcitable segment, interposed between two excitable regions, functions as a purely passive resistance-capacitance circuit (12, 37, 67, 200). The stagnation is caused by cessation of active transmission at the inexcitable element, which can be crossed by electrotonic current bringing distal excitable cells to threshold. This mechanism would therefore depend on N cells becoming inexcitable at short cycle lengths. It has indeed been shown that in N cells recovery of excitability occurs at a later time than completion of repolarization (125). This delayed recovery of excitability may be crucial in explaining failure of AV nodal conduction of premature or successive rapid impulses.

V. WHAT CAUSES AV NODAL DELAY?

A host of factors is involved in slowing down the cardiac impulse as it traverses the AV nodal area, and it is next to impossible to evaluate the relative contribution of each of the factors in causing AV nodal delay.

A. Fiber Diameter

It is well known that cell diameter is a factor determining conduction velocity. As pointed out by Noble (142), the differences in conduction velocity between the AV node and, for example, Purkinje fibers cannot be just the consequence of differences in fiber diameter. Conduction velocity is proportional to the square root of fiber diameter. Given a diameter of Purkinje fibers of 50 μm and of 7 μm for an AV nodal cell, the ratio of conduction velocities, if these were only determined by cell diameter, would be 2.7. The actual ratio [2–4 m/s for Purkinje fibers, 5 cm/s for AV node (58)] is much larger: 40 to 80.

B. Passive Electrical Properties

There is general agreement about a paucity of nexus connections between AV nodal cells, suggesting that coupling resistance may be high. This is confirmed by the observations of Pollack (148) that flow of fluorescein, injected into cells of the N zone, was at least three orders of magnitude lower than between cells of other cardiac tissues.

There are several studies in which an attempt has been made to determine some of the passive electrical properties of the AV node (29, 44, 65, 91). Two methods have been used. *1*) Input resistance was measured with a microelectrode connected to a bridge circuit and used to inject current and record the voltage drop from the same cell. The circuit is balanced until no square-wave deflection can be detected; the input resistance is then equal to the measured resistance minus the resistance of the microelectrode. *2*) Current pulses were applied to AV nodal cells via a small suction electrode, and the decay of electrotonic potential with distance was measured via a microelectrode. In essence, the data were analyzed by assuming that the node had a continuous geometry, a negligible extracellular resistance, and behaved as a cable, although it was realized that because no precise morphometric studies of the AV node have been made and thus very little is known about its geometric characteristics, these assumptions are gross oversimplifications (44). Other authors used a more complex analysis, based on a two-dimensional regular lattice (65) or a two-dimensional model of an anisotropic syncytium (29).

The following values for the space constant (in μm) have been reported: 430, 690, 210 $\pm$ 14 [(44, 91, 29); AN zone at input site of crista terminalis]; 286 $\pm$ 17 [(29); AN zone at input site of interatrial septum]; 176 $\pm$ 54 [(29); N zone]; 416 $\pm$ 60 [(29); NH zone]; 970 $\pm$ 64 [(29); His bundle]. The latter study (29) is the only one in which the space constant was measured in two directions, more or less corresponding to longitudinal and transverse directions with respect to fiber axis (the data mentioned above refer to "longitudinal" values). Throughout the node electrotonic anisotropy was found, and in some parts (the input zone from the crista terminalis and the lower node) no electotonic current flow was found in the "transverse" direction in a large percentage of preparations. Space constants reported for other cardiac tissues (in μm) are generally higher: atrial muscle 790 $\pm$ 150 (29) and 660 (23); ventricular muscle 357 (87), 880 (198), and 580 (38). The low value for the space constant of ventricular muscle (357 μm) found by Kleber and Riegger (87) deserves special mention. This value was obtained from experiments on arterially perfused papillary muscles, without the presence of a fluid layer (always present in superfused preparations) acting as an extracellular shunt resistance. In densely packed tissue, extracellular resistance has a value similar to that of intracellular resistance (87). When the space constant was recalculated for the case of a superfused preparation (infinite volume conductor), the value became 528 instead of 357 μm (86). Thus it may be assumed

that in intact hearts the space constant of the densely packed central or compact node, lying deep beneath the endocardial surface where extracellular resistance certainly is not zero, is much smaller than the values quoted above.

Input resistance of N cells was higher than for other cardiac tissues: (in kΩ) for N cells 880, 580 ± 70, and 1,400 (29, 44, 65); for AN cells 590 ± 36, 410 ± 36, 700 (29, 65); for NH cells 390 ± 5, 800 (29, 65). Calculations of specific internal resistance gave values varying from 1.2 (29) to 3.3 kΩ · cm (91), which is markedly higher than values for other cardiac tissue [cf., e.g., 0.165 KΩ · cm for arterially perfused papillary muscle (87)].

