Out-of-Hospital Cardiac Arrest: Getting Beyond the Tip of the Iceberg

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Sudden Cardiac Death – The Scope

Sudden cardiac death (SCD), which is responsible for approximately 300,000 deaths in the United States, refers to an unexpected death from a cardiovascular cause in a person with or without preexisting heart disease. Most studies include cases that are associated with death occurring within 1 hour of an acute change in clinical status, or an unexpected death that occurred within the previous 24 hours\(^1\), but this definition is not specific for sudden arrhythmic death. The most common sequence of events leading to arrhythmic SCD is the degeneration of ventricular tachycardia (VT) into ventricular fibrillation (VF), often followed by asystole or pulseless electrical activity (PEA). The transition of “shockable” rhythms (VT/VF) to more ominous rhythms such as asystole or PEA depends on various factors, but is highly dependent on time – the longer the time interval, the more likely the VT/VF will degenerate to PEA or asystole. While VF and VT together represent the initial rhythm in half of all outpatient cardiac arrests, data suggest that with each passing minute of untreated ventricular fibrillation, the likelihood of survival is reduced by 7% to 10%\(^2\). Preexisting coronary artery disease and its sequelae (e.g., acute myocardial ischemia, scarring from previous myocardial infarction, heart failure) are manifest in 80% of SCD victims. Dilated nonischemic and hypertrophic cardiomyopathies account for the second largest number of SCDs, whereas other cardiac disorders, such as congenital heart disease and underlying genetically determined ion channel anomalies, account for 5–10% of SCDs\(^3\). While the cascade of events triggering SCD are complex and are currently active areas of investigation, the general goals of reducing SCD are focused on: 1) identifying and preventing sudden death in high-risk individuals by using efficacious therapies such as medications and ICDs; 2) organizing resuscitation services to improve response to and efficiency and effectiveness of treatments directed to cardiac arrest.

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victims; and 3) improving survival rates for SCD victims by implementing and organizing
specialized services at hospitals who deliver post-resuscitation care.

Multifaceted approaches have been implemented to reduce the numbers of SCDs. In this
issue of Circulation, Hulleman and colleagues4 assess the role of ICDs in reducing the incidence
of resuscitation for out-of-hospital cardiac arrest (OHCA) caused by lethal ventricular
arrhythmias, the specific target for ICD therapy. They found that the incidence of VF-OHCA
decreased over a 10 year period in North-Holland from 21.1/100,000 inhabitants/year to
17.4/100,000 inhabitants/year and that ICD therapy likely explained approximately one third of
this decrease (1.2/100,000 inhabitants/year). Interestingly, the incidence of non-VF-OHCA
increased during the same time period from 12.2 to 19.4/100,000 inhabitants/year, leading to an
overall increased rate of OHCA.

While many assumptions were made in this report, any one of which could affect the
results, the sensitivity analyses, as well as concordance with other data5-8, suggest that these
estimates have substantial validity. This enables us to use these important data to provide a
global perspective on the tremendous efforts that have been put forth over the last several
decades on prevention of SCD.

SCD Prevention

Response to OHCA

Hulleman et al note that the decline in OHCA VF is overall modest, approximately 17.5%. This
highlights the continued need for efforts to improve our response to OHCA. Many countries
have identified areas to improve OHCA treatment. These efforts focus on “best practices” in
resuscitation medicine and emphasize the need for continuous quality improvement in processes
of care that may translate to improved outcomes for patients with OHCA. This “chain of
survival” includes dissemination of knowledge to improve delivery of bystander CPR, increasing the distribution and early use of AEDs in highly trafficked areas, such as malls and airports, and rapid emergency medical services (EMS) activation and time to initiation of resuscitation efforts.

