A 5-MONTH-OLD INFANT recently adopted from South America is being evaluated for stable persistent cyanosis with arterial oxygen saturation (Sao2) of 70% to 80% since birth. She feeds well and is in the 70th percentile for weight (6.5 kg). An echo done before her arrival at your institution suggests that she has tetralogy of Fallot (TOF). Although she has never been noted to have a "Tet spell," her Sao2 was noted to decrease to 60% during a recent febrile episode. Repeat echocardiogram reveals TOF with severe valvular pulmonary stenosis (PS) and mild subvalvular PS secondary to anterior deviation of the conal septum into the right ventricle outflow tract (RVOT). There is a peak instantaneous gradient of 70 mm Hg across the RVOT as determined by continuous wave (CW) Doppler.

What is tetralogy of Fallot (TOF)?

In 1888, Fallot described a congenital heart defect composed of four characteristics (a) large ventricular septal defect (VSD), (b) right ventricular (RV) outflow obstruction, (c) overriding aorta, and (d) right ventricle hypertrophy (RVH). Broadly defined, TOF is a complex of anatomic malformations consisting of a large malalignment conoventricular VSD, a rightward and anterior displacement of the aorta such that it overrides the VSD, and a variable degree of subvalvular right ventricle outflow tract (RVOT) obstruction due to anterior, superior, and leftward deviation of the conal (infundibular) ventricular septum. In addition, abnormalities in the septal and parietal bands of the crista supraventricularis further exacerbate infundibular obstruction. RVH is the result of chronic RVOT obstruction. The most common associated lesion is a right aortic arch with mirror image arch vessel branching (innominate artery gives rise to left carotid and left subclavian, right carotid and right subclavian arise separately) present in 25% of patients. Two broad subsets of TOF exist: TOF with pulmonary stenosis (TOF/PS) and TOF with pulmonary artery (TOF/PA). A third much less common type of TOF known as TOF with absent pulmonary valve (TOF/ APV) will not be considered here.

Tetralogy of fallot with pulmonary stenosis
TOF/PS involves the features of TOF in conjunction with varying degrees of valvular PS. At one end of the spectrum of TOF/PS the pulmonary valve may be mildly hypoplastic (reduced annulus size) with minimal fusion of the pulmonary valve leaflets. The pulmonary valve is almost always bileaflet. At the other end of the spectrum the pulmonary annulus may be very small with near fusion of the valve leaflets. It is important to point out that the valvular obstruction is a fixed obstruction while the subvalvular obstruction is dynamic. Left uncorrected, RVOT obstruction from both valvular and subvalvular obstruction begets progression of subvalvular obstruction as compensatory RVH increases the mass of the RV and infundibulum. The anatomy of TOF/PS can almost always be definitively delineated (including coronary anatomy) by two-dimensional echocardiography. Cardiac catheterization is rarely necessary or indicated.

**Tetralogy of Fallot with pulmonary artery**

TOF with pulmonary artery involves the features of TOF and infundibular and pulmonary valvular atresia in conjunction with varying degrees of pulmonary arterial atresia. Four groups are said to exist. Group 1 patients have isolated infundibular and pulmonary valve atresia with a main pulmonary artery and distal pulmonary arteries of near normal size and architecture. In some of these patients the main pulmonary artery (PA) may extend to the atretic infundibulum. In others, there is short segment atresia of the main PA. Patients in this group have pulmonary blood flow supplied from a patent ductus arteriosus (PDA). Group 2 patients have absence of the main PA but the PAs are in continuity and supplied by a PDA. Group 3 patients have severely hypoplastic native PAs; the left and right PA may not be in continuity. There are major aortopulmonary collateral arteries (vessels from the aorta to the PA) known as MAPCAs. A PDA may be present as well. Some segments of lung may be supplied only by blood from MAPCAs, some only by the native PAs, and others by both sources. Group 4 patients have no native PAs and all pulmonary blood flow is derived from MAPCAs. The anatomy of MAPCAs in TOF/pulmonary artery can almost never be clearly delineated by two-dimensional echocardiography alone. Cardiac catheterization and/or magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) are necessary to delineate collateral anatomy and to determine Qp : Qs.
Which other abnormalities need to be considered in this patient?

