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Jeremy B. Richards
Renee D. Stapleton *Editors*

Non-Pulmonary Complications of Critical Care

A Clinical Guide

Humana Press

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Preface

Complications of critical illness, both iatrogenic and non-iatrogenic, are common in the intensive care unit (ICU) and can lead to increased morbidity and mortality. Thus, it is extremely important to understand the nature of complications and how to best prevent and treat them when caring for critically ill patients. The first six chapters of this book thoroughly discuss these complications and are organized by organ system (cardiac, renal, neurologic, hematologic, gastrointestinal, and nutritional/endocrinologic). These chapters are followed by a chapter focusing on procedural complications. Finally, the book concludes with a chapter on preventing complications with meticulous supportive care and systems-based considerations in the ICU. Drug-related complications are mentioned throughout the book in relevant chapters. The topics covered in this book will help readers gain understanding of when to anticipate and how to prevent a wide array of potential complications of critical illness. When complications are encountered, these chapters also include detailed information on diagnosis, management, and prognostication.

We wish to thank the series editor, Dr. Sharon Rounds, for allowing us the opportunity to develop this volume and participate in the series. We are also grateful to the contributing authors for their time and effort in writing clear and concise chapters. Finally, we would like to thank Flora Kim, the developmental editor at Springer, whose assistance and dedication throughout the publication process helped to produce an excellent book.

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Chapter 1
Cardiovascular Complications

Ryan D. Clouser and Gilman Allen

Abstract Cardiovascular complications are a common occurrence while caring for the critically ill patient. Problems such as atrial fibrillation (A fib), acute myocardial infarction, cardiac arrest, cardiac tamponade, and ventricular fibrillation are not uncommon in critical illness. Treatment of these conditions should be focused on prompt organized assessment and care to ensure rapid stabilization of the patient. Treatment of A fib should be focused on conversion back to sinus rhythm in some instances versus rate control with nodal blocking agents. Care of acute myocardial infarction requires determination for the need of invasive management versus medical management, as well as antiplatelet medications and systemic anticoagulation. Cardiac arrest should be treated with cardiopulmonary resuscitation and provision of rapid defibrillation for shockable causes of cardiac arrest. Echocardiography should be considered to aid in diagnosis during rapid deterioration of patients. Selected patients who have return of spontaneous circulation post arrest should be quickly evaluated for utility of targeted temperature management in order to attenuate the systemic and neurologic effects of post resuscitation syndrome.

Keywords Atrial fibrillation • Cardiac arrest • Post resuscitation syndrome • Cardiac tamponade • Ventricular fibrillation • Ventricular tachycardia • Myocardial infarction

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Introduction

It is common for clinicians to be faced with a host of cardiovascular complications of critical illness while treating patients in the Intensive Care Unit (ICU). Even in patients admitted to the ICU for non-cardiac primary issues, acute cardiac complications often arise, requiring rapid clinical assessment and response. In this chapter we review the pathogenesis and evidence-based management of common cardiac complications of critical illness.

Atrial Fibrillation

Atrial fibrillation (A fib) is the most common arrhythmia experienced in the ICU [1] and it is often exacerbated by conditions commonly encountered in the ICU, such as acute myocardial ischemia, cardiac surgery, severe sepsis, shock, hypovolemia, and pulmonary emboli. A recent retrospective review of a large database of critical care units in California hospitals assessed the risk of A fib and its associated risks in the setting of severe sepsis. The study found that new onset A fib occurred far more frequently in hospitalized patients with severe sepsis than in those without severe sepsis [2].

General management of A fib depends on the stability of the patient. Loss of the atrial component of cardiac output can, in many cases, be an inciting event that leads to cardiogenic shock or exacerbation of other forms of shock. As a result of compromised diastolic filling, a rapid ventricular response to A fib or flutter can also lead to diastolic dysfunction and acute pulmonary edema, with subsequent respiratory failure. Any unstable patient with new onset rapid A fib should be considered a candidate for direct current cardioversion to sinus rhythm as quickly as possible. Cardioversion must include provision of some form of sedation and analgesia (with airway protection, as indicated) prior to delivery of percutaneous electricity to the patient.

For the hemodynamically stable patient with A fib and rapid ventricular response, it is important to first review the patient's past medical history and determine whether the patient is chronically in A fib, in which case conversion to sinus rhythm (either by pharmacotherapy or cardioversion) is unlikely to be maintained. In the case of chronic A fib, it is more sensible to shift one's focus to pharmacologic rate control with beta blockers, calcium channel blockers, or even digoxin (Table 1.1).

