Evaluation of Cardiogenetic Diseases and Effectiveness of Screening: Weighing of the heart

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Evaluatie van Cardiogenetische Aandoeningen en Doeltreffendheid van Screening: Weging van het hart

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CHAPTER 1

General Introduction

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Inherited primary cardiac arrhythmia (ICA) is a group of diseases responsible for a significant number (20-30%) of sudden cardiac death in young subjects.(1) These diseases are characterized by either functional or structural abnormalities due to genetic mutations. These mutations are affecting cardiac ion channels or their modulatory proteins. ICA consists of four major channelopathies, namely, long QT syndrome (LQTS), short QT syndrome (SQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome (BrS), however, other conditions such as familial atrial fibrillation (FAF), sick sinus syndrome (SSS) and arrhythmogenic right ventricular cardiomyopathy (ARVC) are also considered as ICA.

Despite the uprising advances in genetics and clinical medicine, there are many challenges facing cardiologists all over the world regarding case identification, the effectiveness of family screening, and risk stratification of sudden death for diagnosed cases. In this chapter, current epidemiology, pathophysiology, diagnosis, family screening, risk stratification, and current treatment strategies of different ICA will be discussed.

Epidemiology of ICAs

There is a lack of accurate estimation of different ICA prevalence due to many challenges. Firstly, the incidence of ICA varies dramatically across the globe due to ethnic specific polymorphism which can affect the penetrance of the disease-causing mutations. Secondly, there is lack of large cohorts from non-western populations. Lastly, variable penetrance of disease-causing mutations makes prevalence measurements more complicated.

BrS has a worldwide pooled prevalence of 0.5 per 1000 (95% CI:0.3-0.7). The highest prevalence on the planet was reported in Thailand (6.8 per 1000) and among Asians in general (1.8 per 1000). The lowest prevalence of BrS was reported among Hispanics (0.05 per 1000).(2) The prevalence of LQTS was estimated to be 1 per 2000, however, these results were based on phenotype positive cases. Therefore, the actual prevalence of LQTS causing mutations could be much higher due to variable penetrance.(3) SQTS prevalence estimation has been challenging due to the inconsistency of QTc cut off value used in published results. Studies reported that SQTS has a prevalence of 0.02-0.1% in the adult population and 0.05% in pediatrics.(4-6) The prevalence of CPVT is one of the lowest among ICAs with an estimation of 1 per 100,000.(7) Although there are some reports about founding mutations in different countries such as the Netherlands, Finland and Spanish Canary islands, there is a lack of large cohorts reporting prevalence in different ethnic groups.(8, 9) Regarding ARVC, an estimate of 1 per 1000 has been reported in the general population, however, some studies from Italy and Greece reported a higher prevalence of 4-8 per 1000. (10, 11) Although SSS has a constantly increasing

prevalence (0.8 per 1000 in 2014), the inherited SSS prevalence is expected to be so low and no large cohorts investigated the epidemiology of inherited SSS.(12) Atrial fibrillation (AF) has a prevalence of 1 % of the general population and reports estimated FAF to represent up to one third of all AF cases (3 per 1000). This makes FAF one of the most common ICAs.(13)

Pathophysiology of ICAs

The main driving mechanism of ICAs is genetic mutations in genes coding ion channels or their modulating proteins. These genetic defects disturb either morphology and/or functionality of these channels and lead to altered cardiac action potential (AP). ICAs have an autosomal dominant pattern of inheritance and follow Mendelian rules in the vast majority of cases.(14) There has been a long debate on the mechanism underlying BrS. There are two hypotheses trying to explain the pathophysiological mechanism behind this lethal syndrome, repolarization and depolarization hypotheses. In the *repolarization* hypothesis, a transmural dispersion of repolarization between epicardium and endocardium in the right ventricle is responsible for ST segment elevation and triggers VTA in these patients.(15) On the other hand, the *depolarization* hypothesis suggested that conduction delay in the right ventricular due to functional and sometimes structural abnormalities (fibrosis and decreased gap junctions) is the main mechanism of ECG morphology and the higher risk of VTA.(16) In LQTS, the prolonged QT interval is either caused by loss of function mutations which decrease outward potassium current (LQTS1, LQTS2) or gain of function mutations leading to increased inward sodium current (LQTS3). This current disturbance initiates transmural spatial dispersion of repolarization and triggers ventricular tachyarrhythmia (VTA).(17) In caontrast to LQTS, gain of function mutations in genes encoding potassium channels are the main mechanism behind SQTS.(18)

The main mechanism behind CPVT is the disruption of cellular calcium homeostasis due to mutations in RYR gene. Excessive calcium overload causes delayed afterdepolarization and facilitates VTA.(19) In ARVC, mutations in genes encoding desmosomal proteins are mainly responsible for defects in cardiac cellular adhesions.(20) Moreover, mutations in non desmosomal genes have been reported as causative of ARVC such as RYR2, TMEM43 and TGFB3.(21-23)

In SSS, mutations in both HCN4 and SCN5A genes have been discovered. Mutations in HCN4 lead to decreased cAMP sensitivity in the funny current channels (*If*) and therefore decrease the firing rate of the SA node.(24) However, SCN5A has no role in the AP of the SA node. Conduction block of the AP in atrial tissue adjacent to the SA node (exit block hypothesis) has been suggested as a mechanism for SSS in these patients.(25)

The mechanism behind FAF has received a lot of attention in the last few years due to the advances in molecular techniques and the high prevalence of lone AF cases. Mutations in genes encoding different ion and non-ion channels have been linked to FAF. Moreover, genome-wide association studies (GWAS) showed an association between many single nucleotide polymorphism and increased risk of AF. This topic is discussed in detail through the second chapter this book.(26)

Diagnosis and family screening

There are many different challenges regarding the diagnosis and family screening of ICAs. For instance, this group of patients could present with a lethal cardiac event at a young age without any previous history of medical complaints. Although genetic family screening has the advantage of early detection of pre-symptomatic cases in the affected family, genetic sequencing results did not sufficiently improve risk stratification for the index cases nor offer guidance for management strategies. Moreover, ICAs also have a social and psychological impact on families with one or more affected members.

In BrS, an electrocardiographic pattern is the cornerstone of diagnosis. A spontaneous type I pattern of coved ST segment elevation of ≥ 0.2 mV in one or both of the right precordial leads (V1 and V2) positioned in the 2^{nd}, 3^{rd} or 4^{th} intercostal spaces.(7) In cases with type II or type III BrS pattern, diagnosis can be considered if type II or III patterns converted to type I by using ajmaline test (sodium channel blocker). In order to confirm BrS diagnosis, additional criteria have to be present, namely, documented VTA, syncope due to arrhythmia, family member with coved type I pattern, family history of sudden cardiac death at age <45 or nocturnal agonal respiration.(27) However, BrS has a low disease penetrance in family members carrying disease related mutations, genetic screening is strongly recommended in families with genotype positive member (Class I). For asymptomatic family members with a genetic mutation, follow up and preventive measures are recommended such as aggressive fever treatment, avoidance of certain drugs and excessive alcohol intake.(28) Some data showed that type of SCN5A mutation could determine the level of BrS phenotype aggressiveness. A stop codon and frameshift mutations showed more severe conduction disorder than missense mutations.(29)

The diagnosis of LQTS is mainly based on ECG measurements. Prolonged QTc is the cornerstone of LQTS diagnosis (≥460 for females and ≥440 for males) besides family history and clinical presentation. A diagnostic score has been developed to facilitate the diagnostic process.(30) LQTS has incomplete penetrance and from 10-30% of genetic mutation carriers have normal QTc.(31) Family screening has the ultimate importance for early detection of asymptomatic mutation carriers. Follow up and lifestyle modification is recommended for these subjects.

In SQTS, the latest guidelines recommended QTc ≤340 ms to confirm the diagnosis, however, patients with QTc ≤360 ms could be considered for the diagnosis if there is a family history of sudden cardiac death or a documented event of VTA.(32) It has been recommended not to perform QTc measurement during bradycardia or tachycardia to prevent inaccurate QTc estimation. Genetic family screening has limited value in respect to case detection as only 20 % of SQTS cases have identified causative mutations.

In CPVT, the exercise stress test is the cornerstone of the diagnostic process. Increasing frequency of single ventricular extrasystoles develops into bigeminy extrasystoles then extrasystolic couplets and could initiate non-sustained or polymorphic ventricular tachycardia (VT). Genetic screening is indicated for families with a diagnosed CPVT patient as 60-70 % of cases carry a causative mutation in RYR2 gene.(33) In ARVC, diagnosis is guided by a set of modified Task Force Criteria.(34) This set has major and minor criteria to facilitate confirmatory diagnosis of cases. Around 60% of diagnosed cases are carrying a causative mutation, therefore, genetic screening is recommended for first degree relatives of these index cases.(35)

The diagnosis of SSS is based on clinical symptoms and ECG findings. Around half of the cases present with syncope and end organ hypoperfusion.(36) Patients with SSS can present with different ECG findings such as bradyarrhythmia, tachyarrhythmia or atrial fibrillation with a slow ventricular response. However, the average age of SSS diagnosis is above 65 years. Reports showed that hereditary SSS can be detected early in families carrying the causative mutations.(37, 38)

The main hallmark of FAF diagnosis is ECG finding of AF at the age of less than 60 without any structural abnormalities. Studies showed that around 40% of lone AF patients reported a family history of AF.(39, 40) Lone AF patients with family history showed earlier onset and were significantly more symptomatic than other AF patients.(41) Some studies showed that genotyping may have clinical implications and prognostic value for FAF. However, the Heart Rhythm Society/European Heart Rhythm Association statement doesn't recommend genetic screening for AF.(42-44)

Risk stratification

Risk stratification is one of the most challenging points in the management of ICA cases due to many reasons. Firstly, ICAs have variable penetrance and this leads to an unclear genotype-phenotype relationship as the risk of developing VTA differs among the carriers of causative mutations. Secondly, the heritability of ICAs is still not fully explained. Among all 21 genes found to be related to BrS phenotype, only SCN5A gene mutations have the definitive evidence to be disease-causing.(45) Thirdly, many clinical and non-

invasive ECG risk markers are not well defined especially for asymptomatic patients and many of these markers should be tested in large multicenter cohorts.

In BrS, there has been a lot of efforts to quantify and predict the risk of developing VTA in such population. From a clinical perspective, the male gender shows a predominance in BrS diagnosis and association with VTAs, however, gender is not independent predictor of VTA events in different cohorts.(46, 47). A recent study showed that ethnicity has an effect on the gender distribution of VTA events as symptomatic Asian BrS patients have a 9 fold higher chances to be male than Caucasian BrS patients.(48)

Family history of sudden cardiac death at age <45 years is an independent risk factor of developing VTA in this population.(49) ECG parameters have received meticulous attention in the many studies trying to identify high risk BrS patients. Some of these markers showed consistent predictive value for VTA events and many other markers showed controversial results. Patients with spontaneous type I BrS pattern were at higher risk than patients with drug induced BrS pattern.(50) Other ECG parameters have been investigated such as fragmented QRS in leads V1-V3, QRS duration in leads II, V2 and V6, R wave sign in lead aVR and S wave sign in lead I.(51-53) Moreover, inferolateral early repolarization, signal averaged ECG, T wave alternans and T peak-T end dispersion may be useful as non-invasive risk stratification markers for BrS.(54-56)

Since 1957, LQTS has been considered one of the most investigated ICA. Despite the relatively high efficiency of management strategies such as antiadrenergic drugs, there are patients at risk of therapy failure and VTA events. Syncope has been a predictor for a subsequent fatal cardiac events in these patients with six-fold increase of the risk.(57) The effect of gender on the risk of VTA in this population has been a matter of debate. Women and children have a higher penetrance and a higher risk to develop VTA. Androgens have a shortening effect on the QT interval and are possible protective factor for VTA in post-pubertal boys and men.(58) Moreover, the QTc interval is an independent predictor for VTA events.(59) The maximum QTc interval was the strongest predictor of VTA events during follow up therefore, periodic QTc measurements are justified. (60) Combining QTc, gender and genetic loci has been introduced as a promising risk stratification tool. For instance, QTc was an independent predictor of VTA in patients with LQT1 and LQT2 mutations. On the other hand, gender was a predictor for VTA in LQT3 mutation carriers.(59) In SQTS, a history of cardiac arrest has been the only risk sign for this population.(61) On contrary to LQTS, QTc failed to stratify high risk patients in this population. In CPVT, a history of aborted cardiac arrest and young age at the time of diagnosis were independent predictors for fatal cardiac events.(62)

Risk stratification for ARVC patients is a dynamic process due to the progressive nature of the disease. There are many risk factors that have been recognized in this population. Firstly, males and a history of sustained VTA regardless of hemodynamic stability showed a higher risk for a lethal cardiac events.(63) Frequent premature ventricular complexes in 24-hour Holter and non-sustained VT are also a high risk marker for a sustained VTA. Secondly, the most extensive involvement of the right and left ventricle such as the large areas of scar tissue or a higher number of T-wave inversions on the ECG is associated with a higher risk for VTA.(64, 65) Lastly, mutations in certain genes such as TMEM43 are related to fetal arrhythmia in affected subjects.(23)

With respect to FAF, there are only few studies that included single nucleotide polymorphisms in a prediction model for AF and ischemic stroke, known as the AF-genetic risk score. These studies showed promising results, however, they lack external validity and are based on relatively small sample sizes.(66, 67)

Treatment

Tailoring a treatment strategy for ICA patients faces different challenges. The risk stratification process is still limited capable to quantify the risk of a fatal cardiac event. The incomplete penetrance and complex genotype-phenotype correlation limit development of mechanism driven therapies. The relatively young age of most affected patients makes an invasive treatment like an ICD implantation a challenging. Most of the studies investigating treatment strategies are limited to either case reports or retrospective data reports due to the impossibility of conducting randomized clinical trials for most of ICAs. Firstly, lifestyle modification has the ultimate importance for these patients. For instance, fever can be a trigger for VTA in BrS and LQTS and has to be treated aggressively. There is also a list of restrictions as avoiding excessive alcohol intake and drugs known to be responsible for increased risk of VTA in BrS.(68) Moreover, QT prolonging medications are absolutely contraindicated in LQTS patients. Certain physical activities are restricted for patients with LQTS1 and CPVT as swimming and avoiding sudden loud voices. Most of the consensus reports recommended against competitive sports for ICAs patients, though new data showed a more liberal eligibility decision making process. (69) Finally, family members of affected patients need to be trained in cardiopulmonary resuscitation techniques.

Pharmacotherapy has a prophylactic role in many ICAs. For instance, β-blockers are recommended for patients with LQTS and CPVT as primary and secondary prophylaxis. Quinidine is also used for BrS patients with a history of arrhythmic storms or in case of either ICD contraindication or refusal by the patient.(70) Moreover, Quinidine showed

efficiency as primary prophylaxis for SQTS patients with a strong family history of fatal cardiac events besides efficacy in preventing ICD shocks.(71)

ICD implantation has been the cornerstone of the treatment strategy for the majority of symptomatic ICA patients. Despite the mortality benefits of ICD implantation, this management strategy has many cons especially for young patients and can heavily affect their quality of life. Adverse events such as infection, lead dislodgment and inappropriate shocks have been reported.(72) ICD implantation strategy is mainly recommended for symptomatic high-risk patients. For LQTS and CPVT patients a left cardiac sympathetic denervation has been considered as an effective intervention.(73) Recent data showed that ICD implantation for CPVT patients did not offer improved survival compared to β-blockers and sympathetic denervation but on the other hand showed a high incidence of complications.(74) In BrS, RVOT epicardial ablation showed promising results regarding BrS pattern normalization and the prevention of VTA events.(75) RVOT ablation for asymptomatic BrS patients is still a matter of debate.(76)

For SSS patients, implantation of an AAI pacemaker is the first line of treatment for symptomatic patients. SSS patients with atrioventricular conduction abnormalities should receive a dual chamber pacemaker. AF associated SSS patients should receive anticoagulation therapy as they are at high risk of embolic events. In patients with FAF, a few studies investigated the effect of genotype on standard treatment and prediction on the outcome of different therapeutic approaches.(44, 77, 78) However, these studies have many limitations such as small sample sizes and lack of randomization.

Thesis outline

Despite the advances in our knowledge about the heritability of AF, we still facing many challenges in epidemiological and clinical playgrounds. **In chapter 2** we discussed rare and common variants role in pathophysiology of FAF. We also highlighted results of epidemiological studies as well as their clinical implications.

Data on the incidence and time course of AF and other SVTs in patients with different ICA diseases are scarce. Therefore, **in chapter 3** we discussed the impact of SVT on these patients. **In chapter 4**, we investigated the incidence and recurrences of fVPC and nsVT and their interrelationship among different cardiogenetic diseases during a long-term follow-up.

Risk stratification of BrS is facing many challenges. Defining accurate non-invasive risk markers is of significant importance. RVOT conduction delay has a major role in pathophysiology of VTA in BrS. This delay in RVOT conduction can be monitored using ECG

lead aVR. Therefore, **in chapter 5,** we investigated the positive R-wave sign in lead aVR as an independent predictor for development of VTA. Moreover, other RVOT conduction delay markers have been described to monitor conduction abnormalities in that area. **In chapter 6**, we investigated three RVOT conduction delay markers in our BrS population. Conduction delay in RVOT area is caused by scattered electrical waves. This dispersion of depolarization vector can be monitored using voltage-dependent parameters such as QRS 3-dimentional vector magnitude. **In chapter 7**, we investigated the value of QRSvm in predicting VTA in BrS using the regression related Frank-lead technique of Kors.

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CHAPTER 2

2

The Genetic Puzzle of Familial Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common clinical tachyarrhythmia. In Europe, AF is expected to reach a prevalence of 18 million by 2060. This estimate will increase hospitalization for AF to 4 million and 120 million outpatient visits. Besides being an independent risk factor for mortality, AF is also associated with an increased risk of morbidities. Although there are many well-defined risk factors for developing AF, no identifiable risk factors or cardiac pathology is seen in up to 30% of the cases. The heritability of AF has been investigated in depth since the first report of familial atrial fibrillation (FAF) in 1936. Despite the limited value of animal models, the advances in molecular genetics enabled identification of many common and rare variants related to FAF. The importance of AF heritability originates from the high prevalence of lone AF and the lack of clear understanding of the underlying pathophysiology. A better understanding of FAF will facilitate early identification of people at high risk of developing FAF and subsequent development of more effective management options. In this review, we reviewed FAF epidemiological studies, identified common and rare variants, and discussed their clinical implications and contributions to developing new personalized therapeutic strategies.

Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia with a rapidly increasing prevalence.(1) By 2050, the prevalence of AF is expected to rise to 5.6-15.6 million in the USA.(2, 3) AF is associated with an increased risk of complications such as stroke and heart failure.(4) Many risk factors are related to the incidence of AF such as age, sex, valvular heart diseases, obesity, alcohol consumption, and hypertension. However, up to 30% of AF cases have no known cardiac pathology or known risk factors (Lone AF).(1) Inherited AF was first reported in the thirties of the last century.(5) Recently, the heritability of AF has been recognized and investigated in depth.(6-8)

The importance of studying the genetic contribution to AF comes from the high percentage of lone AF cases and the prevalence differences according to gender and among certain ethnic groups. Understanding the heritable component of AF will also facilitate early identification of people at high risk of developing AF later in their lives. For a long time, the limited value of AF animal models especially murine ones obfuscated the investigation of inherited AF. However, after emerging advances in the molecular genetics, many studies identified both rare and common genetic variants related to AF.

In this review, we highlight the findings of familial AF epidemiological studies, the role of both rare and common genetic variants as well as their clinical and therapeutic implications.

Epidemiological studies

In the Framingham offspring study, those who had one parent with a history of AF had a 1.8-fold increase in the risk of developing AF. Interestingly, the risk was 3-fold higher in subjects less than 75 years.(9) In the Mayo clinic AF registry, 5% of all patients and 15% of lone AF patients had a family history of AF.(10) Among 5000 Icelanders, the first degree relatives of AF patients were 1.77 times more at risk of developing AF than the general population.(7) This relative risk reached 4.67 in patients less than 60 years. In the Danish twins' study, recurrence risk of AF was 12% for monozygotic twins and 22% for dizygotic twins.(8) In another Danish cohort, the incidence rate ratio for lone AF was 3.48 in subjects who had affected first degree relatives and 1.64 in those whose second degree relatives were affected.(11)

Rare genetic variants

In the past two decades, many researchers tried to elucidate the genetic base of AF by using different types of studies such as linkage analysis, candidate gene analysis and whole-genome next-generation sequencing. In 1997, Brugada and his coworkers

reported the first genetic locus (10q22-q24) related to AF using the linkage analysis approach.(12) A few years later, similar studies reported more genetic loci related to AF, namely 6q14-16, 5p13, 10p11-q21, 20q12-13 and 5p15.(13-16)

In 2003, Chen et al. reported the first gain of function mutation ((KCNQ1) in the potassium voltage-gated channel in affected Chinese family. However, the candidate gene analysis was costly, time-consuming and restricted to a small number of scanned genes. Also, the causality effect theory of these variants was not clear as more than 30 different variants have been discovered in potassium channels genes.

