Epidemiology and genetics of ventricular fibrillation during acute myocardial infarction

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Abstract
Sudden cardiac death (SCD) from ventricular fibrillation (VF) during coronary artery disease (CAD) is a leading cause of total and cardiovascular mortality, and in more than half of SCD cases VF occurs as the first symptom of CAD. Several epidemiological studies have shown that sudden death of a family member is a risk factor for SCD and VF during acute myocardial infarction (MI), independent of traditional risk factors including family history of MI, suggesting a genetic component in the susceptibility to VF. To prevent SCD and VF due to MI, we need a better understanding of the genetic and molecular mechanisms causing VF in this apparently healthy population. Even though new insights and technologies have become available, the genetic predisposition to VF during MI remains poorly understood. Findings from a variety of different genetic studies have failed to reach reproducibility, although several genetic variants, both common and rare variants, have been associated to either VF or SCD. For this review, we searched PubMed for potentially relevant articles, using the following MeSH-terms: “sudden cardiac death”, “ventricular fibrillation”, “out-of-hospital cardiac arrest”, “myocardial infarction, myocardial ischemia”, “coronary artery disease”, and “genetics”. This review describes the epidemiology and evidence for genetic susceptibility to VF due to MI.

Keywords: Family history; Genetics; Myocardial infarction; Sudden cardiac death; Ventricular fibrillation

1 Introduction
Sudden cardiac death (SCD) is a worldwide leading cause of all death (15%–20%) and more than half of all cardiovascular deaths.[1–8] Coronary artery disease (CAD) and its ultimate consequence, myocardial infarction (MI), are believed to underlie 75% of SCDs and is an even more common cause of death among the elderly.[1,9] During the acute phase of MI, studies have suggested that 3%–12% of all MI cases develop ventricular fibrillation (VF) resulting in sudden cardiac arrest (SCA), the real number is beyond doubt higher as many are found dead.[10–14] SCD is one of the main challenges to clinicians, because in more than half of the cases CAD has not previously been recognized clinically, and SCD occurs as its first symptom.[15,16] Previous studies have shown that a family history of sudden death is a risk factor for SCD and VF due to MI,[10,17–20] independent of traditional risk factors for CAD including a family history of MI,[10,19] strongly suggesting a genetic component. However, the underlying genetic factors are largely unknown and the predisposing genetic architecture is complex and most likely polygenetic.[7] The understanding of the risk factors and underlying genetic cause of VF due to MI have major clinical implications and there is an urgent need to understand the underlying pathophysiological mechanisms in order to predict and prevent development of VF and SCD. The ultimate goal is to prevent adverse cardiac events through early identification of individuals at risk. Identification of genetic susceptibility factors will provide deeper insight into the mechanisms of VF caused by MI, which might result in better targets for prevention and development of new therapies. Therefore, this review will focus on describing the epidemiology and the evidence for genetic susceptibility to VF due to MI.

2 Method
We searched PubMed for articles published the last 20 years, last search 10th January 2016. The full search strategy in PubMed included the following MeSH-terms: Death, Sudden, Cardiac AND Ventricular Fibrillation AND Myo-
cardiac Infarction OR Myocardial Ischemia OR coronary artery disease (399 hits), Out-of-Hospital Cardiac Arrest AND Ventricular Fibrillation AND Myocardial Infarction OR Myocardial Ischemia OR coronary artery disease (26 hits), Genetics AND Death, Sudden, Cardiac OR Ventricular Fibrillation (102 hits). Both abstracts and full-text papers were reviewed. In addition, references from reviewed articles were searched for other relevant articles.