Table 1.1 Agents for management of atrial fibrillation

Amiodarone	150 mg loading dose, continuous infusion 1 mg/h × 8 h then 0.5 mg/h
Metoprolol	2.5–5 mg IV
Esmolol	0.5 mg/kg loading dose, 309825 continuous infusion 0.05 mg/kg to 0.3 mg/kg/min
Diltiazem	10–20 mg loading dose, continuous infusion 5–20 mg/h
Digoxin	0.5 mg IV load, 0.25 mg every 6 h × 2 doses, then 0.125 mg daily
Magnesium	37 mg/kg bolus followed by 25 mg/kg/h for 24 h

In the critically ill patient with new onset A fib, pharmacologic conversion to sinus rhythm has been extensively studied. The rates of conversion to sinus rhythm with amiodarone administration ranges between 50 and 70 % within 12 h of initiation of the drug, and about a 50 % stable conversion rate by 24 h [3, 4]. One study found that magnesium (37 mg/kg bolus followed by 25 mg/kg/h for 24 h) actually achieved a higher rate of conversion to sinus rhythm compared to amiodarone (77 versus 50 % at 24 h) [4], but this finding has not been replicated elsewhere. Conversion rates to sinus rhythm have also been reported with more traditional rate-controlling drugs, such as esmolol and diltiazem. Conversion rates were found to be higher with esmolol than with diltiazem (68 versus 33 %), but both agents were equally efficacious at rate control [5].

Aside from rate control, it is important to consider the risk of stroke and need for anticoagulation in a patient with either chronic or acute A fib in the ICU. The decision to provide systemic anticoagulation is often complicated in the critically ill, particularly following recent trauma or surgery, or in the setting of gastrointestinal bleeding, hematological malignancy, or disseminated intravascular coagulation (DIC) from sepsis. Thus, the risks and benefits should be weighed carefully, specifically taking into account the daily risk of thromboembolic complications (including cerebrovascular accidents) attributable to A fib. One important consideration is the presence of severe sepsis at the time of diagnosis of new onset A fib. New onset A fib in severe sepsis is associated with a six-fold higher incidence of ischemic stroke compared to patients without severe sepsis [2], and this should be factored into any decision regarding anti-coagulation for A fib in ICU patients.

Myocardial Infarction

Non-ST Elevation Myocardial Infarction

Non-ST elevation myocardial infarction (NSTEMI) and/or ST elevation myocardial infarction (STEMI) are common in the ICU setting. NSTEMI may be the reason for admission to the ICU when associated with refractory chest pain, pulmonary edema or acute respiratory failure, but can also be associated with or occur during the clinical course of other critical illnesses (such as severe sepsis). Clinical signs and symptoms of NSTEMI can be difficult to ascertain in intubated and sedated ICU patients. Early signs of NSTEMI include chest pain and/or pressure, which can often radiate into the jaw or left arm. An intubated and sedated patient may not be aware of or be able to report these symptoms to clinicians.

Diagnostic workup of acute coronary syndromes such as NSTEMI is dependent on the presence of symptoms and classic electrocardiogram (ECG) changes. The astute intensivist may note ST changes on continuous telemetry monitoring, but a 12-lead ECG should always be obtained as soon as concern for myocardial ischemia is entertained. ECG findings consistent with NSTEMI include ST depression of

>1–2 mm, typically in contiguous leads that correspond with one of the main coronary artery territories. Inversion of T waves is also a worrisome marker for ischemia but not nearly as sensitive or specific as deep ST depression [6]. Cardiac biomarkers are also an important part of the workup for NSTEMI and should be sent as soon as possible. Troponin assays, which are very sensitive, will become elevated within hours of active myocardial ischemia and should be followed serially until they peak. Continued elevation or rising of cardiac troponin should raise serious concern for ongoing myocardial necrosis and infarction.

There are numerous potential causes of NSTEMI in critically ill patients. The most common and classic cause of NSTEMI is the development of non-occlusive arterial thrombus within a coronary artery which leads to a mismatch in myocardial oxygen supply and Verbose and unnecessary demand. This pathophysiologic mechanism explains why critically ill patients are at increased risk for NSTEMI: myocardial oxygen demand is higher in the critically ill. This process is initiated by the rupture of an unstable coronary plaque within a native coronary vessel. The rupture of the plaque leads to activation of platelets and the coagulation cascade, which can progress to further myocardial injury as coagulation and platelet plugs form within the vessel lumen, decreasing vascular luminal diameter and decreasing myocardial oxygen delivery (in the setting of increased myocardial oxygen demand).

