Special review

The Physiology and Clinical Applications of Vasopressin in Critical Illness

J. C. RUSSELL, P. J. GLOVER

Regional Intensive Care Unit, Royal Group of Hospitals, Belfast, NORTHERN IRELAND

ABSTRACT

Objective: *To present the physiology of vasopressin, and review published data on its use in critically ill patients.*

Data sources: *A review of articles on the clinical use of vasopressin in critical care medicine up to 2002 and identified through a MEDLINE search.*

Summary of review: *Vasopressin (antidiuretic hormone) acts via vasopressinergic receptors to maintain osmotic and baroreceptor homeostasis. It has complex and varying effects depending on serum levels, coexisting disease states and organs studied. Synthetic vasopressin is available for clinical use. In large doses (e.g. 40 U) it has vasoconstrictor effects comparable to epinephrine during cardiopulmonary resuscitation. The use of much lower "replacement" doses (e.g. 0.04 U/min) may have a marked vasopressor effect in clinical states associated with vasopressin deficiency; for example sepsis, the organ donor and after cardiopulmonary bypass. These doses are much lower than those leading to cardiovascular effects in healthy patients and may avoid the adverse vasoconstrictor effects seen at "pharmacological" doses. The use of vasopressin to reduce portal pressure and bleeding in oesophageal varices is well established.*

Conclusions: *Vasopressin has widespread effects throughout the body and has several important clinical applications in the critically ill patient.* (**Critical Care and Resuscitation 2002; 4: 181-191**)

Key words: Vasopressin, physiology, critical care, sepsis, shock, brain death, oesophageal varices

Vasopressin or 8-argininine vasopressin (i.e. antidiuretic hormone or ADH), is a cyclical nonapeptide with a disulphide bridge joining two cysteine molecules (Figure 1). It is synthesised in magnellocellular neurosecretory neurones, primarily in the supraoptic, but also in the paraventricular and accessory nuclei of the hypothalamus. The initial biologically inactive precursor macromolecule, pre-pro-vasopressin, is a 164 amino acid protein, which is sequentially cleaved to provasopressin and then to the biologically active peptide, vasopressin. Vasopressin, along with its binding protein, neurophysin II, and the glycoprotein, co-peptin, are transported in neurosecretory granules down the non-myelinated axons from the hypothalamus through the median eminence and stored in nerve terminals in the posterior pituitary. From here the granules are released either directly into the circulation from terminal endings on capillary endothelial cells, or on cells which adjoin the vessel wall. Neurophysin II, which dissociates from the vasopressin molecule prior to secretion, does not appear to have any other significant physiological role. The amount of hormone secreted from axon terminals in the posterior pituitary correlates with the degree of activity of magnocellular

Correspondence to: Dr.J.C. Russell, Regional Intensive Care Unit, Royal Group of Hospitals, Grosvenor Road, Belfast, Northern Ireland BT12 6BA. (e-mail: conn@doctors.org.uk)

secretory cells.[1] Other central projections are also involved in overall vasopressin regulation.
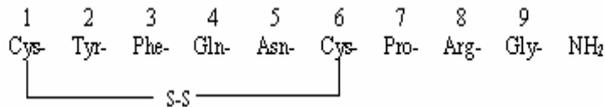

Figure 1. Structure of vasopressin.

The two major physiological roles of vasopressin are serum osmoregulation and mediation of baroreceptor reflexes, although non-osmotic and non-baroreceptor mediated mechanisms also exist. The regulation of vasopressin release from the posterior pituitary is dependent primarily on two mechanisms: (a) osmotic and (b) non-osmotic/volume.

Physiological control of the synthesis and release of vasopressin is related mainly to changes in plasma osmolarity which are detected by specialised osmoreceptors in regions of the anterior hypothalamus which lie outside the blood-brain barrier (e.g. in the sub-fornical organ and the organum vasculosa of the laminae terminalis).[2,3] The osmoreceptor cells generate electrical impulses, which travel along the axons resulting ultimately in vasopressin release by the posterior pituitary. Mechanosensitive cation channels are thought to have a role in the translation of plasma osmotic changes into changes in vasopressin secretion.[4]

Although the precise pathways connecting osmoreceptor activation to vasopressin release remain to be determined, nitric oxide has recently been shown to be an inhibitory modulator of the hypothalamo-neuro-hypophysial system in response to osmotic stimuli.[5]

Vasopressin release can also occur in the absence of changes in plasma osmolality. The non-osmotic stimuli to vasopressin release include pain, emotional stress, emesis, hypoxia, exercise, hypoglycaemia, isotonic volume depletion, cardiac failure, liver disease, cholinergic agonists, beta-blockers, angiotensin, prostaglandins and adrenal insufficiency. They appear to be mediated by changes in autonomic neural tone. Afferent vagal and glossopharyngeal pathways from the left atrium (i.e. low pressure) and carotid sinus (i.e. high pressure) baroreceptor modulate this non-osmotic regulation of vasopressin.

Plasma volume expansion is associated with a reduction in vasopressin secretion release particularly from the perinuclear zone of the supraoptic nucleus. Stretch receptors at the atriocaval junction appear to have a prominent role in this response rather than arterial baroreceptors, although the perinuclear zone is also important with regard to arterial baroreceptor

inhibition of vasopressin release.[6] In addition, an inhibitory pathway relates blood pressure to the release of vasopressin (e.g. an increase either in arterial blood pressure detected by baroreceptors or in central venous pressure detected by cardiac volume receptors inhibits release of the hormone via a neuronal projection from the ventrolateral medulla).[7]

Importantly, non-osmotic mechanisms are less sensitive stimuli for vasopressin release than are osmotic stimuli (e.g. a 1 % change in blood osmolality will evoke a comparable release of vasopressin as a 5 - 10% change in blood volume). Osmotic stimuli are also a higher gain system, as quantitatively larger amounts of vasopressin are released by this mechanism.[8] Genetic variability exists with regard to individual thresholds and sensitivity for vasopressin release.

Vasopressin receptors

Peripheral vasopressin receptors have been classified on the basis of both the second messenger system coupled to the receptors, and the affinity of a series of vasopressin analogues with enhanced selectivity for a certain receptor type.[9] Molecular cloning has revealed that vasopressin receptors belong to the G-protein-coupled receptor superfamily.