Despite these advances in out-of-hospital cardiopulmonary resuscitation, survival to hospital discharge after cardiac arrest in most major metropolitan centers in the United States remains poor. Survival to hospital discharge was recently estimated to be 5-10% among OHCA victims treated by emergency medical services personnel. In addition, the majority of SCDs occur at home, often where the event is unwitnessed. As a result, AEDs, which improve resuscitation rates for witnessed arrests, may have limited effectiveness in reducing overall mortality from SCD. Delays in EMS personnel reaching a witnessed SCD victim, not having an AED readily available, and not initiating immediate CPR may contribute to rapid deterioration of a life threatening ventricular tachyarrhythmia to asystole. Importantly, unwitnessed SCD carries a grave prognosis, largely because the time to resuscitation efforts is delayed and resuscitation efforts may not even be initiated in one-third of cases. It is important to note that improvement in post-arrest therapies and approaches are not likely to influence the number of OHCA victims, only the outcome.

Although there are significant limitations in delivering optimal services to OHCA victims, some metropolitan areas adopting systems of care and organized approaches to resuscitative medicine have shown that overall rates of survival from OHCA – in particular witnessed VF -- can improve over time. Time to first shock has averaged 6 minutes in Rochester, MN, and between 2006 and 2008, survival to hospital discharge for bystander-witnessed events in which victims presented with VF exceeded 50%.
 Prevention of OHCA

These coordinated efforts to provide rapid response to SCD victims are complemented by approaches to prevent SCD. Prevention requires a synergy of efforts including proper medical therapy and ICD placement in appropriate high-risk individuals. The work by Hullemen et al is important because it specifically places into context the role of ICDs in reducing VF-OHCA in light of important changes in the epidemiology of disease and other factors in North Holland. As ICD use explained only 33% of the reduced incidence of OHCA VF in this study, this implies that additional factors are significant contributors to the decline in VF OHCA incidence.

Medication use

Improved use of medical therapies, such as beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, potassium sparing diuretics, and polyunsaturated fatty acids that may impact SCD likely have had an impact on the declining incidence of VF-OHCA. These therapies most likely confer their antiarrhythmic potential indirectly by inhibiting or delaying adverse structural remodeling in a diseased heart and by modulating upstream inflammation and neurohormonal pathways, thereby contributing to electrophysiologic stability. Specifically, the authors point out that beta-blocker use, which has been reported to decrease sudden death by up to 50%, may have reduced the incidence of VF. Yet, there are potentially important ramifications of these therapies, particularly in light of the reported increase in nonVF OHCA. OHCA victims taking beta blockers were 5 times more likely to present with non-VF than VF as the first documented rhythm. A recent trial using implantable loop recorders in a population of post-MI patients with left ventricular dysfunction reported that VF and bradyarrhythmias accounted for equal proportions of recordings at the time of death. Even though VT/VF was the terminal rhythm and was associated primarily with SCD,
intermittent high degree AV block was also a strong predictor of cardiac death\textsuperscript{14}. It is conceivable that beta-blockers not only reduce the incidence of VT/VF, but may alter the electrophysiologic milieu in such a manner as to “convert” terminal VF-OHCA events to non-VF events. Further efforts to ensure proper medical therapy and to understand the interactions of medical therapy with the diverse mechanisms of SCD are necessary.

**Declines in Coronary Heart Disease (CHD) Rates**

A second potential reason for reduction in OHCA VF incidence is a concomitant decline in coronary heart disease burden over time. This can likely be explained by improvements in diagnosis and treatment of co-morbidities associated with CHD, such as diabetes, hypertension, and dyslipidemia, and improved targeted therapies and interventions for CHD. Because CHD is the leading cause of SCD in the world, decline in CHD rates should parallel the reduction in VF-OHCA rates to some degree. As the authors note, the decline in VF-OHCA may also be attributed to other changing biological mechanisms in the population at risk for VF.

**Future approaches to OHCA**

The impact of the ICD in reducing the population based problem of SCD is clearly significant, but is far from enough. Certainly one of the factors limiting the population impact of ICDs is the consistent finding that most patients who experience SCD fall outside the current guidelines for consideration of an ICD. Substantial impact on VF-OHCA can be achieved by improving our ability to identify patients at risk for SCD prior to them experiencing a life-threatening event. Importantly, enhancing our risk-stratification armamentarium of tools, genetic markers, and other techniques to provide adequate discriminatory power to manage individual patients requires rigorous and ongoing research\textsuperscript{15}.