Input resistance increased by the elevation of extracellular calcium and by the addition of ouabain (65). Elevation of extracellular calcium did not alter resting membrane potential and increased maximum rate of rise and amplitude of the action potential upstroke, yet it prolonged AV nodal conduction time (65). In this study, input resistance was assumed to be equal to one-fourth times the square root of the product of longitudinal intracellular resistance and membrane resistance. It was argued that the increase in input resistance was due to a reduction in cellular coupling, since elevation of extracellular calcium could be expected to decrease membrane resistance, secondary to an increase in K^+ conductance. It was therefore suggested that reduced cellular coupling could be a factor in slowing AV conduction. As pointed out by De Mello (44), the high coupling resistance makes conduction extremely vulnerable to changes in membrane resistance. Small reductions caused, for example, by acetylcholine, which decreases the space constant by 38%, could lead to failure of conduction.

In view of the uncertainties of the measurements, it is very difficult to quantify the effect of the high coupling resistance in the AV node on conduction velocity. Conduction velocity in a linear cable is proportional to the square root of the series resistor (e.g., longitudinal extra- and intracellular resistance) (66). If we assume that extracellular resistance is equal in the AV node and in, for example, ventricular myocardium and that intracellular resistance is higher by a factor of 10, conduction velocity in the AV node would be about three times less than in ventricular muscle. Since conduction velocity in ventricular myocardium is in the order of 50–60 cm/s (87), AV nodal conduction velocity would be ~20 cm/s when determined only by coupling resistance, which still is ~10 times higher than actual values observed in the N zone.

C. Nature of Inward Current in AV Nodal Cells

One of the most conspicuous features of N cells is the slow upstroke velocity of the action potential. As early as 1969, it was suggested that the slow inward current was responsible for the action potential upstroke (157, 190), and subsequent work has confirmed the dominant role of the slow inward current in the depolarization of AV nodal cells. Until now, the ques-

tion whether N cells have no fast sodium channels at all or whether they are merely inactivated by the low resting membrane potential has not been settled. Observations that support the concept that N cells are depolarized only by inward current flowing through slow channels and have no fast channels are the following. *1*) Application of hyperpolarizing current to N cells did not result in an increase in the maximum upstroke velocity (dV/dt) (57) or even decreased it (11, 120). *2*) Verapamil (205), D 600 (143), and manganese ions (213) suppressed action potentials in the N zone, whereas tetrodotoxin (TTX) was without effect (2, 143, 192, 213). In contrast to these observations are the findings of others. *1*) In several studies, the application of hyperpolarizing current resulted in an increase in the amplitude and dV/dt of the action potentials of typical nodal cells (169, 185). *2*) Voltage-clamp studies of very small pieces dissected from the AV node (91) or of single cells isolated from the AV node (141) revealed that hyperpolarization to −83 mV restored the availability of the fast sodium channels: the rate of rise of the upstroke of the "anodal break" action potential was sensitive to TTX. Previous studies in intact AV nodal preparations had shown that the action potential upstroke of AN and N cells could be divided into two components, the first one being depressed by TTX and the second one by manganese ions (158). The action potential upstroke would therefore be a mixture of fast and slow inward currents, the relative contribution of each component changing gradually as one approached the N zone, where the slow inward current was the dominant component.

Several factors make a comparison between these studies difficult. In the first place, to evaluate the effects of application of electrical current to the AV node, one has to know the resulting changes in membrane potential throughout the node. It is, for example, possible that the application of hyperpolarizing current to the N zone leads to a "reciprocal" depolarization of the proximal node. The depressed action potentials of the AN zone would then provide insufficient axial current to the N zone, with, as a result, depressed action potentials in the hyperpolarized N cells. Second, the results on isolated cells or on very small isolated pieces of AV nodal tissue can only be evaluated if it is known precisely from which part of the node these preparations have been taken. In view of the variability of the distribution of AN, N, and NH cells in the rabbit heart (18, 19), it is quite possible that late AN cells or early NH cells have been analyzed. It is noteworthy in this respect that Mendez (119) showed that, in intact preparations, hyperpolarization decreased maximal upstroke velocity in typical N cells but increased upstroke velocity in AN cells.

The recovery kinetics of the slow inward current are slow [for review see Coraboeuf (33)]. In only one study has the refractory period of AV nodal cells been determined, by applying stimulating current through an intracellular microelectrode and, after a short latency, recording from the same microelectrode (125). It was indeed demonstrated that in the N zone recovery of excitability was delayed and lagged behind full repolarization.