Potassium channel variants

Since 2003, many studies reported gain of function mutations in genes coding potassium channels (table 1). Most of the reported variants were gain of function mutations though, loss of function mutation was also reported. The gain of function mutations result in shortening of the effective refractory period thereby increasing AF vulnerability. Other gain of function mutations have also been identified in KCNE1, KCNE2, KCNE, KCNE5, KCNQ1 and KCNJ2 genes.(17-24)

Mutations of KCNE1 and KCNQ1 affect Iks potassium channels by a gain of function effect which accelerates repolarization and hence, shortens the refractory period. However, mutations of KCNA5 affect Ikur potassium channels but with a loss of function mutation. (25, 26) This mutation introduced an alternative mechanism for AF including delayed repolarization and prolongation of the effective refractory period.

Sodium channel variants

In 2005, Olson et al. was the first to report an SCN5A mutation related to AF.(27) These reported mutations are encoding α-subunit in Na 1.5 sodium channel. α-subunit gene mutations including genes encoding the four regulatory β-subunits (SCN1B, SCN2B, SCN3B and SCN4B) are all related to AF (Table 1). (27-29) Uncovering the underlying mechanisms of these mutations has multiple challenges such as the mixed phenotypes reported, how both loss and gain of function mutations could cause these different phenotypes and the lack of an animal model with pure AF phenotype. Mutations in the SCN10A gene are related to AF. This gene encodes the NA 1.8 sodium channels which is believed to be responsible for late sodium currents and can be modulated by SCN5A level of expression.(30)

Table 1: summary of gene loci associated with familial atrial fibrillation.

Gene	*Locus*	*Mode of inheritance*	*Functional effect*
KCNQ1	11p15.5	Autosomal dominant	Gain of function(17, 86, 87)
KCNE1	21q22.1	Autosomal dominant	Gain of function(21)
KCNE2	21q22.1	Autosomal dominant	Gain of function(20)
KCNE3	11q13.4	Autosomal dominant	Gain of function(88)
KCNE5	Xq23	X-linked	Gain of function(22)
KCNJ2	17Q23.1	Autosomal dominant	Gain of function(24)
KCNJ5	11q24.3	Autosomal dominant	Gain of function(89)
KCNJ8	12p12.1	Autosomal dominant	Gain of function(90)
KCNH2	7q36.1	Autosomal dominant	Gain of function,(91) Loss of function(92)
KCNA5	12p13.32	Autosomal dominant	Gain of function,(93) Loss of function(25)
KCND3	1p13.2	Autosomal dominant	Gain of function(94)
HCN4	15q24.1	Autosomal dominant	Loss of function(95)
MYH6	14q11.2	Autosomal dominant	Loss of function(96)
ABCC9	12p12.1	Autosomal dominant	Loss of function(97)
RYR2	1q43	Autosomal dominant	Gain of function(98)
CACNB2	10p12	Autosomal dominant	Loss of function(99)
CACNA2D4	12p13.33	Autosomal dominant	Loss of function(99)
CAV1	7q31.2	Autosomal dominant	Loss of function(100)
SCN1B	19q13.11	Autosomal dominant	Gain of function,(101) Loss of function
SCN2B	11q23.3	Autosomal dominant	Loss of function(102)
SCN3B	11q24.1	Autosomal dominant	Loss of function(103)
SCN4B	11q23.3	Autosomal dominant	Loss of function(104)
SCN5A	3p22.2	Autosomal dominant	Gain of function,(28) Loss of function
SCN10A	3p22.2	Autosomal dominant	Gain of function, Loss of function (105, 106)
GATA4	8p23.1	Autosomal dominant	Loss of function(107)
GATA5	20q13.33	Autosomal dominant	Loss of function(108)
GATA6	18q11.2	Autosomal dominant	Loss of function(109)
GJA1	6q22.31	Autosomal dominant	Loss of function(110)
GJA5	1q21.2	Somatic mutation	Loss of function(32)
ZFHX3	16q22.2-q22.3	Autosomal dominant	Loss of function(100)
GREM2	1q43	Autosomal dominant	Gain of function(111)
JPH2	20q13.12	Autosomal dominant	Loss of function(51)
LMNA	1q22	Autosomal dominant	N/A(112)
NUP155	5p13.2	Autosomal dominant	Loss of function(113)
SYNE2	14q23.2	Autosomal dominant	N/A(100)

Table 1: summary of gene loci associated with familial atrial fibrillation. (*continued*)

Gene	*Locus*	*Mode of inheritance*	*Functional effect*
NKX2-5	5q34	Autosomal dominant	Loss of function(114)
NKX2-6	8p21.2	Autosomal dominant	Loss of function
NPPA	1p36.22	Autosomal dominant	Loss of function(115)
PITX2c	4q25	Autosomal dominant	Loss of function(116)

Intracellular calcium channel variants

Increased diastolic Ca2+ leak is one of the pathophysiological pathways to AF. Phosphorylation of RyR at PKA or CAMKII sites would lead to increased RyR opening probability and increased Ca2+ leak from sarcoplasmic reticulum (SR). Recently, a study showed that AF patients have less miRNA-106b-25 cluster with consequent increase in RyR expression and Ca2+ leak.(31)

Non ion channel variants

Gollob et al. described the first three somatic mutations in GJA5 gene related to AF; these mutations are responsible for impaired cell to cell coupling.(32) This impairment is caused by depletion of atrial specific connexin 40. Moreover, Christophersen et al. described a germline mutation in the same gene. Mutations in gene encoding atrial natriuretic peptide (ANP) have been reported to be related to AF. It is believed that this mutation in ANP protein would shorten the action potential. In 2008, a mutation in the NUP155 gene encoding nucleoporin of the nuclear envelope was discovered. This mutation leads to alteration in nuclear envelope permeability. Many mutations in transcription factors genes have been reported to be related to AF such as NKX2-5, PITX2, ZFHX3, GATA4, GATA5 and GATA6 genes. GATA and PITX2 genes affect the development of the pulmonary venous myocardium which is involved in the initiation of AF (Table 1). Several studies reported an increased risk of AF with polymorphism of RAAS system genes encoding angiotensin converting enzyme inhibitor, angiotensin gene promotor, and angiotensinogen. (24, 33)

Limitations of in vitro methods

In vitro methodologies for functionally characterizing the role of ion channels variants have drawbacks. For instance, AF cell lines continuously proliferate and are affected by rapid maturation, increased number of cells, and disorganized three-dimensional structure. In addition, not all areas within cell lines have the same metabolic activity. The evolving induced pluripotential stem cells is one step closer to the optimal in vivo conditions such as conduction properties, contraction and relaxation velocity, action potential duration and repolarization fraction . Repolarization fraction is a parameter to distinguish between atrial and ventricular like human induced pluripotent stem cells

(hiPSCs) and it is calculated based on the following equation: (APD90 – APD50)/APD90), APD90; is action potential duration at 90 % repolarization and APD 50 is action potential duration at 50 % repolarization. However, these type of cells are electrophysiologically different from adult atrial cardiomyocytes in respect to Ca2+ handling and the predominance of ventricular like cells; ventricular contribution to the cell population can be minimized to less than 10 % by using timed retinoic acid exposure.

Murine Models

In recent decades, murine models have drawn the attention of many investigators attempting to decode electrophysiological mechanism underlying AF. Murine models were considered a good candidate because of the conservation of development and signaling pathways between homo sapiens and mice, the ease of genetic manipulation, and rapid maturation.

Potassium channels mutation models have been studied such as the knockout models for KCNE1and SK2 channels..(34-37) Moreover, sodium channel genes have been a target for transgenic models. ΔKPQ-SCN5A models showed more susceptibility to atrial arrhythmia.(38-42) SCN3B subunit knockout models also showed conduction disturbances.(43) Non ion channels models also showed promising results such as connexin 40 and 43models(44-46), Ankyrin B(47) and PITX2.(48) Knock out mice of spinophilin-1 leads to increased RyR phosphorylation and increases Ca2+ leak.(49) The same results were also shown in junctophilin and FKBP-12.6 knock out models.(50, 51)

Despite the value of these murine models, they have several limitations. One of the main limitations of these models is that AF was always induced in a non-physiological way. Other factors involved in clinical AF such as environmental factors, diet, and abuse of toxic substances were omitted. Although there is similarity in signaling pathways between mice and humans, there are important differences in heart rate, ion currents, calcium handling, and predominant myosin isoform.

Genome wise association studies (GWAS)

In 2007, the first GWAS study on AF was published. By using a p-value of <5x10-8 to minimize false positives, variant frequencies were compared between affected and non-affected subjects. The first detected locus was on chromosome 4q25.(52) However, this locus is in a non-coding area; studies revealed its role in regulating the closest gene (PITX2). This gene is essential for cardiac development and suppression of a sinus node development in pulmonary vein myocardium (left-right asymmetry). PITX2 knockout mice model showed a decrease in sodium and potassium channels expression and caused a conduction block at the atrioventricular node.(53) Herraiz-Martínez

et al. recently investigated whether chr4q25 risk variants alter the intracellular calcium homoeostasis. Patients carrying the rs13143308T risk variant show increased SERCA2a expression, SR calcium load, and RyR2 phosphorylation. These changes lead to excessive calcium release and a higher risk for AF.(54)

In 2009, a novel locus on chromosome 16q22 was described in a cohort of European descent.(55) The closest single nucleotide polymorphism (SNP) to this locus was intron to the zinc finger homeobox 3(ZFHX3). This motif binding factor is required for regulation of the Pituitary-specific positive transcription factor 1 (POU1F1) which interacts with the PITX2 gene. In 2010, Ellinor et al. described a novel locus on chromosome 1q21. This SNP is located near KCNN3 gene which encodes voltage-independent calcium-activated potassium channel protein. These SK3 channels are essential for the repolarization phase of the cardiac action potential.(56) These SK3 channels are also located in the inner mitochondrial membrane and opening of these channels using agonists have a protective effect against oxidative stress-induced injury resulting from Ca2+ overload. (57)

Chromosome 15q24 also contained a locus related to AF and sinus node dysfunction. The closest gene to this SNP was HCN4 which encodes channels proteins regulating funny current of the sinoatrial node in the left atrium.(58) Recently, two SNPs were discovered in the Japanese population on chromosome 12q24. The first SNP is located near NEURL gene. Knocking out this gene in zebrafish lead to action potential prolongation. The other SNP was intronic to CUX2 gene, however, the mechanism leading to AF is not clear yet.

An AF GWAS risk SNP on chr14q23 in the SYNE2 encodes nesprin-2 which is part of nuclear outer membrane and sarcomere.(59, 60) Another non ion channel gene showed AF related SNP on chromosome 7q31, this locus is intronic to CAVI (caveolin-1) which has a role in repolarization phase of action potential and also has a structural role by regulating TGF-β-1and fibrosis.(61)

Recently, many studies investigated the role of cytoskeletal proteins in the pathogenesis of FAF. Two Islandic cohorts reported two novel SNPs in MYH6 and MYL4 genes.(62, 63) MYH6 encodes the alpha myosin heavy chain subunit. Mutations in this subunit have been reported to affect cardiac contractility and muscles fibers integrity.(64, 65) MYL4 encodes the essential myosin light chain subunit which is known as atrial light chain1. In vitro experiments on zebrafish with mutant MYL4 revealed loss of cardiac contractility and absence of sarcomere structure.(66, 67) Another study supported the role of myocardial structure in FAF by the discovery of a missense variant in the PLEC gene.(68) This

gene encodes a cross-linking protein (plectin) which has a role in keeping the integrity of cardiac muscles. These studies suggest a strong role of cytoskeletal proteins in the pathogenesis of AF. A recent large GWAS meta-analysis showed that AF is associated with variants in 18 structural genes and also variants in 13 genes with a cardiac fetal developmental role such as ARNT2 and EPHA3.(69) This could explain the pathophysiology of AF as a result of atrial cardiomyopathy via cardiac structural remodeling either during fetal development or during adult life.

Another large GWAS study identified 134 AF associated loci among 93,000 AF cases and more than 1 million referents.(70) This study showed that TBX3, TBX5 and NKX2-5 genes encode transcriptional factors that regulate development of the cardiac conduction system. This study also highlights the overlap between AF and other atrial arrhythmias and the pleiotropy of genes which are responsible for cardiac morphology and function. Nielsen et al. showed the relationship between AF and cardiac development and suggested that AF variants play a role in the developing heart or in reactivating fetal genes or pathways during adulthood as a response to stress and remodeling.(71)

Despite the revolutionary output of GWAS studies, this approach of investigating heritability of FAF has several limitations. A large number of detected loci has only explained a small fraction of the missing heritability. This fact limits the clinical usage of outcomes of GWAS studies and urges the need for studies investigating gene-gene and gene-environment interactions. Another challenge is that approximately 80% of the discovered SNPs are in non-coding regions of the genome and this requires additional research to explore the exact causal variant by deploying techniques such as fine mapping, functional analyses, and evolutionary genetics.

Clinical implications

There is no doubt that FAF is part of the uprising field of personalized medicine. Technological advances in genetics and a large amount of newly available data have encouraged many researchers to investigate the possible clinical value of this data to develop more efficient prediction models and personalized management strategies. The ORBIT-AF registry showed that FAF patients experienced more symptoms than non FAF patients. However, there was no difference between the two groups regarding AF recurrences, hospitalization rate, complications, and all-cause mortality.(72, 73) On the other hand, risk stratification based on genotype showed promising results. Husser et al. and Shoemaker et al. showed that patients with 4q25 SNP rs2200733 had an increased risk of developing recurrent AF after ablation.(74, 75) Another study showed that AF patients with the same 4q25 SNP also had higher risks of developing AF recurrences after direct current cardioversion (HR:2.1, 95% CI: 1.21-3.3; P=0.008).(76) The main limitations

of these results are the small sample sizes and using the time to the first symptomatic episode which is a poor quantitative metrics for AF. Time to the first symptomatic AF episode does not take into account the frequency and length of AF episodes. Advances in continuous rhythm monitoring devices and AF detection algorithms will facilitate using AF burden as a more realistic, accurate and quantitative parameter for AF and also as a surrogate outcome after treatment. The effect of genotype on the success of ablative therapy was tested; likewise, response to antiarrhythmic drugs. Parvez et al. showed that the SNP rs10033464 at 4q25 is an independent predictor for success in rhythm control in both discovery and validation cohorts. Furthermore, they showed this same SNP is a predictor for AF recurrence in the same cohorts.(77) Another study showed that flecainide potency is increased in AF patients with β1AR Arg389Arg genotype. (78) Also, AF patients with the same genotype have a better response to rate control therapy and required lower doses of these drugs.(79) One of the main limitations of these studies is the lack of randomization. Data were analyzed retrospectively and drug response was evaluated a priori without knowledge of the genotype.

Few studies tried to implement genotype into prediction models of de novo AF. In 2013, AF-genetic risk score (AF-GRS) was introduced. This score consisted of 12 risk alleles in nine loci. They investigated the predictive value of this score in 20000 females without cardiovascular disease at baseline. Adding this score to the main prediction model increased the area under the curve to (0.74).(80) In 2014, Tada and his colleagues showed that multiple single nucleotide polymorphisms can improve the prediction to develop AF and ischemic stroke. GRS score showed a potential value as an indicator for anticoagulant therapy.(81) The main limitation of these studies is their lack of external validity to other ethnic groups such as Africans or Asians.

For postoperative AF, few studies have tried to replicate this approach but results are still controversial to improve prediction models performance as these studies lacked large sample sizes and did not use continuous ECG monitoring to identify AF episodes.(82-84) In 2016, Lin and his colleagues investigated if gene-gene interaction would affect AF susceptibility. However, this study could not find any significant association and a larger cohort containing participants from other ethnic groups is indeed justified.(85)

Translational challenges

Translating the advances achieved in genetic technology into clinical practice still has many limitations with respect to genetic based prediction models and personalized therapeutic strategies.

Firstly, prediction models still have insufficient discriminative ability between low and high-risk individuals for several reasons such as testing small number of variants, potential gene-gene interactions and gene-environment interactions. Moreover, the cost and logistic aspects have to be considered while moving this prediction model into clinical use. Secondly, applications of pharmacogenetics guided therapy are limited.

Another limitation is that pathophysiological pathways underlying AF genetic variants are not clear which delays attempts to target certain pathways caused by specific genetic variants. The multifactorial complex nature of AF could also limit the efficacy of any new drug development. In addition, involvement of multiple genetic variants in a patient is more challenging for a personalized efficient treatment strategy.

Future directions

Despite the advances in our understanding of FAF, there are still many challenges and questions to be addressed. Firstly, large cohorts are needed to study the effect of gene-gene and gene-environment interactions on AF. These cohorts should consider larger sample sizes, participation of non-European ancestry and analyzing interactions between more than two variants. Secondly, randomized controlled trials are needed to validate the effect of genotype guided treatment strategies. Advances in rhythm monitoring devices and rhythm detection algorithms are needed in addition to using AF burden as a reliable parameter to quantify AF.

Larger cohorts are needed to investigate the effect of genotype guided prediction models of AF incidence, AF complications and mortality. Last but not least, large and effective screening studies for families with FAF is advised to uncover part of the missing heritability of FAF. For instance exome sequencing and whole genome sequencing projects would discover more missing rare and structural variants which GWAS studies cannot identify.

Conclusion

Genetic basis and heritability of AF is part of the complexity of this arrhythmia and a lot of progress has been achieved in many aspects such as risk stratification for AF, identification of novel therapeutic targets, and genome-based prediction models. There is no doubt that better understanding of AF heritability will not only improve AF prediction models but will also be the next step towards more efficient personalized treatment strategies.

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CHAPTER 3

3

Impact of Supraventricular Tachyarrhythmia in Patients With Inherited Cardiac Arrhythmia

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Abstract

Supraventricular tachyarrhythmia (SVT) especially atrial fibrillation (AF) has been observed in patients with inherited cardiac arrhythmia (ICA). Data on the time course of SVT and the occurrence of other SVT than AF is limited. In this study, we examined the prevalence, co-existence and the time course of different types of SVT in patients with various ICAs. In this retrospective study, we selected 393 patients (median: 49 years, range:17-87, 57% male) from a cohort of patients visiting the outpatient clinic for cardiogenetic screening of ICA. Patients medical records were examined for the occurrence of AF and other SVT. AF/SVT were found in 49 patients (12%, 31 male 42±17 years). Patients presenting with only AF (N=12, 3%) were older than patients presenting with only SVT (N=28, 7%), respectively 52±18 versus 37±14, P=0.007. Nineteen patients (5%) had multiple episodes of either AF (N=7, 2%) or SVT (N=12, 3%). Alternating episodes of AF and SVT occurred in 9 patients (2%). Intervals between second and third AF episodes were significantly shorter than between first and second episodes (P=0.02). An implantable cardioverter defibrillator (ICD) was implanted in 158 patients (40.2%) and 26 patients (16%) had inappropriate ICD shocks (SVT:25, AF:1), particularly those with multiple SVT episodes (P=0.003). In patients with a variety of ICAs, episodes of AF/SVT occurred in 12%. In patients with multiple AF episodes, intervals between consecutive episodes became significantly shorter over time. AF/SVT episodes are associated with inappropriate ICD shocks and aggressive therapy of AF/SVT is therefore justified.

Introduction

Inherited cardiac arrhythmia (ICA) are responsible for 2 to 4% of the total number of sudden cardiac deaths.(1) Hundreds of genetic variants are at present known to cause defects in the ion channels or other membrane components which predispose subjects to ventricular tachyarrhythmia (VT) and sudden cardiac death.(2) However, not only ventricular but also supraventricular tachyarrhythmia (SVT) have been reported in patients with ICA.(3,4) Previous studies have examined the prevalence of atrial fibrillation (AF) mainly in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and Brugada syndrome (Brs).(5,6) There are so far no studies reporting on the incidence of SVT in other ICA. In addition, there is limited data on the prevalence of other different types of SVT than AF and the time course of either AF or SVT in this population. We therefore examined the prevalence of AF and all other SVT in a large cohort of patients with various ICA and also studied time courses and coexistence of AF and SVT episodes.

Methods

This retrospective study is part of the 'EvaluatioN of CardiOgenetic Disease and Effectiveness of scReening' (ENCODER) project, which was approved by the local ethics committee in the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2014-313). All data, including clinical characteristics and test outcomes, were collected from the medical records of the patients. Therefore, informed consent was not required.

Patients were selected from a database containing adult patients, visiting the outpatient clinic for cardiogenetic screening in the Erasmus Medical Center Rotterdam, the Netherlands. Indications for screening include unexplained palpitations, syncope and/or abnormal electrocardiogram (ECG) suggestive of ICA, documented VT of unknown cause, survival of an out of hospital cardiac arrest (VF/OHCA unknown cause), screening with or without diagnosis of an ICA in the family, carriers of cardiogenetic mutations. We excluded symptomatic patients with ischemic heart disease (IHD), Wolff-Parkinson White syndrome and hypertrophic or non-compaction cardiomyopathy or when data regarding the diagnostic process (i.e. test outcomes and patient or family history) was missing.

