Anaphylaxis is clinically defined as a severe systemic allergic reaction of rapid onset, the hallmarks of which are acute cardiovascular and pulmonary dysfunction. In anaeasthetics the incidence of this severe complication is between 1:5,000 and 1:2,500, and it is one of the few remaining causes of mortality directly due to general anaesthesia. During cardiac surgery, children are exposed to multiple foreign substances that have the potential to induce a life-threatening allergic reaction. The most frequent agents involved are antibiotics, neuromuscular blocking agents, blood and blood products, intravascular volume expanders, polypeptides and, more rarely, heparins.1

Pathophysiology
Cardiovascular collapse due to anaphylaxis is a vasodilatory shock characterised by vasodilatation, enhanced vascular permeability and intravascular volume depletion. Multiple mediators from mast cells such as kinins, leukotrienes and prostanoids are implicated in promoting vasodilatation, but histamine seems to play a very important role.2 Despite a few studies suggesting an alteration of myocardial contractility3–5 and the presence of histamine receptors6,7 in the heart, cardiac abnormalities during anaphylactic shock are usually due to an underlying cardiac disease or the side effects of catecholamines administered rather than the anaphylaxis itself.8 Despite the existence of different pathogenetic mechanisms characterising various forms of vasodilatory shock, common mechanisms of vasodilatation and catecholamine resistance have been demonstrated, such as activation of the adenosine-5'-triphosphate (ATP)-sensitive potassium channels (KATP channels), activation of the inducible form of nitric oxide (NO) and deficiency of the vasopressin hormone.

Activation of the ATP-sensitive Potassium Channels in the Plasma Membrane of the Vascular Smooth Muscle
The KATP channels exert a crucial role in regulating the resting potential of vascular smooth muscle membrane. These channels are physiologically closed in their inactive form. Two mechanisms are involved in their activation and opening: a fall of the intracellular pH due to low ATP concentration and increasing hydrogen ions and lactate levels9,10 (a mechanism that links cellular metabolism with vascular tone and blood flow),11 and NO release through the cyclic guanosine monophosphate (cGMP)-dependent mechanisms.12 The KATP opening results in K efflux, cellular hyperpolarisation, closure of the voltage-gate calcium channels and intracellular calcium decrease with a final vasodilatory effect. This impaired free calcium movement through the sarcolemma further contributes to the catecholamine resistance characteristic of vasodilatory shock.

Activation of the Inducible Form of Nitric Oxide
Stimulation of H1 receptors on endothelium cells activates both NO- and prostacycline-mediated vasodilating pathways. NO overexpression contributes to vasodilatation and poor sensitivity to catecholamine administration, as demonstrated by the vasoconstrictive effects and reduction in the inotropic requirements of inhibitors of NO synthesis. These vasodilating and negative inotropic effects are mediated by NO-sustained myosin dephosphorylation and, as mentioned above, by the activation of the KATP and KCa of the vascular smooth-muscle membrane.

Deficiency of the Vasopressin Hormone
Finally, both prolonged low systemic hyperfusion with tissue hypoxia and lactic acidosis can be the cause of all of the described pathophysiological mechanisms, and can induce a relative deficiency in vasopressin plasma concentration, which further amplifies the vasoplectic scenario.13 As well as the NO release at the posterior pituitary gland, several other mechanisms can be involved in inappropriately low vasopressin concentrations, such as exhaustion of the pituitary stores, autonomic dysfunction and the inhibitory effect of the increased norepinephrine concentrations. The inappropriately low plasma vasopressin concentration is the third main pathophysiological mechanism of vasodilatory shock, a finding that has been proved in septic shock, haemorrhagic shock unresponsive to volume replacement and catecholamine administration and vasodilatory shock after cardiopulmonary bypass.

