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# Pathophysiology, risk stratification, and management of sudden cardiac death in coronary artery disease

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## Abstract

*Management of sudden cardiac death (SCD) is undergoing radical change in direction. It is becoming increasingly appreciated that besides depressed left ventricular systolic function and the conventional risk stratification tools, new markers for plaque vulnerability, enhanced thrombogenesis, specific genetic alterations of the autonomic nervous system, cardiac sarcolemmal and contractile proteins, and familial clustering may better segregate patients with atherosclerotic coronary artery disease (CAD) who are at high risk of SCD from those who may suffer from nonfatal ischemic events. Better understanding of pathophysiologic processes such as post-myocardial infarction remodeling, the transition from compensated hypertrophy to heart failure, and the increased cardiovascular risk of CAD in the presence of diabetes or even a pre-diabetic state will help to improve both risk stratification and management. The rapidly developing fields of microchips technology, and proteomics may allow rapid and cost-effective mass screening of multiple risk factors for SCD. The ultimate goal is not only to change the current direction of management strategy of SCD away from increased ICD utilization, but to identify novel methods for risk stratification, risk modification, and prevention of SCD that could be applied to the general public at large.* (Cardiol J 2010; 17, 1: 4–10)

**Key words: sudden cardiac death cascade, diabetes and sudden cardiac death, the autonomic nervous system, post infarction remodeling, systolic dysfunction, genetics**

## Coronary artery disease and sudden cardiac death cascade (Fig. 1)

The majority of sudden cardiac death (SCD) occurs in patients with atherosclerotic coronary artery disease (CAD) (65–85%) [1]. However, there is considerable evidence that traditional markers of CAD, such as hypertension, obesity, smoking, diabetes, and lipid abnormalities, are not specific enough to identify patients at high risk for SCD [2]. Patients with similar risk factors for CAD may suffer from SCD or nonfatal ischemic events. The reason for this difference is not clear. Exciting evidence has been made in recent years in genetic studies of CAD and myocardial infarction (MI). One disease-causing gene for CAD and MI has been identified as MEF2A, which is located on chromosome 15q26.3 and encodes for a transcriptional factor with high level of expression in coronary endothelium [3]. Approximately 1% to 2% of CAD patients may carry an MEF2A mutation. Several other susceptibility genes have been identified using genome-wide association studies or genome-wide linkage studies [3]. There is a new understanding of the

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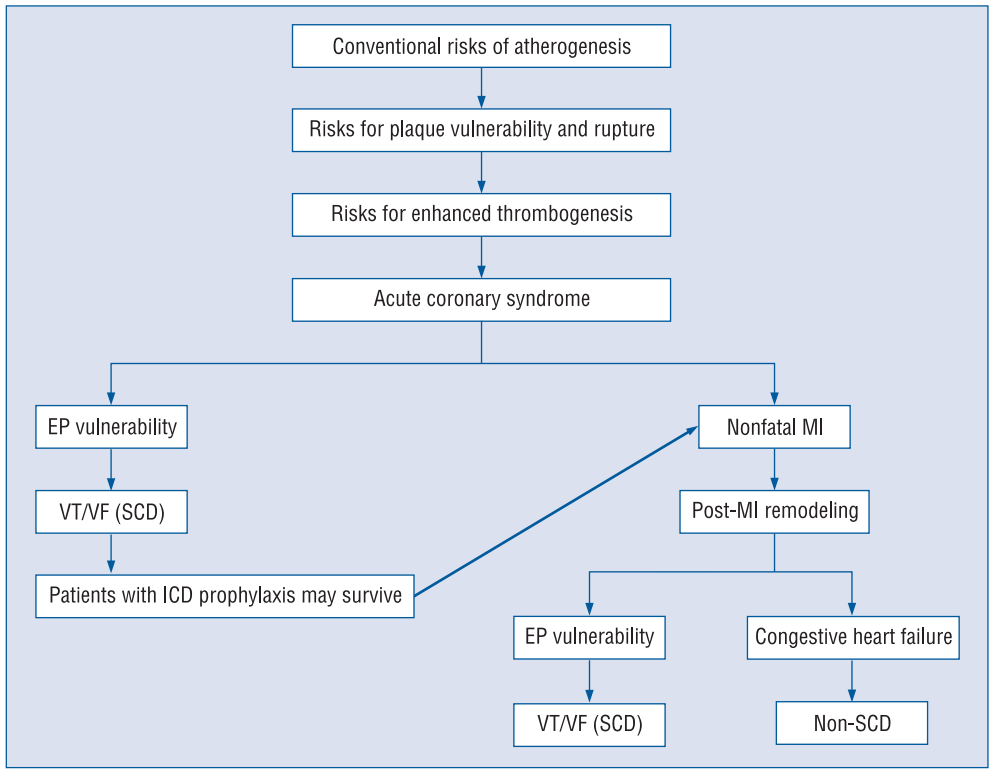


