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# Cardiac Arrest: the Changing Incidence of Ventricular Fibrillation

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## Opinion statement

There are more than 300,000 out-of-hospital cardiac arrests (OHCA) in the USA annually, which can be grouped into those presenting with tachyarrhythmic (shockable) rhythms and those presenting with non-tachyarrhythmic rhythms. The incidence of tachyarrhythmic rhythms, which include ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), has been noted to be progressively decreasing in multiple studies of OHCA. Improved medical and surgical therapies for ischemic heart disease, and the widespread use of implantable cardiac defibrillators (ICDs), have likely contributed to a declining incidence of VF arrest and may result in conversion of an otherwise VF event into a pulseless electrical activity (PEA) arrest. As the incidence of VF has declined, it is unclear if the absolute incidence of non-tachyarrhythmic rhythms has increased or remained largely unchanged. This article discusses the changing rates of presenting rhythms in sudden cardiac arrest, the underlying cellular mechanisms of PEA, the factors contributing to the relative increase in the rate of PEA arrests, and current treatment options.

### Keywords

Pulseless electrical activity; Ventricular fibrillation; Cardiopulmonary resuscitation; Sudden cardiac arrest

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This article is part of the Topical Collection on *Arrhythmia*

Compliance with Ethics Guidelines

Conflict of Interest

Steven P. Keller and Henry R. Halperin each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

## Introduction

Deaths from sudden cardiac arrest (SCA) represent approximately 50 % of total deaths attributable to heart disease [1], and it is estimated that half of patients experiencing SCA have that arrest as the first manifestation of previously undiagnosed coronary disease [2, 3]. Heart disease remains the leading cause of death in the USA with an estimated 600,000 people dying from heart disease in 2010, which represents 24 % of total deaths [4]. SCA is categorized by the initial cardiac rhythm and is classified into tachyarrhythmic and non-tachyarrhythmic categories. The category of tachyarrhythmic arrest includes ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT), while the non-tachyarrhythmic category includes pulseless electrical activity (PEA), ventricular asystole, and extreme bradycardia. A recent report from the National Heart, Lung, and Blood Institute workshop on pulseless electrical activity defined PEA as a syndrome in an unconscious patient with no palpable pulse and with an electrocardiogram demonstrating organized activity other than a ventricular tachyarrhythmia and with the absence of a rapid spontaneous return of adequate organ perfusion and consciousness [5•].

The distinction between presenting cardiac rhythms in SCA is an important one due to the markedly different survival rates and the therapeutic role of defibrillation. The importance of early defibrillation in the management of VF was demonstrated in a study of in-hospital cardiac arrest in which patients that received prompt defibrillation had a survival to discharge rate of 39.3 % when compared to patients in whom defibrillation was delayed by 2 min or more from the onset of VF who had a survival to discharge rate of 22.2 % [6]. This finding was confirmed in a Swedish study of OHCA in which patients with VF undergoing defibrillation with minimal delay had a survival rate at 1 month of approximately 50 % while those with a delay of 15 min had a survival rate of only 5 % [7].

Study of non-shockable rhythms is becoming increasingly more important because of the larger numbers of arrests with those rhythms as well as their significantly worse outcomes. A prospective multicenter observational study of in-hospital arrests from 2000 to 2004 noted a relatively low prevalence of VF as the initial rhythm compared with other rhythms [8]. This study found VF or pulseless VT as the initial rhythm in only 23 % of adult patients compared with a 32 % prevalence of PEA and a 35 % prevalence of asystole with the remaining 10 % of patients having an undocumented rhythm. Patients with VF or pulseless VT had a 36 % survival to discharge rate compared with a rate of 11.2 % for PEA and 10.6 % for asystole. Approximately 54 % of these study patients were admitted for non-cardiac reasons. Similar results were reported from a prospective observational study at more than 400 hospitals involving more than 50,000 patients experiencing in-hospital SCA from 1999 to 2005 [9]. This study found VF or pulseless VT as the initial rhythm in 24 % of patients compared with PEA for 37 % and asystole for 39 %. Survival to hospital discharge was 37, 12, and 11 % for VF or pulseless VT, PEA, and asystole, respectively, which was nearly identical to the rates observed in the prior study.

