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Vasoconstrictors – friend or foe?

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INTRODUCTION

The use of vasoconstrictors in the management of intraoperative hypotension (IOH) is ubiquitous and associated with a not insignificant cost.

The purpose of this article is to explore the rationale for administering vasoconstrictors to treat IOH and whether their administration may be associated with complications. Comparisons of outcomes with and without administration of vasoconstrictors may prove challenging in the current setting, where blood pressure (BP) control is regarded as paramount and withholding vasoconstrictors may not receive approval from ethics committees.

There are many definitions of IOH but no agreed standard definition.[1-3] Nonetheless, vasoconstrictors are commonly used to restore BP to within variable pre-determined limits. The reason used as justification is to maintain "perfusion pressure" based on the premise that BP drives flow. The dogma behind such reasoning may trigger an inappropriate use of vasoconstrictors, which may adversely affect tissue blood flow as well as cause harm. As a simple example, cases of vasopressor-induced digital ischaemia in the context of haemorrhage and attempts to restore blood pressure are evident in the literature.

The author questions the logic and potential reflexive action of "treating a number" without considering the true outcomes desired and inadequately engaging with an understanding of the factors contributing to the blood pressure reading.

A systematic review of the literature was undertaken with respect to the complications attributed to IOH having specific regard to stroke, myocardial ischaemia, and postoperative cognitive dysfunction (POCD). Possible mechanisms for these are considered and whether the associated complications of IOH are caused by hypotension.

DISSECTING BLOOD PRESSURE VERSUS PERFUSION

Regulation of regional blood flow

The combined effects of neurohumoral and local metabolites are responsible for altering vessel calibre, and hence resistance with consequent effects on distribution of blood flow at the tissue level.

The effect of vascular resistance is highlighted when comparing the systemic circulation with the pulmonary circulation,[4] which is a low resistance circulation. In the normal heart, cardiac output from both left and right ventricles is the same, but because of the lower resistance in the pulmonary vasculature, this output is achieved at only one-fifth of the pressure of the systemic side. It is difficult to reconcile this observation if pressure is a driver of flow.[5]

There are multiple postulated mechanisms for regulation of blood flow across the microcirculation demonstrating increasing sensitivity from small arteries to terminal arterioles.[6] The metabolic theory proposes that as flow exceeds local tissue needs the washout of metabolites stimulates contraction of the vascular smooth muscle leading to constriction of the vessels.[7] The corollary being that where flow is inadequate to meet local demands there is a local build-up of metabolites that provokes relaxation of the vascular smooth muscle leading to vasodilatation.

Hypertension

Hypertension is a clinically well-established and well-studied disease associated with recognised complications including, but not limited to, cerebral and cardiac events.[8-10]

Normotension and blood pressure control

In the context of circulatory homeostasis, BP has been credited with a central role. Maintenance of normotension is considered to be the goal. Part of the reason for this is historical, in that the ability to measure blood pressure preceded the ability to measure flow by two hundred years.[21,22]

Notwithstanding the acceptance that tissue perfusion is the critical function of the circulation, the inability to directly measure flow led to BP becoming the surrogate for flow. The focus in medicine on targeting the metrics of a situation while losing sight of the intended outcome is a rampant problem that is often propagated by the overwhelming number of responsibilities each of us are constantly tasked with.

Hales is reputed to be the first to have measured BP by cannulating an artery in 1733.[11] Non-invasive techniques were used in the early 1800s, and in 1901 Harvey Cushing is reputed to have instituted BP monitoring as a regular feature during anaesthesia. It was not until the mid-1900s that the Fick Principle was first used to deduce flow, and it was significantly later that doppler technology matured sufficiently to be an accurate tool for measuring blood flow. It is not surprising then that blood pressure became so ingrained as an indicator of perfusion, and that circulatory function is centred on BP.

While the population mean systolic BP is around 120 mmHg, the range of "normal" is variable, with the "normal" resting systolic BP for some people being as low as 80 mmHg systolic.[12] This raises the question as to why there is such variability and how the body sets its baseline.

