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REVIEW ARTICLE

Review article: Part one: Goal-directed resuscitation – Which goals? Haemodynamic targets

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Part 2: Goal Directed Resuscitation – Which Goals? Perfusion Targets will follow in the next issue.

Abstract

The use of appropriate resuscitation targets or end-points may facilitate early detection and appropriate management of shock. There is a fine balance between oxygen delivery and consumption, and when this is perturbed, an oxygen debt is generated. In this narrative review, we explore the value of global haemodynamic resuscitation end-points, including pulse rate, blood pressure, central venous pressure and mixed/central venous oxygen saturations. The evidence supporting the reliability of these parameters as end-points for guiding resuscitation and their potential limitations are evaluated.

Key words: *end-point, goal directed, perfusion, resuscitation, shock.*

Introduction

Circulatory shock is a common emergency characterized by decreased tissue perfusion and frequently accompanied by hypotension. The misconception that hypotension is necessary to define shock persists, despite evidence and international consensus recommendations to the contrary.[1] Shock can be defined as a life-threatening, generalized maldistribution of blood flow resulting in failure to deliver and/or utilize adequate amounts of oxygen, leading to tissue dysoxia.

Inadequate oxygen delivery typically results from poor tissue perfusion, but may occasionally be caused by an increase in metabolic demand.[2] If the cycle of shock is not halted, it could lead to irreversible cellular injury. Irrespective of the underlying cause of shock, the treatment includes initial resuscitation with volume expansion, vasopressors and additional therapy for multi-organ dysfunction, while concomitantly correcting the underlying cause.[3]

Rivers *et al.* demonstrated, by randomizing patients with severe sepsis or septic shock to either early goal-directed therapy or usual care, early aggressive resuscitation guided by continuous central venous oxygen saturation ($ScvO_2$), central venous pressure (CVP), and mean arterial pressure (MAP) monitoring reduced 28 day mortality rates from 46.5% to 30.5%.[4] This has seen goal-directed resuscitation, using global

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Table 1. Global haemodynamic targets

Modality	Principle	Advantages	Disadvantages
Blood pressure	The pressure waveform of the arterial pulse is transmitted through a column of fluid to provide a systolic and diastolic pressure.	Universally available. Reliable/reproducible. Cheap. Continuous measurement.	Variation in normal blood pressure. Blood pressure may not predict perfusion.
Central venous pressure	Pressure transduction from the superior vena cava may reflect the preload state.	Easily measured. Trends possibly useful.	Poor correlation between assessments of pressure and preload under many conditions.
Mixed venous oxygen saturation (SvO_2)	Gold standard measure of the balance between oxygen delivery (DO_2) and demand. Decreases when DO_2 is compromised or systemic oxygen demands exceed supply.	Gold standard measure of venous oxygen saturation.	Requires a pulmonary artery catheter with its associated risks.
Central venous oxygen saturation ($ScvO_2$)	$ScvO_2$ provides a surrogate measure of SvO_2.	Easily measured. Reliable alternative for SvO_2.	Requires central access. At times not a reliable measure of mixed venous blood.
Arterial pulse waveform analysis	Continuous cardiac output derived from interpretation of arterial pressure waveform, which is proportional to stroke volume.	Minimally invasive. Continuous cardiac output. Additional information, including volume status, may be generated.	Reliability affected by arrhythmias. Extremes of vascular tone may affect validity of measurements.
Oesophageal Doppler monitoring	Measures blood velocity and with a given aortic cross-sectional area allows for determination of cardiac output.	Real-time cardiac output.	Requires expensive equipment. Training and credentialing required.
Echocardiography	Uses standard ultrasound techniques to provide real-time images of the heart.	Real-time information on both cardiac anatomy and function.	Requires expensive equipment. Training and credentialing required.

haemodynamic targets, regain popularity; however, it is possible this strategy suffers from being poorly reflective of changes at the microcirculatory or cellular level.

The art of managing shock involves timely intervention and resuscitation to maintain acceptable haemodynamic parameters, while concurrently defending systemic perfusion. There remains a fine balance between oxygen delivery and consumption, and when this is perturbed, an oxygen debt may ensue.[5] Use of a range of resuscitation targets/end-points may facilitate early detection and appropriate management of shock (Table 1). In part one of this narrative review, the value of the global haemodynamic resuscitation end-points is considered, and in part two, newer technologies that may have a valid application in the ED are evaluated.

Methods

MEDLINE (1990 to July 2011), EMBASE (2000 to July 2011) and CINAHL (1998 to July 2011) databases were searched using MeSH and key terms for (targeted resuscitation OR goal directed therapy OR resuscitation end-points OR resuscitation guidelines) and (intensive care OR critical care OR emergency medicine). The search was limited to human and English language studies, including clinical trials, cohort studies, case series and reviews. A manual search of the reference lists of all the retrieved articles was conducted to identify any further relevant papers. Abstracts were screened by the authors who then obtained the relevant full-text articles. This process has facilitated the writing of a narrative review.

Blood pressure

Targeting blood pressure in the management of the shocked patient is intuitive. Most clinicians use the maximal (systolic) and minimal (diastolic) arterial pressure to assess circulatory status. These pressures are easily established by either invasive or non-invasive means. The arterial pressure wave provides information from both its steady and pulsatile components. The steady component is MAP = diastolic pressure + 1/3 (systolic pressure – diastolic pressure), which is considered constant from aorta to peripheral large arteries. It is apparent from this formula that diastolic pressure contributes substantially more to MAP than the systolic pressure. Non-invasive oscillometric devices measure MAP (point of maximal oscillation), where systolic and diastolic pressures are derived from various device-specific commercial algorithms. This measurement might be inaccurate in patients with alterations in peripheral vascular tone secondary to sympathetic compensation or vasoactive agent use.[6] Therefore, patients with circulatory shock are probably better served with an intra-arterial catheter to obtain more reliable arterial pressure measurements.