Over the last few decades there have been changes in the prevalence of the presenting arrhythmia underlying SCA in out-of-hospital arrests. The incidence of OHCA attributed to ventricular fibrillation in Rochester, Minnesota, has been noted to progressively decrease

from a reported 26.3 per 100,000 population during 1985–1989 to 18.2 during 1990–1994 to 13.8 during 1995–1999 to 7.7 during 2000–2002 [10]. A similar trend was noted in Helsinki, Finland, where a 48 % decrease in the incidence of out of hospital VF from 1994 to 1999 has been reported [11]. The decline in VF in Helsinki occurred without a commensurate increase in the incidence of asystole or PEA. Interestingly, the decreasing incidence of VF occurred at the same time that the paramedic response time in Helsinki decreased from an average of 9 min to 6 min which presumably would have resulted in earlier detection of VF events prior to devolution into asystole. Study of OHCA in Goteborg, Sweden, from 1970 to 1987 resulted in similar observations with a decrease in the rate of VF as the initially recorded rhythm from 39 to 32 % over that time [12•]. Data from Seattle evaluating the initial rhythm in patients suffering from OHCA noted a 56 % decrease in the incidence of VF from 1980 to 2000 [13•]. The decreased incidence was mostly noted in men, regardless of race, while the decline of VF in women over that period was negligible. The incidence of PEA and asystole over that period was largely unchanged. A similar decline in the rate of VF was noted in a review of OHCA in Milwaukee, Wisconsin, in which the rate of VT/VF arrests decreased from 37.1 per 100,000 population in 1992 to 19.4 in 2002 [14]. The rate of PEA remained largely unchanged over the study period with a rate of approximately 20 per 100,000 population while the rate of asystole increased from 27.3 to 44.9. This study found that a higher fraction of VT/VF arrests occurred in public places and were witnessed arrests with a negative correlation between paramedic response time and the rate of VT/VF arrest.

## Mechanisms of disease

The pathophysiological basis of PEA is unclear with its understanding hampered by a lack of laboratory models relevant to clinical experience. Asphyxia has been the typical experimental model for the induction of PEA arrest [15] but is limited in its clinical applicability due to being an uncommon cause of death in humans. Part of the challenge in developing a model has been the number of underlying conditions associated with PEA arrest. A review of more than 1000 cases of cardiac arrest occurring in a tertiary care center found that only 13 % of patients with non-cardiac etiologies for arrest presented in ventricular fibrillation while 62 % presented in PEA and the remaining 25 % presented in asystole [16]. Non-cardiac etiologies for arrest in this report included hypoxia, pulmonary embolism, aortic dissection, intoxications and drug reactions, exsanguination, sepsis, and intracranial hemorrhage among multiple other listed causes.

Echocardiographic evaluation of patients in presumed PEA arrest has demonstrated the presence of ventricular wall motion despite the lack of a palpable pulse resulting in an entity termed pseudo-PEA. This condition may be a common presentation with one study demonstrating 19 of 22 patients in presumed PEA having evidence of synchronous ventricular wall motion activity [17]. In a study of patients in presumed PEA, the presence of ventricular wall motion activity on echocardiography has been associated with return of spontaneous circulation (ROSC) [18]. In this study, 8 of 11 patients with sonographic evidence of ventricular wall motion experienced ROSC compared with 0 of 23 patients with no evidence of ventricular activity subsequently obtaining ROSC.