Patients with the following ICA diagnoses were enrolled: ARVC, BrS, cathecholaminergic polymorphic ventricular tachycardia (CPVT), idiopathic ventricular fibrillation (IVF), long QT syndrome (LQTS), short QT syndrome (SQTS), carriers of a pathogenic cardiogenetic mutation related to ICA without phenotypic manifestation of cardiac disease, and famil-

ial sick sinus syndrome. ARVC was diagnosed as definite, borderline or possible ARVC according to the 2010 revised Task Force Criteria.(7)

The diagnosis of BrS was made according to the criteria as described in the consensus report in 2013.(8) CPVT is diagnosed in the presence of unexplained or catecholamine-induced bidirectional VT or polymorphic premature beats or VT in patients younger than 40 years; diagnosis of CPVT was also confirmed in patients with pathogenic mutation in RYR2, CALM1, CASQ2 or TRDN genes.(9-11) Familial IVF was diagnosed after documented VF/OHCA or pathogenic mutation in the *DPP6* gene was detected.(12) LQTS and SQTS were diagnosed according to the criteria in the expert consensus recommendations in 2013.(11,13)

ECGs, 24-hours Holter registrations and ICD read outs obtained in the initial screening and follow-up visits were evaluated. SVT were subdivided into AF and all other SVT except AF. Diagnosis of SVT were made according to ACC/AHA/ESC clinical guidelines. (14-15) Patients visited the outpatient clinic at least twice per year. The VT zone was programmed between 141 and 220 beats/min and VF zone between 207 and 240 beats/mins. For every inappropriate shock, it was analyzed whether it was caused by AF, SVT or inappropriate sensing.(16)

Continuous variables (expressed as mean ± SD) were compared using unpaired Student's *t* tests or ANOVA tests to compare patient groups. Skewed data is depicted as median and range; Kruskal-Wallis tests were used to compare groups. Categorical data were denoted by percentages and compared with the McNemar test, X^2 test or Fisher's exact test.

Adjusted hazard rates were compared by multivariate Cox proportional-hazards regression analysis. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS, version 21 (IBM, Armonk, New York).

Results

A total of 393 patients (225 male, 57%) were enrolled in August 2015 with a median age of 49 at last follow up. Diagnosis included ARVC (N=41), borderline ARVC (N=16), possible ARVC (N=18), BrS (N=126), IVF (N=105), LQTS (N=48), SQTS (N=1), familial sick sinus syndrome (N=6), CPVT (N=9) and carriers of a cardiogenetic mutations (N=23). Characteristics of the study population are summarized in Table 1. During the last follow up visit, 158 patients (40.2%) had an ICD (DDD-ICD: N=38; DDI-ICD: N=4, VVI-ICD: 42, s-ICD: N=30). Inappropriate ICD shocks (SVT: N=25 AF: N=1) occurred in 26 patients (16%).

One or more AF or SVT episodes were found in 49 patients (12%) at a mean age of 42±17 (range 9 - 82) years. Figure 1 shows age at the moment of the first documented SVT and/or AF episode for patients having only SVT episodes (N=28, 7%), AF episodes (N=12, 3%) or both SVT/AF episodes (N=9, 2%) separately.

Patients with only documented AF episodes were significantly older than patients with only SVT, (52±18 (17-82) years versus 37±14 (17-68) years, P=0.007). In patients who had both documented SVT/AF episodes, age at the initial AF or SVT episode was 48±20 (9-67) years. Gender did not affect age of the first documented SVT episode (males:44±16 (17-67) years; females: 40±18 years (9-82) years, P=0.42).

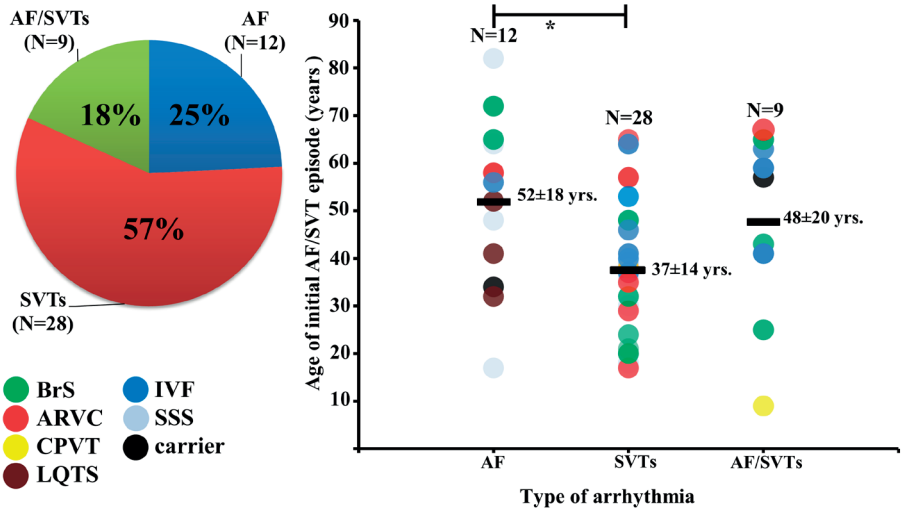

Figure 1. Left panel: Pie chart demonstrating the relative frequency distribution of SVT and AF in our 49 patients with various ICA. Right panel: Scatterplot demonstrating ages at the moment of the initial presentation of different SVT/AFs. ARVC: Arrythmogenic right ventricular cardiomyopathy, IVF: Idiopathic ventricular tachycardia, LQTS: Long QT syndrome, SQTS: Short QT syndrome, VF/OHCA: Ventricular fibrillation/Out of hospital cardiac arrest, VT: Ventricular tachycardia, CPVT: Cathecholaminergic polymorphic ventricular tachycardia.

Multiple episodes of SVT were found in 17 patients (4%); 5 of them had both SVT and AF. Seven patients (7/37, 19%) used beta-blockers at the moment of the first SVT episode. The median interval between the first and second episode was 6 months and between the second and third 22 months. Patients who had multiple SVT episodes were significantly more susceptible for inappropriate ICD shocks (N=12/17, 70%, P=0.003). Ten patients (10/393, 3%) had multiple AF episodes; 3 of them also had SVT episodes. Two patients (20%) used beta-blockers for rate control at the time of the first documented

AF episode. Median interval between the first and second AF episode was 17 months and between the second and the third episode was only one month, P=0.02 (Figure 2).

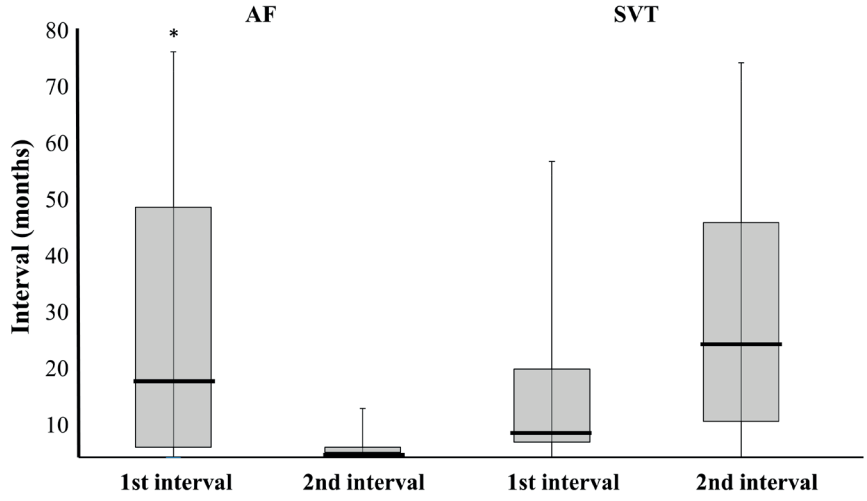

Figure 2. Intervals between multiple episodes
Box plot demonstrating difference between intervals of multiple episodes of AF and SVTs, *P=0.02.

In the entire study population, both AF and SVT episodes were found in 9 patients (2%, 6 male, 48±20 years, 2%; BrS: N=3, ARVC: N=1, IVF: N=3, CPVT: N=1, carrier of cardiogenetic mutation: N=1, Figure 1). Five patients initially presented with AF and four initially with SVT; mean intervals between documentation of consecutive episodes was respectively 27±11 months and 21±17 months.

At least one inappropriate ICD shock occurred in 26 patients. Inappropriate shocks were identified in only 2 patients with a S-ICD compared to 24 patients with a transvenous ICD (2/30 vs 24/128, P=0.084). Inappropriate ICD shocks could not be predicted by age >65, gender, previous history of AF, ICD indication (primary or secondary prevention) or patients beta-blockers usage (Table 2).

Table 2. Cox analysis to identify predictors of inappropriate ICD shocks.

	Univariate		Multivariate	
	Hazard ratio	**P-value**	**Hazard ratio**	**P-value**
Age >65	1.545 (0.02-11.92)	0.67	0.978 (0.943-1.014)	0.222
Gender	1.035 (0.449-2.383)	0.936	1.129 (0.434-2.937)	0.803
History of AF	1.032 (0.302-3.523)	0.960	0.659 (0.162-2.674)	0.559
Secondary prevention	0.530 (0.236-1.186)	0.122	0.506 (0.205-1.247)	0.139
B-blocker	0.625(0.183-2.142)	0.455	0.419 (0.107-1.639)	0.211

Table 1. Prevalence of AF, SVTs and coexistence of AF/SVTs for each ICA

	Arrythmogenic right ventricular cardiomyopathy			Brugada Syndrome	Idiopathic Ventricular Fibrillation	Long QT Syndrome	Short QT Syndrome	Sick Sinus Syndrome	Cathecholaminergic polymorphic ventricular tachycardia	Carrier
	(Definite)	(Borderline)	(Possible)							
N	41(9%)	16(4%)	18(4%)	126(30%)	105(27%)	48(11%)	1(0.2%)	6(1%)	9(2%)	23(6%)
Male	66%	19%	61%	66%	64%	40%	100%	33%	22%	44%
Age (years)	47±16	48±17	51±14	46±15	51±15	43±15	26	58±28	28±9	47±16
Implantable cardioverter-defibrillator	63%	25%	22.2%	28%	73%	21%	0%	83%	44%	13%
Prevalence AF	2 (4%)	0%	0%	5 (4%)	4 (4%)	3 (6%)	0%	4 (67%)	1 (11%)	2 (9%)
SVTs	6 (15%)	1 (6%)	0%	9 (7%)	17 (16%)	1 (2%)	0%	0%	1 (11%)	2 (9%)
AF/SVTs	1 (2%)	0%	0%	3 (2%)	3 (3%)	0%	0%	0%	1 (11%)	1 (4%)
Age 1st episode AF (years)	62±6	N/A	N/A	55±18	56±11	42±10	N/A	53±28	9	46±16
SVTs	45±21	29	N/A	35±15	42±13	39	N/A	N/A	12	39±31

Discussion

To our knowledge, this the first study examining the prevalence and time course of AF and SVT in a large cohort of patients with various ICA. AF/SVTs were observed in 12% of our patients. In the general population, the prevalence of AF and SVT is respectively 2% and 0.23% and the average age of the AF and SVT patient is approximately 75-80 and 57 years.(15) In our population, we observed a higher prevalence of both AF (3%) and SVT (7%) and age at the moment of the initial presentation was younger (AF: 52±18 years, SVT: 37±14 years). Multiple AF and SVT episodes were observed in respectively 3% and 4% of our study population and these patients were more susceptible to inappropriate ICD shocks. About 10% of our patients will develop permanent AF after one year of the first AF manifestation and this risk increases 5% per annum.(17) In contrast to patients with multiple SVT episodes, intervals between consecutive AF episodes became significantly shorter over time. Time intervals between consecutive AF episodes were variable, but could be as long as 72 months. AF can affect the patients' quality of life dramatically as it may cause serious complications such as thrombo-embolic events, heart failure and impaired cognitive function. AF is associated with doubled risk of death, five folds risk of stroke and subsequently a 1.5-fold increase in health care costs.(14) SVT are an infrequent cause of hospitalization, however, they are a common cause of both emergency and primary care visits.(18)

ICA are responsible for 4% of all sudden cardiac deaths. Mutations in sodium, potassium and calcium channels or mutations in cardiac desmosomes are the main pathological changes detected in this populations.(19) Many of these mutations were reported as a cause of AF. Gain of function mutations such as KCNE2, KCNQ1 and KCNJ2 are responsible for decreased action potential duration and then facilitate AF. Loss of function KCNA5 and SCN5A gene mutations lead to increased action potential duration and AF by initiating afterdepolarizations.(20)

In patients with LQTS, prolongation of action potential duration and increased atrial effective refractory period are the main mechanisms underlying SVTs.(21) About 17 genes are linked to LQTS either by gain of function sodium channel mutations or loss of function potassium channel mutations.(22) In patients with SQTS, AF is associated with shortening of the atrial refractory period and increased dispersion of repolarization due to either gain of function mutations in potassium channels or loss of function mutations in the L-type calcium channels is the main mechanism initiating AF in this population. In patients with BrS, intra-atrial conduction delay due to sodium channel loss of function SCN5A mutations is the main substrate underlying AF.(23,24) Calcium leak from the sarcoplasmic reticulum due to dysfunction of ryanodine calcium release

channel (RYR2) or cardiac calsequestrin (CASQ2) is associated with AF in patients with CPVT. Mutations in RYR2, CASQ2, CALM2 and TRD genes were identified in 30-80% of these patients.(25) In SQTS, shortening of ERB and increased dispersion of repolarization due to either gain of function mutations in potassium channels or loss of function mutations in the L-type calcium channels is the main mechanism initiating AF in this population.(26) Major precipitating factors for SVT such as congenital heart defects affecting atrial anatomy or atrial volume/pressure overload were absent in our population. The increased propensity of SVT and AF observed in our study population indicates that not only the ventricles, but also the atria in ICA patients are affected.

Patients diagnosed with ICA should be regularly screened for the presence of SVT/AF, particularly when they are not continuously monitored by an implantable device such as an ICD. The presence of multiple SVT or AF episodes are associated with inappropriate ICD shocks which will also affect the patients' quality of life significantly and proper ICD programming is therefore important. In patients with ARVC, atrial arrhythmia is related to moderate to severe tricuspid regurgitation and enlarged right ventricle.(5) Though the guidelines recommend to start with antiarrhythmic drug therapy, first-line treatment with ablative therapy of SVT may be justified in this patient group. Pharmacological therapy of AF is difficult as many anti-arrhythmic drugs are contra-indicated in BrS and LQTS patients. In addition, drugs may cause side effects such as bradycardia, which is inconvenient in this young patient population. Reduction of sympathetic innervation could decrease the incidence of ventricular tachyarrhythmias in patients with CPVT.(25) In patients with BrS and paroxysmal AF, pulmonary vein isolation has a success rate of 67% during long-term follow-up and reduces the incidence of inappropriate ICD shocks.(27,28)

Our study has several limitations. First, it was a retrospective study and some subpopulations were small. Second, a part of our study population was not continuously monitored and arrhythmia episodes could therefore have been missed.

In patients with a variety of ICAs, episodes of AF/SVT occurred in 12%. In patients with multiple AF episodes, intervals between consecutive episodes became shorter over time. Both AF and SVT episodes are associated with inappropriate *ICD* shocks and aggressive therapy of AF/SVT is therefore justified.

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CHAPTER 4

Ventricular Dysrhythmias during Long-Term Follow Up in Patients with Inherited Cardiac Arrhythmia

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Background

Reports on development of frequent ventricular premature beats (fVPB), (non)sustained ventricular tachycardias ((n)sVT) or ventricular fibrillation (VF) and their interrelationship in patients with different inherited cardiac arrhythmia (ICA) have sofar not been reported. The aim of this study is therefore to examine incidences and recurrences rates of sVT and VF ('malignant ventricular tachyarrhythmias',VTA) in addition to the incidence of fVPB and nsVT ('ventricular dysrhythmias, VDR') in patients with various ICA during long-term follow up.

Methods

Patients (N=167, 88 male, age 45 15yrs) with ICA including definite/borderline arrhythmogenic right ventricular cardiomyopathy (ARVC, N=47), Brugada syndrome (BrS, N=71), catecholaminergic polymorphic ventricular tachycardia (CPVT, N=7), long QT syndrome (LQTS, N=41) or short QT syndrome (SQTS, N=1) who had frequent 24-hr Holter monitoring during a follow-up period of 4.6 ±4.4 years.

Results

Fifteen patients had a history of malignant VTA. During the initial screening visit, fVPB and nsVT was observed in respectively 19% (OHCA/VF/sVT:N=9) and 13% (OHCA/VF/sVT:N=4) of all patients. Compared to the ARVC group, patients with BrS and LQTS had less frequent fVPB and nsVT (fVPB: OR 0.20, 95% CI 0.08-0.49, $p < 0.000$, and OR 0.09, 95% CI 0.02-0.33, $p<0.000$; nsVT:OR 0.17, 95% CI 0.06-0.50, $p= 0.001$ and OR 0.09, 95% CI 0.02-0.46, $p = 0.003$). The recurrence rate of malignant VTA was 33%.

Conclusion

A variety of VDR and malignant VTA were found during long-term follow up in patients with ICA. During nearly a five year follow up period, the recurrence rate of malignant VTA was considerable. fVPB, nsVT and malignant VTA were most often found in patients with an ARVC.

Abstract

Introduction

Inherited cardiac arrhythmias (ICA), including channelopathies and cardiomyopathies, are responsible for approximately 5-10% of all sudden death cases (1, 2) and they are diagnosed in up to 50% of the family members.(3)

Cardiac channelopathies comprise a group of diseases with mutations in genes associated with various cardiac membrane channels. (4) Arrhythmogenic right ventricular cardiomyopathy (ARVC) is nowadays considered to be a bridge between channelopathies and inherited cardiomyopathies. (5) The clinical spectrum of ICA ranges from asymptomatic to SCD caused by life-threatening ventricular tachyarrhythmias (VTA). (4, 6)

Prior studies have attempted to identify ICA patients at high risk of SCD. In certain types of Long QT syndrome (LQTS), patients with a history of cardiac events in their first year of life are considered to be high risk patients.(7) Priori et al. identified a history of syncope, spontaneous Brugada type I electrocardiogram (ECG), ventricular refractory period <200 ms and QRS fragmentation as high risk factors for development of VTA in patients with Brugada Syndrome (BrS).(8) For the majority of the patients, it is difficult to determine whether they have a low, intermediate or high risk for SCD. Most studies evaluate the risk of developing life-threatening VTA in populations with a specific ICA.

Reports on development of frequent ventricular premature beats (fVPB), nonstained ventricular tachycardias ((n)sVT) or ventricular fibrillation (VF) in patients with different ICA during long-term follow up and their interrelationship are scarce. The aim of this study is therefore to examine incidences and recurrences rates of fVPB, (n)sVT and VF in patients with various ICA during a long-term follow up period.

Methods

This retrospective, single center study is part of the 'EvaluatioN of CardiOgenetic Disease and Effectiveness of scReening' (ENCODER) project, which was approved by the local ethics committee in the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2014-313). Informed consent was not required because all data, including patient characteristics and test outcomes, were collected from patients' medical records.

Study Population

Patients older than 18 years who visited the cardiology outpatient clinic between 2004 and 2015 for cardiogenetic evaluation were included. They had survived VF/an out of hospital cardiac arrest (OHCA), had episodes of either non-sustained VT (nsVT) or sustained VT (sVT), complaints with suspicion of ICA, were family members of a patient with (suspicion of) an ICA or were referred by the department of clinical genetics (mutation carriers). Patients with myocardial ischemia, anatomical abnormalities and intoxications were excluded. In this study, we selected a subgroup of patients diagnosed with an ICA who had Holter monitoring during the initial cardiogenetic evaluation and yearly follow up visits. These patients visited the outpatient clinic once a year. Examinations included history taking, registration of surface ECGs and 24-hour Holter monitorings.

Diagnosis of ICA

ARVC, BrS, LQTS, Short QT Syndrome (SQTS) and catecholaminergic polymorphic VT (CPVT) were according to criteria defined in the 2015 ESC guideline for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. {Priori, 2016 #395}. Diagnosis is based on ECG abnormalities, family history or pathogenic mutations. ARVC is further differentiated into possible, borderline and definite ARVC but in this study we only included definite and borderline patients.(9)

Analysis of Rhythm Registrations

In this study, VPB and nsVT were defined as ventricular dysrhythmias (VDR) and sVT and VF as 'malignant' VTA. All 24-hour holter monitorings from every visit were reviewed for the occurrence of VDR and malignant VTA. fVPB are defined as VPBs with a frequency of more than 10 per hour or more than 240 VPBs per 24 hours.(10) If patients had an Implantable Cardioverter Defibrillator (ICD), we evaluated the approriateness of every shock using the ICD printouts.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation. The Shapiro-Wilk or Kolmogorov-Smirnov test was applied to evaluate whether continuous variables were normally distributed. Categorical data were denoted by percentages. A binary logistic model was used to compare the risks of developing VDR between the different ICA. A P value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, NY).

Results

Study Population

Characteristics of the 167 selected patients are summarized in Table 1. The majority of patients had definite/boderline ARVC, BrS, or LQTS. Most patients were refered to the cardiology outpatient clinic because of complaints with suspicion of ICA (N=50, 30%) and screening of family members of patients diagnosed with an ICA (N=44, 26%). Twenty-one patients were initially referred with documented VT (sVT: N=9, nsVT: N=6) or they were VF/OHCA (N=6) survivors. During follow up, 52 (37%) patients received an ICD; ICD indications were either primary (N=37) or secondary prevention (N=15).