There is no universally accepted goal MAP in the resuscitation of shock. Indeed, the optimal MAP probably depends not only on the type of shock, but also the individual patient and their pre-existing physiology. Current septic shock resuscitation guidelines recommend an MAP of 65 mmHg or greater be achieved and maintained, in order to avoid additional organ hypoperfusion.[7] Targeting supranormal physiology, by increasing the MAP to 85 mmHg or more, does not result in improved tissue oxygenation or regional perfusion.[8]

It is particularly difficult to establish an ideal target blood pressure in the management of haemorrhagic hypovolaemic shock. Several animal studies have demonstrated increased blood loss with restoration of normal blood pressure before surgical control of bleeding.[9] Fluid resuscitation to achieve a 'normal' MAP may not only result in a dilutional coagulopathy, but enhanced pressure might be deleterious to thrombus formation.[5] An animal trial has identified reduced oxygen delivery in the setting of normotensive resuscitation of haemorrhage shock.[10] In a landmark trial, Bickell *et al.* demonstrated improved survival in hypotensive patients, following penetrating torso trauma, who received delayed resuscitation compared with those undergoing immediate normotensive resuscitation.[11] However, this has not been a consistent finding in trauma, with some studies failing to demonstrate a disadvantage with normotensive resuscitation.[12] Therefore, the optimal blood pressure goal remains elusive, but hypoperfusion and over-resuscitation are to be avoided.

The shock index, described by the heart rate divided by the systolic blood pressure, might be more useful than either parameter in isolation, with values falling outside the normal range (0.5–0.7) being supportive of shock. Although an elevated shock index heralds an increased risk of mortality, its sensitivity remains low and it cannot be used in isolation to target shock therapy.[2]

Central venous pressure

Central venous pressure is commonly used as a measure of preload in the care of the critically ill patients, and has been included in many algorithms designed to achieve optimal resuscitation.[13] Based largely on the early goal-directed therapy trial completed by Rivers *et al.*,[4] the Surviving Sepsis Campaign guidelines[7] recommend a CVP of 8–12 mmHg as the 'goal of the initial resuscitation of sepsis-induced hypoperfusion'. Despite these guidelines, the reliability of CVP measurements as an indicator of volume status continues to be controversial. Marik *et al.*, in a recent systematic review (which included 803 patients in 24 studies), demonstrated there is a very poor relationship between CVP and blood volume; furthermore, this analysis concluded that the changes in CVP were unable to predict responses to fluid challenges.[13] Many physicians still accept that a very low CVP measurement and in the presence of low arterial pressure is probably indicative of hypovolaemia and predicts the need for volume expansion. The converse does not, however, follow: an elevated CVP does not always indicate an adequate intravascular volume status. CVP is affected by a myriad of intrinsic and extrinsic factors, including patient positioning, intrathoracic pressures, heart rate, contractility, myocardial and venous compliance.[14] If CVP is chosen as a target, it is the pressure just at the onset of the c-wave, before closure of the tricuspid valve and the beginning of ventricular systole, which best represents the atrial pressure used as a surrogate for ventricular end-diastolic pressure. The 2006 International Consensus Conference on haemodynamic monitoring in shock recommended that preload measurement alone not be used to predict fluid responsiveness.[1] These shock guidelines suggested that low filling pressures should result in immediate fluid

resuscitation and that a fluid challenge should be performed (250 mL over 10 min) to predict fluid responsiveness with the intention of achieving an increase in CVP of greater than 2 mmHg.

Central and mixed venous oxygen saturations

Central and mixed venous oxygen saturations refer to the haemoglobin saturation of blood in the superior vena cava and pulmonary artery, respectively.[15] Rearranging the Fick equation demonstrates venous oxygen content (CvO_2) is determined by the difference between arterial oxygen content (CaO_2) and oxygen consumption (VO_2).

$$\text{Cardiac output } (CO) = CaO_2 - CvO_2 / VO_2$$

$$CvO_2 = CaO_2 - VO_2 / CO$$

It is apparent from this relationship that if haemoglobin concentration, VO_2 and arterial saturation are constant, then changes in mixed venous oxygen saturation (SvO_2) will be a reflection of CO. SvO_2 is true mixed venous saturation providing an indication of global oxygen extraction. In order to obtain an SvO_2 measurement, a pulmonary artery catheter is required and this is neither practical nor justified in the ED. Although measurements of $ScvO_2$ often mirror those of SvO_2, they are not identical.[16] $ScvO_2$ could be considered a surrogate for SvO_2; however, $ScvO_2$ is only representative of the perfusion of those organs drained through the superior vena cava and excludes those served by the inferior vena cava. Under normal physiological conditions, $ScvO_2$ is slightly lower than SvO_2, but the converse is true in septic shock.[17] Reinhart *et al.* were able to demonstrate that $ScvO_2$ changed in parallel with SvO_2 in 90% of the instances, where the change was greater than 5%.[18] Furthermore, it is important to recognize that $ScvO_2$ from a femoral vein is not reliable and should not be used routinely to guide resuscitation.[19]

It is widely acknowledged that a decreased $ScvO_2$ obtained from a central venous catheter might reflect an oxygen demand/supply mismatch and therefore be indicative of global tissue hypoxia.[20] There is a growing body of evidence supporting the use of $ScvO_2$ as an indicator of shock severity.[17] Decreased values have been documented in cardiogenic shock.[21] Madsen *et al.* produced human experimental work demonstrating that reduced central blood volume is better reflected in $ScvO_2$, than it is by the CVP.[22] There have been several reports of the value of $ScvO_2$ in guiding resuscitation in traumatic hypovolaemic shock[23] and importantly the futility of targeting supra normal levels of tissue oxygenation.[24] Rivers *et al.* employed 'early goal-directed therapy' to ensure a balance between systemic oxygen delivery and oxygen demand in septic patients.[4] This balance was achieved through manipulation of cardiac preload, contractility and afterload. The process relied heavily on $ScvO_2$-directed interventions and despite this study being the subject of much debate, it has seen the inclusion of $ScvO_2$ in the 'Surviving Sepsis Campaign' guidelines.[25] Therefore, in the appropriate clinical setting a low $ScvO_2$ value may be an important indicator of inadequate systemic oxygen delivery. It does not, however, provide an aetiology for the inadequacy or indeed a therapeutic solution. Furthermore, the recording of either a normal or high $ScvO_2$ value does not guarantee adequate tissue oxygen delivery.[26] Central venous catheter insertion is common practice in Australasian EDs and has the potential to generate continuous or intermittent $ScvO_2$ measures depending on the commercial brand of catheter used. Interestingly, the Australasian resuscitation of sepsis evaluation (ARISE) group demonstrated that Australian and New Zealand patients presenting with sepsis to the ED are not routinely managed with a protocolized, $ScvO_2$-directed resuscitation strategy.[27] This group of investigators are currently evaluating the benefit of an early goal-directed protocolized approach to sepsis that includes $ScvO_2$.

