EBM vs. EBM: combining evidence-based and experienced-based medicine in resuscitation research

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Purpose of review
To discuss the clear rationale for evidence-based medicine (EvBM) in the challenging realms of resuscitation research, yet also provide case examples in which even the well designed, multicentered randomized clinical trial may have had unrecognized limitations, and thus misleading results. This is where experienced-based medicine (ExBM) helps to resolve the issue.

Recent findings
Recent publications have brought to task the conclusions drawn from various clinical trials of resuscitative interventions. These articles have indicated that some major clinical trials that later determined the universal guidelines for resuscitative protocols may have been affected by unrecognized confounding variables, effect modifiers and other problems such as delayed timing. Many interventions, deemed to be ineffective because of these study factors, may actually have lifesaving effects that would have been confirmed had the proper circumstances been in place. With the right mindset, the clinician-researcher can often identify and address those situations.

Summary
When clinical trials indicate ineffectiveness of an intervention that worked very well in other circumstances, both preclinical and clinical, clinician-investigators should continue to re-search the issues and not always take conclusions at face value.

Keywords
amiodarone, cardiac arrest, cardiopulmonary resuscitation, chest compressions, clinical trials, CPR, epinephrine, evidence based medicine, impedance threshold device, research, resuscitation

INTRODUCTION

In the 1960s and 1970s, a new breed of resuscitation scientists took critical care to the streets and homes of entire populations in an effort to save lives from major trauma and heart disease [1–4]. The early pioneers empirically brought along many intuitive interventions and, in some cases, the interventions were overtly life-saving, particularly early defibrillation following the early provision of basic cardiopulmonary resuscitation (CPR) by bystanders [2,4]. Prehospital endotracheal intubation (PHETI) and intravenous epinephrine (adrenaline) administration were provided and infusions of antiarrhythmic drugs in select cases [2,3,5■,6■■,7]. Since that time, however many of these latter interventions have been called into question citing evidence-based approaches [5■,6■■,7–9].

But the issue is not whether these treatments are simply good or bad for the patient. It may be the circumstances as well—harmful in some instances,

helpful in others. Those pioneer prehospital care physicians learned early on that 'it depends'. Especially as patient care transitioned to paramedics in parts of the world such as Australia, Canada and the United States, many interventions became subject to protocols and prioritization with the limited number of on-scene personnel and logistics of providing care in homes, ambulances, and other

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KEY POINTS

- Evidence-based approaches have been shown to not only prevent unnecessary therapies, but also demonstrate harm from what appeared to be empirically reasonable approaches to resuscitative care.

- Many lifesaving interventions may also be detrimental depending on the given circumstance, context and timing of the intervention.

- Although multicenter, randomized clinical trials may still be considered the gold standard approach to documenting the effectiveness of a given intervention, the results may be obscured by unrecognized/unmeasured confounding variables/effect modifiers such as inadequate CPR, overzealous ventilation, delayed timing to the intervention or lack of appropriate stratification.

- Re-analyses of randomized clinical trial data can play an important role in better defining evidence-based approaches to clinical practice and the conclusions ultimately drawn from those research efforts.

difficult settings. These factors often created significant delays in the delivery of certain interventions, likely rendering them ineffective, but perhaps only because of those delays [6""].

For example, use of an automated external defibrillator (AED) has been shown to provide a 75% chance of (neurologically intact) survival for the patient with ventricular fibrillation in those settings where it has been used within minutes [10]. However, if there is a 10-min delay in use, especially without the advantage of basic CPR being performed by bystanders, the results would be grim. Therefore, if a clinical trial were to be performed in which the AED consistently is not used for 10 min (with no other preceding intervention), the results, taken at face value, might lead one to conclude that the 'evidence' shows that AEDs are ineffective. In fact, the experienced clinician-researcher would quickly challenge any statement like, 'the evidence failed to demonstrate that AEDs are effective'. The conclusion of that study might be accurate if it stated that AEDs were found to be ineffective, but that simple conclusion by itself would not be *true* unless it were qualified with the caveat that AEDs are ineffective when use is delayed for 10 min and no other intervention was provided [11]. The *truth* is that AEDs can be dramatically life-saving and to conclude otherwise without qualification would be inappropriate, yet such absolute pronouncements are frequently made in regard to other interventional data. If such 'evidence' were to be used to

determine a guideline that AEDs should not be used altogether, that would not only be a mistake, it would result in many lives being lost. Some interventions, lifesaving in some circumstances, can also result in harm if not used properly [5",12]. In the following dialogue, the quest for evidence-based medicine (EvBM) will be tempered with insights from experience-based medicine (ExBM). Using both previous and more current examples, the discussion will warn against unquestioned acceptance of so-called EvBM in resuscitation research, particularly when the intervention, found to be helpful in other circumstances, clinical or preclinical, is not proven to provide a distinct survival advantage in a given study [13–16].

