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REVIEW ARTICLE

Autoantibodies for Cardiac Channels and Sudden Cardiac Death and its Relationship to Autoimmune Disorders

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Abstract: ***Background*:** Sudden Cardiac Death (SCD) is an unexpected death caused by heart dysfunction. Autoantibodies against cardiac proteins may be potentially involved in the occurrence and progression of cardiac disease and SCD. The first report on the role of autoantibodies in idiopathic dilated cardiomyopathy appeared in the 1980s. In recent years new studies on the effects of the presence of specific autoantibodies and their relationship to ventricular arrhythmias and SCD were published. The purpose of the current mini-review is to analyze the results of the research studies focused on the relationship between anti-cardiomyocyte autoantibodies and SCD with respect to autoimmune disorders.

***Conclusion*:** According to our analysis, more research is needed to understand the role of these autoantibodies against cardiac proteins in the SCD pathogenesis, and potentially employ this knowledge for improving prognosis of SCD.

Keywords: Sudden cardiac death, autoantibodies, channels, autoimmune disorders, heart dysfunction, cardiomyopathy.

1. INTRODUCTION: SUDDEN CARDIAC DEATH (SCD)

Sudden Cardiac Death (SCD) is an unexpected sudden death due to heart dysfunction which claims approximately 450,000 lives annually in the United States [1]. Studies report cardiac-related deaths as SCDs if either the patient expires within 1 hour of an acute hemodynamic change or within 24 hours of a patient's last known well [2, 3]. The general population of patients who are subject to SCD typically have no prior history of heart disease [4]. This is one of the primary reasons preventing SCDs which is challenging and there is a need for risk stratification.

A recent study proposes a risk score that considers 12 risk factors that have been shown to be associated with SCDs (*e.g.*, age, male sex, black race, systolic blood pressure, smoking, diabetes mellitus, *etc*.) [4] Many of these risk factors are shared by those for Coronary Artery Disease (CAD). In fact, 76% of patients over the age of 35 who had an SCD had an associated CAD [5]. SCD is also found to be exacerbated by non-traditional cardiovascular risk factors such as sleep apnea [1]. By better understanding SCDs, there has been an improvement in prognosis and survival rate in recent years. Despite these advancements and improved risk stratification, the survival rate for an Out-of-Hospital Cardiac Arrest (OHCA) remains poor at about 8.3% [6].

2. CHANNEL GENE MUTATIONS AND CARDIOMYOPATHIES

It has been found that mutation of channel genes may produce cardiac channelopathies, a group of genetic disorders due to mutations in genes responsible for the ion channels which affect their activity and function allowing for the propensity to develop dangerous and often deadly arrhythmias. The most common channelopathies are Long QT (LQT) syndrome with others being Short QT (SQT) syndrome [7-9]. Brugada syndrome [10, 11]. and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) [9, 12]. It has been found that LQT syndrome is secondary to loss-of-function mutations in potassium channel genes (KCNE1, KCNE2, KCNQ1, KCNH2, KCNJ2, and KCNJ5) and gain-of-function mutations in sodium channel genes (SCN4B and SCN5A) and a calcium channel gene (CACNA1C) [9, 13]. Further, Brugada syndrome is commonly secondary to loss-of-function mutations in cardiac sodium genes [12, 13]. Patients with CPVT have a gain-of-function mutation in RYR2, a contributing factor to RYR2

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channels that mediate calcium release, and a contributing disease to SCDs.

3. CARDIOMYOPATHIES AND AUTOANTIBODIES AGAINST CARDIAC PROTEINS

Because finding a link between mutations in various channel proteins and cardiomyopathies confirms the role of cardiomyocyte channels in the cardiac dysfunctions (cardiomyopathies/channelopathies), one can suggest that autoantibodies against cardiac channels and other proteins of cardiomyocytes can be potentially involved in the pathogenesis of SCD. For example, those specific autoantibodies can be either risk factors of SCD or/and perhaps are directly involved in SCD pathogenesis. If it is true, the autoimmune screening can be potentially employed in SCD prognosis. Due to an absence of reliable preventive methods to reduce the risk of SCD, further testing the autoimmune approach seems to be necessary and promising.