Until further results are available, targeting an $ScvO_2$ of 70–75% would seem a reasonable resuscitation goal with a sound scientific rationale underpinning this strategy.

Continuous arterial pulse waveform analysis

There are significant limitations with the use of static preload indicators, such as CVP measurement. The use of pulmonary artery catheters, previously considered the gold standard, has steadily declined in many Australasian critical care centres and has not been widely used in the ED. On this background, there is growing enthusiasm for minimally invasive continuous arterial pulse waveform analysis, which is both an attractive and readily available technology. This

methodology relies on an intra-arterial catheter and in some cases a central venous catheter to provide continuous CO monitoring.[28]

The PiCCO device (Pulsion Medical Systems, Munich, Germany) utilizes arterial pulse contour analysis calibrated by transpulmonary thermodilution using a central line with a temperature sensor located on its distal lumen and a proximally sited arterial catheter. The CO derived from the cold-saline thermodilution is used to calibrate the arterial pulse pressure contour, which then facilitates continuous CO monitoring. Proprietary, computer-based mathematical analysis of the thermodilution curve can then provide 'estimates' of cardiac filling volumes (Global end diastolic volume), intrathoracic blood volume and extravascular lung water. The LidCO/PulseCO system (LidCO, Cambridge, UK) also uses pulse contour analysis to estimate stroke volume (calibration with lithium dilution). The lithium dilution method has the advantage of only requiring a peripheral vein catheter and a peripheral arterial line; however, it does not provide cardiac volumes or extravascular lung water measures.[29] The Vigileo/FloTrac system (software version 1.01; Edwards Lifesciences, Irvine, CA, USA) was introduced into clinical practice in 2005 and determines CO, without calibration, by analysis of the arterial pulse wave obtained from a standard peripheral arterial cannula without the requirement for central access. There were initial difficulties with the accuracy of the proprietary algorithm; however, recent studies have validated its accuracy to within 30% of values obtained from pulmonary artery catheterization.[30]

Positive pressure ventilation in a patient without spontaneous respiratory effort is associated with a cyclical increase in right atrial pressure on inspiration. In volume-depleted patients, right ventricular (RV) filling will then consequently decrease in a cyclical manner. This cyclical variation in RV filling subsequently induces a variation in left ventricular (LV) filling. This variation in LV filling will ultimately result in a cyclic variation in LV stroke volume and arterial pulse pressure in volume-depleted patients.[31]

Variations in LV stroke volume, which are termed stroke volume variation (SVV), are calculated as the maximal to minimal stroke volume values over their mean and measured over a defined time interval (e.g. 20 s), have proved useful in assessing response to volume loading.[32,33] Michard *et al.* demonstrated systolic pressure variations of 13% or more in mechanically ventilated septic patients with a tidal volume of 8 mL/kg were highly sensitive and specific for preload responsiveness.[34] A recent meta-analysis, including 23 studies with 568 patients, concluded that SVV is a good predictor of fluid responsiveness in critically ill patients.[32] Arterial pulse pressure variation (PPV), calculated in a similar way as SVV, also accurately predicts preload responsiveness, with a $\geq$13% PPV predicting a $\geq$15% increase in CO following a 500 mL fluid challenge.[31] Recent animal models favour the use of PPV over traditional pressure-derived volumes obtained using pulmonary artery catheters.[35]

There is a scarcity of recommendations with respect to using SVV and PPV as resuscitation targets.[31] However, given their minimal invasiveness and potential to predict volume status or response to therapy, an expanding role for these technologies in guiding resuscitation could be anticipated. It is important to appreciate that these parameters require a constant R–R interval and therefore lose their predictive value under conditions, such as atrial fibrillation. Furthermore, they also require constant tidal volumes, and if there is breath to breath variation, such as may occur with occasional spontaneous breaths, the accuracy may be significantly compromised.[36]

Passive leg raising to 45 degrees is a reversible manoeuvre that mimics rapid volume expansion and has recently emerged as an alternative method for predicting fluid responsiveness. The passive leg-raising test is the only method that has been repeatedly shown to be reliable in predicting volume responsiveness in spontaneously breathing patients.[37] Appropriate utilization of this test requires a real-time assessment of its effects on systemic blood flow. Preau recently demonstrated that changes in stroke volume, radial pulse pressure and peak velocity of femoral artery flow induced by passive leg raising are accurate indices for predicting fluid responsiveness in non-intubated patients.[38] This is potentially an under-utilized technique that allows the emergency physician to rapidly and reversibly provide a volume challenge that could then provide a volume target.

Doppler monitoring

Oesophageal Doppler monitoring was first introduced in the 1970s as a minimally invasive means to measure aortic blood flow and was then refined in 1989.[39] Doppler allows for the determination of the mean velocity of blood in the descending thoracic aorta during ventricular systole. The mean systolic blood velocity together with an estimate of aortic diameter is then used