Other potential causes of NSTEMI in the ICU setting include "demand-related" ischemia resulting from mismatch between the decreased supply of well-oxygenated hemoglobin (and blood flow) and the typically high myocardial demand imposed by an often hyperdynamic myocardium, particularly in patients with severe sepsis and septic shock. Demand-related ischemia is common and is frequently encountered in patients with shock and overall poor perfusion from any cause. Insufficient oxygen supply to the myocardium during shock states can cause impaired ventricular contractility and a secondary, superimposed cardiogenic process that further compounds the hemodynamic effects of the pre-existing, primary cause of shock.

Finally, coronary artery vasospasm can cause NSTEMI in critically ill patients. Coronary vasospasm is a rare but recognized complication of administration of high doses of vasopressors. The vasopressors most likely to cause vasospasm are those with unopposed alpha-adrenergic properties [7]. Coronary vasospasm is also a recognized early-complication of coronary bypass surgery [8] and can also be a complication of recreational cocaine use and/or overdose [9].

Treatment of NSTEMI in the ICU should be focused on providing supportive care and treating underlying and potentially causative conditions, while maximizing oxygen delivery to the myocardium and delivering antiplatelet and anticoagulation therapy as soon as possible. In an intubated patient, it is imperative to ensure that the patient is adequately sedated and provided with good analgesia to ensure that excessive work of breathing or ventilator dyssynchrony are minimized, as both processes may increase respiratory muscle work and myocardial oxygen demand. Airway management and mechanical ventilation should be provided to the critically ill patient with NSTEMI and concomitant acute respiratory failure due to pulmonary edema. When treated expeditiously with non-invasive positive pressure ventilation (NIPPV), patients with acute pulmonary edema due to a NSTEMI may avoid the need for intubation and invasive mechanical ventilation. Early NIPPV may potentially even reduce

overall mortality in this patient population [10]. Administration of non-invasive continuous positive airway pressure (CPAP) can decrease work of breathing and improve oxygenation, presumably by reducing upper airway resistance [11] and helping to partially recruit fluid-filled and collapsed alveoli. Both non-invasive and invasive positive pressure mechanical ventilation can help decrease left ventricular afterload by raising intrathoracic pressure and effectively reducing transmural pressure across the left ventricle during systole [12]. Non-invasive bi-level positive airway pressure (BiPAP) can help to further reduce patients' work of breathing and similarly improve oxygenation. Of note, some concerns were raised early on by the finding of an increased frequency of myocardial infarction with the use of BiPAP for treatment of pulmonary edema in early observational trials [13], but these concerns have not been substantiated in more recent and larger trials. As such, current guidelines based on contemporary evidence support the use of BiPAP for selected patients with acute pulmonary edema and acute coronary syndrome to minimize the risk of needing endotracheal intubation and invasive mechanical ventilation [14, 15].

In addition to supportive care and treating underlying systemic causes, medical management of a NSTEMI should focus on treatment of the acute myocardial infarction (MI). Aspirin should be given as soon as possible. If no enteral access is available in an intubated patient, an orogastric tube should be placed for administration of aspirin. If there is a contraindication for aspirin administration through the gastric route, rectal aspirin should be given. Without a contraindication to anticoagulation, a patient with a NSTEMI should be systemically anticoagulated with a continuous IV infusion of heparin. Low molecular weight heparin (LMWH) is an alternative consideration for treatment of acute coronary syndrome [16]; however, LMWH should be used with caution in the ICU setting due to its poor reversibility after subcutaneous administration, particularly as critically ill patients are at increased risk for acute bleeding complications.

In addition, treatment of the patient with NSTEMI should include secondary antiplatelet therapy with an ADP receptor antagonist such as clopidogrel. Rate control with beta-blockers should be initiated if clinically possible; however, beta-blockade is often not possible in critically ill patients due to concomitant hypotension and shock. As soon as possible, consultation with a Cardiologist should be obtained to identify the utility of further management options. Specifically, cardiology's early input regarding the risks and benefits of continued medical management versus cardiac catheterization and percutaneous coronary intervention (PCI) is critical, as delayed catheterization may have significant clinical consequences. Glycoprotein IIb/IIIa inhibitors (GPIs) should be initiated when recommended by cardiology, and are typically provided for patients undergoing catheterization.