The V_2 antidiuretic hormone receptor is located in the basolateral membrane of principal cells of the distal tubule. Vasopressin-induced increases in adenyl cyclase activity results in an increase in intracellular cAMP promoting the insertion of a water channel, aquaporin 2 (AQP2), into the luminal surface of the collecting tubules, thus increasing water reabsorbtion. Vasopressin has a dual role in regulating water homeostasis: (i) by regulating the fast shuttling of AQP2 to the cell surface and (ii) by stimulating the synthesis of AQP2-encoding mRNA.[10]

Aquaporins are a family of water channels. Five of these membrane integral proteins are distributed in mammalian tissues ranging from erythrocytes to the lens of the eye where they mediate water transport,[10] but only one aquoporin is vasopressin-sensitive (i.e. AQP2). This recently cloned molecule is located in the apical membranes of collecting duct cells and within the cytoplasm,[11] where they appear to be stored in vesicles called aggraphores.[12] In the presence of vasopressin, there is an immediate increase in the presence of AQP2 in the apical membranes and an increased movement of aggraphores toward these membranes, followed by a longer-term increase in AQP2 production within the cells.[13] There is evidence that microtubules might be implicated in vasopressin-stimulated water transport,[14] perhaps associated with the movement of aggraphores to the apical membrane.

V_2 receptors have also been identified extra-renally

(e.g. endothelial cells), with stimulation of endothelial cell V_2 receptors promoting coagulation factor $VIII_c$ and von Willebrand factor release.[15] Although vasopressin has physiological actions at multiple sites including the vasculature and the central nervous system, its principal physiological effect is the well-described increase in water reabsorption that takes place in the renal collecting ducts in the presence of an osmotic gradient. This results in an antidiuresis, hence its synonym, anti-diuretic hormone (ADH).[16]

At higher concentrations than those at which V_2 receptors are normally stimulated, vasopressin will bind to V_{1a} receptors. These are distributed widely in vascu-lar smooth muscle where they mediate vasoconstriction. They are also found in the liver, platelets, kidney, bladder, myometrium, testis and in the central nervous system. Their role in many of these areas is as yet unknown. Stimulation of the V_1 receptor increases intra-cellular levels of diacylglycerol and inositol triphosph-ate leading to Ca^{2+} release from intracellular stores. Activation of the V_{1b} receptor stimulates the release of adrenocorticotropin from the anterior pituitary. A similar mode of action as proposed for V_1 receptor stimulation occurs at the V_{1b} receptor.

These classification criteria have led to the distinc-tion of V_{1a} vasopressin (found in liver, vascular smooth muscle cells and most peripheral tissues expressing vasopressin receptors), V_{1b} vasopressin (found in the adenohypophysis), V_2 vasopressin (found in the kidney) and oxytocin receptors (found in the uterus and mammary gland).[8]

An alternative form of nomenclature suggests that V_{1a} receptors are classifed as V_1, V_{1b} classified as V_3 and V_2 remain as V_2.[9]

Vasopressin and cardiac disease

A systemic inflammatory response resulting in vasodilated shock may occur in up to 8% of patients following coronary artery bypass grafting. Pre-operative risk factors for the development of this syndrome include low pre-operative ejection fraction and angio-tensin converting enzyme inhibitor usage.[17] Serum vasopressin levels have been found to be inappropriat-ely low, with the degree of vasodilatation correlating inversely with the vasopressin concentration, possibly due to impaired baroreflex-mediated secretion of vasopressin.[18] Administration of exogenous vasopressin improves arterial blood pressure with a reduction in the requirements for other inotropes and pressors.[19]

Vasopressin, when given in small doses (e.g. 6 U/min), also improves the haemodynamic stability of patients with left ventricular assist devices leading to a reduction in inotrope requirements. This may also be seen in patients following cardiac transplantation.[20] The

use of vasopressin in these cases has not been associated with any increased end-organ dysfunction.[21]

Vasopressin may also have a role as an adjunct to phosphodiesterase inhibitors in the management of severe heart failure. Instigation of milrinone therapy to improve cardiac index can lead to arterial hypotension due to systemic vasodilatation and necessitate catecholamine infusions. However, in one study the addition of vasopressin (1.8 - 4.2 U/hr) had no effect on the cardiac index but increased arterial blood pressure significantly due to vasoconstriction, leading to a reduction in catecholamine administration. This was associated with an increase in urinary output. The postulated mode of action of vasopressin was an inhibition of the milrinone-induced accumulation of intracellular cyclic nucleotides.[22] The development of vasopressin antagonists as pharmacological agents in the treatment of chronic heart failure is currently being pursued.[23]

Vasopressin and desmopressin stimulate the release of von Willebrand factor from endothelial cells due to increased intracellular cyclic AMP.[14] Vasopressin levels are elevated in both type I and type II diabetes mellitus, and while this may beneficial in the short term by limiting the amount of free water required to excrete a solute load, in the longer term renal hypertrophy, glomerular hyperfiltration and albuminuria occur due to V_2 receptor mechanisms. Albuminuria can be inhibited experimentally by the administration of a V_2 receptor antagonist.[24]

Vasopressin in cardiopulmonary resuscitation

Epinephrine is currently the drug of choice for the maintenance of the coronary and cerebral circulations in shock-resistant ventricular fibrillation.[25] Experimental evidence suggests that epinephrine improves haemody-namic parameters and resuscitation rates in animals.[26,27] However, there are very little data in humans demonstrating the benefit of epinephrine over other agents in resuscitation, although the difficulties of studying this population are considerable.

