Peri-operative Goal-directed Haemodynamic Therapy – Why Are We Where We Are Now, and What Is Needed to Move Forward?

a report by

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What you should be measuring, how you should be treating and how the interaction between measurements and treatments affect patient outcome have long been subjects of debate in medical practice. For centuries there were few scientific links between measurements that could be taken from patients and the subsequent treatments employed, but as technology developed to allow continuous recording of, for example, pulse rates and blood pressure, the question of which values were normal or abnormal, which values were acceptable in a clinical situation or needed action to redress them and which values should be the targets of treatment became important. In critical care medicine, particularly following the development of the pulmonary artery flow-directed catheter, a whole raft of directly measured or indirectly calculated parameters were created that represented the complexity and increased understanding of the cardiovascular system. Although early investigation had been able to characterize various normal ranges for these variables, whic are frequently measured in healthy people, it was not known how important variations from normal were in disease states, how treatment should be adjusted or which were the most crucial variables to try to target. One approach to investigate the relative importance of the different measurements was to look at differences between the values exhibited by survivors and non-survivors of critical illnesses.

Higher-risk patients undergoing surgery proved to be a perfect model for study as these patients could be observed before a physiological and pathological challenge, during the surgery itself and in the recovery phase. For a long time, anaesthesiologists and critical care practitioners had targeted treatment to maintain relatively normal blood pressure and to avoid tachycardia and bradycardia in operative cases, but this did not seem to differentiate between the survivors or non-survivors of surgical procedures and there was little evidence that any particular treatment effected outcome, although it was accepted that at extremes outcome in terms of morbidity and mortality worsened. The question arose of whether the additional parameters now available from increasing the invasive measure methods of monitoring could add additional insight into the physiological changes that might initially predict mortality, and might subsequently be used as targets of treatment themselves. There had been hints in the previous decade that a low cardiac index and arterial hypoxia were indicators of non-survival,[1] but now this could be studied in a much easier way.

During the late 1970s and early 1980s, a number of studies started to recognise the fundamental importance of various parameters that measured the physiological process of tissue perfusion and oxygenation. Of particular importance in this field was the work of Shoemaker and colleagues. Shoemaker began his professional life as a surgeon and moved into the new field of critical care in the early 1970s, becoming a leading figure in the Society of Critical Care Medicine. His group and others showed in a number of publications that there was little difference in routinely measured parameters such as heart rate and blood pressure between survivors and non-survivors of surgical procedures selected from a high-risk group; however, parameters indicating cardiac output, blood flow, oxygen delivery to the tissues and oxygen consumption were significantly different between survivors and non-survivors.[2,3] Much more recent work has confirmed these findings, showing that oxygen transport values change before the more commonly monitored variables and, in patients who die or have complications,[4] vital signs usually remain in the normal range until the terminal event, while oxygen transport variables start to change some hours previously. Furthermore, if the cumulative tissue oxygen debt is calculated during the period of operation, it is found that patients who survive have the smallest oxygen debt and patients who do not survive have the largest; patients with organ failure who survive have intermediate oxygen debts.[5] Shoemaker's group went on to suggest in a pragmatic fashion that the median values exhibited by survivors should be used as targets of treatment in all patients.[6]

This concept seems so appealing that a number of groups started to use various techniques of physiological targeting to manipulate cardiac output and tissue perfusion as well as the more usual targets of pulse rate and blood pressure in various higher-risk patients, and dedicated pre- and post-operative spaces were designated for this.[7] These groups reported good success, but this was far from a randomised scientific approach. In 1984, a randomised study was published concerning

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patients with fractured necks or femurs undergoing a physiological work-up prior to surgery. This included increasing cardiac output with an infusion of inotropes if required, and the results showed marked improvement in morbidity, mortality and hospital length of stay.[8] A better semi-randomised study was published in 1988 by Shoemaker[9] that showed reductions in morbidity, mortality and hospital costs and stays using an approach of peri-operative targeting of additional blood-flow-related parameters, specifically cardiac output and oxygen delivery, as well as more routine variables such as pulse rate, blood pressure and urine output in a group of high-risk surgical patients.

