# SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

**TRIVANDRUM, KERALA**

## PROJECT REPORT

*Submitted during the course of*
*DM Cardiology*

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**DM Trainee**

## DEPARTMENT OF CARDIOLOGY

**Jan 2013-Dec 2015**

# DECLARATION

*I, **Dr Aamir Rashid** , hereby declare that the project in this book was undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.*

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***Forwarded***

*The candidate, **Dr Aamir Rashid** , has carried out the minimum required project.*

*Thiruvananthapuram* **Prof. Dr Jagan Mohan Tharakan**
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# TITLE

# CLINICAL, DEMOGRAPHIC AND TREATMENT PROFILE OF BRUGADA SYNDROME AND LONG QT SYNDROME PATIENTS IN INDIAN POPULATION


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## ACKNOWLEDGEMENT

At the outset I would thank Almighty Allah, Creator of the universe for being with me always despite my shortcomings.

I deeply thank my guide Dr Narayanan Namboodiri for his constant guidance throughout the project.

I am very grateful to my HOD Sir and guide Dr Jagan Mohan Tharakan for his immense support, kind-heartedness and inspiring attitude.

Special thanks to Dr Anees Thajudeen for his valuable suggestions.

Lots of thanks to my parents, wife and little daughter for their support.

My sincere thanks to technical staff of SCTIMST for their extreme co-operation and support

Finally I express my gratitude to all my patients, with whose cooperation this study has been possible

**Aamir Rashid**

# I N D E X

# Introduction

Sudden Cardiac Death in young is significantly contributed by inheritable cardiac arrhythmia syndromes according to western studies. The apparent prevalence in community, the clinical profile and the natural history of these conditions is becoming better known in these populations. The most prevalent and well-studied of them are Brugada Syndrome, and QT-pathies – long QT syndrome (LQTS) and short QT syndrome (SQTS). The relatively higher prevalence of these conditions in populations as compared to other lesser characterised cardiac channelopathies - and probably those with lesser SCD risk- is already known. Brugada syndrome (BS), an inheritable syndrome which carries an increased risk of sudden cardiac death has a characteristic coved-type ST-segment–elevation in right precordial leads from V1 to V3.(1) Long QT syndrome is a genetic cardiac channelopathy which has variable penetration and is associated with increased propensity of sudden cardiac death in young patients with structurally normal heart.(2) These inherited arrhythmia syndromes are well known to vary in their clinical manifestations and relative risk potential to result in SCD in response to many biophysical factors like age, gender, drug exposure, physical stimuli. “Patchy geographical distribution” of these channelopathies is

also known, though more and more cases are being reported from different populations.

Delineation of natural history and clinical profile of patients affected with these conditions in our population has not been systematically approached so far. Although there are isolated case reports on these potentially lethal conditions, the exact prevalence of these syndromes in Indian population is not known. It is also not clear that the clinical features of these inheritable arrhythmia syndromes are different in Indian population as compared to the western counterparts. Many patients with these conditions are misdiagnosed even when they present with warning symptoms and signs or after resuscitated cardiac arrest. The fortunate patients who survive the first episode of SCD are also not evaluated and investigated to recognise if these conditions are present. The scenario is equally worse for the relatives of the proband who are at risk for SCD in many cases.

To author's knowledge there has been no comprehensive study focussed on Brugada Syndrome and Long QT Syndrome at present in India. It is also not clear that the clinical features of these inheritable arrhythmia syndromes are different in Indian population as compared to the western counterparts.

The potential application of such a study is that many patients at potential risk of SCD can be identified, and can be studied for the clinical manifestations and natural history. Any features unique to our population can be identified. Many of the relatives of the proband affected by these genetic conditions can be identified and treated before the symptomatic presentation. This is particularly relevant in some of these conditions with very high likelihood of the initial presentation itself being lethal.

The study is intended to have insight into clinical profile of these common channelopathies in our population, though it is limited because the data is hospital-based. It can also identify the clinical profile and presentation of patients with channelopathies in our community, which is yet not defined in our country. Generating our own data about these channelopathies can help us in better understanding of disease pattern and treatment outcomes in our population which can help in future for optimal management of these patients.

This study aims to give a better insight about clinical presentation, risk stratification, treatment outcome of Brugada syndrome and Long QT syndrome in our population, which are largely unknown in our population.

# Aims and Objectives

This study aims to delineate the clinical, demographic characteristics and treatment outcomes of inheritable arrhythmia syndromes (Brugada syndrome and Long QT Syndrome) presenting to a tertiary care centre in South India.

# Materials and Methods

- History Of Resuscitated Cardiac Arrest
- Type 1 Brugada Sign In Family Members
- Family history of sudden cardiac death in age less than 45 years
- Inducible VT on electrophysiological testing
- Nocturnal agonal breathing, Arrythmogenic syncope.
- Type 2 and Type 3 Brugada signs were diagnosed as Brugada syndrome if on administration of flecainide they changed to Type 1 pattern and also satisfied any of the criteria previously mentioned.

Type 1 Brugada sign was defined as coved ST elevation in right precordial leads with J wave or ST elevation more than 2 mm at its peak followed by a negative T wave in more than one precordial leads V1-V3.

Type 2 Brugada Sign was defined as ST elevation of ≥ 2 mm resulting in saddle back configuration, trough of ST elevation of at least 1mm followed by a positive or Biphasic T wave.

Type 3 Brugada Sign was defined ST elevation of less than 1 mm with either saddle back or coved morphology.(3)

**Study Centre**: Cardiology outpatient and inpatient service, Sree Chitra Tirunal Institute for Medical Sciences and Technology. All patients presenting to OPD or getting admitted as in patients with the specific inclusion criteria and after proper clinical evaluation were recruited. Only those patients consenting to be part of study were included.

The ethical committee of the SCTIMST approved the study.

**Study Design**: Observational Retrospective –Prospective Single Centre Study from Hospital Based Registry.

**Study Period**: Jan. 2013 – Aug. 2015

**Patient population:**

All patients attending SCTIMST from 2000 to 2015 were included in our study that satisfied the inclusion criteria.

**INCLUSION CRITERIA:**

**Brugada Syndrome**

All patients with Type 1 Brugada sign were diagnosed as Brugada syndrome if they satisfied one of the following conditions:

- Self Terminating Polymorphic VT
- Documented Ventricular fibrillation (VF)

**Long QT Syndrome:**

LQTS was diagnosed:

- In presence of corrected QT interval for heart rate using Bazetts formula (QTC) ≥500 ms in repeated 12 –lead electrocardiogram and in absence of a secondary cause for QT prolongation or
- In presence of an LQTS Shwartz risk score ≥ 3.5 in the absence of secondary cause for QT prolongation or
- In presence of a QTC between 480 and 499 ms in repeated 12 lead ECG in patient with unexplained syncope in the absence of secondary cause for QT prolongation.(4)

The QTC interval was measured from lead II (or lead I or III if it could not be measured in lead II) from 12 lead electrocardiogram. With use of Bazzets formula Long QT syndrome (LQTS) was further Stratified as Type 1, type 2 or Type 3.

- LQTS Type1 was identified with typical broad based T wave patterns.
- LQTS type 2 was identifies with notched, bifid low amplitude T waves.

- LQTS type 3 was identified with late onset peaked or biphasic T wave.

**EXCLUSION CRITERIA:**

1. Patient on drugs known to cause QT prolongation or any other secondary cause for prolonged QT.
2. Patient on drugs that can cause Brugada like pattern on ECG or any other condition which can produce Brugada Pattern on ECG.
3. Patients incompetent to give informed consent in case of adults.

The patient selection criteria was designed so as to include all patients who presented with documented Arrhythmia or who were at risk for near fatal or fatal arrhythmias, and suspected to have any of the two cardiac channelopathies. .

All patients were subjected to 2 levels of evaluation as a part of the clinical evaluation protocol

1. **Assessment of clinical characteristics:** This involved confirmation of a cardiac cause for symptoms, and then try to correlate to a particular clinical profile to a known type of genetic arrhythmia syndrome. This was as per standard protocol being followed up in our institute at present. The armamentarium of tests included 12-

lead electrocardiogram, chest X-ray, echocardiogram, ambulatory ECG (Holter) monitoring, MRI in indicated cases. These tests are done in all arrhythmia syndromes, irrespective of the specific etiology/ diagnosis in our institute.