PRIMUM NON NOCERE

First do no harm is a basic tenet and a strong motive for applying EvBM in resuscitation medicine [17]. For example, in the early days of emergency medical services (EMS) systems, the pneumatic antishock garment PASG), also known as the medical anti-shock garment (MAST), was required equipment on every ambulance across much of the United States and it was an integral part of Advanced Trauma Life Support protocols as well [18,19]. Why it was thought to be therapeutic was because it could elevate system arterial blood pressure (SABP) noninvasively in patients with signs of presumptive internal hemorrhage. However, the presumption that elevating SABP would always improve the chances of survival had not been proven [18].

One of the first challenges to a standard of care in EMS trauma resuscitation was the implementation of controlled clinical trials addressing the PASG [17,18]. Reseachers were unable to demonstrate any survival advantage to the PASG and, in fact, there was a trend toward worse outcomes in patients with penetrating injuries to the abdomen [18]. These first attempts at EvBM in prehospital trauma care established a new mindset that empiric therapies might not only be a waste of effort, but they may also be harmful for previously unrecognized reasons [17,18]. Eventually, those early PASG studies generated the hypothesis that elevating blood pressure prior to control of internal bleeding may be deleterious. That led to another clinical trial of intravenous fluid infusions prior to control of bleeding [20]. Again, if anything, early application of that standard of care (intravenous fluids) was harmful and that concept has since taken root and likely saved many lives from harm [21].

Nevertheless, even this evidence-based 'conclusion' should be qualified in that researchers never stated that the PASG or IV fluids were altogether

deleterious. Stated qualifications included inability to *demonstrate* any distinct value of the interventions with the current study and that there still might be potential benefit depending upon the timing of the intervention or perhaps the type of injury. For example, intravenous fluids and elevation of blood pressure might be helpful once bleeding has been controlled or in nonpenetrating type injuries or traumatic brain injury.

The main thesis here is that such interventions should not be considered in terms of absolutes, either bad or good. Instead, 'it depends'. The same can be said for tranexamic acid in that very early use in the first hour after the traumatic event may be lifesaving for the bleeding patient, but also detrimental if given after 3 h of the initial event [12].

On another front, for many years it was also taught that 'hyperventilation' with positive pressure breaths may be helpful in cardiac arrest patients or patients with severe volume depletion to reverse acidosis and hypoxemia [22]. However, it has now been well documented (with evidence) that excessive ventilation with positive pressure breaths can be very deleterious if not deadly, especially in states of cardiac arrest and severe traumatic hypotension [23,24]. Thus, EvBM needs to be an essential part of resuscitation medicine, but EvBM must also be tempered with the wisdom and insight that comes with ExBM.

IS THE GOLD STANDARD CLINICAL TRIAL ALWAYS RIGHT?

The notion of EvBM takes on many forms and can even be assigned to meta-analyses and other various levels of evidence. In most circles, the multi-centered, double-blinded randomized controlled clinical trial has long been considered the gold standard for determining whether or not a given intervention is effective and worthy of being promulgated as a standard of care [25■,26■].

Unfortunately, the results of such gold standard trials may sometimes lead to the wrong conclusion. The reason is not always that the study design was flawed, but very often because of unrecognized confounding variables or effect modifiers that were not accounted for in the results, even when conscientiously recognized *a priori*.

The multicenter, double-blinded randomized controlled clinical trial of the impedance threshold device (ITD) for use in cardiac arrest is a recent illustration of this concern [14]. The elegant design included the methodology that every patient received an ITD, removing that level of bias. Half of the devices, randomly assigned, were inactivated, blinding the rescuers and investigators alike. Among other design advantages, EMS crews had to meet certain CPR performance standards before becoming study participants and CPR performance was recorded electronically in most cases. In essence, this clinical trial of a cardiac arrest resuscitation intervention exemplified the 'gold standard' in EvBM research efforts [14,24].

Despite excellent performance in the laboratory setting and other successful clinical trials, the 'gold standard, EvBM' results from that study failed to show a survival advantage from the ITD [14]. In turn, subsequent guidelines recommended that It would not be reasonable for EMS agencies to use these devices.

But ExBM can also motivate the questioning of such a finding. Analysis should go beyond the usual questions of sample sizes, timing of interventions, setting differences, subgroup stratifications, and precision medicine considerations [16,26■,27■,28]. For example, during the study period, the American Heart Association consensus guidelines (which actually guided the study protocol) had changed. Among other recommendations, the guidelines for chest compressions rates had changed from 80 to 100 per minute to rates more than 100 per minutes. Studies later examining the data from that same ITD trial, identified that the chest compression rate (CCR) had an effect on outcomes including better survival chances with the ITD when in that targeted zone [29■]. The study further identified a 'sweet spot' for the CCR, with and without the ITD [29■]. Using the same database, others had found optimal zones for chest compression depth (CCD) and chest compression fraction (CCF), the percentage of a given time interval during which chest compressions are actively being performed [30,31].