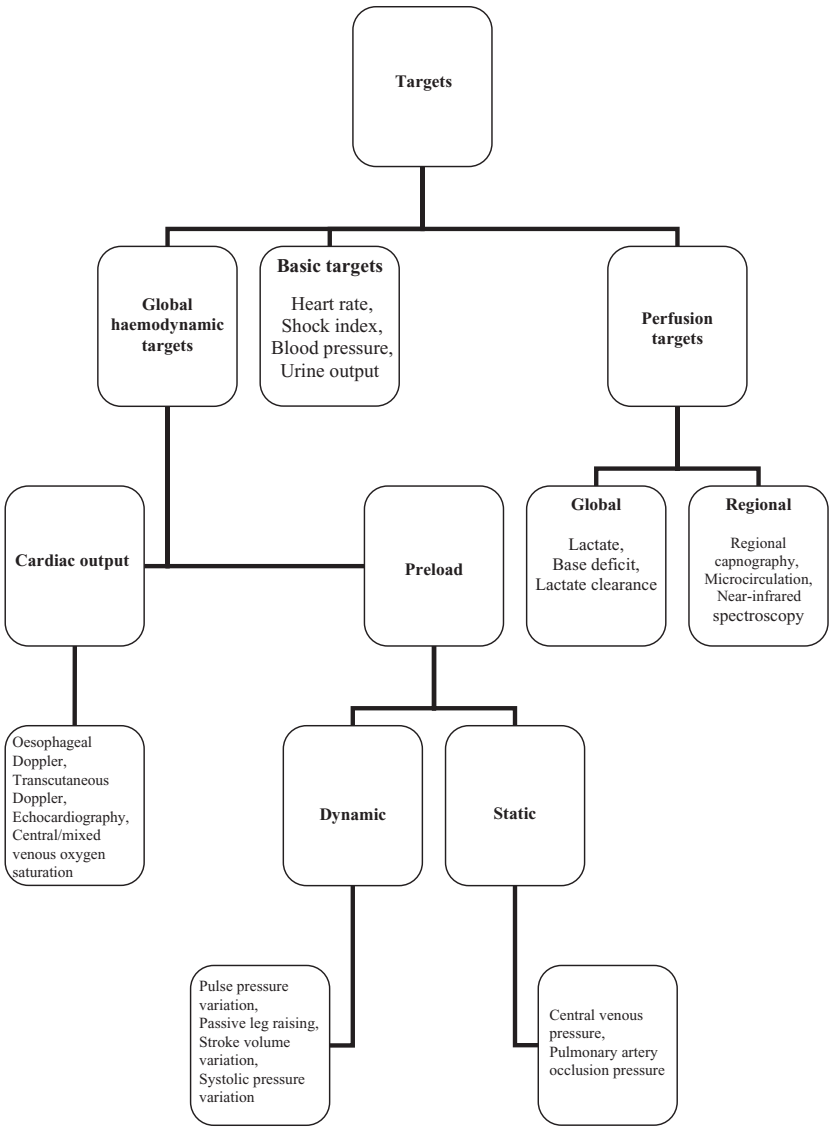

Figure 1. Overview of global and regional perfusion targets.

to reliably establish LV stroke volume and hence CO (CO = HR × SV, where HR stands for heart rate, and SV for stroke volume).[40,41]

Intraoperatively, it has been effectively used to direct fluid administration, resulting in a significant reduction in duration of hospital stay and an improved outcome.[42]

There are several limitations to the use of oesophageal Doppler. Aortic cross-sectional area must be accurately assessed because even small changes in aortic area can significantly affect CO determinations. Furthermore, oesophageal Doppler measures blood flow in the descending aorta, and neglects flow to the aortic arch vessels. The descending aortic blood flow is approximately 70% of CO with 30% going to the cephalic blood vessels, and therefore a correction factor of 30% is required to account for blood flow to the arch vessels. Although valid in young healthy patients, this ratio might not be constant because of changes in metabolic activity between different organs, or hemodynamic status. Numerous studies in the anaesthetic/operative setting have demonstrated improvement in patient outcome with oesophageal Doppler goal-directed fluid therapy.[43] Although the accuracy depends on image quality, sample site, angle of insonation and the velocity

signal-to-noise ratio.[44] To date, there are no studies employing oesophageal Doppler in the emergency room, but certainly the concept of goal-oriented therapy directed by a non-invasive CO measurement is attractive.

Recently, a prospective, observational cohort study of 116 ED patients assessed the value of non-invasive transcutaneous Doppler CO monitoring using USCOM-1A (Uscom, Sydney, Australia) and trans-thoracic echocardiography.[45] Unfortunately, the USCOM-1A haemodynamic monitoring technology showed poor correlation and agreement with standard trans-thoracic echocardiography measures of cardiac function. The utility of USCOM-1A in the management of critically ill patients therefore remains to be determined. It is likely that this technology will further be developed and potentially provide a simple, non-invasive guide to direct resuscitation.

Echocardiography

Echocardiography is unique in that it provides real-time information on both cardiac anatomy and function.[46] Echocardiography could facilitate rapid diagnosis as to the cause of shock in the haemodynamically compromised patient. This technology facilitates global assessments of LV and RV function; furthermore, ventricular volume, ejection fraction and CO may all be determined.[47] Echocardiography also detects segmental wall motion abnormalities, pericardial effusions or cardiac tamponade, whereas the use of Doppler technology allows atrial filling pressures to be reliably determined.[48] The trans-thoracic approach is non-invasive, highly portable and easily performed providing valuable information rapidly in the shocked patient; however, it might be limited by failure to provide adequate image quality. The trans-thoracic approach failure rate, in the critical care setting, has been estimated to be as high as 40%.[49] Continual technological advances, including contrast and digital technology, are resulting in greater success with trans-thoracic echocardiography. This together with the non-invasive or minimally invasive nature of echocardiography makes echocardiography a highly attractive modality for assessing the shocked patient. Bruch *et al.* reported a prospective study of surgical ICU patients where echocardiography was shown to alter management in 43% patients (n = 115).[50] Alterations in management induced by the echocardiography findings included administration of fluids and initiation or discontinuation of inotropic agents. There have been several attempts to define the training requirements for non-cardiologists using echocardiography. Although there is as yet no consensus, the training required to competently perform a focused study is very achievable for the acute care specialties.[51,52] Almost certainly echocardiography represents the new 'global haemodynamic frontier' for the acute care physician to target resuscitation.

Conclusion

Successful management of shock requires early detection and correction of circulatory insufficiency. Not only must global CO and oxygen delivery be adequate, it should also be appropriately distributed to meet the metabolic demands, hence preventing the development of multi-organ dysfunction with its subsequent morbidity or even death. Goal-directed therapy using estimates of global oxygen supply–demand balance has been shown to improve survival among patients in shock states. It is likely that several modalities need to be employed (Fig. 1) and quite probably it is the simple step of establishing and striving for physiologically plausible goals that results in improved outcomes. The ideal modality of measuring global perfusion or indeed the target range still remains elusive.