ST Elevation Myocardial Infarction

Acute STEMI is a true cardiac emergency necessitating rapid evaluation and timely decision making regarding treatment. STEMI is caused by acute plaque rupture and complete occlusion of a coronary artery by formation of an intra-vascular platelet

plug. A STEMI presents with sudden onset of severe chest pain or pressure that can be associated with diaphoresis, nausea, and shortness of breath. ECG is diagnostic and will reveal downward concave ST segment elevation in contiguous leads representative of the affected coronary artery territory. Acute ST elevation may be noted on continuous telemetry lead monitoring in the ICU, but the symptoms can be difficult or impossible to detect in an intubated and sedated patient. Acute hemodynamic and/or respiratory decompensation of a previously stable critically ill patient should trigger prompt obtainment of an ECG to ensure that acute myocardial infarction is not the cause of the patient's deterioration. STEMI can have devastating consequences if not treated rapidly, as an untreated STEMI can quickly progress to acute cardiogenic shock with hypotension, acute respiratory failure, and multi-organ failure.

Treatment of a STEMI should initially focus on immediate medical management with anti-platelet therapy with aspirin (PO [per os, or by mouth], PGT [per G-tube] or PR [per rectum]), and anticoagulation with a continuous infusion of unfractionated heparin IV. GPIs may be reasonable in selected patients, and should be initiated in concert with cardiology consultation and recommendations. Best outcomes are achieved with timely restoration of coronary artery patency, coronary artery blood flow, and myocardial perfusion. Clinical options for restoring coronary artery patency include thrombolytic therapy, invasive PCI via cardiac catheterization, or coronary artery bypass grafting (CABG) surgery. PCI is preferred in most patients as it is associated with less adverse outcomes than thrombolytic therapy, specifically a lower prevalence of major bleeding events. Given the significant risks of surgery in critically ill patients, PCI is generally preferred to CABG in most circumstances.

Post-PCI care focuses on continued systemic anticoagulation with the guidance of the cardiology service. Rate control, medical management of potential reperfusion arrhythmias, and vasopressor administration as needed for post-STEMI/post-PCI cardiogenic shock, are all components of post-intervention management. The optimal vasopressor for management of post-STEMI cardiogenic shock is controversial. However, a recent randomized, prospective, head-to-head trial demonstrated that norepinephrine causes fewer adverse events than dopamine in a heterogenous group of critically ill patients with shock [17]. Specifically, norepinerphine caused less tachyarrhythmias than dopamine in all patients, and was associated with decreased mortality in the subgroup of patients with cardiogenic shock [17]. The utility of intra-aortic balloon pump (IABP) counter-pulsation has recently been called into question by a randomized, prospective study that demonstrated that IABP did not confer any mortality benefit over medical management alone in patients with acute myocardial infarction complicated by cardiogenic shock [18].

Cardiac Arrest

Despite aggressive monitoring and care, cardiac arrest and circulatory collapse are still common complications of critical illness. Furthermore, many patients arrive in the ICU after return of spontaneous circulation (ROSC) following an out-of-hospital

cardiac arrest. Rapid response teams in the inpatient setting may decrease the rate of cardiac arrest on the general medical and surgical wards and shift the incidence of arrest to the ICU by transferring patients to a higher level of care earlier in their critical illness. There are several underlying causes of cardiac arrest that we review in this section. A large review of registry data from of 51,919 in-hospital cardiac arrests between 1999 and 2005 revealed that the first documented arrhythmia during cardiac arrest was ventricular tachycardia in 3,810 (7 %), ventricular fibrillation in 8,718 (17 %), pulseless electrical activity (PEA) in 19,262 (37 %) and asystole in 20,129 (39 %) of cases [19]. Survival to discharge from the hospital was no different if the initial rhythm at the time of arrest was ventricular tachycardia or ventricular fibrillation (37 %). PEA and asystole were both associated with significantly lower rates of survival to discharge at 12 and 11 %, respectively [18]. Evidence is limited as to what constitutes the best management of in-hospital cardiac arrest, but there are recent data that suggest that post-arrest targeted temperature management (TTM) may confer higher rates of favorable neurologic recovery and survival in patients with PEA and in-hospital cardiac arrest [20, 21], as has already been demonstrated in out-of-hospital arrest due to ventricular fibrillation [22, 23].

For all of the arrhythmogenic causes of cardiac arrest, the key elements of immediate management include performing a primary survey (assessing airway, breathing and circulation), obtaining adequate IV access, providing early defibrillation if clinically indicated, and delivering consistent high-quality chest compressions with minimal interruption.