Alpha-adrenoreceptor agonism leads to vasocon-striction and maintenance of coronary and cerebral blood flow. A "toxic adrenergic state", largely due to β-adrenergic effects, may be seen post-cardiac arrest following epinephrine administration with features such as arrhythmias, lactic acidosis, increased myocardial oxygen demand and myocardial dysfunction. However, studies have failed to demonstrate the benefit of pure α-agonists over epinephrine during cardiac arrest,[28-30] although a recent case series demonstrated the effective-ness of phenylephrine in resuscitation when epinephrine had failed.[31]

Endogenous vasopressin is released in very high levels during cardiac arrest,[32] with levels higher in survivors than non-survivors.[33] In an animal experimental model of cardiac arrest, pigs who received a vasopressin antagonist had a reduced myocardial blood flow during resuscitation compared with control animals and also were unable to be resuscitated.[34] The administration of vasopressin during ventricular fibrillation in pigs resulted in a greater myocardial blood flow compared with epinephrine-treated animals, but there was no difference in resuscitation rates or neurological outcomes.[35,36] Intraosseous administration of vasopressin appears to be as effective as epinephrine by the same route[37] and administration via the endobronchial route results in similar outcomes compared with the intravenous route.[38] The consistent beneficial effects of vasopressin administration in animal models of cardio-pulmonary resuscitation may also be related to the en-hanced adrenocorticotropic hormone release and plasma cortisol levels that occur.[39]

In a small randomised trial in patients with shock-resistant ventricular fibrillation, administration of vasopressin (40 U) resulted in a higher rate of return of spontaneous circulation and survival at 24 hr compared with those receiving epinephrine (1mg).[40] As in animal studies, vasopressin administration may lead to improved haemodynamic parameters compared with epinephrine but with no improvement in outcome.[41] In the largest randomised controlled trial to date comparing vasopressin and epinephrine in cardiac arrest, there was no improvement in short or long-term survival or neurological outcome with vasopressin.[42]

The international guidelines for resuscitation currently recommend a single intravenous dose of 40 units of vasopressin as an alternative to epinephrine for the treatment of adult shock-refractory ventricular fibrillation.[43] The evidence is quoted as IIb: acceptable; fair supporting evidence. It is also suggested that vasopressin may be effective in patients with asystole or pulseless electrical activity, but insufficient data are available to recommend vasopressin over epinephrine in these circumstances.

However, the European resuscitation council and the resuscitation council of the United Kingdom continue to recommend epinephrine as the drug of choice until further evidence becomes available.[44] A multicentre trial comparing the use of vasopressin with epinephrine for out-of-hospital cardiac arrest is ongoing.

Vasopressin in septic shock
Septic shock is characterised by profound vasodilation with hypotension and end-organ hypoperfusion.[45] The vasodilation of sepsis is mediated by activation of vascular adenosine 5`-triphosphate regulated potassium

channels and hyperpolarisation of vascular smooth muscle through voltage-gated calcium channels. Mortality remains at over 50%, despite advances in pharmacology, ventilation and cardiovascular support.[46] Catecholamine vasopressor or inotropic agents are frequently required but vascular sensitivity to catecholamine vasopressors decreases in sepsis,[47-49] partly due to receptor downregulation.

Catecholamines also have systemic effects that may be undesirable in the septic patient, such as tachyarrhythmias, increased myocardial oxygen demand, and altered endocrine functions. However, persistent hypotension and vasodilation are associated with a poor outcome in sepsis[50,51] and vasopressor catecholamines may improve outcome.[49,52]

Vasopressin plays little role in the maintenance of blood pressure in normal circumstances,[53,54] but appears to be crucial in circumstances when the blood pressure is threatened.[55,56] There is an intricate interplay between the adrenergic, renin-angiotensin and vasopressor systems,[57] with all three systems being activated in times of stress. The sympathetic nervous system function is abnormal in sepsis and there is a decreased sensitivity to circulating catecholamines. Blood levels of vasopressin are initially high in septic shock,[56] as with other types of shock, but soon fall to levels considered to be inappropriately low. Levels of vasopressin are much lower than those seen in cardiogenic shock. Furthermore, septic patients respond to vasopressin in doses that do not cause vasopressor effects under normal conditions.[58]

Although vasopressin uses the same second messenger system as the adrenergic system (e.g. cAMP),[59] vasopressin receptors are not subject to the same receptor down-regulation that is found with prolonged adrenoreceptor stimulation. Vasopressin reduces the vasodilation in sepsis by inhibiting the activation of ATP-regulated potassium channels[60] and reducing calcium entry through voltage-gated calcium channels. The nitric oxide induced accumulation of cyclic guanosine 3`, 4`-monophosphate is also inhibited.[61]

Several reasons have been postulated for impaired vasopressin secretion in septic shock. Increased metabolism of vasopressin is unlikely as a constant low dose vasopressin infusion produces stable levels.[58] Neurohypophyseal stores have been found to be reduced[62] and high dose catecholamines, exogenous or exogenous, may inhibit the release of vasopressin.[63] The most favored explanation seems to be an impaired baroreceptor-mediated release of vasopressin due to "autonomic failure". This concept of sepsis-induced autonomic failure is supported by the effectiveness of vasopressin in other states when sympathetic function is

impaired; such as primary autonomic failure and after cardiac bypass.[17,64]

Brattleboro rats lack the ability to release vaso- pressin, but have intact autonomic and renin-angio- tensin systems.[65] Infusion of endotoxin in normal and Brattleboro rats resulted in a much greater hypotensive response in the vasopressin-deficient rats and a reduced survival in response to various forms of shock in these animals.[66] Interestingly, pretreating the Brattleboro rats with steroids attenuated the hypotensive response so that it resembled that which was found in the control animals. Also, administration of exogenous vasopressin to shocked Brattleboro rats led to restoration of blood pressure to the expected levels.[67]

Vasculature sensitivity to norepinephrine is decrea- sed during septic shock.[47] In a rat model, the vascular sensitivity to vasopressin increased greatly as shock progressed, whilst the sensitivity to norepinephrine decreased, suggesting that vasopressin may be essential for supporting the arterial pressure during endotoxin shock.[68] Furthermore, vasopressin increases the sensitivity of the vasculature to norepinephrine and the combination of the two drugs produces a much greater vasoconstrictive effect than either drug alone.[69]

A similar vascular sensitivity to vasopressin in humans has been noted. In a small case series, patients with vasodilatory shock receiving high doses of catech- olamine vasopressors, were commenced on vasopressin (0.01 - 0.05 U/min). There was a marked improvement in haemodynamic parameters and a decrease in catech- olamine requirements, with four of the five patients requiring vasopressin as their sole vasopressor.[70] Previous work has showed no vasopressor effect in normal patients when infusions were used up to 0.26 U/min,[64] and the results were consistent with vaso- pressin hypersensitivity in vasodilatory shock. Vaso- pressin levels in septic shock have been found to be much lower than cardiogenic shock (3 pg/mL *vs* 23 pg/mL). Subsequent infusion of vasopressin at 0.01 U/min in a septic group to achieve "appropriate" levels of around 30 pg/mL resulted in a marked vasopressor effect, with an average systolic blood pressure rise from 83 to 115 mmHg.[58]