2. **Advanced evaluation:** This level of evaluation was done to characterize the cases further in accordance with recommendations including published guidelines on the management of these specific syndromes. The evaluations in the advanced evaluation (level 2) were done depending on the certainty of diagnosis based on other levels. Certain tests specific to either of two channelopathies were also done. These tests (pharmacological challenge tests, electrophysiological study, long-term monitoring with implantable loop recorder etc.) are also routinely performed in our institute for these conditions. Once the condition was confirmed, the first degree relatives were screened for the arrhythmia which is being routinely done in our institute.

Documentation of the demographic data including age at presentation, gender and ethnicity, past medical and family histories, and details of investigations performed during initial evaluation and during subsequent hospital visits. The enrolled cases were followed up

at regular intervals. The management of these patients was based on current guidelines and practices in our context. All patients were followed up regularly in the pacemaker –arrhythmia clinic as per the institute protocol. Clinical follow up included detailed history, physical examination and ECG and other relevant investigations if needed. All clinical data was recorded regularly. ICD patients were initially followed after 1 week, then after 3 months, thereafter 6 monthly. All ICD parameters were checked on follow up. All electrograms of appropriate and inappropriate shocks were analysed by expert electrophysiologist. Appropriate shocks were defined as shocks for VT or VF and inappropriate shocks were defined as shocks in absence of any ventricular arrhythmia. All Long QT Syndrome patients also underwent regular check up at pacemaker clinic and pacemaker programming was done and parameters were checked at each visit.

**DETAILS OF TESTS/INVESTIGATIONS:**

All patients underwent standard 12 lead Electrocardiogram. All baseline and drug-induced 12-lead ECGs were recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV .One intercostal space above ECG was used in cases were typical Brugada pattern was not seen in usual ECG. ECGs of family members were also recorded after taking

proper consent. QTc was calculated in lead II (or lead III or I if it could not be obtained from lead II). Repeat ECG was taken to ensure reproducibility. All ECGs were preserved. ECGs were analyzed by expert electrophysiologists.

Treadmill Test and 24 hr holter testing was carried out when indicated as per standard protocol.

All patients underwent Echocardiography to rule out structural heart disease

Cardiac MRI was done in some patients to rule out any structural heart disease if there was suspicion from initial investigations.

Some patients also underwent neurological evaluation if clinically indicated.

Tilt Table testing as per standard guidelines was done if syncope was thought to be vasovagal.

Flecainide challenge was performed when patients had Type 2 or Type 3 Brugada pattern on ECG and had other features as mentioned in Inclusion criteria previously.

Flecainide challenge was carried out as per standard protocol. Patient was kept fasting for 6 hrs .Baseline ECG was recorded. It was not done if there was any evidence of sinus node dysfunction, second or third degree AV block or bundle branch blocks .IV access was taken. Defibrillator was kept ready .Oral preparation of 400 mg of flecainide was administered after taking informed consent. Serial ECGs were recorded. Initial ECG's were taken after every 15 minutes for 1 hour and then after every 30 min till 6 hrs or changes normalized. QRS widening, PR interval and any conduction disturbance were monitored. Positive test was defined as type 1 Brugada sign on ECG.

Selected patients underwent electrophysiological testing as per institute protocol. Electrophysiological study included basal measurements of conduction intervals and programmed ventricular stimulation done as per standard protocol. The protocol used a single or double site of stimulation (right ventricular apex and or RVOT) and introduction of 1, 2, and 3 ventricular premature beats down to a minimum of 180 ms. Positive response was defined as sustained ventricular arrhythmia (Ventricular fibrillation, sustained polymorphic or monomorphic VT lasting more than 30 seconds or requiring DC version)

For Long QT patients with equivocal diagnosis, Adrenaline challenge test was done as per standard mayo protocol.

Those patients who required a pacemaker or ICD, it was accomplished as per standard guidelines. Single or double chamber ICDs were implanted taking into consideration previous history of supraventricular arrhythmia or sinus node dysfunction. ICD settings were kept based on individual clinical history and were adjusted to avoid any inappropriate therapy.

Statistical Analysis of Data are presented as mean ± SD or as absolute values and percentages, where appropriate. Comparison between continuous variables was performed using the unpaired Student t test or paired t test as appropriate. The $\chi 2$ test or Fisher exact test were used to compare categorical variables. P value $<0.05$ was considered statistically significant. Statistical analyses were conducted using the SPSS software for windows.

# Review of Literature

The two cardiac channelopathies (Brugada Syndrome and Long QT syndrome) are inherited cardiac diseases with structurally normal heart which are important cause of sudden cardiac death (SCD) in young. They have varied presentation. Many patients with these disorders remained asymptomatic throughout their life while others present with recurrent arrhythmic events and sudden cardiac death. The incidence, prevalence, clinical features of these disorders is largely unknown in Indian population due to scarcity of data. Both these disorders can mimic other conditions and can result in misdiagnosis. A detailed research and understanding of these conditions is required in our set up for better patient care.

Brugada syndrome was first described by Pedro Brugada and Joseph Brugada in 1992. They studied eight patients who had survived sudden cardiac arrest of which 6 were males and 2 were females. They excluded any cause for the characteristic ECG pattern of RBBB with ST elevation in right precordial leads like ischemia, structural heart disease or electrolyte abnormalities. The cause of aborted cardiac arrest in these patients was polymorphic VT initiated by a short coupled VPC. EPS was done in these patients which showed high VT inducibility rates (4 of the 7 patients). HV was prolonged in 4 patients. They implanted ICD in

4 patients who remained alive on long term follow up. They prescribed beta blocking agent in 2 patients for arrhythmia control and 1 patient had pacemaker while other one died. Brugada syndrome was thus first described and cause of this was unknown.(1)

The prevalence of Brugada syndrome is about 1 in 10,000 worldwide but is higher in Asian and South Asian countries reaching about 5-10 in 10,000 and is lower in European countries about 1.1 in 10,000.(3) Studies have accounted for this difference and suggested that this difference is due to an Asian specific sequence in promoter region of SCN5A.(5)

Brugada syndrome is 8-10 times more common in males (3). The cause of increased male predominance has been explained by Di deigo et al by showing increased transient outward current (Ito) in males in animal studies (6) while Shimizu et al reported higher testosterone levels responsible for predominant male presentation (7).

Begona et al 2008 studied the differences in phenotype in men and women with BrS. Total of 384 patients were studied. 272 males and 112 females. Syncope and sudden cardiac death history was significantly more common in males as compared to females.(18%, 6% vs. 14% ,1% p=0.04). Type 1 ECG pattern, degree of ST elevation and VT inducibility

was significantly higher in males as compared to females ($p<0.001$) . However conduction parameters and QTc were significantly more increased in females in response to Na channel blockers ($p=0.03$,$p=0.001$ respectively). On mean follow up of 58±48 months higher cardiac events (SCD, VF) occurred in males as compared to females. (11.6 % vs. 2.8%) ($p=0.003$). They concluded that Males present with more worse clinical profile than females and previous symptoms are risk factor for future events in male population where as in females, conduction system abnormalities can be used to risk stratify individuals for future events.(8)

The mean age of presentation of Brugada Syndrome patients is 41±15 years. Childhood presentation is rare (3). Family history of sudden death is present in 20-40% of western patients and 15-20% of patients from Japan (3,8,9,10).

