The Relationship of Transmembrane Potential to Surface Morphology of Human Atrial Muscle and Cardiac Hemodynamics

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SUMMARY

A correlative study of transmembrane potential characteristics, surface morphological features of human atrial muscle, and cardiac hemodynamics was carried out in 41 patients, who were divided into 2 groups based on the level of the mean maximum diastolic potentials (MDP). Group A consisted of 19 patients with MDP values ranging from -60.0 to -82.0 mV ($\text{mean} \pm \text{S.D.} = -65.70 \pm 6.63$ mV). Group B included 22 patients who had abnormally low MDP (range -36.0 — -58.5 mV, $\text{mean} \pm \text{S.D.} = -48.14 \pm 6.72$ mV). The differences in electrophysiological data were statistically significant. However, there were no significant differences in the hemodynamic data between the 2 groups. Furthermore, there was poor correlation between the electrophysiological and hemodynamic data in both groups. In group A, scanning and transmission electron microscopy revealed either no changes or only mild alterations in the surface morphology of the atrial myocardium. Various degrees of surface morphological changes, including a focal loss of the endothelium which was always associated with endocardial fibrosis, irregular thickening and lamination of the glycocalyx, disruption of the sarcolemma and complete destruction of the surface membrane structures were more often observed in group B.

These results provide valuable evidence that sarcolemmal changes may underlie the electrophysiological alterations in diseased human atria. We suggest that the principal pathogenetic mechanisms leading to the transmembrane potential changes are the altered surface morphology of atrial myocardial cells, resulting from underlying disease processes.

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IN the past decade, much attention has focused on the study of electrophysiological properties of isolated human heart muscle.¹⁾⁻¹⁰⁾ Of particular interest in the previous reports was the identification of the contributions of a large proportion of atrial myocardial cells to abnormally low diastolic membrane potentials ($= < -60$ mV), which occurred predominantly in diseased atria^{3), 6)-9)} and may be implicated in the genesis of cardiac arrhythmias.¹¹⁾⁻¹⁷⁾ Since the transmembrane potentials are created by the membrane's selective permeability to specific ions¹⁸⁾⁻²¹⁾ the key to the clarification of the pathogenetic mechanisms of the electrophysiological alterations of human atrial fibers clearly must lie in an understanding of the sarcolemmal surface morphology. In view of paucity of available published reports dealing with the correlation between electrophysiological properties and surface morphology of the human atria, it is the purpose of the present study to define the relationship between transmembrane potential characteristics, surface morphological features of human atrial muscle and cardiac hemodynamics. More specifically, we have investigated the correlation between abnormally reduced diastolic potentials and sarcolemmal surface alterations of atrial myocardial cells.

MATERIALS AND METHODS

A total of 41 patients (26 men and 15 women) with various forms of heart diseases were included in this study. Their ages ranged from 2 to 60 years. The clinical diagnoses, which were confirmed by cardiac catheterization and surgical operation, were tetralogy of Fallot (T. F.) in 16 cases, interatrial septal defect (ASD) in 11 cases, interventricular septal defect (VSD) in 6 cases, and chronic rheumatic heart disease (RHD) in 8 cases. Prior to surgery, informed consent was obtained from all patients. Digitalis and antiarrhythmic agents were discontinued at least 3 days before operation. Small pieces (approximately 1 cm²) of atrial myocardium were excised from the anterior free wall of the right atrium as part of the routine cannulation procedure for cardiopulmonary bypass during open heart surgery.

The tissues were immediately immersed in cool Tyrode's solution after excision from the atrium and rapidly transported to the laboratory. Then the specimens were transferred to a tissue chamber and superfused with Tyrode's solution warmed to 37°C and equilibrated with a gas mixture of 95%

O₂ and 5% CO₂. The superfusate flow rate was 8 ml/min. The Tyrode's solution (pH 7.2–7.4) had the following composition (mM/L): NaCl, 137; CaCl₂, 2.7; KCl, 4.0; NaHCO₃, 12; MgCl₂, 0.5; NaH₂PO₄, 1.8; glucose, 5.5. The tissues were allowed to recover while stimulated electrically at a rate of 60/min for about 20 min. When the atrial myocardium beat spontaneously after termination of the drive stimulus, transmembrane potentials were measured with glass capillary microelectrodes filled with 3 M KCl, having tip diameters smaller than 0.5 μ , and resistances between 10 and 25 M Ω . Potentials were measured at 10 sites in each tissue sample. The membrane potentials were monitored on a dual beam cathode ray oscilloscope (Nihon Kohden Co, VC-9), photographed with a recording camera (Nihon Kodon Co, PC-3A), and recorded simultaneously with an eight-channel strip-chart recorder.

