Vasoconstrictor Responses to Vasopressor Agents in Human Pulmonary and Radial Arteries

An In Vitro Study

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ABSTRACT

Background: Vasopressor drugs, commonly used to treat systemic hypotension and maintain organ perfusion, may also induce regional vasoconstriction in specialized vascular beds such as the lung. An increase in pulmonary vascular tone may adversely affect patients with pulmonary hypertension or right heart failure. While sympathomimetics constrict pulmonary vessels, and vasopressin does not, a direct comparison between these drugs has not been made. This study investigated the effects of clinically used vasopressor agents on human isolated pulmonary and radial arteries.

Methods: Isolated pulmonary and radial artery ring segments, mounted in organ baths, were used to study the contractile responses of each vasopressor agent. Concentration–response curves to norepinephrine, phenylephrine, metaraminol, and vasopressin were constructed.

Results: The sympathomimetics norepinephrine, phenylephrine, and metaraminol caused concentration-dependent vasoconstriction in the radial (pEC_{50}: 6.99 ± 0.06, 6.14 ± 0.09, and 5.56 ± 0.07, respectively, n = 4 to 5) and pulmonary arteries (pEC_{50}: 6.86 ± 0.11, 5.94 ± 0.05 and 5.56 ± 0.09, respectively, n = 3 to 4). Vasopressin was a potent vasoconstrictor of the radial artery (pEC_{50} 9.13 ± 0.20, n = 3), whereas in the pulmonary artery, it had no significant effect.

Conclusions: Sympathomimetic-based vasopressor agents constrict both human radial and pulmonary arteries with similar potency in each. In contrast, vasopressin, although a potent vasoconstrictor of radial vessels, had no effect on pulmonary vascular tone. These findings provide some support for the use of vasopressin in patients with pulmonary hypertension. **(Anesthesiology 2014; 121:930-6)**

VASOPRESSOR drugs are commonly used to increase systemic arterial pressure and maintain organ perfusion in states of circulatory failure, including ventricular failure and sepsis.[1] In patients with pulmonary hypertension, however, administration of these drugs may potentially induce pulmonary vasoconstriction, and adversely affect right ventricular function.[2] Clinically used vasopressor agents include the sympathomimetics norepinephrine, phenylephrine, and metaraminol, which act predominantly on vascular smooth muscle α_1-adrenoceptors. Vasopressin, a nonapeptide, is also used clinically to increase vasomotor tone and elevate arterial pressure via activation of smooth muscle V_1 receptors.[3,4] Variation in the distribution and density of receptor subtype influences the vascular response to these agonists within each vascular bed.[5] In surgical patients with pulmonary hypertension, the ideal vasopressor drug is one that can selectively cause systemic vasoconstriction, with a minimal effect on pulmonary vascular tone. While vasopressor drugs are commonly used for hemodynamic support in critically ill and cardiac surgical patients, little data exist comparing the direct effect of these drugs on human systemic and pulmonary vessels. Identifying the relative drug potency between vessels is particularly relevant in the choice of vasopressor drug, and for determining optimal infusion rates when combination therapy is used.[6]

The aim of this study was to measure the efficacy and potency of clinically used vasopressor drugs on human isolated pulmonary artery compared with the radial artery.

What We Already Know about This Topic

- Vasopressors used in clinical practice to maintain organ perfusion have potential to reduce perfusion to specialized vascular beds such as the lung and impair right heart function
- A direct comparison of the relative potencies of commonly used vasopressors to constrict human radial and pulmonary arteries has never been performed

What This Article Tells Us That Is New

- Sympathomimetics were potent vasoconstrictors of human radial and pulmonary arteries while vasopressin produced vasoconstriction only in radial arteries suggesting a potential advantage of vasopressin use in patients with pulmonary hypertension

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Materials and Methods

Experiments using human tissue were approved by the Melbourne Health Human Research Ethics Committee, Melbourne, Australia (HREC ethics number 2011.11). Informed written consent was obtained from patients before undergoing cardiothoracic surgery.

Tissue Collection

Excess segments of radial artery (internal diameter ~3.5 mm) and pulmonary artery (internal diameter ~5.0 mm) were obtained from patients undergoing either coronary artery bypass graft surgery or lung resection surgery at the Royal Melbourne Hospital, Melbourne, Australia. Tissues were immediately harvested and placed in cold Krebs' physiological salt solution (PSS mM): NaCl, 119; KCl, 4.69; $MgSO_4 \cdot 7H_2O$, 1.17; KH_2PO_4, 1.18; glucose, 5.5; $NaHCO_3$, 25; $CaCl_2 \cdot 6H_2O$, 2.5; EDTA, 0.026 mmol/l, and saturated with carbogen (O_2, 95%; CO_2, 5%) at pH 7.4.

