Familial Atrial Dysrhythmia with A-V Block
Intracellular Microelectrode, Clinical Electrophysiologic, and Morphologic Observations

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SUMMARY
This study is of a family with a syndrome of atrial fibrillation or flutter with advanced or complete atrioventricular (A-V) block, involving four members in two generations. Less serious arrhythmias were documented in another 15 members (three generations). Inheritance was by autosomal dominance with varying degrees of expression. An atrial biopsy was obtained in one of the members, a 40-year-old female who had atrial flutter with advanced A-V block proximal to the His bundle (H-V interval of 39 msec). Intracellular action potential (IAP) recordings from this tissue revealed: 1) partially depolarized cells with depressed IAP amplitude, 2) phase IV diastolic depolarization with spontaneous firing, 3) diminished excitability and responsiveness, and 4) decremental conduction with local block and re-entry. Histological findings revealed vacuolar degeneration, hypertrophy, and early necrosis of atrial cells.

In conclusion, the multiple IAP and pathologic abnormalities provide a basis for atrial dysrhythmia in this family. The etiology of the disease is unknown.

Additional Indexing Words:
Atrial fibrillation
Atrial flutter
Action potential
His bundle electrogram
Sick sinus node
Pacemaker

In 1901, Morquio described a family with a syndrome of Stokes-Adams attacks, slow pulse rates, and sudden death. Since this first description of familial arrhythmias, other families have been reported with sinus node disease, atrial standstill, atrioventricular (A-V) dissociation, first degree A-V block, atrial fibrillation, sinus bradycardia with A-V block, bundle branch block (uni-, bi-, and trifascicular block), and bidirectional tachycardia. In most instances of familial arrhythmia the mode of inheritance has been that of autosomal dominant with varying degrees of expression.

Pathological and electrophysiological observations in patients with familial arrhythmias have been limited. We have recently had the opportunity of examining a large family with atrial arrhythmia and A-V block. An atrial biopsy specimen was obtained in one of the members at the time of epicardial pacemaker implantation. In this report, the electrophysiological and pathological characteristics of this tissue are described, and the relevance of these findings in regard to familial conduction disease are discussed.

Methods
The propositus (third generation), a 40-year-old female, was referred to the University of Illinois for evaluation of atrial arrhythmia. Information concerning other members of the family was obtained from direct interviews, correspondence with family physicians, and examination of hospital records. Specimen electrocardiograms were obtained on all second, third, and fourth generation members of the family. Diagnostic cardiac catheterization and His bundle recordings were performed on the propositus utilizing standard techniques. A specimen of right atrial appendage was obtained during implantation of an epicardial permanent pacemaker; this specimen was subjected to pathological and electrophysiological studies.

Pathological Studies
Serial sections were cut and every tenth section was retained. Tissues were stained with hematoxylin-eosin,
Weigert-van Gieson, Periodic-acid Schiff, Gomori's trichrome, and hematoxylin-basic fuchsin-picroc acid. Sections were also stained for amyloid.

Electrophysiological Studies

Immediately following excision, a portion of the atrial specimen was placed into a thermost containing oxygenated modified Tyrodes solution, which had previously been equilibrated with 95% O2 and 5% CO2. The specimen was subsequently transferred to a bath and perfused with oxygenated Tyrodes solution containing NaCl, 137 mM; KCl, 4 mM; CaCl2, 2.7 mM; Na2CO3, 12 mM; NaH2PO4, 1.8 mM; NaCl, 0.5 mM; glucose, and 5.5 mM at a temperature of 37 ± 0.5°C and a pH of 7.38.

Transmembrane potentials were recorded with standard glass microelectrodes filled with 3 M KCl and having dc resistances of 15 to 24 megaohms and tip potentials of 5 mV or less. Microelectrodes were coupled to a conventional cathode follower (Bioelectric, type NF1) using an Ag/AgCl/3 M KCl junction. Recordings were obtained during spontaneous beating and stimulation at rates ranging from 30–180 beats/min. Stimuli were provided by pulse and waveform generators (Tektronix, 161 and 162), isolated from ground by means of radio-frequency oscillators, and applied to the surface of the specimen through bipolar silver wire electrodes which were teflon coated except at the tips. Intracellular potentials were displayed on a Tektronix type 555 oscilloscope and recorded on 35 mm film along with reference signals for provision of time and voltage calibrations. Data collection was first initiated following a one-hour equilibration period and was substantially complete two hours later.