After completion of action potential studies, the atrial specimens were immediately prepared for electron microscopic observations. The specimens were fixed with iced 3% glutaraldehyde in 0.1 M phosphate buffer (pH 7.2–7.4) for 2 hours. Subsequently, the atrial tissues were rinsed with cold 0.1 M phosphate buffer several times, and postfixed with a 2% phosphate buffered osmium tetroxide solution (pH 7.2–7.4) for an additional 2 hours. The tissues were then dehydrated in graded concentrations of chilled ethanol. For scanning electron microscopy, the dehydrated tissues were subjected to critical point drying. The samples were then placed in liquid nitrogen, fractured with a pre-cooled razor blade, mounted on specimen stubs for SEM, and coat-

Fig. 1. Different action potential configurations with a reduced maximum diastolic potential, recorded at different sites in the same specimen from a patient with rheumatic heart disease (case 18 in group B).

Table I. Hemodynamic and Electrophysiological Data in Patients with Resting Membrane Potentials Greater than -60 mV (Group A)

No. of Cases	Sex	Age (yrs)	Diagnosis	Dilatation of RA	Hemodynamic Data			Electrophysiologic Data		
					O ₂ Saturation (%)		Pressure (mmHg)	MDP (mV)	OSP (mV)	APA (mV)
					RA	SA	RA (mean)			
1	M	9	T. F.	+	69.5	88.5	2.0	-70.5	+10.0	80.6
2	M	13	T. F.	-	73.0	84.0	6.0	-66.5	+11.5	78.0
3	F	20	T. F.	-	78.0	86.0	4.0	-65.0	+14.0	79.0
4	F	14	T. F.	-	70.5	80.0	3.5	-61.5	+10.0	71.5
5	M	3	T. F.	+	47.0	51.5	2.5	-60.8	+16.3	77.1
6	F	6	T. F.	+	56.5	76.0	0.6	-60.5	+13.0	73.5
7	M	3	T. F.	-	80.5	94.5	1.5	-60.0	+22.0	82.0
8	M	16	T. F.	-	79.0	80.0	2.0	-60.0	+14.0	74.0
9	F	21	ASD	-	90.0	95.0	1.5	-82.0	+19.0	101.0
10	M	27	ASD	+	91.5	95.5	5.0	-78.0	+13.0	91.0
11	M	30	ASD	-	88.0	97.5	2.0	-66.0	+17.0	83.0
12	F	4	ASD	-	76.0	94.0	1.0	-61.0	+17.0	78.0
13	F	13	ASD	+	89.5	95.0	5.0	-60.0	+15.8	75.8
14	M	4	VSD	-	75.5	93.5	4.5	-78.0	+15.0	93.0
15	M	18	VSD	-	74.5	93.0	1.0	-62.5	+18.5	81.0
16	M	6	VSD	-	73.0	93.0	3.5	-64.0	+9.0	73.0
17	M	29	RHD	+	68.0	96.0	5.0	-68.0	+13.0	81.0
18	M	33	RHD	+	65.0	93.5	6.5	-64.0	+7.0	71.0
19	M	12	RHD	-	77.0	93.5	1.0	-60.0	+14.0	74.0

Abbreviations: M=male; F=female; T. F.=tetralogy of Fallot; ASD=atrial septal defect; VSD=ventricular septal defect; RHD=rheumatic heart disease; RA=right atrium; SA=systemic arteries; MDP=maximum diastolic potential; OSP=overshoot potential; APA=action potential amplitude.