Competing interests

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REVIEW ARTICLE

Review article: Part two: Goal-directed resuscitation – Which goals? Perfusion targets

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Abstract

Haemodynamic targets, such as cardiac output, mean arterial blood pressure and central venous oxygen saturations, remain crude predictors of tissue perfusion and oxygen supply at a cellular level. Shocked patients may appear adequately resuscitated based on normalization of global vital signs, yet they are still experiencing occult hypoperfusion. If targeted resuscitation is employed, appropriate use of end-points is critical. In this review, we consider the value of directing resuscitation at the microcirculation or cellular level. Current technologies available include sublingual capnometry, video microscopy of the microcirculation and near-infrared spectroscopy providing a measure of tissue oxygenation, whereas base deficit and lactate potentially provide a surrogate measure of the adequacy of global perfusion. The methodology and evidence for these technologies guiding resuscitation are considered in this narrative review.

Key words: *end-point, goal directed, perfusion, resuscitation, shock.*

See also Part one: Goal-directed resuscitation – Which goals? Haemodynamic targets in EMA 2012; 1: 14–22.

Introduction

Traditional assessment of oxygen delivery has largely relied on the global measures of perfusion, such as cardiac output, mean arterial blood pressure and central venous oxygen saturations. These parameters were considered in part one of this series. However, these measures remain crude predictors of tissue perfusion and oxygen supply at a microcirculatory or cellular level. Many patients appear to be adequately resuscitated based on normalization of global vital signs; however, they might in fact have occult hypoperfusion with ongoing tissue acidosis. In part two, this review of goal-directed resuscitation end-points will focus on measures of global and cellular perfusion (Table 1). There are far fewer technologies available to the clinician in this category; however, they could constitute the new frontier in shock diagnosis and goal-directed resuscitation.[1]

Methods

MEDLINE (1990 to April 2010), EMBASE (2000 to July 2011) and CINAHL (1998 to July 2011) databases were searched using MeSH and key terms for (targeted

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Table 1. Global and regional perfusion targets

Modality	Principle	Advantages	Disadvantages
Near-infrared spectroscopy	Near-infrared light penetrates soft tissue and is absorbed by oxygenated chromophores. Tissue oxygen saturation (StO_2) is derived from a complex algorithm of the ratio of absorption between the individual chromophores.	Non-invasive. Skeletal muscle StO_2 shows good correlation with measurements of systemic oxygen delivery. Minimal training required.	Equipment expensive. Not yet universally accepted.
Sidestream dark field video microscopy	Direct visualization of the microcirculation using scattered green light that is absorbed by haemoglobin of red blood cells contained in superficial vessels.	Density and perfusion of sublingual vessels correlate with shocked state.	Image interpretation time-consuming. Not universally accepted. Requires training. Equipment expensive.
Regional capnometry	Sublingual and gastric capnometry utilize increases in tissue PCO_2 to reflect an abnormal oxygen delivery state.	Minimally invasive. Immediate results.	Equipment is being refined. Significant variability in tissue. PCO_2 levels within normal individuals.
Lactate	Inadequate oxygen delivery to the tissues results in significant metabolic acidosis.	Easily measured. Inexpensive. No training requirement.	Serum lactate affected by factors other than inadequate tissue perfusion.
Base deficit	Base deficit is a surrogate marker of metabolic acidosis. Inadequate tissue oxygen delivery results in a metabolic acidosis.	Easily measured. Inexpensive. No training requirement.	Shock not the only factor that alters base deficit 0. Predictive value varies depending on patient population.

resuscitation OR goal directed therapy OR resuscitation end points OR resuscitation guidelines) and (intensive care OR critical care OR emergency medicine). The search was limited to human and English language studies, including clinical trials, cohort studies, case series and reviews. A manual search of the reference lists of all the retrieved articles was conducted to identify any further relevant papers. Abstracts were screened by the authors who then obtained the relevant full-text articles. This process has facilitated the writing of a narrative review.

Lactate

The basis for lactate measurement, as an indicator of severity in circulatory shock, is that hypoperfusion results in inadequate oxygen delivery with ensuing mitochondrial hypoxia and hence anaerobic glycolysis with lactate production. In patients with shock, the blood lactate concentration varies in proportion to the ongoing tissue oxygenation deficit. Serial measures, demonstrating reduction in blood lactate concentration, may indicate restoration of oxygen delivery with the institution of effective resuscitation.[2]

In both experimental and clinical situations, serum lactate levels have been well correlated with tissue hypoperfusion. Furthermore, elevated blood lactate levels in shock and their subsequent failure to normalize during resuscitation are associated with both increased morbidity and mortality providing valuable information with respect to adequacy of resuscitation.[3] Lactate trends over time are, however, more predictive of mortality than initial values.[4,5] Lactate measured in the prehospital setting has demonstrated a clear relationship with outcome.[6] It is important to recognize that other factors related to critical illness might affect lactate levels and must be considered when interpreting lactate results. Lactic acidosis can result from an overproduction or decreased hepatic removal of lactate despite maintained oxygen delivery to the tissues.[7] Other aetiologies include: hypoglycaemia/glycogen storage disease, diabetes mellitus, ethanol, hepatic failure, malignancy and drugs (biguanides and nucleo-

side analogue reverse transcriptase inhibitors). A recent prospective comparison of arterial, venous and capillary lactate levels in septic shock patients demonstrated an excellent correlation between arterial and central venous lactate (0.992). They also demonstrated a good correlation between arterial and capillary lactate levels (0.945), suggesting these three measures are interchangeable.[8]

Blow *et al.* reported that early recognition and aggressive resuscitation targeting correction of high serum lactate reduced morbidity and improved survival in severe trauma patients.[9] The results of a recent large multicentre randomized controlled trial, which included 300 patients, compared two strategies of early sepsis resuscitation and suggest that targeting a 10% lactate clearance generates survival rates at least as good as using $ScvO_2$ monitoring as the resuscitation end-point.[10] In this study, patients in the group resuscitated to a lactate clearance $\geq$10% had a 6% lower in-hospital mortality compared with those resuscitated to a $ScvO_2$ of $\geq$70%. The authors conclude that their data support the substitution of peripheral venous lactate measurements as a safe and efficacious alternative to spectrophotometric catheter-generated $ScvO_2$ measurement-guided sepsis resuscitation. The current available evidence would support the use of serial venous lactate measurements and its reduction as an appropriate resuscitation goal in shock. The emergency physician must consider the potential limitations when utilizing this strategy.