D. Effects of Neurotransmitters

Early studies showed that acetylcholine produced the following changes in action potentials of the AV node: slowly rising low-amplitude action potentials, with notches or slurring of the upstroke (36, 62). The notches were thought to indicate that nodal fibers were excited by impulses traveling along separate paths toward the recording site and that acetylcholine changed the timing of arrival of these wave fronts, so that they no longer reached the impaled cell simultaneously. The changes in the action potentials appeared to occur in the absence of an appreciable change in resting membrane potential (62). The depression of nodal action potential was thought to be secondary to a decrease in amplitude of the action potential of fibers at the atrial margin of the node, because during application of acetylcholine in a dosage that blocked anterograde AV nodal transmission and caused severe depression of action potentials in the N zone, retrograde excitation caused by stimulation of the His bundle still produced a full-sized action potential at the recording site (57). West and Toda (201) introduced the method of transmural electrical stimulation of intracardiac cholinergic and adrenergic nerve fibers in isolated preparations. They found that stimulation of vagal fibers induced hyperpolarization in AN, N, and NH zones, the amount being largest in the latter two zones. Atrionodal action potentials persisted despite AV conduction block, whereas action potentials from N and NH cells were abolished or severely depressed. During retrograde conduction, action potentials in the NH and N region were also abolished by nerve stimulation, although activity of the AN cells persisted at the spontaneous frequency of the sinoatrial node. These experiments indicated that the effects of acetylcholine were caused by effects of N and NH cells on the membrane. Later studies employing postganglionic vagal stimulation confirmed and expanded these results (110). Brief bursts of vagal stimulation produced hyperpolarization in the N zone, and action potentials became small and showed steps in the upstroke. The greater the hyperpolarization at the moment of arrival of an atrial impulse, the greater the prolongation of conduction time. The effects of vagal stimulation were inhomogeneous and led to fragmentation of the excitatory wave. For example, despite conduction block in the impaled fiber, conduction often continued to the His bundle, presumably using other fibers that were less affected. Second depolarizations in the response of an N fiber occurring after the inscription of the His bundle electrogram indicated possible reentry. The effects of brief bursts of vagal stimulation depended on the phase of the cardiac cycle during which they were applied: after the initial hyperpolarization (occurring with a latency of 50–75 ms), diastolic depolarization was enhanced [possibly due to activation of the hyperpolarization-activated current I_f (or I_h) (91)]. Arrival of an atrial impulse at the time N cells were more depolarized than normally led to a shorter conduction time (presumably because the difference between actual membrane potential and threshold potential for activation of the slow inward current was smaller so

that less axial current was necessary to activate the N cells). This could explain the "paradoxical" shortening of AV conduction time after a single vagus nerve volley in the in situ canine heart (104).

Whereas amplitude and rate of rise were diminished in hyperpolarized N cells, the effect of hyperpolarization on NH cells was the opposite, leading to an increase in maximal rate of depolarization (110). These results therefore support the concept that in N cells inward current is carried exclusively through slow channels, since muscarinic cholinergic substances decrease the slow inward current [for review see Reuter (153)]. The slow inward current in the AV node is carried by both calcium and sodium ions (2, 91, 192). In NH cells and also in AN cells, the contribution of the fast inward current becomes larger and larger the more removed from the N zone the fibers are.

Sympathetic stimulation and catecholamines enhance AV nodal conduction (100). Since the calcium-dependent slow inward current is increased by epinephrine (152), it comes as no surprise that catecholamines increase the amplitude and rate of rise of the upstroke of action potentials of AV nodal cells, in particular of AN and N cells, without changing maximum diastolic potential (106, 210). Furthermore, the slope of diastolic depolarization of NH cells is increased (184).

The recent finding that the cardiac nodes contain large amounts of bioactive neuropeptides that have an effect on AV nodal conduction (51, 197) may open a new field of investigation concerning the action of neurotransmitters and their modulators on cellular electrophysiology of AV nodal cells.

E. Dual Input and Summation

It has been suggested that in the AN zone excitation of a nodal cell is the result of activity arriving more or less synchronously over several afferent routes (36, 59). This suggestion was based on the observation that action potentials from the AN zone frequently showed steps or notches on the upstroke, especially under the influence of acetylcholine, and that at the time a very low-amplitude action potential was recorded during anterograde conduction under the influence of acetylcholine, a full-sized action potential could be seen during retrograde conduction. The concept that summation of impulses is an important feature in AV nodal transmission was strengthened by several subsequent observations. Thus Merideth et al. (125) stimulated nodal cells with an intracellular microelectrode and observed that successful excitation sometimes occurred without subsequent propagation to atrium or His bundle: lack of summation was thought to prevent propagation. Watanabe and Dreifus (195) showed an example where successful propagation only occurred when two apparently independent wavefronts simultaneously arrived at a junctional point. Stimulation of the interatrial septum at a rapid rate resulted in 2:1 AV block, whereas stimulation of the crista terminalis at the same rate gave rise to 1:1 conduction (74). It was suggested that stimula-

tion of the interatrial septum caused a less effective input, possibly because the wavefront gave rise to less summation than when the wavefront was elicited by stimulation of the crista terminalis. The clearest examples of summation were provided by the study of Zipes et al. (214), in which both nodal inputs were separated by making a cut through the roof and the floor of the coronary sinus. Premature stimulation of each input separately gave rise to a small-amplitude local response in a nodal cell, and simultaneous stimulation of each input resulted in a full-sized action potential, which propagated to the His bundle. Simultaneous excitation of both inputs in an intact preparation sometimes resulted in a slightly shorter conduction time to the His bundle (77, 92), but it was also observed that propagation time was considerably prolonged (77). This latter observation was explained by collision and cancellation of wave fronts in the AN zone, which caused a "weaker" wave front that eventually excited elements closer to the His bundle. It does seem that a fine tuning of wave fronts arriving over the two inputs into the node is an important factor for AV conduction. Stimulation of different input sites not only alters the sequence of AV nodal activation but also influences the refractory curve. Thus, in the rabbit, the functional refractory period is shorter when the crista terminalis is stimulated than when the interatrial septum is paced (109). Similar findings have been reported for the human heart (15). Shortening of AV conduction time in the human heart during pacing from the coronary sinus has been reported by several authors (7, 98), indicating that also in the human AV node the input site is a factor determining conduction through the node.