Ventricular Tachycardia and Ventricular Fibrillation

Ventricular tachycardia (V tach) is a wide complex regular and fast rhythm that is frequently associated with a loss of perfusion to the vital organs, and can result in loss of pulse and cardiac arrest. It is categorized as either V tach with a pulse, or pulseless V tach. Ventricular fibrillation (V fib) results from disorganized electrical activity within the ventricular and is characterized by the lack of discernible QRS complexes on ECG or telemetry monitoring. V tach and V fib most commonly occur as a result of active cardiac ischemia and/or severe electrolyte disturbances, such as hypokalemia or hypomagnesemia. In the ICU, irritation from indwelling vascular access devices, such as central lines or PICC (peripherally inserted central venous catheter) lines inadvertently placed into the ventricle, can also precipitate ventricular ectopy and sustained V tach. V tach and V fib can also be seen in patients with cardiomyopathy or underlying conduction system disturbances from scar tissue involving the ventricular conduction system, the latter resulting from remote myocardial infarction or other inflammatory cardiomyopathies, such as sarcoidosis or viral myocarditis (among other causes).

Treatment of V tach initially hinges on assessing whether or not the patient is hemodynamically stable. For intermittent V tach in a patient who is conscious and hemodynamically stable, administration of an intravenous (IV) beta blocker will often suppress further ectopy. Longer sustained runs of stable V tach are more

appropriately managed with IV amiodarone or lidocaine. Amiodarone is generally delivered as a 150 mg IV bolus followed by an infusion, typically at 1 mg/h. Second line agents, such as lidocaine, are less effective than amiodarone and should only be considered if amiodarone is unavailable or contraindicated. Hemodynamically unstable V tach (characterized by patients who are hypotensive or confused, but who have a palpable pulse) is treated similarly to all hemodynamically unstable tachycardias, beginning with immediate *synchronized* cardioversion. If at any point while managing a patient with V tach there is uncertainty regarding the presence or absence of a palpable pulse, it is reasonable to begin cardiopulmonary resuscitation (CPR) and specifically initiate the appropriate pulseless arrest algorithm (e.g., V fib/pulseless V tach or asystole/PEA).

Pulseless V tach and V fib should both be treated emergently with immediate *defibrillation* (unsynchronized) and initiation of resuscitation based on the American Heart Association Advanced Cardiac Life Support Protocol. Defibrillation is now carried out in a stepwise process to ensure the patient receives uninterrupted chest compressions between each delivered shock prior to assessment of rhythm and evaluation for ROSC. Medical therapy for V fib or pulseless V tach arrest refractory to defibrillation is either a one-time dose of vasopressin 40 units IV or epinephrine 1 mg IV every 3–5 min for the duration of the event.

While animal studies have suggested that vasopressin may lead to improved blood flow to organs and better neurological outcomes after prolonged cardiac arrest [24], the results of vasopressin have been less compelling in human clinical studies. A landmark randomized controlled trial of patients who suffered in-hospital cardiac arrest compared 40 units of vasopressin to 1 mg of epinephrine as initial medical management during cardiac arrest [25]. Patients who did not respond to the first dose of either vasopressin or epinephrine received subsequent doses of epinephrine as a rescue therapy. Of the patients enrolled and randomized, 104 patients received vasopressin and 96 patients were treated with epinephrine. Primary outcomes of survival-to-hospital discharge, survival-to-one-hour, and neurological function were all equivalent between the two groups [25]. A second multicenter, randomized controlled trial compared the use of combined vasopressin plus epinephrine to epinephrine alone for out-of-hospital cardiac arrest [26]. This trial included nearly 3,000 patients and the primary outcome was on survival-to-hospital admission. Secondary outcomes included ROSC, survival-to-hospital discharge, good neurologic recovery, and 1-year survival [26]. This trial again also failed to demonstrate any significant difference between the two medications. Of note, this trial did re-verify the overall poor prognosis associated with out-of-hospital cardiac arrest, with approximately 20 % of patients surviving to hospital admission, 29 % of patients achieving ROSC, and a staggering 2 % of patients surviving to both hospital discharge and to 1 year post-arrest [26].

Lidocaine was previously the agent of choice for medical treatment of refractory V tach and V fib but has since been replaced by amiodarone in the most up-to-date Advanced Cardiac Life Support (ACLS) algorithms. An earlier randomized controlled trial of patients with out-of-hospital cardiac arrest and refractory V tach or V

Table 1.2 Causes of PEA and asystolic cardiac arrest

Common causes of PEA and asystolic cardiac arrest
Hypovolemia/hypotension
Severe metabolic acidosis
Hyperkalemia/hypokalemia
Hypothermia
Hypoxemia
Thrombosis (acute MI/PE)
Toxins (overdose)
Tension pneumothorax
Tamponade

fib demonstrated a significant increase in survival-to-hospital admission with administration of 300 mg of amiodarone when compared to placebo (44 versus 34 %, $p=0.03$) [27]. Another randomized trial 3 years later demonstrated a statistically significant increase in survival-to-hospital admission in patients with shock-resistant, out-of-hospital V fib patients who received amiodarone versus lidocaine (22.8 versus 12.0 %, $p=0.009$) [28].

