Critical Care Cardiology Research
A Call to Action

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The breadth and volume of cardiovascular research have outpaced those of most other medical specialties over the past few decades. These investigations have had an enormous impact on improving care and clinical outcomes, including patients in emergency and critical care settings. Over this same time frame, the spectrum of illnesses within coronary care units (CCU) has changed markedly. In its original concept, the CCU was designed for arrhythmia monitoring and treatment of patients with acute coronary syndromes. Today, the CCU has evolved into a critical care environment that delivers care both to patients with acute single-system cardiovascular illness and to patients with more comorbidities and multisystem organ dysfunction. The prevalence of heart failure, renal failure, and multisystem organ failure has increased in recent years; accordingly, the use of mechanical ventilation and vasoactive infusions has also risen steadily. The changing profiles of patients, drugs, and devices reflect recent medical evolution and represent future clinical and research opportunities.

In light of these developments, the American Heart Association recently released a scientific statement advocating for staffing, structural, and training transformations in CCUs; however, the necessary concurrent critical care cardiology research strategy was less clearly defined. Although our knowledge of cardiac disease treatment has markedly progressed, clinical research in the population of cardiac patients with multisystem failure has been much more limited. Although some studies of complex patients such as those with acute myocardial infarction and cardiogenic shock have been conducted, significant knowledge and treatment gaps persist. In this article, we discuss the important historical advances in the care of critically ill cardiology patients and highlight the perceived research needs, barriers, and potential solutions that could improve conduct and impact of critical care cardiology research.

Important Accomplishments and Achievements
Several randomized trials and observational reports in the cardiac intensive care setting have advanced cardiac disease treatment, but comparatively few have advanced the treatment of the critically ill. In an early study of 250 patients, using a before-and-after design, Killip and Kimball attributed an improved mortality in myocardial infarction patients to the early recognition and treatment of life-threatening arrhythmias. This finding contributed to the worldwide creation of CCUs. In the same era, the management of malignant arrhythmias was improved by a case series describing closed-chest compressions and defibrillation that formed the foundation of modern life-saving cardiac arrest treatment algorithms. Furthermore, modern cardiac arrest management has been enhanced by the application of mild therapeutic hypothermia in ventricular tachycardia or fibrillation cardiac arrest survivors after 2 randomized, controlled trials showed that it improved survival and neurological outcomes. Observational studies have also shown that patients with cardiac arrest have better outcomes when cared for in environments in which primary percutaneous coronary intervention for ST-segment–elevation myocardial infarction (STEMI), therapeutic hypothermia, and goal-directed care are used. This has led to policy statements for the regional development of integrated cardiac arrest systems of care.

In STEMI patients, fibrinolytic and mechanical reperfusion (coupled with regional strategies to reduce ischemic time) have markedly reduced mortality and complications. The management of patients with cardiogenic shock after STEMI has similarly been changed by urgent coronary revascularization. The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, perhaps the most important single trial in cardiac patients with critical illness that has led to a Level IA recommendation for immediate revascularization in patients with acute myocardial infarction complicated by cardiogenic shock, did not show a significant improvement in its primary outcome of 30-day mortality (although it showed improved long-term survival). This highlights some of the challenges in doing research in the acute critically ill patient population, discussed further below.

Patients with acute heart failure include those with acute pulmonary edema and impending shock. Although the majority of trials with acute decompensated heart failure have not included patients with acute shock or enrolled patients exclusively from critical care settings, lessons learned from recent randomized trials from the National Heart, Lung, and Blood Institute Heart Failure Network have been helpful to define the risks and benefits of furosemide dosing and neseritide therapy in acute
decompensated heart failure.\textsuperscript{15,16} Similarly, a randomized trial of ventricular assist devices in transplant-ineligible patients with very advanced heart failure mainly managed with inotropic agents has reported improved survival.\textsuperscript{17}

**Critical Care Research Needs**

Despite many randomized trials that have improved acute cardiac care, the management of the cardiac patient with multisystem organ failure remains challenging, given the high in-hospital mortality rate and the paucity of research in this population. Herein is an opportunity to fill this knowledge gap, but it requires an understanding of the barriers and challenges. The Table outlines possible areas of research to address unanswered questions in critical care cardiology research.