The existence of stretch receptors, which in the circulation have been termed baroreceptors, fuels the perception that the body controls BP. However, this warrants further consideration. For example, what is actually being sensed? Is there some kind of manometer in the circulation and if so, what is the baseline? In his article, Raven[13] poses several questions and suggests that changes in mean arterial pressure are accompanied by a resetting of the baroreceptor reflex function curve with preservation of sensitivity to acute changes in BP. While this explanation reflects neural adaptation to stimuli and re-setting of thresholds, it does not exclude the primary stimulus being volume rather than pressure.

Baroreceptors, located in the aortic arch and the carotid sinus, derive their name on the presumption that they sense pressure. However, they are stretch receptors and as such are sensitive to volume change, which is determined by stroke volume. In her article, Lau[14] correctly identifies uniaxial stretching of baroreceptor neurons mimicking the *forces* exerted on blood vessels that elicit an increase in intracellular Ca^{++} in baroreceptor neurons, but then goes on to consider pressure as if the two are interchangeable. Despite identifying that stretch reflects the forces acting on the receptors the subsequent discussion reverts to current views, centring on pressure.

The baroreceptor reflex invokes inotropic responses designed to alter contractility as well as invoking chronotropic responses affecting heart rate, the combination of which determines cardiac output. It could be argued then, that the body's primary circulatory aim is to control cardiac output and any BP changes are coincidental to alterations in cardiac output and vascular resistance.

Autoregulation

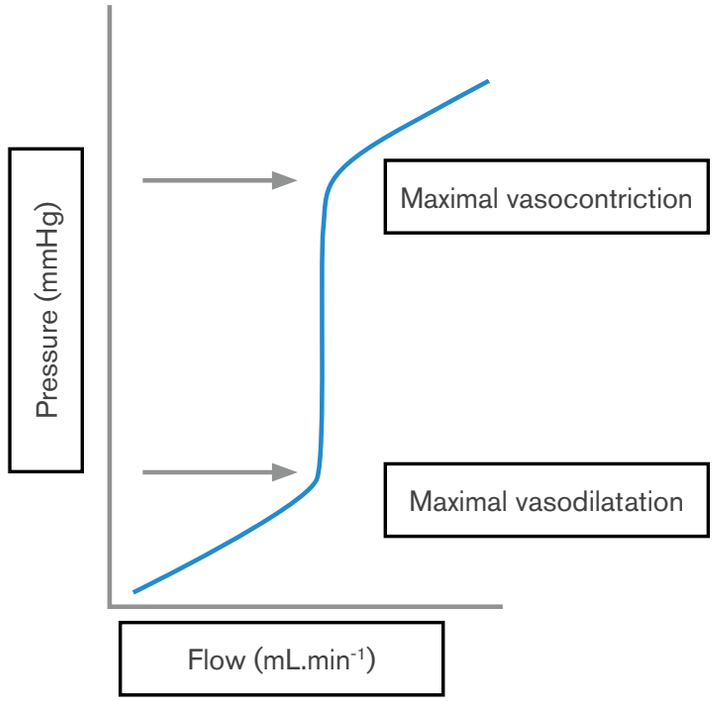
Autoregulation is described as the ability of tissues to maintain a relatively constant local regional flow within a range of "global" BP such as measured in the arm or leg.[15,16] BP measured in this way bears little resemblance to pressures and flows at the tissue level. At any given BP reading, regional flows and pressures may vary significantly depending on local tissue needs.

There are several postulated theories for the mechanism of autoregulation that include the myogenic theory, tissue metabolic theory, tissue fluid pressure theory, and renin-angiotensin theory (in the kidney only).[17] They all have in common the fact that local tissue demands invoke changes in vessel resistance to adjust flow and ensure their localised needs are met. This occurs independently of global pressure measured at any distant site.

The autoregulation argument is predicated on the assumption that pressure drives flow, which begs the question that if BP drives flow, why doesn't flow increase with increasing BP, and instead remains constant over a wide range of pressures? Could it be that BP is not the independent variable?