Indeed, a formation of autoantibodies and their interaction with specific antigens of the human body is responsible for many autoimmune diseases where the immune system reacts to self-antigen and leads to autoimmune inflammation, organ dysfunction and/or destruction [15]. Moreover, there is a growing body of evidence that autoantibodies may be involved in the occurrence and progression of cardiac diseases and SCD [14-16] and the term 'autoimmune cardiac channelopathies' are proposed to describe a novel mechanism of cardiac arrhythmias [17]. The rest of this mini-review covers the results of studies focused on relationships between anti-cardiomyocyte autoantibodies and SCD. In the context of cardiomyopathies, most prominent types of autoantibodies are autoantibodies against β1-adrenergic receptors, Ca-channels, Na-K-ATPase (sodium-potassium pump), and hERG-potassium channel.

4. ROLE OF ANTI-β1-ADRENERGIC RECEPTOR AUTOANTIBODIES IN THE SCD PATHOGENESIS

Autoantibodies against β1-adrenergic receptors that regulate many cardiac functions and belong to cardio-pathogenic agents [16, 18, 19]. The β1-adrenergic receptors are responsible for positive chronotropic, dromotropic and bathmotropic effects and apoptosis of cardiomyocytes [20]. It has been found that patients with Congestive Heart Failure (CHF) may produce autoantibodies against β1-adrenergic receptors. Moreover, the CHF patients demonstrated improvement of hemodynamics, disease state, cardiac function and other clinical parameters of disease activity after the removal of autoantibodies against β1-adrenergic receptors [21, 22]. The autoantibodies may decrease the cardiovascular function [23] increase cardiac mortality [24], worsen ventricular arrhythmia and lead to SCD [25-27].

A study of 104 patients with dilated cardiomyopathy who were screened for these autoantibodies and followed for a mean of 31 months showed that ventricular tachycardia and premature ventricular contractions were more commonly seen in patients who were found to be positive for the autoantibody against β1-adrenergic receptors [26]. The presence of autoantibodies and a low Left Ventricular Ejection Fraction (LVEF) were independent predictors of ventricular tachycardia. SCD was independently predicted by the presence of autoantibodies as well as a low LVEF, although only a low LVEF predicted overall mortality in these patients. The suggested mechanism leading to SCD is the electrical instability created by increased beating frequency in cardiac myocytes. Long-term β1-adrenergic receptor stimulation by autoantibodies may induce instability via calcium overload; this phenomenon is abolished by beta-1 selective antagonism [26].

In another study, 2062 patient with CHF were compared to a control panel of 824 patients over a median follow-up of 36 months [27]. It has been found the anti-β1-adrenergic receptor autoantibodies were more frequently found in the patients with CHF than in the control subjects. Relying on this, the researchers concluded that presence of the anti-β1-adrenergic receptor autoantibodies is an independent predictor for SCD in the CHF patients; the β1-adrenergic receptor autoantibody-positive patients have a four- to five-fold increase in the risk of SCD, as well as the rise in all-cause mortality in dilated and ischemic cardiomyopathy. The same group also studied potential relationships between SCD and autoantibodies to the M2 muscarinic receptor, however, the presence of this kind of autoantibodies in the CHF patients did not affect the patient outcome [27].

Relying on our literature analysis of the data on anti-β1-adrenergic receptor autoantibodies, we conclude the following.

1. Anti-β1-adrenergic receptor autoantibodies are generated in the patients with cardiomyopathies resulted in SCD;
2. Autoantibodies against β1-adrenergic receptors are probably involved in the pathogenesis of cardiomyopathies leading to SCD;
3. Presence of these autoantibodies can be a potential independent predictor of a higher mortality and SCD;
4. Removing these anti-β1-adrenergic receptor autoantibodies leads to improving clinical parameters and survival of patients with cardiomyopathies;
5. Potential pathogenic mechanism of the autoantibodies against β1-adrenergic receptors is based on generating electrical instability via calcium overload.