**Figure 1.** Coronary artery disease (CAD) and sudden cardiac death (SCD) cascade; EP — electrophysiological; ICD — implantable cardioverter defibrillator; MI — myocardial infarction; VT/VF — ventricular tachycardia/ventricular fibrillation.

cascade that relates the distal events of atherosclerosis to the proximal event of SCD. New risk markers for SCD in CAD are likely to cluster under factors that may directly facilitate the development of acute coronary syndromes, specifically those factors that may facilitate transient triggering events, including plaque rupture, enhanced thrombogenesis, and coronary artery spasm [4, 5]. There is significant data showing correlation between SCD and 1) markers of plaque vulnerability, such as heritable alterations of specific matrix metalloproteinases [6]; 2) markers of enhanced thrombogenesis, such as increased D-dimer, increased apo-B, and decreased apo-A1 [7]; polymorphism in platelet glycoprotein receptors [8]; 3) genetic variations that predispose to vasospasm, such as variations in the vascular endothelial nitric oxide synthetase (eNOS) system [9, 10]; and 4) markers of inflammatory response, such as C-reactive protein [11].

## Diabetes, coronary artery disease, and risk of sudden cardiac death

Cardiovascular disease is the leading cause of death in individuals with type 2 diabetes, which affects about 15 million Americans [12]. This is compatible with the "common soil" hypothesis, which postulates that both diabetes and cardiovascular disease have common genetic and environmental antecedents, i.e., "they spring from the same soil" [13]. There is evidence that diabetes is a significant risk factor for SCD but not for nonfatal MI [14]. The increased risk of death and mortality rates associated with diabetes are compounded by the fact that many diabetic individuals are unaware that they suffer from the metabolic syndrome. There is strong evidence that the elevated risk for cardiovascular disease starts to increase long before the onset of clinical diabetes, confirming the so-called "ticking clock" hypothesis [15]. The incidence of impaired glucose tolerance and diabetes may be as high as 39% and 31%, respectively, in patients admitted with acute MI [16]. Recent studies have documented increased inflammation, neovascularization, and intraplaque hemorrhage in human diabetic atherosclerosis [17]. Because of vulnerability of diabetic patients to plaque rupture and acute MI, a question of considerable importance is whether patients with CAD, diabetes or prediabetes, and relatively preserved left ventricular (LV) systolic function (left

ventricular ejection fraction — LVEF ≥ 35%) can benefit from primary implantable cardioverter--defibrillator (ICD) prophylaxis.

## The autonomic system and enhanced susceptibility to sudden cardiac death

Autonomic neural influences, especially increased adrenergic and decreased cholinergic activity, can modulate the susceptibility to SCD following MI. Resting heart rate has been shown to be an independent risk factor for SCD in middle-aged men [18]. There are data showing the heritability of heart rate variation [19]. Adrenergic agonists are known to trigger ventricular arrhythmias, and their circulating levels have similar diurnal patterns as SCD events [20]. Genetic polymorphism of $\beta$-adrenergic receptors have been associated with increased susceptibility to SCD in ischemic deart disease [21]. The association between plasma nonesterified fatty acids and SCD may be related to increased adrenergic tone or the effect on ion channel and transporters [22]. Further, mental stress was found to be associated with lateralization of mid brain activity resulting in imbalanced activity in right and left cardiac sympathetic nerves and increased dispersion of repolarization, predisposing to arrhythmia [23]. Recently a third type of $\beta$-adrenergic receptors, $\beta$-3 adrenergic receptors were found in the human heart [24]. In both failing and post-MI myocardium, $\beta$-3 adrenergic receptors stimulation may have protective effects against $\beta$-1 and $\beta$-2 catecholaminergic stimulation [25]. This makes $\beta$-3 adrenergic receptors a very attractive target for pharmacologic therapy of cardiac arrhythmias related to cardiac sympathetic nerve stimulation.