Because approximately 8% of children with congenital heart disease have other congenital abnormalities, it is prudent to consider and define these defects. For example, patients with tetralogy of Fallot with pulmonary stenosis (TOF/PS) and TOF/pulmonary artery have a higher incidence of 22q11.2 deletion, a defect associated with DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndromes leading to hypocalcemia, immunodeficiency, facial dysmorphia, palate anomalies, velopharyngeal dysfunction, renal anomalies, and speech and feeding disorders as well as neurocognitive, behavioral, and psychiatric disorders. Tracheal stenosis and bronchomalacia may be a serious problem for TOF/pulmonary artery patients who have undergone tracheoesophageal fistula repair. Needless to say many of these defects can seriously complicate airway management.

In general, what NPO guidelines will you follow and what premedication will you give to a child with congenital heart disease?

Generally speaking the rule of 2, 4, 6, 8 can be used as the nothing by mouth (NPO) interval for neonates, infants and children with congenital heart disease:
- Two hours for clear liquids
- Four hours for breast milk
- Six hours for formula
- Eight hours for solid food
Premedication before induction can be used to facilitate a number of objectives. In older children it can be used to alleviate anxiety before an intravenous or inhalation induction. In younger children, premedication eases separation of the child from the parents. In infants judicious premedication alone or in combination with inhaled nitrous oxide can greatly simplify placement of an intravenous catheter in an otherwise struggling infant. Midazolam 1.0 mg per kg orally in infants and younger children who have not had prior cardiac surgery is useful. In children older than 1 year who have undergone prior operative procedures oral ketamine 7 to 10 mg per kg in combination with midazolam 1.0 mg per kg works well. These children are remarkably tolerant to midazolam as the result of either heightened anxiety or previous intra- and postoperative exposure to benzodiazepines. In circumstances where premedication is deemed important and the child will not take oral medication the intramuscular route can be used. Ketamine 2 to 3 mg per kg and glycopyrrolate (10 mg/kg) alone or in combination with midazolam 0.1 mg per kg works well.


How will you induce anesthesia in this patient if intravenous access cannot be obtained?

An alternative to intravenous induction in infants and neonates with difficult peripheral intravenous access is intramuscular induction with ketamine (3 to 5 mg/kg), succinylcholine (5 mg/kg), and glycopyrrolate (10 mg/kg). Glycopyrrolate is recommended to reduce the airway secretions associated with ketamine administration and to prevent the bradycardia, which may accompany succinylcholine administration. This technique provides prompt induction and immediate control of the airway with tracheal intubation and is useful in circumstances where it is anticipated that initial intravenous access will have to obtained through the external jugular vein, femoral vein,
or internal jugular vein. This technique is hampered by the fact that the short duration of action of succinylcholine limits the period of patient immobility. An alternative technique combines intramuscular ketamine (4 to 5 mg/kg), glycopyrrolate (10 mg/kg) and rocuronium (1.0 mg/kg). This technique is hampered by the longer time interval until attainment of adequate intubating conditions and the longer duration of action of rocuronium as compared to succinylcholine.


**Why would end-tidal carbon dioxide (ETCO2) monitoring be of particular use in a patient with tetralogy of Fallot with pulmonary stenosis (TOF/PS)?**

ETCO2 monitoring is routinely employed in patients with congenital heart disease with the caveat that the difference between Paco2 and ETCO2 will vary as physiologic dead space varies and that in some circumstances the difference may be large (>10 to 15 mm Hg). Any acute reduction in pulmonary blood flow (decreased cardiac output, pulmonary embolus, increased intracardiac right-to-left shunting) will increase this gradient. In a patient with TOF/PS a gradual reduction in ETCO2 will often precede a decrease in arterial oxygen saturation (Sao2) as the first manifestation of the increased right-to-left intracardiac shunting associated with a "Tet spell."