5. ROLE OF ANTI-Ca-CHANNEL AUTOANTIBODIES IN THE SCD PATHOGENESIS

Another clinically important target for generation of autoantibodies in the course of cardiomyopathies is Ca-channels. In a prospective, case follow-up survey, 80 patients with dilated cardiomyopathy were investigated for whether autoantibodies against the L-type Ca-channel can be seen as a predilection to arrhythmias resulted in SCD [28]. These cases demonstrated premature ventricular beats and ventricular tachycardia were more common in patients who were anti-Ca channel autoantibody positive as opposed to negative and showed this autoantibody to be the only independent predictor of ventricular tachycardia (odds ratio: 8.65, 95% confidence interval: 2.51-26.33, $P< 0.0001$).

During the 32-month follow-up period, the incidence of SCD was also higher in these patients, although no signifi-

cant difference was seen in all-cause mortality. The suggested explanation for this occurrence was autoantibody activity against an adenine nucleotide translocator which ordinarily cross-reacts with Ca-channels and could pathologically enhance the inward calcium current causing an overload that would eventually result in myocyte damage. This would subsequently lead to prolonged action potential duration, and induced early after-depolarization, ultimately provoking a ventricular tachycardia [28].

The 2014 study evaluated the ability of anti-Ca-channel autoantibody presence to predict prognosis in CHF patients [29]. 2096 patients with CHF as well as 834 as controls for a median follow-up time of 52 months were studied. When analyzing the deaths over the follow-up time, approximately 39% of them were deemed SCD due to non-ischemic or ischemic cardiomyopathy. Autoantibody positivity was significantly higher in a patient with CHF versus control subjects and further analysis showed that the presence of anti-Ca channel autoantibodies could independently predict SCD (HR 3.191, 95% CI 1.598-6.369 for dilated cardiomyopathy; HR 2.805, 95% CI 1.488-5.288 for ischemic cardiomyopathy) and all-cause mortality (HR 1.733, 95% CI 1.042-2.883 for dilated cardiomyopathy; HR 2.219, 95% CI 1.461-3.371 for ischemic cardiomyopathy) in CHF patients [29].

Relying on the research studies focused on the role of anti-Ca-channel autoantibodies in cardiomyopathies we conclude the following.

1. The antibodies against Ca-channels are an independent predictor of ventricular tachycardia;
2. Positivity for anti-Ca-channel autoantibodies is a potential independent predictor for all-cause mortality and SCD, thus it cannot be an exclusive prognostic factor for SCD.
3. The potential pathogenic mechanism of anti-Ca-channel autoantibodies is based on enhancement of the inward Ca current causing an overload that may eventually result in myocyte damage, prolonged action potential duration, early after-depolarization, and a ventricular tachycardia.

6. ROLE OF ANTI-Na-K-ATPASE AUTOANTIBODIES IN THE SCD PATHOGENESIS

Autoantibodies against sarcolemmal Na-K-ATPase (also known as a sodium-potassium pump) can be involved in the SCD pathogenesis. The electrophysiologic function of the autoantibodies is not well understood, however, it is thought that they may produce a delayed after-depolarization that causes the arrhythmias and SCD [30]. The autoantibodies cause abnormal intracellular Ca^{2+} handling by reduced Na-K-ATPase activity leading to PVCs and VT. Therefore, these autoantibodies against Na-K-ATPase may exert an arrhythmogenic effect in potentially susceptible patients leading to SCD [30].

