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Cardiac autonomic function in adolescents operated by arterial switch surgery

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ABSTRACT

Background: Children with transposition of the great arteries, in whom an arterial switch operation (ASO) is performed, have been shown to have an increased incidence of sudden death, which may be due to cardiac autonomic imbalance and repolarisation instability. We hypothesised that i) cardiac norepinephrine (NE) kinetics and ii) arterial baroreflex sensitivity (BRS), reflecting sympathetic activity and vagal function respectively, are altered in this group.

Methods and results: 17 children (15.8 ± 1.5 years of age) with ASO-surgery in the neonatal period were studied. 17 had cardiac BRS assessed by spontaneous fluctuations of systolic blood pressure and RR-interval, and repolarisation was measured as QT variability index. Matched healthy subjects were controls. Cardiac vagal function and repolarisation pattern were unchanged following ASO-surgery. At cardiac catheterisation, we infused tritiated NE in 8 of these children to examine total body and cardiac sympathetic function at baseline and following 5 min of adenosine infusion to induce reflex sympathetic activation. Blood was sampled simultaneously from the aorta and coronary sinus. Cardiac fractional extraction of $^{[3H]}$NE was substantially lower in operated children, being 56 ± 10 vs. 82 ± 9% ($p = 0.0001$). Following i.v. adenosine in the operated group, NE total body spillover doubled vs. baseline ($p < 0.002$) and the coronary venous-arterial concentration gradient of $^{[3H]}$dihydroxyphenylglycol increased 4-fold ($p = 0.04$).

Conclusions: Arterial switch operation performed neonatally appears to leave cardiac vagal function intact and, although cardiac sympathetic activation in response to adenosine occurs, cardiac neuronal NE reuptake is impaired. This may be pro-arrhythmic by reducing removal capacity of NE from the cardiac synaptic cleft.

1. Introduction

1.1. Background

Children born with transposition of the great arteries, in whom an arterial switch operation (ASO) is performed, have been shown to suffer from ischemic events and increased incidence of sudden death [1–5]. The ASO creates a suture line across the ascending aorta and pulmonary trunk as well as around the coronary ostia. The majority of the sympathetic nerves that enter the heart do so via the great arteries [6]. A large proportion of the sympathetic nervous inflow is therefore severed at the time of surgery, and denervation supersensitivity could perhaps account for the increased incidence of sudden death that occurs without evident coronary occlusion following the ASO [1]. While the mechanisms remain unknown they are likely to be associated with disturbances in the autonomic control of the heart, perhaps involving both the sympathetic and parasympathetic divisions. A recent report by us demonstrated elevated sympathetic activity and reduced cardiac baroreflex function in adults who had undergone Fontan surgery during childhood [7].

It has been shown that one month after ASO there is virtually no $^{[123]}$metaiodobenzyl-guanidine uptake in sympathetic nerve terminals in the heart [8], thereby indicating that either the heart is denervated or that the norepinephrine (NE) transporter is not functional. After a year, in a fashion similar to what is observed following heart transplantation [9,10] NE uptake is increased, suggesting partial reinnervation similar to that seen in adult patients following heart transplantation [8,10]. In agreement with these data, physiological studies in piglets subjected to ASO have demonstrated increased sensitivity to circulating NE 6–7 weeks after surgery, probably due to defective re-uptake [11].

Normally, most of the released NE (>80% in the heart) is taken up into the sympathetic nerve terminal via the uptake-1 mechanism [12]. Given the simultaneous process of release and uptake of NE, a measurement that adequately reflects NE release rate from an organ must take into account the active extraction of NE by that organ. By assessing total and cardiac NE kinetics [13,14] it is feasible to examine the fractional extraction of NE across the heart as an index of NE reuptake. In addition, one may also measure the fall in NE specific activity, by means of radioisotope dilution, during a single passage through the

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heart, which also provides a valid index of released NE from cardiac sympathetic nerves [15]. Following reuptake into the sympathetic axoplasm, some NE is metabolised to dihydroxyphenylglycol (DHPG), which then diffuses into the plasma compartment [15]. Hence, [3H] DHPG produced from cardiac sympathetic nerves reflects infused [3H] NE that is taken up by neuronal uptake (uptake-1) [12,15].