To illustrate this, the author has taken the liberty of interchanging the axis variables as normally depicted for autoregulation, with blood flow as the independent variable on the X-axis and pressure as the dependent variable in the Y-axis (Figure 1). This allows an alternative perspective.

Figure 1. Plot of autoregulation curve with pressure as the dependent variable



With maximal vasodilatation (minimal resistance), pressure changes little in parallel with an increase in flow and reflects changes in preload. Once flow exceeds the tissue's needs it induces increasing local vasoconstriction to progressively increase local resistance, thereby maintaining constant flow to the tissue despite the rise in BP. Finally, when the tissue has reached its maximum capacity for vasoconstriction, local flow becomes predominantly dependent on cardiac contractility.

IOH

Given the lack of an agreed definition of IOH, it is difficult to reconcile the real incidence of complications and the variable levels at which interventions occur.

Sequelae attributed to hypotension include, cerebral,[18-20] cardiac,[21] increased 30-day mortality,[22-24] and postoperative cognitive dysfunction (POCD).[25-27] The inference is that BP needs to be maintained in order to perfuse tissues and prevent these events. However, at the local tissue level, regional pressures will vary with changes in regional flow, yet the BP measured in the arm may remain constant.

Hypoperfusion secondary to hypotension is regarded as the underlying mechanism causing these outcomes. Consequently, the almost ubiquitous response to managing hypotension is to administer vasoconstrictors in order to elevate the BP back to "normal," on the assumption that flow (and thus perfusion) will increase in response. However, Newton's second law of motion reveals that a force must be applied to a body to change its momentum or direction or both. It is considered to be one of the most important laws in all of physics.[28] In determining the motion of a mass (blood), it is clear that only a force is capable of influencing the motion of any mass, and not pressure.

The interaction and balance of forces within the circulatory system determine the magnitude and direction of blood flow.[5] In this context, the administration of vasoconstrictors has a detrimental effect on blood flow[29,30] despite any rise in BP.

Another factor considered to drive flow is the pressure gradient. Vasoconstriction results in elevated pressures in vessels proximal to the constriction but a fall in pressure distally, which is observed as an increase in pressure gradient. Despite the increase in pressure gradient, flow decreases and is accompanied by an increase in flow velocity, which may of itself be detrimental.

Stroke associated with IOH

Embolism is considered the primary cause of postoperative ischaemic stroke,[31] which may be related to presence of atrial fibrillation or surgery-induced hypercoagulability in combination with vulnerable plaques in carotid or major cerebral arteries.[17,18]

IOH is considered a major contributor to hypoperfusion and cited as a factor associated with postoperative stroke,[21-23] however, no association has been found between IOH and postoperative stroke in patients undergoing non-cardiac surgery.[32-34]

On the other hand, studies have demonstrated that increased blood velocity and turbulence can damage intimal cells and dislodge plaques.[35] Consequently, it could be that in those studies where a positive association between IOH and stroke exists, that vasoconstrictors were administered resulting in increased blood velocity/momentum and turbulence promoting plaque dislodgement with subsequent embolisation.

Surgery in the beach chair position is regarded as a particular risk to cerebral hypoperfusion with dependency on adequate BP. However, the administration of vasoconstrictors may not be the solution, and indeed may be the enemy. Cho's paper[36] in which prophylactic administration of vasoconstrictors to patient undergoing shoulder surgery in the beach chair position was associated with regional cerebral oxygen desaturation on upright positioning,[36] casts doubt on the merits of vasoconstriction to maintain cerebral perfusion.

Regarding haemorrhagic stroke, the administration of vasoconstrictors could conceivably be a contributory factor by promoting velocity-related turbulence to disrupt cerebral microaneurysms and subsequent rupture.

For a description of the physics and biophysical mechanisms underpinning these processes the author directs readers to Hademenos and Massoud's book.[37]

Myocardial ischaemia associated with hypotension

Walsh et al,[24] in their retrospective analysis of 33,000 patients, examined mean arterial pressure to determine predictors of postoperative morbidity and mortality. They concluded that mean arterial pressure (MAP) less than 55 mmHg predicted adverse cardiac and renal outcomes.

