Phenylephrine: in or out?

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Introduction

Phenylephrine is a synthetic, non-catecholamine, predominantly α-adrenergic agonist when used at clinically relevant dosages. It does have some β-effects, but only at very high doses.

It has traditionally been used in cardiac patients for a number of specific applications:

- During the period surrounding and including cardiopulmonary bypass (CPB).
- For the management of vasoplegic shock post-CPB and shock associated with sepsis in the intensive care unit (ICU).
- As part of the management of right ventricular (RV) failure, when low systemic pressures threaten RV coronary perfusion.

Cardiopulmonary bypass

Optimal perfusion pressure on CPB is undecided.[1] Originally, mean arterial pressure (MAP) on CPB was chosen based on cerebral autoregulation limits thought to be in the range of 50-150 mmHg. Recent work by Olsen et al[2] has shown that there is considerable variability in autoregulatory ranges in normotensive adults. The lower limit of "normal" may be as high as 73-88 mmHg. A number of large studies have now suggested that a subgroup of patients will benefit from higher perfusion pressure, both neurologically, and from a multi-organ dysfunction point of view. This subgroup tends to have risk factors for large- and small-vessel vasculopathy.[3-5]

The use of phenylephrine in this setting has some problems. Cardiac surgery and CPB have both been shown to induce microcirculatory changes associated with hypoperfusion, shunting and ischaemia that temporally last well into the post-surgical recovery period, and are paralleled by serum lactate levels.[6] In recognition of its widespread use, and using similar microcirculatory quantification techniques, phenylephrine, when used on CPB, has been shown to diminish microcirculatory blood flow and increase shunting.[7]

Taking into account that some patients will benefit from higher MAP on CPB, and that phenylephrine is likely to worsen microcirculatory oxygen and nutrient delivery, the question needs to be asked: are any other vasopressors any better? The studies showing the benefit of higher mean pressures on CPB have used varying protocols with phenylephrine, noradrenaline, adrenaline or vasopressin. Techniques recognising patients benefiting from higher perfusion pressures are in their infancy. As a result, there are no head-to-head comparisons of the various vasopressor options. Current consensus guidelines recognise the need for tailored pressure management, but do not distinguish between the pharmacological agents.[1]

The available literature on other questions in this field with regard to phenylephrine is sparse. There are nine studies in total:

- Arterial graft spasm: Two small studies have showed a benefit, and one small study showed harm.[8]
- Renal dysfunction: Creatinine clearance was not altered compared to angiotensin infusion in a small prospective study.[8]
- Gut ischaemia: Phenylephrine, more than noradrenaline, increased mesenteric oxygen extraction in one small crossover study.[9]
- Atrial arrhythmias post-surgery: A retrospective study showed vasopressor use is an independent risk factor for postoperative arrhythmias. Phenylephrine is the safest though.[8]

Vasoplegic shock

Vasoplegic shock has an incidence between 5-25% in the peri-CPB period.[8,10] The goal of maintaining vital organ perfusion by returning vascular tone to acceptable levels seems prudent.

- Only seven studies show that phenylephrine is effective in increasing MAP in this setting.

- Dinardo et al[11] showed that a dose of 0.87 ± 0.37 µg/kg/minute increased MAP by 19 mmHg. This increase was accompanied by no change in pulmonary capillary wedge pressure (PCWP), heart rate (HR), central venous pressure (CVP) and cardiac index.
- No head-to-head studies with noradrenaline are available at present.
- There are currently six studies showing good results in vasoplegic shock post-CPB utilising methylene blue. It is a potent inhibitor of both NO synthase and cylic guanylate cyclase.[10]

Vasoplegic shock due to sepsis in ICU has long been a fertile ground for research:[12]

- There are many head-to-head trials of drugs like adrenaline, noradrenaline, vasopressin, terlipressin, phenylephrine and dobutamine.
- At this stage, no strong evidence supports the use of any single agent or combination of agents over any others.
- The most rational and evidence-based approach refers to early goal-directed restoration of tissue oxygen delivery using a patient-tailored targeted approach, as advocated by the surviving sepsis guidelines.[13]

Right ventricular failure

We will examine the setting of acute RV failure when pulmonary artery pressures approach or exceed systemic pressures, and RV coronary blood flow slows, or stops during systole.

Vasoconstrictors have an accepted, but not evidentially supported role to maintain diastolic coronary perfusion pressures and prevent worsening ischaemic RV myocardial dysfunction. This is a weak recommendation in a situation where outcomes are poor (60% mortality).[14,15] Consensus guidelines tend to favour noradrenaline over phenylephrine on the basis of increased pulmonary vessel resistance (PVR) observed in the higher dosage ranges of phenylephrine. This PVR effect has not been borne out by studies in the congenital heart disease literature or by animal models. As yet, with regard to humans, there is no evidence that favours one over the other.

Lack of evidence-based medicine

There is a distinct lack of evidence when it comes to choice of inotropes. The literature favours a case-by-case targeted approach utilising the strengths of each agent to achieve specific goals. Therefore, the answers may lie in modern monitoring modalities.

Near-infrared cerebral oximetry is a leader in monitoring of the microcirculation. Work by Murkin and Slater suggests that a protocol-based interventional approach to cerebral desaturation on CPB may improve both neurological and multiorgan dysfunction outcomes in cardiac surgery. Vasoconstrictor and perfusion pressure are only one component of their management algorithms.[16,17]

Modern Swan-Ganz technology, with continuous cardiac output, end-diastolic volumes and continuous mixed venous saturations, permits accurate characterisation of the individual's response to vasopressor therapy.

The more universal use of transoesophageal echo-cardiography has already resulted in significant changes in decision making in cardiac theatres. The subtleties of ventricular interdependence, frequency of RV dysfunction and adequacy of preload are only some of the distinct benefits offered in the setting of stunned hearts. Previously unrecognised effects of vasopressor therapy are now commonly diagnosed.

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