Regional capnometry

The rationale underlying the use of regional carbon dioxide (CO_2) monitoring, as a modality to evaluate shock, is that CO_2 tissue levels increase rapidly in the presence of hypoperfusion. The increase in CO_2 follows intracellular bicarbonate buffering of excess hydrogen ions generated by anaerobic metabolism during tissue dysoxia.[11] The finding that the splanchnic vascular bed is affected very early in shock and tracks recovery with resuscitation generated great interest in gastric tonometry as a means of following and detecting early signs of tissue hypoperfusion.[12] In order to measure gastric CO_2, a specially designed nasogastric tube with a CO_2 permeable silicone balloon is placed into the stomach. CO_2 from the gastrointestinal tract diffuses into the normal saline-filled balloon over a period of 20–90 min (alternatively a gas-filled balloon technique can be employed), and the CO_2 of the balloon content is then measured.[13] This $PaCO_2$ measurement together with arterial bicarbonate facilitates calculation of intramucosal pH (pHi) by a modified Henderson–Hasselbalch equation.[14] Gastric intramucosal acidosis (pHi) and intramucosal hypercarbia (PCO_2 gap) have been demonstrated to be a marker of gastric mucosal dysoxia and a predictor of morbidity and mortality in critically ill patients.[15–19] The CO_2 gap is the difference between mucosal (gastric or sublingual) and the arterial CO_2 pressure.[20] Despite initial optimism, gastric tonometry has never been universally adopted into clinical practice. Gastric tonometry is logistically difficult and this might be a significant factor inhibiting widespread use of this technology.[21] There has only been a single study utilizing gastric pHi as a therapeutic index of tissue oxygenation, demonstrating that therapeutic interventions guided by gastric tonometry were able to improve survival.[15]

Sublingual capnometry, however, has more recently been proposed as a measure of regional hypoperfusion that is technically more easily applied than gastric tonometry. The system for measuring sublingual PCO_2 ($PslCO_2$) consists of a disposable PCO_2 sensor attached to a battery-powered handheld instrument (CapnoProbe N80, Nellcor, CA, USA). A CO_2 sensing optode containing a fluorescent indicator is excited by the light conducted through an optical fibre, which then transmits the fluorescent emission back to the instrument where they are converted to a numerical value of PCO_2. The PCO_2 sensor is positioned in the sublingual space to facilitate CO_2 measurement.[12,21] Jin *et al.* hypothesized that the sublingual mucosa could represent an appropriate site for measurement of tissue PCO_2.[22] Although the internal carotid artery provides lingual blood flow, it performs physiologically as if it was part of the 'splanchnic circulation'. It has since been demonstrated that blood flow to the tongue and splanchnic bed decline in parallel when subjected to decreased perfusion pressures.[22] Marik demonstrated excellent correlation between the gastrointestinal mucosal PCO_2 and $PslCO_2$ in a diverse collection of critically ill patients.[13] Furthermore, several authors have demonstrated an increase in $PslCO_2$ directly correlated with decreases in arterial pressure and cardiac index during haemorrhagic or septic shock.[23,24]

In a study of 46 critically ill patients admitted to the ED or ICU, the authors found higher $PslCO_2$ values in patients with circulatory shock, which were also highly correlated with arterial lactate concentrations. When $PslCO_2$ exceeded a threshold of 70 mmHg, its positive predictive value for the presence of physical signs of

circulatory shock was 1.00. When it was <70 mmHg, it predicted survival with a predictive value of 0.93.[23]

Marik[13] and Rackow *et al.*[25] measured $PslCO_2$ in haemodynamically unstable patients during the first 24 h of their ICU admission. Independently, both studies demonstrated that the $PslCO_2$ gap was statistically higher in non-survivors than in survivors. A further study confirmed that the $PslCO_2$ gap is a useful prognosticator, observing that patients with an initial $PslCO_2$ gap greater than 25 mmHg had higher mortality rates than those with a gap less than 25 mmHg.[26] In their study, despite optimization of traditional haemodynamic end-points, the $PslCO_2$ gap decreased but importantly remained higher in the non-survivors than in the survivors.

In a prospective, observational trial of 86 trauma patients, the authors used sublingual capnography as an adjunct to diagnose the severity of haemorrhagic shock and monitor adequacy of resuscitation.[27] $PsLCO_2$ was equivalent to lactic acid levels and base deficit in predicting the severity of shock and more importantly was able to predict survival in hypotensive trauma patients. $PsLCO_2$ has also been shown to correlate with volume of blood loss in penetrating trauma patients.[28]

There is currently a commercially available device: the MI-720 CO_2 electrode (Microelectrodes: Londonderry, NH, USA), which has been used in many of the described studies.[29]

Sublingual capnometry might therefore be considered a non-invasive tool allowing the assessment of tissue perfusion in shocked patients. However, despite the work to date, widespread adoption of sublingual capnometry monitoring in the ED has been limited by the requirement for new equipment, and difficulties with obtaining accurate and reproducible measurements.[30,31]

The scientific rationale for measuring $PsLCO_2$ appears robust, but further studies are required to determine the clinical utility of $PslCO_2$ as an end-point guiding resuscitation.

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) offers a novel monitoring strategy for use in the critically ill patients, measuring the saturation of haemoglobin in the skeletal muscle and providing an index of perfusion.[32,33] NIRS utilizes fibre-optic light (700–1000 nm) to non-invasively determine the percentage of oxygen saturation of chromophores (e.g. haemoglobin, myoglobin and cytochrome aa3 oxidase) based on spectrophotometric principles.[34] Tissue oxygen saturation (StO_2) is derived from a complex algorithm of the ratio of absorption between the individual chromophores.[32] Unlike pulse oximetry, NIRS measures not only arterial, but also venous oxyhaemoglobin saturation at the microcirculatory level. This measurement, therefore, is a reflection of both oxygen delivery and oxygen consumption of the tissue bed sampled.[33]

The InSpectra StO_2 Tissue Oxygenation Monitor (Hutchinson Technology, Hutchinson, MN, USA) is the currently available monitoring system that measures an approximated value of per cent haemoglobin StO_2 through a sensor placed on the thenar eminence. It illuminates tissue approximately 15 mm below the sensor with four calibrated wavelengths of near-infrared light, and its algorithm accounts for total haemoglobin differences between patients, as well as light-scattering variables, such as fat and tissue density.[35]

Lima *et al.* found that patients who consistently exhibited low StO_2 levels following an initial resuscitation had significantly worse organ failure than did patients with normal StO_2 values. Interestingly, they demonstrated that StO_2 changes had little relationship to global haemodynamic parameters.[36] In septic shock patients, StO_2 below 78% have been shown to be associated with an increased mortality at day 28. Further investigations are required to determine whether the goal-directed correction of an impaired level of StO_2 improve the outcome of these patients.[37] The use of a vascular occlusion test in combination with StO_2 analysis has been proposed to enhance the value of NIRS. Various parameters that can be derived from this simple test are shown in Figure 1. The StO_2 occlusion slope is a function of tissue oxygen consumption. The slope is also affected by the amount of metabolically active tissue in the region being sampled and the volume of haemoglobin in the tissue. Following release of the vascular occlusion, a StO_2 reperfusion slope is then generated allowing for evaluation of tissue flow reperfusion and vascular recruitment.