The abbreviations in the subsequent tables are the same.

ed with gold. Then the specimens were examined with a Hitachi H-5010 SEM operated at 25 KV. For transmission electron microscopy, the dehydrated tissues were embedded in Epon-Araldite. The specimens were sectioned with a Sorvall MT-2B Porter-Blum ultramicrotome using glass knives and stained with uranyl acetate and lead citrate. The ultrathin sections were examined with a Hitachi H-500 electron microscope operated at 75 KV.

The following clinical data were available for correlation with transmembrane potential characteristics: mean right atrial pressure (mRAP), oxygen saturation of the right atrium and systemic arteries, and right atrial size (estimated from posterior-anterior projection of chest roentgenogram, the electrocardiogram and observed during surgery as normal or dilated). All data were analysed statistically with Student's paired *t* test. A *p* value of less

Table II. Hemodynamic and Electrophysiological Data in Patients with Resting Membrane Potentials Less than -60 mV (Group B)

No. of Cases	Sex	Age (yrs)	Diagnosis	Dilatation of RA	Hemodynamic Data			Electrophysiologic Data		
					O ₂ Saturation (%)		Pressure (mmHg)	MDP (mV)	OSP (mV)	APA (mV)
					RA	SA	RA (mean)			
1	F	5	T. F.	+	57.5	76.0	0.6	-58.5	+13.5	72.0
2	M	17	T. F.	-	57.5	75.5	1.5	-57.2	+17.5	74.7
3	M	5	T. F.	+	55.0	69.0	4.5	-55.3	+12.5	67.8
4	M	5	T. F.	-	67.5	82.0	2.5	-52.0	+10.7	62.7
5	F	26	T. F.	-	67.5	94.5	1.2	-51.8	+12.6	64.4
6	F	4	T. F.	-	66.0	78.5	2.5	-51.0	+10.0	61.0
7	F	13	T. F.	-	73.5	79.0	1.5	-49.0	+12.0	61.0
8	F	30	T. F.	-	68.5	76.0	3.0	-46.0	+8.0	54.0
9	M	11	ASD	+	90.5	95.0	1.0	-52.4	+8.8	61.2
10	M	18	ASD	-	86.0	95.0	3.0	-50.8	+14.0	64.8
11	M	9	ASD	-	81.0	95.5	1.0	-50.3	+15.7	66.0
12	M	20	ASD	+	86.5	95.0	6.0	-45.0	+12.0	57.0
13	M	7	ASD	-	91.0	96.0	1.5	-41.3	+11.3	52.6
14	F	20	ASD	-	85.0	96.0	2.0	-40.0	+4.5	44.5
15	M	2	VSD	-	74.5	95.5	1.5	-53.0	+10.0	63.0
16	M	6	VSD	-	69.0	94.5	1.0	-52.7	+18.3	71.0
17	M	8	VSD	+	76.5	96.0	1.5	-50.0	+15.2	65.2
18	F	26	RHD	-	70.0	94.5	6.0	-54.0	+14.0	68.0
19	F	35	RHD	+	76.0	95.5	1.0	-38.0	+4.5	42.5
20	F	57	RHD	+	68.0	96.0	5.5	-37.6	+9.2	46.8
21	M	60	RHD	+	78.0	94.0	1.5	-37.3	+10.0	47.3
22	M	42	RHD	+	79.0	96.0	1.0	-36.0	+10.0	46.0

than 0.05 was accepted as the limit of significance. All data are reported as a mean $\pm$ standard deviation.

RESULTS

Various patterns of action potential configurations, with variability in the level of maximum diastolic potential (MDP), were often obtained from multiple impalements at different sites in the same specimen (Fig. 1). According to a recent study of Hordof et al.^(6),7) 41 patients were divided into 2 groups based on whether the mean MDP from the 10 impalements in each preparation was greater than or less than -60 mV. Group A consisted of 19 patients with MDP greater than -60 mV. The 22 patients with MDP less than -60 mV were included in group B. The hemodynamic parameters

