Consequences of Arterial Switch Operation in Children Born with Transposition of the Great Arteries

-A clinical and experimental study of the autonomous nervous system in the heart

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssal Tallen, Drottning Silvia Barn och Ungdomssjukhus, Göteborg

Fredagen den 15 februari 2013 kl 13.00

av

Cecilia Falkenberg

Fakultetsopponent:
Professor Lars Lind
Institutionen för medicinska vetenskaper, Kardiovaskulär epidemiologi,
Akademiska Sjukhuset, Uppsala

Avhandlingen baseras på följande delarbeten:

I **Falkenberg C**, Östman-Smith I, Gilljam T, Lambert G, Friberg P.
Cardiac autonomic function in adolescents operated by arterial switch surgery.
Accepted for publication in International Journal of Cardiology 25-Dec- **2012.** In press.
DOI:10.1016/j.ijcard.2012.12.063

II **Falkenberg C**, Ekman M, Gilljam T, Friberg P. **Heart rate variability in adolescents who as neonates underwent neonatal arterial switch operation.** (Manuscript)

III **Falkenberg C,** Hallhagen S, Nilsson K, Östman-Smith I**. Anaesthetic, surgical and bypass techniques allowing long term survival after complex cardiac surgery in piglets.** (Manuscript)

IV **Falkenberg C,** Hallhagen S, Nilsson K, Nilsson B, Östman-Smith I. A **study of the physiological consequences of sympathetic denervation of the heart caused by the arterial switch procedure**. Cardiology in the Young (**2010**), 20, 150–158

UNIVERSITY OF GOTHENBURG

Abstract

Background*:* The introduction of the arterial switch operation (ASO) made it the procedure of choice for surgical correction of transposition of the great arteries. A majority of the sympathetic nerves innervate the heart alongside the great vessels; these are therefore likely to be damaged during the surgical procedure; imposing new challenges and questions that need to be addressed. The main aim for this thesis was to assess the long-term cardiac consequences on the autonomic nervous system after surgery (paper I and II) and to create an animal model allowing for cardiac physiological studies (paper III and IV).

Methods: Long-term follow-up in adolescents who had undergone ASO as neonates (n=17, 1 female, mean fractional shorting 32±5%) was performed. This included sympathetic nervous system function assessed through infusion of tritiated Norepinephrine ($^{[3H]}$NE) during heart catheterisation (n=8)(controls n=15) and blood samples analysed with high performance liquid chromatography. Samples were obtained both before and after adenosine stimulation as a response to sympathetic excitation. 24-hour heart rate variability (HRV)(n=15 in both groups) was measured both during the day and night using different algorithms. Baroreflex sensitivity and QT variability index (QTVI) (n=17 in both groups) were measured in awake patients. An animal model was developed using complex open heart surgery during cardiopulmonary bypass to mimick the arterial switch operation in piglets 8 weeks of age. The piglets surviving at least 5 to 6 weeks post-operation had follow-up of physiological response to catecholamines and were studied in vivo and in vitro using the Langendorff perfusion system.

Result*s:* In both groups the specific activity of $^{[3H]}$NE decreased from the artery to the coronary sinus, but to a lesser extent in the ASO group. The extraction fraction in the ASO group was 56±10% compared to 82±9% in the healthy subjects (p<0.001). The arterial to coronary sinus plasma concentration of $^{[3H]}$ dihydroxyphenylglycol (DHPG) was significantly increased in the healthy group (70%, p=<0.0001) but was not so in the ASO group (8%, p=0.5). The difference of endogenous DHPG increase from the arterial to the coronary sinus was significantly smaller in the ASO group (p=0.008). After adenosine infusion, the total body NE spillover increased in the ASO group (p=0.002), reflecting major sympathetic activation. $^{[3H]}$DHPG step-up from the artery to the coronary sinus increased 4-fold following adenosine. HRV frequency-domain at night-time, when cardio-parasympathetic drive is likely to be most pronounced, showed a significant decrease of normalized high frequency in the ASO group (52±20) compared to healthy subjects (68±15)(p=0.018). Time-domain showed no statistical difference between the two groups, neither during day-time nor night-time. Baroreflex sensitivity and QTVI did not show significant differences between groups. The animal model resulted in 14 out of 19 piglets surviving the mimicked ASO. Piglets operated with mimicked ASO had a significantly higher basal heart rate both in vivo (p=0.042) and in vitro (p=0.0056).

Conclusion*:* A disturbed but functioning sympathetic cardiac innervation was found in the ASO patients at long-term follow-up. The vagal tone seemed normal in terms of BRS, however, frequency-domain analysis showed a decreased parasympathetic tone at night time in the ASO group. The surgical challenges due to translocation of the coronary arteries and the consequences of an injured autonomic nervous system impose risks of decreased myocardial perfusion and arrhythmias. Thus, the present data suggest that these patients ought to have follow-up that includes autonomic nervous system assessment.

Key Words: Transposition of the great arteries, arterial switch operation, autonomous nerves system, norepinephrine, heart rate variability, cardiopulmonary bypass, piglets

ISBN 978-91-628-8542-7