The risk of myocardial injury rose markedly with duration of hypotension when MAP was less than 55 mmHg in comparison with MAPs above this level. This association is clearly demonstrated in their paper. However, these findings warrant further consideration. Those patients in ASA categories III and IV constituted the greater proportion of patients with MAP < 55 mmHg at all durations. Such patients are at higher risk as predicted by their ASA status, which may include morbidity such as pre-existing poor cardiac function, or alternatively a reflection of more extensive major surgery with accompanying hypovolaemia.

The study by Walsh et al does not consider whether vasoconstrictors were administered, and if so, at what point. Administration of vasoconstrictors may have provoked adverse effects on blood flow and contributed to increased morbidity and mortality. It needs to be established whether vasoconstrictors were used and then compare outcomes with and without vasoconstrictors.

In an article by Howell, they propose that high arterial pressures are associated with high levels of afterload and cardiac work.[10] This serves as a logical explanation for the mechanism responsible for cardiac complications observed with hypertension. The combination of the need to meet tissue oxygen demand along with vessel rigidity and narrowing, results in hypertrophy of the myocardium with subsequent impairment of critical sub-endocardial blood flow. If myocardial demand exceeds reserves, and the ability to provide the necessary flow, then susceptible patients are at risk of developing ischaemia.

While this provides an explanation in patients with chronic hypertension, the same mechanism may contribute to similar outcomes when treating BP with vasoconstrictors. Overzealous or injudicious use of vasoconstrictors intraoperatively may precipitate a cardiac event in those prone to developing ischaemia due to the increase in afterload and therefore myocardial work and myocardial oxygen demand.

Aside from the increased afterload accompanying vasoconstriction, but equally important, is the effect of increased velocity of blood flow as vessels narrow, resulting in turbulent flow with intimal stress/disruption, and potential dislodgement of plaque within the coronary circulation.

Postoperative cognitive dysfunction

Deterioration in cognitive function following anaesthesia is the subject of considerable investigation and continues to be a focus as a major health concern. Several factors have been implicated, with anaesthesia being one of the most recently identified.[26]

One of the mechanisms under investigation is adequacy of cerebral perfusion and the need to maintain BP levels, although there is little evidence to indicate the appropriate level or target BP.[11] Hirsch et al concluded that absolute or relative hypotension was not predictive of postoperative delirium but rather it was the fluctuations in BP.[26]

Fluctuations in BP under anaesthesia arise because of numerous factors, including the administration of anaesthetic medications and other vasoactive drugs, including vasoconstrictors.

Further research comparing bolus administration of vasoconstrictors with infusions may shed some insight into whether it is the swings resulting from bolus administration that are the problem, or whether such problems occur even with constant infusions, in which case vasoconstrictors may be implicated irrespective of the means of their administration.

While earlier research suggested that the anaesthesia technique used, and selection of general anaesthesia was a contributing factor to POCD, more recent research is favouring other mechanisms on the basis that there appears to be no difference in the incidence of postoperative cognitive dysfunction between general anaesthesia and spinal or epidural techniques.[38,39] One of the hypotheses used to explain this observation is that regional techniques are often supplemented by the administration of sedative medications or sub-hypnotic doses of hypnotics.

However, another factor common to both general anaesthesia and regional anaesthesia is the intention to control BP, which is essentially achieved through the use of vasoconstrictors. This may explain the absence of any difference between general anaesthesia and central neural blockade, as vasoconstrictor administration is known to be associated with swings in BP irrespective of the anaesthesia technique.

VASOCONSTRICTORS – FRIEND OR FOE?

There is undoubtedly a place for the judicious use of vasoconstrictors, such as their direct and localised application to minimise blood flow to a region. This may include their local administration to minimise surgical bleeding, as with endoscopic sinus surgery,[40] for example. Administration of vasoconstrictors to the local surgical site increases local vascular resistance and, along with concomitant administration of vasodilators, systemically reduces systemic resistance thereby diverting flow away from the surgical site.

