Human Atrial Repolarization: Effects of Sinus Rate, Pacing and Drugs on the Surface Electrocardiogram

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OBJECTIVES

We studied the effects of rate and some cardioactive drugs on the atrial surface electrocardiogram (ECG).

BACKGROUND

In atrioventricular block, atrial surface ECG is unmasked. The effect of rate alone permits detection of the effect of other exogenous stimulations such as drugs in the presence of rate alterations.

METHODS

High fidelity, high gain ECG leads I, II and III were recorded from 51 patients with heart block. Durations of P and Ta waves and the total PTa interval were measured from nonconducted atrial events.

RESULTS

No relationship was found between sinus cycle length and PTa, P or Ta in 31 patients. In 20 patients, progressively decreasing the atrial pacing cycle length from 853 ms to 381 ms resulted in a linear reduction of the PTa interval from 444 to 291 ms (rho = 0.76, slope = 0.24). This was largely due to shortening of Ta. A linear rate correction formula was derived:

\[
\text{corrected } \text{PTa} = \text{PTa} - 0.24 (\text{PP} - 1000).
\]

Atropine (0.02 mg/kg) shortened the PP interval (p < 0.001) and the PTa interval (p < 0.01). Propranolol (0.1 mg/kg) prolonged the PP interval (p < 0.001) but did not alter the PTa interval. Neither disopyramide (2.0 mg/kg) nor flecainide acetate (2.0 mg/kg) altered the PP interval, but both prolonged the PTa interval (p < 0.001). This was largely due to P wave lengthening after flecainide (p < 0.001) and to Ta prolongation after disopyramide (p < 0.001).

CONCLUSIONS

In heart block, PTa, P and Ta waves can be measured reliably. The effects of pacing and some antiarrhythmic drugs on the atrial myocardium are similar to those known at the ventricular level. (J Am Coll Cardiol 1999;33:358–65) © 1999 by the American College of Cardiology

Compared with the QRS complex, the electrocardiographic (ECG) deflection due to atrial depolarization is small in both amplitude and area. Atrial repolarization is usually hidden by the ensuing QRS complex (1). Atrioventricular (AV) block may be used as a model to study atrial depolarization and repolarization (2–4). We developed a high gain, high fidelity technique of recording ECG atrial activity in patients with 2:1 or complete AV block.

The properties of atrial repolarization might give rise to atrial arrhythmias in the same way as ventricular repolarization relates to ventricular arrhythmia (5). It is therefore important to determine the normal variations of the atrial ECG complex, the PTa interval, to recognize abnormalities. Changes in heart rate may result in changes in PTa interval duration and morphology. The knowledge of the effect of rate alone on the atrial surface ECG permits detection of the effect of drugs or any other physiopathologic intervention in the presence of related rate alteration.

Clinical determination of the effect of drugs on the ventricular myocardium is usually based on changes induced in ECG activity, but similar studies on the atrial myocardium have not been undertaken. We selected atropine, an antimuscarinic drug the effect of which on the human atrial myocardium is still controversial (6–8), and propranolol, a nonselective beta-adrenergic receptor blocking agent. Disopyramide, a class Ia antiarrhythmic drug, and flecainide acetate, a class Ic agent (9), are both effective in converting atrial fibrillation to sinus rhythm when given intravenously (10,11), making therefore their effect on surface atrial ECG of interest.