3 Burden of SCD and VF caused by MI

SCD is a major public health problem affecting millions of people each year worldwide.\(^1\)\(^{-}\)\(^{20}\) The incidence of SCD and SCA increases with age,\(^27\)\(^{-}\)\(^{28}\) and therefore most commonly affecting older persons. Although studies indicate that incidence of SCD\(^20\) and VF as a cause of out-of-hospital cardiac arrest\(^30\) is declining, VF itself is the most common underlying arrhythmia in SCDs.\(^1\)\(^,\)\(^8\)\(^,\)\(^15\)\(^,\)\(^31\) In the thrombolytic era, the incidence of ventricular arrhythmias in patients with acute MI ranged from 3.7%–10.2% in large randomized studies.\(^32\)\(^{-}\)\(^{34}\) However, in the era of primary PCI, the incidence of ventricular arrhythmias appears to be lower.\(^1\)\(^,\)\(^35\) In two separate studies among 5745 and 5373 enrolled ST-elevation myocardial infarction (STEMI) patients with primary percutaneous coronary intervention (PCI), VF or VT occurred in 5.7% and 9.3%, respectively.\(^1\)\(^,\)\(^35\) Nevertheless, the true incidence of VF is underestimated as individuals who suffer SCD out-of-hospital are not covered by these studies. Investigating the epidemiology of the phenotype is complicated by the fact that patients that develop VF during acute MI have a high mortality.

4 Pathophysiology of VF caused by MI

The pathophysiology of VF during MI is complex and is associated with both environmental and genetic causes.\(^1\)\(^7\),\(^1\)\(^9\),\(^1\)\(^0\),\(^2\)\(^0\),\(^2\)\(^3\),\(^3\)\(^7\) VF in the setting of MI is most likely the result from the complex interaction of multiple factors, including ongoing ischemia, hemodynamic alterations, electrolyte abnormalities, macro-reentry due to different conduction velocities in ischemic and non-ischemic areas, genetic, and environmental triggers.\(^3\)\(^8\)\(^{-}\)\(^{42}\) Acute obstruction of the coronary flow will affect the resting membrane potential and inward and outward ionic fluxes during the action potential leading to alterations in conduction, refactoriness, and automaticity in cardiac muscle cells.\(^43\) Most common VT provoked by early after depolarization that degenerates first to VF, followed by an increase in VT frequency and QRS width, and later to asystole.\(^6\)\(^,\)\(^4\)\(^4\) Experimental studies have found that there are different phases of in which post-MI VF occurs.\(^4\)\(^3\),\(^4\)\(^5\) The first phase (phase 1a or “immediate ventricular arrhythmias”) occurs between 2–10 min after occlusion, with the highest incidence of arrhythmias at 5–6 min, and the second phase (phase 1b or “delayed ventricular arrhythmias”) occurs from 12–30 min after occlusion, with a peak at 15–20 min.\(^6\)\(^3\)

5 Risk factors associated with VF caused by MI

Clinically, it is difficult to assess the risk of SCD and VF due to MI in the general population, because most episodes occur mainly in low risk subgroups without known risk factors as pointed out by Huikuri, et al.\(^1\)\(^5\) The majority of the VF and SCD cases is thought to occur in asymptomatic individuals without a preexisting structural cardiac disease and represents the first manifestation of CAD.\(^1\)\(^5\),\(^1\)\(^6\),\(^3\)\(^1\),\(^4\)\(^6\),\(^4\)\(^7\)–\(^4\)\(^\)\(^8\) Patients with similar risk factors for MI may suffer from VF/SCD, while others do not. Over the last decades, manifold screening strategies to lower the burden of SCD in the general population have been discussed.\(^4\)\(^9\)–\(^5\)\(^1\) The optimal way of lowering the burden of SCD is to prevent MI. One approach is finding patients at risk before the triggering MI event where angina is the classical symptom, even among the young patients experiencing SCD due to CAD.\(^5\)\(^2\) Recent reviews have focused on existing and novel risk stratification tools for SCD due to ventricular arrhythmias.\(^5\)\(^3\),\(^5\)\(^4\) They highlighted that the majority of SCDs occur in individuals without known heart disease, where risk prediction of the unpredicted is difficult. However, in most of these studies it is difficult to differentiate between risk factors for MI and risk factors for VF due to MI. In an attempt to narrow the phenotype, identify a population with a similar pathology and phenotype, two studies have investigated VF during first STEMI.\(^1\)\(^0\),\(^1\)\(^9\) The first study to differentiate between risk factors for STEMI and risk factors for the development of VF in the acute phase of STEMI was the AGNES (Arrhythmia Genetics in the Netherlands) study.\(^1\)\(^9\) In AGNES, patients with their first acute STEMI with VF (cases, \(n = 330\)) were compared to patients with their first STEMI without VF (controls, \(n = 372\)). Interestingly, hypercholesterolemia was significantly lower in patients who developed VF during their first STEMI than those who did not have such arrhythmia.\(^1\)\(^9\) However, these findings were not confirmed in our Danish nationwide prospective GEVAMI (GEnetic causes of Ventricular Arrhythmia in patients with first ST-elevation Myocardial Infarction) case-control study among patients with first STEMI with VF (cases, \(n = 219\)) and without VF (controls, \(n = 441\)) before PCI.\(^1\)\(^0\) Furthermore, a similar result to our GEVAMI
study was found in the Nurses’ Health Study from the US, which reported that a history of hypercholesterolemia was not a significant predictor for SCD.\[31\] In addition, there is considerable evidence that traditional cardiovascular risk factors, such as hypertension, obesity, smoking, lipid abnormalities and diabetes, are not specific enough to identify patients at high risk to VF and SCD caused by MI\[10,15\]. However, in the GEVAMI study, we identified several patients characterized associated with a significantly higher risk of VF before PPCI after adjusting for common cardiovascular risk factors, infarct location, and thrombolysis in myocardial infarction (TIMI) flow.\[10\] These independent risk factors included younger age (< 60 years), a family history of sudden death, the absence of pre-infarction angina, statin use, a history of atrial fibrillation, and alcohol intake greater than seven units/week.\[10\]