While the field of risk stratification for prevention of SCD is currently focused on using
certain approaches to identify appropriate ICD candidates, the importance of this research endeavor transcends this specific treatment. Patients found to be at significant risk for SCD could be treated with a host of therapies including lifestyle modifications (i.e. exercise, diet), more aggressive medical therapy, and newer medical or other novel therapies. Examples of the latter could include vagus nerve stimulators or spinal cord stimulators meant to modulate the autonomic nervous system effects on the heart.

The final challenge in addressing the vast public health problem of SCD is that in a sizable percentage of individuals, SCD is the first manifestation of cardiac disease. Improved public education and screening for cardiovascular disease are modalities that may impact SCD in this subpopulation. Because of the number of susceptible patients who would not be identified as candidates for an ICD using current guideline approaches, it remains important to continue to focus on rapid identification and efficient response systems to OHCA and successful restoration of spontaneous circulation. Continued improvements in this field, such as greater dissemination of AEDs, rapid and early CPR, the development and implementation of hypothermia protocols and other systems of care will also further impact SCD outcomes, and lead to improved survival rates in OHCA. In Philadelphia, for example, a comprehensive multidisciplinary treatment protocol for patients resuscitated from OHCA and its implementation strategy led to survival rates that improved from 22% of OHCA admitted to the hospital with a pulse surviving to discharge to more than 50%.

The future clearly holds significant opportunity to reduce the population burden of OHCA (Figure 1). Our greatest opportunity appears to stem from unlocking the mechanisms and triggering events leading to VF in at-risk individuals and disseminating appropriate therapies to these individuals to limit this risk. Our greatest challenge may be in preventing and treating...
non-VF OHCA, where the triggering events for SCD remain elusive. Because non-VF OHCA represents a sizeable portion of all OHCAs, a better understanding of this mode of SCD and its precursors is required in order to have a tangible impact. The future – as suggested by Hulleman and colleagues – may bring further shifts in OHCA from VF to non-VF cases.

Improvements in risk stratification and identification of individuals as appropriate candidates for medical and device therapy, advancements in medical therapy to limit progression of cardiac disease, and enhancements in resuscitative services collectively will lead to incremental and continued declines in the incidence of VF-OHCA and overall SCD rates. Further studies will be necessary to continue to track the epidemiological impact of all these efforts on OHCA.

Conflict of Interest Disclosures: Dr. Goldberger is Director of the Path to Improved Risk Stratification, NFP, a not-for-profit think tank on risk stratification for prevention of sudden cardiac death, which has received unrestricted educational grants from Medtronic, Boston Scientific, and St. Jude Medical. Drs. Goldberger and Ilkhanoff have received past honoraria from Medtronic, Biotronik, and St. Jude Medical.

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Figure Legend:

**Figure 1.** The universe of out-of-hospital cardiac arrest (OHCA) is divided into those with ventricular fibrillation (VF) and non-VF arrest, with a slight preponderance of the latter based on Hulleman et al. Within each major mode of OHCA, there are opportunities for improved prevention (the middle slices) and improved response (the top two slices), with some of the potential approaches listed. In some cases (the bottom two slices), OHCA is a terminal event for which no preventive or response measures could be effective, termed “Zone of futility.” The sizes of the slices are meant to be relative, not absolute; for example, more non-VF OHCA are likely terminal events than VF-OHCA, and there is greater opportunity for prevention of VF-OHCA than non-VF OHCA.
Out-of-hospital Cardiac Arrest

Opportunity for Improved Response
- Faster EMS response
- AED deployment
- Advances in CPR/ACLS

VF

Opportunity for improved prevention
- Improved risk stratification
- Better utilization of current therapies
- New therapies

nonVF

Opportunity for improved prevention
- Improved mechanistic insights

Zone of futility
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