Treatment of Anaphylactic Shock
The most important requirements in the treatment of anaphylaxis are prompt diagnosis and the maintenance of coronary and cerebral perfusion. The underlying congenital heart disease makes the patient extremely intolerant to the adverse cardiocirculatory effects of anaphylactic shock; nevertheless, in the presence of physicians skilled in the rapid diagnosis and management of acute cardiovascular dysfunction and with the patient haemodynamically monitored, any adverse events that take place in the operating theatre can be quickly diagnosed and immediately treated. The cornerstone of treatment is airway maintenance with 100% oxygen and intravascular volume expansion, the latter being effectively guided by transoesophageal echocardiography. Epinephrine has been widely accepted as being the standard medical therapy to reverse cardiovascular collapse and bronchospasm in anaphylaxis.13 As a last resort, a rapid placement onto cardiopulmonary bypass with a perfusion strategy based on high flow in moderate hypothermia with a normal haematocrit value may help to achieve a positive final outcome by maintaining adequate end-organ perfusion while adjusting the pharmacological treatment.14 Second-line treatment consists of corticosteroids, which may have value in the early hours of any post-resuscitation period, and β2 agonists (terbutaline or albuterol) administered by inhalation via the endotracheal tube in order to treat bronchospasms. Epinephrine administration is the first-line treatment for anaphylactic shock, regardless of the existence of human studies that are not entirely supportive of its use.15,16 In fact, there are strong pathophysiological findings sustaining its efficacy: due to its α- and β-adrenergic effects, epinephrine inhibits further vasodilating mediator release, whereas corticosteroids may be less efficacious in reversing the release of mediators from mast cells, which are involved in the pathogenesis of anaphylaxis.
release from basophils and mast cells, reduces bronchoconstriction, increases vascular tone and improves cardiac output. Nevertheless, inotropic resistance has been widely described in vasodilating shock, and epinephrine therapy may not always be effective in reversing hypotension.16–18 This event makes the risk–benefit ratio of the catecholamine therapy clinically intolerable. In fact, excessively increased myocardial oxygen consumption and arrhythmias are undesirable complications of high catecholamine concentration,19 and are particularly risky in cardiac patients and in patients being treated with beta blockers.17 In this setting, when catecholamine therapy is ineffective in rapidly restoring haemodynamics, the use of doses of vasopressin between 0.0003 and 0.008IU/kg/minute has been reported to be of great use.

Rationale for Vasopressin Administration
Vasopressin is a peptide hormone released by the pituitary gland that has multiple physiological effects of central importance in a vasoplastic scenario. It induces vasconstriction by activating vasopressin-1 receptors on vascular smooth muscle, a mechanism distinct from that of adrenergic vasoconstriction. In addition, vasopressin is synergistic with other vasopressors, enhancing the sensitivity of the vasculature to catecholamines.20,21 Vasopressin also stimulates corticotropin secretion by increasing adrenocorticotropic hormone production and release. Finally, vasopressin actively works on several pathophysiological mechanisms of the vasodilatory shock by:

- decreasing the synthesis of inducible NO synthetase;
- blocking the target enzyme of the NO pathway;15
- blunting the increase in CgPM induced by NO;22 and
- directly inactivating KATP channels in vascular smooth muscle.23

The effectiveness of low doses of exogenous arginine–vasopressin (AVP) in restoring blood arterial pressure in patients suffering from catecholamine-resistant vasodilatory shock has been reported in various clinical settings;24–28 however, there are only a few experimental studies and case reports supporting vasopressin’s efficacy during anaphylactic shock.29–31 A vasopressin dose of 0.08IU/kg has been demonstrated to be effective in restoring haemodynamics and improving survival in an animal model of anaphylactic shock.32 Case reports exist documenting vasopressin’s efficacy in restoring haemodynamics in patients suffering from catecholamine-resistant anaphylactic shock for both adults33 and children.

Recently, we reported on a case of intra-operative heparin-induced anaphylactic shock in a six-year-old male patient scheduled for ventricular septal defect repair. The patient was initially treated according to the first-line treatment with volume resuscitation, 100% oxygen ventilation, epinephrine in boluses and continuous infusion. CPB was promptly instituted in order to optimise the systemic oxygen delivery. Haemodynamic stabilisation and normal systemic vascular resistance were achieved only five minutes after the beginning of a 0.0003SU/kg/minute dose of vasopressin infusion. During the first six months post-operatively, the patient was successfully weaned from CPB and vasopressin was progressively reduced and stopped.14

Conclusion
In conclusion, treatment of severe anaphylactic systemic reaction during paediatric cardiac surgery is substantially similar to the first-line treatment of anaphylactic shock. It consists of volume resuscitation (in this case guided by transoesophageal echocardiography) ventilation with a fraction of inspired oxygen (FiO2)=1, intravenous bolus of low dose epinephrine titrated on the pressure effect (no more than three doses of 10–25mg/kg), followed by 1.0–3.0mg/kg/minute in continuous infusion. A low dose of vasopressin (0.0003–0.003IU/kg/minute) is strongly recommended in addition to the standard medical therapy (especially in catecholamine-refractory states) in order to promptly guarantee the increase in systemic vascular resistance and the adequacy of cerebral and coronary perfusion pressure, avoiding the deleterious effects of high doses of catecholamines.