Cardiogenic shock has undergone comparatively little research outside the setting of acute myocardial infarction. Despite improvements with acute revascularization, mortality rates in STEMI patients with cardiogenic shock are $\approx50\%$.\textsuperscript{14,18,19} The high mortality rate presents an opportunity for new investigational agents to show benefit; however, no other therapies have been shown to improve outcomes in shock, and the few prospective pharmacological trials that have been performed have been disappointing. A randomized trial of nitric oxide synthase inhibition (Tilarginine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock [TRIUMPH] trial) was negative.\textsuperscript{20} In a trial evaluating pressor strategies (Sepsis Occurrence in Acutely Ill Patients II [SOAP II]), patients with cardiogenic shock receiving dopamine as a first-line vasopressor had a higher mortality than patients receiving norepinephrine; however, the unreported rate of many prognostically important cardiac variables may limit the external validity of this trial.\textsuperscript{21} A potential difficulty in exploring treatments for cardiogenic shock is the known hemodynamic heterogeneity whereby the inflammatory response syndrome, with or without superimposed infection, results in marked systemic vascular resistance variability.\textsuperscript{22} Patients with low or normal systemic vascular resistances may hemodynamically resemble heart failure patients with distributive shock (such as sepsis) in whom there is equally little high-quality evidence to guide management. In both these patient types, customizing treatment through better pathophysiologic and hemodynamic shock characterization may be required. Unfortunately, the routine use of pulmonary artery catheters has not been shown to be beneficial, but specific application may be useful.\textsuperscript{23} Finally, the appropriate fluid management strategy remains a challenge in patients with cardiogenic shock. Intensive care unit (ICU)–based studies have shown that fluids are an important component of early goal-directed therapy, that net fluid accumulation during a patient’s ICU stay is associated with an increased mortality, and that volume restriction in noncardiogenic pulmonary edema is associated with reduced length of stay and ventilation days.\textsuperscript{24–28} Unquestionably, the hemodynamic profiles and volume statuses of patients in these ICU trials are very different from those in patients in cardiogenic shock. Nonetheless, whether a negative, euvoletic, or positive fluid balance should be targeted in cardiac shock patients in the resuscitative and subacute phases is an interesting unanswered clinical question.

The delivery of care to the critically ill represents an attractive area of future study. Cardiac procedural volumes are known to be an important determinant of mortality.\textsuperscript{27,28} It has yet to be examined, but it is logical to assume that the frequency with which healthcare teams care for critically ill cardiac patients may also influence clinical outcomes. Possible delivery strategies aimed at improving caregiver volume and skills that may merit prospective evaluation include (1) examining the relationship between patient outcomes and the number of weeks per year of service required by CCU cardiologists; (2) studying whether outcomes can be improved by centralizing the care of critically ill cardiac patients into a single regional CCU with physicians, nurses, and team members who routinely provide complex cardiac care; (3) exploring whether outcomes can be improved with regional systems that link, streamline, and protocolize the care of critically ill cardiac patients through the prehospital setting, the emergency department, the critical care unit, and cardiac rehabilitation; (4) studying the role of consultant services in the critical care setting, including night time coverage; and (5) evaluating whether and how critical care training among cardiologists improves outcomes.\textsuperscript{2} Multidisciplinary team interventions, along with pharmacist-, nursing-, and physical therapist–led protocols, have resulted in meaningful improvements in critical care and cardiology patients.\textsuperscript{29–31} Defining and studying how interprofessional team members can harmoniously improve outcomes in critically ill cardiac patients merit further study.\textsuperscript{32}