6 Heritability of VF, familial aggregation

Several studies have previously demonstrated a familial aggregation of SCD/SCA and sudden death, suggesting a possible influence of genetic factors on SCA and SCD risk.\[10,17–20\] The first of these studies was published in 1998 by Friedlander, et al.\[17\] showing that a family history of MI or primary cardiac arrest was independently associated with an increased risk of primary cardiac arrest (RR = 1.57; 95% CI: 1.27–1.95). Furthermore, the authors reanalyzed their data by differentiating between family history of MI and family history of sudden death among first-degree relatives and found that a parental history of early onset (age < 65 years) of sudden death was associated with an increased risk of primary cardiac arrest (OR = 2.69; 95% CI: 1.35–5.36), after adjustment for parental history of MI and other risk factors.\[55\] However, a major limitation of this case-control study is that the matched control group consisted of healthy volunteers without a history of cardiovascular disease, and not patients with CAD. The observational Paris Prospective Study I confirmed that parental sudden death is an independent risk factor for sudden death in middle-aged men (n = 7746).\[18\] A family history of sudden death on either the paternal or the maternal side of family was associated with a nearly 2-fold increased risk of sudden death, and if both parents had a history of sudden death, there was a 9-fold increased risk of dying suddenly. Furthermore, the study indicated that even though a family history of sudden death increased the risk for sudden death it did not increase the risk for acute MI, suggesting the possibility of different risk factors for sudden death and MI.\[13\] However, important is that these two initial studies\[17,18\] did not distinguish between the different phenotypes of sudden death (arrhythmic vs. non-arrhythmic), nor between underlying CAD (STEMI vs. non-STEMI).

The pioneering Dutch AGNES study was the first study to suggest an association between family history of sudden death and VF caused by first STEMI.\[19\] In this population, recruited at multiple Dutch heart centers, they demonstrated that individuals with a history of sudden death in a parent or siblings had 3.3 times the odds of VF compared with individuals with no family history of sudden death, even after adjustment for SCD risk factors, including degree of ST-segment elevation. In our own Danish GEVAMI study,\[10\] familial sudden death occurred significantly more frequently among cases than controls (38% vs. 26%, respectively) resulting in an odds ratio of 1.80 (95% CI: 1.27–2.56; P = 0.001). These data support a strong role for heritable factors in the risk for VF during a first MI.\[10,19\] Moreover, in contrast to previous studies, these two studies\[10,19\] only included patients who experienced their first acute coronary event, because the risk factors and mechanisms of SCD may differ significantly between those with and without a prior MI. Another study, from Finland showed that the risk of SCD appears to be high if two or more first-degree relatives have experienced SCD.\[20\] Subjects with a family history of SCD among first-degree relatives have an increased risk of dying suddenly during an acute coronary event. Despite the different population characteristics and methods in the studies above,\[10,17–20\] the results taken together demonstrated that there is a familial aggregation of VF during STEMI and SCD, suggesting that shared genetic variants may influence vulnerability to VF due to MI and SCD.