Table III. Statistical Analyses of Electrophysiological and Hemodynamic Data

	Electrophysiologic Data						Hemodynamic Data					
	MDP (-mV)		OSP (+mV)		APA (mV)		O ₂ Sat. of RA (%)		O ₂ Sat. of SA (%)		mRAP (mmHg)	
	Gr. A	Gr. B	Gr. A	Gr. B	Gr. A	Gr. B	Gr. A	Gr. B	Gr. A	Gr. B	Gr. A	Gr. B
Mean	65.70	48.14	14.16	11.55	79.84	59.70	74.84	73.81	88.84	89.04	3.05	2.30
SD	6.63	6.72	3.63	3.47	7.59	9.31	10.93	10.09	10.44	8.85	1.81	1.65
P value	<0.001		<0.50		<0.001		>0.20		>0.20		>0.10	

Abbreviations: SD=standard deviation; Gr.=group; Sat.=saturation.

Table IV. Correlation between Electrophysiological and Hemodynamic Data

	Group A			Group B		
	MDP	OSP	APA	MDP	OSP	APA
RAO ₂	0.39	0.34	0.50†	-0.50*	-0.30	-0.47†
SAO ₂	0.33	0.08	0.33	-0.50*	-0.14	-0.41
mRAP	0.24	-0.54*	-0.04	-0.04	-0.02	-0.04

Numbers are the correlation coefficients.

* $0.02 > p > 0.01$; † $0.05 > p > 0.02$

RAO₂=oxygen saturation of right atrium; SAO₂=oxygen saturation of systemic artery; mRAP=mean right atrial pressure.

and electrophysiological data, including MDP, overshoot potentials (OSP), and action potential amplitude (APA) in groups A and B are summarized in Tables I and II, respectively.

The relationship between transmembrane potential characteristics and cardiac hemodynamic parameters

In group A the MDP ranged from -60.0 to -82.0 mV, with a mean of -65.70 ± 6.63 mV, OSP ranged from +7.0 to +22.0 mV, with a mean of $+14.16 \pm 3.63$ mV, and APA ranged from 71.0 to 101.0 mV, with a mean of 79.84 ± 7.59 mV. In group B the MDP was between +36.0 and -58.8 mV, with a mean of -48.14 ± 6.72 mV, OSP between +4.5 and 18.3 mV, with a mean of $+11.55 \pm 3.47$ mV, and APA between 42.5 and 74.7 mV, with a mean of 59.70 ± 9.31 mV.

Right atrial dilatation, as estimated from the radiographic findings, electrocardiograms and surgical observations was noted in 7 (36.8%) and 9 (40.9%) patients of groups A and B, respectively. The hemodynamic data in group A (Table I) showed that oxygen saturation of the right atrium varied between 47.0 and 91.5%, with a mean of $74.8 \pm 10.93\%$. Oxygen saturation of the systemic arteries was between 51.5 and 97.5%, with a mean of $88.84 \pm$

10.44%, and the mRAP between 0.6 and 6.5 mmHg, with a mean of 3.05 ± 1.81 mmHg. The hemodynamic data from group B (Table II) showed that oxygen saturation of the right atrium ranged between 55.0 and 91.0%, with a mean of $73.81 \pm 10.09\%$, oxygen saturation of the systemic arteries ranged between 69.0 and 96.0%, with a mean of $89.04 \pm 8.85\%$, and the mRAP ranged between 0.6 and 6.0 mmHg, with a mean of 2.30 ± 1.65 mmHg. The statistical analyses of electrophysiological and hemodynamic data in both groups are shown in Table III. The differences in the electrophysiological data between groups A and B, particularly the MDP and APA, were highly significant ($p < 0.001$). However, there were no significant differences in the hemodynamic data between these 2 groups. Table IV showed the correlation between electrophysiological and hemodynamic data. In general, there was a poor correlation between these parameters.