Arteries were trimmed of excess fat and connective tissue, cut into 3 mm long ring segments, and placed into 20 ml organ baths. Tissues were mounted between two L-shaped wires (550 μm diameter) and connected to a force transducer (Grass Instruments FT03C, Quincy, MA) and an adjustable leg, connected to a data acquisition system (Powerlab, AD Instruments, Sydney, Australia). Organ baths were filled with PSS, continuously bubbled with carbogen to stabilize partial pressure of carbon dioxide (pCO_2),[7] and maintained at 37.0 ± 0.1 °C. Tissues were allowed to equilibrate for 30 min.

Experimental Protocol

In vitro analysis of isolated vessels is a robust and sensitive approach that enables assay of agonist–receptor interactions. Tissues were normalized by passive stretch to an equivalent transmural pressure of 100 mmHg for radial arteries or 20 mmHg for pulmonary arteries.[8] Tissues were allowed to equilibrate for a further 15 min before exposure to potassium depolarizing solution (KPSS; PSS with an equimolar substitution of K^+ for Na^+; K^+ 124 mM) to determine the viability of the artery, and provide a reference maximum contractile force. Tissues were then washed with PSS and allowed to relax to baseline.[9]

For each patient multiple 3 mm long segments of the harvested radial or pulmonary vessel were mounted. A single concentration–response curve to either norepinephrine (0.1 nM to 10 μM), phenylephrine (1 nM to 30 μM), arginine vasopressin (10 pM to 3 μM), or metaraminol (1 nM to 30 μM) was then constructed in each ring to allow comparison among the pressor agents. These drugs were added in cumulative half-log_{10} increments allowing time for the response to plateau between additions. Contractions to each concentration of pressor agent were expressed as %KPSS maximum contraction within artery. To take account of the variation in artery diameter, the maximum contraction (E_{max}) to each pressor agent was measured in g force for the 3 mm ring segment and divided by the internal circumference ($g/\pi D$). The vessels were then washed with drug-free PSS.

To test the integrity of the endothelium, each ring of radial and pulmonary artery was precontracted to a steady force with norepinephrine 1 μM or phenylephrine 3 μM before applying acetylcholine 1–3 μM.

To investigate whether vasopressin causes relaxation in isolated pulmonary arteries, some vessels were precontracted to 60–75% KPSS maximum with U46619 (thromboxane A_2 receptor agonist; 10 to 30 nM). A cumulative concentration–relaxation response curve to arginine vasopressin (0.1 nM to 3 μM) was then completed. Vasopressin was added in cumulative half-log_{10} increments allowing time for responses to plateau between additions. Time control experiments were also undertaken to determine the effect of time on U46619 tone. Pulmonary arteries that had not previously been exposed to vasopressin were precontracted to 60–75% KPSS maximum with U46619 (10 to 30 nM) and a vehicle equivalent (MilliQ H_2O, 20 μl) was added every 5 min.

Drugs

Drugs and suppliers were as follows: arginine vasopressin (AusPep, Parkville, Victoria, Australia), metaraminol (Sandoz, Holzkirchen, Germany), norepinephrine bitartrate (Sigma, St Louis, MO), phenylephrine hydrochloride (Sigma), and thromboxane mimetic U46619 (Sigma). All drugs were prepared using MilliQ water and stored as stock solutions at 4 °C until required.

Statistical Analysis

All data are expressed as mean ± 1 standard error of the mean (SEM) of *n* experiments. Sigmoidal concentration–response curves were fitted using Prism 5 (GraphPad Prism Software, San Diego, CA) for each individual experiment. The potency pEC_{50} (the negative logarithm of the molar concentration required to elicit 50% maximum response) and efficacy taken as maximum responses of each drug were compared between groups with one-way analysis of variance (ANOVA) and Dunnett's *post hoc* (2-sided) test using SPPS Statistics 22 software (IBM, Armonk, NY). For experiments assessing vasopressin relaxation, concentration–relaxation curves were analysed by Repeated Measures ANOVA to determine change in tone over time.

In all cases, $P < 0.05$ was accepted as statistically significant.