Table 1. Clinical Characteristic

	All (N=167)	ARVC (N=47)	BrS (N=71)	LQTS (N=41)	CPVT (N=7)	SQTS (N=1)
Male N(%)	88 (53)	23 (49)	45 (63)	17 (42)	2 (29)	1(100)
Age (mean ± SD) years	45±15	48±16	45±15	45±15	27±14	26
Indication for Cardiogenetic Evaluation N(%)						
Documented VT	15 (9)	11 (23)	2 (3)	1 (2)	1 (14)	0(0)
Genetic Screening, Known Diagnosis	44 (26)	13 (28)	23 (32)	6 (15)	2 (29)	0(0)
Genetic Screening, Unknown Diagnosis	22 (13)	6 (13)	10 (14)	4 (10)	2 (29)	0(0)
Complaints suspected for ICA	50 (30)	8 (17)	33 (47)	7 (17)	1 (14)	1(100)
Carriers	17 (10)	3 (6)	2 (3)	12 (29)	0 (0.0)	0(0)
VF/OHCA	6 (4)	4 (9)	1 (1)	1 (2)	0 (0.0)	0(0)
Other Diagnosis	13 (8)	2 (4)	0 (0.0)	10 (25)	1 (14)	0(0)

ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy); BrS (Brugada Syndrome); LQTS (Long-QT Syndrome); CPVT (Catecholaminergic Polymorphic Ventricular Tachycardia); SQTS (Short QT Syndrome); VT (Ventricular Tachycardia); ICA (Inherited Cardiac Arrhythmia); VF (Ventricular Fibrillation); OHCA (Out of Hospital Cardiac Arrest)

Frequent Ventricular Premature Beats

fVPB were found in 32 (19%) patients during the initial screening at the outpatient clinic; 6 of them were referred for prior sustained VT and 3 patients were VF/OHCA survivors. Figure 1 shows that fVPB during the initial Holter monitorings were most often observed in the ARVC group (N=19, 40%; prior sVT: N=4, VF/OHCA: N=4) compared to the CPVT (N=1, 14% with prior sVT), BrS (N=8, 11%) and LQTS (N=3, 7%; prior sVT: N=1) group.

Non-Sustained Ventricular Tachyarrhythmias

nsVT was present in 21 (13%) patients during the initial screening. Comparable to fVPB, Figure 1 shows that nsVT also occurred more frequently in ARVC patients (N=9, 19%; prior sVT: N=2, VF/OHCA: N=2) followed by BrS (N=5, 7%), CPVT (N=1, 14%) and LQTS (N=1, 2%). In the latter 3 groups, none of these patients had a history of malignant VTA.

Recurrent Malignant Ventricular TachyArrhythmia

Median duration of the follow up period was 5 years (IQR 5 years). Figure 2 shows the development of various VDR over time.

In the entire study population, malignant VTA only developed in patients with an ICD. Out of 52 patients with an ICD, 15 patients (ARVC: N=6, BrS: N=4, LQTS: N=3, CPVT: N=2) experienced appropriate shocks (AS), as shown in Figure 3. Five of them (ARVC: N=2, BrS: N=1, LQTS: N=1, CPVT: N=1) were referred with a history of malignant VTA. Thus, the recurrence rate of malignant VTA is 33%. Inappropriate shocks (IS) were detected in 5 patients and were caused by supraventricular tachycardia (N=4) or dysfunction of the RV lead (N=1).

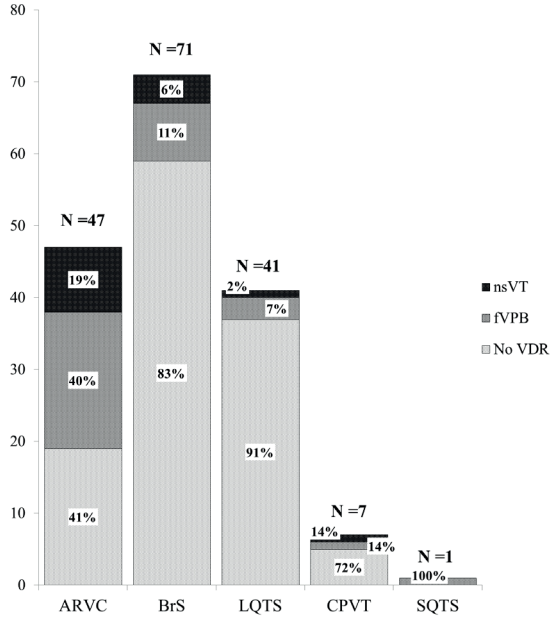

Figure 1. Bars demonstrating the percentage of patients presenting with fVPB and NSVT during initial screening in each group of patients.
nsVT (Non Sustained Ventricular Tachycardia); fVPB (frequent Ventricular Premature Beats); VDR (Ventricular Dysrhythmia); ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy); BrS (Brugada Syndrome); LQTS (Long-QT Syndrome); CPVT (Catecholaminergic Polymorphic Ventricular Tachycardia); SQTS (Short QT Syndrome).

Table 2 shows that BrS (OR 0.20, 95% CI 0.08-0.49, $p < 0.000$) and LQTS (OR 0.09, 95% CI 0.02-0.33, $p < 0.000$) patients are less likely to develop fVPB than ARVC patients. Similary, Table 3 shows that BrS (OR 0.17, 95% CI 0.06-0.50, $p= 0.001$) and LQTS patients (OR 0.09, 95% CI 0.02-0.46, $p = 0.003$) are also less likely to experience nsVT compared to ARVC patients. Patients with CPVT and SQTS were not included in the analysis because of the small number of patients.

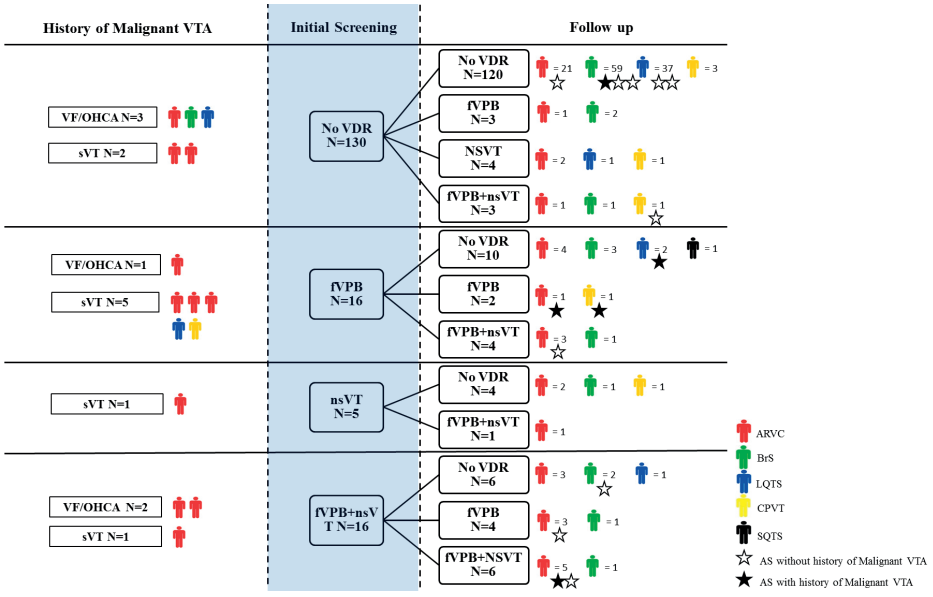

Figure 2. Flowchart demonstrating development of various VDR during long term follow up.
See text for detailed explanation.
VDR (Ventricular Dysrhythmias); fVPB (frequent Ventricular Premature Beats); nsVT (non-sustained Ventricular Tachycardia); sVT (sustained Ventricular Tachycardia); VF (Ventricular Fibrillation); ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy); BrS (Brugada Syndrome); LQTS (Long-QT Syndrome); CPVT (Catecholaminergic Polymorphic Ventricular Tachycardia); SQTS (Short QT Syndrome)

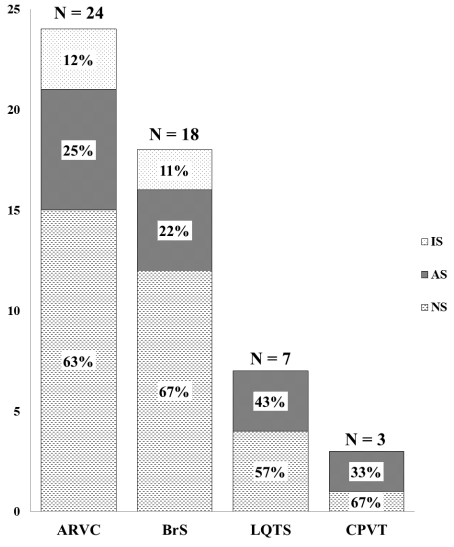

Figure 3. Bars demonstrating the distribution of (in)appropriate shocks in patients with an ICD.
AS (Appropriate Shock); Inappropriate Shock); NS (No Shock); ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy); BrS (Brugada Syndrome); LQTS (Long-QT Syndrome); CPVT (Catecholaminergic Polymorphic Ventricular Tachycardia); SQTS (Short QT Syndrome)

Table 2. Binary logistic regression model - predictors of fVPB in BrS and LQTS patients compared to ARVC patients

VPB>10	OR	*CI 95%*	*p*
BrS	0.20	0.08-0.49	0.000
LQTS	0.09	0.02-0.33	0.000

fVPB (frequent Ventricular Premature Beats); ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy); BrS (Brugada Syndrome); LQTS (Long-QT Syndrome).

Table 3. Binary logistic regression model - predictors of nsVT in BrS and LQTS patients compared to ARVC patients

nsVT	OR	*CI 95%*	*p*
BrS	0.17	0.06-0.50	0.001
LQTS	0.09	0.02-0.46	0.003

nsVT (non-sustained Ventricular Tachycardia); ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy); BrS (Brugada Syndrome); LQTS (Long-QT Syndrome).

Discussion

Key Findings

A variety of VDR and malignant VTA were found during long-term follow up in patients with ICA. The recurrence rate of malignant VTA was as high as 33%. Compared to BrS and LQTS, ARVC patients had more VDR and malignant VTA.

Ventricular Dysrhythmias

Although VPB are common in the general population (11, 12) they are considered to be benign. Frequent ventricular ectopy may, however, induce a cardiomyopathy.(13, 14) The Framingham Heart Study demonstrated that in men without apparent coronary artery disease, asymptomatic ventricular ectopy is associated with a twofold increase in risk for all-cause mortality.(15) Other studies also showed that fVPB increase the risk of SCD significantly in apparently healthy men (adjusted relative risk = 3.0; $p < 0.025$). (16). VPB trigger VT episodes which in turn may progress into VF and asystole.(17) (18, 19) Although these findings could not be derived from our ICA patients, the presence of VPB or nsVT indicated a higher probability to develop malignant VTA.

The majority of patients with fVPB or nsVT in this study population were ARVC patients; and they were also more likely to develop fVPB and nsVT than BrS and LQTS patients. The combination of increased ventricular ectopy and structural abnormalities in ARVC patients may explain why ARVC patients have a higher susceptibility to develop VDR and eventually malignant VTA. Patients with ARVC have regional fibrofatty replacements of ventricular myocardium which result in localized abnormalities in morphology, espe-

cially in the right ventricle (RV). However, as ARVC progresses, fibrofatty replacements extends to other RV areas and finally also the left ventricle (LV). (20)

In this study, only a few BrS patients had VDR or VTA during follow up. Similar observations were made in a Canadian study population of 105 BrS patients of whom only 6.7% had VF or monomorphic VT.(21) Likewise, Rodríguez-Mañero et al. found that 4.2% (35 from 834 patients) of BrS patients with an ICD experienced VTA (monomorphic ventricular tachycardia).(22) However, apart from the ARVC group, BrS patients had more both VDR and malignant VTA compared to the remainder of the study population. Recent studies demonstrated that similar structural abnormalities found in ARVC are also present in the right ventricular outflow tract of patients with BrS.(23-26) There may also be an overlap in the pathophysiology between BrS and ARVC patients. (27-29) The presence of structural abnormalities could explain why BrS patients presented with more VDR and malignant VTA compared to other channelopathies in this study.

Mechanisms underlying development of VDR may not only differ between patients with various ICA but may also differ between patients with the same ICA. For example, both reentry and triggered activity due to delayed afterdepolarization have been suggested as the main mechanism of arrhythmias in patients with BrS.(30) On the other hand, different degrees of overlap could be present between group of diseases as mentioned above.

Study Limitations

The small sample size in some ICA groups hampered comparison of development of VDR between all ICA groups. Selecting only patients with holter recordings can produce a selection bias in this study. Also, not all patients had an ICD and were thus not continuously monitored which implies that episodes of fVPB and nsVT could have been missed. For that reason, we only reported the recurrence rate of malignant VTA.

Conclusion

In patients with ICA, the recurrence of malignant VTA was considerable during a nearly 5-year follow-up period. Compared to BrS and LQTS, fVPB, nsVT and malignant VTA were most often found in patients with ARVC patients.

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CHAPTER 5

5

Usefulness of the R-Wave Sign as a Predictor for Ventricular Tachyarrhythmia in Patients With Brugada Syndrome

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Abstract

Brugada syndrome (BrS) is an autosomal dominant channelopathy which is responsible for a large number of sudden cardiac deaths in young individuals without structural abnormalities. The most challenging step in management of patients with BrS is identifying who is at risk for developing malignant ventricular tachyarrhythmia (VTA). In patients with BrS, conduction delay in the right ventricular outflow tract (RVOT) causes a prominent R wave in lead aVR. This electrocardiographic parameter can be useful to detect these high risk patients. The goal of this study is to test the significance of R wave elevation in lead aVR as a predictor for VTA in patients with BrS. In this retrospective study, we included 132 patients with BrS (47±15 years, 65% male) who visited the outpatient clinic for cardiogenetic screening. Patients' medical records were examined for the presence of a positive R wave sign in lead aVR and VTA. A positive R wave sign in lead aVR was observed in 41 patients (31%). This sign was more frequently observed in patients who experienced VTA (N=24) either before the initial diagnosis, during electrophysiological studies or during follow up ($P < 0.001$). The positive R wave sign occurred more frequently in symptomatic patients with a history of an out of hospital cardiac arrest, VTA or syncope, than asymptomatic patients (60% versus 26%; $P = 0.002$). During the follow up period, this sign was more frequently detected in patients who developed either de novo (50%) or recurrent (80%) VTA ($P = 0.017$). Multivariable regression analysis showed that R wave sign is an independent predictor for VTA development (OR 4.8, 95% CI 1.79-13.27). The presence of a positive R wave sign in lead aVR is associated with development of VTA. In conclusion, positive R wave sign in lead aVR can be used to identify BrS patients at risk for malignant VTA.

Introduction

Brugada syndrome (BrS) is an inherited channelopathy characterized by ST segment elevation in the precordial leads. BrS is one of the causes of sudden cardiac death in predominantly young males without underlying cardiac diseases. It is inherited as an autosomal dominant disorder and is related to mutations in 17 different genes.(1) Risk stratification is very challenging because of the heterogeneity of the clinical presentation and the dynamic Brugada pattern on the surface electrocardiogram (ECG). Many studies tried to evaluate the prognostic value of family history, history of ventricular tachycardia (VT) or ventricular fibrillation (VF) and electrocardiographic features.(2-4) There is strong evidence that the right ventricular outflow tract (RVOT) contains the arrhythmogenic substrate for ventricular tachyarrhythmia in patients with BrS.(5-7) Vectorcardiographic studies in BrS patients could detect a right end conduction delay (RECD) in the right superior and posterior quadrant of vectorcardiograms (VCG)s.(8) This areas of VCG are corresponding to lead aVR in ECG and they are located opposite to RVOT anatomically. Therefore, any RECD in mentioned areas can be detected by prominent R wave in lead aVR. In this cohort study, we tested the prognostic value of a prominent R wave in lead aVR in BrS patients for developing VTA, (including VT and VF) during long-term follow-up.

Methods

This retrospective study is part of the 'EvaluatioN of CardiOgenetic Disease and Effectiveness of scReening' (ENCODER) project, which was approved by the local ethics committee in the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2014-313). Informed consent was not required. All data, including clinical characteristics and tests outcomes, were collected from digital medical records.

Patients with BrS according to the criteria defined in the latest consensus report were selected from a database containing patients with suspicion of channelopathies who visited the outpatient clinic for cardiogenetic evaluation in the Erasmus Medical Center Rotterdam, the Netherlands.(9) Patients were excluded when data regarding the diagnostic process (i.e. test outcomes and patient or family history) were missing. Medical letters, 12-lead ECGs, 24h- Holter monitor registrations, signal-averaged electrocardiograms, drug (ajmaline) challenging tests, electrophysiological studies, Implantable Cardioverter Defibrillator (ICD) print outs and reports of genetic testing for SCN5A gene were reviewed.

According to the latest expert consensus document, diagnosis of BrS was based on the presence of either spontaneous or sodium channel blockers induced type I morphology (coved pattern) ST segment elevation ≥2 mm in ≥ 1 of the right precordial leads V1-V3. Type II diagnosis was defined as conversion of type II morphology (saddle-back) ST segment elevation to type I morphology after provocative drug test in ≥1 lead among the right precordial leads V1-V3.(10) All ECGs were screened for the presence of a Brugada pattern type I or type II. Amplitude of the R wave and QRS duration in lead aVR in the ECGs were measured. A R wave amplitude more than 0.3mV in lead aVR was defined as a positive R wave sign (Figure 1).

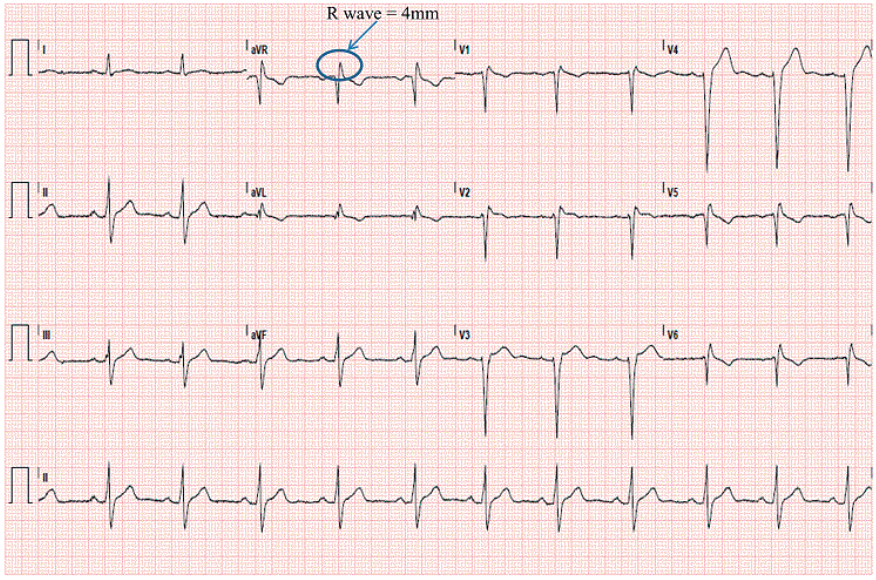


Figure 1. Typical ECG example of a Brugada patient demonstrating a prominent R wave in lead aVR.

Drug challenging tests were performed with intravenous ajmaline (1mg/Kg,10 mg/2min) during a 10 minutes ECG recording. This test was considered positive when either Brugada pattern type I occurred or when a type II pattern converted into a type I pattern. Infusion of ajmaline was stopped immediately if there was a >30 % increase in QRS duration, appearance of Brugada pattern, occurrence of premature ventricular complexes PVC's or VT, sinus arrest or atrioventricular conduction block.

During an electrophysiology study, ventricular tachyarrhythmia were induced using a standard induction protocol as previously described in detail.(11) Using the right femoral vein, catheters were introduced into the right ventricular apex or the RVOT. Fixed cycle length pacing (S1) of eight beats were delivered and immediately followed by

single, double and triple ventricular extrastimuli (S2, S3, S4) at a drive cycle length of 600ms and 400ms. An electrophysiology study was defined as positive when polymorphic ventricular tachycardia lasting more than 10 beats or ventricular tachyarrhythmia requiring cardioversion developed.

During the follow up period, all patients visited the cardiology outpatient clinic once a year and ICD check-ups were performed twice a year. ECGs, Holter recordings and ICD print outs were reviewed for the occurrence of VT or VF and ICD shocks.

Continuous variables were expressed as mean ± standard deviation. The ANOVA test was used to compare patient groups. Categorical data were denoted by percentages and compared with the McNemar test, X2 test or Fisher's exact test. Kaplan-Meier survival curves were plotted, and a log rank test was used to compare the curves. Receiver operator characteristic (ROC) curves were used to evaluate the sensitivity and specificity. The relationship between development of VTA and different independent variables was assessed using multivariable regression model, the independent variables included different patients characteristics and some electrocardiographic parameters. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, New York).

Results

One hundred thirty-two patients were selected from the source database; BrS type I pattern was detected in 114 patients (86%) and type II pattern in 18 patients (14%). Mean age at the time of the initial diagnosis was 43±15 years. Four patients presented with an OHCA (3%), 16 (12%) with syncope and 112 (85%) were asymptomatic. Age and gender at the moment of the initial diagnosis did not differ between patients with and without symptoms (respectively 40±16 versus 44±15 years, P=0.291; male: 83 (66%) versus female: 43 (34%), P=0.123). The follow up period after the initial diagnosis was 44±33 months. Mean age at the moment of the last follow up was 47±15 years. Ajmaline testing was positive in 109 patients (83%). Forty-eight patients (36%) were screened for SCN5A. Mutations were detected in 10 patients (21%); three of these patients had a history of syncope and 7 patients were asymptomatic (P=0.257). An ICD was implanted in 35 patients (28%), either for primary (N=15, 11%) or secondary prevention (N=20, 15%). Eight patients (6%) used quinidine; two of them also had an ICD (Table 1).