The relationship between transmembrane potential characteristics and surface morphological findings

The surface characteristics of entire tissue specimens from the endocardium to myocardium could be readily appreciated, even at the subcellular level, with scanning and transmission electron microscopy (TEM). In group A, the scanning electron microscopic observations showed that there were, at most, only mild alterations on the surface morphology from the endocardium to myocardium. The endocardium generally exhibited an intact endothelium. The individual endothelial cells were clearly delineated (Fig. 2). Although focal areas of endothelial desquamation were observed in 7 of 19 group A patients (2 in T. F., 2 in ASD, and 3 in RHD), the denuded subendothelial surface was rather smooth (Fig. 3), and the underlying exposed myocardial cells appeared normal (Fig. 4). The muscle cells in the myocardium usually showed mild or almost no pathologic alterations on the cell surface with distinct cell boundaries (Fig. 5). The cell membranes of atrial myocardial fibers were comprised of three distinct layers when viewed with TEM (Fig. 6). The glycocalyx (basement membrane) present on the external surface of the plasmalemma was composed of two layers, termed the surface coat and external lamina.²²⁾⁻²⁴⁾

In 13 of 22 group B patients (3 in T. F., 4 in ASD, 1 in VSD, and 5 in RHD), particularly in patients with RHD, the focal loss of the endothelium, associated with endocardial fibrosis, was a common finding (Fig. 7). The myocardial cells often showed surface morphological changes which were characterized by various degrees of surface defects, including a complete loss of the surface details and intercellular borders (Fig. 8). These scanning electron microscopic findings were compatible with transmission electron micro-

Fig. 2. Scanning electron micrograph of normal endocardium showing an intact endothelium with a corrugated surface. Individual endothelial cells are marked by nuclear bulges (arrows). $\times 3,600$. Horizontal bar = 5μ .

Fig. 3. Scanning electron micrograph of the endocardium, showing endothelial desquamation with a smooth, denuded subendothelial surface (large arrows). Note the individual endothelial cells are clearly delineated with microvilli on the cell surface (small arrows). $\times 3,600$. Horizontal bar = 5μ .

Fig. 4. Scanning electron micrograph of the denuded subendothelial surface exposing the underlying myocardial cells (large arrows). Individual endothelial cells exhibit a number of microvilli on the cell surface (small arrows). $\times 3,600$. Horizontal bar = 5μ .

Fig. 5. Scanning electron micrograph of normal myocardial cells in the myocardium showing smooth cell surfaces with distinct cell boundaries (arrows). $\times 3,600$. Horizontal bar = 5μ .

Fig. 6. Transmission electron micrograph, showing the three layers of the myocardial cell membrane (arrows). The glycocalyx (G), composed of surface coat (small arrow head) and external lamina layer (large arrow head), is closely applied to the plasmalemma (P). Mf=myofilaments; Z=Z line. $\times 90,000$.

Fig. 7. Scanning electron micrograph of the endocardium, exhibiting a focal loss of the endothelium associated with endocardial fibrosis (arrows). $\times 3,600$. Horizontal bar= $5\ \mu$.

Fig. 8A and B. Scanning electron micrographs of the myocardial cells, showing various degrees of surface structural changes. A: Small defects (small arrows) are observed on the cell surface. $\times 3,600$. Horizontal bar = 5μ . B: Extensive destruction of the cell surface, exposing internal structures (large arrows), is associated with ill-defined intercellular borders. $\times 3,600$. Horizontal bar = 5μ .

Fig. 9A and B. Irregular thickening and lamination of the glycocalyx (G). A: Focal thickening of the glycocalyx is evident (arrow heads). P=plasmalemma (arrow); M=mitochondria; Mf=myofilaments. $\times 36,000$. B: Lamination of the glycocalyx is illustrated (arrows). Mf=myofilaments. $\times 72,000$.

Fig. 10. Transmission electron micrograph of myocardial cells, showing a loss of the triple-layered structure of the cell membranes (large arrows). P = plasmalemma (small arrows); G = glycocalyx (arrow heads); Mf = myofilaments; Z = Z line. $\times 63,000$.

Fig. 11 A and B. Various patterns of pathological destruction of the sarcolemma (S) of myocardial cells. A: A focal defect of the sarcolemma is shown (large arrows). $\times 45,000$. B: Disruption of the sarcolemma is illustrated (large arrows). $\times 45,000$.

Fig. 12. Scanning electron micrograph of rigid and small myocardial cells with an irregularly wrinkled surface. $\times 3,600$. Horizontal bar = 5μ .