The impact of autoantibodies against sarcolemmal Na-K-ATPase on the development of ventricular tachycardia and sudden cardiac death in cases of dilated cardiomyopathy was studied in the case-control study on 100 patients suffering from dilated cardiomyopathy were matched with controls and screened for anti-Na-K-ATPase antibodies [30]. The Na-K-ATPase activity was discovered to be lower in dilated cardiomyopathy patients who were positive for the autoantibody as compared to patients with dilated cardiomyopathy and no autoantibodies. This effect was not observed in the control group [30].

The incidence of ventricular tachycardia was found to be more common in patient with autoantibodies independent of a low LVEF or plasma norepinephrine. SCD could be independently predicted by autoantibody positivity as well as a low LVEF. The study speculated that an electrical instability could be generated due to the reduced Na-K-ATPase activity resulting from abnormal levels of intracellular calcium and delayed after-depolarizations. This delayed after-depolarization arises from an increase in intracellular sodium because of a reversal of the Na/Ca exchanger [30].

Summarizing the data described above, we can conclude the following.

1. Autoantibodies against sarcolemmal Na-K-ATPase can be actively involved in the SCD pathogenesis;
2. The potential pathogenic mechanism of these autoantibodies can be based on raising abnormal levels of intracellular K^+, Na^+, and Ca^{2+}, and a formation of the delayed after-depolarization that causes the arrhythmias and SCD.

7. ROLE OF hERG-POTASSIUM CHANNEL ANTIBODIES IN THE SCD PATHOGENESIS

Anti-Ro/SSA antibodies are frequently found in patients with connective tissue diseases, particularly in those with Sjögren syndrome (up to 95%) and systemic lupus erythematosus (up to 50%), but also in the healthy population (up to 2.7%) [31]. These autoantibodies may also produce an arrhythmogenic effect in the adult heart [32]. Anti-Ro/SSA antibodies biochemically cross-react with L-type and T-type Ca-channels and thus significantly inhibit the Ca-currents, that play a key role in the slow action potential in cardiomyocytes of the heart conduction system [14, 33].

It was recently demonstrated that autoantibodies against the Ro/SSA region (fragment with MW=52 kDa) of hERG-potassium channels are responsible for a novel form of acquired LQT syndrome of autoimmune origin, by directly cross-reacting with the extracellular loop of the hERG-potassium channel pore-forming region, resulting in inhibition of cardiac rapidly activating rectifier potassium (IKr) channels and prolongation of an Action Potential Duration (APD) [34]. A high prevalence of hERG-binding and IKr blocking anti-Ro/SSA-52kDa antibodies were found in a prospective cohort of unselected TdP patients, in most cases without any history of autoimmune disease [35].

Relying on the available data, we can conclude that:

1. Autoantibodies against the Ro/SSA region of hERG-potassium channels are involved in cardiac syndromes that may result in the SCD pathogenesis.
2. A potential pathogenic mechanism of these autoantibodies is linked with cross-reacting with the extracellular loop of the hERG-potassium channel pore-

forming region, resulting in IKr inhibition and APD prolongation. Besides, these antibodies may cross-react with L-type and T-type Ca-channels and thus significantly inhibit the Ca-currents.

8. SCD IN AUTOIMMUNE DISEASES WITH INCREASED CARDIOVASCULAR MORBIDITY AND MORTALITY

Certain autoimmune conditions pose an increased risk for cardiovascular disease. Long-standing inflammation is the hallmark of the autoimmune disease, this eventually leads to atherosclerosis [36].

It has been studied that T-cell abnormalities also play a role in plaque instability and acute coronary syndrome; autoimmune disease is notorious for T-cell abnormalities which can increase the risk for cardiovascular complications [37] such as acute myocardial infarction, stroke and SCD [38]. In general CD4CD28null T- cells are known to have defects in apoptotic pathways which results in persistent clonal expansion of these cells. CD4CD28null T cells have been found accumulated in plaque lesions which suggest they have a role in plaque instability. These T cells produce high amounts of IFN-y which has been associated with the acute phase response which results in stimulation of macrophages and production of tissue destructive metalloproteinases and may also cause release of oxygen free radicals [39]. Lazzerini *et al*. compared peripheral blood samples of patients with Unsable Angina (UA), Stable Angina (SA), and coronary vessel tissue and plaque sampling of fatal myocardial infarctions and found that a subtype of T cells called CD4+CD28null was increased in peripheral blood of patients with Unstable Angina (UA) but not in Stable Angina (SA). In addition they found increased levels in of CD4CD28null cells in the tissue analysis of unstable plaque but none in the stable plaque [40].

