The Relationship of Human Atrial Cellular Electrophysiology to Clinical Function and Ultrastructure

Luc Mary-Rabine, A. Albert, T.D. Pham, Allan Hordof, John J. Fenoglio, Jr., James R. Malm, and Michael R. Rosen

From the Departments of Pharmacology, Pediatrics, Pathology, and Surgery, Columbia University College of Physicians and Surgeons, and The University of Liège, Liège, Belgium

SUMMARY. Although previous studies have described the electrophysiological and ultrastructural characteristics of human cardiac fibers, no attempt has been made as yet to describe quantitatively the relationship between the ultrastructural and cellular electrophysiological derangements occurring with cardiac disease, and their clinical manifestations. In this study, we used standard microelectrode techniques to record the action potential characteristics of human atrial fibers obtained during cardiac surgery and correlated the electrophysiological parameters with clinical and ultrastructural data. Ultrastructure was studied by optical and electron microscopy. We found a multiple linear regression among maximum diastolic potential, atrial size and pressure, P wave duration and ultrastructure changes. Proliferations of Z band material, widening of intercalated discs, and degenerative changes were quantified and correlated with electrophysiological and clinical data. These studies emphasize the relationship between hemodynamic anomalies and resultant changes in both human atrial fiber structure and electrical function. Finally, the likelihood of occurrence of arrhythmias can be predicted using the analytic method described. (Circ Res 52: 188-199, 1983)

The first attempts to record membrane potentials from human ventricular and atrial fibers were reported 20-25 years ago (Bromberger-Barnea et al., 1959; Trautwein et al., 1962; Woodbury et al., 1957). However, a systematic investigation of normal atrial myocardium was not performed until Gelband and co-authors (1972) described the electrophysiologic properties of 22 preparations obtained from patients with no evidence of atrial disease. Those studies of normal human atrium revealed levels of maximum diastolic potential, action potential amplitude, and maximum upstroke velocity of phase 0 (Vmax), that were consistent with those seen in normal canine atrium (Hogan and Davis, 1968).

Other studies of diseased human atrium reported low levels of resting membrane potential, action potential amplitude, and Vmax (Fabianto and Fabianto, 1971; Singer and Ten Eick, 1971; Singer et al., 1967; Singer et al., 1973; Sleator and de Gubareff, 1964). In one such study, we reported 22 patients with clinical evidence of atrial disease, and concluded that the depression of the resting and the action potentials seen was associated with and presumably explained by chamber dilation (Hordof et al., 1976). Moreover, we found a statistical association between the low resting membrane potential and a prolonged P wave duration.

Although the previous studies have shown qualitatively the association between cardiac disease and its electrophysiological and ultrastructural manifestations, we are unaware of any study that has identified which abnormalities induced by cardiac disease are associated with and presumably are the cause of specific structural changes that occur, as well as of the electrophysiological abnormalities that may cause cardiac arrhythmias.

Therefore, the purpose of the present study was to identify which of the hemodynamic and structural abnormalities that occur in diseased atria are associated with the electrophysiologic abnormalities noted. Moreover, we intended to determine whether any clinical findings might be identified as providing accurate indicators of the deterioration in cellular electrophysiological properties and ultrastructure and of the likelihood of arrhythmias. To attain these ends, data from 121 patients were analyzed using multiple stepwise regression techniques and logistic discriminant analysis.

**Methods**

The atrial tissues studied were obtained from the hearts of 121 consecutive patients undergoing corrective cardiac surgery requiring cardiopulmonary bypass. Prior to surgery, informed consent was obtained. All patients had been followed by the Divisions of Pediatric or Adult Cardiology for at least 1 year before surgery. Standard ECG's and physical examinations were performed as indicated clinically. No patient had ECG evidence of preexcitation. For all patients, the following information was available: history (including that of atrial arrhythmias), drug therapy, standard 12-lead electrocardiograms, right and/or left cardiac catheterization data, and angiocardiography. Twelve- to 24-hour Holter monitoring was done only in certain of the patients (those with paroxysmal tachycardias).

At the time of surgery, the size of the atrium from which tissues was to be removed was estimated by the surgeon as normal (+), or slightly (++), moderately (+++), or mark-
grids and approximately 400 cells were studied in each with a Philips 300 electron microscope at 80 kV. The volume was 2 ml. The tissues were impaled with 3 M KCl-fused with Tyrode’s solution warmed to 37°C and equilibrated with 95% O₂, 5% CO₂. The composition of the Tyrode’s solution (mM/liter) was: NaCl, 137; NaHCO₃, 12; NaH₂PO₄, 1.8; MgCl₂, 0.5; CaCl₂, 2.7; KCl, 4; dextrose, 5.5. The superfusate flow rate was 15-17 ml/min; chamber volume was 2 ml. The tissues were impaled with 3 M KCl-filled glass capillary microelectrodes having tip resistances of 10–30 MΩ. The electrodes were coupled to a 3 M KCl interface to an Ag-AgCl bar which led to an amplifier having a high input impedance and input capacity neutralization. The output was displayed on a cathode ray oscilloscope (Tektronics model 565). The tissue chamber was connected to ground through a salt bridge and an Ag-AgCl junction. The methods used to calibrate the equipment have been described previously (Rosen et al, 1973a). The preparations were stimulated at a cycle length of 1000 msec through Teflon-coated bipolar silver wire electrodes (Rosen et al., 1973). After the tissue had stabilized in Tyrode’s solution for 20 minutes, measurements were made of action potential amplitude and overshoot, maximum diastolic potential, and maximum upstroke velocity of phase 0 depolarization (V̇max).