## Cardiac gene mutations and enhanced susceptibility to sudden cardiac death

There is compelling evidence that a genetic mechanism may increase a patient susceptibility to SCD following MI. Subtle genetic variations such as single nucleotide polymorphisms can influence the phenotypic expression of low penetrance ion channel mutations and increased the propensity to VA and SCD [26]. One clue of the role that genetic factors may play in SCD has been evidence of "family clustering" of SCD victims. Population studies have reported that familial clustering of SCD events is an important independent factor in multifactorial analyses of SCD risk. This may be related to shared environmental or genetically transmittable abnormalities. Evidence favoring a focus on genetic factors was presented in epidemiologic studies that suggested not only that familial risks for SCD appear substantial, but that they are statistically distinct and separable from familial risks of MI [27––30]. In one study parental history of SCD increased the relative risk of SCD to 1.8 after adjustment for conventional CAD risk factors, but it did not elevate the risk for deaths coded as non-sudden. In a small subset in which there was a history of both maternal and paternal SCD events, the relative risk for SCD in offspring was up to 9.4 [28].

Further, the role of modifier genes (gene–gene interaction) is beginning to be appreciated.

Modifier genes are genes that are not involved in the genesis of the disease but modify the severity of the phenotypic expression. The final phenotype is the result of interactions among causal genes, modifier genes, and environmental factors. Identification of modifier genes will complement the results of studies of causative genes and could enhance genetic-based diagnosis, risk stratification, and implementation of preventive and therapeutic measures of SCD [31].

## Post-myocardial infarction remodeling and sudden cardiac death

Patients who suffer from a nonfatal MI as well as those who survive SCD in the setting of acute MI later undergo post-MI remodeling. Ventricular remodeling is the process by which ventricular size, shape and function are regulated by mechanical, neurohormonal, and genetic factors [32–34]. Remodeling may be physiological and adaptive during normal growth or pathological due to MI, cardiomyopathy, hypertension, or valvular heart disease. Post-MI remodeling is a complex time-dependent process that involves structural, biochemical, neurohormonal and electrophysiologic alterations. The acute loss of myocardium results in an abrupt increase in loading conditions that induces a unique pattern of remodeling involving the infarcted border zone and remote noninfarcted myocardium [35]. Post-MI remodeling is associated with time-dependent dilatation, distortion of ventricular shape, and hypertrophy of the noninfarcted myocardium. Following a variable period of compensatory hypertrophy, deterioration of contractile function may develop resulting in congestive heart failure.

In recent years the understanding of the signal transduction pathways for cardiac remodeling in the post-MI heart [36, 37] has provided opportunities for novel therapeutic interventions.

