The arterial switch operation (ASO) is recognized as the procedure of choice for the treatment of children with transposition of the great arteries (TGA). Although sufficient growth of aortocoronary anastomoses has been demonstrated in animal and human studies, coronary dysfunction with attenuation of the coronary flow reserve (CFR) and stress-induced perfusion defects has been demonstrated in previous studies using positron emission tomography (PET).

Sympathetic nerves may be interrupted by the ASO with denervation of the heart. Several studies have demonstrated that signals from cardiac efferent sympathetic nerves play an important role in modulating the ability of the coronary vasculature to dilate and thus increase the myocardial blood flow during periods of activation of the sympathetic nervous system, such as physical activity or mental stress.

The objective of the present investigation was to measure the integrity of myocardial sympathetic innervation in long-term survivors of the ASO by PET-imaging using C-11 epinephrine (EPI) as an analog of norepinephrine. The results were compared with TGA patients after the Rastelli procedure, having the same inborn cardiac anomaly but not having transection of the great arteries and coronary reimplantation.

**Methods**

**Study Population**

A total of 18 patients with TGA without limitations precluding...
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Results

Treadmill Exercise Tolerance Test

The patients (groups 1 and 2) were fully active and asymptomatic; no patient was on cardiovascular medication.

All patients could be exercised to exhaustion and achieved the anaerobic threshold; because the gas exchange ratio (RER) at peak exercise exceeded 1.0 in all individuals, we are confident that all patients and controls performed near maximal exercise. Maximal oxygen uptake (VO₂max; groups 1 and 2) was within the normal range (32.4±6.9 ml kg⁻¹ min⁻¹) compared with the group of healthy volunteers (36.2±4.1 ml kg⁻¹ min⁻¹); despite a tendency to having lower VO₂max in Rastelli patients, there was no significant difference between the 2 patient groups (35.6±2.9% vs. 33.9±3.85 ml kg⁻¹ min⁻¹, NS) (Table 1).

None of the patients had ECG evidence of ischemia or ectopic activity during or after exercise.

All patients remained asymptomatic and did not complain of chest pain.

Echocardiography

Echocardiographic measurements of fractional shortening and ejection fraction were normal in all patients. LV ejection fraction and LV end-diastolic volume did not differ significantly between the patient subgroups with absent or positive EPI-retention. No patient showed depressed contraction <0.45 in ejection fraction or regional wall motion abnormalities of the LV at rest or after maximal exercise and there was no significant difference detected in comparison with the healthy volunteers. There was no evidence of hemodynamic abnormalities such as relevant RV outflow tract obstruction, aortoventricular regurgitation, aortic regurgitation or width of the ascending aorta.

Sympathetic Innervation

The initial qualitative assessment of myocardial perfusion with 13-N ammonia was homogeneous in all patients. Perfusion defects were not detected, confirming myocardial integrity at the time of PET scanning. The presence and extent of catecholamine uptake in cardiac sympathetic nerve terminals were evaluated with 11-C EPI, an analog of norepinephrine, that has the same mechanism of uptake and storage as the naturally occurring neurotransmitter.

LV myocardial EPI-retention as a measure of the intensity of innervation ranged from 6.1% to 15.9%/min (mean 12.7±4.3%/min) in all patients of groups 1 and 2.

No statistical significant difference could be found between patients of groups 1 and 2. The maximal LV EPI-retention in group 1 was 12.8±1.4%/min (range: 6.1–14.8%/min) and 12.6±1.41%/min (range: 6.5–15.9%/min) in group 2.

Patients in both groups who had undergone more than 1 operation had a significant lower maximal EPI-retention than those with primary repair (1-stage repair: 13.9±2.8%/min vs. 2-stage repair: 8.23±2.8%/min, P<0.001). Two patients had EPI-retention <7%/min, indicating complete denervation. One of the patients, in the Rastelli group, had reoperation because of homograft stenosis; the other had a mechanical aortic valve implantation because of severe aortic insufficiency after ASO (Table 2).

A significant positive correlation was found between EPI-retention and the time interval between corrective surgery and investigation for both patient groups (r=0.81, P<0.001); no difference existed between groups 1 and 2.

Maximal EPI-retention was significant higher in patients undergoing corrective cardiac surgery at an earlier age than in those who had surgery in adolescence (P<0.001); again, there was no significant difference between patients after ASO or Rastelli repair.

Clinical data such as weight, height, body mass index, LV ejection fraction at rest and after exercise, maximal oxygen uptake VO₂max and ECG pattern at rest and during exercise did not correlate with EPI-retention and did not differ between groups 1 and 2.