Several studies have found StO_2 occlusion slopes to be abnormal in shocked patients and to differentiate between survivors and non-survivors in severe sepsis.[36,38,39] Nanas *et al.* demonstrated that NIRS can detect tissue oxygenation deficits and impaired microvascular reactivity in critically ill patients, as well as discriminate among groups with different disease severity.[40] Lima *et al.* demonstrated in a prospective, observational study that low StO_2 at the completion of early goal-directed therapy is associated with worse outcome. They performed repeated StO_2 measurements in critically ill patients to test the hypothesis that the persis-

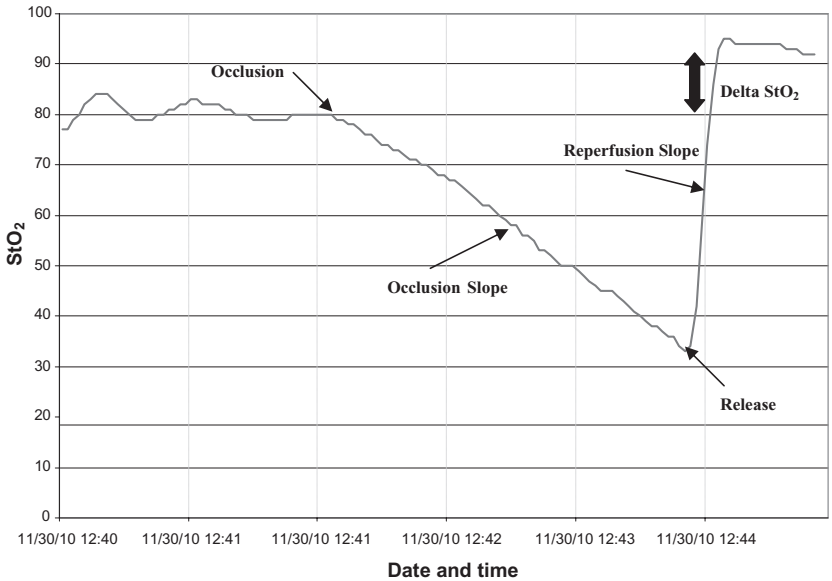

Figure 1. Vascular occlusion test on healthy subject using the Hutchinson Technology InSpectra StO_2 Tissue Oxygenation Monitor (Model 650; Hutchinson Technology, Hutchinson, MN, USA). Graph generated using InSpectra StO_2 Case Graphing software (Hutchinson Technology, Hutchinson, MN, USA). (Monitor supplied courtesy of Critical Assist Australia.) StO_2, tissue oxygen saturation. (—) InSpectra StO_2.

tence of low StO_2 levels during the early resuscitation phase of therapy is associated with more severe organ dysfunction. An important finding was that patients who failed to normalize StO_2 during early treatment in the ICU subsequently had more severe organ dysfunction and disease severity, as determined by Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. The authors also concluded that StO_2 abnormalities are more closely related to regional perfusion than macrohaemodynamics.[36]

The Delta StO_2 (Fig. 1) has also been postulated as a measure of microcirculatory reactivity.[41] In addition, these monitors provide tissue haemoglobin index, a measure of the amount of haemoglobin in the tissue being sampled in arbitrary units. A recent study hypothesized that NIRS-derived StO_2 could assist in identifying shock in casualties arriving to a combat support hospital, as well as predict the need for life-saving interventions and blood transfusions. Arriving casualties had NIRS-derived StO_2 recorded in the ED. The measurements included minimum StO_2, initial 2 min averaged StO_2 and tissue haemoglobin index for all 147 casualties studied. NIRS-derived StO_2 values were able to predict the need for blood transfusion in casualties who initially seemed haemodynamically stable (as defined by a systolic blood pressure greater than 90 mmHg).[42]

Cohn *et al.* performed a prospective observational study involving seven US trauma centres recruiting 381 patients.[43] They used StO_2 monitoring in the ED to determine whether thenar StO_2 and base deficit could equally predict multiple organ failure (MOF) and death. The StO_2 measurements were obtained within 30 min of the patient's arrival in ED. StO_2 performed as well as both base deficit and systolic blood pressure in predicting the 50 patients that subsequently developed MOF. There were 55 deaths out of 381 study patients, and in this group it was also apparent that StO_2 outperformed base deficit and systolic blood pressure in predicting this outcome.

Near-infrared spectroscopy is encouraging as a new non-invasive technology that appears capable of providing useful information about regional perfusion. It however remains unclear what role this modality will play at the bedside with respect to enhancing existing goal-directed therapy strategies.[44] Almost certainly widespread clinical application remains well into the future.

The microcirculation

The fundamental role played by the microcirculation in regulating oxygen delivery to the tissues supports the

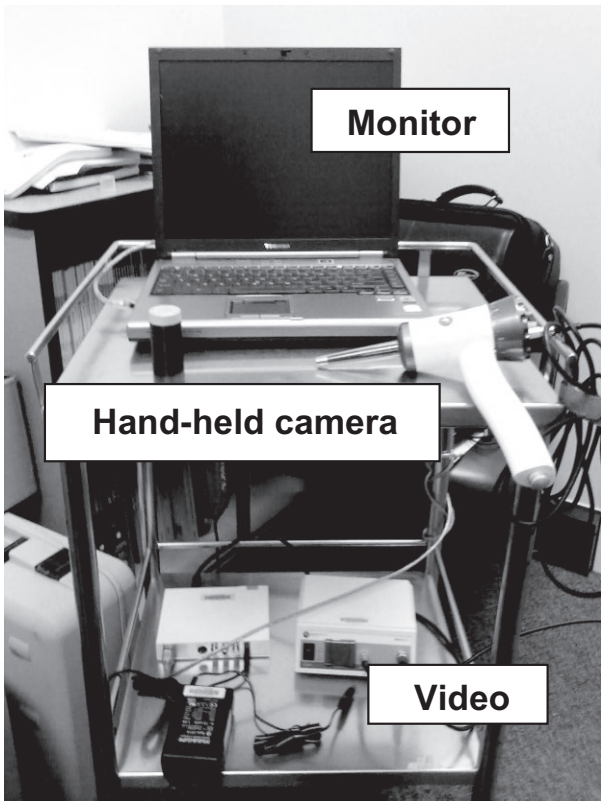

Figure 2. Sidestream dark field image camera with monitor.