Pattara et al in 2015 studied the prevalence of fever induced Brugada syndrome in Thailand. They noted ECG patterns of febrile and non febrile patients attending emergency department and found out higher prevalence of BrS in febrile group as compared to non febrile group (8% vs 0.4% $p=0.03$). Brugada pattern disappeared after fever subsided. Their study showed high incidence of fever induced Br pattern on ECG. (11)

Cardiac events in Brugada syndrome patients occurs more frequently (70-80%) during night or during sleep. Matsuo et al first described in 1999 about the circadian pattern of VF in patients with Brugada syndrome (12). Later on in 2008 Takigawa reported about the seasonal and circadian variation in the distribution of VF in patients with BRS. Takigawa et al found out that ICD shocks in BRS patients were more common between March and June (spring to early summer) ($p=0.03$) and from midnight to 6am ($p=0.0001$) (13). Mizumaki et al reported in 2004 that vagal activity influences the ST segment elevation in daily life in Brugada patients. They found the spontaneous augmentation of ST elevation occurred more frequently in patients who had history of VF as compared to those who were asymptomatic (5.7 ±2.5 times vs. 2.3 ± 2.4 times) ($p<0.01$). ST elevation was higher in the VF group when compared with the non VF group (14). Atrial fibrillation is associated with 10-20% of patients in West while as in Japanese population it occurs in 20-30% of cases. Morita H et al assessed atrial vulnerability in patients with BrS. They found out that intra atrial conduction time was prolonged in BRS patients as compared with controls (168.4 ± 17.5 vs. 131.8 ± 13.0 ms) (p 0.001) although atrial effective refractory period was same in two groups. Atrial potential duration was prolonged in BRS

group (80.3 ± 18.0 vs. 59.3 ± 9.2 ms) (p 0.001). AF was induced in 8 out of 18 patients in BrS group and in no patient in controls and thus concluded that BRS patients have increased atrial vulnerability, abnormal intra atrial conduction may be responsible for high induction rates of AF in this population (15).

The first consensus report in 2002 described the three ECG patterns in Brugada patients which have been discussed before. Several studies have been done to elucidate the natural history of BRS patients. The data from Brugada registry showed that patients presenting with initial history of resuscitated cardiac arrest or Ventricular fibrillation are at high risk of recurrence (with recurrence upto 69% on mean follow up of 54 ±54 months) .Patients with syncope and type 1 ECG had recurrence rate of 19% for follow up of 26 ± 36 months. Brugada et al also reported a recurrence rate of 8% in asymptomatic patients in their registry (16). The data from FINGER registry which studied the prognosis and risk factors of Brugada syndrome patients from France, Italy, Netherlands, and Germany however had different results. This registry recruited 1029 patients (745 men; 72%) with a mean age of 45 years from 11 tertiary centres and 4 European countries. The patients had presented with sudden cardiac arrest (6%) syncope (30%) and 64% were asymptomatic.

On median follow up of 31.9 months 5 % had cardiac events. In patients with aborted SCD, cardiac event rate per year was 7.7%, while as those with syncope it was 1.9%, and only 0.5% in asymptomatic patients. They also found out that syncope and Type 1 ECG pattern as predictors of arrhythmic events (17). The Japanese registry showed a lower rate of arrhythmic events than those of the Brugada registry. The annual rate of arrhythmic events in patients with Type-1 Brugada ECG was 10.2% in VF group, 0.6% in syncope and 0.5% in the asymptomatic group (18).

As management is not clear in asymptomatic patients several investigators have looked into other parameters to better risk stratify an individual. Makimoto H et al has investigated the significance of ST segment augmentation in early recovery phase of exercise Tread Mill test for risk stratification of individuals. TMT was performed in 93 patients with BrS (22-VF, 35-syncope, and 36 were asymptomatic) and 102 healthy controls. Augmentation of ST elevation ≥0.05mV in V1-V3 as compared with baseline was observed in 37% of BRS patients and in no patient in the control group. The group of BRS patients with augmentation of ST Segment in early recovery had higher VF events on follow up as compared to patients who had no ST segment elevation augmentation in early recovery (44% vs. 16%) (p=0.0004) (19).

Youichi et al in 2005 analyzed various factors in risk stratifying individuals with BRS. They showed that only late potentials on SAECG were significantly more common in symptomatic group as compared to asymptomatic group (92.6% vs. 42%) (p=0.0004). They showed that cut off value of RMS40 <15 microvolt had higher rates of recurrences of VF as compared to RMS40 >15 microvolt (p=0.04) (20). Morita et al analyzed the incidence of fragmented QRS in 115 BRS patients. They found out that fragmented QRS was significantly observed in more patients presenting with VF as compared to patients presenting with syncope or who were asymptomatic (VF 85%, syncope 50%, and asymptomatic 34%) (P<0.01). On follow up of 43±25 months they found out that among those without fragmented QRS and history of VF and syncope, VF occurred only in 6% as compared to patients who had fragmented QRS in which VF occurred in 58% on follow up (P<0.01) (21). Prelude registry data in 2012 also showed that presence of fragmented QRS was useful in selecting patients for ICD implantation. QRS fragmentation was a significant predictor of arrhythmic events (HR 4.94) (22). Many studies have investigated the role of programmed ventricular stimulation in risk stratifying patients with Brs. Gasparani et al in 2002 studied 21 BRS patients, EPS was done in all patients.

Stimulation was done from RVA, RVOT. Upto 3 extra stimuli were given. BCL was 600,500,400. VT inducibility rate was 18%. No patient had any event on follow up of 34±40 months (23). Brugada et al. in 2002 demonstrated that VT inducibility on programmed electrical stimulation can help in risk stratifying patients. They showed a higher incidence of cardiac events on follow up in patients with positive VT induction study as compared to patients with negative VT induction study (17 % vs. 2%) (p=0.007)(24). Brugada et al in 2003 again reported in separate study that those patients with positive VT induction have high rate of cardiac events on follow up as compared to those with negative EP study (13% vs 1.1%) (25). Juan et al from Brugada group in 2015 which is the latest large study analysed 403 patients with mean age of 43.2±16.2 years of which 58.2% (235) were males. VT inducibility was seen in 18.1% (73) patients. The mean follow up was 74 ±53 months and on follow up total of 25 arrhythmic events occurred .16 events occurred in EPS positive patients and 9 events occurred in EPS negative patients. VT inducibility had a hazard ratio for events of 8.3 ($p<0.01$). They concluded that VT inducibility is good predictor of events in BRS patients especially in asymptomatic individuals (26). Benito et al. in 2008 (Brugada group) reported a prospectively studied 384 patients for mean follow-up period

of 58 months. They found out that rate of cardiac events was significantly higher in male patients who had inducible ventricular arrhythmias as compared to those who did not have inducible ventricular arrhythmias (74.1% vs. 27.6%) (p <0.001). Inducibility of ventricular arrhythmias at PES remained an independent predictor of cardiac events with multi analysis (HR, 2.93; p=0.02) (27) Delise et al. reported in 2011 a combined clinical and electrophysiological approach for risk stratification in Brugada syndrome patients. They performed VT Induction in 245 patients with type 1 Brugada pattern ECG and no previous Cardiac arrest. During a median follow-up period of 40 months, VF or Sudden cardiac death occurred in 14% of patients with inducible ventricular arrhythmias, in no patient without inducible ventricular arrhythmias, and in 5.3% of patients without PES (p < 0.001). However they could not find single clinical risk factor, to identify patients at high risk. But they found out that Patients at the highest risk were those who had spontaneous Type 1 Brugada ECG with at least 2 risk factors: syncope, family history of sudden death, and positive PES. Combination that was best able to predict major arrhythmic events was of spontaneous type 1 Brugada, syncope, family history of sudden death, and Positive VT induction (C-statistic, 0.87; 95% CI, 0.82–0.90) (28).

PRELUDE registry (2012) was designed so as to find out the utility and predictive value of inducible arrhythmias on EPS and other predictors of cardiac events in BRS patients. They included 308 individuals (247 men, 80%; median age 44 years). VT induction was done at enrolment, and patients were followed 6 monthly. At median follow-up of 34 months, 14 (4.5%) arrhythmic events occurred (13 appropriate shocks, and 1 cardiac arrest). Nine of the 14 events occurred in the group in which VT/VF was not inducible. Factors predictive of future events included history of syncope and spontaneous Type 1 ECG (HR: 4.20), ventricular refractory period <200 ms (HR: 3.91), and QRS fragmentation (HR: 4.94) while as VT inducibility failed to show any significance for prediction of future cardiac events. (22). Eckardt et al. studied VT inducibility in 188 patients with type 1 Brugada ECG. On follow up of 40 months, only 9 patients experienced an arrhythmic event, of which 5 (56%) had inducible ventricular arrhythmias. Kaplan–Meier analysis showed that VT/VF inducibility was not a predictor of cardiac events (10). In the FINGER registry 638 individuals (62%) underwent PES. Ventricular tachyarrhythmia were inducible in 262 (41%). Previously symptomatic patients had higher rate of inducible ventricular tachyarrhythmia as compared to asymptomatic population. (46% Vs 37% p=0.02). On