Baseline heart rate and rate pressure product (RPP) as an index of cardiac work at rest was within the normal range in all patients and there was no significant difference between groups 1 and 2.

Heart rate and RPP at maximal exercise levels tended to be significantly higher in patients with higher EPI-retention (P<0.001).

Aortic cross-clamp time during corrective surgery inversely correlated with maximal EPI-retention (r=−0.72, P<0.001); bypass time, time in the intensive care unit and ventilation time did not correlate with sympathetic innervation (Table 3).

Discussion

As a result of major achievements in cardiac surgery and clinical care, a growing number of patients with congenital heart disease reach adulthood. Besides psychosocial factors, which influence mental health, complications may arise from postoperative sequelae, residual defects and acquired comorbidities. In particular, alterations in myocardial perfusion can be a concern in the long-term follow-up of patients with TGA after the ASO. Several studies demonstrate attenuated myocardial blood flow, impaired CFR and reversible stress-induced perfusion defects while the patients are clinically asymptomatic.

Several factors contribute to an alteration of myocardial blood flow, and impairment of the microcirculation seems to be most likely.

Abnormal vasomotor activity because of an increase in myocardial oxygen demand, progresed intima proliferation induced by coronary reimplantation, endothelial dysfunction, attenuated coronary perfusion pressure because of increased stiffness of
the ascending aortic wall, or reimplantation of the coronary arteries out of the aortic sinus, and sympathetic denervation of the myocardium have to be discussed.

Coronary microcirculation is modulated through changes in arteriolar vascular resistance responding to alterations in blood flow, metabolic tissue demands and neurohumoral stimuli. An increase in sympathetic activity produces dilatation of coronary resistance vessels and thus increases myocardial blood flow. The increase in coronary flow response to sympathetic stimulation correlates with the magnitude of regional stores of norepinephrine in cardiac sympathetic nerve terminals, which correlates with contractility, oxygen demand and reactive metabolic vasodilatation or direct activation of β-adrenergic receptors on smooth muscle- and endothelial cells in the vessel wall.

Coronary vasodilatation may also result from the direct stimulation of alpha 2-adrenergic receptors in intact endothelial cells and the release of nitric oxide, presumably through the activation of local kinin synthesis.

Postganglionic sympathetic nerve fibers, which travel from the stellate ganglia along the arterial structures to the myocardium, are transected in patients undergoing ASO, resulting in axonal degeneration and depletion of norepinephrine from nerve terminals.

It is hypothesized that dissection of the great arteries and coronary reimplantation may have some adverse effect on myocardial perfusion contributing to an attenuated CFR, which creates potential for a mismatch between perfusion and energy demand.

In our study, there were signs of reinnervation in most of the patients after ASO and only 1 patient in each group showed complete denervation with EPI-retention <7%/min, indicating complete denervation as demonstrated in patients early after heart transplantation.

There was no difference in the intensity of EPI-retention between patients after ASO or after Rastelli repair, indicating that sympathetic denervation is not the major point contributing to impairment of myocardial blood flow and CFR in long-term survivors of the ASO.

Initially after the ASO, there is relevant sympathetic denervation leading to an attenuation of myocardial perfusion, as has been demonstrated in animal models and clinical studies.

Early denervation supersensitivity and inhomogeneity of sympathetic innervation, which is likely to be present during the reinnervation phase, predispose to arrhythmias, which occur in 9.6% of 1-year survivors.

Regrowth of nerve fibers takes time and it is apparent that the intensity of myocardial EPI-retention, which represents sympathetic reinnervation, is positively correlated to the length of time after surgery. Patients operated on at an earlier age had positive EPI-retention more frequently and more extensively than those operated on at an older age.

Similar findings have been demonstrated in patients after transplantation.

The fact that patients after Rastelli repair had a similar pattern of EPI-retention as patients after ASO, and the fact that a Rastelli patient had complete denervation indicates that the process of sympathetic denervation and reinnervation also takes place in patients who do not undergo arterial transection and coronary reimplantation.

Potential mechanisms are transient myocardial deterioration and surgical damage. Sympathetic nerves also pass along the postero-medial surface of the superior vena cava, the right atrium and both the ascending aorta and the main pulmonary artery and pulmonary veins. Transection and dissection of cardiac structures and removal of the pericardium overlying the surface of the right atrium and the superior vena cava during cardiac surgery may damage sympathetic neuronal innervation; subclinical myocardial damage, such as ischemia during cardiac surgery, may be another reason.

