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Negative chronotropic response to low-dose atropine is associated with parasympathetic nerve-mediated cardiovascular response in postoperative patients with congenital heart disease

Hideo Ohuchi[a,*], Yuji Hamamichi[a], Tamaki Hayashi[a], Tamao Watanabe[a], Osamu Yamada[a], Toshikatsu Yagihara[b], Shigeyuki Echigo[a]

[a]*Department of Pediatrics, National Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan*
[b]*Department of Thoracic Surgery, National Cardiovascular Center, Osaka, Japan*

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Abstract

Objectives: To investigate the negative chronotropic response (NCR) to low-dose atropine in postoperative patients with congenital heart disease (CHD).
Background: Low-dose atropine causes a NCR through the central nervous system muscarinic receptor and is attenuated in adult heart failure patients. It has never been evaluated in CHD patients.
Methods: NCR corrected for basal heart rate (HR) (minimal HR/basal HR=cNCR) was determined after low-dose atropine (3 μg/kg) administration in 124 postoperative CHD patients (97 biventricular repair and 27 Fontan patients) and 11 controls and was compared with the cardiac autonomic nervous and functional status.
Results: The cNCR in simple CHD (post atrial or ventricular septal defect closure), complex biventricular CHD, and Fontan patients were 0.92±0.04, 0.94±0.04 and 0.96±0.04, respectively, and higher than in controls (0.87±0.03, $p<0.001$). In the complex CHD patients, higher cNCR was mainly associated with the lower pharmacologically determined cardiac parasympathetic nervous tone (PST), HR variability, high atrial natriuretic peptide, and lower right ventricular ejection fraction ($p<0.0001$). In Fontan patients, the lower β sensitivity of the sinus node and the PST mainly determined the higher cNCR ($p<0.01$) and the cNCR did not correlate with either hemodynamics or exercise capacity.
Conclusions: NCR is attenuated in proportion to the impaired cardiac parasympathetic nervous system and hemodynamics in postoperative complex biventricular CHD patients. In addition to PST, β sensitivity of the sinus node significantly influences the NCR in Fontan patients.

Keywords: Congenital heart defects; Atropine; Heart rate; Heart failure; β sensitivity of the sinus node

1. Introduction

A dose-dependent biphasic heart rate (HR) response to atropine is a well-recognized phenomenon in humans and the negative chronotropic response (NCR) to low-dose atropine is believed to be caused through muscarinic receptors in the central parasympathetic system [1–3]. Abnormal cardiac autonomic nervous activity (CANA) is closely associated with pathophysiology in heart failure patients [4–8] and altered parasympathetic control of HR is observed in the early stages of heart failure [9]. Because delayed HR decline, possibly related to withdrawal of parasympathetic activity, is associated with high mortality in both normal and cardiac patients [10,11], the importance of the parasympathetic nervous system in protecting against adverse cardiac events has been emphasized. As NCR is closely related to the central parasympathetic nervous system, its evaluation is not only useful to stratify cardiac status but also provides valuable information on the pathophysiology in heart failure

* Corresponding author. Tel.: +81 6 6833 5012; fax: +81 6 6872 7486.
E-mail address: hohuchi@hsp.ncvc.go.jp (H. Ohuchi).

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patients [12,13]. On the other hand, abnormal CANA has been demonstrated in various kinds of postoperative patients with congenital heart disease [14,15] and may be a substrate for future adverse cardiac events, such as arrhythmias. In biventricular repair patients, CANA indices as well as neurohormonal factors are useful guides for evaluating postoperative functional status, especially parasympathetic nervous activity index in relatively mild heart failure patients [16]. Our hypothesis is that NCR is impaired in CHD patients and correlates with CANA indices, especially with parasympathetic nerve-mediated indices such as heart rate variability (HRV) and arterial baroreflex sensitivity (BRS). Our study is the first investigation of NCR and its clinical significance in postoperative biventricular CHD and Fontan patients.