The measurements for each tissue sample were obtained from 20–115 impalements in the first subendocardial cell layer. All impalements were made at least 3 mm from the cut edges of the preparation. The number of impalements performed in a given preparation depended on the variability in membrane potentials recorded. Where transmembrane potential characteristics of 20 fibers impaled at different subendocardial sites showed little to no variation (±10%), no more impalements were made. As variability increased, more impalements (up to 115) were made. To report the membrane potential of any one preparation, the mean value for all impalements made in that preparation was determined. As such, equal weight was given to all impalements. After the control transmembrane potential characteristics for each preparation had been determined, the drive stimulus was discontinued, and the tissue was allowed to initiate spontaneous activity.

After the electrophysiological study was completed, the tissue was fixed in phosphate-buffered (pH 7.3) 2.5% glutaraldehyde as previously described (Fenoglio et al., 1979). All tissue was fixed overnight in glutaraldehyde, and post-fixed for 1 hour in chilled 1% osmium tetroxide in 0.1 M phosphate buffer (pH 7.3). The tissue was rinsed in phosphate buffer, dehydrated in graded acetone, and embedded in Swiss araldite. Flat silicone embedding molds were used and areas until the study was completed. We analyzed (1) the following clinical data: sex, age, diagnosis, history of cyanoisis and arrhythmias, drug therapy; (2) the following catherization data: atrial size, atrial pressure (mean, a wave, v wave), pulmonary artery wedge pressure, and, when present, cardiovascular shunts; (3) the following ECG data: rate and rhythm, PR interval, P wave duration, P wave amplitude; (4) the following surgical data: atrial size; (5) the following electrophysiological data: maximum diastolic potential, action potential amplitude, and overshoot, and maximum upstroke velocity of phase 0 (V̇max); (6) the following structural data: Z band and intercalated disc changes, degenerative changes, mean cellular diameter.

Statistical analysis of the data was performed using analysis of variance, multiple stepwise regression techniques, and logistic discriminant analysis (Snedecor and Cochran, 1967). This statistical procedure utilizes as few variables as possible and weighs them to derive the optimal polynomial equation that separates subjects into two distinct groups. By considering the interaction among variables, this technique pairs the list to an optimal combination of predictive variables (see Appendix). Results are expressed as mean ± 1 s.

Results

Clinical Data

Clinical information was documented completely in 118 of the 121 patients, of whom 53.3% were male and 46.7% were female. The diagnoses are listed in Table 1. Patients with congenital heart disease were 8 months to 58 years old (mean: 9 years; median: 4.0 years) and the age distribution was skewed ("lognormal"). Patients with acquired heart disease were 25–78 years old (mean: 52.7 years; median: 54.0 years) and the age distribution was symmetrical ("normal"). Cyanosis was evident in 24 patients, all of them with congenital heart disease.

Fifty-four patients did not receive any cardiotonic, antiarrhythmic, or diuretic medication. Forty-three patients were taking digoxin and/or diuretic therapy for treatment of congestive heart failure. Sixteen patients received propranolol and/or nitroglycerine for angina pectoris. Five patients were taking quinidine or procaaine amide. For all patients receiving cardioactive...
and the right atrium was moderately to markedly dilated.

This group was 4.0 ± 2.3 mm Hg and the atrium was 23.5 ± 11.7 mm Hg and the left atrium was 27.2 ± 12.7 mm Hg. For these patients, the mean Qp/Qs was 2.9 ± 1.5.

Twenty-three had elevated mean atrial pressures (>8 mm Hg), and the overall mean right atrial pressure for all 91 patients was 0.8 ± 3.3 mm Hg, while the mean right atrial pressure in this group was 7.3 ± 5.7 mm Hg. Of these 91 patients, 20 had a left-to-right shunt at the atrial level. For these patients, the mean Qp/Qs was 2.5 ± 1.1. In 29 cases, the atrium was slightly enlarged (++), in 33 cases it was moderately enlarged (+++), in 16 cases it was moderately enlarged (+++), in 33 cases, markedly enlarged (+++). Right atrial pressure was measured in 91 patients. The dimension of the atrium from which each tissue sample was obtained (right atrium in 117 cases, left atrium in 4) had been evaluated at cardiac catheterization using a qualitative angiographic assessment. This was corroborated by the surgeon at the time of surgical correction. Thirty-nine patients had atria of normal size (+); in 29 cases, the atrium was slightly enlarged (+), in 16 cases it was moderately enlarged (++), in 33 cases, markedly enlarged (+++).