7 Genetics, susceptibility to ischemic VF

Even though the literature mentioned above indicates a genetic predisposition to VF during acute MI, little is known about the exact genetic component that increases the vulnerability to VF caused by MI in the general population. The allelic architecture of complex disorders such as VF due to MI and SCD are likely to involve both common variants with modest effect and rare variants with stronger effects.\[56\] Several studies have examined the association of common and rare genetic variants to either SCA and/or SCD.\[37,57–80\] However, only few of the variants identified in these studies have been replicated, and many do not yet have a clear functional implication, and furthermore, a minority of the studies have focused on VF and SCD in the context of CAD (Table 1).

The genetic component of VF and SCD due to MI have primarily been investigated using either candidate gene or genome-wide approaches, however, the rapid expansion and
7.1 Common genetic variants

The first GWAS to identify common genetic variants, single nucleotide polymorphisms (SNP), associated with VF during acute MI was in the Dutch AGNES study. This GWAS was conducted in a set of 972 individuals, 515 cases (STEMI patients with VF) and 457 controls (STEMI patients without VF). The most significant association with VF was found at 21q21 (rs2824292, OR = 1.78, 95% CI: 1.47–2.13; P = 3.3x10^-10) and was replicated in an independent case-control set consisting of 146 cases of out-of-hospital cardiac arrest, individuals with MI complicated by VF from the ARREST study and 391 individuals who survived an acute MI (OR = 1.49, 95% CI: 1.14–1.95; P = 0.004). Interestingly, the closest gene to this SNP is CXADR, which encodes a coxsackievirus and adenovirus receptor previously implicated in myocarditis and dilated cardiomyopathy and which has been identified as a modulator of cardiac conduction. However, this locus has not been implicated in arrhythmia susceptibility. Even though this SNP reached GWAS significance, the SNP was not replicated in a smaller German case-control study (cases = 90; controls = 167). In a large scale meta-analysis of several GWAS two SNPs (rs6730157 in the RAB3GAP1 gene...
on chromosome 2q21 and rs2077316 in the ZNF365 gene on chromosome 10q21 were associated with SCD due to CAD.\[74\] Furthermore, in a combined meta-analysis among 1283 SCD cases from five separate studies and 20,000 control individuals, all of European ancestry, a locus at chromosome 2q24.2 (rs4665058) was found to be associated with SCD with a relatively strong effect size (OR:1.92, 95% CI: 1.57–2.34).\[67\] However, this SNP was not found in the AGNES study. Another GWAS reported 11 gene associations for SCA due to VF in patients with CAD, including validation of 4 previous published gene associations for SCA.\[66\] A novel genetic locus, GPC5, for SCA due to CAD was identified in the ongoing Oregon Sudden Unexpected Death Study (Oregon-SUDS), and further validated in 2 other cohorts.\[65\] The minor allele of GPC5 (GLYPICAN 5, rs3864180) was associated with a lower risk of SCA (OR = 0.85).

Previous candidate studies have reported that common variants in genes encoding ion-channel subunits contribute to SCD risk.\[57–62\] A systematic candidate-gene study reported that common variants in or near CASQ2, GPDL1 and NOS1AP were associated with increased risk of SCD in patients with CAD.\[58\] They observed and validated significant associations between SCD risk and SNPs in genes previously associated with relatively rare inherited forms of arrhythmias. Furthermore, in a combined analysis of six prospective cohort studies, two common intronic variants in KCNQ1 and SCN5A were associated with SCD in individuals of European ancestry.\[57\] The SNPs rs2283222 in KCNQ1 and rs11720524 in SCN5A were significantly associated with SCD (OR = 1.30 and 1.36, respectively).\[57\] However Marcusa, et al.\[80\] were unable to reach a significant signal for rs11720524 in a heterogeneous SCD cohort. In this case-control study they included both established and probable ischemic cardiac death cases (n = 360) and age-matched controls (n = 300).\[80\]

It should be noted that these studies mentioned above identified a variety of variants without detecting variants from the other studies. There is no obvious explanation for this disparity. Several reasons exist for a failure to replicate SNPs. First, it could be insufficient power to detect the modest effect size. Second, it could be because of differences in the clinical phenotypes. Third, the effect of the risk allele may differ between populations because of gene-gene or gene-environment interactions.\[85\] This lack of replication highlights the difficulties, which is commonly seen in genetic studies related to SCD and VF, and probably relates to the heterogeneity, both within and between studies. Larger sample sizes and homogenous enriched subgroups will be needed to identify and replicate additional genetic variants associated with VF during acute MI. More studies need to be done to uncover a causal relationship. Using well-defined phenotype subset of individuals with a certain disease can facilitate gene discovery from complex traits, such as VF during STEMI.