F. Reentry

Reentry (a conduction disturbance in which an impulse meets an area of unidirectional block, travels along alternate pathways around the area of block to activate distal tissue with delay, and then retrogradely invades the area of block to reexcite the tissue proximal to the zone of block) was considered to occur in the AV connection of the heart of the electric ray by Mines in 1913 (129). The first report on reentry in the human heart was a clinical case report by White in 1915 (202). During AV dissociation, idioventricular beats were sometimes conducted back to the atria, and the retrograde inverted P wave, was followed by a QRS complex. There was an inverse relationship between retrograde conduction time (long R-P interval) and anterograde conduction time (short P-R interval). The explanation given was that during retrograde conduction to the atrium only part of the AV node was able to conduct, the other part still being refractory. Conduction to the atrium was slow enough to enable this part to recover its excitability and to be available for antegrade conduction to the ventricles. This so-called reciprocal rhythm was studied in the canine heart in 1926 (163), and in this report the term "functional longitudinal dissociation" of the AV node was introduced. In this

study reciprocal beats [also called "return extrasystoles" or later "ventricular echoes" (153)] were elicited by premature stimulation of the ventricles under conditions whereby AV conduction was impaired. Early studies (133, 155, 169) were devoted to ventricular echoes. Reciprocation in the other direction, in which an atrial impulse turns back into the AV node to reexcite the atria as an echo, was considered at a later stage (85).

When techniques for intracardiac recording and stimulation during cardiac catheterization were developed, many reports on both atrial and ventricular echoes in humans appeared (17, 151, 164, 165). Echo beats could be elicited by premature stimulation in hearts without apparent AV conduction abnormalities, so that functional longitudinal dissociation was considered to be a property of the normal AV node (165). Animal studies, in which echoes were induced in a similar way, supported this idea (121, 128, 133). In some animal studies, it was possible to induce repetitive AV nodal reciprocation, leading to supraventricular tachycardia (78, 122, 132, 209) but in humans with normal AV nodal function this has not been observed. In patients with spontaneous paroxysmal reciprocal tachycardia, however, premature stimulation of the atrium easily induces repetitive AV nodal reentry (17, 34, 151). All these studies necessarily considered the AV node as a "black box," and the analysis of the function of the AV node consisted in essence of the measurement of time intervals between signals recorded from atrium, His bundle, and ventricles in response to various stimulation patterns of atria and ventricles. Such analysis sometimes led to the conclusion that in humans three functionally different pathways existed in the normal AV node (86, 164).

More direct evidence for functional longitudinal dissociation within the AV node was obtained from studies in which echo beats or sustained tachycardias were elicited during microelectrode recording from the AV node; all these studies were performed on isolated, superfused preparations of the rabbit heart (64, 77, 78, 107, 122, 144, 193, 209). The first direct evidence that the upper part of the AV node was functionally and spatially divided into two pathways, called α and β, was given by the experiments of Mendez and Moe (122). An atrial premature beat could be blocked in the α-pathway while being conducted via the β-pathway. Somewhere in the distal node, these pathways were joined together, and when the impulse reached the junction, the α-pathway was retrogradely excited and the impulse returned to the atrium as an echo. Many variations of this type of reentry are possible. The returning wave front through the α-pathway may fail to reach the atrium ("abortive echo" or "concealed reentry"); the atrial echo may again penetrate into the β-pathway and set up a sustained circus movement tachycardia, or it may penetrate the β-pathway but be blocked before reaching the junction with the α-pathway. It must be emphasized that, in the studies employing microelectrodes, recordings have been made from only very few cells simultaneously (from 2 to 6) and that reconstruction of the reentrant pathway depends on the assumption that the same pathway is followed during repetitive induction of the echo beat or tachycardia. In fact, in only one study was a complete reentrant pathway mapped (64). In this study, the perinodal fibers

above the ostium of the coronary sinus appeared to be an essential link of the reentrant circuit. Depending on the site of stimulation, premature atrial impulses could be blocked in one of the input regions (crista terminalis or interatrial septum) of the AV node or in the perinodal fibers. For example, during stimulation of the crista terminalis, block occurred in the input region of the crista, but conduction occurred through the perinodal fibers and the impulse entered the AV node via the interatrial septum input; reentry occurred then via retrograde conduction through the node. Surgical interruption of the perinodal fibers prevented reinitiation of the echo.

Functional longitudinal dissociation of the AV node is supposed to be the result of differences in refractory periods of α- and β-pathways, but this has never been proven. No anatomic delineation of α- and β-pathways has been found, although the two input regions could very well be their anatomic counterparts (64, 77, 107; see sect. II*A5*). Simultaneous microelectrode recordings from α- and β-pathways during a sustained reentrant tachycardia showed that both pathways were in electrotonic contact (78). It is therefore quite possible that instead of two anatomically defined pathways that are electrically insulated from each other, the complex architecture of the upper AV node, with different coupling resistances in different directions (29) and with many branching sites, could lead to functional longitudinal dissociation based on tissue anisotropy rather than on differences in refractoriness.