Pulseless Electrical Activity

PEA is a common cause of cardiac arrest in the ICU. PEA is characterized by continued electrical activity on telemetry monitoring without effective cardiac output, systemic circulation, or a palpable pulse. In addition to prompt cardiopulmonary resuscitation, the underlying causes of PEA must be considered and directly treated to provide the patient the best chance of surviving an acute PEA arrest. The most common causes of PEA arrest include severe hypovolemia, hypoxia, acidosis, hyperkalemia and hypokalemia, hypothermia, tension pneumothorax, pericardial tamponade, drug ingestion, myocardial infarction, and massive pulmonary embolism (Table 1.2).

The immediate management of a PEA arrest is similar to a V tach/V fib arrest, as clinicians should rapidly perform a primary survey, ensure there is adequate IV access, initiate high-quality chest compressions, and provide fluid resuscitation based on the standard ACLS protocol. Again, the focus of the ACLS algorithm is high-quality, uninterrupted chest compressions. While performing immediate CPR, clinicians should consider potentially treatable causes of the patient's acute decompensation and PEA arrest. Medical therapy for PEA is epinephrine 1 mg IV every 3–5 min for the duration of the resuscitation. Additional medications such as IV calcium, sodium bicarbonate, insulin, and glucose are also frequently provided during resuscitation, particularly when hyperkalemia or severe acidosis is suspected as a potential or probable cause of PEA. Atropine is no longer advised by the American Heart Association as part of the standard medical treatment algorithm for PEA.

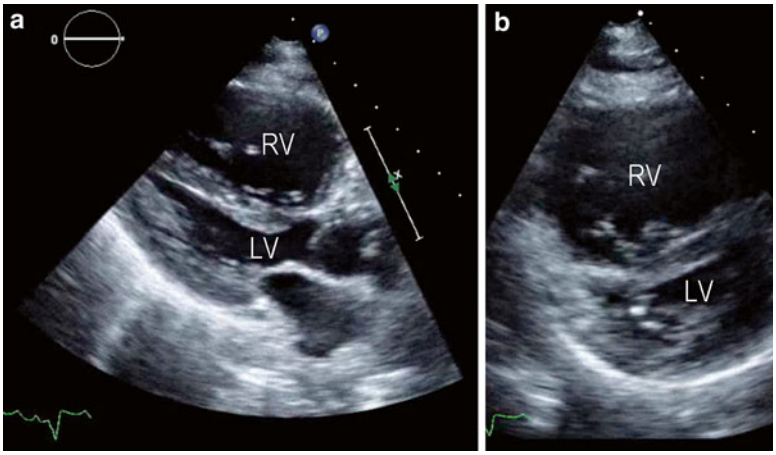

Fig. 1.1 Para-sternal long axis (*panel A* on *left*) and short axis (*panel B* on *right*) views from echocardiogram, demonstrating under-filled left ventricle (LV) and dilated right ventricle (RV) with septal flattening during late systole, leading to asymmetry of left ventricle in cross-section (*panel B*, LV), commonly referred to as the "D-sign", consistent with RV pressure and volume overload, which should raise suspicion for a hemodynamically significant pulmonary embolism

Bedside echocardiogram can be very helpful in evaluating and guiding treatment of patients in PEA arrest. Rapid assessment of cardiac contractility during brief pauses in CPR can allow for differentiation between true PEA (absence of echocardiographic cardiac activity) and "pseudo-PEA", in which electrical conduction and cardiac contractility are coupled but the cardiac output is insufficient to generate adequate perfusion and a palpable pulse.

Bedside ultrasound can also aid in the assessment of potential causes of PEA by rapidly assessing the structure of the heart and lungs. Using bedside echocardiography it is possible, with proper training, to rapidly assess for the presence of pericardial tamponade, pneumothorax, and acute right ventricular pressure and volume overload, which may raise clinical suspicion for massive PE (Fig. 1.1).

With regard to both bedside echocardiography and bedside ultrasound, it is important to emphasize that chest compressions should not be stopped for these evaluations and resumption of chest compressions should not be delayed by these assessments. Rapid and timely use of ultrasound can be helpful in ruling in or ruling out possible causes of PEA, but resuscitative efforts should not be held or delayed simply to perform ultrasonography.