In other small studies, systemic blood pressure impr- ovements and a reduction in cathecholamine requirem- ents with vasopressin have been confirmed. These have been associated with a small decrease in cardiac index and heart rate, and an improvement in other features such as acidosis, urine output and creatinine clearance.[71-73] Doses of greater than 0.04 U/min were not associated with increased effectiveness, and five cardiac arrests occurred at doses greater than 0.05 U/min.[73] A bolus of vasopressin may cause a rise in

pulmonary vascular resistance, but it appears that a low dose infusion has little effect on pulmonary vasculature, and may even cause pulmonary vasodilation. Although heart rate may slow, bradycardia has not been reported in septic patients with low dose infusions. Terlipressin, a long acting vasopressin analogue, led to a significant rise in blood pressure in septic patients and enabled the discontinuation of norepinephrine.[74]

The effects on renal function are complex and variable. There is an increase in urine output with no evidence of excessive water retention. Low dose vasopressin infusions may have a natriuretic effect through inhibition of proximal tubular sodium absorption.[75] The vasoconstrictor effects appear more marked in the efferent than the afferent arteriole,[76] thereby causing an increase in glomerular filtration pressure.

There has been some concern expressed over the possibility of excessive vasoconstriction caused by vasopressin. Pharmacological doses have been shown to cause significant coronary and mesenteric ischaemia[77] and it has been suggested that vasopressin should be used cautiously, if at all, in patients with symptomatic coronary artery disease.[73] In endotoxic models of sepsis, there is evidence of vasopressin-induced gut hypoper- fusion and mucosal damage and vasoconstriction is seen in human gastroepiploic arteries, even at low doses.[69,78] Clinical trials of vasopressin in septic patients have not, however, shown any clear evidence of mesenteric ishaemia. Vasopressin has been reported to cause less vasoconstriction of the coronary, mesenteric and cerebral circulations[79] and there is some evidence of NO-mediated vasodilation of these areas.[80,81] In one study, an infusion of low dose vasopressin led to no alteration in gastric mucosal carbon dioxide levels, or change in ST segments on electrocardiograph.[72]

In addition to potential vasoconstrictive effects, vasopressin is known to promote platelet aggregation.[82] These effects have been used to advantage in patients with abnormal platelet function, but, on the other hand, may induce further microcirculatory thrombosis in patients with a systemic inflammatory response syndrome.

Studies into the therapeutic use of this agent in patients with sepsis have been small, and generally lack randomisation. Physiological doses have consistently shown beneficial effects on haemodynamic parameters, and may avoid many of the adverse effects seen with pharmacological doses that are used in non-septic patients. Data concerning the clinically important adverse effects of vasopressin are lacking, this has been confounded by small study sizes and wide patient variability.

Vasopressin and portal hypertension

The development of gastro-oesophageal varices from portal hypertension in patients with cirrhosis is associated with an increased morbidity and mortality. Variceal haemorrhage occurs in up to 35% of people with cirrhosis and the index bleed itself has a mortality approaching 30%.

Increased portal venous blood flow due to increased arteriolar vasodilatation and increased intrahepatic vascular resistance to flow contribute to the development of portal hypertension. The increased resistance to portal venous blood flow in cirrhosis occurs not only due to the distorted liver structure but also because of contraction of myofibroblasts, activated stellate cells and vascular smooth muscle cells of intrahepatic veins. There may also be an imbalance between vasodilator and vasoconstrictor stimuli, with the latter predominating in cirrhosis. However, the arteriolar vasodilatation is caused by, among other things, an increase in nitric oxide production, which may have a primary role.[83-85]

Vasopressin has been used in the treatment of bleeding varices for almost four decades, acting via V_1 receptors to cause splanchnic arteriolar vasoconstriction and a secondary reduction portal venous flow and pressure.[86,87] Similar decreases in portal venous and superior mesenteric arterial blood flows of 30% in cirrhotic patients during vasopressin infusions have been documented, while there was an even greater decrease in oesophageal variceal blood flow (e.g. 48%) suggesting that vasopressin may also selectively affect variceal blood flow.[88] The continuous administration of vasopressin is not associated with tachyphylaxis or a rebound increase in portal venous pressure after discontinuation of the infusion.[89] Vasopressin has been administered both systemically and intra-arterially,[90,91] but delivery via the intravenous route is easier to perform and is just as efficacious as an infusion directly into the superior mesenteric artery.[92]

Administration of vasopressin in patients with oesophageal varicies has been limited due to the various adverse effects. These include systemic hypertension and bradycardia, reduced cardiac output[93] and arrythmias.[94,95] Regional circulatory adverse sequelae include mesenteric ischaemia and infarction, rhabdomyolysis and skin necrosis.[96-99] Gut ischaemia may also contribute to the development of bacterial peritonitis.[100]

Vasopressin administration for the control of variceal haemorrhage has not been shown to be more efficacious than placebo in many randomised trials and has also fallen out of favour because of the development of drugs with better safety profiles.[101,102] Concomitant administration of nitrates either intravenously, sublingually or transdermally reduces the incidence of the adverse effects of vasopressin and may increase the efficacy of haemorrhage control.[103-105] However, although vasopressin does achieve better variceal bleeding control when compared with placebo, it has not been shown to improve mortality.[106] Control of bleeding is also inferior when compared with balloon tamponade.[107]

Vasopressin and brain death

Brainstem death is associated with well-established haemodynamic changes,[108] but variable endocrine and metabolic abnormalities have also been described. Thyroid hormone abnormalities consistent with a sick euthyroid variant are commonly found, but other hormones dependent on anterior pituitary function such as prolactin, growth hormone, gonadotropins and cortisol are usually not deficient.[109,110] Hyperlactataemia is common in 'brain-dead' patients.[110] However, a persistent feature is impaired posterior pituitary function, with decreased serum vasopressin concentrations.[111] Consequently diabetes insipidus is reported in up to 78% of organ donors[109] and may occur in up to 50% of patients prior to the onset of brain death. If not properly treated, this may lead to water losses and electrolyte abnormalities, which can impair donor organ function and adversely affect the outcome of transplantation.