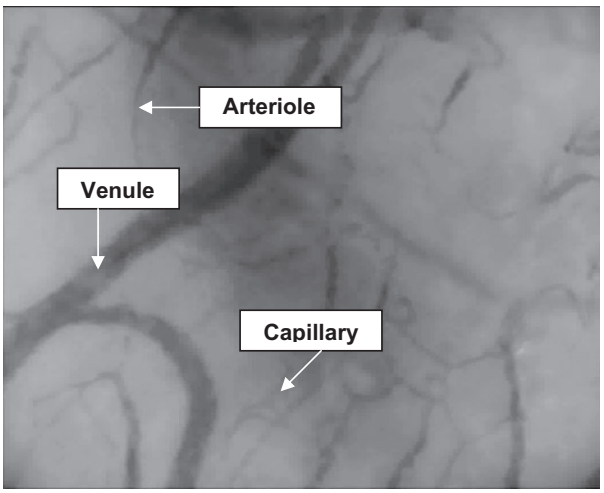

Figure 3. Sidestream dark field image of the sublingual microvasculature in a healthy volunteer.

notion that alterations in microvascular perfusion seen in shock are implicated in both organ dysfunction and MOF.[45] The relationships between systemic haemodynamics and microcirculatory changes during resuscitation are complex as evidenced by underperfusion of the microcirculation persisting despite restoration of macrohaemodynamics.[46] This situation could partially be explained by the different mechanisms implicated in regulation of the microvascular perfusion and macrovascular circulation. Microvascular perturbation can be attributed to a range of factors, including endothelial cell dysfunction, altered leukocyte adhesion, microthrombi formation and rheological abnormalities, all of which result in functional shunting at a microcirculatory level.[47] Clearly, maintenance of adequate tissue oxygenation should be considered a fundamental objective of any goal-directed resuscitation strategy. It is impossible to appreciate the state of the microcirculatory perfusion by simply assessing the macrohaemodynamics; therefore, defining the adequacy of resuscitation requires attention to both global and regional perfusion.[48] Ideally, we should be able to reliably, accurately and reproducibly measure oxygen supply/utilization in specific tissues at the bedside. However, it is only recently that technology has evolved to a point where this is routinely achievable in clinical practice.[1]

Sidestream dark field video microscopy is a minimally invasive method of imaging the microcirculation deep to the mucosal surfaces.[49] The technique consists of a handheld videomicroscope containing a ring of stroboscopic light-emitting diodes. Green light that penetrates up to 3 mm tissue depth is applied to the superficial vascular bed (Fig. 2). This is then absorbed by haemoglobin, so that red blood cells appear dark, yielding high-contrast video of blood flow in the submucosal microvasculature.[1] Figure 3 demonstrates a typical image obtained using sidestream dark field video microscopy.

In critically ill patients, the sublingual area is the most easily investigated mucosal surface, and this has been seen as one of the limitations of the method. The relevance of the sublingual area has always been questioned, as it might not be representative of other organs.[45] Some recent experimental data have shown that sublingual and gut microvascular blood flow had a similar evolution in a model of endotoxic shock,[50] suggesting the sublingual area is an appropriate site for microcirculatory observation.

In order to avoid subjectivity in the image analysis, consensus guidelines have been produced facilitating semi-quantitative reporting.[51] The scoring of the microcirculation should include an index of vascular density,

assessment of capillary perfusion and a heterogeneity index, hence there are two commonly employed scoring systems – the De Backer score[52] and the microcirculatory flow index.[53]

Recently, Trzeciak and colleagues demonstrated that improvement in microcirculatory perfusion (detected using sidestream dark field technology) during protocol-driven resuscitation of patients with septic shock resulted in less multi-organ failure at 24 h.[54] Given the observed relationship between persistent microcirculatory distress syndrome and adverse outcomes, targets for resuscitation in the future are likely to involve 'microcirculation recruitment' and the 'defence' of tissue oxygenation.

It is too soon to recommend exact targets, but achieving more than 80% perfusion of the observed microcirculatory vessels might be reasonable. It might well be that it is time to consider 'microcirculatory goal-directed therapy' as a new strategy to restore cellular function and prevent the onset of multiple organ dysfunction in the critically ill patients.

Conclusion

It is well established that monitoring techniques themselves do not directly affect outcome. It is the appropriate application of available technology that can guide clinical interventions that potentially impact on patient outcomes.[55] The optimal goals for quantitative resuscitation of shock remain uncertain, as do the most appropriate modalities for such assessment. However, what is clear is that a structured approach to the haemodynamic targets in shock is required. Adequate organ perfusion is the goal of supportive and therapeutic critical care. Blood pressure and standard global measures fail to provide an adequate indication of low cardiac output or indeed the distribution of that cardiac output. Certainly, lactate and its clearance is a practical and valid tool. Strategies that directly assess or measure organ oxygenation potentially offer the possibility of improved recognition and treatment of shock. The additional merits of using end-points for resuscitation are to have uniformity of resuscitation terminology and uniformity of goals that would avoid under- or over-resuscitation. Target uniformity also serves as a basis to compare outcome measures in resuscitation-based clinical trials.[56] The fundamental principle in utilizing haemodynamic monitoring should be to define specific goals and end-points. It will ultimately be a combination or 'bundle' of targets evaluating both global and regional perfusion that allows titration of therapy to predetermined end-points. Frequent and reliable re-evaluation of target parameters will be critical to the success of such a strategy.

Competing interests

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