Without the availability of ultrasound, treatment of PEA arrest will typically focus on rapid detection and treatment of acid/base and electrolyte abnormalities using point-of-care testing, restoration of circulating volume, and potentially empiric needle decompression of the chest or pericardiocentesis in the setting of suspected pneumothorax or pericardial tamponade. It is also not uncommon in the critically ill patient to have more than one cause of PEA present. Thus, it is crucial that the clinician continue to work his or her way through the entire list of possible causes when one intervention fails to restore cardiovascular circulation.

Asystole

Asystole is diagnosed by absence of cardiac electrical activity on telemetry monitoring ("flatline"). The common causes for asystole are similar to the causes of PEA. Asystole is commonly preceded by progressive sinus or junctional bradycardia.

Treatment of asystole is focused on airway management, oxygenation, and chest compressions. When an airway cannot be immediately secured, there should be no delay in initiating CPR and delivering high-quality chest compressions. Oxygen should be delivered by face mask while chest compressions are provided at a rate of 100 compressions per minute. Epinephrine should be administered at a dose of 1 mg IV every 3–5 min for the duration of the arrest. Sodium bicarbonate was formerly considered a therapeutic option for the prolonged arrest; however, it has been removed from the most recent algorithms due to a lack of efficacy and concern that it might promote increased intracellular acidosis. The overall survival rate from aystolic cardiac arrest is poor, even in the ICU setting.

Reperfusion Injury/Post-resuscitation Syndrome/ Targeted Temperature Management

Despite aggressive measures and advances in technology, long-term outcomes and survival from cardiac arrest, both in and out of the hospital, remain poor. Care of the post-arrest patient should focus on the restoration of blood flow and oxygen delivery to vital organs and minimization of reperfusion injury. The post resuscitation syndrome is characterized by anoxic brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia with reperfusion injury, and a subsequent systemic inflammatory response [29]. The degree of post-resuscitation syndrome is based on a number of factors, including the underlying comorbid state of the patient, the underlying cause of the arrest, the duration of no-flow state, and the adequacy of restoration of perfusion.

The pathophysiology of post-cardiac arrest syndrome is not completely understood but appears to involve several cellular pathways. Global ischemia activates the systemic inflammatory response and causes increased production of cytokines, including IL-1, IL-6, IL-8, TNF-α and increased complement activation, arachadonic acid metabolites, expression of leukocyte adhesion molecules, and chemotaxis of neutrophils into the ischemic tissue [30]. Lack of oxygen delivery to cells leads to decreased ATP synthesis, depletion of intracellular ATP stores, and produces a depolarization of the cellular membrane, opening of the voltage-dependent calcium channels, and decreased mitochondrial membrane potential [30]. This results in an influx of calcium into cells which results in cellular damage. Restoration of oxygen delivery to injured cells can accelerate the production of free radical and reactive oxygen species, including superoxide anions, hydrogen peroxide and free radical hydroxyl groups, all of which can lead to further cytotoxic injury [30].

The global systemic inflammatory response also triggers the coagulation cascade, leading to micro-vascular thrombosis, which can potentially lead to added and prolonged ischemia, and ultimately to multi-organ failure and death. Ischemia of the gut can result in breakdown in the epithelial mucosal membrane, which can allow for bacterial translocation into the circulation and subsequent sepsis and multi-organ failure.

Post-cardiac arrest hypotension is a mixed form of cardiogenic and distributive shock [31]. Typically this shock state is characterized by severe and global, but reversible, left ventricular dysfunction, which begins quickly after ROSC and generally resolves within 48–72 h [31]. Management of post-arrest hypotension should be focused on rapid evaluation of left ventricular function with beside echocardiography and initiation of vasopressors and ionotropes to maximize cardiac output and reperfusion. Oxygen should be delivered to a point sufficient to restore cellular oxidative metabolism, but with care to avoid excessive oxygen tension. A large multicenter cohort study of 120 hospitals and 6,326 patients found that post-arrest patients treated with hyperoxia within 24 h of arrest ($PaO_2 > 300$ mmHg) had a significantly higher in-hospital mortality of 63 versus 45 % among patients with more physiologically normal PaO_2 levels [32]. Carbon dioxide levels should be kept within normal range by adjusting of patients' minute ventilation while they are mechanically ventilated. Excessive hyperventilation can lead to decreased $PaCO_2$ and resultant vasoconstriction of the cerebral vasculature with compromise of cerebral perfusion and added threat to favorable neurologic recovery.