median follow-up period of 31.9 months VT/VF inducibility was not independent predictor of cardiac events in multivariate analysis, (p=0.48) (17). Takagi in 2007, performed PES in 146 patients of which 31 had VF, 52 had syncope and 63 were asymptomatic. VF / VT inducibility was observed in 23 (74%), 41 (79%), and 50 (79%) patients in the VF, syncope, and asymptomatic groups, respectively (p=0.23) (29). The same group studied again in 2013 the utility of VT/VF inducibility. They performed EPS in 334 patients of which 62 had VF, 91 syncope and 181 were asymptomatic. VF/ VT inducibility was seen in 37 (60%), 66 (73%), and 121 (67%) patients in VF, Syncope, and asymptomatic groups, respectively (p=0.25). On follow up of 50 months VT/VF inducibility failed to show significance for prediction of cardiac events (p=0.2 in all patients) (30). Gehi et al did Meta analysis of 30 prospective studies consisting of total of 1545 patients. Relative risk and risk difference of an event which included syncope, ICD shock, or SCD was evaluated for various risk factors in Brugada syndrome. 785 patients underwent PES. With mean follow-up period of 32 months, VF or VT inducibility was not found to be an independent predictor of these events (HR, 1.88; p=0.27) (31). Paul et al. meta analysed 15 studies including total of 1217 patients with BrS. 1036 patients (85%) underwent PES. They found that VF or VT

inducibility was higher in symptomatic than in asymptomatic individuals (66% in VF, 55% in syncope and, 25% in asymptomatic groups). At mean follow-up period of 34 months, the VF or VT inducibility at PES failed to show an independent predictive value for the occurrence of VF or VT (HR, 1.5; p=0.399) (32). Due to conflicting results, studies involving uniform protocol of PES were conducted. Makimoto et al performed uniform PES protocol in 108 patients with type 1 Brugada ECG of which 26 had VF, 40 had syncope and 42 were asymptomatic. They delivered maximum of 3 ventricular extra stimuli delivered from the RVA and RVOT either up to ventricular refractoriness or coupling interval of upto 180 ms. First they stimulated RVA up to 2 extras then RVOT up to2 extras followed by RVA by triple extra and then RVOT by triple extra. Basic cycle length was 500 milliseconds. In 4 patients, VF or VT was induced by a single extra stimulus, while in 41 patients VT/VF got induced by double extra stimuli, and 36 patients had VT/VF inducible by triple extra stimuli. VT/VF more inducible from RVOT as compared to RVA (70% vs 30%). Mean follow-up period was 79 months. There was no increased risk of VF on follow up with inducibility of VF/VT (p=0.78). However, they noted that those patients who had inducible VF or VT by single or double extra stimuli had worse prognosis as compared to those

who got inducible VF or VT by triple extra stimuli among all the patients (p=0.004) and those without any documentation of VF (p=0.001). VF/VT with upto 2 extra had better positive and negative predictive values (36%, 87%, respectively) as compared to those with 3 extras (23%, 81%, respectively). Single or double extra stimuli at PES were found out to be adequate for a prognostic indicator in Brugada syndrome and stimulation site and coupling interval of extras had no prognostic value as indicator in Brugada patients (33). Munetake et al in 2002 examined the ECG and electrophysiological characteristics in relation to PES induced VF, and also on effect of PES-induced VF on the recurrence of cardiac events in symptomatic Brugada syndrome. 34 patients Of Brugada syndrome were studied, 22 had inducible VF while as 12 had no inducible VF. They found out that Positive EPS patients had longer QRS duration, more incidence of RBBB and late potentials, longer HV interval and longer conduction time at extra stimulation from the RVOT to the left ventricle as compared to those in the non-induced VF group. However, they were not able to find any significant difference in the recurrence of cardiac events between the two groups (36% vs. 58%) during follow up of 38 months. They concluded that induction of VF by PES actually is dependent on severity of depolarization abnormalities,

however does not predict future occurrence of cardiac events thus suggesting both depolarization and repolarization abnormalities are important in development of VF in Brugada syndrome patients. (34) Koji et al in 2014 studied the usefulness of the combination of several electrocardiographic markers on risk assessment of ventricular fibrillation patients with Brugada syndrome. The analyzed 246 patients (236 males; mean age, 47.6 ± 13.6 years) with Brugada-type electrocardiogram. 13 patients had history of VF and 40 patients with history of syncope episodes. During the mean follow-up period of 45.1 months, VF occurred in 23 patients and one patient had sudden cardiac death. QRS duration of more than 120 ms and fragmented QRS and repolarisation abnormalities including inferolateral early repolarisation were shown to be associated with future cardiac events. Inferolateral ER pattern and fragmented QRS, history of syncope and VF were independent predictors of cardiac events on multivariate analysis ($p < 0.05$). Presence or absence of ER and fragmented QRS pattern showed worse or better prognosis on Kaplan-Meier Curves (log-rank test, $p < 0.01$). Hence they concluded that VF events occurrence is associated with combination of depolarization and repolarization abnormalities and combination of these abnormalities may be helpful in

detecting high risk and low risk individuals. (35) Takashi et al in 2002 reported mechanism of the ST-T change in Brugada syndrome. Using contact electrode method they obtained monophasic action potentials from 3 patients with Brugada pattern ECG and 5 controls during open chest surgery and recorded epicardial maps. They noted a spike-and-dome configuration from epicardial sites of the RVOT in all Brugada patients but not in control patients. No abnormality was noted on recordings from RVOT endocardium in Brugada patients. A transmural current is induced because of deeply notched action potential in RV epicardium that leads to ST elevation in the right precordial leads and T wave inversion occurs due to rapid reversal of transmural gradients due to spike and dome configuration of action potential (36). Vincent et al reported the first study on Brugada syndrome in Children. They studied 31 children with mean age of 8±4 years. 10 patients had spontaneous type 1 ECG while others needed drug challenge for documentation of Type I ECG pattern. Children presented variedly including aborted sudden cardiac death in 1, syncope in 10, SVT in 1, and 17 patients were detected as part of family screening for Brugada syndrome. Fever precipitated syncope in 5 cases. ICD was implanted in 5 children; 1 patient had pacemaker and 4 children were on hydroquinidine. They

were followed for 37±23 months. On follow up, 1 child had sudden cardiac death while 2 children received an appropriate shock. There was 1 device related infection and required explantation. The patients who received shock, all were symptomatic and had spontaneous Type I ECG. (37) Giulio et al (Brugada group) reported in recent study in 2015 about the follow up of ICD events in Brugada syndrome patients. They included total of 176 patients who had undergone ICD implantation. The mean follow up was 83.8 ±57.3 months. Appropriate ICD shocks occurred in 15.9 % (28) patients while as inappropriate ICD shocks occurred in 18.7% (33) patients. Only 8 (4.5%) patients died, Spontaneous sustained Ventricular arrhythmias occurred in 17% (30) patients. 2.3% (4) patients had Electrical storm. 16% (28) patients had device-related complications. VA inducibility on PES and history of sudden cardiac death were independent predictors of appropriate shock on multivariate Cox regression analysis. They concluded that ICD therapy was helpful in treating life threatening arrhythmias in 17% of patients. Appropriate shocks were significantly associated with history of sudden cardiac death, however they also occurred in 13% of asymptomatic patients. ICD is associated with Device related complications and inappropriate shocks continue to occur despite careful programming (38).