Sudden cardiac death is usually hard to assess, especially with co-existent of an autoimmune disease, however it does exist. Several autoimmune conditions have a high proclivity for cardiac pathology; for example, in systemic lupus erythematosus (SLE) cardiac involvement can be seen in up to 50% of patients, this includes arrhythmias and conduction disorders [41]. Several studies have demonstrated the risk of SCD in autoimmune conditions. SLE is known to several mortality peaks, and the second mortality peak is usually unexpected and is therefore thought to be linked SCD. This was proved by Abu-Shakra *et al*., in a study with 665 SLE patients, using a univariate analysis they identified that sudden death as the fourth most common cause of death during 20 years of follow-up [42]. Another study compared SLE patients with and without conduction disturbances noted on EKG, they found 17.5% of patients developed conduction abnormalities and had a higher mortality rate after 10 years than compared to SLE patients without conduction disturbances [43]. Another study that evaluated SLE patients for 33 years found that EKG changes is an independent risk factor for mortality and has a high prognostic value [44]. The pathogenesis of SCD related to autoimmune conditions, and specifically SLE, has not been completely clarified. It is thought to be a result of the inflammatory process of myocardium and pericardium, atherosclerotic myocardial ischemia, or as a result of vasculitis of small vessels with collagen and fibrotic deposits in the myocardium that affects the conduction system.

Rheumatoid arthritis is also associated with increased cardiovascular morbidity and mortality as well as SCD. Solomon *et al*. evaluated women with and without RA to assess their increased risk for SCD which included acute myocardial infarction. They found that women with RA possess more than a 2 fold risk for SCD [38].

Systemic Sclerosis (SSc) also has cardiac manifestation that can eventually lead to SCD. SSc manifests with sporadic fibrosis in the myocardium causing left ventricular hypertrophy, systolic or diastolic dysfunction. Cardiac involvement can be seen on autopsy in 33-75% of cases, and 5-40% can have EKG disturbances. SCD in SSc is likely due to ventricular failure leading to sustained arrhythmias [45].

9. SCD AUTOANTIBODIES IN AUTOIMMUNE CONDITIONS

Several autoantibodies that can potentially cause SCD are found in autoimmune disorders. Anti-Ro/SSA antibodies are frequently found in patients with connective tissue diseases, particularly in those with Sjögren syndrome (up to 95%) and SLE (up to 50%). These autoantibodies may also produce an arrhythmogenic effect in the adult heart [32]. Anti-Ro/SSA antibodies biochemically cross-react with L-type and T-type Ca-channels and thus significantly inhibit the Ca-currents, that play a key role in the slow action potential in cardiomyocytes of the heart conduction system [14, 33]. Another explanation is called the "*calcium channel hypothesis*". Extended contact of anti-Ro/SSA antibodies can cause calcium channel internalization, leading to apoptosis, cell death, and inflammation. The inflammatory damage eventually results in fibrosis and calcification of the cardiac conduction system leading to fatal arrhythmias.

One study reported that patients who were anti-Ro positive had a significantly higher prevalence of myocarditis and conduction defects then compared to anti-Ro negative patients [46]. Congenital heart block is also associated with transplacental migration of anti-SSA/Ro-SSB/La antibodies and can be seen in 95% of fetuses or newborns with the congenital atrioventricular block.

10. SCREENINGS & INTERVENTIONS FOR SCD IN AUTOIMMUNE DISEASES ASSOCIATED WITH AUTOANTIBODIES

Since SCD is relevant in autoimmune conditions, we must pay close attention to possible inciting factors that can lead to SCD.