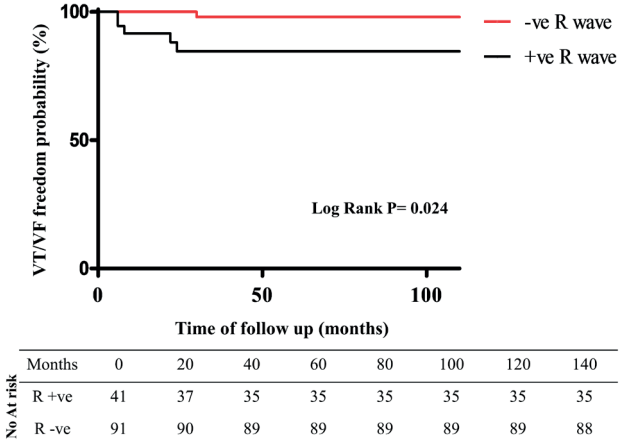
The mean QRS duration was 114±17ms; QRS duration in lead aVR did not differ between symptomatic (history of OHCA, VTA, or syncope) and asymptomatic patients (113±16ms

versus 115±17ms, P=0.553). Fifty-three patients (40%) underwent an electrophysiological study and VT/VF was inducible in 7 patients (5%). During the follow up period, VTA occurred in a total of 9 patients (7%), 4 patients (3%) developed de novo VF at the mean age of 53±11 years; 3 (2%) of them received ICD shocks because of recurrent VTA. Five patients (4%) who initially presented with an OHCA (N=2) or syncope (N=3) had recurrent VT/VF for which they received ICD shocks (VF: N=3, VT: N=2).

Table 1. Baseline characteristics of the study populati

Variable	Overall population (N=132)	Symptomatic cases (N=20)	Asymptomatic cases (N=112)	P value
Age (years)	47±15	44±16	47±15	0.398
males	86 (65%)	15 (75%)	71 (67%)	0.316
Age of diagnosis (years)	43±15	40±16	44±15	0.291
Spontaneous Type 1 Brugada syndrome pattern	114 (86%)	14 (70%)	100 (89%)	0.021
SCN5A mutation	10/48 (21%)	3 (15%)	7 (6%)	0.257
Probands	71 (54%)	16 (80%)	55 (49%)	0.009
Implantable Cardioverter Defibrillator	35 (28%)	15 (88%)	20 (18%)	< 0.001
Quinidine	8 (6%)	4 (18%)	4 (4%)	0.005
QRS	115±17	113±16	115±17	0.553
Signal-averaged ECG	52/86 (39%)	3 (15%)	49 (44%)	0.05
Positive R wave sign	41 (31%)	12 (60%)	29 (26%)	0.002

A positive R wave sign was observed in 41 patients (31%). This sign was more frequently observed in patients who experienced VTA either at the moment of the initial presentation, during an electrophysiological study or during the follow up period (N=14/41, 34% versus 10/91, 11%, P= 0.001). Comparing symptomatic (history of OHCA, VTA or syncope) and asymptomatic patients, the positive R wave sign occurred more frequently in symptomatic patients (N=12/20 (60%) versus N=29/112 (26%), P=0.002). During the follow up period, the positive R wave sign was more frequently detected in patients who developed VTA after the initial diagnostic screening (N=6/41 (15%) versus N= 3/91(3%), P= 0.017).



No At risk	Months	0	20	40	60	80	100	120	140
	R +ve	41	37	35	35	35	35	35	35
	R -ve	91	90	89	89	89	89	89	88

Figure 2. Kaplan-Meier curve demonstrating the cumulative freedom of ventricular tachyarrhythmic events for patients with and without a positive R wave sign between the moment of the initial diagnosis and end of the follow-up period.

Four patients (4/5, 80%) with recurrent VTA had a positive R wave sign and two asymptomatic patients (2/4, 50%) who developed new onset VTA had this sign as well. Inappropriate shocks due to supraventricular tachycardia (N=10) occurred also more frequently in patients with positive R wave sign (P=0.04) (Table 2). Kaplan-Meier analysis of freedom from VTA episodes during follow up in patients with and without the R wave sign showed significant better prognosis for patients who had no positive R wave sign (P=0.026, Figure 2).

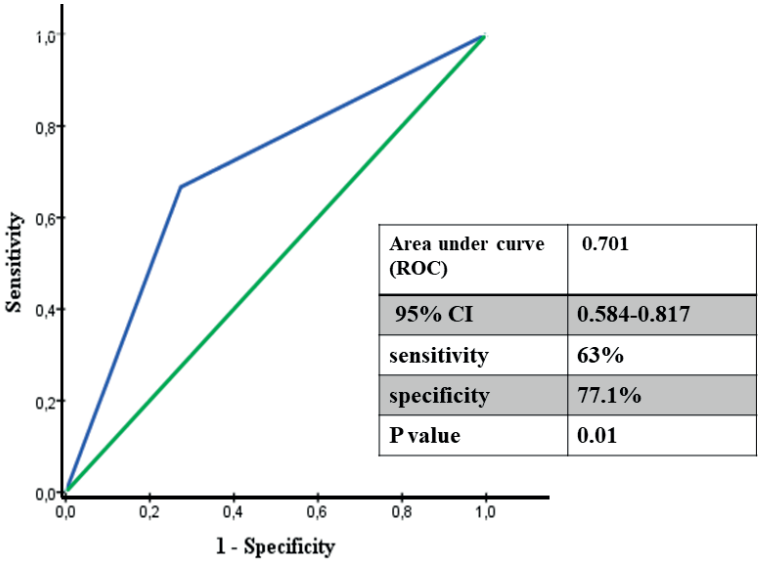


Figure 3. Receiver operator characteristic (ROC) curve demonstrating the sensitivity of the positive R wave sign as a predictor for the occurrence of VTA episodes in BrS patients.

In multivariable regression analysis, R wave sign was the independent predictor for VTA development P=0.002; patients with positive R wave sign have 4.8 fold risk of developing VTA (OR 4.8, 95% CI 1.79-13.27, Table 3). ROC curve for R-wave elevation > 0.3mV had an area under the curve of 0.701 (95% CI: 0.584-0.817, sensitivity: 63%, specificity:77.1%, Figure 3). Patients with a negative or positive R wave sign did not differ in age and gender (45±15 vs 48±15, P=0.268, 73% males versus 56%, P=0.194). There was no significant difference between the appearance of a positive R sign and the presence of genetic mutations (P=0.733), positive ajmaline tests (P=0.493) or electrophysiological studies (P=0.379).

Table 2. Differences in patient's characteristics between patients with and without a positive R wave sign.

Variable	Positive R wave (n=41)	Negative R wave (n=91)	P value
Age (years)	45±15	48±15	0.268
Males	30 (73%)	56 (62%)	0.194
Spontaneous Type 1 Brugada syndrome pattern	33 (80%)	81 (89%)	0.187
+ve Ajmaline test (N=109)	35 (85%)	74 (81%)	0.493
SCN5A mutation	4 (11%)	6 (7%)	0.733
Probands (N=71)	26 (63%)	45 (49%)	0.0682
Total documented VT/VF events (N=24)	14 (34%)	10 (11%)	0.001
+ve Electrophysiological study (N=7)	3 (7%), (2:1Extrastimulus,1:3 Extrastimuli)	4 (4%) (3:3Extrastimuli,1: Extrastimulus)	0.379
Ventricular tachyarrhythmia during follow up (N=9)	6 (15%)	3 (3%)	0.017
Implantable Cardioverter Defibrillator shocks			
VT/VF shocks	6 (15%)	2 (2%)	0.006
Inappropriate shocks	6 (15%)	4 (4%)	0.04

Table 3. Multivariable regression analysis of different patient characteristics with documented Ventricular tachyarrhythmia.

Independent variables	Multivariable Analysis OR (95% CI)	P value
Gender	1.82 (0.63-5.26)	0.26
Age of diagnosis (years)	1.02 (0.985-1.06)	0.24
+ve Signal-averaged ECG	1.11 (0.98-1.26)	0.07
+R wave	4.8 (1.79-13.27)	0.002
QRS duration	0.98 (0.95-1.01)	0.24
SCN5A mutation	2.44 (0.91-6.5)	0.07
Implantable Cardioverter Defibrillator carriers	20.32 (6.29-65.61)	<0.001

Discussion

In our study population, a positive R wave sign appeared significantly more often in BrS patients who had history of VTA and in patients who developed either de novo of recurrent VTA during follow up. The R wave sign is an independent predictor for VTA development and positive R wave sign patients have a 4.8 fold risk of developing VTA. The positive R wave sign was present in 50% of the patients who developed new onset of VTA during the follow up, 80% of patients who developed recurrent VTA and 60% of patients with history of VTA before screening and diagnosis with BrS. Our findings emphasize further investigation of the R wave sign in lead aVR to identify patients at high risk for development of VTA.

BrS is an autosomal dominant channelopathy and is responsible for at least 4% of all sudden deaths and 20% of deaths in patients without underlying heart diseases.(12,13) BrS is the second leading cause of death in men <40 years old in certain Asian countries.(14) There is no accurate data about the prevalence of this syndrome because of the dynamic ECG patterns and wide range of symptoms at the initial presentation. Initial presentation of this syndrome could be incidental diagnosis, syncope, palpitation or sudden death due to ventricular fibrillation. Risk stratification is the most challenging step in management of BrS patients.(15,16) There are many factors which influence management of BrS including family history of BrS, history of previous syncope or episodes of VTA, spontaneous ECG pattern of BrS, inducibility of VTA by electrophysiological studies and the presence of SCN5A gene mutations. Many ECG parameters were tested in previous studies including late potentials, f-QRS and early repolarization in peripheral leads in order to identify patients at risk for developing VTA.(17-19)

Prior studies demonstrated that the mechanism of VTA in BrS consists of loss of the action potential dome in the right ventricular epicardium resulting in a transmural dispersion of repolarization. This gives rise to local re-excitation via phase 2 reentry facilitating development of VTA.(20) Other studies showed prolongation of the epicardial action potential in the right ventricular outflow tract as the underlying mechanism.(21,22) Experimental studies suggested that conduction delay caused by tissue discontinuities in the RVOT epicardium play a major role in development of VTA in patients with BrS.(5,6,23-25)

Peréz-Riera et al. studied vectorcardiograms of BrS patients and found that RECD appeared at the end of QRS loop and this RECD was located in the right superior quadrant in 90% of the cases. Anatomically, this area is opposite to RVOT and very close to lead aVR (-150°) (Figure 4).(8)

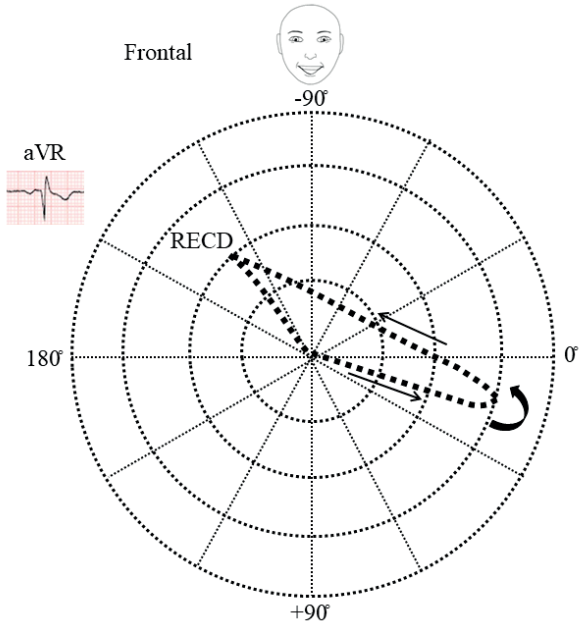


Figure 4. Vectorcardiogram (Frontal plane) demonstrates right end conduction delay (RECD) of QRS loop in the right posterior quadrant.

Other investigators demonstrated that cardiac neural crest cells are responsible for abnormal development of the RVOT causing BrS phenotype.(26) In our cohort study, we measured the R wave amplitude in lead aVR which reflects conduction delay especially in the RVOT and basal part of the interventricular septum. As the presence of a prominent R wave in lead aVR was significantly related to the history of VTA and arrhythmic events during the follow up period, our observations support the assumption that the RVOT contains the arrhythmogenic substrate in patients with BrS. In patients with tricyclic antidepressant toxicity, elevation of R wave more than 0.3 mV in lead aVR has the largest specificity (negative predictive value: 94%) and is used to predict seizures VTA.(27)

Babai et al. demonstrated in a small number of patients (N=24) with BrS a correlation between a positive R wave sign and development of VTA.(28) In a larger cohort study containing 325 patients, the R wave sign correlated with the presence of right bundle branch block and fascicular block.(29) Juntilla et al. tested the r`/s wave amplitude ratio in lead aVR of Brs patients but did not find a difference between symptomatic and asymptomatic BrS patients.(30)

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CHAPTER 6

6

Prediction of ventricular tachyarrhythmia in brugada syndrome by right ventricular outflow tract conduction delay signs

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Background

Brugada syndrome (BrS) is an autosomal dominant disease responsible for sudden cardiac death in young individuals without structural anomalies. The most critical part in the management of this channelopathy is identification of high-risk patients, especially asymptomatic subjects. Prior studies have shown that conduction delay in the right ventricular outflow tract (RVOT) is the main mechanism for developing ventricular tachyarrhythmia (VTA) in BrS patients. The aim of this study was to investigate the significance of electrocardiographic RVOT conduction delay parameters as predictors for development of VTA in patients with BrS.

Methods and results

We retrospectively analyzed electrocardiograms obtained from 147 BrS patients (43 ± 15 years, 65% men) and assessed the following electrocardiographic parameters: (1) Tzou criteria (V1R > 0.15 mV, V6S > 0.15 mV, and V6S:R > 0.2), (2) prominent S wave in lead I, lead II, and lead III, (3) SII > SIII, and (4) prominent Q wave in lead III as possible predictors of VTA occurrences during follow-up. Prominent SI, SII, SIII, SII > SIII, QIII, and +ve Tzou criteria occurred more frequently in patients who either presented with VTA or developed VTA during the follow-up of 56 (IQR: 40–76) months. SII > SIII has the highest area under the curve for prediction of VTA (AUC: 0.84, sensitivity: 80%, specificity: 89%). Multivariable regression analysis showed that prominent S waves in lead I, SII > SIII and +ve Tzou criteria are independent predictors for VTA in BrS patients.

Conclusion

Prominent S in lead I, SII > SIII and +ve Tzou criteria can be used as effective signs for predicting VTA in patients with BrS.

Abstract

INTRODUCTION

Brugada syndrome (BrS) is an autosomal dominant channelopathy characterized by an increased risk of sudden cardiac death in young individuals without structural abnormalities. ST-segment elevation in the precordial leads spontaneously or after provocation testing is the main diagnostic criterium.(1, 2) Risk stratification especially in asymptomatic patients is very challenging. Many investigators tried to identify electrocardiographic signs to quantify the risk of developing ventricular tachycardia (VT) or ventricular fibrillation (VF) in this heterogeneous population.(3-6) However, controversial outcomes and dynamicity of these electrocardiographic signs make identification of high-risk patients challenging. There is strong evidence that conduction delay in the right ventricular outflow tract (RVOT) is the main pathophysiological mechanism. Prior studies demonstrated that there are electrocardiographic signs that can detect conduction abnormalities in this area such as a prominent R wave in lead aVR, a prominent S wave in lead I, II, III, and a larger S wave in lead II compared to lead III (SII > SIII pattern). (7-9) However, only a prominent R wave in lead aVR and S wave in lead I have been related to BrS. Furthermore, several electrocardiographic signs have been proposed which also predict VT in nonischemic cardiomyopathies such as V1R > 0.15 mV, V6S > 0.15 mV, and V6S:R > 0.2 .(10)

In this study, we tested whether in patients with BrS these different electrocardiographic signs are predictors for development of ventricular tachyarrhythmia (VTA, including VT and VF) during long-term follow-up.

METHODS

This retrospective study is part of the "EvaluatioN of CardiOgenetic Disease and Effectiveness of screening" (ENCODER) project, which was approved by the local ethics committee in the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2014-313). Informed consent was not required. All data, including clinical characteristics and tests outcomes, were collected from digital medical records.

Study population

According to the criteria defined in the latest consensus report, we selected patients with definitive BrS diagnosis from the database of patients with suspicion of cardiac channelopathies visiting the outpatient clinic for cardiogenetic evaluation in the Erasmus Medical Center Rotterdam, the Netherlands.(11) Patients were excluded when data

regarding the diagnostic process (i.e., test outcomes and patient or family history) were missing.

Diagnosis of type I BrS was based on the presence of either spontaneous or sodium channel blockers induced type I morphology (coved pattern) ST segment elevation ≥2 mm in ≥1 of the right precordial leads V1–V3. Type II diagnosis was defined as conversion of type II morphology (saddle-back) ST segment elevation to type I morphology after drug provocation test in ≥1 lead among the right precordial leads V1–V3.

Electrocardiographic analysis

Amplitude of S waves in leads I, II, III were measured; a S amplitude ≥ 0.15 mV was considered as prominent S wave.(12) We also compared the amplitudes of S waves between lead II and lead III (SII > SIII pattern).(9) Tzou criteria (V1R > 0.15 mV, V6S > 0.15 mV, and V6S:R > 0.2) were tested and patients with two or more positive signs were considered as positive (Figures 1 and 2).(10) To test repolarization homogeneity, we calculated QT, QT-QTp (Tp-Te), and Tp-Te/QT in lead V1.(13, 14)

Follow-up

During the follow-up period, all patients visited the cardiology outpatient clinic at least once a year and implantable cardioverter defibrillators (ICD) were checked twice a year. ECGs, Holter recordings, and ICD print outs were reviewed for the occurrence of VT or VF and ICD shocks.

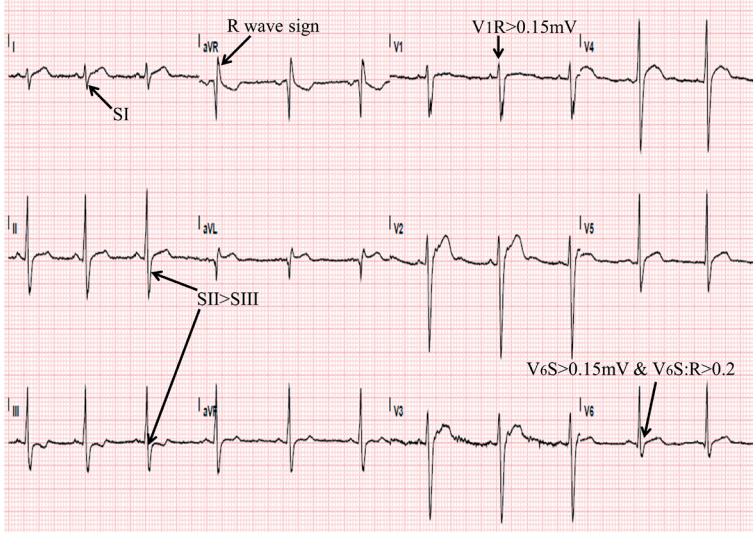


Figure 1. Electrocardiogram of a symptomatic BrS patient during follow up showing a SII>SIII pattern, prominent S wave in lead I, R wave sign in lead aVR and positive Tzou criteria.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. ANOVA tests were used to compare patient groups. Categorical data were denoted by percentages and compared with the McNemar test, chi-square test, or Fisher's exact test. Receiver operator characteristic (ROC) curves were used to evaluate sensitivity and specificity of electrocardiographic parameters. The multivariable regression model was used to assess the relation between development of VTA and independent variables including the different electrocardiographic parameters. A P-value of < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, NY, USA).

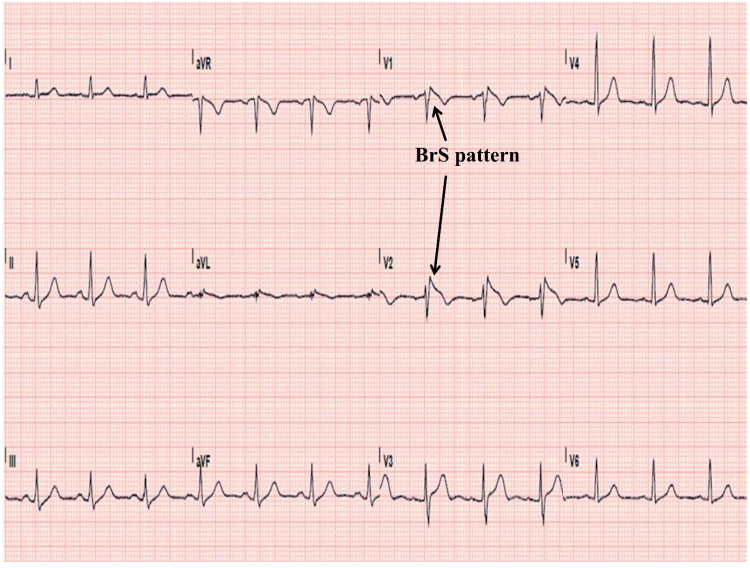


Figure 2. Electrocardiogram of an asymptomatic BrS patient without any of the RVOT conduction delay signs.

