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Epinephrine and left atrial and left ventricular diastolic function decrease in normal subjects

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ABSTRACT

Background: We assessed the effect of epinephrine over left atrial and left ventricular diastolic function in subjects without structural heart disease.
Methods: Twenty-seven, 34.6 ± 17.2 year-old patients without structural heart disease were included. Intravenous epinephrine (50 to 100 ng/kg/min) was infused. Left atrial and ventricular functions were evaluated by means of echocardiography before and during the epinephrine infusion.
Results: No complications were observed. Significant increases in heart rate and systolic blood pressure were recorded. Both left atrial (minimal and maximal) volumes increased but increase in the minimal volume was more pronounced, and the ejection fraction diminished. Left atrial expansion index decreased and the fraction of left ventricular inflow volume resulting from atrial contraction increased. Two patients displayed abnormal left ventricular diastolic function. During epinephrine infusion, E/A and e′ decreased, and isovolumetric relaxation time increased.
Conclusions: In this group of young adults without structural heart disease, epinephrine infusion was safe, did not produce any complications, and induced a small but significant decrease in left atrial function and left ventricular diastolic function.

1. Introduction

Epinephrine and norepinephrine are the main neurotransmitters of the sympathetic nervous system that is activated in response to stress [1]. Both neurotransmitters are available for human administration and have been widely used for various medical purposes. With the widespread medical use of cathecolamines, some reports showed serious adverse effects after the administration of cathecolamines and beta-receptor agonists [2]. Indeed, a clinical entity named *stress related cardiomyopathy* is today related to cathecolamines toxic effects on the cardiovascular system [3].

Traditional textbooks of medicine state that epinephrine increases cardiac contractility and cardiac output and enhances the rate of relaxation [1]. However, other publications report conflicting results about the effect of cathecolamines on left ventricular diastolic function. For example, Niwa et al. studied the effect of epinephrine and norepinephrine on left ventricular diastolic function when these were administered with local anesthetics and found that norepinephrine induced diastolic dysfunction while epinephrine did not [4].

A significant role has been assigned to the left atrium function as a modulator of left ventricular filling and cardiovascular performance [5]. In an excellent review on the topic, Hoit describes the left atrium functions as "a *reservoir* for pulmonary venous return during ventricular systole, a *conduit* for pulmonary venous return during early ventricular diastole, and a *booster pump* that augments ventricular filling during late ventricular diastole" [5]. Both left atrial function and left ventricular diastolic function can be echocardiographically assessed [6,7].

Stratton et al. reported that an intravenous epinephrine infusion (25–100 ng/kg/min) produced significant increases in the plasmatic epinephrine concentration that reached values similar to those reported during isotonic exercise [8]. Stratton et al. also reported significant increases in left ventricular stroke volume and ejection fraction, heart rate, systolic arterial pressure and peripheral vascular resistance [8].

In our Electrophysiology and Arrhythmias Section (University Hospital of The Andes, Mérida, Venezuela), we recently validated the use of epinephrine as an alternative to isoproterenol to produce sympathetic stimulation and facilitate arrhythmia induction [9]. Most of the patients who are referred to us for the ablation of supraventricular tachycardia do not have structural heart disease. During the electrophysiological evaluation, patients are submitted to an intravenous epinephrine infusion. In a PubMed search, we did not find any study that investigated the effects of epinephrine on the left atrial mechanical function in patients without structural heart disease. This is why we

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decided to echocardiographically evaluate the left atrial mechanical function and left ventricular diastolic function in patients without structural heart disease who receive an intravenous infusion of epinephrine.

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

After explaining the study protocol in detail and obtaining the patients' written informed consent, we enrolled the patients without structural heart disease who had been admitted for catheter ablation. The patients were evaluated by a cardiologist. An X-ray, an ECG and a transthoracic echocardiogram were obtained before performing the ablation.

If structural heart disease was ruled out, all pharmacological treatments (especially the antiarrhythmic drugs) were discontinued by at least 5 half-lifes. Midazolan was administered for conscious sedation.

Heart rate, blood pressure, and a transthoracic echocardiogram were recorded before and 5 min after confirming the appearance of sympathetic stimulation induced by the intravenous epinephrine infusion (see below).

2.2. Epinephrine infusion

Our epinephrine infusion protocol is described elsewhere [9]. Briefly, epinephrine was intravenously injected at a dose of 50 ng/kg/min. Arterial pressure and heart rate were monitored to verify that at least a 10% increase in heart rate was obtained. If heart rate did not increase, the infusion rate was then raised up to 100 ng/kg/min.

