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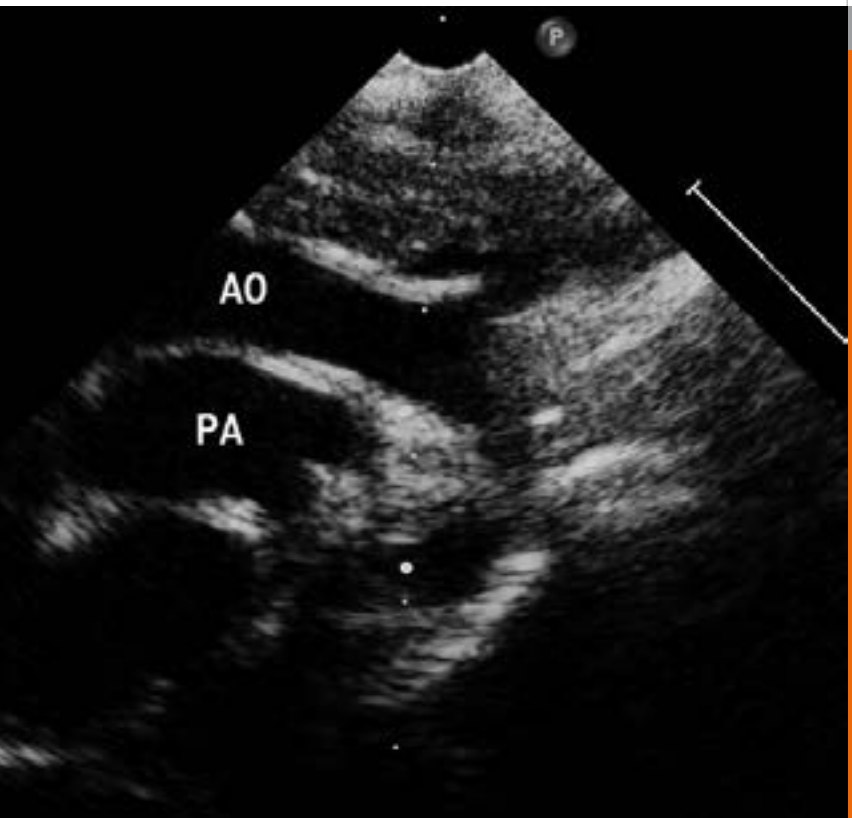
Outcome of a 20-day-old term infant with d-TGA and severe hypoxemia



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INTRODUCTION

D-transposition of the great arteries (d-TGA) is the most common cyanotic congenital heart defect to present in the 1st week of life (1), affects 2.4 per 10,000 births (2), and goes along with progressive, moderate to severe postnatal hypoxemia (SpO2 ~ 40-85%). Most patients with d-TGA/intact ventricular septum (iVS) are now successfully treated with prostaglandin E infusion, balloon atrial septostomy (BAS, Rashkind procedure) (3) and arterial switch operation in the first week of life (4). Several investigators found an association between both early BAS (5) and one stage arterial switch operation (4) on the one hand, and post-interventional stroke/brain damage (5) as well as mid- to long-term neurological impairment of d-TGA patients (4) on the other. Here, we report on a 3-week-old term infant with d-TGA/iVS, who had chronic, slowly worsening, and finally severe hypoxemia, underwent late BAS and two-stage arterial switch operation, but did not suffer from brain damage associated with significant neurodevelopmental delay at preschool age.

CASE REPORT

In May 2002, a 3-week-old boy from Pakistan with postnatally diagnosed cyanotic congenital heart disease, arrived at the airport in Munich. Pregnancy had been uneventful, and was followed by a normal vortex term delivery of the mother's fourth child in a private hospital in Pakistan (birth weight 3400 g). Apgar scores were 5 at 1 minute and 10 at 10 minutes. On DOL 2, tachypnea and central cyanosis were

noticed. A provisional diagnosis of bronchopneumonia was made and the baby was transferred to an NICU in Lahore, Pakistan. The baby was treated with IV antibiotics although bacterial cultures remained negative. It was not until DOL 10, when persistent cyanosis was investigated further (Fig. 1). An echocardiogram showed d-transposition of the great arteries, intact ventricular septum (d-TGA/iVS) and a restrictive patent foramen ovale (PFO), i.e. 3 mm in diameter with an estimated interatrial pressure gradient (LAP > RAP) of 6 mmHg. Postductal SpO2 at that time were 70-72%. Given the urgent need for cardiovascular surgery, the parents finally (i.e., 10 days later) managed to schedule public airline transport to Munich. On the day of departure (DOL 19, approx. 20 hours before the patient's arrival in Munich) vital signs indicated progression of hypoxemia (heart rate 130 bpm, 45 breaths/minute, postductal SpO2 62%).