Alternatively, vasoconstrictors may be beneficial when aiming to reduce regional flow to minimise capillary leakage, as occurs with anaphylaxis and septic shock.

However, for control of trauma or damaged organ bleeding, any increase in generalised vascular resistance tends to aggravate blood loss due to the diversion of blood flow away from the general circulation to the damaged organs, which have lost the ability to alter their local vascular resistance. Use of vasodilators is often helpful in these settings by producing generalised vasodilatation, which facilitates diversion of blood flow away from the surgical site or damaged organ.

The assumption that BP determines flow promotes the intraoperative use of vasoconstrictors to treat hypotension and restore blood pressure back to "normal," for which there are consequences.

Arguments that have been proposed to support the use of vasoconstrictors include:

- Vasoconstriction diminishes peripheral flow with consequent diversion of blood volume centrally to maintain flow to brain, heart, and kidney. However, this is not supported by the distribution of alpha-1 receptors within the circulation. These receptors are widespread in the vascular smooth muscle of genitourinary, intestinal, cardiac,[41] and brain[42] and consequently, these organs are subject to the effects of alpha-1 agonists. While vasoconstriction aims to support BP on the premise that blood flow will be maintained to the central organs, this may not be the case, and in fact may prove to be harmful.
- Diastolic filling of coronary arteries can be maintained or improved as a result of vasoconstriction, which may have a beneficial effect on cardiac output. While coronary blood flow is maximal during diastole, it is also true that any increase in afterload results in an increase in wall tension, which decreases subendocardial flow and may precipitate an ischaemic event. Furthermore, the determinants of cardiac output are preload, afterload, and contractility. Administration of vasoconstrictors increases cardiac work and consequently may disproportionately increase oxygen/blood flow demand with likely adverse effects.
- Increasing afterload leads to an increase in left ventricular end-diastolic volume (LVEDV), with consequent increase in stroke volume and cardiac output. However, any increase in the LVEDV secondary to an increase in afterload has to be the consequence of reduced systolic emptying, which suggests that cardiac output is in fact diminished. This will then be compensated by an increase in contractility (and myocardial work) resulting from the increased myocardial muscle fibre length but represents an encroachment on myocardial physiological reserves.

- Administration of vasoconstrictors to avoid reductions in blood pressure in patients with left ventricular outflow tract obstruction is thought to be of benefit with regard to maintaining cardiac output in these patients. The problem with outflow tract obstruction being a resistance to flow is that it acts as a force opposing the propulsive force of myocardial contraction. Adding any additional opposing resistive force, in series with the outflow tract obstruction, despite the aim of maintaining blood pressure on the premise that this drives flow, can only have deleterious effects on cardiac output.
- Not all vasoconstrictors are the same and demonstrate varying alpha and beta receptor effects. This is indeed a valid argument to support the judicious use, which suggests that beta receptor agonists are indicated to support cardiac contractility where this is compromised. However, the use of pure alpha receptor agonists to manipulate blood pressure is regarded by the author as dubious.

CONCLUSION

IOH is not an uncommon event under anaesthesia, predominantly being attributable to changes in vascular resistance and to some degree, myocardial depression.

Vasodilatation under anaesthesia, with concomitant hypotension, presents a low resistance circulation with blood flow accompanied by reduced myocardial work. What then is the true benefit of administering vasoconstrictors to rectify a BP reading that may not in fact reflect flow?

Vasoconstrictors have an important application in surgery to reduce blood flow to surgical areas, with the aim of minimising bleeding and optimising the surgical field. However, intravenous administration to manage BP is another matter.

Regarding the effects of vasoconstrictors in increasing vascular resistance, increasing blood flow velocity with subsequent turbulence and intimal capillary damage, fluctuations in BP, or all of these combined, further research is required to establish the risks of vasoconstrictors and whether IOH is an indication for their use.

Hopefully, challenging accepted thinking and asking questions will provoke the research necessary to support further investigation and more refined answers.

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