METHODS

Patients. The study population consisted of 51 patients (34 men) aged from 26 to 86 (mean 61) years. Thirty-eight of them suffered with complete 3rd degree AV block and 13 with 2nd degree Mobitz II AV block. The cause of their conduction defect was degenerative in 39, congenital in 2, therapeutic catheter ablation of AV conduction in 9 and...
aortic valve replacement in 1. All were awaiting implantation of a permanent pacemaker system. None of the patients was suffering from hypertension or ischemic heart disease. Their hearts were radiologically within normal limits for their age. The echocardiographic examination revealed no enlargement or other abnormality of the atria. Mitral and tricuspid valves were normal. None of the patients had abnormal atrial depolarization and repolarization intervals in sinus rhythm; patients with interval durations \( P > 125 \text{ ms} \) and \( \text{PTa} > 465 \text{ ms} \) were excluded (3,12). Patients whose morphology of atrial depolarization and repolarization were biphasic, bifid, abnormally slurred or of an electrical gradient very different from 0 were also excluded. None of them had taken any antiarrhythmic medication for at least five elimination half-lives before the recordings were made. Twenty-four–hour ECG monitoring confirmed the absence of atrial arrhythmias except in the nine patients who had undergone His bundle ablation as a therapeutic measure for paroxysmal atrial flutter and atrial fibrillation and recurrent paroxysmal sinus tachycardia.

All patients had a transvenous 5-F or 6-F bipolar pacing electrode catheter positioned in the apex of the right ventricle, and 20 of these patients also had a temporary transvenous J pacing electrode catheter placed in the right atrial appendage. All studies were done with the patient lying supine and with the ventricle paced on demand mode at 40 bpm after informed consent was obtained.

**Validation study.** The technique was validated on 17 patients.

**Study in sinus rhythm.** Atrial surface ECG recordings were obtained from 31 patients in sinus rhythm at rest. The durations of the PTa, P and Ta intervals were measured and correlated with the sinus PP interval.

**Atrial pacing study.** In the group of 20 patients with atrial pacing electrodes, the effect of pacing the atrium at pacing intervals varying between 863 and 381 ms (rates varying between approximately 70 and 150 bpm) was determined. Each patient was paced at two to nine different rates. The atrium was paced for 3 min at each rate before any recording was made to allow steady state to be reached (12,13). The PTa and Ta intervals and the P wave duration were correlated with the paced PP intervals. A linear regression equation was derived to predict the effect of changes in PP intervals on PTa, P and Ta.

**Drug administration study.** Propranolol was administered at a dose of 0.1 mg/kg to 8 patients, atropine, at a dose of 1.2 mg to 12 patients, disopyramide at a dose of 2 mg/kg (10) to 9 patients and flecainide at a dose of 2 mg/kg (11) to 10 patients. To obtain steady state, all drugs were administered intravenously, over 2 min for atropine and over 15 min for propranolol, disopyramide and flecainide.

**Method.** Standard bipolar leads I, II and III of the conventional surface ECG were recorded directly onto half-inch FM magnetic tape using a Racal store 7 recorder. The amplification through a Biodata low noise physiologic amplifier ranged from 1,000 to 10,000 times (a factor of 10 to 100 times the gain used for standard ECG recordings), depending on the input signal level. Extraneous noise was reduced by collecting the signals over a narrow frequency band of 0.16 to 30 hertz (3 dB points). For analysis, the signals were transferred to computer memory via a 12-bit analog to digital converter at a sampling rate of 256 samples per second. Once in the computer memory, good quality, low noise recordings were displayed directly on a Tektronix 4010 graphics terminal. In occasional cases, when the recorded signals, particularly the repolarization Ta wave, were too small in amplitude or when reduction of myogenic noise or mains interference was necessary, it was possible to subject the signals to further computer analysis, providing further amplification (up to a factor of 4) and/or further digital filtration (low pass filter) (Fig. 1).

The total duration of the atrial ECG event, the PTa interval, was measured from the beginning of the P wave...
(atrial depolarization) to the end of the Ta wave (atrial repolarization). The end of the P wave (and the beginning of the Ta wave) was arbitrarily defined as the point at which the ECG trace crossed the isoelectric line (Fig. 1). Only complete PTa complexes, not interrupted by a ventricular QRS complex or T wave or deformed by an artifactual change of the baseline, were measured. Measurements were made from the lead with the clearest PTa complex recorded in each patient. Care was taken to measure the same lead in any one patient. For each recorded value of PTa, five unencumbered PTa complexes were measured to determine the coefficient of variation (CV) of the measurements.