Reentry, whether concealed or manifest, has obvious consequences for conduction time through the AV node of both the impulse that induces reentry and subsequent impulses. When the junction of α- and β-pathways is reached by only one wave front, the excitatory current to more distal elements will be less than when both wave fronts arrive more or less simultaneously at the junction. This can lead to slower conduction or even conduction block in the lower node (185). An example in which total conduction time through the AV node was prolonged in the presence of reentry in the upper node has been published (77). In the case of concealed reentry, part of the return pathway will be refractory, and this may cause prolongation of the conduction time of a subsequent impulse.

VI. AUTOMATICITY IN THE AV NODE

Hoffman (58) and Hoffman and Cranefield (59, 60) found phase four depolarization resulting in normal automatic firing only in cells of the NH and H regions of the rabbit AV node. These findings, indicating that the pacemaker region of the AV node is located in its most distal part, have largely been confirmed by others (45, 73, 75, 196). Watanabe and Dreifus (196) found that of 290 isolated rabbit heart preparations 23 had a spontaneous AV nodal rhythm. They mapped activity of the AV nodal area in 19 of these preparations and found that in 15 hearts the NH region was the earliest activated site and in 4 hearts the AN zone was earliest. In another report (75) automatic activity in a preparation showing complete block between atrium

and the AV node was found in what was designated as an N cell. The focus could be overdrive suppressed by rapid stimulation of the His bundle. Since the authors recognized that N potentials could be recorded from the very beginning of the atrioventricular bundle (178), they agreed with Hoffman and Cranefield (59, 60) that normal automatic activity occurs in the distal AV node. In contrast to these findings are the results of Tse (183). This author exposed the AV node of isolated dog hearts by peeling off the endocardium and atrial fibers overlying the node and His bundle. He found that diastolic depolarization was present in all fibers of AN, N, and NH zones and that it was steepest in fibers of middle and lower nodal regions. All fibers showed the characteristic feature of normal automaticity, overdrive suppression (189). Often, separation of the His bundle from the rest of the preparation resulted in an increase in the firing rate of automatic AV nodal fibers. It was suggested that in intact preparations atrial muscle might prevent pacemaker activity in the upper node by electrotonic interaction with cells of AN or N zones (183). This concept is supported by studies in which AV nodal tissue was dissected into very small specimens, in the order of 0.5×0.5 mm (90, 143, 207) or in clusters consisting of a small number of isolated cells (173). Thus, in intact AV nodal preparations, average resting potential was -62 mV, whereas in the small dissected preparations it was -48.6 mV (90). Similar values were found for very small clusters consisting of 3–10 cells isolated from the rabbit's AV node (173). This partial depolarization and the fact that most of the dissected pieces were spontaneously active was attributed to the absence of electrotonic influence of the atrial myocardium, as well as to possible damage due to the dissection procedure.

It is not quite clear which currents are responsible for pacemaker activity in AV nodal cells. A voltage-dependent K^+ channel that was blocked by ATP has been described in a study applying the patch-clamp technique to single cells from the AV node (79). It cannot be determined from which zone in the AV nodal region the cells were obtained. This channel shared some properties with the K^+ channel that plays a role in generating the pacemaker potential in other cardiac tissue. However, its role in causing automaticity in AV nodal cells remains to be elucidated, since it will only contribute to spontaneous diastolic depolarization when intracellular ATP concentration falls below 1 mM (79).

Hyperpolarization of isolated clusters of AV nodal cells activated a slowly increasing inward current, the amplitude of which was much smaller than that of AV nodal or SA nodal multicellular preparations (173). This finding was taken to indicate that a hyperpolarization-activated I_f (or I_h) current did not significantly contribute to pacemaker activity (173).

VII. ROLE OF THE AV NODE IN ATRIAL FIBRILLATION

Atrial fibrillation is one of the most common arrhythmias in humans (27, 166). It is not infrequently observed in dogs and horses (21, 28, 40, 41, 111, 116, 147), whereas it is hardly ever seen in smaller animals such as cats,

rabbits, and rats (28) or dogs with a body weight below 20 kg (111). One of the important functions of the AV node is to limit the number of impulses that reach the ventricles during rapid atrial arrhythmias. This property ensures the survival of individuals suffering from atrial fibrillation.

The duration of the longest R-R intervals during spontaneous atrial fibrillation is different in various species. In the dog it rarely exceeds 1 s and in the untreated human 1.5 s; in the horse it may be as long as 3–4 s (118). This could be accounted for by an increase in the functional refractory period of the node in the larger species, by an increase in concealed conduction in the AV node or the bundle branches, or by differences in nodal architecture, but no data are available concerning these factors. One reason why, in horses, contrary to dogs and humans, the ventricular rhythm is not random is the fact that the very long R-R intervals cause a drop in blood pressure, resulting in baroreflex activity and influence of the autonomic nervous system on AV nodal conduction properties (25, 114).