RESULTS

Characteristics of study population

One hundred forty-seven BrS patients (97 male, 65%) were selected from a database containing patients with cardiogenetic disease. Baseline characteristics are summarized in Table 1. Diagnosis of type I BrS (spontaneous BrS pattern) was confirmed in 116 patients (79%) and diagnosis of type II (after provocation test) in 31 patients (21%). Mean age at the time of the initial presentation was 43 ± 15 years. The duration of the follow-up period was 56 (IQR: 40–76) months and age at the moment of the last follow-up visit was 47 ± 15 years.

The majority of the patients (N = 117, 80%) remained asymptomatic during the follow-up period, whereas 30 patients (20%) developed VTA (either documented history or de novo). Seventy-five patients (51%) presented to our outpatient clinic as probands. Genetic screening for BrS related genes was done for 51 patients (35%); 11 patients (22%) had mutations in SCN5A gene. An ICD was implanted in 37 patients (25%), either for primary (N = 16, 11%) or secondary prevention (N = 21, 14%). Quinidine was prescribed for 8 patients (5%) (Table 1).

Table 1. Baseline characteristics of the study population.

	Overall population (N=147)
Age (years)	47±15
Males	97 (65%)
Age of diagnosis (years)	43±15
History of VTA	21 (14%)
De novo VTA	9 (6%)
History of cardiac syncope	17 (12%)
Positive electrophysiological study	7 (5%)
SCN5A mutation	11/51 (22%)
Implantable Cardioverter Defibrillator	37 (25%)
VT/VF ICD shocks	8 (5%)
Inappropriate ICD shocks	10 (6%)

Electrocardiographic findings

A prominent S wave in lead I, II, and III was present in, respectively, 34 (23%), 75 (51%), and 77 (52%) patients. These signs were more frequently observed in symptomatic than asymptomatic patients: prominent S in lead I (N = 21/30, 70% vs. N = 13/117, 11%, P < 0.001), lead II: (N = 30/30, 100% vs. N = 45/117, 38%, P < 0.001) and lead III: (N = 27/30, 90% vs. N = 50/117, 43%, P < 0.001).

By comparing the depth of S waves in lead II and lead III, a SII > SIII pattern appeared in 37 patients (25%). SII > SIII was also more frequently observed in symptomatic patients (N = 24, 80% vs. N = 13, 11%, P < 0.001). Prominent Q waves in lead III appeared in 11 patients (7%) and 8 of them were symptomatic (P < 0.001). Tzou test was positive in 37 patients (25%) and was significantly more positive in symptomatic patients (N = 19/30, 63% vs. N = 18/117, 15%, P < 0.001). QT, QTp, QT-QTp, and QT-QTp/QT did not differ between symptomatic and asymptomatic patients (Table 2).

During the follow-up period, SI, SII > SIII, and Tzou criteria were more frequently detected in patients who developed VTA (SI: n = 6 of 34 [18%] vs. n = 3 of 113 [3%], P = 0.005, SII

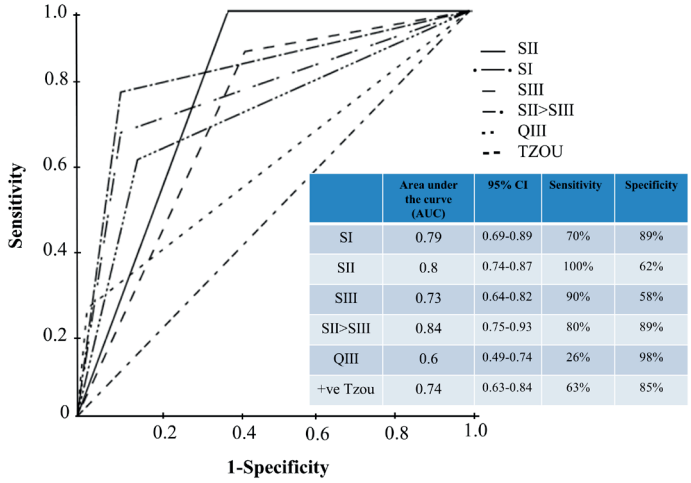
> SIII: n = 5 of 37 [14%] vs. n = 4 of 110 [4%], P = 0.04, +ve Tzou: n = 6 of 37 [16%] vs. n = 3 of 110 [3%], P = 0.008).

ROC curve for the various electrocardiographic parameters showed that a SII > SIII pattern had the largest area under the curve (AUC) of 0.84 (95% CI: 0.75–0.93) with a sensitivity of 80% and a specificity of 89%. A prominent SII had the highest sensitivity of 100% but a specificity of 62% (AUC: 0.8, 95% CI: 0.74–0.87); prominent QIII had the highest specificity of 98% but a sensitivity of only 26%. The AUC of +ve Tzou criteria was 0.74 (95% CI: 0.63–0.84, sensitivity: 63%, specificity: 85%), as demonstrated in Figure 3.

Table 2. Various electrocardiographic parameters tested within the study population.

	Overall population (N=147)	**Symptomatic cases (N=30)**	**Asymptomatic cases (N=117)**	**P value**
SI	34 (23%)	21 (70%)	13 (11%)	< 0.001
SII	75 (51%)	30 (100%)	45 (38%)	< 0.001
SIII	77 (52%)	27 (90%)	50 (43%)	< 0.001
SII>SIII	37 (25%)	24 (80%)	13 (11%)	< 0.001
QIII	11 (7%)	8 (27%)	3 (3%)	< 0.001
V1R	30 (20%)	20 (67%)	10 (9%)	< 0.001
V6S > 0.15mV	37 (25%)	19 (63%)	18 (15%)	< 0.001
V6S:R > 0.2mV	35 (24%)	18 (60%)	17 (15%)	< 0.001
+ve Tzou criteria	37 (25%)	19 (63%)	18 (15%)	< 0.001
QT	80±10	100±10	80±8	NS
QTp	60±9	70±10	60±8	NS
QT-QTp	20±4	20±6	20±4	NS
QT-QTp/QT	0.25±0.4	0.25±0.5	0.25±0.4	NS
R wave sign	48(33%)	20(67%)	28(24%)	< 0.001

In multivariable regression analysis, a SII > SIII pattern, prominent SI, and +ve Tzou criteria are independent predictors for VTA events in BrS patients. Patients with prominent SI or +ve Tzou test had a fourfold higher risk to develop VTA (SI: OR: 4.15, 95% CI: 1.2–16.9, P = 0.025, positive Tzou test: OR: 3.7, 95% CI: 1–13.58, P = 0.049). Patients with positive SII > SIII pattern had the highest odds ratio to develop VTA (OR: 8.3, 95% CI: 1.82–37.85, P = 0.006, Table 3).



	Area under the curve (AUC)	95% CI	Sensitivity	Specificity
SI	0.79	0.69-0.89	70%	89%
SII	0.8	0.74-0.87	100%	62%
SIII	0.73	0.64-0.82	90%	58%
SII>SIII	0.84	0.75-0.93	80%	89%
QIII	0.6	0.49-0.74	26%	98%
+ve Tzou	0.74	0.63-0.84	63%	85%

Figure 3. Receiver operator characteristic curve demonstrating the sensitivity of different electrocardiographic parameters.

Table 3. Multivariable analysis of different electrocardiographic parameters.

Independent variables	Multivariable analysis OR (95%CI)	P-value
SI>0.15mV	4.15 (1.2-16.9)	0.025
SII>0.15mV	0.385 (0.74-6.4)	0.997
SIII>0.15mV	0.566 (0.65-4.9)	0.566
SII>SIII pattern	8.30 (1.82-37.85)	0.006
QIII	4.13 (0.585-29.16)	0.155
+ve TZOU	3.7 (1.0-13.58)	0.049

DISCUSSION

This study reveals in addition to a positive R wave sign in aVR and a prominent S wave in lead I, novel electrocardiographic signs related to VTA in BrS patients, including prominent S waves in lead II and III, a SII > SIII pattern, and +ve Tzou criteria. In addition, multivariable regression analysis revealed that a SII > SIII pattern, SI, and +ve Tzou criteria are independent predictors of VTA.

Several studies investigated the arrhythmogenic substrate in BrS patients and found that conduction abnormalities in the RVOT are the main underlying mechanism of VTA in this population.(15-19) There are two prevailing mechanisms underlying BrS including the "depolarization and repolarization" theory.(20) In the repolarization theory, conduction abnormalities are caused by transmural dispersion of repolarization due to loss of action potential dome in the epicardium, which in turn facilitates local reexcitation via phase

2 reentry.(21) The depolarization theory is supported by observations using vector-cardiographic analysis in BrS patients that showed right-end conduction delay (RECD) in the right superior and posterior quadrant within in the frontal plane.(22) RECD in this area can be detected by different ECG signs such as the R sign in lead aVR, prominent S wave in lead I, a SII > SIII pattern, rS in lead V1, and prominent S in lead V6.

As demonstrated in Figure 4, the QRS loop of the frontal plane is dexo-rotated resulting in an electrical axis of +30° in the first part of the loop and –150° in the second part. A maximum vector of 30° justifies the appearance of a Q wave in lead III and a prominent S wave in lead I while the other –150° vector justifies the appearance of a SII > SIII pattern and a R wave sign in lead aVR. The QRS loop of the horizontal plane moves anteriorly, and this explains the appearance of rS in lead V1 and prominent S in lead V6.

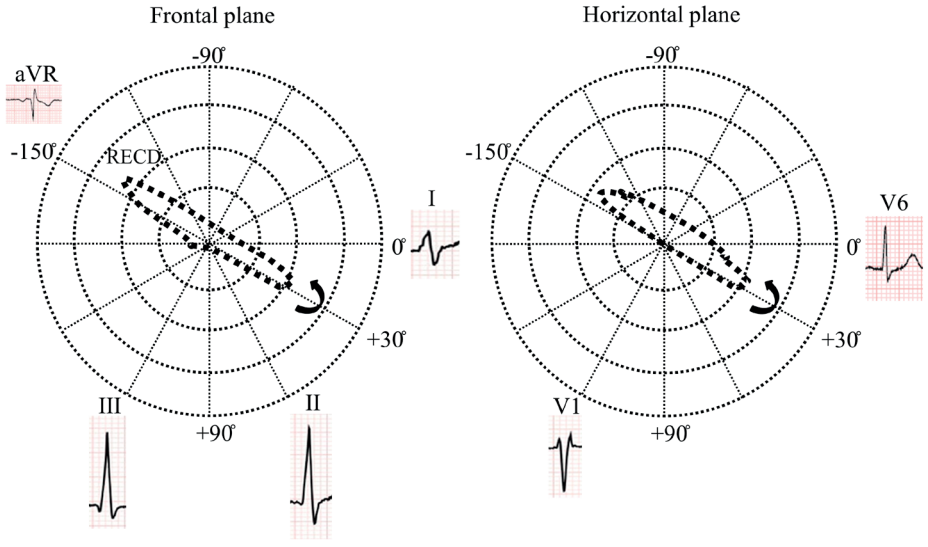


Figure 4. Vector cardiogram demonstrating (A) dexorotation of the QRS loop in the frontal plane and (B) anterior deviation of the QRS loop in the horizontal plane.

Several studies tried to stratify high-risk patients based on RVOT conduction delay electrocardiographic signs.(3, 5, 6) Ikeda et al. tested the predictive value of late potentials measured by signal averaged ECGs in 124 BrS patients and found that the presence of late potentials was the only significant electrocardiographic sign in the univariable analysis (hazard ratio: 7.9, specificity: 46%, positive predictive value of 15%).(23) Other electrocardiographic signs such as fragmented QRS complexes are also associated with VTA events in BrS patients. Morita et al. showed that this sign appeared more often in symptomatic compared to asymptomatic patients (85% vs. 34%).(4) Other investigators also found hazard ratios of this sign ranging between 2.3 and 8.9.(24, 25) Calò et al.

showed that a SI larger than ≥ 0.1 mV and longer than ≥ 40 ms is an independent sign for development of VTA in BrS patients.(8) Ragab et al. recently also showed the prognostic value of a prominent R wave in lead aVR.(7)

Spatial velocity ECG techniques showed that right ventricular conduction delay in the anterosuperior subpulmonary Purkinje network (26-28) causes the appearance of SII > SIII patterns.(29, 30) Bayés de Luna et al. showed that the appearance of this pattern can be explained by the presence of a right antero-superior zonal conduction block.(2) They also demonstrated that a SII > SIII pattern can also appear in normal individuals, which could be explained by an abnormal distribution of right Purkinje fibers causing RVOT conduction delays. Tzou criteria h ave been proposed as predictors of VT in patients with nonischemic cardiomyopathy with a sensitivity of 0.86 and specificity of 0.88.(10) In the present study, testing of these Tzou criteria in BrS patients was based on Bayés de Luna experimental findings that a right antero-superior zonal conduction block causes a rS pattern in lead V1 and a prominent S wave in lead V6.(9)

Our study was retrospective with a relatively small number of patients, and our observations should therefore be verified in a multicenter study with larger registry of BrS patients. Nevertheless, we can conclude that a SII > SIII pattern, a prominent S wave in lead I, and positive Tzou criteria can be useful noninvasive prognostic electrocardiographic signs to identify BrS patients at high risk for VTA.

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CHAPTER 7

7

QRS Vector Magnitude as Predictor of Ventricular Arrhythmia in Patients With Brugada Syndrome

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Abstract

Risk stratification is the most challenging part in management of patients with Brugada syndrome (BrS). Conduction delay in the right ventricular outflow tract (RVOT) is the major mechanism underlying ventricular tachyarrhythmia (VTA) in BrS. However, QRS duration was not useful in stratifying high-risk patients in large registries. Reconstructing the traditional 12-lead ECG into QRS vector magnitude (QRSvm) can be used to quantify depolarization dispersion and identify high-risk BrS patients. The aim of the study is to test the significance of the QRSvm as a predictor for VTA in patients with BrS. In this retrospective cohort, we included 136 patients (47±15 years, 66% male) who visited the outpatient clinic for cardiogenetic screening. All medical records were examined, all 12- lead ECGs were reconstructed into QRSvm using Kors' quasi-orthogonal method and were assessed for the presence of electrocardiographic signs indicative of RVOT conduction delay including; R wave sign, deep SI, SII>SIII pattern, Tzou criteria. QRSvm was significantly lower in patients who either presented with VTA or developed VTA during follow up (1.24±0.35mV vs 1.78±0.42mV, P<0.001). Positive RVOT conduction delay signs occurred more frequently in symptomatic patients (20% vs 7%, P<0.001).The area under receiver operator characteristic curve for QRSvm was 0.85 (95% CI: 0.77-0.92). Using QRSvm cutoff of 1.55mV, sensitivity and specificity were 89% and 71% respectively. Multivariate regression analysis showed that QRSvm and RVOT signs are independent predictors for VTA in BrS patients (QRSvm: OR: 3.68, 95% CI: 2.4-6.2, P=0.001, RVOT: OR: 2.6, 95% CI: 1.4-4.9, P=0.001). In conclusion, not only electrocardiographic signs indicative of RVOT conduction delay but also QRSvm can be used as a predictor for VTA events in BrS patients.

Introduction

Brugada syndrome (BrS) is an autosomal dominant channelopathy characterized by an increased risk of sudden cardiac death in young subjects without structural anomalies.(1) This channelopathy has an incidence of 0.05% to 0.6% in the general population and can be diagnosed by ST-segment elevation in the right precordial leads either spontaneously or after provocation test using sodium channel blockers.(2) Stratifying the high-risk patients is the most challenging part of BrS management. Many investigators reported on testing different electrocardiographic parameters to quantify the risk of ventricular tachyarrhythmia (VTA) especially in asymptomatic patients. The controversial outcomes make this task unfortunately very challenging.(3, 4, 5) However, there is a strong evidence that conduction delay in right ventricular outflow tract (RVOT) is the main mechanism underlying VTA in BrS yet, time parameters such as QRS duration did not have strong prognostic value in large registries.(6, 7) Voltage-dependent vectorcardiographic parameters have proved to add diagnostic and prognostic value to the 12-lead surface electrocardiogram (ECG).(8, 9, 10) Voltage-dependent QRS 3-dimensional vector magnitude (QRSvm) is a promising parameter for predicting VTA in patients with tetralogy of Fallot (TOF).(11, 12) Lower QRSvm indicates scattering of slowly propagating electrical waves, resulting in dispersion of depolarization vectors. As a consequence, the QRS magnitude decreases. In this study, we tested if QRSvm can be a useful predictor for VTA including VT and VF during long-term follow-up

Methods

This blinded retrospective study is part of the "EvaluatioN of CardiOgenetic Disease and Effectiveness of scReening" (ENCODER) project, which was approved by the local ethics committee in the Erasmus Medical Center Rotterdam, the Netherlands (MEC-2014-313). Informed consent was not required. All data, including clinical characteristics and tests outcomes, were collected from digital medical records. During the follow-up period, all patients visited the cardiology outpatient clinic at least once a year and implantable cardioverter defibrillator (ICD) were checked twice a year. ECGs, Holter recordings signal-averaged electrocardiograms (SAECG) and ICD print outs were reviewed for the occurrence of VTA or ICD shocks. Patients were excluded when data regarding the diagnostic process (i.e., test outcomes and patient or family history) were missing.

We selected patients' definitive BrS diagnosis from the database of patients with suspicion of cardiac channelopathies visiting the outpatient clinic for cardiogenetic evaluation in the Erasmus Medical Center Rotterdam, the Netherlands. According to the

criteria defined in the latest consensus report, diagnosis of type I BrS was based on the presence of either spontaneous or sodium channel blockers induced type I morphology (coved pattern) ST segment elevation ≥2 mm in 1 or more of the right precordial leads V1 to V3. Type II diagnosis was defined as conversion of type II morphology ST segment elevation into type I morphology after drug challenge test in 1 or more lead among the right precordial leads V1 to V3.(2) Patients with obesity (body mass index >29.9), Chronic Obstructive Pulmonary Disease (COPD), or BrS patients who developed ischemic heart disease were excluded.

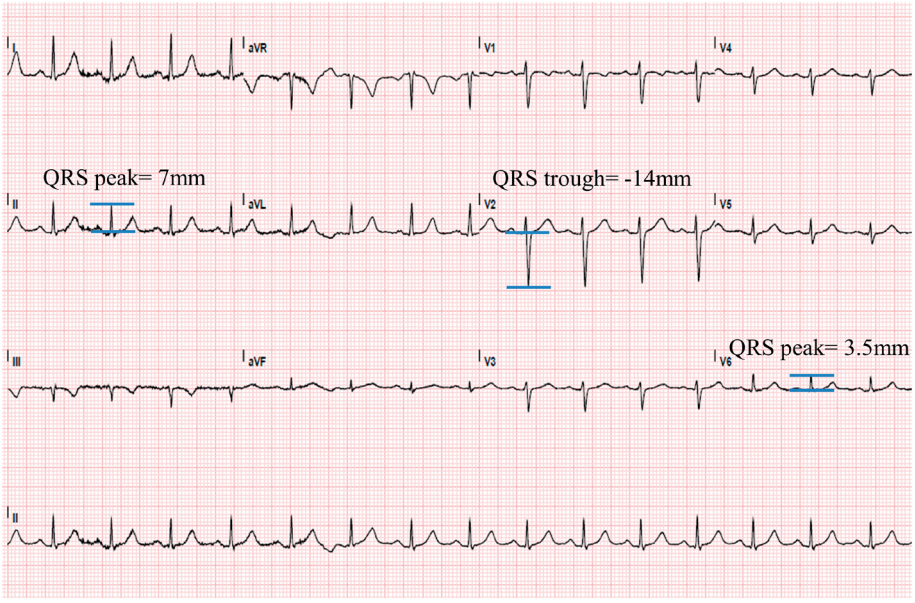
RVOT conduction delay signs were tested, including the R wave sign, deep SI, SII >SIII pattern, Tzou criteria (V1R >0.15 mV, V6S >0.15 mV; and V6S:R >0.2).(13, 14, 15) Patients with 3 or more positive signs were considered as positive for RVOT conduction delay; QRS durations were measured in lead aVR.

Figure 1 demonstrated determination of the QRS vector magnitude (QRSvm). This parameter was tested in all ECGs using the regression-related Frank-lead technique of Kors. (16) The following formula was used for QRSvm estimation:

$$(\sqrt{\{(QRS\ peak\ lead\ II)^2 + (QRS\ peak\ lead\ V6)^2 + (-0.5 * -QRS\ trough\ lead\ V2)^2\}})$$

All peaks were measured manually from digital ECGs (25 mm/s; 10 mm/mV).

Continuous normally distributed variables were expressed as mean ± standard deviation. Continuous not normally distributed variables were expressed as median and interquartile range. Independent samples t test were used to compare patient groups. Categorical data were denoted by percentages and compared with continuity correction chi-squared test. Receiver operator characteristic curves were used to estimate the optimal cutoff and to evaluate sensitivity and specificity of tested parameters. The multivariable regression model was used to assess the relation between development of VTA and independent variables including the different electrocardiographic parameters (R wave sign, deep SI, SII >SIII pattern, Tzou criteria; V1R >0.15 mV, V6S >0.15 mV, and V6S:R >0.2) A p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 21 (IBM, Armonk, New York).



$$\mathbf{QRSVm = SQRT[QRSII^2 + QRSV6^2 + (-0.5*-QRSv2)^2]}$$

Figure 1. Baseline electrocardiogram of an Ajmaline induced BrS patient demonstrating measurement of QRSvm.

