Atrial repolarization in man *Effect of beta-receptor blockade*

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Right atrial monophasic action potentials were recorded using a bipolar suction electrode technique in 29 patients without any present or past atrial arrhythmias.

The monophasic action potential duration measured at the level of 90 per cent repolarization, ranged in these patients between 210 and 413 msec, with a tendency to become shorter at higher heart rates, which was not, however, statistically significant. Five of these 29 patients, as well as 12 additional patients, were given 10 mg alprenolol or propranolol intravenously after the monophasic action potential recording. A second recording 10 minutes later did not reveal any change in duration other than that which might have been expected from the change in heart rate. The antiarrhythmic effect of beta-receptor blockade upon supraventricular tachyarrhythmias is thus probably not mediated via reflex delayed repolarization.

A short myocardial tissue refractory period is theoretically a factor leading to arrhythmias (Hoffman and Cranfield, 1964; Vaughan-Williams, 1970). This was demonstrated in animal experiments and has recently been verified even in the intact human heart (Olsson, Cotoi, and Varnauskas, 1971a). Beta-receptor blocking drugs of different types are well documented as effective therapeutic and prophylactic agents in the treatment of different supraventricular arrhythmias (Gibson and Sowton, 1969). These drugs have, however, failed to prove beneficial in the prevention of relapse from sinus rhythm to atrial fibrillation after DC conversion (Rydén *et al.*, 1972).

The underlying pathological electrophysiological mechanisms in different supraventricular arrhythmias are almost always uncertain or unknown. It has, however, been demonstrated that accelerated atrial muscle repolarization as well as spontaneous diastolic depolarization are proarrhythmic mechanisms which may be present in patients with atrial arrhythmias while these factors could not be found in patients without any arrhythmia (Olsson, 1972). It has also been shown in a single case that injection of a beta-receptor blocker could delay the atrial muscle repolarization, this effect being associated with clinical beneficial effect of the drug (Olsson, 1971b). The present work was, therefore, initiated to outline the general effect of beta-receptor blockade upon atrial repolarization in a larger series of

patients as well as the atrial repolarization in patients free from arrhythmias.

Subjects and methods

All patients were investigated with the technique, by which monophasic action potentials could be recorded from the intact heart (Olsson, Varnauskas, and Korsgren, 1971b). This investigation was performed in connexion with routine diagnostic heart catheterization. After the diagnostic procedure was finished, the recording of monophasic action potentials was done. The patients had been previously informed about the additional procedure and had given their consent to this. In this way 29 patients free from any kind of earlier known supraventricular arrhythmia were investigated. Four of these patients, as well as 5 additional patients who had had supraventricular arrhythmias previously, were investigated, not only during spontaneous sinus rhythm but also 10 minutes after a slow infusion over 10 minutes of 10 mg alprenolol intravenously. Similarly, 7 patients with earlier observed atrial arrhythmias of different types as well as one from the group of 29 arrhythmia-free patients were investigated before and after the intravenous injection of 10 mg propranolol. A disposable radio-opaque close bipolar suction electrode catheter¹ α -monophasic action potential catheter (Fig. 1) was percutaneously introduced from the right femoral vein and placed in the right atrium using fluoroscopic control. The catheter was slightly pressed against the endocardial wall and suction was then applied within the lumen of the catheter. The close bipolar signal between the electrode terminals, one situated inside the lumen of the catheter

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FIG. 1 Radio-opaque catheter for recording monophasic action potentials of the right atrium. Length: 100 cm; outer diameter: 2.8 mm; lumen diameter: 1.4 mm; distance between catheter tip and peripheral catheter electrode terminal (PCET): 3 mm. A stainless steel spring reinforces the catheter to ensure optimal stiffness. Central catheter electrode terminal (CCET) is situated within the lumen of the catheter and can be seen exposed in the figure.