Patients in PEA with no evidence of ventricular activity may represent one end of a continuum of presentations that includes patients in PEA with ventricular activity and patients with evolving shock but with still palpable pulses. Supporting this concept has been the development of a swine model of partial asphyxiation in which a period with persistent ventricular contractions with changes in aortic pulse pressure but with non-palpable peripheral pulses was found to precede the development of PEA with no evidence of ventricular activity [19]. To understand the range of these presentations requires elucidation of the cellular mechanisms underlying the loss of contractile force in the cardiac myocyte. In healthy cardiac muscle, an action potential triggers the entry of calcium ions from the extracellular space into the cytoplasm which in turn triggers a larger release of calcium from stores in the sarcoplasmic reticulum (SR). Calcium ions then bind to troponin C on myofibrils which subsequently allows for the interaction of myosin and actin with the splitting of ATP and the generation of force. The amount of force produced is in part due to variations in the amount of calcium ions released into the cytoplasm from the SR in addition to the sensitivity of the contractile proteins to the concentration of calcium ions. Ischemia may result in diminished contractile force via a reduced transient calcium release from the SR, reduced sensitivity of the contractile proteins to calcium ions, and a reduction of the contractile force activated by calcium [20]. Clinically, acute occlusion of coronary arteries has been implicated in the development of PEA arrest [21]. Of note, changes in coronary perfusion pressure have been found to modulate the intracellular calcium concentration with a subsequent change in contractile force [22]. Utilizing an isolated ferret heart model, Kitakaze and Marban demonstrated a loss of cardiac contractile force with coronary pressure below 60 mmHg with subsequent development of markers of tissue ischemia. The metabolic effects of tissue ischemia are then likely to further impair cardiac contractility [23–25]. Increased intracellular levels of inorganic phosphate, resulting from breakdown of phosphocreatine, has been shown to have a major inhibitory effect on developed contractile force in addition to a smaller effect attributed to the decrease in intracellular pH.

Additional effects on cardiac arrhythmias and contractile force have been attributed to interactions between the heart and nervous system [26]. Primary nervous system dysfunction, secondary to either direct injury or due to environmental conditions resulting in stress, result in elevated levels of circulating catecholamines which can then result in coronary vasospasm or direct injury to myocardial cells. Excessive amounts of circulating catecholamines have been shown to be oxidized to aminochromes, which are highly active quinine compounds, which themselves produce myocardial injury and intracellular calcium ion overload [27]. In a rat model of burn injury, intracellular calcium was found to increase by fourfold compared with control animals with study animals experiencing impairment of cardiac contractility [28]. Of note, levels of circulating catecholamines are elevated in patients with chronic heart failure which may then serve to predispose this patient group to arrhythmias [29].

PEA may then result from a combination of conditions in which impaired coronary pressure results in altered calcium flows in myocardial cells with subsequent loss of contractile force and further loss in coronary pressure. Increased levels of circulating catecholamines, either from chronic stress or perhaps from a new overwhelming stress, may result in further loss of

contrac-tile force resulting in a decoupling of the cardiac action potential from mechanical contraction.

## Potential factors in the increasing incidence of PEA

The crude death rate in the USA fell from 1095 to 799 deaths per 100,000 population from 1935 to 2010 [30]. This actually understates the improvement in the risk of dying as the US population became older over this time period with the age-adjusted death rate over this time period declining from 1860 to 746 per 100,000 population. Cardiac disease has remained the leading cause of death in the USA over this period but has declined markedly as a cause of mortality after reaching its peak in approximately 1968. The age-related death rate per 100,000 population from cardiovascular disease in the USA was 426 in 1950 but had declined to 284 by 1976 [31]. Data from the Framingham heart study noted a 59 % decrease in deaths from coronary heart disease (CHD) from 1950 to 1969 compared with 1990–1999 and a 49 % decrease in the rate of sudden death [32].

The decline in deaths from CHD has been attributed to both improvements in secondary preventive therapies and a change in risk factors associated with the development of CHD [33]. Advances in revascularization therapy, improvements in heart failure management, and improvements in the initial treatment of myocardial infarction have contributed to better secondary preventative therapies. Reductions in total cholesterol, improved blood pressure control, and a decreased prevalence of smoking have all contributed to a change in the risk factors associated with the development of CHD. The decline in death rate attributed to CHD has likely contributed to a decrease in the rate of VF arrests given the association of VF with coronary disease.