Based on these new definitions of what might be optimal CPR in terms of CCR, CCD, and CCF, an increased concern over what constituted quality CPR had evolved and particularly the interaction between the quality of CPR provided and study interventions [32]. Accordingly, in another follow-up analysis of the original ITD study data [14], a new question was asked, 'Did the overall quality of CPR, measuring CCR, CCD, and CCF, affect the outcomes when the ITD was used?' [33■■].

The investigators found that, even when using very liberal criteria for 'quality', less than one in five ($n = 1675$) of the 8719 enrolled patients had documentation of actually having received good quality CPR with respect to CCR, CCD, and CCF despite the well vetted screening process for study participation [33■■]. Among the 1675 patients identified as having received an adequate combination of CCR, CCD, and CCF, those receiving the ITD ($n = 848$) had a very significant lifesaving effect (with good

neurological outcome) compared to controls ($n = 827$). Those subsets of active ITD and deactivated ITD groups receiving quality CPR remained well matched cohorts and the effect of the ITD was compelling when CCR, CCD, and CCF were in the more optimal zones with survival chances with good neurological outcome nearly doubling (7.2 vs. 4.1%; $P = 0.006$). Just as important, within the cohort of patients who did not receive quality CPR, ITD outcomes were worse, returning us to the premise that, depending on the circumstance/context, a lifesaving intervention also could be detrimental. So, although it was accurate to say that ITD made no difference in context of the original study, the EvBM conclusion needs to be qualified with the statement that it provided no distinct advantage when the performance of CPR by rescuers was not taken into account or measured. Consistent with other clinical and preclinical studies, the ITD does indeed save lives, but that specific device requires good CPR to work properly [33■■,34■■].

In this case, the quality of CPR was an important but unrecognized effect modifier for the intervention being studied. With so many other unsuccessful trials primarily in the realm of mechanical CPR, temperature management, and drug administration showing conflicting results or even a lack of effectiveness, the same concerns should probably be raised for those studies as well. Sample size, or lengthy periods of time elapsing before the therapy is given, can result in no confirmed advantage for a given intervention (such as amiodarone had in previous studies). However, other confounding variables also may have been at play in earlier 'gold standard' trials such as the high-dose epinephrine studies published in the 1990s [6■■,13]. Not only did study protocols differ from the laboratory approach, but delivery of ventilation was not controlled [13,17,22–24]. Later it was found that one of the larger agencies contributing many of the subjects to the clinical trial had been using excessive positive pressure ventilation rates for cardiac arrest patients, averaging in excess of 35 min^{-1} [23]. Even 'normal' rates of breathing would be too excessive in the patient with cardiac arrest and investigators from the same system later called this phenomenon, 'death by hyperventilation' [35]. Although only speculative at this time, it is still remains intuitive in retrospect that the unrecognized, unmeasured variable of excessive positive ventilations compromising cardiac output may have obscured any positive contribution from the high-dose epinephrine with the assumption that it would have truly been effective in human studies (as it had been so convincingly in the laboratory setting) [24]. Even when prehospital practitioners are facile at ETI, that

talent may actually lead to more harm if the practitioners' ventilatory practices are improper or excessive [5■,8,24]. This may likely account for clinical trials in the pediatric population in which ETI placement was found to be no better or even inferior to bag valve mask devices [9,24]. With the traditional concept that children need more respiratory support, this unrecognized/unmeasured confounding variable may have been further augmented [9]. For all the same reasons, studies that found no advantage to mechanical CPR devices, drugs, and temperature management may also be affected by such factors as excessive ventilation or prolonged duration of delayed chest compressions while applying the device.

Such presumptions are still speculative even if well founded in the mind of those practicing ExBM. Some will argue a lack of validity for the previously mentioned quality of CPR investigation [33■■] because it was a 'post-hoc' analysis. However, a counter-argument is that a completely new hypothesis was being tested and the data were collectively prospectively and comprehensively [27■,36,37]. Fortifying that concept, the smaller cohorts of ITD and control patients with good CPR techniques were exceptionally well matched in every respect. Also, the ITD had been routinely favoring lifesaving in other controlled trials of cardiac arrest in the laboratory and it was a component of the life-saving experimental interventions in another published trial [38]. All of these supportive studies make the results of the quality CPR follow-up study more compelling [33■■,34■■,38].

CONCLUSION

The central thesis here is not to always jump to absolute conclusions in scientific analysis, even when considering accurately reported, well-designed randomized clinical trials. Especially when the outcomes are neutral and do not fit the pattern of prior work, examination for confounding variables and other dynamic factors should be considered. Most importantly, for those practicing both EvBM and ExBM, research might always be better spelled as 're-search'.

Conflicts of interest

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