(Central Catheter Electrode Terminal=CCET), the other on the outer side of the catheter (Peripheral Catheter Electrode Terminal=PCET), was then amplified with a very high input impedance (10^{11} ohm) differential DC recording system. The signal was recorded on ultraviolet sensitive paper (Olsson *et al.*,

1971b). The signals were also recorded on a Honeywell 5600 14 track FM tape recorder. Fig. 2 has been reproduced from the tape by recording on an Elema Mingo-
graf 34 ink-writer, allowing reproduction from DC to 400 Hz.

Each monophasic action potential recording was

FIG. 2 Recording of right atrial monophasic action potential (MAP) and electrogram (RAE). The principle for construction of baseline and level of 90 per cent repolarization is illustrated. Note the biphasic notch on the upstroke of the monophasic action potential, representing interference from local close bipolar electrogram signal.

analysed with respect to cycle length and duration at the level of 90 per cent repolarization (Fig. 2). The method has been described more extensively elsewhere (Olsson, 1971a).

Results

Fig. 2 depicts a typical recording of a right atrial monophasic action potential. A base-line has been constructed as well as the level of 90 per cent repolarization for calculation of monophasic action potential duration.

The range of monophasic action potential durations in the 29 patients free from any kind of earlier atrial arrhythmia was 210 to 413 msec. Individual values appear in Table 1.

In the patients investigated before and after infusion of alprenolol intravenously, the mean right atrial monophasic action potential duration before injection was 286 msec and after administration of

alprenolol it was prolonged to 292 msec. Concomitantly, the cycle length increased from 792 to 859 msec.

In the 8 patients investigated before injection of propranolol, mean right atrial monophasic action potential duration was 261 msec while this value had increased to 273 msec 10 minutes after the propranolol injection. Similarly the cycle length had increased from 787 to 975 msec. None of the above-mentioned changes of duration of monophasic action potential was significant according to t-test of paired differences. Individual data from the recordings before and after administration of alprenolol or propranolol appear in Table 2.

TABLE 1 *Cycle length and duration of right atrial monophasic action potential in 29 patients with various kinds of heart diseases but presently and earlier devoid of any type of supraventricular dysrhythmia: values in msec*

Case No.	Cycle length	Monophasic action potential duration
1	789	210
2	729	287
3	957	267
4	615	266
5	596	244
6	749	228
7	1010	413
8	462	240
9	748	220
10	573	220
11	816	268
12	683	285
13	1180	277
14	772	246
15	815	327
16	745	296
17	755	270
18	961	320
19	625	259
20	858	250
21	768	267
22	1086	298
23	664	237
24	852	251
25	914	256
26	939	322
27	709	296
28	746	273
29	666	285

TABLE 2 *Cycle length and duration of right atrial monophasic action potential before and 10 minutes after 10 mg alprenolol or propranolol intravenously: values in msec*

Case No.	Cycle length	Monophasic action potential duration	Cycle length	Monophasic action potential duration
<i>Before alprenolol</i>		<i>After alprenolol</i>		
3	957	267	1038	274
4	615	266	666	275
5	596	244	652	318
6	749	228	838	230
30	743	360	888	337
31	789	260	789	272
32	939	329	990	274
33	792	287	761	228
34	950	336	1113	420
<i>Before propranolol</i>		<i>After propranolol</i>		
7	1010	413	1175	385
35	822	173	1050	218
36	445	224	975	255
37	847	285	1006	279
38	832	236	836	262
39	678	288	780	270
40	945	210	1070	235
41	720	258	905	278

Fig. 3 demonstrates individual values as well as the mean square fitted regression line for the relation between monophasic action potential duration and cycle length in the 29 patients without arrhythmias. The figure also includes the mean values of cycle length and monophasic action potential duration from the patient groups who received alprenolol and propranolol before as well as 10 minutes after the drug was administered.

FIG. 3 Relation between cycle length and duration of right atrial monophasic action potential (MAP) in 29 patients free from any kind of atrial arrhythmia (black dots). The regression line for this relation is also indicated as well as mean values of atrial monophasic action potential durations before (A, P) and after (A⊙, P⊙) alprenolol (A) and propranolol (P) respectively. Note the similarity of the slope of the three lines.