This treatment approach soon became known as goal-directed haemodynamic therapy (GDHT) and has led to many further clinical investigations being undertaken in surgical and other patients, but in the late 1980s and early 1990s the concept was met with an extraordinary dichotomy of views. Some intensive care physicians and anesthesiologists considered the whole approach fundamentally flawed with dangers of over-investigation, irrelevant treatment and dangerous treatment that might place added strain on the heart. While other physicians suggested that this type of goal-directed therapy might provide the goals for treatment in a wide range of critical illnesses from high-risk surgery to septic shock, scientific investigation focused on these two areas.

Early investigations in goal-directed therapy in septic shock cases showed little evidence of improvement in outcome,[10] with one study even suggesting that it may cause harm.[11] However, more recently evidence has been emerging that very early attention to goal-directed therapy in septic shock may significantly improve both mortality and morbidity,[12] and this has been adopted as one of the therapeutic recommendations by the influential surviving sepsis campaign.[13] When considering the evidence for peri-operative GDHT, it is interesting to compare the influence of this one positive study in the area of septic shock and a general critical illness with a larger number of negative studies in driving clinicians to change practice.

In more direct surgical applications there have been at least 25 studies undertaken that have investigated adding the targets of increasing tissue perfusion and blood flow to routine practice. The studies have investigated various patient groups, surgical procedures, techniques of measurement, different drugs to reach targets and even different targets of treatment, which has made interpretation of the scientific literature both complicated and controversial. This explains some of the dichotomy of opinion that was referred to earlier, but is hardly surprising given the desire to not simply repeat a previous study but rather to expand on questions highlighted by previous research, use different and new technologies and study different patient groups.

Many of these studies have shown a significant benefit in achieving the end-points studied, and support the use of GDHT. Most studies have used the population of high-risk surgical patients, although some have studied much lower-risk groups, and have shown reductions in mortality, morbidity, hospital stay and costs. A number of meta-analyses (and similar analyses of groupings of papers) have also been undertaken showing similar improvements in the end-points mentioned above.[14–17] Our own analysis of the data identifies 23 studies enrolling a total of 4,494 patients, with a control group mortality of 9.74% and a protocol mortality of 6.70% (OR 0.67, CI 0.54–0.83).

Despite the evidence supporting the use of GDHT in this patient group, it has not been widely adopted by the clinicians caring for these individuals.[18] Contributing to this is the major difficulty in the identification of this patient group. Studies have demonstrated a high-risk group, which accounts for fewer than 15% of surgical procedures but for more than 80% of deaths.[19] Studies trying to identify factors that create a 'high-risk' surgical patient who may benefit have proved difficult, as criteria have varied between the individual studies and, anecdotally, all clinicians believe they can identify this group; therefore, it remains difficult to precisely define and apply to everyday practice.

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The factors influencing the choices that clinicians make in choosing treatments for their patients is neither well understood nor studied extensively, but is likely to be a complex interaction of understandings of applicability to their particular patients, peer pressure, external pressure, difficulty in establishing the proposed new regime, fear of being seen to depart from established practice and an individual interpretation of the evidence base as well as that made by opinion leaders. In the face of the very positive evidence for GDHT, should we not be asking ourselves why GHDT remains widely unused? Below, we propose there are several reasons for this reticence in clinical uptake.

