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Effects of epinephrine over P wave duration and ventricular repolarization in subjects without structural heart disease

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ABSTRACT

Background: Little is known about the effects of epinephrine over atrial electrical function, AV conduction and ventricular repolarization in normal subjects. We intended to study the effects of intravenous epinephrine on the duration of P wave, inter-atrial conduction time, PR, QRS, QT, corrected QT (QTc), QTc dispersion (QTc max–min), the peak-to-end interval of T wave (Tp-e), the Tp-e/QT index, and the middle portion of ventricular repolarization length (QT − (QRS + Tp-e)) in healthy subjects.

Methods: Forty-three, 37.20 ± 17.05 year-old, 25 (58%) female patients without structural heart disease took part in the study. They underwent an electrophysiological study. An epinephrine infusion (50 to 100 ng/kg/min) was administered for 5 min until an increase of at least 10% of the initial heart rate (HR) was achieved.

Results: No complication arose from epinephrine infusion, and the drug facilitated arrhythmia induction. A significant increase in heart rate, systolic blood pressure, QRS, QTc, Tp-e, Tp-e/QT index, and QTc max–min interval duration was documented. No significant effect on diastolic blood pressure, P wave duration, inter-atrial conduction time, and PR, QT and QT − (Tp-e + QRS interval) was observed.

Conclusions: In this group of patients without structural heart disease, epinephrine infusion did not produce any complication and it facilitated arrhythmia induction. It did not modify P wave duration, PR interval or inter-atrial conduction time. Moreover, it significantly increased the duration of depolarization, the final portion of repolarization, transmural dispersion of repolarization, and regional dispersion of repolarization without inducing significant changes in the middle portion of repolarization.

1. Introduction

Epinephrine has been used for a long time in medicine but several adverse effects have been reported in the literature. For example, between 1991 and 2002, Japanese cardiologists described patients who suffered precordial pain after being submitted to emotional stress or catecholamine injection. The majority of the patients were women; their ECG displayed ST segment elevation and/or inverted T waves in precordial leads and QT prolongation. The left ventricular angiogram showed apical aneurysms resembling the traps used in Japan to catch octopuses (Takotsubo) [1–3]. The entity was named Takotsubu cardiomyopathy. Similar changes have been described in patients suffering from acute medical conditions, such as hemorrhagic strokes, surgery, sepsis, pheochromocytoma, cocaine abuse, or catecholamine administration [3–6]. The electrophysiological effects of epinephrine have been studied in a few subjects only, and most reports have been conducted in patients with structural cardiomyopathy.

Stratton et al. studied 10 normal subjects and reported that an epinephrine infusion of 25 to 100 ng/kg/min produced a significant rise of plasma epinephrine concentration that was equivalent to the levels attained performing isotonic exercise in a cycle-ergometer [7]. The subjects also showed significant increases in stroke volume, ejection fraction, heart rate and systolic arterial pressure accompanied by a decrease of systemic vascular resistance [7].

Morady et al. investigated some of the electrophysiological effects of epinephrine in humans [8]. They found a decrease in the atrial and AV node refractory period and an acceleration of the AV nodal conduction, and reported that the epinephrine infusion facilitated arrhythmia induction [8].

Cheema et al. reported a significant prolongation of the signal averaged P wave in normal subjects who received an epinephrine infusion (50 ng/kg/min) [9]. Magnano et al. described prolongation of the QT interval in normal subjects who were administered epinephrine infusion in a dose of up to 300 ng/kg/min [10].

The duration of the QT interval in the ECG approximately reflects the duration of the ventricular action potential [11,12]. QT interval

Abbreviations: QTc, corrected QT interval; QTc max–min, regional QTc dispersion; Tp-e, peak-to-end of T wave interval; QT − (QRS + Tp-e), middle portion of ventricular repolarization length.

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prolongation and increased QT interval dispersion have been considered markers of risk for the appearance of polymorphic ventricular tachycardia [13]. Regional QT interval dispersion has been assessed by measuring the differences in QT interval duration in the different ECG leads [13]. Repolarization has been measured in the different portions of the ventricular wall, and it has been found that midmyocardial cell repolarization last longer than the repolarization of the epicardial and endocardial cells. The intramural dispersion of repolarization reflects the differences in repolarization length between the mid-myocardial cells and those of the epicardial and endocardial layers [14]. Epicardial cell repolarization ends when the peak of the T wave occurs, and the mid-myocardial repolarization process finishes at the end of the T wave. Intramural dispersion of repolarization has been assessed by measuring the interval between the peak and the end of the T wave (Tp-e). Tp-e prolongation has been advocated as a marker of risk for lethal ventricular arrhythmias and sudden death [14–16]. Gupta et al. reported that Tp-e is influenced by body size and heart rate and advocated the relation Tp-e/QT as a more independent and reliable index of transmural dispersion of repolarization [17]. The duration of the middle portion of ventricular repolarization could be measured by subtracting the initial (QRS) and final (TP-E) portions from the QT interval {QT − (QRS + Tp-e)}, but this interval has not been investigated.