Discussion

The effect of different beta-receptor blockers upon the electrophysiology of single cells is well known. The normal enhancement of phase 4 depolarization in specialized conductive tissue cells exerted by adrenaline and similar substances is abolished by beta-receptor blockers, e.g. alprenolol or propranolol (Vaughan-Williams, 1966; Davis and Temte, 1968).

The action of alprenolol or propranolol upon the pure atrial muscle cell is a slowing of the maximal rate of depolarization, of the type also shown with quinidine (Vaughan-Williams, 1966; Davis and Temte, 1968; Singh and Vaughan-Williams, 1970). This is a mode of action which principally has to be separated from the beta-receptor blocking action.

The precise effect of adrenaline upon the atrial muscle action potential is dependent upon the species (Hoffman and Cranefield, 1960). In the dog, a slight shortening of the action potential has been reported (Brooks *et al.*, 1955). However, concentrations of adrenaline, which cause physiological changes in the force of contraction, do not affect the shape of the mammalian atrial muscle action potential (Vaughan-Williams, 1966). It can thus be assumed that the action of adrenaline from humoral and neural sources in the intact human heart prob-

ably changes the configuration of the atrial muscle action potential to a very small extent.

It can be argued that though it is possible to detect changes in the electrophysiology of single cells when a drug is given to a tissue preparation, the drug concentrations and the ionic composition of the perfusate used in such experiments do not correspond to the actual circumstances when the drug is used in clinical routine. The composition of the fluid in a tissue bath is different from that of blood in respect not only of electrolytes but of cells and proteins as well. The influence of protein-bound portion of the drug might thus be obscured in *in vitro* experiments.

The rapid depolarization of the monophasic action potential does not allow interpretation of maximal rate of depolarization of action potentials from single cells (Olsson *et al.*, 1971b) because the monophasic action potential is recorded from a great number of cells. In addition the rapid upstroke of the monophasic action potential signal is often interfered with by a local electrogram signal—a fact clearly shown in Fig. 2.

Though the method used for recording monophasic action potentials in this study does not allow of interpretation of amplitudes of the genuine transmembranal potential nor of the maximal rate of depolarization, the duration of the monophasic action potential as well as the form of repolarization

throughout the different phases 1-4 however can be largely relied upon (Hoffman *et al.*, 1959).

In the patients without earlier atrial arrhythmias, a frequency-dependent change of monophasic action potential duration was found. The slope of the line relating the monophasic action potential duration and the cycle length was, however, not statistically significant. When the mean atrial monophasic action potential durations before and after injection of propranolol or alprenolol were compared it appeared that the monophasic action potential was slightly prolonged after beta-receptor blockade was performed. It is obvious though that this monophasic action potential duration variation can be completely explained by the change in heart rate. Thus it seems unlikely that any reflex vagal inhibition association with beta-receptor blockade of the type suggested earlier should take place (Olsson, 1971b).

In a number of patients with paroxysmal supra-ventricular arrhythmias, two arrhythmia-provoking factors were found (Olsson, 1972). One was a short monophasic action potential duration, the other a spontaneous diastolic depolarization. Neither of these factors could be observed in any of the patients free from earlier arrhythmias in the present series. Neither could any diastolic depolarization be demonstrated in any of the patients given alprenolol or propranolol. Some of these patients had a monophasic action potential duration which was short compared with that of the arrhythmia-free population. It must, however, be stressed that all patients had different kinds of heart diseases and various kinds of cardiotropic drugs, factors which thus presumably affected the atria as well. The present group of patients must therefore not be regarded as representing the normal range of atrial repolarization in man. The desirability of collecting information about the atrial repolarization in healthy people is obvious.

The expected variability in the atrial monophasic action potential duration between successive suction in an individual patient can be expressed as a variation coefficient up to 16.5 per cent (Olsson, 1971a). In this series, the variation coefficient of the monophasic action potential durations before and after beta-blockade is higher in only one case (244 to 318 msec = 18.6%). It is thus likely that the observed variations are mainly caused by the recording at different positions or at different times. Possible monophasic action potential duration changes caused

by beta-receptor blockade may, however, be obscured within the expected normal variability.

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