The error rate thus was 15%, and the predictive value of a positive index 79%. Since drug therapy could bear redundant information (following and not predicting the occurrence of arrhythmia), and since ECG’s prior to the occurrence of an arrhythmia might not always be available or permit accurate reading of P wave duration at standard paper speeds, we reanalyzed our data. This time we considered only sex, age, diagnosis, atrial size, atrial pressure and cyanosis. Again, three parameters (atrial size, age, cyanosis) could discriminate between the presence and absence of atrial arrhythmias (P < 0.05). Table 2A shows for 100 patients (those for whom complete information was available) the classification matrix and the calculated logistic discriminant function (LDF) equation. A large positive LDF value is associated with a high risk of arrhythmia and a large negative value with a low risk. When the cutoff point was taken at LDF = 0, a value which theoretically maximizes the total probability of correct classification, 85 patients were allocated correctly. The error rate thus was 15%, and the predictive value of a positive index 79%. Since drug therapy could bear redundant information (following and not predicting the occurrence of arrhythmia), and since ECG’s prior to the occurrence of an arrhythmia might not always be available or permit accurate reading of P wave duration at standard paper speeds, we reanalyzed our data. This time we considered only sex, age, diagnosis, atrial size, atrial pressure and cyanosis. Again, three parameters (atrial size, age, cyanosis) could discriminate between the presence and absence of atrial arrhythmias (P < 0.05). Table 2B shows for

<table>
<thead>
<tr>
<th>Clinical Diagnoses</th>
<th>Observed</th>
<th>Predicted NSR</th>
<th>Predicted arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>61</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>17</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Endocardial cushion defect</td>
<td>3</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>11</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>2</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>2</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Anomalous left coronary artery</td>
<td>1</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Transposition of the great vessels</td>
<td>8</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>12</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>3</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>2</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Acquired heart disease</td>
<td>57</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>31</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Atherosclerotic heart disease</td>
<td>22</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Atrial myxoma</td>
<td>3</td>
<td>66</td>
<td>5</td>
</tr>
</tbody>
</table>

We believed it would be useful to test whether the clinical data available might be predictive of atrial arrhythmias. We therefore constructed a prognostic index, considering the following variables: sex, age, diagnosis (congenital heart disease, rheumatic heart disease, coronary heart disease), atrial size, atrial pressure, digitalis therapy, and P wave duration. Using the logistic discrimination method with a stepwise variable selection procedure, the most important parameters (in decreasing order of importance) appeared to be P wave duration, cyanosis, and digitalis therapy. One might question why (and whether) atrial pressure was not an important determinant here. As shall be shown later, it was an important determinant of one arrhythmia, atrial fibrillation. However, in considering arrhythmias as a group, the pressure elevation added insignificantly to the predictive value of the equation. As such, the equation, which uses as few variables as possible (see Methods and Appendix I) does not include pressure. Taking P wave, cyanosis, and digitalis therapy into consideration, we could predict the likelihood of the presence or absence of an atrial arrhythmia in the initial study population (P < 0.025). Table 2A shows for 100 patients (those for whom complete information was available) the classification matrix and the calculated logistic discriminant function (LDF) equation. A large positive LDF value is associated with a high risk of arrhythmia and a large negative value with a low risk. When the cutoff point was taken at LDF = 0, a value which theoretically maximizes the total probability of correct classification, 85 patients were allocated correctly. The error rate thus was 15%, and the predictive value of a positive index 79%. Since drug therapy could bear redundant information (following and not predicting the occurrence of arrhythmia), and since ECG’s prior to the occurrence of an arrhythmia might not always be available or permit accurate reading of P wave duration at standard paper speeds, we reanalyzed our data. This time we considered only sex, age, diagnosis, atrial size, atrial pressure and cyanosis. Again, three parameters (atrial size, age, cyanosis) could discriminate between the presence and absence of atrial arrhythmias (P < 0.05). Table 2B shows for

<table>
<thead>
<tr>
<th>Predictive Variables Related to Atrial Arrhythmias</th>
<th>Predicted NSR</th>
<th>Predicted arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. LDF = 2.140 cyanosis * + 1.60 drug† + 0.051 P duration (msec)</td>
<td>7.89</td>
<td></td>
</tr>
<tr>
<td>Observed NSR</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Observed arrhythmia</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>B. LDF = 0.067 age + 0.994 A5 + 2.65 cyanosis * - 6.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed NSR</td>
<td>66</td>
<td>8</td>
</tr>
<tr>
<td>Observed arrhythmia</td>
<td>10</td>
<td>19</td>
</tr>
</tbody>
</table>

NSR = normal sinus rhythm; A5 = atrial size.
* Cyanosis present = 1, absent = 0.
† Drug therapy = 1, no drug = 0.
the 103 patients the classification matrix and the
logistic discriminant function. The error rate here is
17% and the predictive value 70%.

Having derived the two equations in Table 2, we
proceeded to test them in 29 patients who were not
part of the group used to develop the equations. The
data and interpretation are presented in Appendix II.
It is apparent that Equation II-A was not an accurate
predictor of arrhythmias, having an error rate of 21% and
a predictive value of the positive prognostic index of
only 50%. However, the error rate for Equation II-
B was only 10%, and its predictive value was 75%. This is consistent with the result predicted in Table
2B.