Results

The data from the radial and pulmonary arteries were grouped as per their single test vasoconstrictor agent. The internal diameter (D100) of the radial arteries in the four groups ranged from 3.29 to 3.64 mm, whereas the range for the pulmonary arteries (D20) was from 4.37 to 5.55 mm. Despite the larger pulmonary artery diameter, the maximum contractile force to KPSS (KPSS mN) was approximately 20–30% that of the radial arteries (Table 1). By taking the

maximum response to KPSS as 100% within artery, the E_{max} to each of the four constrictor agents ranged from 88% to 103% that of KPSS. In the pulmonary artery, E_{max} to norepinephrine (89 ± 10%) and metaraminol (82 ± 6%) were close to the KPSS response while E_{max} to phenylephrine was not significantly less (64 ± 9%, P=0.10), while vasopressin was without effect (fig. 1 and table 1). Another useful index is to compare the total active force of the 3 mm long artery segment normalized for the internal circumference (πD100) to take account of the variation in artery internal diameter. With this index, the range was 0.99–1.63 g/mm for the four pressor agents compared with 0.13–0.16 for norepinephrine, phenylephrine, and metaraminol in the pulmonary artery. In radial arteries, the sensitivity (pEC_{50}) to vasopressin was 170-fold higher (antilog 2.23) than for norepinephrine which, in turn, was 7-fold (antilog 0.85) more potent than phenylephrine and 27-fold (antilog 1.43) more potent than metaraminol. In the pulmonary artery, the pEC_{50} values and rank order of potency were the same for norepinephrine, phenylephrine, and metaraminol as in the radial artery. This contrasts with the failure of vasopressin to contract the pulmonary artery despite the potent and strong contraction in the radial artery.

Each ring segment of radial and pulmonary artery precontracted with norepinephrine (1 μM) or phenylephrine (3 μM) relaxed completely when acetylcholine 1–3 μM was applied. This test indicated that each ring had sufficient functional endothelial cells to release nitric oxide and functionally antagonize the contraction.

Experiments were conducted to determine whether the failure of vasopressin to contract the pulmonary artery was due to relaxation. Here, arteries were precontracted with U46619 to a steady level of active force between 65% and 85% of KPSS maximum in each pulmonary artery ring. Half-log concentration addition of vasopressin 10^{-10}–$10^{-5.5}$ M added every 5 min over 45 min caused no significant relaxation compared with similarly timed additions of vehicle (fig. 2; P=0.44, Repeated Measures ANOVA).

Drug Treatment

Radial artery segments were removed from patients with a variety of clinical morbidities including hypertension, and were on a wide variety of medications involving some of the following: β-adrenoceptor blockers, statins, angiotensin II-converting enzyme inhibitors, aspirin, glyceryl trinitrate, calcium entry blockers, and prazosin. The donors of the pulmonary arteries were on some of the following: digoxin, carvedilol, nicorandil, diuretics, and bronchodilators. Whether these drugs had been removed from the artery rings in the organ baths after several hours of drug-free PSS is unknown. Clearly, this is a hazard of human arterial tissue research.

Discussion

This is the first study to directly compare clinically used vasopressor agents in human isolated pulmonary and radial arteries. The findings show that constrictor potency (pEC_{50}) for norepinephrine, phenylephrine, and metaraminol is in the same rank order in both the radial and the pulmonary artery and most likely due to the distribution of $\alpha_{1a} > \alpha_{1b} = \alpha_{1d}$ adrenoceptors. Indeed, the density of

Table 1. Vascular Reactivity in Human Isolated Radial and Pulmonary Arteries to Clinically Used Vasopressor Agents

	Norepinephrine	Phenylephrine	Metaraminol	Vasopressin
Radial artery				
n	4	4	5	3
Diameter (mm)	3.53 ± 0.30	3.64 ± 0.60	3.37 ± 0.40	3.29 ± 0.33
KPSS (mN)	204.3 ± 50.6	216.4 ± 58.5	104.3 ± 29.2	100.2 ± 43.3
E_{max} (%KPSS)	88 ± 9	90 ± 12	103 ± 10	90 ± 2
P value		(0.99)	(0.58)	(1.00)
E_{max} (g/mm)	1.63	1.56	0.99	1.26
pEC_{50}	6.99 ± 0.06	6.14 ± 0.09*	5.56 ± 0.07*	9.13 ± 0.20*
P value		(0.01)	(0.01)	(0.01)
Pulmonary artery				
N	4	4	3	4
Diameter (mm)	5.55 ± 0.73	5.17 ± 1.08	4.37 ± 0.96	4.92 ± 0.80
KPSS (mN)	31.7 ± 12.5	33.0 ± 11.1	21.4 ± 12.3	33.8 ± 13.9
E_{max} (%KPSS)	89 ± 10	64 ± 9	82 ± 6	0*
P value		(0.10)	(0.94)	(0.01)
E_{max} (g/mm)	0.16	0.13	0.13	0
pEC_{50}	6.86 ± 0.11	5.94 ± 0.05*	5.56 ± 0.09*	NC
P value		(0.01)	(0.01)	

*P < 0.01 (one-way analysis of variance, Dunnett's *post hoc* comparison to norepinephrine).