It has been known since the beginning of this century that the ventricular response to atrial fibrillation is characterized by its irregularity (48, 56, 153), but the explanation of this phenomenon has puzzled investigators ever since (20, 24, 115). The mechanism often quoted as being the cause for the ventricular irregularity is concealed conduction. Concealed conduction was first described by Engelmann (46), who wrote in 1894, "every effective atrial impulse, even if it does not elicit a ventricular systole, prolongs the subsequent AV interval" (our translation). The phenomenon that atrial premature impulses that were delayed or blocked within the AV conduction system had an effect on the conduction of subsequent impulses was studied in more detail by Lewis and Master (102) in 1925. Langendorf (93) deduced the existence of this phenomenon from the analysis of clinical electrocardiograms, introduced the term concealed conduction, and was the first to prove its existence experimentally in the human heart (96). In its simplest form, concealed conduction may be manifested by an atrial premature impulse that is blocked within the AV node but prolongs its refractory state so that a subsequent impulse will also be blocked, whereas it will be conducted in the absence of the previous blocked impulse. As argued by Abildskov and Moe (1) and Moe et al. (130), the fibrillating atria provide rapid and irregular impulses to the AV node, thereby enhancing the chances for concealed conduction of multiple impulses. They predicted that "cycles containing a concealed impulse may be expected to be followed by other cycles containing concealed beats with greater than random frequency" (1). Thus long ventricular cycles would have a tendency to be followed by other long cycles. Analysis of the R-R intervals during uncomplicated atrial fibrillation in humans, however, showed that the ventricular rhythm is absolutely irregular in the sense that it is a rhythm with random temporal sequences (24, 117). It was also found that in dogs with spontaneous atrial fibrillation the ventricular response was absolutely irregular, whereas in dogs with atrial fibrillation that was induced by rapid stimulation of the atria, there was a nonrandom distribution of ventricular cycles (171). In spontaneous atrial fibrillation, the absolute irregularity of

the ventricular response was attributed to the randomness of atrial fibrillation (20, 24), and concealed conduction alone did not appear to explain the ventricular response fully.

There are several studies in which microelectrode recordings have been made from the AV node and from the ventricular specialized conduction system during experimental atrial fibrillation induced by rapid atrial stimulation (in the order of 20–30 Hz) (108, 134–136, 212). Moore (134, 135) showed that during this form of atrial fibrillation as many as nine subsequent concealed impulses could be recorded from the N zone of the rabbit AV node. Short ventricular cycles were associated with less or no concealment, whereas long R-R intervals followed concealment of multiple atrial responses. Concealed impulses could be blocked at several levels within the AV node (136, 212), and block during atrial fibrillation could also occur in the atrium (212). Moore (135) demonstrated that impulses that had passed through the AV node could be delayed or blocked within the ventricular specialized conduction system of the rabbit, confirming previous findings in the in situ dog heart, where local extracellular electrograms were recorded from various parts of the ventricular conduction system (61). This occurred especially when an impulse arrived very quickly after a blocked AV nodal response because of the increased duration of the action potential of the bundle branches following a long cycle (136).

It has been suggested that concealed impulses could influence the firing of a subsidiary pacemaker in the AV node and that repetitive resetting of such a pacemaker could give rise to a prolonged ventricular cycle (95). In his microelectrode study of the rabbit heart, Moore (135) found no evidence that the ventricular dysrhythmia associated with atrial fibrillation results from AV nodal pacemaking with entrance and exit block. In his study subsidiary pacemakers were only found in the ventricular specialized conduction system. Other studies in which microelectrode recordings were made during atrial fibrillation or other rapid atrial rhythms also did not document phase four depolarization in the AV node (18, 19, 108, 212).

It seems beyond any doubt that during atrial fibrillation multiple successive atrial impulses can be blocked within the AV node. The difficulties in explaining the ventricular response during atrial fibrillation on the basis of concealed conduction seem to stem from the fact that the AV node is usually considered to be a black box with only a single atrial input. Thus, in a recent model in which the ventricular response during atrial fibrillation was successfully imitated, the AV node was represented as a single cell characterized by a refractory period and spontaneous phase four depolarization (32). However, the AV node has more than one input (see sect. II*A5*), and one of the factors that could determine the ventricular response might be the variable pattern of activation of the two major input sites (74). Mazgalev et al. (108) recorded simultaneously from extracellular electrodes on the two input sites and from the His bundle and also from two microelectrodes in AN, N, and NH regions of the rabbit AV node during atrial fibrillation provoked by rapid

atrial stimulation. They could show that increased disparity in activation of AN fibers resulted in prolonged conduction times to the His bundle, and they found multicomponent action potentials in AN and N regions resulting from inhomogeneous conduction caused by asynchronous arrival of wave fronts from the two nodal inputs. The appearance of well-formed AN action potentials with summation of wave fronts was critical for successful transmission to the His bundle. These authors concluded that, during atrial fibrillation, asynchronous conduction, concealed conduction, summation, cancellation of wave fronts, and local reentry may all contribute in determining whether or not the His bundle will be excited. Thus far, no model has incorporated all these different elements to account for the ventricular response in atrial fibrillation.