**What is near-infrared spectroscopy (NIRS) and what does it measure?**

NIRS is an evolving technology that holds promise as a real-time, online monitor of cerebral tissue oxygenation. This technology is based on the physical principle that light of an appropriate wavelength passing through a solution of a colored compound (chromophore) will
be absorbed by the compound. As a result of this absorption the intensity of the light emerging from the solution will be lower than the intensity of the light projected into the solution. This principle through application of the Beer-Lambert equation "log \([I_0/I] = \text{cad}\)" allows quantification of the concentration \((c)\) of a chromophore if the emergent light intensity \((I)\) is measured and the following are known:

- Extinction coefficient \((a)\), a constant that describes the absorption characteristics of a particular chromophore at a given wavelength of light.
- Thickness of the solution \((d)\)
- Incident light intensity \((I_0)\)

NIRS technology is particularly suited to use in neonates and infants because the thin skull and small head allow light to be transmitted through one side of the head and detected on the other side, a technique known as transmission spectrometry.

Cerebral oxygen saturation \((\text{ScO}_2)\) as measured by all NIRS technology is the combined oxygen saturation of an uncertain mix of arterioles, capillaries, and venules. Traditional pulse oximetry differs in this respect from NIRS because it is capable of isolating and measuring the arteriole component by gating measurements to pulsatility. It has been previously assumed that \(\text{ScO}_2\) represented contributions of cerebral arterial and venous blood in a ratio of 25:75 with the contribution of capillary blood felt to be negligible. More recent data suggests that in children the average ratio is 15:85. The issue is further complicated by the fact that there is significantly variability in the ratio (from 0:100 to 40:60) between patients.


**How does heparin administration and activated coagulation time (ACT) monitoring differ in children as compared to adults?**

Before use of cardiotomy suction, cannulation, and commencing bypass, it is essential that adequate anticoagulation be obtained. Vnfractionated heparin (VFH) is currently the anticoagulant used for cardiopulmonary bypass (CPB). It generally is acknowledged that an ACT in excess of 400 seconds is necessary to ensure adequate
anticoagulation for the safe conduct of CPB. While there is a large heparin anticoagulation monitoring literature in adults there is a very small literature in children. The ACT, commonly used to assess CPB anticoagulation is also prolonged by hypothermia, hemodilution, platelet dysfunction, and low coagulation factor levels. As a result, in children the ACT will overestimate the antifactor IIa and Xa effects of heparin. Most institutions use an age or weight based protocol to administer the initial pre-CPB dose of heparin such as: patients less than 30 kg-200 IU per kg; patients greater than 30 kg 300 IU per kg. The large circuit prime volume to blood volume ratio would be expected to decrease plasma heparin levels with initiation of CPB unless an appropriate quantity of heparin is added to the CPB prime. Most institutions add heparin to the CPB prime as follows: patients less than 30 kg-2.5 IU per mL of CPB prime; patients greater than 30 kg-3.0 IU per mL of CPB prime. Heparin should always be given into a central line through which venous return can be demonstrated easily or as is more common in infants/neonates directly into the heart (usually the right atrium) by the surgeon. This is necessary to ensure that the heparin dose has reached the central circulation. An ACT can be drawn within minutes of heparin administration as peak arterial ACT prolongation occurs within 30 seconds and peak venous ACT prolongation within 60 seconds.


How is heparin reversed?