We must pay close attention to and learn to recognize predicting and prognostic factors that influence that cardiac conduction system leading to arrhythmias and SCD. For many autoimmune disorders, conduction disturbances were noted to have a more detrimental prognostic factor [31, 41, 42, 44, 46]. Cardiac involvement with a cardiomyopathy and ventricular arrhythmias is highly concerning given the possibility of SCD. Patients with autoimmune conditions that have a high predisposition for cardiac involvement such as SLE, SSc, Rheumatoid arthritis etc. should undergo electro-

Table 1. Summary of the different studies that on cardiac channelopathy that lead to sudden cardiac death.

Chart: Studies that Show Sudden Cardiac Death is Potentially Associated with Presence of Autoantibody Against A Cardiac Channel or Receptor		
Autoantibody	**Relationship to SCD**	**Comment**
Beta1-adrenergic receptor autoantibodies	A case-control study with 2062 patients and 824 controls found that, in patients with Ischemic Cardiomyopathy (ICM), beta 1 adrenergic receptor autoantibody was significantly higher in those who had Sudden Cardiac Death (SCD) compared to those who had Non-Sudden Cardiac Death (NSCD).	This study was done among patients with Chronic Heart Failure (CHF) and statistical significance was only shown in ICM patients, not in patients with Dilated Cardiomyopathy (DCM) [27]
	A study of 104 patients showed that presence of auto-antibodies against the second extracellular loop of the beta1 adrenergic receptor was an independent predictor of SCD.	This study was done among patients with idiopathic dilated cardiomyopathy [26]
Antibody against sarcolemmal Na-K-ATPase	A study of 100 patients and age-matched controls showed that the presence of antibody against sarcolemmal Na-K-ATPase was an independent predictor of SCD in DCM.	This study was done in patients with dilated cardiomyopathy [30]
Calcium channel autoantibody	A large-scale prospective study done with 2096 patients and 834 controls showed that the presence of calcium channel autoantibody in CHF patients (due to DCM or ICM) was an independent predictor of SCD.	The study was done in patients with CHF due to DCM or ICM [29]
	Study of 80 patients with DCM showed that calcium channel autoantibodies were the strongest independent predictor of sudden death.	The study was done in patients with DCM [28]
hERG-potassium channel	A high prevalence of hERG-binding and IKr blocking anti-Ro/SSA-52kDa antibodies were found in a prospective cohort of unselected TdP patients in 25 consecutive patients with TdP arrhythmia were prospectively collected independently of ongoing therapies and concomitant diseases.	The study was done in patients with TdP arrhythmia [35]

physiological studies for screening purposes and AICD implantation is recommended in patients with ventricular tachycardia or reduced left ventricular ejection fraction [45, 47].

Inflammatory changes and tissue accumulation as a result of the immunologic reaction can potentially result in arrhythmias. The interventions and treatment that can inhibit the cardiac disease progression and prevent SCD include medication for the specific underlying autoimmune condition, catheter ablation, and implantable electronic cardiac devices such as pacemakers and defibrillators.

Therefore, increasing the awareness and knowledge of arrhythmias in patients with autoimmune rheumatic conditions is essential to prevent SCD and must be further established.

CONCLUSION

Over the last decade, a potential involvement of autoantibodies against cardiac proteins in the pathogenic processes that either cause or accelerate SCD has been studied. The most data in this field have been obtained in the studies focused on the role of anti-β1-adrenergic receptor autoantibodies in SCD pathogenesis (Table **1** for the list of studies performed), much less information is available about the autoantibodies generated against Ca-channels, Na-K-ATPase (sodium-potassium pump), and hERG-potassium channels. No doubt, more research is needed to understand the relationships between anti-cardiomyocyte autoantibodies and SCD development, especially in relation to autoimmune disorders, and employ this knowledge for improving prediction and prognosis of SCDs.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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