Title
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Journal
ANNALS OF EMERGENCY MEDICINE, 72(4)

ISSN
0196-0644

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Publication Date
2018-10-01

DOI
10.1016/j.annemergmed.2018.06.007

Peer reviewed

Does Point-of-Care Ultrasound Improve Clinical Outcomes in Emergency Department Patients With Undifferentiated Hypotension? An International Randomized Controlled Trial from the SHoC-ED Investigators

EDITORIAL

But it makes sense physiologically…

Sara E Crager and Jerome R Hoffman

Point-of-care ultrasound (POCUS) is increasingly being used as a tool to support medical decision making in patients with undifferentiated shock. This is based on a series of assumptions about the physiology of shock, and the ability of POCUS to differentiate assorted pathophysiologic states for which the optimal treatment is believed to vary. A number of small studies have suggested POCUS can improve disease oriented end-points (DOEs), including diagnostic accuracy at the bedside; if this is true, the thinking goes, it should lead to improvements in what really matters – patient oriented end-points (POEs), including morbidity and mortality.

Many readers will therefore be disappointed that the first randomized controlled trial of emergency physician use of POCUS in undifferentiated shock looking at POEs was completely negative. What does this mean, and where does it leave us?

There are many reasons a trial can be negative, the most obvious being simply that the hypothesis is wrong, and the intervention being studied is not beneficial. But there are other possibilities, and just as a single positive trial is rarely definitive, the same is true for a single negative study – even if the study is carefully conceived and performed. No study is perfect, and even minor methodologic issues and biases can produce results that lead to an incorrect conclusion. In addition, any single study can, by chance alone, get the "wrong" results. Alternatively, benefit in a subset of patients can be obscured by absence of benefit – or even harm – in a different subset, making the results seem uniformly negative, even though the intervention is useful in an important subgroup. Furthermore, if the intervention distracts us from other more important tasks, the net effect of even a "useful" intervention may be neutral. Finally, even if an intervention like POCUS provides information that could be useful, it will not be so unless and until we know how to utilize that information; if our pathophysiologic reasoning is mistaken, or if the clinicians involved in the study misunderstand or misapply this reasoning, even the "best" data may lead to actions that harm as many patients as they help.

As is true of virtually any study, the RCT of POCUS by Atkinson et al has substantial limitations. We believe two of the most important are as follows: the protocol utilized a single ultrasound – which makes it impossible to benefit from the purported utility of POCUS in guiding on-going therapy via serial assessments. Perhaps even more critical, the study was substantially underpowered, with a sample size intended to detect an extremely ambitious 10% reduction in mortality. It is hard to identify any single intervention that has this much impact on mortality in acutely ill patients; to put this in perspective, the absolute risk reduction in mortality conferred by aspirin in acute MI is something on the order of ~3%. If application of POCUS in undifferentiated shock could

decrease mortality by even 3%, it would be a resounding success – but a study of this size would be extremely unlikely to find such a benefit.

Despite these concerns, it is worth noting that this carefully done trial did not show even a trend toward benefit. While it is true that this negative trial is far from definitive, it also continues to be true that there is no evidence that POCUS actually improves the POEs that truly matter.

But how can it hurt?

Absent anything close to definitive evidence, we still have to decide what to do at the bedside. Despite the results of this trial, then, advocates may claim that we should keep using POCUS, because it might ultimately prove useful … and how can it hurt?

Unfortunately, such reasoning has proven to be terribly wrong in many cases, at great harm to patients. Examples include the use of antiarrhythmics in acute MI, decompressive craniotomy for elevated ICP that is refractory to all standard therapies, and tight glucose control in ICU patients, among many others.

Still, one might ask what possible downside is there of using a diagnostic imaging modality that is relatively inexpensive and does not expose the patient to ionizing radiation. One obvious potential harm is that POCUS could divert time and energy away from more important interventions. Time and resource allocation in the emergency department is a zero-sum game both on an individual provider and departmental level, so focusing on an unproven intervention at the expense of proven interventions is an obvious concern. Adding POCUS to an ever-expanding list of things that need to be done can also lead to harmful neglect of other patients in the department. In addition, as is true of any imaging modality, major downstream harm could result from unnecessary work-up and treatment of incidentalomas and overdiagnosis. Finally, in the acutely unstable patient, major false positives and false negatives could cause significant harm, and increasing clinician certainty about potentially incorrect conclusions would obviously be very worrisome.