Results

The study population consists of 136 BrS patients (90 male, 66%); characteristics are summarized in Table 1. Mean age at the time of diagnosis was 47 ± 15 years. The median duration of the follow-up period was 57 (interquartile range 39 to 75) months and mean age at the time of the last follow-up was 47 ± 15 years. Whole genome sequencing was done in 43 patients (32%) and 8 (6%) of them had SCN5A mutation. An ICD was implanted in 34 patients (25%) either for primary (n = 14, 14 of 136, 10%) or secondary prevention (n = 20, 20 of 136, 15%).

Most patients (n = 101, 74%) remained asymptomatic during the follow-up period. Thirty-five patients developed VTA either before diagnosis (n = 22, 16%) or de novo events during follow-up (n = 13, 10%). During the follow-up period, 8 patients (5%) received appropriate ICD shocks and 10 patients (7%) received inappropriate ICD shocks caused by supraventricular arrhythmia. Six patients used Quinidine and none of them developed VTA (Table 1). Fifty-one patients (38%) underwent electrophysiological study

and VT/VF was inducible in 7 patients (5%). The SA-ECG was positive for late potentials in 56 patients (41%).

There were no differences between symptomatic and asymptomatic patients with respect to age, gender, or age of diagnosis. Also, mean QRS duration in lead aVR and late potentials did not differ between symptomatic and asymptomatic patients (respectively, 113 ± 17 vs 117 ± 17 ms, p = 0.26 and 10 of 35, 29% vs 46 of 101, 46%, p = 0.07).

Positive RVOT signs (3 or more) appeared in 25 patients (18%), RVOT signs were more frequently observed among symptomatic patients (54% vs 6%, p < 0.001).

By comparing QRS peak in lead II, QRS peak in lead V6 and QRS trough in lead V2, symptomatic patients showed smaller QRS peak or trough than asymptomatic patients (QRS II: 8 ± 3 vs 12 ± 4 mm, p < 0.001; QRS V6: 8 ± 3 vs 11 ± 3 mm, p < 0.001; QRS V2: 9 ± 4 vs 12 ± 4 mm, p < 0.001; Table 2). As demonstrated in Figure 2, QRSvm was significantly lower in patients who developed VTA (at the time of presentation or de novo) than patients who did not (1.24 ± 0.35 vs 1.78 ± 0.42 mV, p < 0.001).

Table1. Baseline characteristics of study population.

	Overall population (N=136)
Age (years)	47±15
Males	90 (66%)
Age of diagnosis (years)	42±14
Symptoms at the moment of diagnosis	22 (16%)
De novo VTA events during follow up	13 (10%)
SCN5A mutation	8/43
Implantable Cardioverter Defibrillator	34 (25)
VT/VF ICD shocks	8 (5%)
Inappropriate ICD shocks	10 (7%)
Positive late potentials	56 (41%)

Area under receiver operator characteristic curve for QRSvm was 0.85 (95% confidence interval [CI] 0.77 to 0.92; Figure 3). Using QRSvm cutoff of 1.55 mV, sensitivity and specificity were, respectively, 89% and 71%. Area under receiver operator characteristic for RVOT was 0.74 (95% CI 0.633 to 0.85) with a sensitivity of 54% and specificity of 94%.

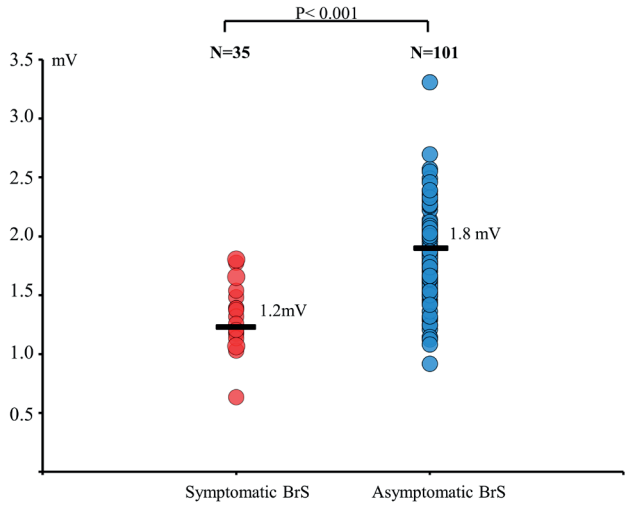


Figure 2. Scatterplot demonstrating the QRSvm of symptomatic and asymptomatic BrS patients.

In multivariable regression analysis, both QRSvm and positive RVOT signs are independent predictors for VTA events in BrS. Patients with lower QRSmv had fourfold higher risk to develop VTA (odds ratio [OR] 3.68, 95% CI 2.4 to 6.2, p = 0.001), whereas patients with positive RVOT signs had threefold higher risk (OR 2.6, 95% CI 1.4 to 4.9, p = 0.001).

Table 2. Differences in electrocardiographic parameters between symptomatic and asymptomatic BrS patients.

	Symptomatic cases (N=35)	**Asymptomatic cases (N=101)**	**P-value**
Age (years)	48±15	46±15	0.53
Male	23 (66%)	67 (66%)	0.23
Age of diagnosis (years)	42±13	42±15	0.86
QRS duration (ms)	113±17	117±17	0.26
QRS peak lead II (mm)	8±3	12±4	<0.001
QRS peak lead V6 (mm)	8±3	11±3	<0.001
QRS trough lead V2 (mm)	9±4	12±4	0.001
QRS vector magnitude (mV)	1.24±0.35	1.78±0.42	<0.001
Positive RVOT signs	19 (54%)	6 (6%)	<0.001
Positive late potentials	10 (29%)	46 (46%)	0.07

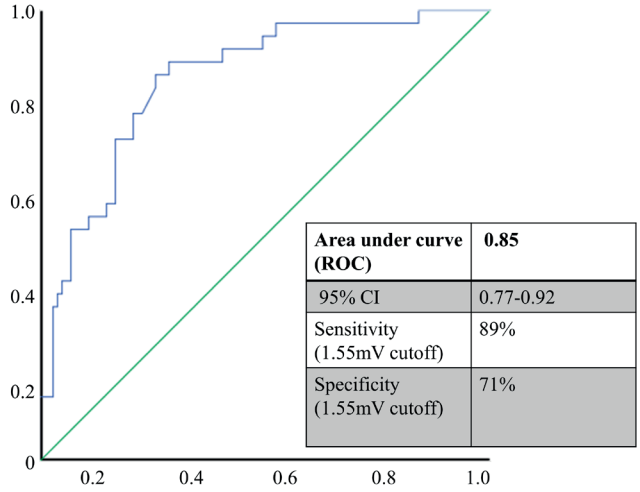


Figure 3. Receiver operator characteristic curve demonstrating the sensitivity and specificity of QRSmv parameter.

Discussion

In this study, we demonstrate the significance of QRSvm and positive RVOT signs as predictors for VTA in BrS. Patients with QRSmv lower than 1.55 were 4 times more likely to develop VTA. Moreover, patients with 3 or more positive RVOT signs have a threefold higher risk of VTA.

BrS is an autosomal dominant channelopathy responsible for 4% to 12% of all sudden cardiac deaths. The highest prevalence of BrS is among Asians.(17) BrS is more prevalent among men and they also have worse prognosis compared with women.(18) BrS patients are either diagnosed incidentally or present with a wide range of symptoms such syncope, seizures, or VTA. Risk stratification of BrS patients is the most challenging part in the management of this channelopathy. Many investigators reported on to testing of electrocardiographic markers to identify high-risk BrS patients.(4, 19, 20, 21) These markers include f-QRS and QRS duration in V2.(22) However, we still do not have clear noninvasive predictors for VTA, specifically for asymptomatic patients. QRS duration showed a promising prognostic value in some studies but it did not show value in large registries.(6, 7) In addition, other diagnostic and prognostic parameters than QRS duration and ECG-derived vectorcardiographic parameters such as spatial QRS-T angle have been evaluated for stratifying high-risk patients in different populations. Borleffs et al (9) showed that a wide QRS-T angle is a strong predictor for appropriate ICD shocks in patients with ischemic heart disease. In another study, a wide spatial QRS-T angle is also

associated with diabetes type 2, impaired glycemic control, and decreased left ventricular function.(8) Kardys et al (23) showed that spatial QRS-T angle is a strong predictor of cardiac mortality in the elderly.

Quantifying the scattering of electric waves by calculating the QRSvm showed a prognostic value in recent studies. Cortez et al(11) tested the significance of QRSvm as a predictor of VTA in TOF patients who underwent pulmonary valve replacement with a negative predictive value of 95% and OR of 34 (95% CI 3.9 to 293.3). They also showed that QRSvm can predict VTA inducibility in TOF patients with area under receiver operator characteristic curve of 0.75 and relative risk of 2.59 (95% CI 1.48 to 4.71).(12) Nagase et al (24) showed that low voltage type 1 ECG of BrS is highly and independently associated with VTA. The recent subxiphoid epicardial mapping approach revealed that the RVOT of symptomatic BrS patients showed areas of low voltage and delayed fragmented potentials and ablation of the anterior aspect of RVOT epicardium normalized BrS pattern in most of these patients.(25, 26) In line with these results, our study not only supports that low voltage is associated with high risk of VTA in BrS, but also introduced a noninvasive ECG-derived parameter to identify these high-risk patients.

Positive RVOT conduction delay signs were tested by our group in 2 previous studies. (13, 14) In this study, we combined all variables into 1 and still showed an independent predictor for VTA with odds ratio of 2.6 (95% CI 1.4 to 4.9, $p = 0.001$) and area under receiver operator characteristic of 0.74 (95% CI 0.633 to 0.85).

In conclusion, QRSvm and positive RVOT conduction delay signs can be beneficial noninvasive independent predictors of VTA in BrS patients. However, our observations need to be further evaluated in a multicenter study with larger number of BrS patients.

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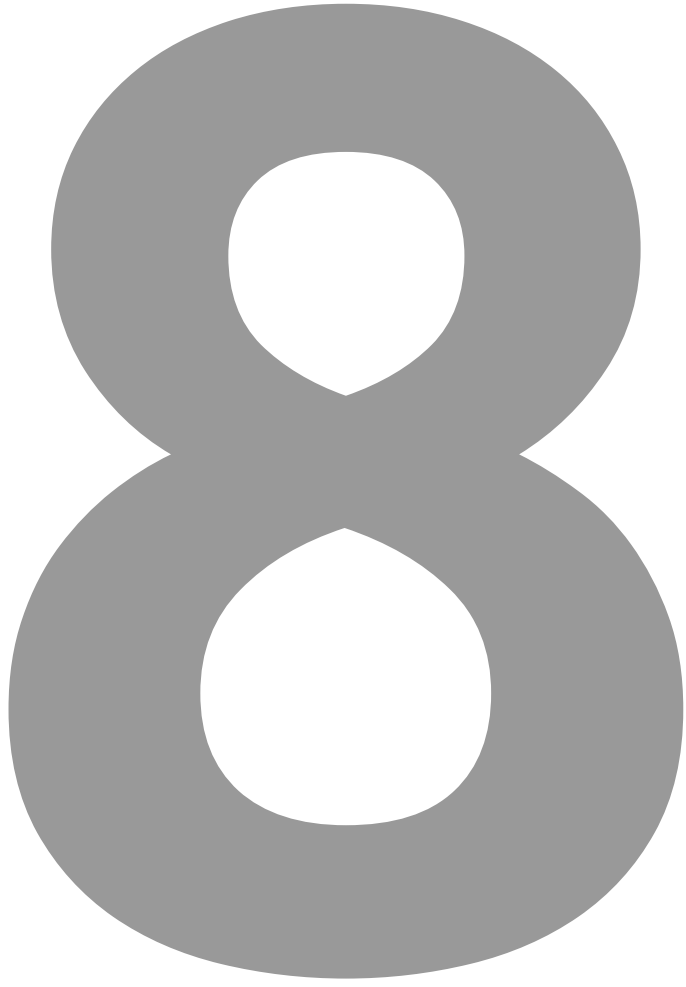
CHAPTER 8



GENERAL DISCUSSION

Ahmed Ragab

Cardiogenetics and Atrial Fibrillation

Atrial fibrillation (AF) is the most common clinical arrhythmia affecting millions of subjects all over the planet. Some researchers described it as " an epidemiological time bomb" and one of the 21st century epidemics. By 2060, it is expected that AF prevalence will exceed 18 million in the EU. AF comes with a huge burden on the whole healthcare system for instance AF costs around 0.9-1.6% of the national health service (NHS) total budget every year and this number is expected to reach 4.27% in the upcoming two decades.(1) Over 120 million outpatient visits are expected due to the massive increase in AF prevalence. Despite the fact that most of the risk factors for developing AF is well defined, there is one third of AF cases with no identified cardiac pathology or known risk factors (previously labelled as Lone AF).(2) The relatively young age of "lone" AF cases besides the unknown risk factors point out the role of genetics in the pathophysiology of this condition. The heritability of AF has been investigated since the first report of familial atrial fibrillation (FAF) in the 30s of the last century. A better understanding of the underlying mechanisms of FAF would support preventive and management strategies. In chapter 2, we discussed FAF from an epidemiological and clinical perspectives. Despite the huge advances in genetic technology, we are still facing challenges and limitations regarding experimental models, interpretation of the results of epidemiological studies, and translating them into efficient prediction models and therapeutic strategies. Firstly, Murine models have many limitations regarding the difference in structure and electrophysiological pathways such as calcium handling. Secondly, genome-wide association studies (GWAS) only explained a very small part of the inheritability of AF as 80% of the discovered single nucleotide polymorphism (SNPs) are located in non-coding regions. Moreover, studies tried to implement genotype to predict therapy response and to quantify the risk of developing de novo AF, but these studies lack external validity, randomization and the usage of time to the first symptomatic AF episode is a limited method as a quantitative parameter for AF.(3-5)

Cardiogenetics and Supraventricular Tachyarrhythmia

Supraventricular tachyarrhythmia (SVT) have been observed in patients with different cardiogenetic disorders. However, the vast majority of these disorders are affecting the ventricles with a high risk to develop ventricular tachyarrhythmia (VT) and sudden cardiac death. Reports on the incidence and the time course of AF/other SVTs in this population are scarce.

In chapter 3, we investigated the impact of SVT on patients with different cardiogenetic disorders, AF/SVT were observed in 12% of our cohort. Our patients developed SVT at a younger age than the reported age of onset in the general population (AF 52 ± 18 years, other SVT 37 ± 14 years). Recurrence of AF/SVT was observed in respectively 3%

and 4% of our cohort. We investigated the time interval between consecutive AF/other SVT episodes. For AF, the median interval between the first and second episode was 17 months and between the second episode and third was only 1 month, p=0.02. On the other hand, the median interval between the first and the second SVT episodes was 6 months and 22 months for the second and the third. We observed that patients who experienced SVT recurrences are more susceptible to inappropriate ICD shocks (12/17, 70%, p=0.003). Since most patients with an ICD had a traditional transvenous ICD system implanted (128/158, 81%), the cause of these inappropriate shocks is SVT rather than T-wave oversensing.(6) Hense, aggressive treatment such as ablative therapy of AF/SVT is recommended to reduce morbidities and complications such as inappropriate ICD shocks.

Understanding the pathophysiology of AF/SVT in the presence of cardiogenetic diseases has led to challenges with respect to management strategies. Firstly, many antiarrhythmic drugs are contraindicated in LQTS patients such as amiodarone. Moreover, AF can be the first clinical manifestation in Brugada syndrome (BrS) patients. Screening of young patients with "lone" AF can therefore unmask undiagnosed cardiogenetic diseases.(7) Quinidine has been tested in BrS patients and showed promising results in preventing AF/atrial flutter. However, the presence of side effects has led to drug discontinuation.(8) Pulmonary vein isolation showed a 67-83% success rate in eliminating AF and prevented inappropriate ICD shocks in two small cohorts.(9) Finally, using dual-chamber ICD instead of single-chamber ICD and punctuate device programming are recommended to decrease inappropriate shocks.(10)

Cardiogenetics and Ventricular Arrhythmia

The clinical spectrum of cardiogenetic diseases is broad as it ranges from asymptomatic to sudden cardiac death. Long-term follow-up reports on frequent ventricular premature complexes (fVPC) and non-sustained ventricular tachycardia (nsVT) in this group of patients are scarce. In chapter 4, we examined the incidence and recurrences of fVPC and nsVT and their interrelationship in different cardiogenetic conditions during a long-term follow-up. Both BrS and LQTS patients are less likely to develop fVPC and nsVT than ARVC patients. These results were unsurprisingly since the ventricles of ARVC patients are the most affected structurally among all cardiogenetic conditions.

The second highest incidence of fVPC and nsVT was among BrS patients. There is a shred of strong evidence that there is an overlap in the pathophysiology of ARVC and BrS with respect to the presence of structural abnormalities.(11) Recently, Parreira and her colleagues showed a high incidence of Brugada ECG pattern type II and III among patients with idiopathic VPC and a high incidence of low voltage areas outside the transitional

voltage zone.(12) These results suggest that idiopathic VPC might be the first presentation in BrS patients. Therefore, screening young patients presenting with idiopathic VPCs for BrS has been suggested.(13)

Risk stratification of Brugada syndrome (BrS)

Since 1992, many research groups around the globe tried to tackle the major challenge of risk stratification of patients with BrS, a potential life-threatening condition. Although implantation of an implantable cardioverter defibrillator (ICD) for primary prevention has mortality benefits, this preventive measure has serious implications with respect to morbidity and quality of life.

Risk stratification of BrS patients is facing many obstacles. Firstly, BrS has incomplete penetrance with a poor genotype-phenotype relationship as not all causative mutations carriers present with the same phenotype. Secondly, most of the diagnosed patients are asymptomatic and they could present with sudden cardiac death without any previous warning signs. Therefore, early identification of individuals at risk is of paramount importance. Diagnosis of BrS does not just affect the identified individual but also her/his family members and conduction of family screening is therefore essential. Thirdly, there are at present 21 known genes associated with BrS but yet only one gene (SCN5A) has a definitive relation with BrS phenotype. Lastly, accurate non-invasive electrocardiographic risk markers need to be defined or validated in large cohorts.

There are three main categories of variables that have been investigated to quantify the risk of VTA events in this population, namely; clinical profiles, genetic mutations, and electrophysiological markers.

Clinical Profile and risk stratification

Among all clinical variables, a history of previous cardiac arrest or arrhythmic syncope has the highest predictive value for further VTA events. The yearly risk of recurrent VTA in patients with a history of cardiac arrest or syncope is respectively 7% and 2%. Distinguishing between arrhythmic and vasovagal syncope is important during the risk stratification process. In a recent study, Sacher and his colleagues followed patients after separating them into BrS patients with a history of arrhythmic syncope and non-arrhythmic syncope. During a 5 year follow-up period, patients with an arrhythmic syncope had a 5.5% yearly VTA rate compared to no VTA events in the patients with vasovagal syncope.(14) A positive family history of sudden cardiac death had no prognostic value in most BrS cohorts. However, in a Japanese cohort, a family history of lethal cardiac events had a prognostic value for BrS probands.(15) Moreover, a recent study showed

that patients with a family history of sudden cardiac death in multiple first-degree relatives (<35-year-old) have a higher risk for VTA.(16)

The vast majority of VTA events in BrS occur between the age of 20 and 65 years. During long-term follow-up, patients over 70 didn't experience any VTA events.(17) Moreover, BrS is rare among children, and VTA is often triggered by fever. An European cohort study showed that spontaneous type 1 ECG and history of VTA are independent predictors of VTA among BrS children.(18) Despite the high incidence of VF in children during drug-induced testing, the incidence of VTA during the follow-up is low.(19, 20) This is adding more challenges to the risk stratification for young patients and questioning the rationale of this test at a young age.(21) BrS is more prevalent among adult males with a 2 to 7 times higher risk of presenting with VTA. However, gender is not an independent predictor for recurrent VTA events after adjustment to other variables such as a spontaneous type 1 ECG pattern. There are two main hypotheses explaining gender differences in BrS. Di Diego and his colleagues suggested that the presence of a more prominent Ito channels in males' right ventricle epicardium is responsible for the difference in BrS phenotype expression.(22) On the other hand, studies suggested that sex hormones are the main drivers for the observed gender differences since BrS phenotype mainly manifests in males during puberty, A case-control study showed an association between higher testosterone levels in patients with BrS.(23) Moreover, one case report described the disappearance of the BrS pattern in a patient after surgical castration.(24) In a recent study, ethnic differences among BrS patients were investigated. In an Asian cohort consisting of 678 patients, there was a male predominance , and males more often presented with fatal cardiac events and spontaneous type I ECG. However, they less frequently have a family history and SCN5A mutations than Caucasians. This study has a limitation since no patients were included from the two Asian countries with the highest prevalence of BrS (Thailand and Philippines).(25)

Genetic background and risk stratification

Although BrS is a genetic disease, the significance of genetic testing has still implications for risk stratification and management. Many studies failed to show any association between SCN5A gene mutations and the risk of developing VTA during follow-up.(15, 26, 27) However, specific mutations have prognostic values such as mutations resulting in truncated Nav1.5 protein. Moreover, combining a history of sudden cardiac death in first-degree young relatives with SCN5A mutation was indicative of a poor prognosis. (16, 28) Further, recent studies suggested that common polymorphism can affect the severity of disease phenotype by modulating the effect of SCN5A mutations. Hu and her colleagues suggested that the splice variant in SCN5A affects the molecular phenotype of a loss of function mutation (R1512W). (29-31)

Electrophysiological markers of arrhythmic risk

Many studies have investigated the value of electrophysiological parameters to predict VTA and optimize management strategies for BrS patients. These parameters include surface ECG markers, processed ECG signals and programmed ventricular stimulation during electrophysiological studies.