On the runway in Munich, the parents handed the transport team a pale, reasonably warm, shallow but regularly breathing boy (50 breaths/minute) with central cyanosis and moderate dehydration. On auscultation, the heart rate (HR) was regular at 140-150 bpm, 1st and 2nd heart sounds were gentle and no murmur was heard. Initially, no pulse or blood pressure were obtainable. The liver was palpable 3.5 cm below the costal margin. Two separate pulsoximeters indicated an SpO2 of 17% with good wave form both at the upper and lower extremities. The transport team had

Fig. 1

10-day-old term infant born in Pakistan with central cyanosis due to d-TGA/iVS.

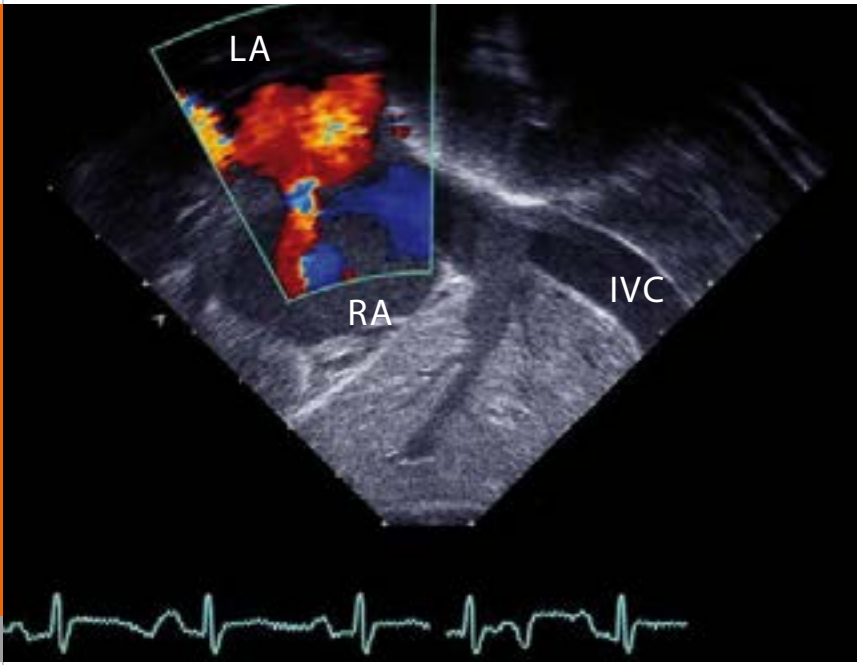

Fig. 2A

Color Doppler echocardiography showing left-to-right atrial shunting via a patent foramen ovale (PFO):

A) restricted interatrial blood flow from the left atrium (LA) through the PFO into the right atrium (RA) as indicated by the narrowing and turbulence of the red signal across the atrial septum; systemic venous return via the inferior vena cava (IVC) into the RA is indicated by blue color.