Helder et al in 2014 assessed the long term prognosis of Brugada patients who had undergone ICD implantation. They implanted ICD in 36 patients with mean age of 41±13 (80%) males. 6 patients (16.7%) had history of aborted sudden cardiac death, 11 (30.6%) patients had history of syncope while as 19 (52.8%) were asymptomatic. 25 (69.4%) patients had Spontaneous type 1 Brugada pattern. 26 (72.2%) underwent EPS, VT/VF inducibility was seen in 84.6% (22) patients. 7 patients (19.4%) had appropriate shocks with annual event rate 2.8% during mean follow up of 74±40 months. These patients had significantly higher history of aborted SCD (54.1% vs. 6.9%; p=0.008) and nonsustained ventricular tachycardia (57.1% vs. 10.3%; p=0.016) on follow-up. Other parameters including Spontaneous type 1 ECG pattern, syncope and VT/VF inducibility had no significant association with appropriate shocks on follow up. Aborted SCD was an independent predictor of cardiac events on follow up with multivariate analysis (HR 8.07, p=0.012). Eight (22.2%) patients had inappropriate shocks during the follow-up period, which was mainly due to sinus tachycardia in five patients and device complications in other two (39). Frederec et al reported in a multicentric study in 2006 about ICD outcomes in BRS patients. Total of 220 patients from 14 centres with 183 of them being males with mean age of 46 ±12

years were included in the study. The various indications of ICD included SCD (18 patients, 8%), syncope (88 patients, 40%), or VT/VF inducibility in asymptomatic patients (99 patients, 45%). Mean follow-up was 38±27 months. 18 (8%) patients had appropriate shocks 26±33 months after follow up. The overall complication rate was 28% in Brugada patients including inappropriate shocks, which occurred in 20% of patients. Annual event rate was low (2.6%). Inappropriate shocks were more common than appropriate shocks and significant device related complications were present. (40) Frederec et al again reported in 2013 in much larger multicentric registry study about ICD outcomes in BRS patients. A total of 378 patients of which 310 were males with mean age of 46±13 years underwent ICD implantation. The various indications of ICD included SCD (31 patients), syncope (181), and 166 were asymptomatic. Mean follow-up was 77±42 months 46 (12%) patients had appropriate shocks. The appropriate device therapies at 10 year were 48% for those with history of SCD, 19% who had presented with syncope and 12% in asymptomatic group. At 10 years the rates of inappropriate shocks were 39% and lead failure rates were 29% Introduction of remote programming , long detection time and single high VF detection (>210-220) zone significantly reduced inappropriate

shocks. They concluded that though appropriate therapies are more common in symptomatic patients but are significant in asymptomatic patients as well (1%/y). Optimal programming can significantly and dramatically reduce inappropriate shock. However, lead failure continues to be a major problem in BRS patients. (41)

Long QT syndrome is genetic cardiac channelopathy characterized by delayed ventricular repolarisation manifested on ECG as prolonged QT interval. (42, 43) In 1957 a family of six siblings was reported by, Dr. A. Jervell and Dr. F. Lange- Nielsen. Four children were deaf and had history of recurrent fainting attacks. Three children had QT prolongation while one had SCD. (44) Later on it was analysed that KCNQ1 mutations result both in prolonged QT interval and sensory deafness. In 1963, Romano et al and Ward reported cases of prolonged QT in families with autosomal dominant inheritance without deafness (45, 46).

Robert G et al described in 1990 twenty three children and young adults with long QTS. The median age was 10 years and 61% had family history of LQTS. Syncope was presenting symptom in 13 (69%) of patients, aborted sudden death in 5 (26%) of patients. During follow up period of 67 patient years, there were total 3 deaths with annual mortality rate of 4.5%. Patients who died and patients who did not

respond to betablockers were significantly younger at diagnosis as compared to rest of patients (P<0.05). TMT showed significant prolongation of QTC with exercise and 24 hr holter showed T wave alterans in two patients who died on follow up (47). Mikael et al in 2015 reported long term follow up of 316 LQTS patients and reported no arrhythmic deaths on follow up. They identified QTC >500 ms to be associated with increased risk of cardiac events as compared with QTC <470 ms (p 0.001). Beta blockers significantly reduced the risk of first cardiac events (HR 0.23; p=0.001). Beta blockers were well tolerated (48). Silvia et al in 2003 reported about risk stratification of LQTS patients. They evaluated total of 647 patients (LQTS mutation type 1 386, Type 2, 206; type 3, 55). They determined according to genotype, sex and QTC interval the cumulative probability of a first cardiac event (Syncope, cardiac arrest or sudden death before 40 years age and before starting therapy). They also divided each genotype into 4 groups as per sex and QTc for analysis of risk stratification. The incidence of cardiac events was lower in LQTS 1 (30%) as compared to LQTS2 (46%) and LQTS3 (42%) (p <0.001). QTC and type of genetic locus were found to be independent predictors of risk in multivariate analysis. QTC was independent predictor of cardiac events in those who had LQTS 1 and

LQTS2 mutation while as sex was independent predictor of events in those who had LQTS 3 Locus mutation (49). Moss AJ et al in 1985 studied 196 patients with LQTS. Mean age was 24 yrs, 64% females and family history of LQTS was present in 88%. The average follow up was 26 months. Four Patients (1.3% per year) had sudden death on follow up and syncope occurred in 27 patients (8.6% per year) on follow up. History of congenital deafness and syncope, female gender and torsades de pointes or VF were independent predictors of cardiac events on multivariate analysis. Beta blockers and left stellate ganglionectomy significantly reduced occurrence of cardiac events on follow up (42). Locati et al in 1998 studied age and sex related occurrence of events in 479 probands and 1041 family members. Among probands females predominated (366- 71%). Male probands had significantly lower age at presentation as compared to female probands (8±7 vs. 14±10 years) and had significantly higher cardiac event rates by 15 years of age as compared to female probands (74% vs. 51%) ($p<0.0001$). In female probands the hazard ratio of experiencing events by 15 years age was 0.48 as compared to 1.87 by 15 to 40 years of age. This age and sex related difference was not seen in LQT2 and LQT3 carriers (50). Moss et al in 1991 prospectively investigated the long term natural course of

3343 LQTS patients from 328 families. They found out that probands usually received attention because of an episode of syncope and probands were younger (21±15 years) and had higher history of syncope, cardiac arrest, congenital deafness, longer QTC as compared to affected and unaffected family members. Syncopal episodes were often misdiagnosed as seizure disorder. Higher cardiac event rates of syncope and death were observed in probands (5% and 0.9% per year respectively) as compared to affected and unaffected family members. They concluded that a longer QTc, prior history of cardiac events and heart rate less than 60 were independent predictors of future cardiac events (43). Elder et al studied the effectiveness of combination of beta blocker and pacemaker in LQTS and showed that cardiac pacing at rates of 70-125 significantly reduced QTC from 541±62 ms to 479± 41 ms and no patient died on follow up of 55± 45 months although 10% had recurrence of symptoms. They also noted that pacemaker problems to adjust rate for QTc shortening and to avoid T wave over sensing are relatively common in this population.(51)