The number of surgical procedures is another factor that affects sympathetic innervation of the myocardium. Only patients undergoing more than 1 operation had EPI-retention <7%, indicating complete denervation of the LV caused by surgical injury as already mentioned. The higher age of the subjects at the time of operation, the reduced ability for generating sympathetic reinnervation and recurrent surgical damage are also possible explanations.

Kondo et al demonstrated that almost all patients operated on in early infancy showed positive uptake of an norepinephrine analog, which was observed in only half of those having the operation in childhood or adolescents, suggesting there is a greater ability for sympathetic reinnervation in younger children.

It is well known that neuronal regeneration is dependent on neurotropins, which are produced and released by the target tissue, as aging has been suggested to be associated with reduced availability of target-derived neurotropin factors, which may explain the relationship between sympathetic reinnervation and the age of the patient. Reduced availability and synthesizing capacity of neurotropins may be responsible for the lower degree of reinnervation in cases of more frequent operations.

Aortic cross-clamp time negatively correlated with EPI-retention in both patient groups. During aortic cross-clamping there is reversible subendocardial ischemia, leading to hibernating myocardium, which affects sympathetic nerve function.

Functional denervation has been observed after brief coronary occlusion, as well as in viable risk areas of reperfused myocardial infarcts, which supports the view that sympathetic nerve function is exquisitely sensitive to ischemia.

The parasympathetic and sympathetic postganglionic pathways to the sinoatrial node follow the free wall of the right atrium and thus are vulnerable to surgical interventions such as incision or cannulation of the right atrium during open heart surgery; this regional injury may induce cardiac arrhythmias, but sympathetic innervation of the ventricular myocardium is not likely to be affected.

PAB did not attenuate sympathetic innervation of the ventricular myocardium; animal models has it been demonstrated that ventricular hypertrophy induced by PAB with slowly progressive pressure overload is not associated with depression of sympathetic innervation.

The present study showed that both the heart rate response to exercise and RPP as an index of cardiac work were attenuated in patients with reduced or absent EPI-uptake. Similar findings have been obtained in patients after transplantation, where the magnitude of peak heart rate and oxygen consumption correlated with the presence or absence of sympathetic reinnervation.

The right stellate cardiopulmonary nerves, including the sympathetic and parasympathetic axons, travel along the postero-medial surface of the superior vena cava; sympathetic as well as parasympathetic innervation from the right stellate cardiopulmonary nerves to the sinus node may be compromised in patients after ASO or Rastelli repair. Chronotropic action because of norepinephrine release into the sinus node artery may be attenuated by such surgical procedures. Clinical parameters such as ventricular performance on exercise and cardio-pulmonary exercise capacity were unaffected by the degree of LV EPI-retention.

Nevertheless, the paucity of sympathetic reinnervation may
have long-term physiological and clinical consequences cardiovascular surgery.

**Clinical Implications**

The study results showed that open heart surgery should be performed as early as possible, because sympathetic reinnervation is more likely in children having corrective cardiac surgery in early infancy. The negative influence of cardiopulmonary bypass should be taken into consideration, as we could demonstrate a negative correlation between aortic cross-clamp time and sympathetic innervation; if possible, prolonged aortic cross-clamp time should be avoided.

**Study Limitations**

The study population was small, which is a major limitation of the study; the clinical variation was wide, but all patients after ASO had dissection of the great arteries, which is thought to be the main reason for sympathetic denervation of the ventricular myocardium with consecutive impaired myocardial blood flow. From the ethical point of view it was not acceptable to investigate children younger than 18 years of age, because of the exposure to radiation and the fact that the clinical impact of the study had no direct therapeutic consequence for the individual patient; because of that, according to the instructions of the ethical committee, only patients older than 18 years of age were included in the study.

**Conclusions**

We found that sympathetic reinnervation occurs in most of the long-term survivors after ASO. There exists no difference in EPI-retention between patients after ASO or Rastelli repair, so factors other than arterial transection and coronary reimplantation may influence sympathetic innervation of the myocardium.

The older the patients were at the time of operation, the more operations they underwent and the longer the aortic cross-clamping lasts, the more diminished is EPI-retention as indicator of sympathetic reinnervation.

Ventricular performance and cardiopulmonary exercise capacity did not correlate with EPI-retention; only peak heart rate and RPP at maximal exercise level positive correlated with the degree of sympathetic reinnervation.

It is unlikely that reduced CFR is related exclusively to an impairment of myocardial sympathetic innervation in long-term survivors of ASO: a multifactorial pathomechanism has to be discussed.

**Disclosures**

None.

**References**