**Electrophysiology of Atrial Myocardium**

We arbitrarily divided the atrial fibers studied into
three groups (Table 3). The first group (A) uniformly
showed action potentials that were fast responses, the
third group (C) action potentials with very slow up-
stroke velocities that probably were slow responses, and
the intermediate group (B) had variable trans-
membrane potential characteristics, including action
potentials with fast and slow upstroke velocities. The
basis for suggesting the action potentials with slow
upstroke velocities were, in fact, slow responses was
as follows: we and others (Hordof et al., 1976; Crane-
field, 1975) have found that slow response action
potentials usually have $V_{\text{max}}$ under 20 V/sec. In the
present study, the group C fibers had a mean $V_{\text{max}}$ of
4 V/sec. Although we did not use slow and fast
channel blockers in the present study to ascertain the
responses of the action potentials to these agents, our
use of verapamil and procaine amide in an earlier
study (Hordof et al., 1976) of comparable action poten-
tials gave results suggesting that they are slow
responses.

Group A included 51 preparations having a rapid
$V_{\text{max}}$. Two types of atrial transmembrane potentials
were recorded in this group, as previously described
(Gelband et al., 1972); those having a prominent
plateau preceding phase 3 repolarization (presumably
specialized fibers) and those with an abbreviated pla-
"teau (presumably muscle). No significant difference
in maximum diastolic potential, action potential am-
plitude, and $V_{\text{max}}$ was observed between these two
types of fibers.

Group B included 45 preparations with significantly
lower maximum diastolic potentials, action potential
amplitudes, and $V_{\text{max}}$ than those in group A. The
action potential characteristics for each atrium in
group B were very variable, with slow responses being
recorded from preparations in which the fast response
predominated.

Group C consisted of 25 preparations having max-
diastolic potentials less negative than $-60$ mV. Of
interest is that there was a far greater heterogeneity
of maximum diastolic potentials in group C than in
group A or B ($F = 3.43; P < 0.01$). The group C action
potentials also showed very slow upstroke velocities of
$<10$ V/sec. In this group, it was impossible to
distinguish between working myocardial and special-
ized fibers.

**Atrial Ultrastructure**

In 62 preparations, atrial structure appeared to be
normal (Pham et al., 1978) (Fig. 1). The muscle cells
were arranged in orderly fashion and measured 6 to
12 μ in diameter at the nuclear level. There was no
evidence of fibrosis. Both side-to-side and end-to-end
intercalated discs were frequent, consisting of fascia
adherens, macula adherens, gap junctions and undif-
ferentiated portions. No abnormalities in disc struc-
ture were found. The cytoplasm was filled with my-
ofibrils, which often extended uninterrupted from one
end of the cell to the other. Usually 4 to 6
myofibrils were present across the cell. Z bands, A
bands, I bands and M lines were distinct and the
sarcomeres measured approximately 2.0 μm in length.

In 29 preparations, focal thickening of the Z bands
and accumulations of abnormal Z band-like material
were found in less than 1% of the cells examined. The
cell organelles (nuclei, mitochondria, Golgi apparatus,
sarcoplasmic reticulum) were intact. The nuclei were
placed centrally in the atrial muscle cells and were
eelliptical in configuration. Mitochondria were inter-
posed between myofibrils. The mitochondria were
round to ovoid and varied considerably in size. The
sarcoplasmic reticulum system was present through-
out the cell and consisted of strands of tubules of
variable size.

In 37 preparations, there was evidence of cellular
degeneration (Fenoglio et al., 1979) (Fig. 2). Degener-
ating cells measured 8–10 μm in diameter and dem-
onstrated myofibrillar loss with preferential loss of
thick filaments, focal accumulations of sarcoplasmic
reticulum, aggregates of mitochondria, and glycogen
granules replacing myofibrillar elements, and myelin
figures and lysosomal bodies. Occasional widening of
the undifferentiated portions of the intercalated discs
was found between degenerating cells. Focal accu-
mulations of Z band material with loss of thick fila-
tments in adjacent sarcomeres were not considered as
evidence of cellular degeneration.

Thirty-two of these preparations had hypertrophic
as well as degenerating cells. Hypertrophy was de-
"fined as a cell diameter greater than 12 μm (12–55
μm). Here we found increased numbers of myofil-
tments, lobulated nuclei, and focal widening of Z
bands. The discs were markedly irregular in contour

---

**Table 3**

<table>
<thead>
<tr>
<th>Transmembrane Potential Characteristics of Human Atrial Fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (51)*</td>
</tr>
<tr>
<td>AP amplitude (mV)</td>
</tr>
<tr>
<td>Overshoot (mV)</td>
</tr>
<tr>
<td>MDP (-mV)</td>
</tr>
<tr>
<td>$V_{\text{max}}$ (V/sec)</td>
</tr>
</tbody>
</table>

* Number of preparations.
† $P < 0.01$ compared to groups A and C.
‡ $P < 0.01$ compared to groups A and B.
FIGURE 1. Normal atrial ultrastructure. The sarcomeres of the right atrial myocardial cells are in register across the cell with distinct Z bands, A bands, M lines, and I bands. The sarcolemma is intact and T-tubules are not present, although focal vacuolated mitochondria and dilated segments of sarcoplasmic reticulum are seen. The mitochondria are ovoid and situated both adjacent to myofibrils and within the perinuclear region. Lipid droplets are present (13,500×).

and were associated with increased deposition of Z band-like material and increased accumulations of fibrillar material especially at fascia adherens.

Relationship of Cellular Electrophysiological to Clinical Data

Table 4 shows the relationship between atrial size and the maximum diastolic potential of human atrial fibers. Mild to moderate dilation had no significant relationship with maximum diastolic potential (P > 0.10). However, maximum diastolic potential was significantly lowered in markedly dilated atria (P < 0.01).