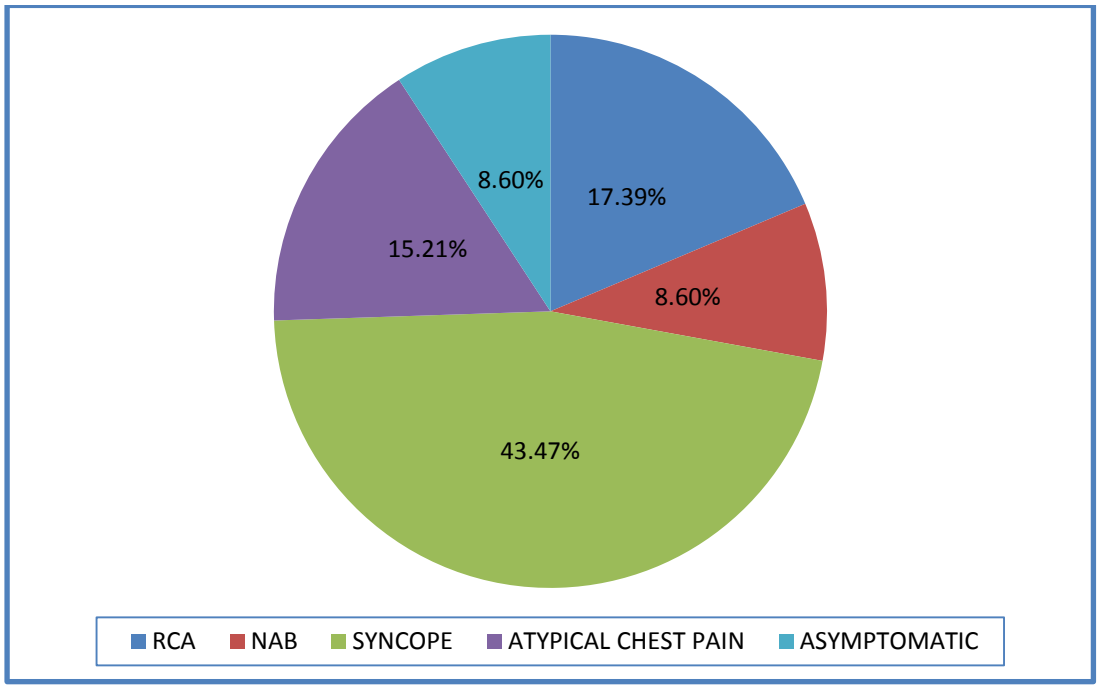
# Observations and Results

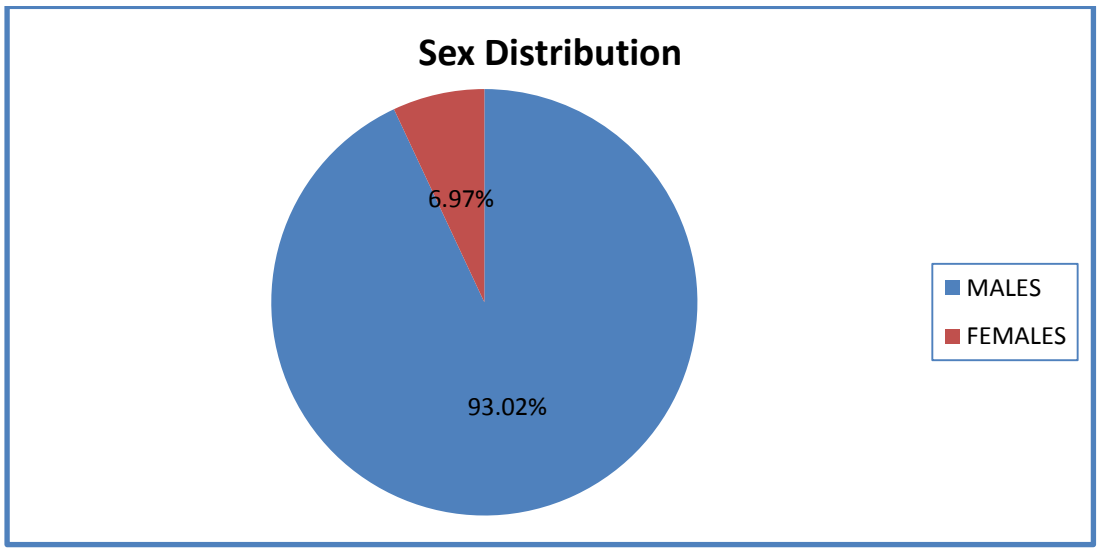
A total of 46 Brugada syndrome patients were studied. Of these 43 were males and 3 were females. The male to female ratio was 14.3:1. The mean age of presentation in our patients was 38.97 ±15.40 years. The various clinical presentations included Resuscitated cardiac arrest in 8 (17.39%), Nocturnal agonal breathing in 4 (8.6%), syncope in 20 (43.47%), atypical chest pain in 7 (15.21%), asymptomatic -4 (8.6%), Fever precipitated syncope in 26.31% of patients. Family history of sudden cardiac death was present in 13 of 46 patients (28.29 %). 3 (6.5%) of patients were misdiagnosed as STEMI, emergency CAG revealed normal coronaries.

**TABLE 1: Clinical Presentation of Brugada syndrome in our Patients**

| **CLINICAL PRESENTATION** | **PERCENTAGE** (Number) |
|---|---|
| RESUSCITATED CARDIAC ARREST | 17.39%(8) |
| NOCTURNAL AGONAL BREATHING | 8.6%(4) |
| SYNCOPE | 43.47%(20) |
| ATYPICAL CHEST PAIN | 15.21%(7) |
| ASYMPTOMATIC | 8.6%(4) |
| FHSCD | 28.29%(13/46) |
| Fever as precipitating factor | 26.31% |

**Pie Diagram of clinical presentations**



**ECG Characteristics of BrS patients**

The Mean heart rate was 64.93 ± 10.36 beat per minute .The mean PR interval was 167.76 ±28.55 ms. The mean QRS axis was 25.81±35.67 degree. The mean QRS duration was 102.34±18.4ms.The mean ST elevation was 3.57 ±1.15 mm .Type 1 Brugada pattern was present in 52.17% (23) patients, type 2 at baseline was present in 21.73% (10) patients and Type 3 was present in 6.5% (3 patients) while as 21.73% (10) patients had both type 1 and type 2 pattern intermittently.

**Table 2 : ECG characteristics of Brugada syndrome patients**

| ECG characteristics | Mean±SD |
|---|---|
| Heart Rate | 64.93 ± 10.36 |
| PR interval(ms) | 167.76±28.55 ms |
| QRS axis(degree) | 25.81 ±35.67 |
| QRS duration(ms) | 102.34 ±18.49 ms |
| ST elevation(mm) | 3.57 ±1.15 mm |
| Type 1 | 52.17%(23) |
| Type 2 | 21.73%(10) |
| Type 3 | 6.5%(3) |
| Type 1,2 | 21.73% (10) |

All patients were divided into two groups as per their clinical presentation. Group 1 included all patients who had more malignant presentation in the form of either resuscitated cardiac arrest or nocturnal agonal breathing. Group 2 included patients which had other presentations including syncope, non specific chest pain or asymptomatic. The two groups were compared in different parameters to find any factor which is more prevalent in the group with more severe presentation. Follow up events were also studied.

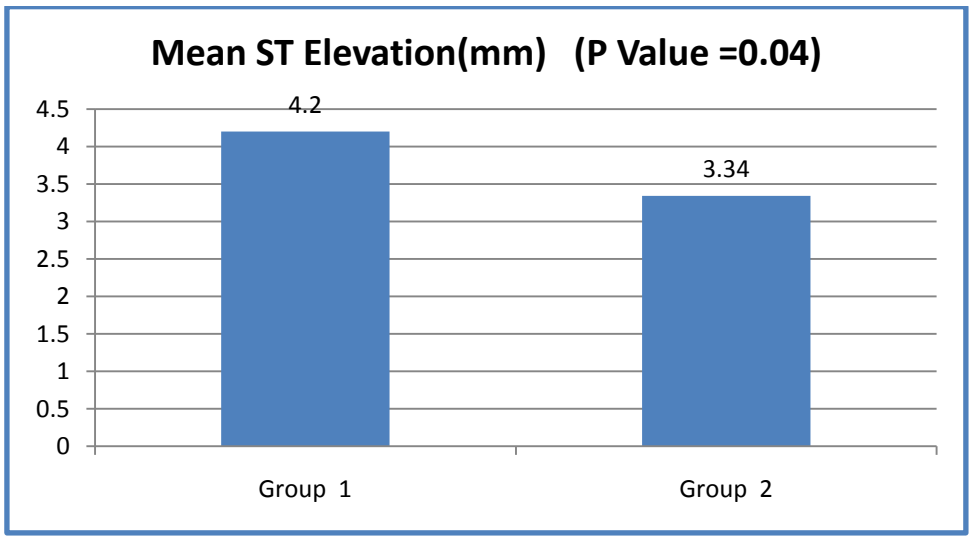
Group 1 included 12 patients, 8 had history of resuscitated cardiac arrest and 4 had history of nocturnal agonal breathing. Group 2 included 34 patients in which 20 patients had history of syncope, 7 had atypical chest pain and 4 were asymptomatic. Male to female ratio in group 1 was 11:1 while as in group 2 it was 16:1. The mean age in group 1 was 45.41 ± 11.85 years while as in group 2 it was 36.48 ±16.04 years (p =0.08). Family history of Sudden cardiac death was present in 16.66% (2/12) in group1 while as it was present in 32.25% (11/34) of patients in group2 (p=0.46).The average PR interval in group1 was 174. 16±31.56ms while as in group 2 it was 165.29±27 ms (p=0.3). The mean QRS duration was 108.58 ± 22.13 ms in group 1 while as it was 99.61±16.55ms in group2 (p=0.14). The mean ST elevation in Group1 was significantly