<table>
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<tr>
<th>Table. Ten Examples of Unmet Needs in Critical Care Cardiology Research</th>
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<tr>
<td><strong>Shock in the cardiac patient</strong></td>
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<tr>
<td>• Defining the best fluid and vasoactive pharmacological management strategies in cardiogenic shock</td>
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<td>• Managing septic shock and inflammatory response syndromes in patients with heart failure</td>
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<td><strong>Cardio-renal syndrome</strong></td>
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<td>• Timing preventive and therapeutic interventions for cardio-renal syndromes</td>
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<td><strong>Cardiac arrest care</strong></td>
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<td>• Improving systems of care and identifying therapies beyond hypothermia that can improve post–cardiac arrest neurological outcomes and survival</td>
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<td><strong>Delivery of care</strong></td>
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<td>• Evaluating whether institutional or physician volumes or regionally centralized care affect the outcomes of critically ill cardiac patients</td>
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<td>• Evaluating whether electronic medical record systems and clinical decision support systems can reduce errors and improve safety</td>
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<td>• Examining the role of cardiology and intensive care cross-training</td>
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<td><strong>Measurement</strong></td>
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<td>• Establishing standardized definitions, processes of care, and outcome measures for patients with advanced cardiac disease and critical illness through registry platforms and databases</td>
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<td><strong>Palliative care</strong></td>
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<td>• Enhancing support of patients and families to ensure optimal decision making about end-of-life care, including administration, withholding or withdrawal of advanced cardiac and other critical care technologies, and integrating palliative care into both the inpatient and outpatient setting</td>
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<td><strong>Training</strong></td>
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<td>• Cross-fertilizing in clinical practice and clinical research for cardiology and critical care trainees</td>
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The growing use of electronic health records could potentially serve as a data collection platform for a large multi-institutional observational data set. We speculate that this type of research platform could be set up with government funding and would ideally have joint cardiology and critical care governance. The resulting data set would potentially allow useful insights into illness trajectories, processes of care, variations in care, and patient outcomes, thereby leading to investigations that could improve the quality and delivery of cardiology critical care similar to the way that foundational registries have provided insights into acute coronary syndrome and cardiac arrest management. This endeavor would also require the establishment of standardized disease definitions, severity indexes, and outcome measures and the identification of validated physiological and biomarker variables. The lack of a uniform definition of, and outcomes for, cardiogenic shock in major clinical trials is a simple example that highlights how consensus measurements and definitions in this field are lacking but would advance the field and help to coordinate investigations in the future.

Much of the science we have on caring for critically ill patients has been garnered from the general intensive care clinical and research experience, wherein only a minority of patients have primary cardiac problems. Although it may be the best evidence available, commonly applied ICU evidence such as resuscitation strategies, sedation strategies, hemodynamic management, ventilator management, or renal replacement therapies (to name a few) were studied in heterogeneous critically ill populations. To what extent the reported results are directly applicable to critically ill patients with dominant cardiac problems remains unclear.

**Historical and Current Research Barriers**

Cardiology has long held a focus on cardiac-specific research, whereas the multisystem failure was historically the clinical and research domain of the critical care community. Unfortunately, this longstanding differentiation remains largely entrenched today. In North America, CCUs and ICUs are often physically separate spaces despite growing overlap between their patient populations. ICU and CCU training programs are similarly segregated so that most programs do not require trainees to spend time on rotations within the other specialty. In academic medical centers, both of these barriers impede the routine exchange of knowledge and management practices at the faculty and trainee levels.

Pharmaceutical industry funding as a major driver of cardiac randomized, controlled trials may also serve as a cardiology critical care research barrier. Companies must make a profit to survive and, in general, want to fund pharmaceutical research that maximizes the chance of proving efficacy and minimizing risk. Including patients with multisystem organ failure with high baseline mortality rates and altered pharmacodynamics is a higher-risk proposition for industry-funded investigations. The excess bleeding observed in patients with renal insufficiency receiving clopidogrel and therapeutic, but not prophylactic, low-molecular weight heparin, illustrates this point.