Reperfusion injury to the brain is a common occurrence following ROSC. Two landmark studies demonstrated that cooling cardiac arrest survivors, specifically after V tach/V fib arrest, to a temperature of 33–34 degrees Celsius (ºC) was associated with decreased mortality and an increase in favorable neurologic recovery [21, 22]. For this reason it has become common practice, and a recommendation by the American Heart Association, to provide TTM immediately following the ROSC in patients who have suffered V fib or V tach cardiac arrest. The application of controlled patient cooling is believed to decrease the harmful effects of reactive oxygen species and cellular calcium influx toxicity, presumably through a reduction in cerebral metabolism and oxidative chemistry. More recent evidence demonstrates that maintaining post-cardiac arrest patients at a temperature of 36 degrees Celsius is non-inferior to 33 degrees, and that avoiding fever with TTM may be the most important intervention to optimize neurologic recovery after ROSC [33].

Evidence to support the use of TTM is strongest for survivors of V tach/V fib cardiac arrest [22, 23], but this practice has been expanded to other causes of cardiac arrest [33]. There is currently no solid evidence available from randomized clinical trials to strongly support the use of TTM for non-shockable rhythms, but the rationale for doing so is the same pathophysiologic processes that occur after V tach and V fib arrest likely occur after PEA and asystolic arrest. The data to support the practice of TTM of non-shockable rhythms include retrospective cohort, non-randomized prospective observational studies, and one large randomized controlled trial and the results are mixed with regard to favorable neurological recovery [21, 34, 35]. A recent meta-analysis of randomized and non-randomized studies appears to support TTM for in-hospital and out-of-hospital arrest due to non-shockable

Table 1.3 Methods to induce cooling via targeted temperature management to achieve therapeutic hypothermia (return of spontaneous circulation is abbreviated as ROSC)

Initiation of therapeutic hypothermia
Determine if patient is appropriate for cooling (comatose [GCS < 8], ROSC < 60 min, hemodynamically stable)
Place ice packs in groin, axilla, and neck
Bolus with 20–30 ml/kg iced saline
Place cooling blankets
Consider medication to manage sedation and prevention of shivering
Anticipate close monitoring and management of serum electrolytes (check levels at least every 4–6 h during initiation and maintenance of therapeutic hypothermia, as well as during rewarming)
Assess and follow coagulation profile

cardiac causes, but the authors acknowledge a substantial risk for bias and poor quality of evidence [20]. As with any clinical intervention, clinicians need to weigh the risks and benefits when deciding whether to initiate TTM for patients who have suffered PEA or asystolic arrest.

Overall, however, TTM should at least be considered for all survivors of cardiac arrest who remain unresponsive or if the GCS remains <8 following ROSC (Table 1.3). There are several important contraindications to the initiation of therapeutic cooling, including severe hemodynamic instability, continued unstable arrhythmias, and the presence of active hemorrhage. Withholding therapeutic cooling should also be considered in patients who have had a prolonged period of compromised perfusion, generally limiting practice to those with less than 60 min before ROSC. The likelihood of favorable neurologic outcome is felt to rapidly diminish beyond this duration of down time.

Rapid induction of cooling can be achieved by applying ice packs in the patient's groin, axilla, and neck, with close attention to the integrity of the skin at least every 15 min after application. In addition to ice packs, rapid cooling can be achieved by administering cold intravenous fluids, typically chilled to 4 ºC and administered as a 20–30 ml/kg bolus (Table 1.2). Care should also be taken during cooling to prevent shivering, which can prolong the time to achieve target temperature. Prevention of shivering can often be achieved with opiates, acetaminophen, buspiprone, intravenous magnesium, and skin counter-warming measures alone [34]. While most effective in shivering prevention, neuromuscular blocking agents are often reserved as a last resort at some centers, while they are used uniformly at others. It is imperative that goal temperature be achieved as quickly as possible and every effort should be made to achieve goal core temperature of 33 ºC within 6 h (ideally 2 h [22]) of ROSC. Core temperature is best monitored with the aid of either a bladder or esophageal probe. Once the goal core temperature has been reached, patients are typically maintained at that temperature for 24 h with the aid of cooling blankets or pads.

TTM is associated with a number of risks. The most common adverse side-effects of cooling include electrolyte abnormalities (particularly hypokalemia and hyperglycemia), hypotension, coagulopathy and bleeding, bradycardia, ventricular arrhythmias, and breakdown in skin integrity due to adherent cooling devices. The majority of these complications can be managed without discontinuation of the hypothermic