The pitfalls of clinical decision-making based on physiologic data

Most of what we do in medicine is not backed by solid evidence, and relies instead on physiologic reasoning to help us make our best guess under suboptimal conditions. This has indeed led to important advances – if a failing heart has trouble pumping against increased resistance, for example, it makes good sense that afterload reduction would seem to be helpful … and indeed so it is. On the other hand, our knowledge of physiology has changed greatly over time, and will surely continue to change in the future. “Treatments” like leeches and blood-letting surely made physiologic sense at one time … which is to say that such physiologic reasoning is only as good as our current understanding of pathophysiology. There are many examples of “scientific” approaches that unfortunately proved to be wrong, and that ended up harming patients.

With regard to the use of POCUS in undifferentiated shock, the most obvious comparator is the use of pulmonary artery (Swan-Ganz) catheters for the hemodynamic monitoring of critically ill patients. The theory behind this seemed impeccable. Using real-time physiologic data to guide management made complete sense – until it was shown that its real-world application in fact likely *worsens* patient outcomes.

Even assuming our understanding of the physiology is accurate, for management based on physiologic data to be helpful, a number of discrete criteria *must all* individually be met. First, the data must mean what we think it does; central venous pressure, for example, is not in fact an accurate predictor of fluid responsiveness. Second, the data must be obtained accurately and reliably. This is often a major problem with skill-dependent procedures such as ultrasound. Furthermore, the data must be interpreted correctly; multiple studies suggest that even trained intensivists frequently misinterpret Swan-Ganz data[1,2,3,4,5]. Finally, the appropriate management in response to the data must be readily apparent. Board-certified intensivists choose to initiate extremely different management strategies when provided with *identical* Swan-Ganz data.[6] Even were this not the case, there is evidence that chasing numbers may lead to over-treatment that is more harmful than helpful.[9,10]

It is also important to note that clinicians often lack insight into our own limitations. A particularly relevant example involves the response of intensivists asked about how well the data derived from pulmonary artery catheterization is understood; most respondents agreed that the understanding of 'other practitioners' was poor, but were confident in their own ability to use such information for the benefit of patients.[6,7,8]

So where does this study leave us?

It is impossible to know to what extent, if at all, clinicians in the current trial were able to meet the above prerequisites for successful use of physiologic data – or even to what extent the information provided by POCUS can accurately define physiology in a way that means what most clinicians think it does. Indeed, current education about POCUS tends to focus on *how to* do the procedure; we believe it needs to place at least as much emphasis on how US can help construct a valid model of physiology.

The study by Atkinson et al thus cannot definitively answer whether some ideal version of POCUS could be *efficacious* in improving POE outcomes in undifferentiated shock. What it does show is that the version of POCUS used in this trial was not *effective*. While answering questions about (real-life) effectiveness are ultimately more important, future studies that wish to answer the former question about efficacy (under ideal conditions) need to address how well POCUS measurements can approximate the relevant physiologic parameters being sought, how accurate and reliable is the data collection and interpretation, and how appropriate and predictable is the response to the data that is gathered. *If* such an ideal version of POCUS could be developed, it could then be possible to test whether or not its application improves POEs. And even if that could be shown, it would still be necessary to study whether or not such an ideal approach could be implemented by large numbers of practicing clinicians. To this end,

clinical research will be most useful *after* POCUS protocols have been specifically designed to allow a broad range of clinicians reliably and accurately to obtain, interpret, and act on the ultrasound data.

In summary, POCUS, as performed in this first RCT to assess patient-oriented endpoints, failed to find benefit; while that doesn't preclude the possibility that a different application of POCUS could be useful, as a general rule the standard for deciding about whether or not to adopt a new management strategy should not be "is it proven to be useless?" but rather "is there is adequate evidence of benefit?"

Still, the practice of clinical medicine routinely obliges us to make decisions about what to do in the absence of definitive evidence. Even thus hamstrung, we must decide what to do, using our best judgment (along with whatever limited evidence that we do have). We therefore don't believe it reasonable to insist that no one incorporate POCUS into the evaluation of undifferentiated shock, even though this first trial is negative. Anyone who chooses to do so, however, should at the very least have a well thought out plan regarding exactly what information to gather, and how to respond to whatever results are obtained. Even that – a firm belief that one's reasoning makes sense – is no guarantee that the plan is actually a good one, or that patients will actually benefit. Furthermore, we should all understand, and take very seriously, two very important, and very disconcerting, truths – that ideas that seem logically unassailable frequently prove to be wrong, and that interventions that seem completely benign can in fact lead to substantial harm. Finally, as a community we need to be concerned that widespread adoption of an unproven approach makes it that much harder to do the studies that could ultimately answer the question as to whether the approach is actually valuable, and – even more important – that much harder to abandon it if and when there is evidence that it is harmful.

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