The historical low success rate of pharmaceutical trials in the intensive care field also highlights the potential difficulty of (and a potential pharmaceutical industry aversion to) including critically ill cardiac patients in randomized trials. In contrast, successful critical care trials have tested a range of drugs and devices, led increasingly by investigator-initiated research consortia, that have blossomed in recent years. Although many such trials have tested currently available approaches to care, industry-funded trials have largely been in the fields of sepsis and septic shock. Given these observations and the high mortality rate of critically ill cardiac patients, it is clear that pharmaceutical development for this population is a high-risk proposition. However, historical failures should not be a reason to dissuade our collective goal of improving patient care.

Whatever their funding source, small trials have historically tended to evaluate surrogate physiological outcomes in critical care and cardiology. Many such trial results raise interesting questions that are later disproved by subsequent appropriately powered analyses. Future studies beyond the phase II stage should strive to avoid the use of surrogate end points, given that implementing the results into clinical practice prematurely can potentially be harmful or nonbeneficial. Appropriately identifying and testing interventions in discrete yet relatively common clinical subpopulations (eg, cardiorenal syndrome or septic shock in patients with heart failure) with clinically meaningful, definitive end points represents an area ripe for future research at the interface of cardiology and critical care.

**Applicability of Ongoing Cardiac Research to Cardiac Critical Care**

In an analysis of all cardiac trials registered with www.clinicaltrials.gov, we sought to examine how applicable future publications will be to the critical care setting. We included all ongoing phase II to IV clinical trials studying adult patients 18 years and older with a cardiac diagnoses using the prespecified search terms cardiogenic shock, myocardial infarction, acute heart failure, cardiac critical care, and cardiac arrest. First, each study was examined for 2 exclusion criteria that could potentially limit the study results to critically ill patients: high or low blood pressure and solid-organ (kidney or liver) dysfunction or failure. These clinical variables were selected because of an increasing prevalence of these conditions in CCUs. A total of 318 unique ongoing studies were identified, and 233 of the studies (73%) excluded patients with 1 of the 2 aforementioned criteria (122 studies imposed blood pressure restrictions; 173, specific solid-organ dysfunction; 62, both). Next, the remaining 85 study protocols (27%) were reviewed to evaluate whether the results of the trials would be applicable to critically ill cardiac patients. We specifically focused on whether critical CCU patients (eg, those with acute STEMI, acute decompensated heart failure, or cardiac arrest) were eligible for enrollment and whether the study end points would be relevant to clinical practice. We determined that only 34 of the registered trials (11%) were relevant to critically ill cardiac patients. Among the 51 excluded studies, 50 studies did not enroll critically ill patients, and 1 trial used a surrogate end point.
The exclusion of large portions of the population in clinical trials is not unique to cardiology. A review of randomized, controlled trials published in high-impact journals reported that 81% of trials excluded patients on the basis of medical comorbidities and that <50% of all exclusion criteria were strongly justified. The clinical consequences of such exclusions can be important, leading to results that do not represent typical patients cared for in practice. Excluded high-risk patients may also be most likely to benefit (or suffer) from an intervention. Achieving the appropriate balance in establishing the efficacy, safety, and generalizability of an intervention is challenging. However, our modest trial analysis highlights only a small proportion (11%) of ongoing clinical trials that are projected to be relevant to the critically ill cardiac patients. Applying the results of cardiac research to critically ill patients is a familiar clinical dilemma to CCU and critical care physicians. For example, how should non-STEMI be treated if the pathogenesis is considered attributable to supply–demand mismatch rather than plaque rupture? Many practitioners caring for critically ill cardiac patients need to make clinical decisions based on previous experience or perceived benefit rather than the crude results of published trials. Perhaps clinical practice in the CCU could benefit from a broadening of eligibility criteria and a more parsimonious selection of exclusion criteria in future cardiac clinical trials.