The endocardial surface of the specimen was extensively explored by using glass microelectrodes. Electrophysiological properties were assessed utilizing conventional recording and stimulating techniques. Conductivity and the characteristics of impulse spread were determined by using conduction times between two microelectrodes 1–2 mm apart on the longitudinal axis of a selected trabeculum and 1 mm distal to a bipolar stimulating electrode.

Results

Report of Cases

Case One (the propositus)

This 40-year-old white female was healthy until approximately two months prior to admission when she developed episodes of marked weakness and light-headedness. Electrocardiograms taken by her family physician revealed atrial flutter with varying block. Cardioversion was performed twice, and electrocardiograms following cardioversion revealed 1° A-V block (P-R of 0.26 sec). Atrial flutter recurred despite maintenance therapy with quinidine. She was then admitted to the University of Illinois Hospital for further evaluation.

Physical examination revealed an irregularly irregular pulse without other cardiovascular abnormalities. Hemoglobin, white blood count, fasting blood sugar, blood urea nitrogen, serum protein electrophoresis, calcium, phosphorous, serum electrolytes, T3 and T4, were within normal limits. Antinuclear antibodies were not present and latex fixation was negative. Chest X-ray revealed no cardiac enlargement.

Electrocardiograms revealed atrial flutter with varying block with periods of advanced A-V block. The patient had one paroxysm of severe weakness during hospitalization and electrocardiograms obtained several minutes later revealed atrial flutter with advanced block. Random 24-hour Holter tape recordings also demonstrated similar episodes of advanced A-V block. An echocardiogram revealed normal mitral valve function and no evidence of idiopathic hypertrophic subaortic stenosis.

Diagnostic right and left heart cardiac catheterization was normal except for elevations of right atrial pressure (mean 12 mm Hg) and right ventricular end-diastolic pressure (14 mm Hg). Left ventricular angiograms, pulmonary artery angiograms, and coronary arteriograms were within normal limits.

Intracardiac electrophysiological studies revealed atrial flutter with a flutter rate of 216 beats/min and varying block proximal to the His bundle (mean ventricular rate of 66 beats/min) (fig. 1). The H-V interval was 39 m sec. Rapid atrial pacing converted flutter to atrial fibrillation, which persisted for 24 hours and then reverted back to flutter.

Because of symptoms associated with periods of advanced A-V block, a permanent epicardial right ventricular demand pacemaker was implanted. Following surgery, the patient has remained asymptomatic.

Case Two

The mother of the propositus was known to have a slow irregular pulse for many years. At age 54 she fell unconscious at her home. Electrocardiograms revealed atrial fibrillation and complete heart block with a ventricular response of 42 beats/min. A permanent pacemaker was implanted at age 56 because of recurrent syncope. She did relatively well until age 62 when after being admitted for pacemaker failure, she died suddenly with ventricular fibrillation. Autopsy was not performed.

Case Three

The maternal uncle of the propositus was found to have first degree A-V block at age 53. Atrial fibrillation with complete A-V block was noted at age 58. In the ensuing years, he developed signs and symptoms of congestive heart failure. A permanent pacemaker was implanted at age 62. Repeated admissions followed for heart failure until his death at age 67.

Case Four

A maternal aunt of the propositus is 66 years old and completely asymptomatic. Her electrocardiogram
reveals atrial fibrillation with advanced A-V block (ventricular response of 33 beats/min).

Familial Involvement (fig. 2)

The family consisted of 61 members. Criteria for diagnosis of definite involvement necessitated the combination of atrial fibrillation or flutter with advanced or complete A-V block. Four members, three in the second generation and one in the third generation, are thus considered to have definite involvement (see cases 1–4 above). Criteria for possible involvement included one of the following: Slow heart rate by history, sudden death under the age of 35 years, atrial fibrillation without A-V block, first degree A-V block, persistent sinus bradycardia, wandering atrial pacemaker, and multifocal atrial premature beats.
Thus, possible involvement was present in three members in the first generation, four members in the second generation, and eight members in the fourth generation. Accordingly, the mode of inheritance appeared to be autosomal dominant with varying expression, in part related to age.