The arterial baroreflex sensitivity (BRS) is a marker of parasympathetic modulation of heart rate in response to blood pressure fluctuations that has been shown to convey prognostic information after a myocardial infarction [16]. Although the mechanisms underpinning the prognostic value of BRS are unclear, data indicate that a normal modulation of cardiac parasympathetic nervous activity could protect against ventricular arrhythmia [17]. Furthermore, increased lability of cardiac repolarisation, either spatial or temporal, is associated with ventricular arrhythmias and sudden cardiac death [18,19]. The QT variability index (QTVI) is a non-invasive measurement of subtle beat-to-beat fluctuations in the duration of the QT interval [20].

Thus, it appears essential to determine the activity in both components of the autonomic nervous system and the value of QTVI in long term survivors, who neonatally underwent surgery for transposition of the great arteries and hence may present with damage or dysregulation of cardiac sympathetic and vagal innervation, to unravel any functional disturbance that could contribute to the reported heart problems in this group. Therefore, the present study explores: i) cardiac sympathetic nerve function in arterial switch operated adolescents using radiolabelled NE to determine cardiac fractional extraction of NE, specific activity of NE across the heart and the production of tritiated DHPG both at rest and during sympathetic activation induced by adenosine infusion, ii) cardiac BRS at rest to determine vagal activity, and iii) QTVI as an indicator of possible repolarisation abnormalities. Findings in these patients were compared with data from young healthy subjects.

2. Methods

2.1. Subjects

28 children born with transposition of the great arteries were operated with ASO in the neonatal period at Sahlgrenska University Hospital during the period from May 1983 to October 1991. 17 of these children underwent a long-term follow-up study of autonomic function. The patients were offered to participate in consecutive order of birth. Four had died, two had moved to other regions, one had moved abroad, one declined the follow up; two participated although not in the investigations included in this article (one was excluded because of existing treatment with beta-blockers due to left ventricular dysfunction) and two did not participate due to unspecified reasons. One child born in 1994 was included because of request of the child's physician. Hence, 17 subjects (16 males/1 female, aged 15.8 ± 1.5 years, weight 64.5 ± 9.7 kg, height 174 ± 10 cm) (see Supplementary table which also includes clinical details) participated in this follow-up study, which included physical examination, electrocardiogram (ECG), pulmonary scintigraphy, BRS, cardiac ultrasound examination and exercise test with spirometry. After an overnight fast, all 17 patients underwent the cardiac catheterization procedure with full hemodynamic investigation. It was possible to achieve a stable catheter-position in the coronary sinus in 8 patients and they received tritiated NE ([3H]NE) for studying cardiac sympathetic function. These subjects were given an antecubital intravenous (i.v.) line in the right arm for infusion of [3H]NE and one i.v. line in the right hand for subsequent adenosine infusion. A catheter was also inserted via a femoral artery and placed in the descending aorta. The coronary sinus was catheterised via a femoral vein, jugular vein or left antecubital vein. During catheterization, anaesthesia was induced with pentobarbiturates 5.3 ± 6.5 mg/kg, and light anaesthesia was maintained with isoflurane. The control group of healthy subjects who received [3H]NE infusion (n = 15) was sourced from the database of healthy subjects at the Baker IDI Heart & Diabetes Institute, Melbourne, Australia. Those subjects were somewhat older than the aforementioned ASO group (19.7 ± 1.0 years of age, p = 0.0006, 1 female, weight 75.3 ± 6.8 kg, p = 0.0006, height 178 ± 11 cm, p = 0.29) and were given radiotracer infusion according to previously described protocols [14].

The study protocols were approved by the local ethics reviewing committee at the Sahlgrenska University Hospital no Ö379-02, and at the Alfred Hospital, Melbourne, Australia, and all subjects, and if below 18 years, also their parents, gave informed consent.

2.2. Radiotracer infusion

During the catheter studies participants received a tracer infusion of ^{3}H-labelled NE (specific activity of 11–25 Ci/mmol; New England Nuclear, Boston, MA, USA) via a peripheral vein at 0.6 to 0.8 μCi/min, after a priming bolus of 12 μCi, for the measurement of NE kinetics by isotope dilution.