Figure 3 illustrates the correlation between maximum diastolic potential and atrial pressure (r = 0.52; P < 0.05). The use of a multiple stepwise regression technique improved this correlation by introducing atrial size into the regression equation (r = 0.59; P < 0.05). Based on these data, Figure 4 shows the relationship expected between maximum diastolic potential and atrial pressure in atria of normal size and in severely dilated preparations. As atrial pressure and dilation increased, the fibers depolarized.

The relationship of the electrophysiological parameters to the clinical diagnoses is illustrated in Table 5. In patients with congenital or atherosclerotic heart disease the diagnosis, itself, did not have a significant relationship with maximum diastolic potential. However, preparations from patients with rheumatic heart disease were significantly depressed and depolarization was related to pressure and volume overload (we cannot rule out rheumatic involvement of the atrial wall as an important additional factor).

The relationship of cyanosis and maximum diastolic potential was assessed in 59 patients with congenital heart disease. In 35 subjects without cyanosis, MDP was −72.8 ± 7.5 mV. In 24 patients with cyanosis, it was −72.4 ± 6.1 mV (P > 0.05).

In the 54 preparations obtained from patients not
receiving medication, MDP was $-72.1 \pm 7.5$ mV and 50% of the preparations initiated automatic rhythms on cessation of the drive stimulus. In the 43 preparations obtained from patients receiving digoxin therapy, MDP was $-62.8 \pm 14.0$ mV and only 33% of the preparations became automatic ($P < 0.01$). Moreover, automatic rate in fibers from this group was slower than in fibers from the nonmedicated patients. Eleven patients were taking propranolol; of these, seven developed automatic rhythms when the drive stimulus was discontinued. MDP in this group was not significantly depressed ($-73.5 \pm 3.0$ mV).

Atrial fibrillation was observed in 23 patients. The preparations obtained from those patients had an MDP of $-57.1 \pm 13.8$ mV as compared to $-71.7 \pm 8.5$ mV in 85 preparations from patients free of arrhythmias ($P < 0.01$). The group of patients with atrial fibrillation could be broken down into two subgroups: the first, of 12 patients, had maximum diastolic potentials in the $-55$ to $-70$ mV range, including a number with fast response action potentials (ranging from 100 to 150 V/sec). These atria were largely from group B. The second group had maximum diastolic potentials of $-40$ to $-50$ mV and were either quiescent or showed slow response action potentials ($V_{\text{max}}$

![Figure 2. Abnormal atrial ultrastructure. In many of the severely degenerating cells, the myofibrils are completely replaced by clusters of small, irregular mitochondria, aggregates of dilated sarcoplasmic reticulum, and clusters of membrane-bound osmophilic bodies which presumably represent lysosomes. Only remnants of myofibrils are present against the sarcolemma. The sarcolemma and associated basement membrane appear normal. Aggregates of glycogen are frequent. These degenerative changes have been called "lysosomal degeneration" (10,500 X).](image-url)
< 20 V/sec). Atria from both groups were markedly dilated (+++) and atrial pressure was 14 ± 9 mm Hg. These atria were from group C.

Finally, two patients had experienced paroxysmal atrial tachycardia. MDP in their right atria was −73.6 ± 1.1 mV.

To determine the relationship of the clinical data to the maximum diastolic potential, 11 variables (age, sex, atrial size, atrial pressure, P wave duration, drug therapy, congenital heart disease, rheumatic heart disease, atherosclerotic heart disease, cyanosis, arrhythmias) were analyzed by stepwise multiple regression. Atrial pressure and P wave duration were the variables best correlated with MDP (r = 0.61, P < 0.01) (see Table 6, Eq. 1). The introduction of atrial size and arrhythmias only slightly improved the correlation coefficient (to r = 0.65; Table 6, Eq. 2).

Relationship of Ultrastructure to Clinical and Electrical Function

When atria with no evidence of disk changes and cellular degeneration were compared to atria with such changes, significant differences in related clinical and electrophysiological characteristics were observed (Table 7). By a stepwise multiple regression, we then

![Figure 3](image-url)  
**FIGURE 3.** Relationship between MDP (in mV, vertical axis) and atrial pressure (in mm Hg, horizontal axis). The filled circles refer to normal or moderately dilated atria, whereas the unfilled circles refer to markedly dilated atria. The correlation coefficient r is 0.52 (P < 0.05).

![Figure 4](image-url)  
**FIGURE 4.** Relationship between MDP, atrial pressure (AP), and atrial size (AS). The broken line describes the relationship expected in atria of normal size between MDP and atrial pressure. The solid line represents the same relationship in severely dilated preparations. Atrial pressure is the variable best correlated with MDP, but the addition of AS significantly improves the correlation (r = 0.59). The lines differ significantly (P < 0.05).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>MDP (mV)</th>
<th>( V_{\text{max}} ) (V/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>61</td>
<td>72.3 ± 7.2</td>
<td>156 ± 68</td>
</tr>
<tr>
<td>ASD</td>
<td>17</td>
<td>70.4 ± 8.9</td>
<td>159 ± 75</td>
</tr>
<tr>
<td>VSD</td>
<td>11</td>
<td>75.2 ± 6.9</td>
<td>182 ± 73</td>
</tr>
<tr>
<td>TGV</td>
<td>8</td>
<td>72.5 ± 7.3</td>
<td>184 ± 31</td>
</tr>
<tr>
<td>Fallot</td>
<td>12</td>
<td>72.3 ± 5.2</td>
<td>144 ± 36</td>
</tr>
<tr>
<td>Atherosclerotic heart disease</td>
<td>22</td>
<td>71.0 ± 9.8</td>
<td>150 ± 69</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>31</td>
<td>61.5 ± 14.8*</td>
<td>84 ± 93*</td>
</tr>
</tbody>
</table>