Electrophysiologic Findings (atrial specimen from case 1)

Transmembrane potentials of atrial endocardial cells differed in many major respects from those reported for comparable specimens of normal human atrium. The most characteristic finding was the presence of large numbers of partially depolarized cells, the mean value for diastolic potential being $-51.5 \pm 4.1 \text{ mV}$ (fig. 3). Amplitude, maximum rising velocity, and time course of repolarization also differed from normal. Action potential amplitude and maximum rising velocity were universally reduced as well. Mean value for action potential amplitude was $52 \pm 4 \text{ mV}$. Upstroke velocity ranged from 0–50 V/sec. Phases I, II, and III of repolarization were slurred together with the result that the action potentials appeared triangular in form.

A second characteristic was the occurrence of spontaneous beating. Gross inspection, at 10–20 $\times$ magnification, suggested the existence of at least six spontaneous foci. These foci were characterized by fibers exhibiting spontaneous (3–5 mV/sec) diastolic (phase IV) depolarization. Spontaneous activity in at least two of the foci, located 2 mm apart, was clearly independent. Spontaneous rates were temperature sensitive, the cells tending to beat more rapidly at $37.5^\circ$ than at $36.5^\circ$. Spontaneous rate fluctuations also occurred independent of temperature changes.

Excitability and conductivity were depressed to a marked degree (fig. 4). Stimulus strengths required to evoke a response capable of propagating at least 1 mm were 3–10 times greater than those required for comparable specimens of normal dog and rabbit atrium. In five of the seven trabecula examined, depression of excitability and conductivity was so profound that a propagated response could not be evoked. In trabeculae which could be excited and in which a propagated response could be evoked, estimated conduction velocities were very slow (0.004 to 0.020 m/sec) as shown in figure 4A. Decremental conduction, Wenckebach type periodicity (figs. 4B and 5B), and local regions of bi- and unidirectional block were observed (figs. 4C, D, and 5C).

Depressed and decremental conduction, local regions of block, and multifocal pacemaker activity found in this preparation are conditions thought to predispose to fragmentation of the excitation wave and development of arrhythmia due to slow conduction and re-entry (fig. 5). Coupled extrasystoles were common.

The coexistence of independent spontaneously beating foci within a small segment of tissue implies the presence of high degrees of local block since each focus must be protected against depolarization by im-
pulses initiated at the other sites. Local block would thus appear to confer many of the characteristics of parasystole on these foci. Figure 5C shows recordings obtained from two closely adjacent sites on a single trabeculum. The cells at one of the two recording sites beat spontaneously. Cells at the second recording site were activated by impulses occurring at the same rate as those initiated by the spontaneous cells. The prolonged interelectrode conduction time (30-50 msec) between the focus and second recording site can be considered a manifestation of exit block about the former. It will also be seen that regular stimulation of an area closely adjacent to both the spontaneous focus (site 1) and to the second recording site resulted in activation of the latter but not the former. Failure to activate the spontaneous focus can be considered entrance block.

Depressed excitability and conductivity could be due to the presence of a large number of cells with low levels of diastolic potential. Alterations in membrane responsiveness were also probably present, in that propagated action potentials could be evoked at levels of membrane potential of -40 mV. This suggested that the membrane responsiveness curve had been shifted upward and to the left, since responses would not normally be expected at this level of membrane potential.

Histological Findings (atrial specimen from case 1)

Some of the atrial cells were enlarged. The cytoplasm of many cells was markedly vacuolated, some of the cells having pyknotic nuclei. The cytoplasm in some cells stained positively with PAS and hematoxylin-basic, fuchsin-picric acid stain (fig. 6). There were no amyloid or vascular changes. There were focal accumulations of neutrophils and a slight focal accumulation of lymphoid cells. Fibrin was present in the pericardium. There was considerable infiltration of fat tissue throughout the atrial tissue (fig. 6). These findings were consistent with acute and chronic vacuolar degeneration and hypertrophy of atrial cells with early necrosis of unknown cause.