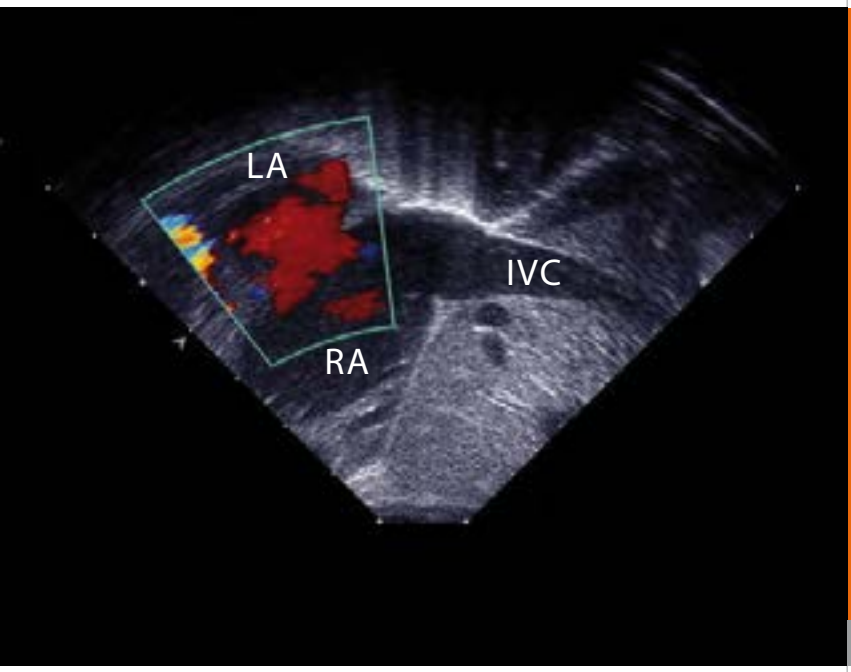

Fig. 2B

Color Doppler echocardiography showing left-to-right atrial shunting via a patent foramen ovale (PFO):

B) after successful ballon atrial septostomy (BAS, Rashkind procedure) with large left-to-right atrial shunt.

been told the boy had d-TGA, had had a Rashkind procedure in Pakistan, and - for the duration of the flight - had been on prostaglandin E (PGE) infusion, and supplemental oxygen as needed.

On arrival, however, the infant had not been seen by any physician for at least 12 hours. Based on the patient's compromised clinical condition, the emergency pediatrician assumed the initial diagnosis was correct, but that both atrial and ventricular septum were intact and the foramen ovale and ductus arteriosus had closed. With supplemental oxygen (100%, 10 l/minute) SpO2 rose to 40%. Two peripheral venous lines were placed. Volume substitution (normal saline) and high-dose PGE infusion (100 ng/kg/minute) were started. The baby continued to breath spontaneously, pulses became detectable (130-145 bpm), and mean arterial blood pressure (MAP) and SpO2 were recorded to be 55 mmHg and 40-50%, respectively.

The infant arrived on the cardiovascular intensive care unit (CVICU) at 18:30h - after 40 minutes of ground transport and additional low-dose sodium bicarbonate infusion (0.7 mEq/kg/dose = 1 mEq/kg/h) - with a HR 155 bpm, MAP 38 mmHg and SpO2 42-55%. After analgosedation, muscle relaxation, endotracheal intubation and positive pressure ventilation with 100% oxygen, SpO2 initially dropped to 29% but increased to 39% over the next 20 minutes. An arterial blood gas analysis (18:56h) immediately after intubation showed

severe hypoxemia (PaO2 13 mmHg) but no acidosis (pH 7.47, PaCO2 36 mmHg, BE +2 mmol/l, lactate 3.2 mmol/l). Volume replacement was continued via a central venous line, however the baby remained borderline hypotensive and severely hypoxemic so that moderate dopamine (8 mcg/kg/min) and norepinephrine (0.07 mcg/kg/min) infusions were started. The initial echocardiogram demonstrated d-TGA/iVS, minimal shunts across the atrial septum and the ductus arteriosus, and impaired biventricular function (Fig. 2). A balloon atrial septostomy was performed 90 minutes after the patient's arrival on the CVICU, leading to a rapid increase of SpO2 > 60%, followed by a continuous rise of SpO2 up to 76% over the next 90 minutes, and discontinuation of PGE infusion (see movie below: catheter was inserted into the femoral vein and placed in the left atrium (LA) via the inferior vena cava, the right atrium (RA) and a patent foramen ovale. A ballon attached to the catheter is rapidly pulled back from the left into the right atrium; note the wide open interatrial communication after the successful procedure).

After stabilization of the infant, comprehensive history taking revealed that d-TGA/iVS had been diagnosed late on DOL 10 in Pakistan, where usual counselling would have been "terminal care". The parents decided to ask for international help and requested urgent BAS as well as international neonatal emergency transport. However, the only capable cardiologist in

