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SERUM TRANSFORMING GROWTH FACTOR-ß1 AS A RISK STRATIFIER OF SUDDEN CARDIAC DEATH

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Abstract

Sudden cardiac death prematurely claims the lives of some 7 million each year worldwide. It occurs primarily in patients with an underlying structural cardiac abnormality, and regardless of the type of the underlying pathology (heart failure, dilated and hypertrophic cardiomyopathies, myocardial infarction and aging), death is almost always caused by ventricular tachycardia (VT) which rapidly degenerates to ventricular fibrillation (VF). Implantable cardioverter defibrillator is an effective but expensive therapy for preventing SCD, and finding a reasonably specific, sensitive and cost-effective risk stratification tool for patients at high risk of sudden cardiac death will have great clinical utility in preventing premature sudden cardiac death. Increased myocardial fibrosis has been shown to develop in a wide range of cardiac diseases all manifesting increased risk of VT and VF. Clinical and experimental studies attribute a major role for fibrosis in the initiation of VT, VF and sudden cardiac death. Transforming growth factor-beta1 (TGF-beta1) has been shown to promote myocardial tissue fibrosis and perhaps more importantly in cardiac conditions associated with increased myocardial fibrosis are shown to be positively correlated with increased serum levels of TGF-beta1. In the present hypothesis we suggest that monitoring the serum levels of TGF-beta1 may be a cost-effective risk stratifier to identify patients at high risk of sudden cardiac death caused by VT and VF.

BACK GROUND AND THE SCOPE OF THE PROBLEM

Sudden cardiac death (SCD) prematurely claims each year the lives of more than 300,000 Americans (1) and some 7 million worldwide, and is almost always caused by ventricular tachycardia (VT) that rapidly degenerates to ventricular fibrillation (VF) (1).

Myocardial tissue electrical heterogeneity and myocardial structural remodeling such as interstitial fibrosis have been traditionally considered to play a major role in promoting activation wave front instabilities (wavebreaks) that degenerate to VF (2–4). Experimental studies have shown that atrial (5) and ventricular (6) fibrosis considerably increase the incidence of atrial fibrillation and VF initiated by triggered activity. At the present there is no reliable pharmacological approach to effectively prevent VT and VF and as such the placement of implantable cardioverter defibrillator (ICD) remains the only effective approach against SCD (4). Identification of non-invasive markers of SCD can be of considerable benefit to reduce premature mortality in high risk patients in a cost-effective manner.

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MYOCARDIAL FIBROSIS; A NEW TARGET FOR SCD PREVENTION

Fibrosis is characterized by increased deposition of collagenous septa forming insulating barriers within bundles of myocardial cells, and increased density of myocardial fibroblasts and their differentiated active phenotype, myofibroblasts. Myocardial fibrosis is a common feature of diverse types of cardiac diseases that are associated with increased risk of VT and VF causing SCD (1). These conditions include myocardial infarction (MI), heart failure in dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM), valvular diseases (eg aortic stenosis), aging, and less common conditions such as right ventricular dysplasia. The ventricles of patients with HCM have an 8-fold increase in matrix collagen (6) and increased collagen turnover rate (7). The DCM variant of heart failure also manifests increased collagen content (8) and increased collagen turnover rate (9,10). Furthermore, patients with aortic stenosis (AS) manifest increased interstitial fibrosis and collagen deposition that positively correlates with increased left ventricular end-diastolic pressure and decreased left ventricular ejection fraction (LVEF) (11) a marker of SCD (12). Increased fibroblast density in myocardial fibrosis promotes heterocellular coupling between cardiomyocytes and myofibroblast causing reduced excitability of cardiomyocytes (due to low resting membrane potential of the myofibroblast) causing ectopic pacemaker activity as shown in recent co-culture cardiac myocytes-myofibroblasts studies (13). The same factor is also likely to reduce repolarization reserve, consistent with our findings of increased propensity for early afterdepolarizations and triggered activity in fibrotic atria (5) and fibrotic ventricles (6). Evidence thus far clearly indicates that increased myocardial interstitial fibrosis facilitates the initiation of VT and VF by various electrophysiological mechanisms including wavebreak and triggered activity.

ANGIOTENSIN-II PROMOTES MYOCARDIAL FIBROSIS BY TGF-ß1 OVEREXPRESSION

The observation that angiotensin-II-mediated hypertrophy and fibrosis were eliminated in mice deficient in TGF-ß1 provided direct evidence for involvement of TGF-ß1 in angiotensin-II-mediated cardiac hypertrophy and fibrosis (14). This observation is compatible with the studies that have shown angiotensin-II upregulates TGF-β1 mRNA and protein in cardiac fibroblasts, myofibroblasts, and cardiomyocytes (15–18). TGF-β1 is known to increase the synthesis of collagen and decrease its degradation so as to promote increased collagen deposition (15–18). TGF-β1 also upregulates profibrotic proteins and extracellular matrix (ECM) protein production, and induces differentiation of cardiac fibroblasts into a more active phenotype, myofibroblasts, which produce collagen at twice faster rates than fibroblasts (19,20). Most importantly cardiac TGF-β1 has been shown to be increased in patients with MI, DCM, HCM, and in patients with valvular diseases (21–30), cardiac conditions that are all associated with increased fibrosis. Sanderson and colleagues demonstrated that in patients with DCM the serum level of TGF-β1 is twice high than controls with no heart disease (31).

Taken collectively the combined experimental and clinical evidence uniformly point to a strong association between increased risk of SCD and increased fibrosis. Furthermore mounting electrophysiological evidence suggests that the positive association between SCD and myocardial fibrosis may well be causally related.

THE HYPOTHESIS

Different orders of evidence indicate that the serum levels of TGF-β1 positively correlate with myocardial collagen production and myocardial tissue fibrosis in diverse cardiac disease conditions that are all associated with increased risk of SCD. Monitoring the serum

levels of TGF-β1 may provide useful prognostic information about the likelihood of future development of myocardial fibrosis. Although imaging tools such as magnetic resonance imaging could assess the extent of myocardial tissue fibrosis, this method however remains qualitative and most probably late (i.e., diagnosis *after* fibrosis has been developed) in preventing an increase in SCD. Because increased myocardial fibrosis has been linked to an increased risk of cardiac wave instabilities, ectopic pacemaking and triggered activity (i.e., dynamic precursor of VT and VF), monitoring serum TGF-β1 levels could provide a non-invasive mean of identifying patients at increased future risk of SCD in a cost-effective manner. We suggest that the serum levels of TGF-β1 could serve as a useful risk stratifier of patients at high risk of SCD.

CONCLUSION

The ICD is an effective therapy for preventing SCD but it still remains an expensive and invasive procedure. Moreover, only ~20% of patients who die suddenly each year meet current clinical criteria for ICD implantation (32). While challenging, finding a reasonably specific, sensitive and cost-effective risk stratification tool to identify high risk patients for SCD has become a much needed end-point to reduce premature mortality. Pharmacological therapy targeting ion channels for preventing SCD failed to provide effective and reliable protection (7–10). Alternative approaches with more upstream strategies targeted against the substrate of the VT and VF rather than downstream strategies targeting specific ion channels may eventually prove to be more effective and useful strategy. Since TGF-ß1increases myocardial tissue fibrosis and fibrosis plays a major role in VT and VF, we propose that monitoring the serum levels of TGF-β1 should be evaluated as a potentially useful marker for stratifying patients at high risk of SCD.

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