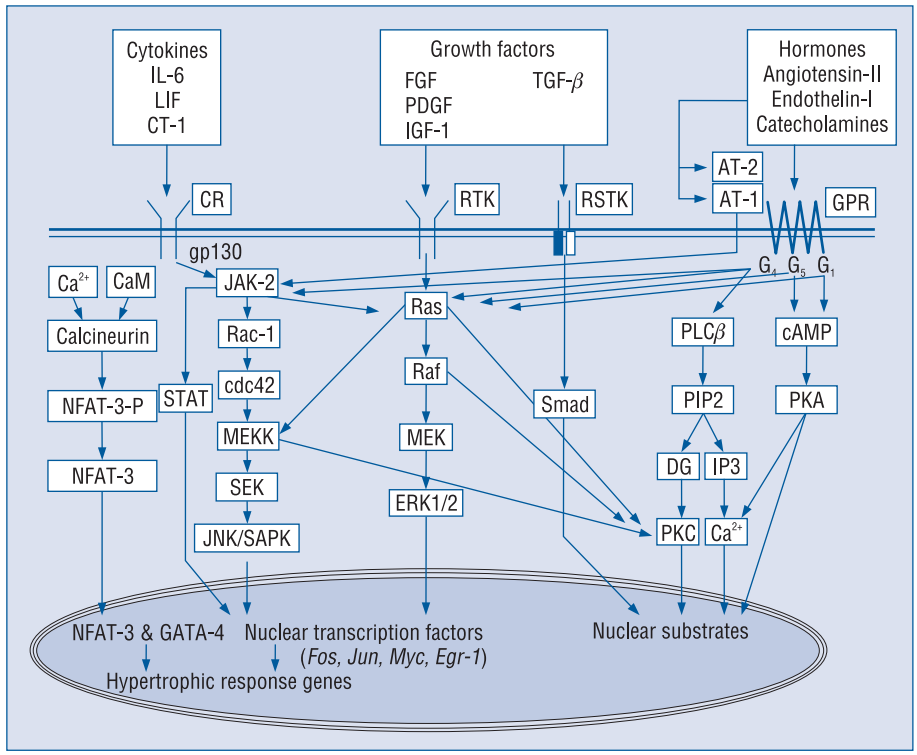


**Figure 2.** Post-myocardial infarction signaling pathways (modified from [34], with permission of Elsevier).

Figure 2 illustrates a proposed scheme for post-MI signaling pathways [31]. Many of these pathways were shown to be activated either in response to ischemia/reperfusion stimuli or to a stretch stimulus using different experimental models and sometimes non-cardiac cell systems. However, cell membrane receptors and intracellular signaling proteins are highly conserved between mammalian species and the triggering events for cellular hypertrophy in humans are likely to resemble closely those in the various animal models used. The diagram shows that a cascade of successive transduction steps allows signal enhancement and diversification at branching points and thus permits combinatorial interactions between multiple pathways. Although multiple signaling pathways may act in synergistic, antagonistic, or permissive way some key pathways may play a dominant role. There is a plethora of experimental and clinical evidence showing that the renin–angiotensin system and the $\beta$-adrenergic system play major roles in post-MI remodeling [34]. This explains the beneficial role that angiotensin converting-enzyme inhibitors, AT-1 receptor antagonists, and beta-blockers in the post-MI period. More recently, other signaling pathways, for example, the calcineurin pathway [38] and the Janus kinase/signal transducer and activator of transcription (JAK-STAT) [39] signaling pathway were also found to play a significant role in post-MI remodeling. Pharmaceutical agents that can block these pathways may provide new therapeutic modalities in the post-MI period.

## Post-myocardial infarction remodeling and electrophysiological vulnerability

A key electrophysiologic alteration in post-MI remodeled heart is down regulation of $K^+$ gene expression and $K^+$ currents resulting in spatially heterogeneous prolongation of action potential duration and increased dispersion of refractoriness [40]. For many years the observation was made that cardiac hypertrophy from whatever cause is consistently associated with down regulation of $K^+$ channel genes and $K^+$ currents. However, recent studies have shown that, in the post-MI heart, this down regulation occurs early and may be dissociated from the slower time course of post-MI remodeled hypertrophy [40]. It is therefore not surprising that the post-MI heart is more sensitive to hypokalemia and the proarrhythmic effects of drugs that depress $K^+$ currents, especially $I_{kr}$ blockers. Some pharmacological interventions that have been shown to reduce the incidence of SCD in post-MI

**Table 1.** Risk stratification of sudden cardiac death.

| Electrophysiological surrogates | Functional, biochemical, and genetic surrogates |
|---|---|
| **Measures of conduction disorder:** | **Funcional markers:** |
| Signal averaged electrocardiogram, % of scar tissue in cardiac magnetic resonance | Left ventricular ejection fraction* |
| **Measures of dispersion of repolarization:** | **New York Heart Association class** |
| QT dispersion, T-wave alternans | |
| **Measures of autonomic nervous system:** | **Biochemical markers:** |
| Direct: sympathetic nerve activity, 1231-MIBG scan | C-reactive protein |
| Electrocardiogram-based: heart rate variability, baroreceptor sensitivity, heart rate turbulence, QT dynamicity | Homocysteine level<br>Serum matrix metalloproteinase<br>Beta natriuretic peptide, etc. |
| **Measures of altered calcium kinetics ???** | **Genetic markers ???** |

*Curently, left ventricular ejection fraction ≤ 35% is the main criterion for primary implantable cardioverter-defibrillator prophylaxis

patients, like magnesium [41] and spironolactone [42] may act by countering the effects of low $K^+$.