7.2 Rare genetic variants

As mentioned above it is possible that VF due to MI is caused by rare variants with variable penetrance. To date, few studies have examined rare variants in genes encoding ion-channels,\[59,62,63,86,87\] such as variants in the SCN5A gene, which encodes the α-subunit of the cardiac sodium channel responsible for cardiac action potential conduction and are known to be risk factors for arrhythmia.\[86,87\] The rare genetic variants that contribute to SCD and VF caused by MI are largely unknown and unexplored. Stecker, et al.\[59\] found no unique or rare allelic variants of SCN5A among the 77 cases of SCA with associated CAD and 91 control individuals. In contrast, Albert, et al.\[62\] identified five unique or rare missense variants in three exons of SCN5A in 60 women with SCD. This study aimed to find mutations in cardiac ion channel genes, so the entire coding sequence and splice junctions of five ion channel genes associated with SCN5A, KCNE1, KCNE2, KCNQ1 and KCNH2, were directly sequenced. A recent study that aimed to investigate the role of SCN5A mutations and polymorphisms in the development of VF during acute MI reported that only two of 49 MI/VF patients (4.1%) demonstrated SCN5A variants that may be the cause of VF.\[86\] A small case-control study of VF survivors with CAD (n = 45) found significantly higher frequency of selected, rare coding variants in five long QT genes.\[88\] Another small study of 19 patients with VF during acute MI found one missense mutation (G400A) in SCN5A.\[89,90\] However, the potential association of SCN5A mutations with VF during acute MI remains unclear, and requires further investigation. These data suggest that mutations or rare variants may contribute to SCD and VF due to MI, but also emphasizes the need for further investigation. Such rare variants are best detected by direct sequencing. Because of the rapid development of next generation sequencing (NGS) technologies, large-scale sequencing projects are becoming possible allowing the examination of rare genetic variants. NGS facilitates rapid sequencing of the entire genome and/or exome in a highly efficient and cost effective manner. However, whole genome and exome methods are still too expensive to use at a large scale for most research groups.

8 Perspectives

VF and SCD caused by MI remains a major public health
problem. Despite tremendous research on risk stratification for predicting VF and SCD, it is still an enormous challenge for physicians to predict risk, especially in the general population.\[53,54,91,92]\) To understand this complex phenotype, we need a solid and complete understanding of clinical, genetic and epigenetic risk factors for VF in the setting of acute MI (Figure 1). Identification of genetic factors that predispose to VF during ischemia is important for further genetic testing which may contributes to a better risk stratification. Identification of genetic susceptibility factors will provide deeper insight into the mechanisms and perhaps identify better targets for prevention and development of new therapies. A recent comprehensive study highlighted that genetic risk scoring can be used to predict the risk of SCD.\[93]\) This study showed that a score formed of the most significant common genetic risk variants for CAD is associated significantly with the occurrence of CAD-related out-of-hospital SCD.\[93]\) Furthermore, in the past years, interest has been focused on epigenetics and the importance of epigenetics alterations which are heritable changes in gene expression or phenotype that do not involve a change in DNA sequence.\[94–96]\) There is a growing evidence that epigenetic factors may modify the genetic variations. Future research needs to incorporate epigenetics for a better understanding of this complex phenotype, and to build a bridge between genes and risk factors. Progress in both the genetic and epigenetic field will have an important impact on our understanding of this unique phenotype.

9 Conclusions

Several studies have shown that a family history of sudden death increases the risk of experiencing a cardiac arrest during acute MI, which suggests a genetic background. Generally, the manifestation of VF during acute MI should be considered as the interaction of several genetic and non-genetic factors. Developing an understanding of genetic contributions to VF during acute MI may support the current management, including risk stratification in the general population, thereby improving our ability to predict and prevent. Ideally, we would have a prediction model including genetic and epigenetic risk factors that allows clinicians to identify patients at risk for VF. This systematic review confirmed that after decades of research, the genetics of VF during acute ischemia and SCD due to MI largely remain to be explained.

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