The coefficient of intraobserver variation for one observer measuring the recordings of 10 patients in sinus rhythm on four different occasions and the variance attributable to the different measurement times by the same observer were assessed. Six different observers measured recordings from the same four patients to assess the interobserver variability. Intraindividual repeatability (14) was tested on 12 patients by recording their atrial ECG in the same conditions on two occasions. To assess the effect of drugs on atrial depolarization and repolarization, the recordings were performed immediately before drug administration and again at the end of the injection of each drug.

PTa intervals were corrected for rate by the use of Bazett’s hyperbolic correction factor designed for the ventricular QT intervals and adapted to the atrial intervals and by a linear correction derived by pacing the atrium of 35 patients.

Statistical analysis. Data are expressed as mean and standard deviation. Between- and within-observer variations were tested using one random factor analysis of variance, and the coefficient of variation was used to express reproducibility. For correlation analysis between two variables, parametric Pearson product–moment correlation coefficient $r$ was calculated. In cases when each data point was not independent of the other (when several data points derived from the same patient), the nonparametric Spearman rank correlation coefficient rho was calculated (15). Student paired $t$ test was used to assess the effect of the different drugs on the PP, PTa, Ta and P intervals. This test was also performed on the values corrected for heart rate. All tests were two tailed, and the statistical significance level was set at 5%.

RESULTS

Validation study. Variation in the measurements, assessed as stated above, varied from 1% to 3% for the full PTa interval. The P wave duration CV varied between 0% and 11% and the Ta interval CV, between 1.5% and 4.5%. The coefficient of intraobserver variation for one observer measuring the recordings of 10 patients in sinus rhythm on four different occasions varied between 1% and 3%. The variance attributable to the different measurement times by the same observer was not significant ($F$ test $= 1.04$, $p = 0.39$, NS). The mean interobserver CV, by six different observers measuring the same four patients’ recordings, was <3.5% in all cases. The variance attributable to observer was not significant ($F$ test $= 0.71$, $p = 0.56$, NS). Intraindividual repeatability (8) tested on 12 patients by recording their atrial ECG in the same conditions on two occasions showed no “occasion” effect or systematic error ($t$ test $= 0.20$, $p = 0.85$, NS).

Study in sinus rhythm. There was no significant correlation between atrial ECG interval duration (PTa, P, Ta) and atrial sinus cycle length.

Atrial pacing studies. Increasing the pacing rate reduced the PTa interval mainly by shortening the repolarization segment, Ta. There was a good linear correlation of the atrial ECG intervals PTa and Ta with the pacing interval PP (Figs. 2 and 3). There was no obvious relationship between P wave duration and pacing intervals (Fig. 4).

From the linear regression of PTa interval upon PP interval was derived a correction equation for the PTa interval which accounted for the effect of atrial rate. To
correct for changes in PP, all values of PTa are expressed as though PP was 1,000 ms (60 beats per minute):

\[
\text{Corrected PTa} = \text{PTa} - 0.24 (\text{PP} - 1000).
\]

**Drug study.** Propranolol slowed the atrial rate, and atropine resulted in an increase in atrial rate (Fig. 5 and 6). Neither flecainide nor disopyramide had a significant effect on rate (Fig. 6).

Propranolol did not significantly alter any of the uncorrected atrial intervals, but atropine significantly decreased all three intervals (Fig. 7). The PTa interval was significantly increased by both disopyramide and flecainide, but disopyramide acted mainly by increasing the Ta interval, whereas flecainide acted by increasing the P wave duration (Fig. 7).

Correction of the PTa interval for drug-induced rate changes using both the Bazzet’s hyperbolic formula and the linear regression equation produced similar results; intervals varied in the same direction with each different drug. Propranolol significantly decreased the PTa interval, whereas atropine had no significant effect on it. Disopyramide and flecainide significantly prolonged the PTa interval (Fig. 8).