Once all the catheters and intravenous lines were in position the radiotracer infusion began. The first resting blood sample was collected after at least 15 min of infusion to ensure a steady state of the plasma concentration of [3H]NE. Blood samples (10 mL) were taken simultaneously from the coronary sinus and the aorta. Adenosine infusion was then started (140 μg/kg/min), and after 5 min additional blood samples were taken simultaneously from the coronary sinus and aorta.

2.3. Assay of catecholamines

All samples were transferred immediately into pre-chilled tubes containing reduced glutathione and heparin. They were centrifuged at 4 °C and plasma separated for storage at −80 °C. NE was extracted from plasma (1 mL) and samples of infusate (10 μl) using alumina adsorption and separated by high performance liquid chromatography [21,22]. Intra-assay coefficients of variation (CV) in our laboratory are 1.3% and 2.3% respectively; inter-assay CVs are 3.8% and 4.5%, respectively.

2.4. Calculations of norepinephrine kinetics

Total body plasma clearance of NE (CL_{TB}) and total body spillover of catecholamines (NE) into plasma (SP_{TB}) were calculated according to Esler et al. [13,14] and cardiac fractional extraction of NE ($EX_{cardiac}$) was calculated as:

$$EX_{cardiac} = \left({}^{[3H]}NE_A - {}^{[3H]}NE_V\right) / {}^{[3H]}NE_A.$$

NE_V is coronary sinus NE concentration (pmol/mL) and $^{[3H]}NE_A$ is arterial concentration of tritiated NE (dpm/mL). The specific activity (SA) was estimated according to the equation:

$$SA_{NE} = {}^{[3H]}NE_{AV} / NE_{AV}$$

where $^{[3H]}NE_{AV}$ and NE_{AV} are the respective arterial-coronary venous increments in plasma concentration of [3H]NE (dmp/mL) and endogenous NE (pml/mL) [15].

Further, the gradient of [3H]DHPG, [3H]NE and DOPA between the descending aorta and coronary sinus was calculated.

2.5. Cardiac baroreflex sensitivity measurements and calculations

Prior to, and separated from the catheterization procedure, cardiac BRS assessment was performed in awake and non-sedated 17 ASO patients. 17 Swedish sex- and age-matched healthy adolescents were used as controls (1 female; age 15.7 ± 0.3 years, weight 61.1 ± 8.6 kg, height 173 ± 7 cm). The BRS measurements were performed in a quiet environment with minimum disturbance. The same experienced research nurse performed all recordings. All individuals refrained from caffeine-containing beverages and exercise for the 12 h prior to the investigation and were fasting since at least 1 h. After 10 min of rest, ECG and beat-to-beat blood pressure were recorded over 20 min by Portapres® equipment (TNO Biomedical, Amsterdam, Netherlands), with the subject in supine position and with spontaneous, non-regulated breathing [23–25].

According to Gao et al. [26] the time series of SBP and RR interval from the entire period of recording (20 min) were scanned to identify baroreflex sequences, which were defined as three or more consecutive beats in which successive SBP and RR intervals concordantly increased or decreased, with the threshold set at 1.0 mm Hg and 5.0 ms, respectively, and a shift of +1 between the blood pressure pulse and the RR interval, as suggested by Bertinieri et al. [27]. Linear regression was applied to each sequence and only those for which the square of the correlation coefficient (r^2) was greater than 0.85 were accepted for further analysis. The spontaneous BRS was calculated, reflecting the average regression slope for all the linear regressions, thus reflecting cardiac vagal activity.

2.6. QT interval variability index

A period of 5 min with less than 5% atrial/ventricular ectopic beats was chosen for the temporal QT interval variability analysis using a computer algorithm [26,28]. RR interval mean (RRm) and variance (RRv) and QT interval mean (QTm) and variance (QTv) were derived from the respective time series. QTVI, which represents the log ratio between normalised QT and RR interval variability, was calculated according to the equation [20,29].

$$QTVI = log_{10}\left[\frac{QTv/QTm^2}{RRv/RRm^2}\right]$$

2.7. Statistical methods

Numerical distributions are presented by their mean ± SD. Mann–Whitney U-test was used for inter-group comparisons, and Wilcoxon rank sum test was performed for paired comparisons given that the distributions of the data from switch-patients were not normally distributed. Statistical significance was defined as $p<0.05$.