ASD = atrial septal defect; VSD = ventricular septal defect; TGV = transposition of great vessels; Fallot = tetralogy of Fallot. *MDP and \( V_{\text{max}} \) were significantly lower in preparations obtained from patients with rheumatic heart disease than in preparations from patients with congenital or atherosclerotic heart disease (P < 0.01).
TABLE 6
Regression Equations, Relating MDP, Degenerative Changes, and Clinical Data

<table>
<thead>
<tr>
<th>Equation</th>
<th>MDP</th>
<th>AS</th>
<th>AP</th>
<th>DC</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>MDP = 80.3 - 3.24 AS - 0.56 AP</td>
<td>r = 0.59</td>
<td></td>
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<td>(2)</td>
<td>MDP = 87.1 - 0.60 AP - 0.14 P dur</td>
<td>r = 0.61</td>
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<td>(3)</td>
<td>DC = 0.017 P dur + 0.059 AP - 1.45</td>
<td>r = 0.66</td>
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<tr>
<td>(4)</td>
<td>MDP = 74.1 - 2.2 disk changes - 4.9 DC</td>
<td>r = 0.72</td>
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MDP = maximum diastolic potential; AS = atrial size; AP = atrial pressure; DC = degenerative changes.

Determined a linear correlation between degenerative changes, P wave duration, and atrial pressure (r = 0.66, P < 0.01) (Table 6, Eq. 3 and 4).

Depolarization of the membrane was increasingly prominent as changes in the intercalated disks and degenerative changes occurred (Table 8). Multiple stepwise regression showed that the degenerative changes of the tissue were the most important factor correlated with depolarization, but this correlation was significantly improved by taking the disk changes into account (r = 0.72, P < 0.01). This relationship is shown in Figure 5 (also see Eq. 4, in Table 6).

Finally, we divided the patients into two groups: those with normal ultrastructure (group I) and those with abnormal ultrastructure (group II). Abnormal ultrastructure (group II) was defined as the presence of degenerative changes in greater than 1% of the cells studied. To discriminate between the two groups of patients, we used the logistic discrimination method, combined with a variable selection technique. Table 9 lists the linear discriminant function that was obtained and the corresponding classification matrix. MDP, P wave duration, age, atrial pressure, and presence or absence of rheumatic heart disease, in decreasing order of importance, allowed prediction of the ultrastructure with an error rate of 5.4%.

**Discussion**

One of our purposes in this study was to determine the extent to which ultrastructural alterations might be associated with abnormalities in electrophysiological function of atrial cells. Because depressed action potentials may occur when cardiac tissue is not hand-

![Figure 5. Relationship between MDP, degenerative changes, and disk alterations. The broken line represents the relationship between MDP and degenerative changes, when there are no disk changes. The solid line represents the same relationship in case of severe disk alterations.](https://www.ahajournals.org/doi/10.1161/01.CIR.83.4.195)
dial surface (Friedman et al., 1975). We observed that when depressed action potentials were recorded from human atrial myocardium, the ultrastructure was usually abnormal. Although Z band changes by themselves were not correlated with changes in electrical function, there was a linear multiple regression relationship between maximum diastolic potential and disc and degenerative changes. The mechanisms by which degenerative changes might modify the electrical properties of atrial myocardial cell membranes are not known; however, Ten Eick and Singer (1971) have suggested that, as a result of cardiac disease, electrogenic pumping may be depressed, resulting in depolarization. Despite the apparent relationship here between ultrastructure and electrophysiological changes, it must be stressed that we are not implying that specific ultrastructural alterations are responsible for the electrophysiological changes, but rather that the two occur in association with one another.

Our second purpose was to test the relationship of the clinical condition of the patient to cellular electrophysiological and ultrastructural characteristics. The association of atrial disease and electrical alterations has been described by many investigators (Fabiato and Fabiato, 1971; Hordof et al., 1976; Mary-Rabine et al., 1980; Singer et al., 1967; Singer et al., 1973; Singer and Ten Eick, 1971; Sleator and de Gubaroff, 1964; Ten Eick and Singer, 1979). Hordof et al. (1976) concluded, on the basis of 22 electrophysiological experiments, that the decrease in MDP was caused by atrial dilation. In this group of patients, all of them children with congenital heart disease, there appeared to be no major relationship between atrial pressure and the electrophysiological changes. Subsequently, in studies of ultrastructure in congenital heart disease, Fenoglio et al. (1979) and Pham et al. (1978) did not find any relation between increased right atrial blood flow and the development of structural changes in the right atrium. In the present study, severe chamber dilation was associated with decreased resting membrane potential, a result consistent with the study of Hordof et al. (1976). However, the present study provides a more definitive evaluation of the relationship between atrial size and maximum diastolic potential than was seen in the 22 patients reported by Hordof et al. (1976). It appears that, although there is a relationship between atrial dilation and maximum diastolic potential, it is not until the atrium is markedly dilated that membrane potential falls below ~60 mV. Hence, the atrium can tolerate moderate degrees of dilation without depolarizing significantly, an observation made in studies of experimentally dilated canine atria as well (Boyd en, 1982).