Hypotension following brain death is a frequent occurrence and catecholamines are often required to maintain arterial blood pressure. However, the administration of catecholamines may be associated with early mortality in the recipient.[112] In one study, the addition of vasopressin to epinephrine in the maintenance of haemodynamic parameters in brain-dead patients was associated with a dramatic prolongation of the time before cardiac arrest (1 day to 23 days).[113] The beneficial effects of vasopressin on survival are dose-dependent, as the addition of antidiuretic doses of vasopressin (0.1 - 0.4 U/hr) to epinephrine to maintain a systolic blood pressure greater than 100 mmHg was associated with a prolongation of the period of survival from 1 to 3 days, while pressor doses of vasopressin (1 - 2 U/hr) increased survival to 17 days. Furthermore, pressor doses of vasopressin alone increased the mean arterial pressure. The cardiac index was unchanged and peripheral resistance increased. When compared with vasopressin, epinephrine alone increased cardiac index, pulmonary capillary wedge pressure and mean circumferential fibre shortening velocity, with no change in peripheral resistance. Interestingly, when a constant pressor dose of vasopressin was infused, the dose of norepinephrine required to maintain arterial blood pressure was 4 times greater that of epinephrine.[114] The use of similar pressor doses of vasopressin (0.3 mU/kg/min) had no effect on the pulmonary vascular resistance, but caused a reduction in catechol-

amine requirements and a trend towards higher myo-cardial ATP concentrations.[115]

In a series of adult organ donors without diabetes insipidus requiring catecholamines to maintain adequate arterial blood pressure, serum vasopressin levels were at the lower end of the normal range or subnormal in the majority of patients, possibly due to an impairment of baroreflex-mediated release. The administration of vasopressin (2.4 - 6 U/hr) increased blood pressure sufficiently to lead to the cessation of catecholamines in 40% and a reduction in another 40% of patients.[116] The administration of vasopressin to brain-dead paediatric patients is also associated with a marked reduction in catecholamine requirements with no impairment of early transplanted organ function.[117] The administration of vasopressin after brain death does not impair hepatic mitochondrial function, as the arterial ketone body ratio, a measure of the redox state of hepatic mitochondria, was maintained compared with the pre-brain death levels.[118]

REFERENCES
1. Renaud LP, Bourque CW. Neurophysiology and neuropharmacology of hypothalamic magnocellular neurons secreting vasopressin and oxytocin. Prog Neurobiol 1991;36:131-169.
2. Thrasher TN, Keil LC, Ramsay DJ. Lesions of the organum vasculosum of the lamina terminalis (OVLT) attenuate osmotically-induced drinking and vasopressin secretion in the dog. Endocrinology 1982;110:1837-1841.
3. Yang CR, Senatorov VV, Renaud LP. Organum vasculosum lamina terminalis-evoked postsynaptic responses in rat supraoptic neurones in vitro. J Physiol 1994;477:59-74.
4. Bourke CW, Oliet SH. Osmoreceptors in the central nervous system. Annu Rev Physiol 1997; 59:601-619.
5. Wang H, Morris JF. Constitutive nitric oxide synthase in hypothalami of normal and hereditary diabetes insipidus rats and mice: role of nitric oxide in osmotic regulation and its mechanism. Endocrinology 1996;137:1745-1751.
6. Grindstaff RR, Cunningham JT. Cardiovascular regulation of vasopressin neurons in the supraoptic nucleus. Exp Neurol 2001;171:219-226.
7. Head GA, Quail AW, Woods RL. Lesions of A1 noradrenergic cells affect AVP release and heart rate during haemorrhage. Am J Physiol 1987;253:H1012-1017.
8. Barberis C, Mouillac B, Durroux T. Structural bases of vasopressin/oxytocin receptor function. J Endocrinol 1998;156:223-229.
9. Birnbaumer M. Vasopressin receptors. TEM 2000;11:406-410.
10. Knepper M. Molecular physiology of urinary concentrating mechanism: regulation of aquaporin water channels by vasopressin. Am J Physiol 1997;272:F3-12.
11. Fushimi K, Uchida S, Hara Y, Hirata Y, Marumo F, Sasaki S. Cloning and expression of apical membrane water channel of rat kidney collecting tubule. Nature 1993;361:549-552.
12. Harris WH, Strange K, Zeidel ML. Current understanding of the cellular biology and molecular structure of the antidiuretic hormone-stimulated water transport pathway. J Clin Invest 1991;88:1-8.
13. Marples D, Knepper MA, Christensen EI, Nielsen S. Redistribution of aquaporin-2 water channels induced by vasopressin in rat kidney inner medullary collecting duct. Am J Physiol 1995;269:C655-664.
14. Phillips ME, Taylor A. Effect of nocodazole on the water permeability response to vasopressin in rabbit collecting tubules perfused in vitro. J Physiol 1989;411:529-544.
15. Kaufmann JE, Oksche A, Wollheim CB, Günther G, Rosenthal W, Vicher UM. Vasopressin-induced von Willebrand factor secretion from endothelial cells involves V2 receptors and cAMP. J Clin Invest 2000;106:107-116.
16. Laycock JF, Hanoune J. From vasopressin receptor to water channel: intracellular traffic, constraint and by-pass. J Endocrinol 1998;159:361-372.
17. Argenziano M, Chen JM, Choudhri AF, et al. Management of vasodilatory shock after cardiac surgery: identification of predisposing factors and use of a novel pressor agent. J Thorac Cardiovasc Surg 1998;116:973-980.
18. Argenziano M, Choudhri AF, Moazami N, et al. Vasodilatory hypotension after cardiopulmonary bypass: risk factors and potential mechanisms. Circulation 1997;96(8S):680-681.
19. Rosenzweig EB, Starc TJ, Chen JM, et al. Intravenous arginine-vasopressin in children with vasodilatory shock after cardiac surgery. Circulation 1999;100(19S):II182-186.
20. Argenziano M, Chen JM, Cullinane S, et al. Arginine vasopressin in the management of vasodilatory hypotension after cardiac transplantation. J Heart Lung Transplant. 1999;18:814-817.
21. Morales DLS, Gregg D, Helman DN, et al. Arginine vasopressin in the treatment of 50 patients with post cardiotomy vasodilatory shock. Ann Thorac Surg 2000;69:102-106.
22. Gold J, Cullinane S, Chen J, et al. Vasopressin in the treatment of milrinone-induced hypotension in severe heart failure. Am J Cardiol 2000;85:506-508.
23. Kim M, Kukin M. New advances in the pharmacological management of chronic heart failure. Expert Opin Pharmacother 2000;1:261-269.
24. Bankir L, Bardoux P, Ahloulay M. Vasopressin and diabetes mellitus. Nephron 2001;87:8-18.