Fig. 13. Scanning electron micrograph of necrotic myocytes covered with fibrous tissue on the cell surface (arrows). $\times 5,400$. Horizontal bar = 5μ .

scopic observations, which showed various degrees of sarcolemmal changes including irregular thickening and lamination of the glycocalyx (Fig. 9), loss of an identifiable, triple-layered structure of the cell membrane (Fig. 10) and various patterns of sarcolemmal destruction (Fig. 11). In many instances, the muscle cells appeared rigid and small with surface irregularities (Fig. 12). Necrotic myocytes were often present, and usually covered with fibrous tissue on the cell surface (Fig. 13).

DISCUSSION

In recent years, a number of studies have examined the electrophysiological properties of isolated heart muscle obtained during open heart surgery in an effort to explore the cellular basis of electrical activity in man.¹⁾⁻¹⁰⁾ The most interesting results have been the identification of a large group of atrial myocardial cells with reduced diastolic membrane potentials (< -60 mV) in diseased human atria.^{3),6),7)} Since the myocardial cells with diastolic potentials less than -60 mV have a preponderance of slow response action potentials, primarily initiated by a slow inward current, they may play a role in the genesis of cardiac arrhythmias.^{6),7),10)-17),25),26)} Thus, particular attention has been paid to the pathogenetic mechanisms resulting in the alterations of human atrial transmembrane potentials. Atrial chamber dilatation and hemodynamic factors may play an important role in the altered electrophysiological properties of the atrial fibers.⁶⁾ In the present study, there was only a slight difference in the incidence of right atrial dilatation between groups A and B, although the differences in the electrophysiological data between the 2 groups were highly significant ($p < 0.001$). Similarly, there were no significant differences in the hemodynamic parameters between these 2 groups. Furthermore, there was no significant correlation between electrophysiological and hemodynamic data in both groups. Thus, our results indicate that atrial enlargement and hemodynamic factors are not the principal determinants of the electrophysiological alterations of atrial fibers.

More recent studies of the electrophysiological characteristics of human atrial fibers have suggested that a substantial decrease in the K^+ conductance⁸⁾ is the basic ionic mechanism involved in the alterations of the atrial transmembrane potential. However, the problem of how the underlying disease processes affect the active and passive electrical properties of the atrial myocardial cell membrane remains obscure. Since the transmembrane potentials are created by ions that pass through the cellular membrane, the permeability of membrane wall to specific ions becomes a key parameter in electrophysiological phenomena.¹⁷⁾⁻²¹⁾ There is little doubt that surface struc-

tural changes can modify the permeability of the cell membrane to ions which further alters the electrophysiological properties of the cells. Since an intact sarcolemmal surface is absolutely necessary for maintenance of the functional integrity of cellular electrical activity,²²⁾⁻²⁴⁾ it is important to understand the relationship of surface morphological changes in the atrial myocardium to pathogenetic mechanisms contributing to the electrophysiological alterations of the atrial fibers. By correlating the electron microscopic findings with the electrophysiological data in the present report, it was evident that various degrees of pathological alterations of the surface morphology of isolated human atria were more often observed in patients in group B with abnormally low diastolic potentials as compared with group A. The abnormal findings observed on the sarcolemmal surface of atrial myocardial cells with the SEM varied from small defects to complete destruction of the surface details, corresponding to the transmission electron microscopic findings which revealed various degrees of sarcolemmal damage. These surface structural changes may modify the ionic movement across the sarcolemma. The resultant disruption of the membrane's selective permeability may further alter the transmembrane potential of atrial myocardial cells.

In conclusion, the present study provides valuable structural evidence that surface morphological changes in atrial myocardial cells may explain electrophysiological alterations in diseased human atria. We suggest that alterations on the sarcolemmal surface of atrial myocardial cells, resulting from the underlying disease processes, were the principal pathogenetic factors contributing to the transmembrane potential changes.