Isoproterenol is not available in Venezuela. This is why, in our electrophysiological studies, we have been using epinephrine infusions to facilitate arrhythmia induction. Since little is known about epinephrine effects in subjects without structural heart disease, we decided to study the effects of an epinephrine infusion over P wave duration, inter-atrial conduction time, PR interval, QRS, QT, corrected QT, QT interval dispersion, and Tp-e, Tp-e/QT and QT − (QRS + Tp-e). Our hypothesis was that epinephrine infusion (50–100 ng/kg/min) does not produce significant collateral effects and that it can modify the above-mentioned electrophysiological parameters.

2. Methods

We certify that we complied with the Principles of Ethical Publishing of the *International Journal of Cardiology*. The study protocol conforms to the ethical guidelines of the 2013 Declaration of Helsinki as reflected in an a priori approval by our Institution's Human Research Committee.

2.1. Population

Written informed consent was obtained from all the patients. Patients were included if they did not have any structural heart disease or conduction disturbances and if they had been admitted to our electrophysiology laboratory to undergo electrophysiological study. A clinical cardiologist evaluated all the patients, and an X-ray, ECG, and a transthoracic echocardiogram were obtained before performing the ablation. Antiarrhythmic drugs were discontinued for at least 5 half-lives. No patient was receiving amiodarone.

2.2. Epinephrine infusion

1 mg of epinephrine was diluted in 250 cm^3 of 0.9% saline solution. Infusion rate begun at 50 ng/kg/min for 5 min, and heart rate was continuously monitored to check whether an increase of at least 10% on the heart rate had occurred. If the heart rate had not increased, the infusion rate was then adjusted to a maximum of 100 ng/kg/min in order to achieve the 10% heart rate increase. If the heart rate did not increase after adjusting the infusion rate, the measurements were then performed at the maximal infusion rate.

2.3. Measurements

The ECG and intracavitary recordings were obtained with a digital polygraph and stored to measure the electrophysiological parameters. The cardiologists responsible for measuring the variables under study were trained in the Electrophysiology Section until an inter-observer variability <6 ms was achieved. When the beginning or the end of the waves was not well defined, the gain and speed of recordings were modified for obtaining precise measurements. Electrocardiographic intervals were measured according to standard recommendations [18]. Depolarization and repolarization measurements were performed in simultaneously acquired 12 lead ECG. The result obtained in each ECG lead was recorded, and the 12 measures were averaged. The variability and dispersion of the measures were computed in an Excel$^{(R)}$ sheet where the values were stored. Tp-e was measured from the maximal voltage of the T wave to its intersection with the basal line. Tp-e/QT was calculated with the Excel sheet were the values were stored. The middle portion of depolarization duration was computed adding the Tp-e to QRS duration and subtracting the result from the QT interval. Interatrial conduction time was measured from the beginning of the A wave recorded with the high right atrial catheter to the beginning of the A recorded with the distal pair of electrodes of the catheter placed in the coronary sinus.

2.4. Statistical analyses

Statistical analyses were performed with Excel$^{(R)}$ and SPSS20$^{(R)}$ statistical packages. Data distribution was assessed with Shapiro–Wilk test. Normally distributed data were compared with paired T-test and Variance analysis. Data that did not fit in a normal distribution were compared with the Wilcoxon Signed Rank and Kruskall–Wallis test. In order to detect differences of 20 ms between the means with 95% confidence intervals and a statistical power of 80%, a sample size (adjusted to 15% missing data) of 42 observations was calculated.

3. Results

3.1. Population

Forty-three patients (25–58% — female) took part in the study. The mean age was 37.2 + 17.02 years. All the patients had normal hearts and preserved cardiovascular function. The left ventricular ejection fraction was 0.61 ± 0.05. No complication arose.

3.2. Heart rate and arterial pressure

Heart rate increased 14% after the epinephrine infusion and reached a mean of 85 beats per minute (see Table 1). Only one patient did not achieve a significant heart rate increase. Epinephrine infusion produced a significant systolic and mean blood pressure increase without significant changes in diastolic blood pressure (see Table 1). In 13 patients, supraventricular arrhythmia was induced only with the epinephrine infusion ($p < 0.05$).

3.3. Electrocardiographic and electrophysiological parameters

In the control situation, the QRS interval was shorter in women than in men (77 ± 8 vs 84 ± 10 ms; $p = 0.018$). The QTc interval difference

Table 1
Arterial pressure and heart rate changes after epinephrine infusion.

	Control		Epinephrine		p value
	Mean	SD	Mean	SD	
SAP (mm Hg)	123.61	25.89	137.18	27.19	<0.0001
DAP (mm Hg)	76.28	16.01	78.34	14.11	0.1200
MAP (mm Hg)	92.09	21.29	99.51	17.98	<0.0001
R-R (mseg)	818	179	700	157	<0.0001

SD = standard deviation. **SAP**: Systolic arterial pressure. **DAP**: Diastolic arterial pressure. **MAP**: Mean arterial pressure. **R-R** = Electrocardiographic R-R interval.