Discussion

The familial disease described in this report is characterized in its advanced form by atrial fibrillation or flutter with complete A-V block. The A-V block is usually symptomatic with spells of lightheadedness and/or syncope necessitating pacemaker implantation. The more advanced rhythm disturbances develop in or after the fourth decade, with abnormalities of less seriousness detectable prior to this. These include first degree A-V block, persistent sinus bradycardia, wandering atrial pacemaker, and multifocal atrial premature beating. Although congestive heart failure has been noted in some of the older family members, and abnormalities of right ventricular function were detected at catheterization in case one, it is not clear whether cardiomyopathy involving ventricular myocardium is definitely part of the disorder.

Resemblance to Other Reported Families

Of the reported families with cardiac arrhythmias, Figure 5

Examples of altered automaticity and conductivity which could predispose to chronic dysrhythmia. Panel A shows records during spontaneous beating. Activity originated in the pacemaker at a different location. Each dominant beat is followed by fixed coupled, re-entrant type response. Panel B shows continuous records from two closely adjacent cells (less than 2 mm apart) during period of spontaneous beating. As was true for A, activity originated at the pacemaker at a different locus. Slow and decremental conduction, local block and beat-to-beat variations in interelectrode conduction time are striking. Note 3:2 Wenckebach sequence in top strip. Panel C shows continuous records from two sites as in figure 4D. Unidirectional block would appear to give the cell in spontaneously active focus (bottom trace in each strip) certain characteristics of parasystole.

Figure 6

Section of atrial biopsy showing degenerative changes. PAS stain (after diastase) × 127. The darkly stained cells show degenerative changes. Also note fatty infiltration.
some bear resemblance to the present family. Atrial fibrillation has been described in two families by Gould and by Phair, with autosomal dominant inheritance, benign course, and absence of A-V block. Familial sinus node disease can present with episodes of atrial tachyarrhythmias; however, sinus arrest or bradycardia are the main features, as described by Spellberg.

Williams et al. reported a family of two generations which demonstrated a progression from sinus bradycardia and first degree A-V block at younger ages to later development of supraventricular tachyarrhythmias with slow ventricular response. Atrial standstill with junctional rhythm developed still later, with the patients becoming symptomatic with syncope and/or signs of congestive failure. Atrial pacing was attempted in one case, but the atrium was inexcitable. Autopsy in one case revealed necrosis and diffuse interstitial fibrosis of atrial muscle.

Sarachek et al. reported a family with sinus bradycardia and heart block. In this study, A-V block was frequently preceded by unifascicular and then bifascicular block with first or second degree A-V block. Although sinus bradycardia was apparent at ages five to 72, the earliest appearance of heart block was at age 44.

In a recent report by Lynch et al., an extensive family pedigree was shown, consisting of five generations including 502 members. In the affected members of this family, progression from first degree A-V block to complete block was usually insidious but occasionally acute. Atrial and ventricular arrhythmias occurred rarely and then only as late complications. Clinically these patients presented with slow heart rates or episodes of lightheadness and syncope, usually in their late thirties. An autosomal dominant pattern with incomplete penetrance was suggested. A ventricular biopsy showed no abnormality and no atrial tissue was studied. Hemodynamic studies were normal.

In the present family, as in most of the other reported families, the mode of inheritance appeared to be that of autosomal dominant with varying degrees of expression. This does not imply that similar disease entities could not be transmitted in the recessive mode. Recognition of families with recessive transmission would be difficult since the probability is high that such cases would appear as isolated cases, although on occasion they might cluster in one generation. It is unfortunate that we were unable to discover a specific electrophysiological or biochemical trait which might lead to identification of such otherwise sporadic and poorly understood cases. Other workers encountering similar families should pursue this problem further.

Electrophysiologic and Pathologic Basis of Chronic Atrial Tachyarrhythmias

Despite a voluminous literature, the mechanisms underlying initiation and perpetuation of chronic atrial flutter and fibrillation have not as yet been entirely clarified. Controversies persist as to whether these dysrhythmias result from enhancement of normal or development of abnormal automaticity in a single ectopic locus or in multiple loci, from slow conduction and re-entry, or some combination of these factors.