**DISCUSSION**

**Study in sinus rhythm.** Atrial intervals did not correlate with PP intervals in 31 patients in whom, of course, interindividual variability in refractoriness and therefore in PTa duration may be expected. Moreover, although all the patients were selected as having normal atria, six of them had documented atrial arrhythmias. This may also explain the lack of linear correlation. Hayashi et al. (3) did find a linear correlation between PTa and PP including only one point for each of 25 patients in atrial sinus rhythm with AV block of whom 20 had no significant cardiovascular diseases and 5 had severe cardiovascular conditions such as ischemia and arrhythmia. Kesselman et al. (16) measured atrial deflections from the surface ECG of 36 patients and concluded that a linear relationship existed between PTa and PP at rates varying between 60 and 300 bpm, with a slope of 0.34 and an intercept of 140 ms. These authors made 50 measurements on the ECGs obtained from 35 patients and 24 measurements on the ECG of a single patient. Three recordings were made at atrial rates of 200 and 300 bpm, one of which was in paroxysmal atrial tachycardia and two in atrial flutter. Clearly, the linear correlation might have been influenced by the inclusion of several measurements recorded from the same patient. Including patients with atrial rates of 200 and 300 bpm, which represent a series of depolarizations with no repolar-
The monophasic action potential reflects cellular refractoriness (17,18). The PTa interval is the spatial summation of all atrial electrical events. The PTa and Ta intervals are only an approximation of the repolarization time and are not a measure of either cellular action potential or monophasic action potentials (MAPs) (12). However, a shortening of the right atrial MAP with decreasing cycle length in individual patients has earlier been pointed out by Shabetai et al. (19), but is not evident in the report by Korsgren et al. (20). Olsson (21) found a linear correlation between atrial monophasic action potential duration and the PP interval in a group of 12 patients in sinus rhythm at rest. However, differences between measurements in the duration of the right atrial MAP between patients as well as in the same patient were obvious; he concluded that there was a wide distribution of the refractory periods in human atria, which can explain the lack of correlation found in our study.

**Atrial pacing study.** The rate-related variation of the PTa interval at different pacing cycle lengths has not been studied previously. The PTa duration is a reflection of atrial refractoriness (12). Correlating the atrial interval duration with the pacing cycle length therefore gives an indication of the variation in atrial refractoriness with rate. In this study, increasing atrial pacing rate decreased the PTa interval mainly by reducing the duration of repolarization. This is concordant with the findings of Denes et al. (22), who reported that atrial effective and functional refractory periods decreased with pacing cycle length in 11 patients with normal atria. Furthermore, Attuel et al. (23) demonstrated a relationship between atrial vulnerability to arrhythmias and failure of the atrial refractory period to shorten with increasing rate.

The P wave duration is little affected by rate. This is analogous to what has been described at the ventricular level (24), where heart rate changes have little or no effect on ventricular depolarization but substantially alter the JT interval.

At the ventricular level, in man, in vitro work on action...
of rate on the duration of depolarization and repolarization of the normal atrium. Although the patients were selected accordingly, they could have had underlying atrial disease. It is well known that there is a higher incidence of sinus node dysfunction in patients with AV block (31). In six patients, AV block had been produced artificially as a therapeutic measure for atrial arrhythmia. Olsson et al. (35) showed that a short atrial refractory period (measured by the technique of the monophasic action potentials) was present in some patients failing to maintain sinus rhythm after direct current conversion of atrial fibrillation. In brief, Wyndham et al. (36) demonstrated that decrease in cycle length potentiates atrial vulnerability to atrial tachyarrhythmia. Attuel et al. (23) suggested that atria with poor or absent rate adaptation of the refractory period are prone to atrial flutter or fibrillation. Dispersion of atrial refractoriness is known to predispose to arrhythmia (17,37); a short refractory period allows development of tachyarrhythmia owing to the possibility of early excitation and initiation of new depolarization in adjacent muscle cells with different refractoriness. The PTa interval records the sum of the atrial electrical phenomena. The six patients with atrial arrhythmia did not have particularly long or short repolarization phases.