The interpretation of statistical data is always open to debate and the opinions of a group of clinicians regarding the validity of a given result will rarely be consistent. In the case of GDHT, where there have been many trials in different patient groups using differing physiological parameters, there is increased scope for debate. This has been compounded by work suggesting that small 'poor-quality' studies tend to show larger treatment benefits than larger 'high-quality' studies.[20] There has been a reluctance to accept the demonstrated treatment effects of smaller single-centre studies of GDHT. Indeed, when only the 'higher-quality' trials have been included in a meta-analysis, no statistically significant improvement in outcome from GDHT could be demonstrated, although this then begs the question of what comprises a 'high-quality' trial, and also raises the question of why so many trials testing treatment in a single centre do not not seem to be able to translate positive results to a larger multicentre environment. Are these effects due to a real lack of efficacy, or have they been masked by differences in treatment consistency, different baseline outcomes and conditions or a lack of highly motivated involvement of the many investigating teams?

There have also been concerns regarding the tools used, although this has been particularly directed at the pulmonary artery catheter. While it is reasonable to state that the majority of clinicians now consider the initial work demonstrating an increased mortality[21] to be flawed, the

debate continues in some circles, with calls for randomised controlled trials of all invasive monitoring before introduction to clinical practice.[22] This may have led to reluctance to use GDHT when tools associated with the technique are under scrutiny; however, with ongoing developments in monitoring technology, increasingly less invasive devices are now able to supply similar data to the pulmonary artery catheter. Thus, we can now separate these different issues and allow GDHT to be investigated in its own right without the aspersions previously cast by association. The tools chosen need to be free from compounding risks and safety issues of their own, effectively excluding the pulmonary artery catheter. With recent advances in less invasive haemodynamic monitoring such as the oesophageal Doppler moniter or LiDCO Cardiac sensor technology, this is not only achievable but a clear possibility. Taking things further, even less invasive techniques may be possible in certain circumstances, with studies demonstrating that techniques such as pulse pressure variation may be worth considering.[23] Whichever of the many currently available techniques are investigated further, it is essential that the chosen technique is easily reproducible using end-points that can be achieved not just in the tertiary centres but also at a regional and local level, where the same specialist equipment and expertise may not be available. It is vital that if widespread use and benefit is achieved, GDHT does not become the property of 'ivory tower' institutions, but instead is a technique that can be used to improve patient care throughout healthcare systems.

> We believe what goal-directed haemodynamic therapy needs now is a large, multicentre, randomised controlled trial.

Perhaps the single most important factor in the slow uptake of GDHT is the perceived potential financial outlay that would initially be required. In an era where medicine is increasingly subjected to cost–benefit analysis, the outlay for such an undertaking needs to be justified beyond doubt; as the debate around this issue continues, it is unlikely that any healthcare system will be in a position to invest in an area where the outcome is not proven, regardless of the degree of potential benefit. The potential for reduction in mortality and morbidity, and thus overall cost, following the widespread introduction of GDHT into clinical practice would also require investment in equipment and training, further increasing the burden on healthcare providers. Despite the fact that a number of individual studies have shown a significant cost reduction[9,24,25] as well as a reduction in mortality, the lack of a strong consensus make such initial investment difficult to justify.

The frustration felt by advocates of GDHT in the face of these issues has recently been expressed, and the challenge remains of how to take this forward into clinical practice and achieve the potential patient benefits. There are several key issues that need to be resolved before GDHT develops a strong enough evidence base to move forward into widespread clinical use. The myths that have arisen need to be dispelled, the tools used reviewed, the statistical analysis strengthened and, perhaps most importantly, to facilitate introduction the long-term patient and financial benefits need to be clearly illustrated. So where does this lead us to now? We believe what GDHT needs now is a large, multicentre, randomised controlled trial using a clear definition of the high-risk patient group that individual clinicians can relate to the patients they are treating on a daily basis; we also need to see the question of healthcare provision cost addressed and the potential patient and cost benefits clearly illustrated to a level of statistical and clinical significance using sound statistical analysis. Only at this point will we have the data and evidence that will be required to lead to the widespread introduction of GDHT.

Such a study is the only way in which these many issues can be addressed and hopefully will provide the body of evidence that is required to facilitate the widespread introduction of a potentially life-saving technique – or at the very least finally resolve the ongoing debate that has become GDHT. ■

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