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REFERENCES

1. Trautwein W, Kassebaum DG, Nelson RM, Hecht HH: Electrophysiological study of human heart muscle. *Circulat Res* **10**: 306, 1962
2. Sleator W Jr, De Gubareff T: Transmembrane action potentials and contractions of human atrial muscle. *Am J Physiol* **206**: 1000, 1964
3. Prasad K: Transmembrane potential and force of contraction of the normal and potassium-deficient human atrial tissue in vitro. *Can J Physiol Pharmacol* **47**: 1015, 1969
4. Fabiato A, Fabiato F: The two components of the human atrial action potential. *Circulat Res* **29**: 296, 1971
5. Gelband H, Bush HL, Rosen MR, Myerburg J, Hoffman BF: Electrophysiologic properties of isolated preparation of human atrial myocardium. *Circulat Res* **30**: 293, 1972

6. Hordof AJ, Edie R, Malm JR, Hoffman BF, Rosen MR: Electrophysiological properties and response to pharmacologic agents of fibers from diseased human atria. *Circulation* **54**: 774, 1976
7. Hordof AJ, Spotnitz A, Mary-Rabine L, Edie RN, Rosen MR: The cellular electrophysiological effects of digitalis on human atrial fibers. *Circulation* **57**: 223, 1978
8. Ten Eick RE, Singer DH: Electrophysiological properties of diseased human atrium. I. Low diastolic potential and altered cellular response to potassium. *Circulat Res* **44**: 545, 1979
9. Mary-Rabine L, Hordof AJ, Danilo P Jr, Malm JR, Rosen MR: Mechanisms for impulse initiation in isolated human atrial fibers. *Circulat Res* **47**: 267, 1980
10. Senges J, Brachmann J, Rizos I, Jauernig R, Hasper B, Beck L, Braun W, Kübler W: Metabolism and the electrical activity of human atrial myocardium. *Cardiovasc Res* **15**: 320, 1981
11. Wit AL, Rosen MR, Hoffman BF: Relationship of normal and abnormal electrical activity of cardiac fibers to the genesis of arrhythmias I-Automaticity. *Am Heart J* **88**: 515, 1974
12. Wit AL, Rosen MR, Hoffman BF: Relationship of normal and abnormal electrical activity of cardiac fibers to the genesis of arrhythmias. Reentry. *Am Heart J* **88**: 664, 1974
13. Surawicz B, Imanishi S: Automatic activity in depolarized guinea pig ventricular myocardium. Characteristics and mechanisms. *Circulat Res* **39**: 751, 1976
14. Cranefield PF: Action potentials, afterpotentials, and arrhythmias. *Circulat Res* **41**: 415, 1977
15. Wit AL: Cellular electrophysiology of cardiac arrhythmias. Part I. Arrhythmias caused by abnormal impulse generation. *Mod Concept Cardiovasc Dis* **50**: 1, 1981
16. Wit AL: Cellular electrophysiology of cardiac arrhythmias. Part II. Arrhythmias caused by abnormal impulse conduction. *Mod Concept Cardiovasc Dis* **50**: 7, 1981
17. Hoffman BF, Rosen MR: Cellular mechanisms for cardiac arrhythmias. *Circulat Res* **49**: 1, 1981
18. Trautwein W: Membrane currents in cardiac muscle fibers. *Physiol Rev* **53**: 793, 1973
19. Van Winkle B, Schwartz A: Ions and inotropy. *Ann Rev Physiol* **38**: 247, 1976
20. Coraboeuf E: Ionic basis of electrical activity in cardiac tissue. *Am J Physiol* **234**: H101, 1978
21. Frank JS, Langer GA, Nudd LM, Seraydarian K: The myocardial cell surface, its histochemistry, and the effect of sialic acid and calcium removal on its structure and cellular ionic exchange. *Circulat Res* **41**: 702, 1977
22. Bennett HS: Morphological aspects of extracellular polysaccharides. *Histochem Cytochem* **11**: 14, 1963
23. Legato KJ: Ultrastructure of the atrial, ventricular and Purkinje cell, with special reference to the genesis of arrhythmias. *Circulation* **47**: 178, 1973
24. Langer GA: The structure and function of the myocardial cell surface. *J Physiol* **235**: H461, 1978
25. Reuter H: Properties of two inward membrane currents in the heart. *Ann Rev Physiol* **41**: 413, 1979
26. Reuter H, Scholz H: A study of the ion selectivity and the kinetic properties of the calcium-dependent slow inward current in mammalian cardiac muscle. *J Physiol (Lond)* **264**: 17, 1976