In general, clinical research for its own sake is not useful. Research needs to integrate into the typical critical care setting and demonstrate how care can be safe and effective. This study speaks of the need to address how to care for an understudied group of patients managed in CCUs around the world. However, it makes a larger point about the danger of research purity losing clinical relevance. Research needs to inform clinicians, not confuse them. Patients need clinicians and systems of care that are informed by directed and relevant research.

**Potential Solutions to Increase Critical Care Cardiology Research**

To facilitate more critical care cardiology research, we propose 6 broad improvement strategies (Figure). First, whenever it is clinically appropriate, the inclusion criteria of many cardiology clinical trials focused on acute cardiac disease could be broadened. Large trials that have included a broader scope of patients not only offer more generalizable results but also provide insights beyond the primary analyses to advance research; for example, since the publication of the SHOCK trial, some contemporary STEMI trials have included patients with cardiogenic shock. The resulting databases have provided researchers the opportunity to perform post hoc exploratory analyses and to describe outcomes in relatively large populations of critically ill patients. In cases in which trial sponsors determine that broadening inclusion criteria to multisytem organ failure is too high risk (particularly for new pharmaceutical compounds), government funding such as that from the National Institutes of Health and Canadian Institutes of Health Research will continue to be a major source of funding of critical care research. The critical care research community can also play an important role in furthering our knowledge. Cardiac patients represent a sizeable portion of all ICU admissions; thus, the critical care community in collaboration with the cardiology community could conduct more trials focused on cardiac conditions.

This call to action encourages not only randomized trials and observational studies but also other scientific endeavors such as cardiac and critical care registries. We propose the creation of new registries, or alternatively, existing cardiac registries could be expanded to include important critical care variables (or vice versa). Leveraging the existing infrastructure and data systems expertise in the latter strategy has the potential setup time and cost efficiency advantages. Critical care and cardiology disciplines should consider collaboratively building on existing clinical and research relationships to advance research interests of joint concern. This could potentially be accomplished by (1) conducting joint trials; (2) establishing shared registries, including through the use of electronic medical records; (3) building new research collaborations; (4) reciprocally increasing the exposure of trainees of each specialty to the other’s service during training; and (5) combining advanced training with the view of developing cardiologist–intensivists focused on clinical research at the watershed areas of interest.

The establishment of working groups could also help forward the goals and ideas put forth in the study. The European Society of Cardiology has a working group on acute cardiac care that has put forth clinical training standards, established...
an annual meeting, and endorsed a peer-reviewed journal dedicated to acute cardiac care. The AHA has an Acute Cardiac Care Committee that could advocate for these issues. The creation of a working group could build on the European experience and play a leading role in recommendations to fill the existing research void.

Conclusions

The CCU has evolved from its beginnings as an arrhythmia monitoring center into an environment that increasingly cares for critically ill cardiac patients with shock, respiratory failure, and multisystem organ failure. Cardiologists have been leaders in clinical medical research, but research in the critical care components of the CCU has not kept pace with the changing case-mix and more complicated clinical practice. A collective focus to identify barriers to more clinically relevant joint research efforts and to identify solutions for advancing the field will help to ensure that promising opportunities can be seized. As we strive to implement the recent scientific goal of new knowledge about how to best care for this growing and challenging population.

Disclosures

Dr Cook is a research chair of the Canadian Institutes of Health Research. Industry relationships of Dr Granger are publically listed at http://circoutcomes.ahajournals.org/Downloaded from. Dr Cook is a research chair of the Canadian Institutes of Health Research. Industry relationships of Dr Granger are publically listed at http://circoutcomes.ahajournals.org/Downloaded from. Dr Cook is a research chair of the Canadian Institutes of Health Research. Industry relationships of Dr Granger are publically listed at http://circoutcomes.ahajournals.org/Downloaded from. Dr Cook is a research chair of the Canadian Institutes of Health Research. Industry relationships of Dr Granger are publically listed at http://circoutcomes.ahajournals.org/Downloaded from.

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