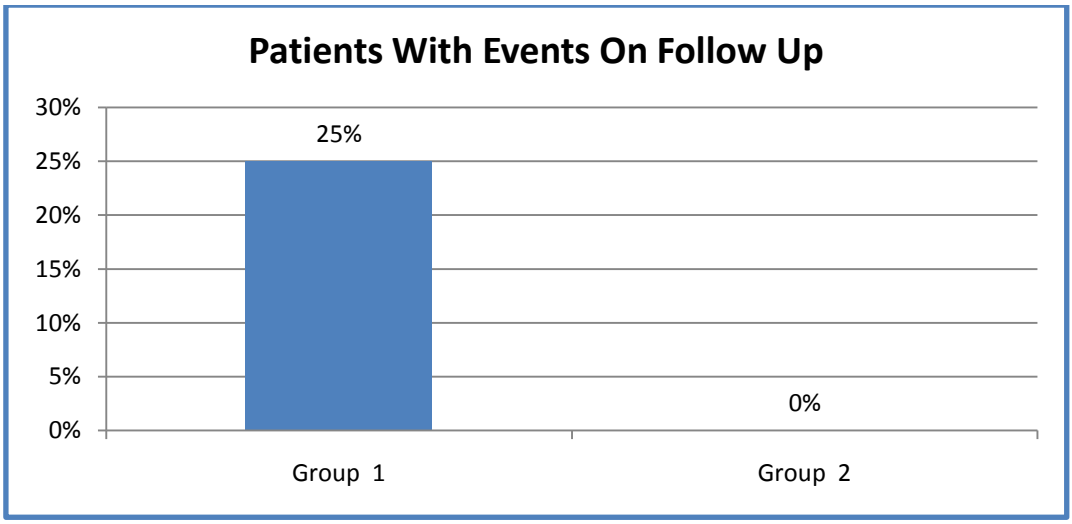
higher as compared to Group 2 (4.22±1.2 mm vs. 3.34 ± 0.97mm) (p=0.04). Type 1 pattern was present in 66.66% (8/12) in group 1 against 50% (17/34) in group 2 (p=0.5). Notched QRS or wide QRS or evidence of early repolarisation in inferolateral leads was present in 25% (3/12) of patients in group 1 as against 8.87% (3/31) in group 2 (p=0.07). The mean follow up of group 1 patients was 30.08±19.58months while as in group2 it was 26.12±22.10 months (p=0.5). **The number of patients with events (ICD shocks, Documented VF) in group1 was significantly higher as compared to group 2. (25 %( 3/12) vs 0%) (p=0.02).**

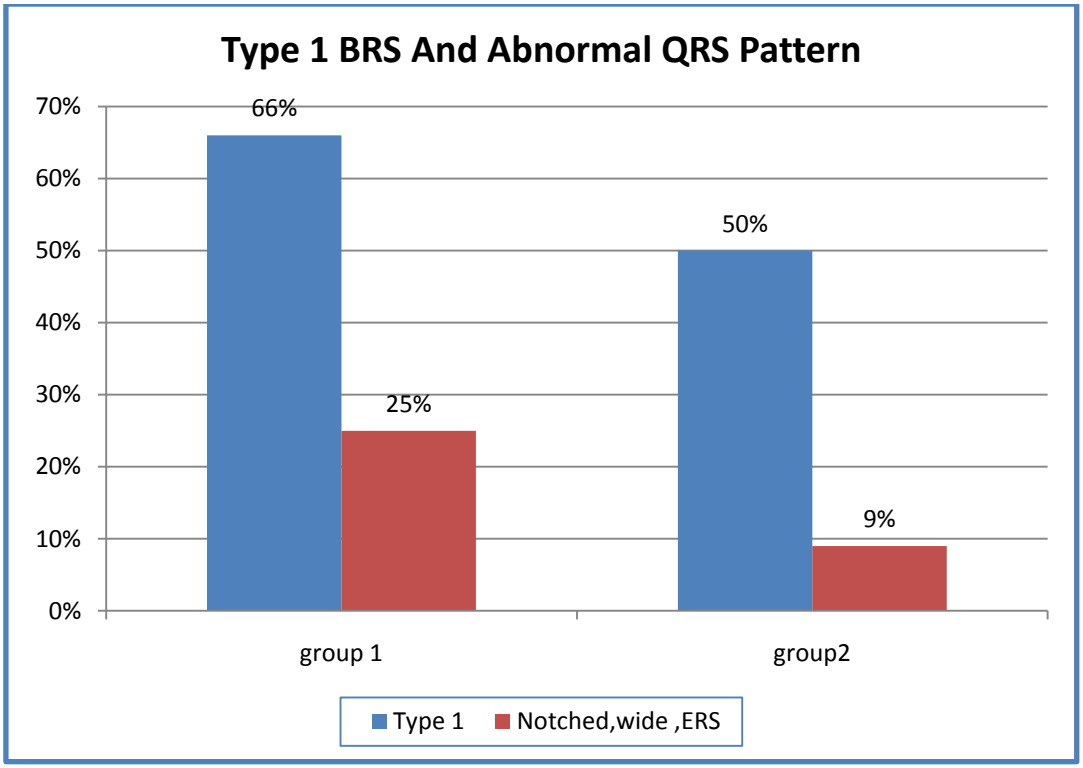
## Table 3: Patient Characteristics According To Clinical Presentation

| Clinical Parameter | Group 1 (RCA,NAB) | Group2 (Syncope, Chest Pain, Asymptomatic) | P value |
|---|---|---|---|
| Number | 26.08%(12/46) | 73.92%(34/46) | |
| Age (years) | 45.41±11.85 | 36.48±16.04 | 0.08 |
| FHSCD | 16.66% (2/12) | 32.35% (11/34) | 0.46 |
| PR(ms) | 174.16±31.56 | 165.29±27 | 0.3 |
| QRS duration(ms) | 108.58± 22.13 | 99.61 ±16.55 | 0.14 |
| **ST elevation(mm)** | **4.22± 1.2** | **3.34± 0.97** | **0.04** |
| Type 1 | 66.66% (8/12) | 50% (17/34) | 0.5 |
| Notched, Wide, ERS | 25% (3/12) | 8.8% (3/31) | 0.07 |
| Follow up (months) | 30.08 ± 19.58 | 26.12 ± 22.10 | 0.5 |
| **Number of patients with events on follow up(ICD shocks, VF)** | 25% (3/12) | 0 | **0.02** |

RCA – Resuscitated Cardiac Arrest, NAB – Nocturnal Agonal breathing, ERS –early repolarization




Patients With Events On Follow Up
30%
25%
20%
15%
10%
5%
0%
25%
0%
Group 1
Group 2


Type 1 BRS And Abnormal QRS Pattern
70%
60%
50%
40%
30%
20%
10%
0%
66%
25%
50%
9%
group 1
group2
Type 1
Notched,wide ,ERS

A total of 26 among 46 (56.52%) patients underwent Electrophysiological study with VT induction. The mean age of patients undergoing VT induction was 43.95 ± 10.49 years. 24 were males and 2 patients were females. All underwent VT induction from RV apex, 4 patients additionally also underwent stimulation from RVOT. 22 patients underwent triple extra stimuli while as 4 patients had double extra stimuli which resulted in VF. 10 patients had positive VT induction study while as 16 patients had negative VT induction study, thus giving a VT inducibility rate of 38.46%. Among those who were positive 10 had VF and 3 had sustained polymorphic VT all needed DC version at time of study to terminate the tachycardia. Of 16 patients who were considered negative for VT induction 4 had ill sustained polymorphic VT and 12 had no VT induced, none required DC version.