2. Methods

2.1. Subjects

We studied 134 subjects (9–36 years), including 124 postoperative CHD patients and 11 controls. Postoperative patients included 17 patients after closure of an atrial or ventricular septal defect, 57 after right ventricular outflow tract reconstruction, 4 after an arterial switch operation for complete transposition of the great arteries, 14 after the Ross operation for aortic valve lesions, 5 after repair of coarctation or interruption of the aorta, and 27 post Fontan operation (Table 1). We divided the CHD patients into 3 groups: 1) simple CHD group of patients after atrial or ventricular septal defect (n=17), 2) complex CHD group which includes biventricular repair patients other than group 1 (n=80) and 3) Fontan group (n=27). The controls were being followed at our institute because of a history of dilatation and/or aneurysm of the coronary arteries due to Kawasaki disease and who underwent selective coronary angiography to evaluate possible stenosis of the coronary arteries. Our controls showed no significant coronary artery stenosis [14–16]. Patients after right ventricular outflow tract reconstruction included tetralogy of Fallot in 35 patients, double outlet right ventricle in 9, transposition of the great arteries after Rastelli operation in 5, atrioventricular discordance in 6 (double switch operation in 5, functional repair in 1), and persistent truncus arteriosus in 2. Of the Fontan patients, a total cavopulmonary connection was created in 17 and an atriopulmonary connection in 10 (Table 1). The follow-up period from the last operation to the present study was at least 1 year. Medications included digoxin (n=13), diuretics (n=28), anticoagulant agents (n=37), and 5 were taking an angiotensin converting enzyme inhibitor. No patients were receiving chronotropic or antiarrhythmic medications and we excluded patients with sick sinus syndrome and/or significant arrhythmias, such as junctional rhythm, or ventricular tachycardia from the study. All patients were in sinus rhythm.

2.2. Cardiac catheterization

Cardiac catheterization under light sedation was performed in 82 biventricular patients, 25 Fontan patients and 7 controls. Parameters determined included right atrial

Table 1
Clinical characteristics of the study patients

Group	Congenital heart disease			Control
	Biventricule		Fontan	–
	AVSD	Complex		
Cases	17	80	27	11
Age (years)	15.1±4.6	15.5±5.0	14.4±5.8	15.6±4.6
Follow-up (years)	1.0±0.1	6.1±5.5	7.3±3.9	–
Disease (repair)	ASD (11), VSD (6)	RVOTR (57)	APC (10), TCPC (17)	Hx of KD (11)
	–	Ross (14), ASO (4)	–	–
	–	CoA/IAA (5)	–	–
Cardiac function	(n=14)	(n=68)	(n=25)	(n=11)
CVP (mm Hg)	4±2	7±3***###	12±3***###!!!	3±1
RVp (mm Hg)	27±5	53±22***###	–	25±5
RVEF (%)	55±8	50±9	–	54±7
SVEF (%)	67±5	61±12	51±14**###!!!	63±7
CI (L/min/m^2)	3.6±0.8	3.0±0.7##	2.2±0.6***###!!!	3.7±0.6
Natriuretic peptides				
ANP (pg/ml)	42±20	60±46**	83±70***##!	17±9
BNP (pg/ml)	19±13	36±42	70±115**##	4±5

ANP=atrial natriuretic peptide, APC=atriopulmonary connection, ASO=arterial switch operation, AVSD=atrial or ventricular septal defect, BNP=brain natriuretic peptide, CoA/IAA=coarctation or interruption of aorta, Hx of KD=history of Kawasaki disease, SVEF=ejection fraction of the systemic ventricle, RVEF=ejection fraction of the right ventricle, and RVp=systolic right ventricular pressure. *: p<0.05, **: p<0.01, ***: p<0.001 vs control, ##: p<0.01, ###: p<0.001 vs AVSD and !: p<0.05, !!: p<0.01, !!!: p<0.001 vs complex. Values are mean±SD.