Some effects of ventricular pacing or of ventricular extrasystoles during atrial fibrillation are difficult to explain. Ventricular extrasystoles are followed by a "compensatory pause" (94, 97, 149). This has been attributed to prolonged refractoriness of the AV node to anterograde conduction, resulting from retrograde penetration (concealed V-A conduction) of the ventricular extrasystole (97). However, both experimental (131, 137) and clinical studies (167) have shown that conduction of an atrial premature impulse can be facilitated by a critically timed ventricular premature beat. Preexcitation of the refractory barrier of the lower AV node by the premature ventricular impulse permits earlier recovery of excitability, thereby allowing conduction of a premature atrial impulse that otherwise might have been blocked. Moe and associates (131) coined the term "peeling back" for this phenomenon. In patients with atrial fibrillation, pacing of the right ventricle can eliminate spontaneous R-R cycles that are shorter than the pacing cycles. During spontaneous atrial fibrillation shortest R-R intervals were in the order of 350 ms, whereas it was possible to pace the ventricles with a cycle length of 700 ms without interference of supraventricular impulses (43, 211). A possible explanation for this phenomenon could be that during atrial fibrillation the lower AV node acts as an automatic focus, protected from supraventricular impulses, the N zone becoming "passive" during the rapid bombardment by fibrillatory impulses. These supraventricular impulses can, however, by providing electrotonic currents, modulate the firing of the pacemaker (12). The random ventricular rhythm would then be the result of the random firing of the electrotonically modulated pacemaker. During ventricular pacing, the pacemaker would be "overdrive suppressed," resulting in regulation of the ventricles at a slower rate than during atrial fibrillation without ventricular pacing. This mechanism is supported by model studies (32, 52, 188), whereas microelectrode studies have not demonstrated pacemaker activity in the AV node during atrial fibrillation or other rapid supraventricular rhythms. The model studies, in which the AV node was described as a periodically pertubed oscillator (32, 52, 188), could accurately predict the ventricular response to extrasystolic and postextrasystolic stimulation (188) and during atrial fibrillation (32).

VIII. COMPARATIVE ASPECTS OF AV NODAL FUNCTION

In the introduction, we made two speculations, namely that the contribution of AV nodal delay to the P-R interval would become progressively less in larger mammals and that in very large mammals the main function of the AV node would be to protect the ventricles from too rapid rates during supraventricular arrhythmias, especially atrial fibrillation. If we examine the little that is known about the comparative aspects of the many factors that cause AV nodal delay and block, we must conclude that no final explanation can be given for the apparent discrepancy between heart weight and P-R interval in large mammals. To begin with morphological aspects, only a limited amount of data is available about the dimensions of the AV node in various mammals (154). Thus the length of the AV node of the rabbit is given as 1.5 mm (22); that of the monkey is given as 1.5–2 mm [young adult, no species indicated (191)]; the length of the human AV node at birth is reported as 2–4 mm, at the age of 1–15 yr as 3–5 mm, and at the age of 15–40 yr as 5–7 mm (204). The AV node of the sperm whale was reported to be short and wide (1.5 × 1 cm) (203). Whereas this shows that AV nodal length increases as the heart gets bigger, no linear relationship from which extrapolations to larger mammals could be made can be derived from these figures. A plot of heart weights for rabbit (5 g) and a human at birth (22 g), from 1 to 15 yr (50–224 g), and from 15 to 40 yr (224–378 g) (6) versus AV nodal length shows too large a variation. Clearly, data for AV nodal dimensions and conduction time have to be obtained from the same mammals using similar techniques. Even then, the caveat of Truex and Smythe (181) that "gross measurements of the AV node mean very little" must be kept in mind. Thus there is as yet no conclusive evidence that the size of the AV node grows proportionally with the size of the heart in large animals, and it may well be that in large hearts the AV node is disproportionately small.

One way to explain the relative short P-R interval in large mammals could be that conduction velocity in the His-Purkinje system increases with heart size. Again, available data do not allow a conclusion on this point, since the reported figures on conduction velocity (in m/s) vary considerably: 0.75 (Purkinje fibers, calf), 1.0–1.5 (His bundle, dog), 2.0–2.5 (Purkinje fiber, dog), 2.2 (Purkinje fiber, kid), 3.0–3.5 (free running Purkinje fiber, dog), and 4.2 (false tendon, ox) (59). There are differences in diameter of Purkinje fibers of small and large mammals [12–32 μm, average 20.87, in the rabbit versus 19–94 μm, average 44.8, in the gray whale (179)]. Since conduction velocity is proportional to the square root of fiber diameter (142), if it depended on only fiber diameter, the conduction velocity in the Purkinje system of the whale would only be a factor 2.2 larger than that in the Purkinje system of the rabbit.

Of the many factors that determine AV nodal conduction delay, nothing at all is known about coupling resistance, the area of cells where inward current is only carried via the slow channels, and the geometry of the node in hearts of large mammals.

The concept that in small hearts the main function of the AV node is to delay the impulse whereas in large hearts it is to protect the ventricles from too rapid rates during atrial fibrillation by blocking atrial impulses (while conducting normal sinus beats with very little delay) is difficult to reconcile with available data. Thus the fact that in N cells inward current is solely carried through the slow channels is one of the important factors causing AV nodal delay. It is also one of the most important factors causing block of premature or too frequent impulses, because of the delayed recovery from inactivation of the slow inward current. It is therefore difficult to conceive an AV node that conducts rapidly but is able to block atrial impulses occurring at a rapid rate. It is, of course, conceivable that in large hearts the filtering function of the AV node is taken over by fibers of the ventricular specialized conduction system. These fibers would have to possess a prolonged action potential duration, which, on an increase in heart rate, would only shorten to a minimal degree. Such a mechanism is, of course, completely speculative. If, on the other hand, the AV node does not delay conduction in the traditional sense but acts as a nonprotected pacemaker (12, 32, 211), delay and protection may yet reside inside the AV node itself. However, without further data this mechanism is speculative as well.