Findings in this study and other studies suggest that the electrophysiologic properties of specimens of atrium from patients with atrial disease and dysrhythmia differ from normal in a number of major respects. The most striking difference was the presence of spontaneously firing cells exhibiting typical pacemaker-like characteristics similar to those found in S-A nodal cells. In most instances, including the specimen under discussion, these cells appeared to be gathered into one or more discrete foci, emphasizing multifocal pacemaker activity as a cause of atrial flutter and fibrillation. It is of interest that these foci were characterized by intense degrees of local block which gave them many of the attributes of parasystole. The specimens also were characterized by the presence of large numbers of partially depolarized fibers, considerable local differences in diastolic potential and in action potential configuration and duration, altered responsiveness, depressed and decremental conduction, multiple regions of local block, and a variety of oscillatory after and pre potentials. Since such conditions might be expected to predispose to fragmentation of the excitation wave and re-entrant excitation, they suggest that altered conduction and re-entry represent a second major factor underlying sustained atrial tachyarrhythmias. Coupled extrasystoles and other forms of re-entrant type activity were, in fact, quite common. The existence of such conditions, particularly the oscillatory potentials and the abrupt local differences in potential, further suggests that the so-called abnormal automatic mechanisms, including boundary currents and after potentials, also may be contributory. The multiplicity of electrophysiologic disturbances within a single specimen makes it tempting to speculate that chronicity of atrial flutter and fibrillation may well be related to the simultaneous operation of multiple mechanisms.

This analysis presumes that the observed changes in the specimens are representative of other portions of the atrium. However, this is not a necessary presumption, since it is possible that multifocal ectopic activity and multiple regions of local block of varying degrees within even a small region, e.g., the atrial appendage.
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could predispose to sustained dysrhythmia irrespective of the condition of the remainder of the atrium. Findings that application of agents such as aconitine to a localized portion of the atrium can induce such dysrhythmias supports this conclusion.\(^1,^2\)

The electrophysiologic disturbances in the specimen from case one are consistent with the occurrence of chronic atrial tachyarrhythmias in this patient. In addition, these electrophysiologic changes are presumably representative of those present in the atria of other affected family members and are also consistent with dysrhythmias exhibited by the latter. This seems reasonable in light of the comparability of changes in the specimen from case 1 with those reported for other patients with chronic atrial disease and dysrhythmia.\(^1,^2\) The validity of this analysis would be enhanced if, as appears likely from the histories on older family members, the patient described in case 1 eventually goes on to develop chronic fibrillation.

The extent to which the morphologic changes in the specimen from case one relate to the observed electrophysiologic disturbances is not clearly defined. The diffuseness of the degenerative changes would appear to correlate well with the diffuseness and severity of the electrophysiologic disturbances, particularly the disorganization of conduction. One striking finding was that, in contrast to a previous study,\(^1,^2\) occurrence of pacemaker-like activity was not associated with the presence of specialized fibers as defined by histologic criteria. Observations such as these emphasize the need for further investigation designed to assess the interrelationships between changes in structure and electrical activity and thus provide added insight into the link between the functional and morphological bases of cardiac arrhythmias.

The pathological basis for the A-V block in this family is unknown since there were no anatomic studies of the A-V conduction system. However, electrocardiographic analysis of all affected members revealed narrow QRS with no evidence of intraventricular conduction disease. His bundle studies in case 1 revealed a site of block proximal to the His bundle with normal H-V interval. These observations suggest that A-V block occurred in the A-V node or in its atrial approaches. Block in the latter site would correspond to our finding of extensive electrophysiologic abnormalities demonstrated in the atrial specimen.

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References

1. MORQUO L: Sur une maladie infantile et familiale caracterisee par des modifications permanents du pouls, des attaques syncopeales et epileptiformes et la mort subite. Arch Med Enfan-\(^\)ts 4: 467, 1901
24. TRAUTWEIN W, KASEBAUM DG, NELSON RM, HECHT HH:


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