Surface ECG markers

A variety of non-invasive ECG markers have been investigated. A spontaneous type I BrS pattern showed twice the risk of developing VTA compared to patients with drug-induced BrS pattern (0.8% per year vs 0.4% per year).(26, 32) The excellent prognosis of patients with drug-induced BrS pattern raised questions and debate about the specificity of the test.(33) A recent study suggested that ajmaline doses >1mg/Kg could decrease the specificity of the test.(34) Moreover, type I BrS pattern in peripheral leads showed a higher risk for developing VTA. Rollin et al. showed that 27% percent of BrS patients with both precordial and peripheral patterns developed VTA compared to 6% of BrS patients with the only precordial pattern.(35) Early repolarization pattern (J-point elevation) in the inferior and lateral leads has been associated with increased risk to develop VTA.(36, 37) Moreover, there are repolarization risk markers that have been investigated as a risk marker such as prolonged T-peak to T- end and increased (T-peak to T-end)/QT ratio.(38, 39) Recently, a study showed that prolonged QT interval of more than 460ms in multiple ECGs is associated with a higher risk for recurrent VTA.(40)

On the other hand, several depolarization risk markers have been studied. Not only QRS prolongation, but also fragmented QRS showed increased risk to develop VTA in BrS patients.(41, 42) Prolonged QRS reflects conduction delay and shortened wavelength whereas, fragmented QRS is a sign of conduction dispersion.(43, 44) Moreover, Epsilon like wave sign appeared more often in symptomatic BrS patients.(45) This sign points towards a conduction delay in RVOT which is also observed in other cardiogenetic diseases (arrhythmogenic right ventricular cardiomyopathy). Cardiac activation mapping suggested that structural abnormalities in RVOT are responsible for current-load-mismatch and conduction changes and hence ST-segment elevation.(46) Another mapping study suggested that discontinuous conduction due to impaired active membrane process is a major conspiring factor besides abnormal functional factors which is triggered by fever and/or SCN5A mutations. These results could explain that most of BrS patients develop VTA after their third decade of life since it takes time to develop structural abnormalities. (47)

In BrS patients, vector-cardiography can be used to detect right end conduction delay in the right superior and posterior quadrant of the vector-cardiographic frontal plane.

These areas are corresponding to the anatomical location of the RVOT and can be monitored by lead aVR in ECG. In chapter 5, we have investigated the positive R-wave sign in lead aVR as one of the RVOT depolarization risk markers. Our cohort showed that the R-wave sign is an independent predictor for the development of VTA with a 4.8 (95% CI:1.79-13.27) higher risk than BrS patients with no R-wave sign. The sign appeared in 50% of BrS patients who developed de novo VTA during the follow-up, in 60% of patients with a history of VTA before diagnosis, and in 80% of the patients with a history of recurrent VTA. Interestingly, the positive R-wave sign was observed in patients with tricyclic antidepressant toxicity.(48) Slowing down depolarization by sodium current inhibition is the main mechanism behind the increased risk of developing VTA among those patients.

Other RVOT conduction delay ECG markers have been defined to monitor conduction abnormalities in this area such as prominent S wave in lead I, S wave in lead II > S wave in lead III, and Tzou criteria. These markers have been described by experimental findings of Bayes and his colleagues and have been tested in other conditions such as ischemic cardiomyopathy as a marker for anterosuperior zonal conduction block.(49) In chapter 6, we, therefore continued to investigate these three RVOT conduction delay markers in our BrS population. All three investigated markers showed an independent prediction of VTA in BrS patients. The strongest risk marker was SII>SIII pattern with an OR of 8.3 (95% CI:1.82-27.85). This sign also showed the highest sensitivity and specificity (sensitivity: 80%, specificity: 89%). Prominent S wave in lead I (>0.15 mV) had OR of 4.15 (95% CI: 1.2-16.9) with a sensitivity of 70% and specificity of 89%. Tzou criteria had OR of 3.7 (95% CI:1.0-13.58) with a sensitivity of 63% and specificity of 85%.

A vector-cardiographic study showed a dextrorotation of the QRS loop in the frontal plane of BrS patients. This rotation is consistent with +30 degrees rotation in the first part of the loop and -150 in the second part and this explains the appearance of Q wave in lead III and a prominent S wave in lead I. On the other hand, the 150 degree dextrorotation in the second part explains the appearance of SII > SIII pattern and a R wave sign in lead aVR. We also investigated ECG markers of repolarization homogeneity such as T, QT-QTp (Tp-Te), and Tp-Te/QT in lead V1, and none of these markers showed any significant predictive value in our cohort.

Conduction delay in the antero-superior sub-pulmonary Purkinje network causes right antero-superior zonal conduction block. This can manifest in the ECG as SII>SIII pattern, not only in BrS syndrome but also in other conditions with the same underlying patho-physiological mechanism. Moreover, Bayes de Luna's findings showed that conduction block in this anterosuperior can be monitored by detecting rS pattern in lead V1 and a

prominent S wave in lead V6 and both of these signs are part of Tzou criteria. We investigated the prognostic value of having three or more RVOT conduction delay signs and it showed OR of 2.6 (95% CI 1.4 to 4.9, p = 0.001) with a sensitivity of 54% and specificity of 94%.

Not only dextrorotation of the QRS loop of vectorcardiogram studies is affected by RVOT conduction delay, but also voltage-dependent parameters. QRS 3-dimensional vector magnitude (QRSvm) showed a value in predicting VTA in patients with tetralogy of Fallot.(50) Dispersion of depolarization vector is caused by scattered slowing electrical waves, therefore, QRSvm decreases in patients with RVOT conduction delay. In chapter 7, we investigated the value of QRSvm in predicting VTA in BrS patients. To calculate this parameter we used the regression related Frank-lead technique of Kors.

Our cohort showed that QRSvm was significantly lower in patients who developed VTA (1.24 ± 0.35 vs 1.78 ± 0.42 mV, p < 0.001). Using 1.55mV as a cut-off, the highest sensitivity and specificity were 89% and 71% respectively. Multivariable regression analysis showed that QRSvm lower than 1.55mV is an independent predictor for developing VTA in our BrS cohort with an OR of 3.68, 95% CI 2.4-6.2).

In chapter 7, we introduce a new noninvasive method to quantify the level of scattering delayed electrical activity in BrS patients. QRSvm showed prognostic value in tetralogy of Fallot patients with an OR of 34. Moreover, BrS mapping studies revealed the presence of low voltage areas with delayed fragmented potentials in RVOT. By targeting those areas during ablation therapy, normalization of BrS pattern was achieved in most patients.(51, 52)

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CHAPTER 9

9

ENGLISH SUMMARY

Ahmed Ragab

In Chapter 1, we discussed the current knowledge on different cardiogenetic diseases such as epidemiology, pathophysiological mechanisms of arrhythmia. In addition, we discussed diagnosis, family screening, risk stratification strategies, and treatment strategies of each inherited cardiac arrhythmia (ICA).

In chapter 2, we reviewed familial atrial fibrillation (FAF) from pathophysiological, epidemiological, and clinical perspectives. We discussed common and rare variants related to FAF. We also highlighted the current challenges facing the usage of animal models in FAF studies. Moreover, we illustrated the clinical implications of current knowledge such as genotype-based AF prediction models and personalized treatment strategies including pharmacogenetics-guided therapy.

In chapter 3, we examined the impact of different supraventricular arrhythmia (SVT) in patients with different ICA. We studied the prevalence, co-existence, and time course of different types of SVT. Among 393 patients (median 49 years, range 17 to 87, 57% male), AF/SVT was observed in 12% (n=49, 31 male, 42 ± 17 years). Patients presented with only SVT were younger than the ones presented with only AF. In patients with AF, interval between episodes became shorter over time. Finally, AF/SVT were associated with inappropriate implantable cardioverter defibrillator shocks.

Data on frequent ventricular premature complexes (fVPC) and non-sustained ventricular tachycardia (nsVT) among ICA patients are limited. **In chapter 4**, we reported the incidence, recurrences, and interrelationship of fVPC and nsVT among different ICA during a long-term follow-up. Patients with arrhythmogenic right ventricular cardiomyopathy had more frequent fVPC and nsVT compared to other ICA. The overall recurrence rate of malignant ventricular tachyarrhythmias (VTA) was 33%.

Identifying the high-risk patients for developing VTA is the most challenging step in the management of Brugada syndrome (BrS) patients. Conduction delay in the right ventricular outflow tract (RVOT) plays a major role in the pathophysiology of VTA in BrS. R-wave elevation in lead aVR indicates RVOT conduction delay. **In chapter 5**, we studied the significance of R-wave sign as a predictor of VTA in BrS patients. A positive R-wave sign was observed in 31% (41/132) of the cohort. This sign appeared more frequently in the ECG of symptomatic patients either before initial diagnosis, during electrophysiological studies, or during follow-up. R-wave sign showed independence in predicting VTA development with an odds ratio of 4.8 (95% confidence interval 1.79 to 13.27). **In chapter 6**, we continued to investigate the significance of other RVOT conduction delay ECG parameters as predictors for VTA development. Prominent S waves in lead I, SII > SIII, and +ve Tzou criteria were independent predictors for VTA during follow-up of 56

(IQR: 40-76) months. SII > SIII had the highest area under the curve for prediction of VTA with a sensitivity of 80% and specificity of 89%. **In chapter 7**, we reconstructed the traditional 12-lead electrocardiogram into QRS vector magnitude (QRSvm) to quantify depolarization dispersion and identify high-risk BrS patients. QRSvm was significantly lower in symptomatic patients (1.24 ± 0.35 vs 1.78 ± 0.42 mV, $p < 0.001$). QRSvm was an independent predictor for VTA with an odds ratio of 3.68, 95% CI 2.4 to 6.2. The highest sensitivity and specificity were 89% and 71% respectively with an area under the curve of 0.85. This was achieved by using a 1.55mV cut-off value.

In chapter 8, the main findings and clinical significance of the studies reported in this thesis were discussed.

CHAPTER 10

10

Nederlandse samenvatting

Ahmed Ragab

In Hoofdstuk 1 bespraken we de huidige kennis over verschillende cardiogenetische ziekten zoals epidemiologie, pathofysiologische mechanismen van aritmie. Daarnaast bespraken we diagnose, familiescreening, risicostratificatiestrategieën en behandelingsstrategieën van elke erfelijke hartritmestoornis (ICA).

In hoofdstuk 2 hebben we familiair atriumfibrilleren (FAF) bekeken vanuit pathofysiologische, epidemiologische en klinische perspectieven. We bespraken veelvoorkomende en zeldzame varianten met betrekking tot FAF. We hebben ook gewezen op de huidige uitdagingen waarmee het gebruik van diermodellen in FAF-onderzoeken wordt geconfronteerd. Bovendien illustreerden we de klinische implicaties van de huidige kennis, zoals op genotype gebaseerde AF-voorspellingsmodellen en gepersonaliseerde behandelstrategieën, waaronder farmacogenetica-geleide therapie.

In hoofdstuk 3 onderzochten we de impact van verschillende supraventriculaire aritmie (SVT) bij patiënten met verschillende ICA. We hebben de prevalentie, het naast elkaar bestaan en het tijdsverloop van verschillende typen SVT bestudeerd. Onder 393 patiënten (mediaan 49 jaar, bereik 17 tot 87, 57% mannen), werd AF/SVT waargenomen bij 12% (n=49, 31 mannen, 42 ± 17 jaar). Patiënten die alleen SVT kregen, waren jonger dan degenen die alleen AF kregen. Bij patiënten met AF werd het interval tussen afleveringen in de loop van de tijd korter. Ten slotte werden AF/SVT geassocieerd met ongepaste implanteerbare cardioverter-defibrillatorschokken.

Gegevens over frequente ventriculaire premature complexen (fVPC) en niet-aanhoudende ventriculaire tachycardie (nsVT) bij ICA-patiënten zijn beperkt. **In hoofdstuk 4** rapporteerden we de incidentie, recidieven en onderlinge relaties van fVPC en nsVT tussen verschillende ICA gedurende een lange termijn follow-up. Patiënten met aritmogene rechterventrikelcardiomyopathie hadden vaker fVPC en nsVT in vergelijking met andere ICA. Het totale recidiefpercentage van maligne ventriculaire tachyaritmieën (VTA) was 33%.

Het identificeren van patiënten met een hoog risico voor het ontwikkelen van VTA is de meest uitdagende stap in de behandeling van patiënten met het Brugada-syndroom (BrS). Geleidingsvertraging in het rechter ventriculaire uitstroomkanaal (RVOT) speelt een belangrijke rol in de pathofysiologie van VTA in BrS. R-golfhoogte in afleiding aVR geeft RVOT-geleidingsvertraging aan.

In hoofdstuk 5 hebben we de betekenis van het R-golfteken als voorspeller van VTA bij BrS-patiënten bestudeerd. Een positief R-golfteken werd waargenomen bij 31% (41/132) van het cohort. Dit teken verscheen vaker op het ECG van symptomatische

patiënten, hetzij vóór de eerste diagnose, tijdens elektrofysiologische onderzoeken of tijdens follow-up. R-golfteken toonde onafhankelijkheid in het voorspellen van VTA-ontwikkeling met een oddsratio van 4,8 (95% betrouwbaarheidsinterval 1,79 tot 13,27).

In hoofdstuk 6 gingen we verder met het onderzoeken van de betekenis van andere RVOT-geleidingsvertragings-ECG-parameters als voorspellers voor VTA-ontwikkeling. Prominente S-golven in lead I-, SII> SIII- en +ve Tzou-criteria waren onafhankelijke voorspellers voor VTA tijdens een follow-up van 56 (IQR: 40-76) maanden. SII > SIII had het hoogste gebied onder de curve voor de voorspelling van VTA met een sensitiviteit van 80% en specificiteit van 89%.

In hoofdstuk 7 hebben we het traditionele 12-afleidingen elektrocardiogram gereconstrueerd in QRS vector magnitude (QRSvm) om depolarisatie dispersie te kwantificeren en risicovolle BrS patiënten te identificeren. QRSvm was significant lager bij symptomatische patiënten (1,24 ± 0,35 vs 1,78 ± 0,42 mV, $p < 0,001$). QRSvm was een onafhankelijke voorspeller voor VTA met een odds ratio van 3,68, 95% BI 2,4 tot 6,2. De hoogste sensitiviteit en specificiteit waren respectievelijk 89% en 71% met een oppervlakte onder de curve van 0,85. Dit werd bereikt door een afkapwaarde van 1,55 mV te gebruiken.

In hoofdstuk 8 werden de belangrijkste bevindingen en klinische significantie van de studies beschreven in dit proefschrift besproken.

CHAPTER 11

11

Appendices

PhD portfolio

List of publications

About the author

Dankwoord

PHD PORTFOLIO

Name PhD student:	Ahmed Adel Y. A. Ragab
Erasmus MC department:	Cardiology
Research School:	COEUR
Thesis title:	**Evaluation of Cardiogenetic Diseases and Effectiveness of Screening: Weighing of the Heart**
Promotors:	**prof. dr. N.M.S. de Groot, prof. dr. B.J.J.M. Brundel**

	Year	ECTS
Academic skills		
Cardiovascular Pharmacology	10-2015	1.5
Cardiovascular Medicine	12-2015	1.5
Arrhythmia Research Methodology	1-2016	1.5
Molecular Biology in Cardiovascular Research	4-2016	1.5
Systematic literature retrieval in PubMed Part I	6-2016	0.3
Research Integrity	8-2016	0.3
Cardiovascular Imaging and Diagnostics Part I	1-2017	0.5
Biomedical English Writing Course for PhD-students	2017	2
Congenital Heart Disease Part I	2-2017	0.5
Course on R	5-2017	1.8
"How to use the latest mapping and ablation technologies" workshop	6-2017	0.5
Cardiovascular Imaging and Diagnostics Part III	6-2017	0.5
"How to get better in PAF treatment" workshop	3-2018	0.5
Symposia and conferences		
COEUR PhD Dag	2016	0.3
EHRA EUROPACE, Vienna	6-2017	1.5
ESC congress, Barcelona	8-2017	1.5
NVVC najaarscongres, Papendal	10-2017	0.6
COEUR PhD Dag	2017	0.3
EHRA, Barcelona	3-2018	1.5
COEUR PhD Dag	2018	0.3
EHRA, Lisbon	2019	1.5
ESC congress, 2020	2020	1.5
ESC congress, 2021	2021	1.5

Presentations		
Is the r wave sign a predictor for ventricular tachyarrhythmia in patients with brugada syndrome ?" EHRA EUROPACE, poster	2017	0.3
Is the r wave sign a predictor for ventricular tachyarrhythmia in patients with brugada syndrome ?" ESC CONGRESS, poster	2017	0.3
Supraventricular tachyarrhythmia in Cardiogenetic diseases, Research Journal, EMC	2017	0.6
Prevalence and the time course of supraventricular tachyarrhythmias in patients with inherited cardiac arrhythmia." EHRA EUROPACE	2017	0.3
"Usefulness of the R-Wave Sign as a Predictor for Ventricular Tachyarrhythmia in Patients With Brugada Syndrome "Dutch Heart House Congress, Arnhem	2017	0.6
"Prediction of ventricular tachyarrhythmia in brugada syndrome by right ventricular outflow tract conduction delay signs. EHRA, Barcelona.	2018	0.6
The Genetic Puzzle of Familial Atrial Fibrillation, Journal club, EMC	2018	0.6
QRS Vector Magnitude as Predictor of Ventricular Arrhythmia in Patients With Brugada Syndrome. EHRA 2019 Lisbon.	2019	0.6
The assessment of the accuracy and credibility of cardiovascular health information on social media platforms, ESC congress	2020	0.6
Other courses		
Dutch language A1	2016	1.5
German Language A2, Goethe institut	2017	1.5
Translational electrophysiology meetings		0.6
TOTAL		**31.5**

List of Publications

1- Usefulness of the R-Wave Sign as a Predictor for Ventricular Tachyarrhythmia in Patients With Brugada Syndrome. **Ragab AAY**, Houck CA, van der Does LJME, Lanters EAH, Burghouwt DE, Muskens AJQM, de Groot NMS. DOI: 10.1016/j.amjcard.2017.04.044

2- Impact of Supraventricular Tachyarrhythmia in Patients With Inherited Cardiac Arrhythmia. **Ragab AAY**, Houck CA, van der Does LJME, Lanters EAH, Muskens AJQM, de Groot NMS. DOI: 10.1016/j.amjcard.2017.08.016

3- Prediction of ventricular tachyarrhythmia in brugada syndrome by right ventricular outflow tract conduction delay signs. **Ragab AAY**, Houck CA, van der Does LJME, Lanters EAH, Muskens AJQM, de Groot NMS. DOI: 10.1111/jce.13496

4- QRS Vector Magnitude as Predictor of Ventricular Arrhythmia in Patients With Brugada Syndrome. **Ragab AAY**, Houck CA, van der Does LJME, Lanters EAH, Muskens AJQM, de Groot NMS. Doi.org/10.1016/j.amjcard.2019.03.018

5- A Rare Case of the Digenic Inheritance of Long QT Syndrome Type 2 and Type 6. Heida A, van der Does LJME, **Ragab AAY**, de Groot NMS. doi.org/10.1155/2019/1384139

6- Ventricular Dysrhythmias during Long-Term Follow Up in Patients with Inherited Cardiac Arrhythmia. Sitorus GDS, **Ragab AAY**, Houck CA, Lanters EAH, Heida A, van Gastel VE, Muskens AJQM, de Groot NMS. doi:10.1016/j.amjcard.2019.07.050.

7- The Genetic Puzzle of Familial Atrial Fibrillation. **Ragab AAY**, Sitorus GDS, Brundel BJJM, de Groot NMS. doi.org/10.3389/fcvm.2020.00014

8- Early and late post-operative arrhythmias after surgical myectomy: 45 years of follow-up. Kharbanda RK, Lodder L, **Ragab AAY**, de Jong PL, Kik C, Brundel BJJM, Taverne YJHJ, de Groot NMS, Bogers AJJC. Int J Cardiol. 2021 Apr 1;328:63-68. doi:10.1016/j.ijcard.2020.11.055.

About the author

Ahmed Adel Ragab was born on 19th of June 1989, in Egypt. In 2006, he graduated from "Lieutenant General Abdel Moneim Ryad" military high school. In 2014, he graduated from Alexandria Faculty of Medicine, Egypt. In 2014, he completed research training at Johns Hopkins Hospital and Adams Cowley Shock Trauma Center, Baltimore, the USA. In 2015, he started his PhD at Erasmus Medical Center, Rotterdam, the Netherlands, supervised by Prof. Dr. N.M.S. de Groot and Prof. dr. B.J.J.M. Brundel. He concomitantly granted his Master of Public Health at the University of Aberdeen, Scotland. He also worked for the Egyptian Ministry of Health, Sharm El-Sheikh International Hospital, and Sharm El-Sheikh Trauma I Center.

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