25. de Latorre F, Nolan J, Colin Robertson C, Douglas Chamberlain D, Baskett P. European Resuscitation Council Guidelines 2000 for Adult Advanced Life Support. A statement from the Advanced Life Support Working Group and approved by the Executive Committee of the European Resuscitation Council. Resuscitation 2001;48:211-221.

26. Brown CG, Werman HA, Davis EA, Hobson J, Hamlin RL. The effects of graded doses of epinephrine on regional myocardial blood flow during cardiopulmonary resuscitation in swine. Circulation 1987;75:491-497.

27. Brown CG, Werman HA, Davis EA, Hamlin RL, Hobson J, Ashton JA. Comparative effect of graded doses of epinephrine on regional brain blood flow during CPR in a swine model. Ann Emerg Med 1986;15:1138-1144.

28. Lindner KH, Ahnefeld FW, Grunert A. Epinephrine versus norepinephrine in prehospital ventricular fibrillation. Am J Cardiol 1991;67:427-428.

29. Turner LM, Parsons M, Luetkemeyer RC, Ruthman JC, Anderson RJ, Aldag JC. A comparison epinephrine and methoxamine for resuscitation from electromechanical dissociation in human beings. Ann Emerg Med 1988;17:443-449.

30. Silfvast T, Saarnivaara L, Kinnunen A, et al. Comparison of adrenaline and phenylephrine in out-of-hospital cardiopulmonary resuscitation. Acta Anaesthesiol Scand 1985;29:610-613.

31. McBrien ME, Breslin DS, Atkinson S, Johnston JR. Use of methoxamine in the resuscitation of epinephrine-resistant electromechanical dissociation. Anaesthesia 2001;56:1085-1089.

32. Lindner KH, Strohmenger HU, Ensinger H, Hetzel WD, Ahnefeld FW, Georgieff M. Stress hormone response during and after cardiac arrest and cardiopulmonary resuscitation. Anesthesiology 1992;77:662-668.

33. Lindner KH, Haak T, Keller A, Bothner U, Lurie KG. Release of endogenous vasopressors during and after cardiopulmonary resuscitation. Br Heart J 1996;75:145-150.

34. Krismer AC, Lindner KH, Wenzel V, et al. The effects of endogenous and exogenous vasopressin during experimental cardiopulmonary resuscitation. Anesth Analg 2001;92:1499-1504.

35. Lindner KH, Brinkmann A, Pfenninger EG, Lurie KG, Goertz A, Lindner IM. Effect of vasopressin on hemodynamic variables, organ blood flow, and acid-base status in a pig model of cardiopulmonary resuscitation. Anesth Analg 1993;77:427-435.

36. Babar SI, Berg RA, Hilwig, RW, Kern KB, Ewy GA. Vasopressin versus epinephrine during cardiopulmonary resuscitation: a randomized swine outcome study. Resuscitation 1999;41:185-192.

37. Wenzel V, Lindner KH, Augenstein S, et al. Intraosseous vasopressin improves coronary perfusion pressure rapidly during cardiopulmonary resuscitation in pigs. Crit Care Med 1999;27:1565-1569.

38. Wenzel V, Lindner KH, Prengel AW, Lurie KG, Strohmenger HU. Endobronchial vasopressin improves

39. Kornberger E, Prengel AW, Krismer A, et al. Vasopressin-mediated adrenocorticotropin release increases plasma cortisol concentrations during cardiopulmonary resuscitation. Crit Care Med 2000;28:3517-3521.

40. Lindner KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. Lancet 1997;349:535-537.

41. Morris DC, Dereczyk BE, Grzybowski M, et al. Vasopressin can increase coronary perfusion pressure during human cardiopulmonary resuscitation. Acad Emerg Med 1997;4:878-883.

42. Stiell IG, Hebert PC, Wells GA, et al. Vasopressin versus epinephrine for in-hospital cardiac arrest: a randomised controlled trial. Lancet 2001;358:105-109.

43. American Heart Association in collaboration with the International Liason Committee on Resuscitation. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care - an international concensus on science. Resuscitation 2000;46:1-448.

44. Lockey AS, Nolan JP. Cardiopulmonary resuscitation in adults. Revised guidelines are more evidence based. BMJ 2001;323:819-820.

45. Parrillo JE. Septic shock in humans: advances in the understanding of pathogenesis, cardiovascular dysfunction and therapy. Ann Intern Med 1990;113:227-242.

46. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time? Crit Care Med 1998;26:2078-2086.

47. Baker CH, Wilmouth FR. Microvascular responses to E. coli endotoxin with altered adrenergic activity. Circ Shock 1984;12:165-176.

48. Zweifach BW, Thomas L. The realtionship between the vascular manifestations of shock produced by endotoxin, trauma and hemorrhage: I. Certain similarities between the reactions in normal and endotoxin tolerant rats. J Exp Med 1957;106:385-401.

49. Chernow B, Roth BL. Pharmacologic manipulation of the peripheral vasculature in shock: clinical and experimental approaches. Circ Shock 1986;18:141-155.

50. Parrillo JE. Pathogenetic mechanisms of septic shock. N Engl J Med 1993;328:1471-1477.

51. Groeneveld AB, Bronsveld W, Thijis LG. Hemodynamic determinants of mortality in human septic shock. Surgery 1986;99:140-153.

52. Meadows D, Edwards JD, Wilkins RG, Nightingale P. Reversal of intractable septic shock with norepinephrine therapy. Crit Care Med 1988;16:663-666.

53. Grollman A, Geiling EMK. The cardiovascular and metabolic reactions of man to the intramuscular injection of posterior pituitary liquid (Pituitrin), Pitressin and Pitocin. J Pharmacol Exp Ther 1932;46:447-460.

54. Graybiel A, Glendy RE. Circulatory effects following the intravenous administration of Pitressin in normal

persons and in patients with hypertension and angina pectoris. Am Heart J 1941;21:481-489.