Diameter = internal diameter at normalization (mm); E_{max} (%KPSS) = maximum response to the vasopressor agent as %KPSS within artery; E_{max} (g/mm) = maximum average response to the vasopressor agent as g force normalized per mm of averaged internal circumference at normalization; KPSS (potassium depolarizing solution) = increase in force (mN) to KPSS for arteries grouped for subsequent test with vasopressor agent; n = number of arteries from separate patients; NC = no contraction; pEC_{50} = negative logarithm of the concentration of vasopressor agent required to elicit 50% maximum response.

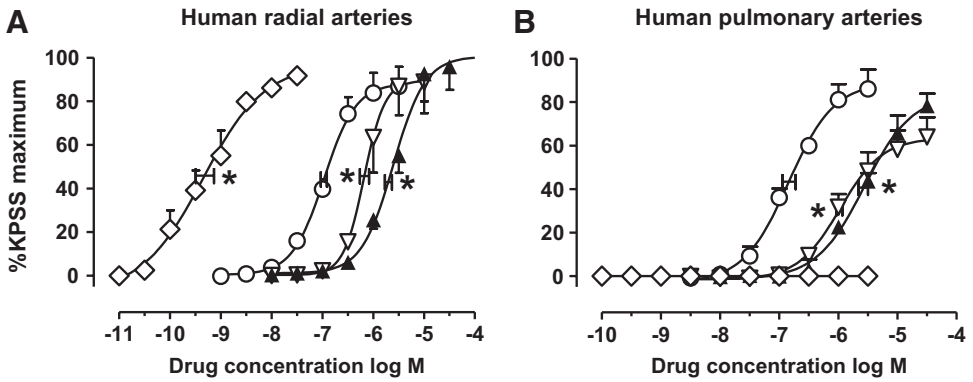

Fig. 1. Contractile responses to vasopressor agents in human isolated (*A*) radial and (*B*) pulmonary arteries. Cumulative concentration–response curves to arginine vasopressin (◇, $n = 4$), norepinephrine (○, $n = 4$), phenylephrine (▽, $n = 4$), or metaraminol (▲, $n = 3$–5) were constructed in each tissue. Data are shown as a percentage of KPSS (potassium depolarizing solution) maximum contraction. *Vertical error bars* are ±1 SEM; where no error bar is visible the SEM is within the symbol. *Horizontal error bars* represent EC_{50} ± 1 SEM. n = number of arteries each from different patients. *$P < 0.01$ (one-way analysis of variance, Dunnett's post hoc comparison to norepinephrine).

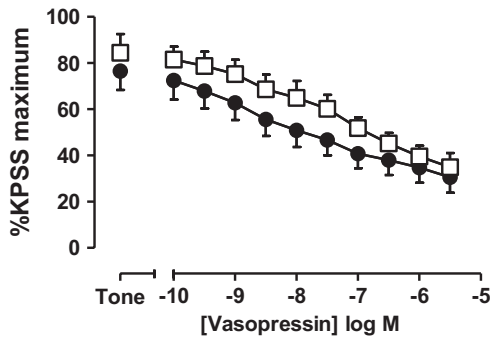

Fig. 2. Lack of relaxation responses to arginine vasopressin (●, $n = 6$) compared to time control (vehicle) equivalent (□, $n = 4$) in human pulmonary arteries pre-contracted with U46619 (to 65–85% KPSS [potassium depolarizing solution] maximum). For time control experiments, vehicle equivalent (MilliQ H_2O, 20 μl) was added every 5 min. Data are shown as a percentage of KPSS maximum contraction. *Error bars* are ±1 SEM. Tone = level of U46619 precontraction on vessel before commencement of vasopressin concentration–response curve or time control experiment. No significant difference between groups ($P = 0.443$).