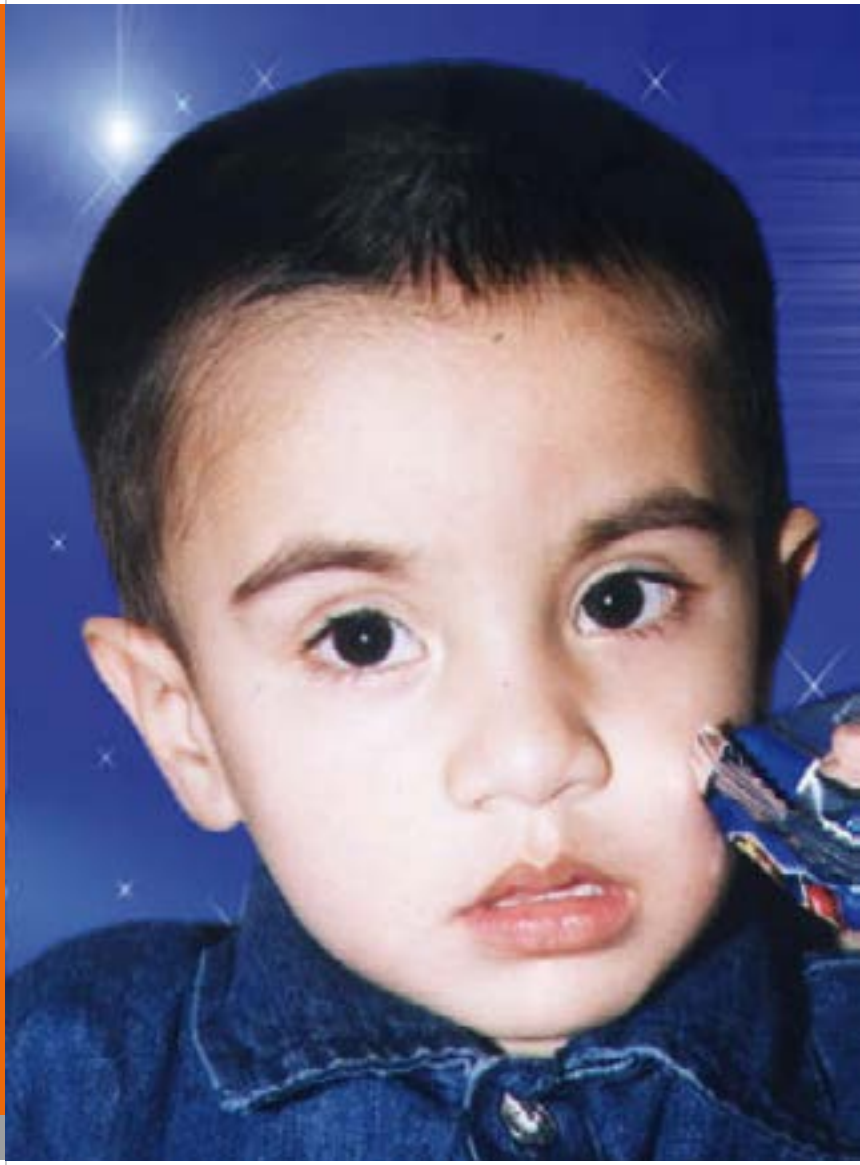

Fig. 3A

The same patient at age of three (A) and four years (B).

Fig. 3B

a 300 km radius had a hand injury on the day of the scheduled procedure so that a BAS, in fact, was not performed. On their own initiative, the parents subsequently scheduled public airline transport during which they had noticed their baby getting even more blue. Biventricular dysfunction in this severely compromised infant lead to the decision for a rapid two-stage arterial switch-operation: Two days after arrival and BAS, a central aortopulmonary shunt (3.5 mm), atrioseptectomy and pulmonary arterial banding were performed to improve systemic oxygenation and to train the left ventricle in anticipation of the arterial switch operation. Postoperatively, multiresistant bacterial sepsis (acquired in Pakistan) was successfully treated, and cardiac function improved. Nine days after the first operation, an uncomplicated arterial switch operation was performed on the then almost 5-week-old infant. The boy was discharged one month later in excellent hemodynamic and neurological condition, with SpO2 95%, a remaining pressure gradient (dP) over the pulmonary artery (PA; dP 55 mmHg at the PA bifurcation on Doppler echocardiography), and normal head ultrasound. Three, four and five years later, the patient was found to be an active, healthy boy (Fig. 3 A, B). Cardiac follow-up showed good biventricular function, regular coronary blood flow, improved right PA stenosis (dP 30 mmHg), and normal ECG, blood pressure and SpO2 (98%). The developmental milestones were assessed on Schedule of Growing Skills (SGS-II) (6) and demonstrated adequate neurodevelopment at 5 years

of age, with mental developmental indices (MDI) of 80-100% for all 8 skills tested. The child currently is 6 years old, in first grade of a regular school and doing well in academics according to school report.