Drug study. It is thought that the atria are predominantly under parasympathetic control (17). In man, variable or no effect of atropine on the atrial refractory period has been reported (6,7). Dhingra et al. (8) showed that atropine shortens atrial functional and effective refractory periods, facilitating conduction, and implied that vagal stimulation prolongs the refractory period in man. Acetylcholine shortens the duration of the action potential in isolated myocardial preparations, but vagal stimulation prolongs the atrial monophasic action potential in man due to the decrease in heart rate. Thus, the effect of bradycardia compensates the direct vagal effect (17). As expected, the atrial rate is increased after atropine injection. The effect on the atrial repolarization expected from previous work on the atrial monophasic action potential (38) was seen. The drug shortened all three atrial intervals, but its effect on the PTa interval was neutralized by the rate correction. The effect of atropine on the intervals is explained by its effect on atrial rate. The drug itself has no independent effect. This is similar to the ventricular response to the drug (38), where atropine shortens the effective refractory period but does not affect the monophasic action potential; however, the ventricle is predominantly under the influence of sympathetic tone. This still confirms the findings of Bisset et al. (7) and contradicts the widely recognized belief based on animal work that atropine prolongs atrial refractoriness (39,40).

As would be expected from a beta-adrenoceptor blocking drug, propranolol slows the atrial rate. Acute administration of intravenous propranolol has no effect on the uncorrected atrial intervals but significantly decreases the PTa corrected for rate change, a finding that has already been documented for the human ventricle (41). Olsson (42) showed no change

**Patients.** This study was conducted to determine the effect of rate on the duration of depolarization and repolarization...
in duration of atrial monophasic action potentials at 90% repolarization 10 min after the intravenous administration of propranolol or alprenolol in 17 patients. Milne et al. (41) found that propranolol decreased the duration of the QT interval corrected for rate but increased or did not change the QT interval duration measured at identical atrial paced rates. Edvardsson et al. (38) showed no effect of acute metoprolol on ventricular monophasic action potential duration and refractory periods using similar methods of constant rates before and after drug administration.

The effects of propranolol and atropine on the atrial ECG at doses used to create partial or total pharmacologic autonomic denervation (43,44) are useful to define and constitute the basis for further studies on autonomic tone at the atrial level.

Disopyramide is a class Ia antiarrhythmic agent with combined characteristics of a membrane-stabilizing or local anesthetic agent (45) and anticholinergic agent (46,47). It prolongs refractory periods at all levels of the heart and prolongs the QT interval by prolonging the JT interval (10). Similarly, at the atrial level, it prolongs the P'Ta interval mainly by prolonging the repolarization interval. It does not modify the atrial rate, and therefore the rate correction applied is consistent, showing the same prolongation of the P'Ta interval. These effects of disopyramide on the atrium are equivalent to those previously reported for the ventricle (32).

The electrophysiologic properties of flecainide acetate have been well documented by a number of authors (11,48,49). Most studies have used intravenous flecainide at doses ranging from 1 to 2 mg/kg. It has been shown to prolong the QT interval by increasing the duration of the QRS interval without any alteration of the JT interval and to slightly prolong atrial and ventricular refractory periods (11,32). The findings in this study for atrial depolarization and repolarization are similar.

Correction for changes in heart rate using Bazett’s correction formula adapted to atrial intervals and the linear regression formula derived here are in agreement. Another way of testing the correction formula would have been to study drug effects while maintaining atrial rate by pacing the atrium. This should be considered in further studies.

**Conclusions.** The effect of pacing on atrial ECG was similar to its effect at a ventricular level on the QRS and QT intervals and permitted derivation of a rate correction formula. Using this formula allowed determination of the intrinsic effect of chronotropic drugs on atrial depolarization and repolarization. It should also permit future investigation of the intrinsic effect of biophysical, pharmacologic, pathologic phenomena on atrial depolarization and repolarization, eliminating their potential effect on atrial rate. However, the correction formula was derived here from the biophysical effect of pacing, and using it to account for changes in atrial rate related to autonomic tone, in particular exercise, should be done cautiously.

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