Protamine is a polyvalent cation derived from salmon sperm that is currently used to neutralize systemic heparinization. Protamine normally is given once stable hemodynamics are maintained after termination of cardiopulmonary bypass (CPB). It should not be administered until the likelihood that having to reinstitute CPB is small. After protamine neutralization of heparin begins, the cardiotomy suction should not be used and removal of the arterial and venous cannulas should proceed. This prevents contamination of the
heparinized CPB circuit with protamine should prompt reinstitution of CPB be necessary and prevents thrombus formation on the cannulas. There are several approaches to the neutralization of heparin with protamine, all with reportedly good clinical results. Some centers use 1.0 to 1.3 mg of protamine for each 100 units of heparin determined to exist at the termination of CPB. This ratio is based on the in vitro protamine-heparin neutralization ratio of 1.3: 1.0. The amount of heparin present is determined by obtaining an activated coagulation time (ACT) when CPB terminates and using reverse extrapolation of the patient's heparin dose response curve to correlate ACT and heparin dose. This method has been criticized because the ACT obtained at the termination of CPB is prolonged by factors other than heparin, such as CPB-induced platelet dysfunction and hemodilution. This may result in an overestimation of the heparin present at the termination of CPB and a larger than necessary protamine dose.

Some centers simply administer a fixed dose of protamine based on the patient's weight (3 to 4 mg/kg) regardless of the heparin dose administered, whereas others administer 1.0 to 1.3 mg of protamine for each 100 units of heparin administered. Obviously, these methods do not rely on any post-CPB assessment of residual heparin effect (ACT) to determine the protamine dose. Nonetheless, these methods have been shown to result in adequate heparin reversal. In the case of the fixed dose regimen, heparin reversal is obtained at much lower protamine doses than predicted by the reverse extrapolation method.

The Hepcon automated heparin protamine titration method measures clotting times enhanced by addition of thromboplastin in several channels that contain varying quantities of protamine. The first channel to clot is the channel in which the protamine to heparin ratio is closest to neutralization. The absolute clotting time is not important; only the determination of the channel with the appropriate ratio. Therefore, the determination should be independent of nonheparin factors that prolong the ACT. In theory this method should allow determination of the appropriate dose of protamine independent of the nonheparin parameters that prolong ACT.

What is the incidence of protamine reactions in children?

The incidence of protamine reactions in children following cardiac surgery is generally believed to be substantially lower than that in adults. A recent retrospective analysis of 1,249 children revealed the incidence of hypotension (at least 25% decrease in mean arterial pressure [MAP]) following protamine administration to be 1.76% to 2.88% depending on the stringency of criteria linking the episode to protamine administration. In this series no episodes of pulmonary hypertension or RV dysfunction were noted. There is a report of pulmonary hypertension and cardiovascular collapse in 6-week-old infant following protamine administration. Clinical experience indicates that pulmonary hypertensive episodes in children following protamine administration are very rare.


What is the role of transesophageal echocardiography (TEE) in this patient?

It has been demonstrated that intraoperative TEE has a major impact on post-CPB decision making (such as return to CPB to repair residual lesions) in approximately 15% of cases when it is used nonselectively. In the subset of patients undergoing valve repair and outflow tract reconstruction TEE provides the best immediate assessment of the adequacy of the operative procedure and if necessary directs its revision. While detection of retained intracardiac air is certainly facilitated by use of intraoperative TEE it remains to be determined what role the technology will play in improving cardiac de-airing algorithms particularly in neonates/infants. The role of TEE in the detection of residual VSDs following repair of both simple and complex defects deserves some discussion. Residual defects less than 3 mm are detectable by TEE but generally do not require immediate reoperation as they are hemodynamically insignificant. The majority (75%) of these small defects are not
present at the time of hospital discharge as determined by transthoracic echocardiography. Residual defects greater than 3 mm detected by TEE require immediate reoperation only if they are associated with intraoperative hemodynamic (elevated left atrial pressure [LAP] and/or pulmonary artery pressure [PAP] in the presence of good ventricular function) and oximetric (Qp : Qs > 1.5 : 1 or right atrium [RA] to PA oxygen saturation step-up with fraction of inspired oxygen (FI02) <0.50) evidence that they are significant.