55. Schwartz J, Reid IA. Role of vasopressin blockade on blood pressure regulation during hemorrhage in concious dogs. Endocrinology 1981;108:1778-1780.

56. Wilson MF, Brackett DJ, Hinshaw LB, Tompkins P, Archer LT, Benjamin BA. Vasopressin release during sepsis and septic shock in baboons and dogs. Surg Gynecol Obstet 1981;153:869-872.

57. Waldron CJ, Hicks PE. Relative contribution of different vascular beds to the pressor effects of α-adrenoreceptor agonists and vasopressin in pithed rats: radioactive microsphere determination. J Auton Pharmacol 1985;5:333-338.

58. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997;95:1122-1125.

59. Bendge MJ. Inositol triphosphate and diacylglycerol as second messengers. J Biochem 1984;220:345-360.

60. Wakatsuki T, Nakaya Y, Inoue I. Vasopressin modulates K-channel activities of cultured smooth muscle cells from porcine coronary artery. Am J Physiol 1992;263:H491-496.

61. Kusano E, Tian S, Umino T, Tetsuka T, Ando Y, Asano Y. Arginine vasopressin inhibits interleukin-1β-stimulated nitric oxide and cyclic guanosine monophosphate production via the V1 receptor in cultured rat vascular smooth muscle cells. J Hypertens 1997;15:627-632.

62. Sharshar T, Carlier R, Blanchard A, et al. Depletion of neurohypophyseal content of vasopressin in septic shock. Crit Care Med 2002;30:497-500.

63. Day TA, Randle JC, Renaud LP. Opposing α- and β-adrenergic mechanisms mediate dose-dependent actions of norepinephrine on supraoptic vasopressin neurones in vivo. Brain Res 1985;358:171-179.

64. Wagner HN Jr, Braunwald E. The pressor effect of the antidiuretic principle of the posterior pituitary in orthostatic hypotension. J Clin Invest 1956;35:1412-1418.

65. Zerbe RL, Bayorh MA, Feuerstein G. Vasopressin: An experimental pressor factor for blood pressure recovery following hemorrhage. Peptides 1982;3:509-514.

66. Altura BM. Evidence that endogenous vasopressin plays a protective role in circulatory shock. Role for reticuloendothelial system using Brattleboro rats. Experimientia 1980;36:1080-1082.

67. Laycock JF, Penn W, Shirley PG, Walter SJ. The role of vasopressin in blood pressure regulation immediately following acute haemorrhage in the rat. J Physiol 1979;296:267-275

68. Baker CH, Sutton ET, Zhou Z, Dietz JR. Microvascular vasopressin effects during endotoxin shock in the rat. Circ Shock 1990;30:81-95.

69. Hamu Y, Kanmura Y, Tsuneyoshi I, Yoshimura N. The effects of vasopressin on endotoxin-induced attenuation of contractile responses in human gastro-epiploic arteries in vitro. Anesth Analg 1999;88:542-548.

70. Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory septic shock. Crit Care Med 1997;25:1279-1282.

71. Malay MB, Ashton RC Jr, Landry DW, Townsend RN. Low dose vasopressin in the treatment of vasodilatory septic shock. J Trauma 1999;47:699-703.

72. Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. Anesthesiology 2002;96:576-582.

73. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. Intensive Care Med 2001;27:1416-1421.

74. O'Brien A, Clapp L, Singer M. Terlipressin for norepinephrine-resistant septic shock. Lancet 2002;359:1209-1210.

75. Walter RSC, Mehta PK, Boonjarern S, Arruda JAL, Kurtzman NA. Conformation considerations of vasopressin as a guide to development of biological probes and therapeutic agents. In: Andreoli TE, Grantham JJ, Rector FC (eds) Disturbances in body fluid osmolality. American Physiologic Society, Bethesda, Md. pp 1-36.

76. Edwards RM, Trizna W, Kinter LB. Renal microvascular effects of vasopressin and vasopressin antagonists. Am J Physiol 1989;256:F274-278.

77. Schmid PG, Abboud FM, Wendling MG, et al. Regional vascular effects of vasopressin: Plasma levels and circulatory responses. Am J Physiol 1974;227:998-1004.

78. Varga C, Pavo I, Lamarque D, et al. Endogenous vasopressin increases acute endotoxin shock-provoked gastrointestinal mucosal injury in the rat. Eur J Pharmacol 1998;352:257-261.

79. Liard JF, Deriaz O, Schelling P, Thibonnier M. Cardiac output distribution during vasopressin infusion or dehydration in concious dogs. Am J Physiol 1982;243:H663-669.

80. Oyama H, Suzuki Y, Satoh S, et al. Role of nitric oxide in the cerebral vasodilatory responses to vasopressin and oxytocin in dogs. J Cereb Blood Flow Metab 1993;13:285-290.

81. Vanhoutte PM, Katusic ZS, Shepherd JT. Vasopressin induces endothelium-dependent relaxations of cerebral and coronary, but not of systemic arteries. J Hypertens 1984; 2:S421-422.

82. Wun T, Paglieroni T, Lachant NA. Physiologic concentrations of arginine vasopressin activate human platelets in vitro. Br J Haematol 1996;92:968-972.

83. Wiest R, Shah V, Sessa WC, Groszmann RJ. NO overproduction by eNOS precedes hyperdynamic splanchnic circulation in portal hypertensive rats. Am J Physiol 1999;276:G1043-1051.

84. Niederberger M, Martin P, Gines P, et al. Normalization of nitric oxide production corrects arterial vasodilation and hyperdynamic circulation in cirrhotic rats. Gastroenterology 1995;109:1624-1630.

85. Pizcueta M, Pique J, Bosch J, Whittle B, Moncada S. Effects of inhibiting nitric oxide biosynthesis on the

systemic and splanchnic circulation of rats with portal hypertension. Br J Pharmacol 1992;105:184-190.