α_1-adrenoceptor (fmol/mg total protein) has reported to be as high in the human pulmonary artery as in the renal artery.[5] In contrast, vasopressin was a very potent constrictor of the radial artery ($pEC_{50} = 9.13$) yet was completely insensitive in the pulmonary artery. In comparing norepinephrine pEC_{50} values in human coronary, internal mammary, inferior epigastric and gastroepiploic arteries, the pEC_{50} values ranged from 5.9 to 6.6 and were not significantly different.[10] The current work shows that among the three sympathomimetics, norepinephrine has the highest potency or is more efficient at contracting both pulmonary and radial arteries than the other two. This is essentially a chemical property of the pressor agent and the receptor occupation and stimulus response coupling.

The total circumferential active force of the 3 mm artery ring generated by the pressor agent will depend on the muscle mass. Generally, the larger the internal diameter of an artery, the larger the wall thickness, and thus active force generated. The normalization of the force by the internal circumference allows for comparison of contractile responses from arteries of different sizes.[11] Because most investigators use a standard 3 mm long artery segment for *in vitro* studies, comparisons can readily be made of E_{max} either as % of the KPSS within artery or, in absolute terms, as g/mm internal circumference. In our work in radial arteries, vasopressin E_{max} was on average 1.26 g/mm, similar to metaraminol (0.99) and less than norepinephrine (1.63) and phenylephrine (1.56; Table 1). By comparison, Wei et al.[12] reported E_{max} of 1.8 ± 0.2 g/mm in radial artery and a very similar pEC_{50} of 9.28 ± 0.11 (compared to 9.13 ± 0.2 in the current study). In striking contrast was that the pressor agents and KPSS were approximately 10 times more powerful in the radial artery compared with the pulmonary artery (0.16 g/mm for norepinephrine, 0.13 for phenylephrine and metaraminol, and 0.22 g/mm for KPSS).

This clearly demonstrates that the human pulmonary artery has a relatively weak constrictor response to vasopressor agents compared with more muscular arterial segments that are exposed to arterial rather than pulmonary artery distending pressure. In addition, the failure of vasopressin to contract the human pulmonary artery gives this pressor agent some advantage over the other agents in clinical use.

A major limitation of this study was that we were unable to access smaller diameter pulmonary arteries that could play a significant role in controlling pulmonary vascular resistance. Because the resistance (R) is proportional to the reciprocal of the internal radius[4] ($R\alpha 1/r^4$), the pharmacodynamic responses in these large conduit vessels may not be replicated in the very small arteries. However, we can be sure that the radial and pulmonary arteries have very different pharmacology as far as vasopressin is concerned. In rats,[13] vasopressin

causes pulmonary vasodilatation, and in dogs, large pulmonary artery segments *in vitro* relaxed to vasopressin apparently due to endothelium-dependent release of nitric oxide.[14] In humans, the results of *in vivo* studies have been inconsistent, with reports of vasopressin causing increased, decreased, or no change in pulmonary artery pressure.[15–18]

The vascular response to vasopressin is influenced primarily by receptor subtype and density, as well as age and disease. Activation of V_1 receptors (Gq/PLC coupled) increases intracellular calcium to induce smooth muscle vasoconstriction.[19] Vasopressin may also elicit vasodilatation by a nitric oxide–dependent mechanism[14] or by activation of vascular smooth muscle V_2 receptors (Gs/cAMP coupled) and possibly oxytocin receptors.[20] Pulmonary vasodilatation may occur in adult lung but not in neonatal lung, an effect attributed to absent neonatal V_1 receptor expression.[21] Such receptor variability determines vascular responsiveness and challenges the use of vasopressin in neonatal pulmonary hypertension. In a guinea pig preparation, vasopressin has been demonstrated to differentially constrict pulmonary veins compared with pulmonary arteries.[22] In humans, such a vascular response could potentially increases lung edema, limiting the use of vasopressin in the treatment of left ventricular heart failure. Infusion of vasopressin in healthy humans does not elevate blood pressure, but may decrease it by inducing muscle vasodilatation, a response attenuated by antagonism of nitric oxide synthase.[23,24] In sepsis, however, changes in receptor affinity and intracellular signaling result in vasopressin hypersensitivity. Low-dose vasopressin is clinically effective in restoring vascular responsiveness to catecholamines,[3] a response mediated by tyrosine kinase and protein kinase C pathways.[25]