DISCUSSION

Acute perinatal hypoxic-ischemic events and associated hyperoxia-reperfusion injury ("birth asphyxia") (7-10) frequently lead to devastating neonatal brain damage (11). Strategies how to treat hypoxic ischemic encephalopathy (HIE) are subject of an ongoing debate (10, 12-15). Our description of a newborn infant with d-TGA surviving chronic, slowly progressing, and finally severe hypoxemia (SpO2 17%, PaO2 13 mmHg), BAS and cardiovascular surgery without any significant neurodevelopmental delay is quite remarkable. Postductal SpO2 was 70-72% on DOL 10, and the worsened postductal SpO2 of 62% on the day of departure from Pakistan (DOL 19) is in line with the natural course of untreated d-TGA (i.e., closing of PDA and PFO, usually in the first two weeks of life). During the intercontinental flight, the flow restriction through the PFO may have worsened or stayed the same, but the small ductus arteriosus (that might have been marginally open before departure) functionally closed. On arrival in Munich, the LA-to-RA shunt and systemic oxygenation increased with the administration of IV volume and high-dose PGE infusion. We might have re-opened the ductus arteriosus to some extent, however, according to the echocar-

diogram performed in Munich, the ductal shunt prior to the Rashkind procedure (BAS) was nevertheless very small. The rapid balloon atrial septostomy dramatically improved all the shunt on the atrial level, systemic oxygenation and hemodynamics, so that subsequently the patient was stable enough to undergo a two-stage arterial switch operation.The PaO2 at which 50% of hemoglobin is saturated (P50) averages 22 mmHg in the newborn (16). Given the sigmoid shape of the oxygen-hemoglobin-dissociation curve, lack of severe acidosis and the reliable pulsoximetric wave form obtained, it can be realistically estimated that the patient's PaO2 in room air on arrival at the airport was approximately 10-16 mmHg (when SpO2 was 17%). We are not aware of any other published case report, describing an older child or adult surviving several days - with arterial oxygen saturations persistently below 65%, followed by a several hour-long period with SpO2 below 20%. This report therefore may suggest a greater tolerance for chronic hypoxia in neonates than in older children or adults. Moreover, the patient's clinical course and follow-up indicates the neonatal brain adjusting better to chronic, slowly worsening hypoxia than to acute hypoxia (11) (e.g., birth asphyxia). Whether this is due to decreased cerebral energy metabolism and/or increased cell survival and resistance to apoptosis in the context of chronic (rather than acute) hypoxia is unknown. Ischemic preconditioning (ischemic tolerance) (17) is the process by which a sub-threshold ischemic insult applied to the brain regulates certain

gene sets and cellular pathways which may reduce damage caused by subsequent ischemic episodes. In fact, cerebral ischemic preconditioning in animal models of stroke provided solid neuroprotection against subsequent ischemic injury (18), and previous transient ischemic attacks were associated with better clinical outcome after subsequent stroke in humans (19). Researchers have just begun to unravel the underlying molecular processes: In a mouse model of cerebral ischemia, preconditioning resulted in downregulation of genes that control metabolism, cell cycle regulation, and ion-channel activity (20). These features mimic specific adaptive neuroprotective strategies seen in hypoxia-tolerant states such as hibernation (which occurs, for example, with therapeutic hypothermia (15)). It is possible that the chronic, slowly worsening hypoxia and hemodynamics in our patient preconditioned the infant's brain (21) to the severe hypoxia-ischemia at the time of critical shunt closure, and to the subsequent periods of cardiopulmonary bypass that is associated with variable degrees of cerebral hypoperfusion and hypoxia. Nevertheless, it should be underlined that children with congenital heart disease continue to have a high rate of cerebral injury on MRI (and even abnormal brain development in utero (22)) and a significant burden of neurodevelopmental disability when compared with their healthy peers (4, 23-24). While some infants with d-TGA/iVS may be severely depressed or even die immediately after birth - presumably due to early and rapid perina-

tal closure of the foramen ovale and ductus arteriosus (25-26) - this case report suggests there might be another subgroup of d-TGA/iVS patients who either resist or tolerate shunt reduction and associated progressing hypoxia for a longer period of time.

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