In conclusion, therefore, many more data need to become available about morphological and functional aspects of the AV node and the ventricular specialized conduction system in different species before an adequate explanation can be given for the apparent discrepancies between heart size and P-R interval throughout the mammalian kingdom.

IX. SUMMARY

The AV node of those mammalian species in which it has been thoroughly investigated (rabbit, ferret, and humans) consists of various cell types: transitional cells, midnodal (or typical nodal cells), lower nodal cells, and cells of the AV bundle.

There are at least two inputs to the AV node, a posterior one via the crista terminalis and an anterior one via the interatrial septum, where atrial fibers gradually merge with transitional cells. The role of a possible third input from the left atrium has not been investigated.

Since the transition from atrial fibers to nodal fibers is gradual, it is very difficult to define the "beginning" of the AV node, and gross measurements of AV nodal length may be misleading. Histologically, the "end" of the AV node is equally difficult to define. At the site where macroscopically the AV node ends, at the point where the AV bundle penetrates into the membranous septum, typical nodal cells intermingle with His bundle cells.

A conspicuous feature, found in all species studied, is the paucity of junctional complexes, most marked in the midnodal area. The functional counterpart of this is an increased coupling resistance between nodal cells.

An electrophysiological classification of the AV nodal area, based on

transmembrane action potential characteristics during various imposed atrial rhythms (rapid pacing, trains of premature impulses), into AN (including ANCO and ANL), N, and NH zones has been described by various authors for the rabbit heart. In those studies in which activation patterns, transmembrane potential characteristics, and histology have been compared, a good correlation has been found between AN and transitional cells, N cells and the area where transitional cells and cells of the beginning of the AV bundle merge with midnodal cells, and NH cells and cells of the AV bundle. Dead-end pathways correspond to the posterior extension of the bundle of lower nodal cells and to anterior overlay fibers.

During propagation of a normal sinus beat, activation of the AN zone accounts for at least 25% of conduction time from atrium to His bundle, the small N zone being the main source of AV nodal delay. Cycle length-dependent conduction delay is localized in the N zone. Conduction block of premature atrial impulses can occur both in the N zone and in the AN zone, depending on the degree of prematurity.

Several factors determining AV nodal conduction delay have been identified. During normal sinus rhythm (or during regular atrial pacing at a rate close to that of the sinus rate), the most important determinants seem to be the fact that depolarization of AV nodal cells largely depends on the slow inward current and the high coupling resistance between nodal cells. Both of these factors are most marked within the N zone. The small diameter of AV nodal cells may play a minor role in causing slow conduction within the AV node.

The recovery kinetics of the slow inward current are slow, and this may underly the fact that at short cycle lengths the N zone becomes inexcitable and acts as a passive segment, capable only of transmitting electrotonic current between late AN cells and early NH cells. This would explain the observation that, with the introduction of atrial premature impulses, the increase in AV nodal transmission time is due to "stagnation" between N and NH zone.

Atrioventricular nodal architecture, especially the dual input into the node, also plays a role when the atria are prematurely excited or activated at a rapid rate. Within the AN zone, summation and cancellation of wave fronts and local reentry determine the efficacy of the excitatory wave that converges toward the N zone.

All factors involved in producing AV nodal conduction delay and block (slow recovery of excitability in fibers depending on the slow inward current, increased coupling resistance, cancellation and summation of wave fronts, and local reentry in the upper node due to asynchronous activity in the two nodal input sites) play a role in protecting the ventricles from stimulation rates that are too rapid during supraventricular arrhythmias, especially atrial fibrillation. As an additional safety factor, impulses that pass the AV node may be blocked in fibers of the ventricular specialized conduction system. An alternative explanation may be that, at least during atrial fibrilla-

tion, the AV node acts as a pacemaker that is electrotonically modulated by concealed atrial impulses. These would produce subthreshold depolarizations in the pacemaker cells, which, depending on their timing, may postpone or accelerate the firing of the pacemaker, thus causing an irregular ventricular rhythm. Microelectrode studies, however, have failed to find evidence for AV nodal pacemaker activity during atrial fibrillation or other rapid supraventricular rhythms.

Most studies agree that only the cells of the distal NH zone show pacemaker activity in intact preparations. This pacemaker activity is overdrive suppressed when NH cells are excited at a rate more rapid than their intrinsic rate.

The divergence from a linear relationship between P-R interval and heart size in larger mammals can still not be explained in terms of AV nodal anatomy and electrophysiology. Clearly, more comparative data are needed before our speculations that the AV node in large mammals produces little conduction delay but still is able to protect the ventricles against atrial fibrillation can be substantiated.

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Address for reprint requests: F. L. Meijler, Interuniversity Cardiology Institute, POB 19258, 3501 DG Utrecht, The Netherlands.

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