2.3. Transthoracic echocardiogram

The transthoracic echocardiogram was obtained according to the guidelines of the American Society of Echocardiography [10,11]. All measurements were performed in sinus rhythm and with heart rates that allowed clear separation of the E and A waves of the mitral Doppler. The echocardiograms were stored and randomly analyzed by an experienced cardiologist who was unaware of the phase of the study (control vs. intervention) during which the echo was recorded.

2.4. Left atrial function

2.4.1. Volumetric indexes of left atrial function

The maximal (measured just before the mitral valve opening) and minimal (measured at the closure of the mitral valve) left atrial volumes were measured in the 4-chamber apical view. The left atrial ejection fraction (EF) was calculated by subtracting the left atrial minimal from the left atrial maximal volume and by dividing it by the left atrial maximal volume [5]. As an index of the reservoir function of the left atrium, we calculated the left atrial expansion index by subtracting the left atrial minimal from the left atrial maximal volume and by dividing it by the left atrial minimal volume [5].

2.4.2. Spectral Doppler index of left atrial function

To estimate the fraction of stroke volume resulting from atrial contraction which represents the relative contribution of atrial booster pump function, we calculated the atrial filling fraction as the ratio of the A-wave velocity–time integral to the total mitral inflow velocity–time integral [5,11,12].

2.5. Left ventricular diastolic function

The Doppler mitral inflow was acquired with a sample volume of 1 to 3 mm at the level of the tips of the mitral leaflets during diastole. To acquire mitral annular velocities, the pulsed wave Doppler sample volume was positioned at the septal and lateral insertion sites of the mitral leaflets. Placing the cursor of the continuous wave Doppler in the left ventricular outflow tract, the isovolumetric relaxation time was measured from the end of the aortic ejection to the onset of mitral inflow. E/A velocity ratio, e′ velocity, a′ velocity, E/e′, isovolumetric relaxation time, and E wave deceleration time were systematically recorded.

2.6. Statistical analyses

The raw data were stored in Excel® sheets and were analyzed by means of Excel® and SPSS 20® Statistical packages. For continuous variables, the fit to a normal distribution was assessed by means of the Shapiro–Wilk test in order to decide the type (parametric or non-parametric) of tests that should be used for the analyses. Analysis of variance, T-test, Wilcoxon Signed Rank and Kruskall–Wallis test were employed. In our study, the patients were their own controls.

In order to have an 80% statistical power and a 95% confidence interval, a sample size of 27 patients (including a 15% estimate of loss) was calculated as adequate.

3. Results

Twenty-seven patients were included. Fifty-two percent were female. The mean age was 34.6 ± 17.2 years. The mean left ventricular EF was 61 ± 4.5%, and no patient had evidence of structural heart disease. No complication arose.

3.1. Blood pressure and heart rate

Systolic arterial pressure and heart rate significantly increased (see Table 1). The mean heart rate obtained with epinephrine was around 92 beats/min (15% more than control); it did not interfere with the echocardiographic measurements.

3.2. Volumetric and Doppler indexes of left atrial function

Both maximal and minimal atrial volumes increased after epinephrine infusion. The minimal atrial volume increase was more pronounced, and left atrial EF decreased significantly (see Table 2). The left atrial expansion index decreased, and the left atrial filling fraction significantly increased (see Table 2).

3.3. Left ventricular diastolic function

The E wave velocity did not change significantly after epinephrine infusion (0.92 ± 0.29 vs. 0.89 ± 0.24 m/seg; p = 0.3). The A wave velocity significantly increased (0.72 ± 0.25 vs. 0.80 ± 0.18, p = 0.025). In terms of the E/A ratio, 2 patients changed their normal pattern to a grade I diastolic dysfunction pattern after epinephrine infusion. As

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

	Control		Epinephrine		p value
	Mean	SD	Mean	SD	
SAP	137.037	22.896	147.629	25.692	0.00066271
DAP	81.222	14.598	82.222	13.250	0.515887868
MAP	100.851	20.633	104.592	19.329	0.058357393
HR	79.55	12.36	91.59	14.19	≤0.0001

The values correspond to the mean ± the standard deviation. SAP = systolic arterial pressure in mm Hg. DAP = diastolic arterial pressure in mm Hg. MAP = mean arterial pressure. HR = heart rate in beats/min. SD = standard deviation.