Although there are minor differences between the present study and the earlier one of Hordof et al. (1976), the overall values for membrane potentials reported in both studies are quite similar. In fact, the group C (Table 3) atria in the present study show maximum diastolic potentials nearly identical to those of the markedly dilated atria in the study by Hordof et al. (1976), whereas the group A and B atria (Table 3) bracket the values reported in the more normal atria in the earlier study. These values also are consistent with those reported in other studies of human atria (e.g., Hordof et al., 1978; Mary-Rabine et al., 1980).

The importance of hemodynamic changes to the electrical and ultrastructural changes in the present study is seen in reviewing the atrial pressure and sizes. The correlation of pressure or volume changes with electrophysiological and ultrastructural alterations is consistent with experimental studies of constriction of the pulmonary artery in the cat in which chronic right ventricular hypertension has resulted in similar electrical abnormalities (Gelband and Bassett, 1973). It also was reported that, in cats with spontaneous cardiomyopathy, severe atrial dilation was associated with low resting potentials (Boyd en, 1977).

In considering the role of electrophysiological abnormalities in the genesis of arrhythmias, it is instructive for one to review the ranges of maximum diastolic potentials in the more diseased as compared to the healthier atria. The standard deviations for maximum diastolic potentials in the markedly dilated atria (Table 3, group C) and in atria from patients with rheumatic disease (Table 5) were greater than the standard deviations in other groups. As heterogeneity of resting and action potentials may be predisposing factors for cardiac arrhythmias, it is possible that the greater variability seen in tissues from the group C patients was of importance in inducing arrhythmias.

Our results also support previous suggestions that the presence of atrial fibrillation is related closely to the degree of atrial dilation (Henry et al., 1973; Watson et al., 1977). However, right atrial dilation, even of severe degree, is not necessarily associated with atrial fibrillation. In fact, atrial pressure appears, if anything, to be an even more important determinant than atrial size. This observation is consistent with a postulate of Probst et al. (1973). Moreover, our own recent study of atrial fibrillation also suggests strongly that the atrial pressure increase is an important requisite for atrial fibrillation to occur (Rosen et al., 1982). Three other factors related to atrial fibrillation

| Table 9 |
| Discriminant Analysis of Clinical and Electrical Variables Related to Cellular Ultrastructure |

| LDF = | $-0.24 \, \text{MDP} + 0.029 \, \text{P dur} + 0.085 \, \text{age} + 0.585 \, \text{AP}$ | $+ \{1.63 \text{for non-rheumatic heart disease}$ |
| | $+ 1.39 \text{for rheumatic heart disease}$ |

<table>
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</thead>
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<tr>
<td>II</td>
<td>3</td>
<td>24</td>
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</tbody>
</table>

Group I = normal ultrastructure; group II = abnormal ultrastructure. AP = atrial pressure; P dur = P wave duration; MDP = maximum diastolic potential.
were: first, the patients with chronic fibrillation were
the oldest patients in the group (age 55.5 ± 9 years)
and had the longest history of arrhythmias; second,
as a group, their atria showed the lowest levels of
membrane potential and most depressed action po-
tentials; third, their atrial ultrastructure was the most
abnormal of any of the subgroups, regardless of
whether their disease was rheumatic or non-rheu-
matic. The mean membrane potentials of the atrial
fibrillators were −66.3 ± 3.9 mV for those in group
C. These membrane potentials are similar to those
described by Ten Eick and Singer (1979) of −58 ± 8.1
mV for 21 patients with atrial fibrillation. Other sim-
ilarities between our findings and those of Ten Eick
and Singer (1979) are the fact that there appeared to
be greater differences in cell-to-cell voltage gradients
in the fibrillating atria (and in group B and C atria in
general) than occurred in atria from group A. Such
disparities in membrane potential may be an impor-
tant predisposing factor for arrhythmias.

Considering the relationship of clinical variables to
atrial arrhythmias, it appears that, in addition to atrial
size (and pressure), cyanosis and age provide strong
predictive indices (see Table 2B). One might wonder
at the inclusion of cyanosis here. Although it is true
that most of our patients with arrhythmias were adults
with acquired heart disease (as demonstrated in the
“clinical data” section), three adult patients with con-
genital heart disease had atrial fibrillation as well. All
were cyanotic. It also must be stressed that cyanosis
achieved its major predictive value in considering
patients in the pediatric age group. In young children,
age (and P wave duration) were less important than
they were in adults in predicting arrhythmias, whereas
atrial size retained its importance and cyanosis
achieved great importance. One might wonder why—
given the importance of cyanosis in predicting arr-
hythmias—a clearer role for cyanosis in the genera-
tion of low membrane potentials was not demon-
strated. In evaluating this, we must stress that the
tissues were normally oxygenated during the experi-
ments. Hence, even though hypoxia might reversibly
depress membrane potential when the tissues are in
situ, this effect would not be seen when the tissues
are excised and superfused with normal Tyrode’s
solution.