Changes in the use of beta-blockers have also likely contributed to changes in presenting rhythms in SCA. A review of 179 cases of SCA presenting to a single hospital from 2001 to 2006 demonstrated an odds ratio of 3.7 for the use of beta-blockers in patients presenting in PEA compared to VF [34]. The use of beta-blockers has also increased over the past few decades as evidenced by a community-based cohort of newly diagnosed heart failure patients in whom beta-blocker use increased by 2.4 % annually from 1989 to 2000 [35]. A British study reported that the use of recommended beta-blockers in male patients being treated for heart failure increased from 6.1 to 27 % of male patients over a 5-year period with a similar increase noted in female patients [36]. Beta-blocker therapy has also been shown to decrease cardiac events in patients with newly diagnosed CHD and a recent myocardial infarction [37] and had previously been noted to decrease the likelihood of sudden cardiac death following myocardial infarction [38]. The increasing use of beta-blockers has likely contributed to a decreased incidence of OHCA due to ventricular fibrillation.

Following the successful use of external defibrillators, implantable cardiac defibrillators (ICDs) were developed with the first devices being implanted in 1980 [39]. Since that time, multiple trials have demonstrated a survival benefit for patients suffering from prior cardiac arrest [40–42] with a subsequent broadening range of clinical indications for ICDs increasing the total number of patients with devices [43, 44]. In 2009, more than 225,000 patients in the USA had ICDs with 133,000 devices implanted in that year alone [45]. A

review of all cases of OHCA in the North Holland province of the Netherlands found that the incidence of VF arrest decreased from 21.1 per 100,000 population in 1995–1997 to 17.4 in 2005–2008 and attributed approximately 33 % of this decline as being due to increased use of ICDs [46•]. A study of 320 patients with ICDs experiencing sudden death found that the most common cause, accounting for 29 % of cases, was PEA occurring after delivery of a shock for treatment of VF [47]. Based on these findings, it is likely that ICDs have both decreased the incidence of VF arrest while also contributing to cases of PEA arrest.

In 1979, chronic lower respiratory diseases became one of the top five causes of death in the USA [30]. By 2000, there were an estimated 10 million adults in the USA with physician diagnosed chronic obstructive lung disease (COPD) and an estimated 24 million adults with impaired lung function [48]. Over the past two decades, the prevalence of COPD has stabilized and subsequently declined while the overall death rate has remained roughly constant from 1999 to 2009 [49]. Over this period, the gender balance has changed with the number of women dying from COPD exceeding the number of men since 2000. Given that women have a lower prevalence of CHD when compared to men combined with increasing numbers of women dying from COPD may be a secondary contribution to the relative increase in the number of PEA arrests.

From 2000 to 2010, the number of hospital deaths in the USA decreased by 8 % even while the number of hospitalizations increased by 11 % [50]. Over this period, the number of deaths attributed to sepsis increased by 11 %. In a prospective study of 173 adult patients presenting to an urban hospital following OHCA 38 % were found to be bacteremic with 91 % of these patients presenting in either PEA or asystole [51]. While the overall significance of these findings is unclear, an increasing burden of patients experiencing multiorgan failure and higher rates of sepsis may contribute to a relative increase in PEA arrests.

## Treatment of PEA

The guidelines for cardiopulmonary resuscitation (CPR) classify PEA and asystole as non-shockable rhythms and call for continued CPR while identifying and managing reversible non-cardiac causes of arrest [52]. Resuscitation guidelines list hypoxia, hypovolemia, acidosis, hypothermia, myocardial ischemia, pulmonary thromboembolism, hyper- and hypokalemia, and drug overdose as potentially reversible causes of PEA. While attempting to reverse the underlying cause of arrest, maintaining cardiac and cerebral perfusion via closed chest cardiac massage is the mainstay of conventional management of PEA arrest.

The mechanism by which chest compressions produce blood flow has been thoroughly explored and appears to be due to changes in intrathoracic pressure that occur with compression of the thorax [53–55]. During compression, increased intrathoracic pressure results in movement of blood out of the thoracic aorta into the brain, abdomen, and periphery. During decompression, the negative pressure gradient from the thorax to the other venous beds results in venous return to the heart. The amount of flow produced from compressions appears to be a function of the pressure gradient achieved and also requires adequate intravascular volume [56].