## Sudden cardiac death and systolic dysfunction

Although the exact mechanisms involved in the strong correlation between decreased LV systolic function and increased incidence of SCD are not clearly defined, it is now recognized that one way to combat SCD following MI is to try to halt or improve the deterioration in LV function. The mechanism(s) for the transition from compensated to decompensated heart failure is under intensive investigation and it is clear that multiple factors are involved [43]. The role of continuous loss of cardiomyocytes to apoptosis in the noninfarcted myocardium; the negative consequences of remodeling of the interstitial matrix; the downregulation of the $\beta$-adrenergic receptor-G protein-adenylyl cyclase pathway; the downregulation of the L-type calcium current, and the alterations in calcium regulated excitation-contraction coupling are some of the major mechanisms involved. Recent years have seen significant advances in the treatment of ventricular systolic dysfunction and heart failure. The therapeutic armamentarium includes not only pharmacological agents, but also electrical and surgical devices. Besides the cornerstone drugs for heart failure like digoxin, diuretics, angiotensin converting--enzyme inhibitors, and $\beta$-blockers, newer agents like the aldosterone receptor antagonist spironolactone, the endothelin antagonist bosentan, the vasopeptidase inhibitor omapatrilat, and the brain natriuretic peptide (BNP) neseritide have been investigated in multicenter trials with varying results [44]. BNP level was shown to be a strong predictor of SCD in patients with chronic heart failure [45]. On the other hand, electrical devices like biventricular pacing in selected groups of patients can improve LVEF and mortality [46]. Further, surgical procedures like passive external support have been shown in experimental studies to reverse remodeling with reduced systolic wall stress and improved adrenergic signaling [47]. The success of the LV assist devices [48] has shown that even in an advanced stage of heart failure, the remodeling process could be reversed with significant improvement of ventricular function. Finally, clinical research has demonstrated that gene transfer is a potential therapeutic option to restore diseased cardiomyocytes and rescue the failing heart [49].

## Risk stratification of sudden cardiac death in the post-myocardial infarction period (Table 1)

In 2005, the Centers for Medicare and Medicaid Services (CMS) approved primary implantable cardiac cardioverter defibrillator for patients in the post-MI period who have LVEF of 35% and New York Heart Association (NYHA) class II or III heart failure [50]. These criteria were based on data from MADIT II [51] and SCD-HeFT [52]. Implantation is approved only after 40 days or more have elapsed from the time of MI, on the basis of data from DINAMIT [53]. One area of uncertainty of these criteria is the unreliability of LVEF measurements as well as evolution of LVEF over time and the way in which this influences risk [54]. There is general consensus that there is a need for more robust risk stratification of SCD beyond LVEF.

All completed SCD primary ICD prophylaxis trials addressed patients with one or more conven-

tional risk factors for SCD (Table 1) [31]. The electrophysiological surrogates for SCD, including measures of myocardial conduction disorders, dispersion of repolarization, and autonomic imbalance, are based on sound scientific evidence. However, the majority of conventional electrophysiological risk stratifiers of SCD have a relatively low positive predictive value that would preclude their wide application as guidelines for ICD implantation in patients known to be at risk for SCD. This is not to mention the impracticality of their use for risk stratification in the general asymptomatic public. It is not therefore surprising that the current main criteria for SCD primary ICD prophylaxis are measures of ventricular dysfunction, i.e., LVEF and NYHA class. There is general consensus that these criteria may have strong predictive value for total cardiac mortality but are not specific enough for arrhythmic mortality. This explains the continued effort to identify additional risk factors with independent or additive predictive power for arrhythmic death. These may include the use of newer techniques of nuclear magnetic resonance with contrast material to define anatomy of the infarct [55] as well as possible future use of genetic risk profiling.

## Conclusions

The immediate future goals for risk stratification and management of SCD post-MI could be summarized as follows:

1. Identification of novel clinical, biochemical, and genetic markers for SCD and assessment of the functional consequences of sequence variants identified in human genetic studies as well as relevant environmental-genetic interactions.
2. Determination of the heritability of genetic risk factors for SCD as well as the factors involved in ethnic-specific differences in risk of SCD.
3. Identification of a battery of a relatively limited number of incrementally cumulative low-intermediate risk variants and development of a "signature" combination of clinical, biochemical, and genetic markers of SCD. However, we should not be surprised that the positive predictive value of some of the new risk factors, similar to conventional risk factors, will be relatively low, especially if these are applied to large populations who are at low risk. In fact, the true value of risk stratification of SCD in the future may be to identify low-risk populations who do not warrant prophylactic intervention with therapy that demonstrated efficacy, e.g. the ICD.
4. Identification of novel pharmacological and non-pharmacological approaches for risk modification and prevention of SCD. One example is the interest in clinical prevention of SCD by n-3 polyunsaturated fatty acids. Although this relatively new diet-heart hypothesis that underlies this therapeutic modality is yet to catch the attention of the clinical community at large, several experimental and clinical evidence point to the validity of this approach [56].
5. Wider collaboration among different academic and industrial institutions by sharing research results as well as resources such as clinical data, blood and other tissues from Biorepository centers. The ultimate goal is not only to change the current direction of management strategy of SCD away from increased ICD utilization, but primarily to identify novel methods for risk stratification, risk modification, and prevention of SCD that could be applied to the general public at large.

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