The relationship of digitalis therapy to the maxi-
imum diastolic potential and the presence of arrhyth-
mas is complex. We have shown that atria from
patients receiving digitalis had a significantly lower
(i.e., less negative) maximum diastolic potential than
either those from patients receiving no medication or
those from patients receiving propranolol. The lower
maximum diastolic potential in the digitalis group
probably reflects the fact that most of the patients
taking digitalis had elevated atrial pressures, large,
atria, and—in many—atrial fibrillation. Of interest as
well is that only 33% of atria from patients receiving
digitalis therapy developed automatic rhythms,
whereas 50% of those from patients not receiving
medication became automatic. In a previous study
(Hordof et al., 1978), we have shown that human atrial
preparations superfused with ouabain in concentra-
tions that are not toxic show a decrease in the slope of
phase 4 depolarization and automaticity. This effect
of ouabain is similar to that of acetylcholine and is
blocked by atropine. Presumably, this action of oua-
bain is related to its interaction with parasympathetic
fibers supplying the heart and acetylcholine release at
vagal terminals. In the present study, we can speculate
that the lesser incidence of automaticity in atria of
patients receiving digoxin therapy is the result of the
same vagal interaction. In no instance did we see
delayed afterdepolarizations in these atria. These os-
cillations are the result of the toxic effects of digoxin
(e.g., Rosen et al., 1973a). Their absence is consistent
with the fact that none of the patients was suspected
to be digitalis toxic prior to surgery, and no patient
received digitalis within the 24 hours prior to surgery.

In conclusion, as shown in Tables 6 and 7, it is
possible to relate the clinical, ultrastructural, and
electrophysiological manifestations of cardiac disease
mathematically in such a way that the derangement
in maximum diastolic potential and—with this—in
the action potential becomes predictable. Moreover,
the clinical variables studied, in themselves, can pre-
dict the likelihood of cardiac arrhythmias (Table 2).
In considering the clinical variables, it appears that
when Equation II-B is applied to a group of patients
not previously included in our analysis (Appendix II),
it provides an error rate and a predictive accuracy that
might be of some clinical value. In only 1 of 21
instances where the equation predicted sinus rhythm
did an arrhythmia occur, and in 8 instances where
arrhythmias were predicted, these were documented
in 6. It might be possible to improve upon the accu-
rracy of the equation if the frequency of arrhythmias
were evaluated by means of the Holter monitor in-
stead of the ECG’s used in the present study. The
resultant data should help improve the accuracy of
the prognostic index in assessing the likelihood of
arrhythmias in individual patients.

Appendix I

The logistic discrimination method is based on the
assumption that the relationship between posterior
probabilities and linear discriminant function has the
logistic form—that is, if

\[ L(x) = a_0 + a_1 x_1 + \cdots + a_i x_i \]  

(1)
denotes the linear discriminant function based on the
i variables and \( Pr (II/x) \) represents the posterior prob-
bility of group II conditional to the observation of
the i variables \( x = (x_1, \cdots, x_i) \), then

\[ Pr (II/x) = \frac{\exp(L(x))}{1 + \exp(L(x))}. \]  

(2)

It immediately follows that the posterior probability
of group I is given by the relation:

\[ Pr (I/x) = 1 - Pr (II/x) = \frac{1}{1 + \exp(L(x))}. \]  

(3)
It is known that relations 2 and 3 hold for many multivariate distributions, including both continuous and discrete variables; thus the method is particularly suitable to the problem here. The coefficients $a$ of the discriminant function are estimated directly from the training sample using an iterative maximum likelihood procedure. All calculations were carried out on a PDP 11/45 (Digital Equipment).

### Table 10

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<th>Cyanosis</th>
<th>Drug</th>
<th>P dur (msec)</th>
<th>Age (years)</th>
<th>Atrial size (1-4+)</th>
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* 1 = yes.
† 0 = no.

Nevertheless, it may be that, among these variables, some are correlated and bear only redundant information. Therefore, variables were introduced in a stepwise manner starting from the most discriminant and adding the remaining variables one at a time until no significant improvement was observed in the discrimination. We decided to base our stopping criteria not only on the increase of the log likelihood ratio, (which is distributed asymptotically as a $\chi^2$ with 1 degree of freedom), but also on the error rate.

### Appendix II

We used the two formulas presented in Table 2 to predict the likelihood of arrhythmias in 29 patients who were not included in the present series.

#### A

$$LDF = 2.14 \text{ cyanosis} + 1.6 \text{ drug} + 0.051 \text{ P duration} - 7.89$$

#### B

$$LDF = 0.067 \text{ age} + 0.994 \text{ atrial size} + 2.65 \text{ cyanosis} - 6.49$$

In Tables 10 and 11 are listed the patient variables evaluated, the LDF calculated using each formula, and the presence or absence of an atrial arrhythmia.

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Address for reprints: Michael R. Rosen, M.D., Department of Pharmacology, Columbia University, College of Physicians & Surgeons, 630 West 168th Street, New York, New York 10032.

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INDEX TERMS: Atrial arrhythmias • Cardiac action potentials • Congenital heart disease • Rheumatic heart disease

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L Mary-Rabine, A Albert, T D Pham, A Hordof, J J Fenoglio, Jr, J R Malm and M R Rosen

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