86. Merigan T, Plotkin G, Davidson C. The effect of intravenous pituitrin on hemorrhage from bleeding esophageal varices. N Engl J Med 1962;266:134-135.
87. Chan CC, Lee FY, Wang SS, et al. Effects of vasopressin on portal-systemic collaterals in portal hypertensive rats: role of nitric oxide and prostaglandin. Hepatology 1999;30:630-635.
88. Iwao T, Toyonaga A, Oho K, et al. Effect of vasopressin on esophageal varices blood flow in patients with cirrhosis: comparisons with the effects on portal vein and superior mesenteric artery blood flow. J Hepatol 1996;25:491-497.
89. Ready JB, Robertson AD, Rector WG Jr. Effects of vasopressin on portal pressure during hemorrhage from esophageal varices. Gastroenterology 1991;100:1411-1416.
90. Mallory A, Schaefer JW, Cohen JR, Holt SA, Norton LW. Selective intra-arterial vasopression infusion for upper gastrointestinal tract hemorrhage: a controlled trial. Arch Surg 1980;115:30-32.
91. Robinette C, Gerlock AJ. Intra-arterial vasopressin infusion in treating acute gastrointestinal bleeding. South Med J 1980;73:209-213.
92. Chojkier M, Groszmann RJ, Atterbury CE, et al. A controlled comparison of continuous intraarterial and intravenous infusions of vasopressin in hemorrhage from esophageal varices. Gastroenterology 1979;77:540-546.
93. Millette B, Huet PM, Lavoie P, Viallet A. Portal and systemic effects of selective infusion of vasopressin into the superior mesenteric artery in cirrhotic patients. Gastroenterology 1975;69:6-12.
94. Faigel DO, Metz DC, Kochman ML. Torsade de pointes complicating the treatment of bleeding esophageal varices: association with neuroleptics, vasopressin, and electrolyte imbalance. Am J Gastroenterol 1995;90:822-824.
95. Melo JA, Lee M, Munoz J, Levine SM. Severe hyponatremia and bradycardia associated with intravenous vasopressin therapy for variceal hemorrhage. J Clin Gastroenterol 1995;20:266-268.
96. Lambert M, de Peyer R, Muller AF. Reversible ischemic colitis after intravenous vasopressin therapy. JAMA 1982;247:666-667.
97. Brearley S, Hawker PC, Dykes PW, Keighley MR. A lethal complication of peripheral vein vasopressin infusion. Hepatogastroenterology 1985;32:224-225.
98. Pierce ST, Nickl N. Rhabdomyolysis associated with the use of intravenous vasopressin. Am J Gastroenterol 1993;88:424-427.
99. Lin RY, Du SL, Yeh HS, Wang WM. Vasopressin-induced amber-like skin necrosis. Dermatology 1997;195:271-273.
100. Bar-Meir S, Conn HO. Spontaneous bacterial peritonitis induced by intra-arterial vasopressin therapy. Gastroenterology 1976;70:418-421.
101. Corley DA, Cello JP, Adkisson W, Ko WF, Kerlikowske K. Octreotide for acute esophageal variceal

bleeding: a meta-analysis. Gastroenterology 2001;120:946-954.
102. Imperiale TF, Teran JC, McCullough AJ. A meta-analysis of somatostatin versus vasopressin in the management of acute esophageal variceal hemorrhage. Gastroenterology 1995;109:1289-1294.
103. Gimson AE, Westaby D, Hegarty J, Watson A, Williams R. A randomized trial of vasopressin and vasopressin plus nitroglycerin in the control of acute variceal hemorrhage. Hepatology 1986;6:410-413.
104. Tsai YT, Lay CS, Lai KH, et al. Controlled trial of vasopressin plus nitroglycerin vs. vasopressin alone in the treatment of bleeding esophageal varices. Hepatology 1986;6:406-409.
105. Bosch J, Groszmann RJ, Garcia-Pagan JC, et al. Association of transdermal nitroglycerin to vasopressin infusion in the treatment of variceal hemorrhage: a placebo-controlled clinical trial. Hepatology 1989;10:962-968.
106. Schweitzer EJ, Kerr JC, Swan KG. Clinical use of vasopressin in the management of bleeding esophageal varices. Am Surg 1982;48:558-562.
107. Teres J, Planas R, Panes J, et al. Vasopressin/nitroglycerin infusion vs. esophageal tamponade in the treatment of acute variceal bleeding: a randomized controlled trial. Hepatology 1990;11:964-968.
108. Scheinkestel CD, Tuxen DV, Cooper DJ, Butt W. Medical management of the (potential) organ donor. Anaesth Intens Care 1995;23:51-59.
109. Howlett TA, Keogh AM, Perry L, Touzel R, Rees LH. Anterior and posterior pituitary function in brain-stem-dead donors. A possible role for hormonal replacement therapy. Transplantation 1989;47:828-834.
110. Powner DJ, Hendrich A, Lagler RG, Ng RH, Madden RL. Hormonal changes in brain dead patients. Crit Care Med 1990;18:702-708.
111. Gramm HJ, Meinhold H, Bickel U, et al. Acute endocrine failure after brain death? Transplantation 1992;54:851-857.
112. Wahlers T, Cremer J, Fieguth HG, et al. Donor heart-related variables and early mortality after heart transplantation. J Heart Lung Transplant 1991;10:22-27.
113. Yoshioka T, Sugimoto H, Uenishi M, et al. Prolonged hemodynamic maintenance by the combined administration of vasopressin and epinephrine in brain death: a clinical study. Neurosurgery 1986;18:565-567.
114. Iwai A, Sakano T, Uenishi M, Sugimoto H, Yoshioka T, Sugimoto T. Effects of vasopressin and catecholamines on the maintenance of circulatory stability in brain-dead patients. Transplantation 1989;48:613-617.
115. Pennefather SH, Bullock RE, Mantle D, Dark JH. Use of low dose arginine vasopressin to support brain-dead organ donors. Transplantation 1995;59:58-62.
116. Chen JM, Cullinane S, Spanier TB, et al. Vasopressin deficiency and pressor hypersensitivity in hemodynamically unstable organ donors. Circulation 1999;100[suppl II]:II-244-246.
117. Katz K, Lawler J, Wax J, O'Connor R, Nadkarni V. Vasopressin pressor effects in critically ill children

during evaluation for brain death and organ recovery. Resuscitation 2000;47:33-40.

118. Manaka D, Okamoto R, Yokoyama T, et al. Maintenance of liver graft viability in the state of brain death. Synergistic effects of vasopressin and epinephrine on hepatic energy metabolim in brain-dead dogs. Transplantation 1992;53:545-550.