In the setting of right heart failure, a clinical concern is that vasopressor agents may induce pulmonary vasoconstriction, and potentially impair right ventricular function. However, clinical experience suggests that norepinephrine can be used safely when carefully monitored in patients with pulmonary hypertension and right heart failure.[26,27] Norepinephrine appears superior to other sympathomimetic vasoconstrictor agents, such as phenylephrine.[2] This may be explained by norepinephrine's β-adrenoceptor agonism, with β_1-adrenoceptor activation improving right ventricular contraction and cardiac output, whereas β_2-adrenoceptor activation is believed to simultaneously decrease pulmonary vascular resistance.[28] Because right coronary artery blood flow occurs during both systole and diastole, an augmented increase in mean arterial pressure will also improve coronary perfusion and right ventricular function. Importantly, norepinephrine also increases automaticity at the sinoatrial node, maintaining heart rate. In contrast, phenylephrine and other vasopressor agents are associated with significant bradycardia and decrease in cardiac output, via activation of the baroreceptor reflex.[29]

Therefore, vasopressin remains an attractive option for hemodynamic support in patients with pulmonary hypertension or right heart failure. A number of case reports have supported the safe use of vasopressin in both acute[30] and chronic pulmonary hypertension.[31,32] Comparison of vasopressin with sympathomimetics, particularly norepinephrine with its intrinsic β_1-adrenoceptor activity, has not been fully evaluated. The vasopressin and septic shock trial (VASST)[6] compared low dose vasopressin with norepinephrine in patients with septic shock. Although vasopressin did not decrease mortality, an effect possibly related to dose, it was shown to be as safe as norepinephrine. In cardiac arrest, vasopressin has been effective in acute resuscitation, however, randomized control trials have failed to demonstrate that vasopressin is superior to epinephrine.[33] In arrested patients with pulmonary hypertension, however, vasopressin may theoretically improve the chances of successful resuscitation.

In the acute respiratory distress syndrome, intrapulmonary shunt is significant, and vasoconstrictor drugs may benefit oxygenation by enhancing hypoxic pulmonary vasoconstriction.[34] This intrinsic pulmonary vascular response improves oxygenation with regional vasoconstriction to direct blood flow away from nonventilated alveoli and prevent shunt.[35,36] Phenylephrine has been demonstrated to improve oxygenation in acute respiratory disease syndrome,[36] in contrast to norepinephrine which showed no improvement.[34] These drugs, however, have not been compared in the same study, and while sympathomimetics are likely to augment hypoxic pulmonary vasoconstriction, this mechanism has not been established.

A limitation of the current study is that *in vitro* experiments were carried out under normoxic conditions. In disease states, however, the pulmonary vascular response may be influenced by hypoxia or hypercarbia resulting from lung dysfunction.[13] Future study of pulmonary vascular responses under hypoxic conditions may better simulate disease states. Second, the responses observed in radial arteries were interpreted as a representative measure of systemic vascular responsiveness (or resistance). Because radial vessels are predominately conduit rather than primary resistance vessels, the results in this artery may not truly reflect arteriolar responses.

After coronary artery bypass grafting vasopressor agents are commonly used in low cardiac output states to increase coronary perfusion pressure, and vasoconstriction may impact on both native and graft coronary flow. In recent years, extensive investigation of vessel reactivity to numerous pharmacological drugs has been performed in assessing the suitability of both arterial and venous conduits for coronary artery bypass graftings.[37] Early work using canine vessels showed norepinephrine and phenylephrine to have potent vasoconstrictor effects in internal mammary arteries and saphenous veins.[38] Similarly, in humans, clinically used vasopressor drugs have been shown to have the potential to constrict vascular grafts.[28,29] Increased plasma levels of catecholamines and vasopressin have been demonstrated postcardiopulmonary bypass and may be implicated in arterial graft

spasm[12,39] In a recent study of patients undergoing coronary artery bypass grafting, norepinephrine or vasopressin infusions were given to increase the arterial pressure by 20%.[40] Norepinephrine increased internal thoracic artery graft flow (35%) as the resistance in this bed fell (11%). Vasopressin slightly increased internal thoracic artery flow 3% but increased the internal thoracic artery resistance (15%). Importantly, vasopressin but not norepinephrine decreased the pulmonary resistance by 14%. Both drugs increased the systemic vascular resistance by 12–13%. This study and the current work support the concept that vasopressin spares both the large and small pulmonary arteries.

In summary, these results demonstrate that catecholamine-based vasopressor agents constrict both human radial and pulmonary arteries, and that vasopressin also potently vasoconstricts radial vessels, but has no effect on pulmonary vascular tone. These findings support the use of vasopressin in patients with pulmonary hypertension.

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Competing Interests

The authors declare no competing interests.

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