A variety of mechanical devices have been developed in an effort to improve the efficacy of chest compressions provided to patients in cardiac arrest. Active compression and decompression devices utilize an integral suction cup to promote return of the chest to the neutral position with the goal of increasing negative intrathoracic pressure to augment venous return [57, 58]. Impedance threshold devices are connected in line with a patient's ventilatory support and are designed to augment negative intrathoracic pressure again with the goal of improving venous return [59]. Animal studies of these devices have shown increased blood flow during CPR [60, 61] while a meta-analysis of clinical trials of impedance threshold devices demonstrated significant improvement in favorable neurological outcome following arrest compared with standard resuscitative measures [62]. Load-distributing band devices have also demonstrated improved hemodynamics during resuscitation compared with traditional compressions [63], although clinical trials have yet to reliably demonstrate higher survival to discharge rates in test groups [64, 65]. An especially promising treatment is the use of chest compressions synchronized to cardiac systole to augment blood flow. Given the importance of maintaining cardiac and cerebral perfusion while treating underlying causes of PEA, further efforts to improve the efficacy of chest compressions remain an important area of investigation.

Due to the public health interest in improving the survival rate of OHCA and in increasing the participation of bystanders in performing CPR, there has been an emphasis on prompt initiation of chest compressions with a decreased focus on providing respiratory support [66–69]. Animal studies demonstrate that chest compressions produce airway collapse which may impair ventilation [70] while efforts to quantify the amount of ventilation produced solely from chest compressions suggest that it is not sufficient to provide for adequate ventilation [71, 72]. Animal studies have also demonstrated that cerebral oxygen delivery falls to negligible amounts in compression-only CPR within a few minutes after the onset of VF arrest [73]. Despite these findings, a large trial of compressions-only bystander CPR failed to show inferiority in patient survival to hospital discharge compared with traditional CPR [69]. Additionally, patients who had an advanced airway placed during OHCA were noted to have worse neurological outcomes compared with patients ventilated only through bag-mask ventilation [74].

Initial clinical trials demonstrated a role for post-arrest cooling as a means to improve neurological outcomes following VF arrest [75, 76]. However, these trials were criticized for not controlling for hyperthermia in the standard therapy group leading to concerns that the benefits observed were attributable not to hypothermia but rather for limiting the harmful effects of fever. A recent randomized controlled trial comparing the effects of targeted temperature management to a goal of 33 versus 36 °C failed to find a significant difference in survival or neurologic outcome between treatment groups [77]. This study was also notable for a very high rate of long-term survival among patients who survived to hospital admission when compared with historical averages. However, a porcine model of coronary occlusion in which intra-resuscitation hypothermia was found to significantly reduce myocardial infarct size indicates that there may still be a role for early hypothermia in the management of SCA [78].

In addition to efforts to improve the efficacy of CPR and reduce the physiological and long-term consequences of SCA, efforts to provide for mechanical cardiopulmonary support via extracorporeal oxygenation (EMCO) are currently ongoing. A propensity score-matched observational study found improved survival to discharge and 1-year survival in patients undergoing extracorporeal CPR compared with traditional CPR [79]. Despite a lack of randomized controlled trials, the American Heart Association has proposed the use of ECMO for management of cardiac arrest patients in whom the duration of arrest is brief and in whom reversible causes of arrest are readily identified [80]. While many technical hurdles remain before this becomes an accessible and widely used alternative to conventional CPR, its potential makes it an area of ongoing investigation.

## Conclusions

The relative increase in the incidence of PEA arrest is likely due in part to successes in the treatment of heart disease. Improved treatment of CHD and modification of underlying risk factors, the use of ICDs, and the widespread use of beta-blockers have all likely contributed to the decreased incidence of VF arrest. These factors may have contributed to increasing the number of PEA arrests by altering the presenting rhythm from what would have previously presented as a VF arrest. Additional factors include an aging population with an increasing incidence of multiorgan failure and sepsis that are more frequently present in PEA. Given the dismal survival rates for PEA arrest, ongoing efforts to improve understanding of the mechanisms of PEA arrest, to improve the efficacy of traditional cardiopulmonary resuscitation, and to explore alternative treatment technologies remain the needed areas of investigation.

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