## Table 4: Clinical Profile Of Patients Who Underwent EP Testing

| S NO | AGE/SEX | SITE | DCL | Extras | NO STIMULI | INDUCED ARRYTHMIA | DC VERTED | POSITIVE NEGATIVE |
|---|---|---|---|---|---|---|---|---|
| 1 | 50/M | RVA | 450 | 240/220/200 | 3 | VF | Yes | P |
| 2 | 40/M | RVA RVOT | 500 | 240/200/200 | 3 | NIL | No | N |
| 3 | 33/M | RVA | 550 | 240/200/200 | 3 | SPVT | Yes | P |
| 4 | 53/M | RVA | 500 400 | 230/220/200 | 3 3 | NIL | No | N |
| 5 | 43/M | RVA | 500 | 290/210/200 | 3 | VF | Yes | P |
| 6 | 52/M | RVA | 600 | 240/220/200 | 3 | NIL | No | N |
| 7 | 36/M | RVA | 500 | 290/250 210 | 3 | ISPVT | No | N |
| 8 | 59/M | RVA | 600 | 260/220/200 | 3 | NIL | No | N |
| 9 | 24/M | RVA RVOT | 500 450 | 230/220/200 240/200/200 | 3 3 | NIL | No | N |
| 10 | 52/M | RVA | 400 | 260/220/180 | 3 | SPVT | Yes | P |
| 11 | 49/F | RVA | 500 | 230/220/200 | 3 | ISPVT | No | N |
| 12 | 53/M | RVA | 500 | 240/220/180 | 3 | NIL | No | N |
| 13 | 45/M | RVA | 400 600 | 230/220/200 230/220/200 | 3 3 | NIL | No | N |
| 14 | 46/M | RVA | 500 | 230/220/210 | 3 | ISPVT | No | N |
| 15 | 60/F | RVOT | 600 | 270/230/230 | 3 | NIL | No | N |
| 16 | 50/M | RVA | 600 | 290/250/230 | 3 | NIL | No | N |
| 17 | 31/M | RVA | 500 | 240/200 | 2 | VF | Yes | P |
| 18 | 47/M | RVA | 400 | 220/180 | 2 | VF | Yes | P |
| 19 | 32/M | RVA | 400 | 240/200 | 2 | VF | Yes | P |
| 20 | 58/M | RVA | 500 | 260/220/180 | 3 | NIL | No | N |
| 21 | 58/M | RVA | 600 | 230/220/210 | 3 | SPVT | Yes | P |
| 22 | 48/M | RVA | 500 | 230/220/200 | 3 | NIL | No | N |
| 23 | 29/M | RVA RVOT | 600 400 | 270/230/210 280/220/200 | 3 3 | NO ISPVT | No No | N N |
| 24 | 66/M | RVA | 600 400 | 230/220/210 230/220/210 | 3 3 | VF | Yes | P |
| 25 | 34/M | RVA | 500 | 240/220/200 | 3 | NIL | No | N |
| 26 | 48/m | RVA | 400 | 220/200 | 2 | VF | Yes | P |

RVA – Right Ventricle apex, SPVT – Sustained polymorphic VT, ISPVT – Ill sustained polymorphic VT, N – Negative, P - Positive

**Table 5: Baseline Characteristics Of Patients Undergoing EP Study**

| Parameter | Overall (26) | EPS positive (10) | EPS negative (16) |
|---|---|---|---|
| Age(Years) | 46.12 ± 10.49 | 46.22 ±12.26 | 46.06 ±10.69 |
| Sex M:F | 25:1 | 10:0 | 15:1 |
| Type 1 ECG | 73.07% (19/26) | 80% (8/10) | 68.75% (11/16) |
| RCA | 19.23% (5) | 40% (4/10) | 6.25% (1/16) |
| NAB | 11.5% (3) | 0 | 18.75% (3/16) |
| Syncope | 38.46% (10) | 30% (3/10) | 43.75% (7/16) |
| Atypical chest pain | 19.23% (5) | 20% (2/10) | 18.75% (3/16) |
| Asymptomatic | 11.53% (3) | 10% (1/10) | 12.5% (2/16) |
| FHSCD | 26.92% (7/26) | 20% (2/10) | 31.25% (5/16) |
| ICD Implantation | 36% (9) | 60% (6/10) | 18.75% (3/16) |

RCA:Resusciated cardiac arrest. NAB:Nocturnal agonal breathing,FHSCD :family history SCD

The mean age of patients undergoing VT induction was 43.95 ± 10.49 years. The mean age of patients who had positive EP study was 46.22 ±12.26 years while as mean age of patients who had negative EP study was 46.06 ±10.69 years. In total population, Type 1ECG pattern was present in 73.07% (19/26) patients. In all patients who underwent EP study, 5 (19.23%) presented with history of resuscitated cardiac arrest, 3 (11.5%) with nocturnal agonal breathing, 10 (38.46%) with syncope, 5 (19.23%) with atypical chest pain and 3 (11.53%) patients were asymptomatic. Family history of SCD was present in 26.92% (7/26) of patients. 36% (9/26) patients underwent ICD implantation. In EPS

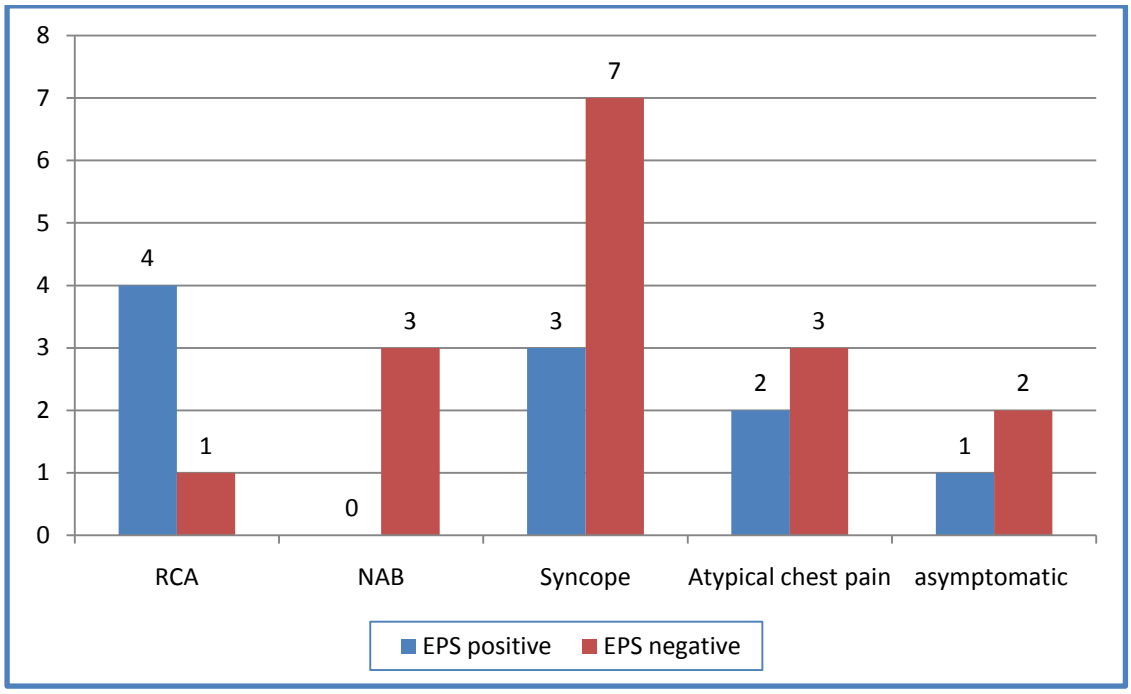
positive patients all were males while as among EPS negative patients one was female and 15 were males. Those who were EPS positive, 80% had type 1 Brugada pattern on ECG while as those negative 68.75% had type 1 Brugada pattern on ECG. EPS positive patients had history of RCA in 40% (4/10), Nocturnal agonal breathing in 0 patients, syncope in 30% (3/10), atypical chest pain in 20% (2/10), asymptomatic in 10% while as in EPS negative group these percentages were 6.25% (1/16), 18.75% (3/16), 43.75% (7/16), 18.75% (3/16), 12.5% (2/16) respectively. Family history of SCD was present in 20% (2/10) in EPS positive group while as it was 31.25% (5/16) in EPS negative group. 60% (6/10) of EPS positive patients underwent ICD implantation while as 18.75% in EPS negative group underwent ICD implantation.

Patients were analyzed as per their presenting symptom and VT inducibility rates. Those patients who presented with resuscitated cardiac arrest had VT inducibility of 80% (4/5), those with Syncope had VT inducibility of 30% (3/10), those with atypical chest pain 40% had inducible VT, asymptomatic had 33.33% of VT inducibility rate while those with nocturnal agonal breathing none had inducible VT.

**Table 6: Presenting Symptom Of EP Studied Patients**

| Clinical presentation | EPS positive | EPS negative |
|---|---|---|
| RCA | 4/5 (80%) | 1 /5 (20%) |
| NAB | 0 /3 | 3/ 3 (100%) |
| Syncope | 3/10 (30%) | 7/10 (70%) |
| Atypical chest pain | 2 /5 (40%) | 3/ 5 (60%) |
| Asymptomatic | 1/ 3 (33.33%) | 2 /3 (66.67%) |

RCA – Resuscitated Cardiac Arrest, NAB – Nocturnal Agonal breathing




All patients were divided into two groups, those who presented with history of resuscitated cardiac arrest and other presentation.

5 patients had presented with history of resuscitated cardiac arrest while 21 patients had other presentation.

Of 5 patients who presented with history of resuscitated cardiac arrest 4 had positive VT induction study (80%).

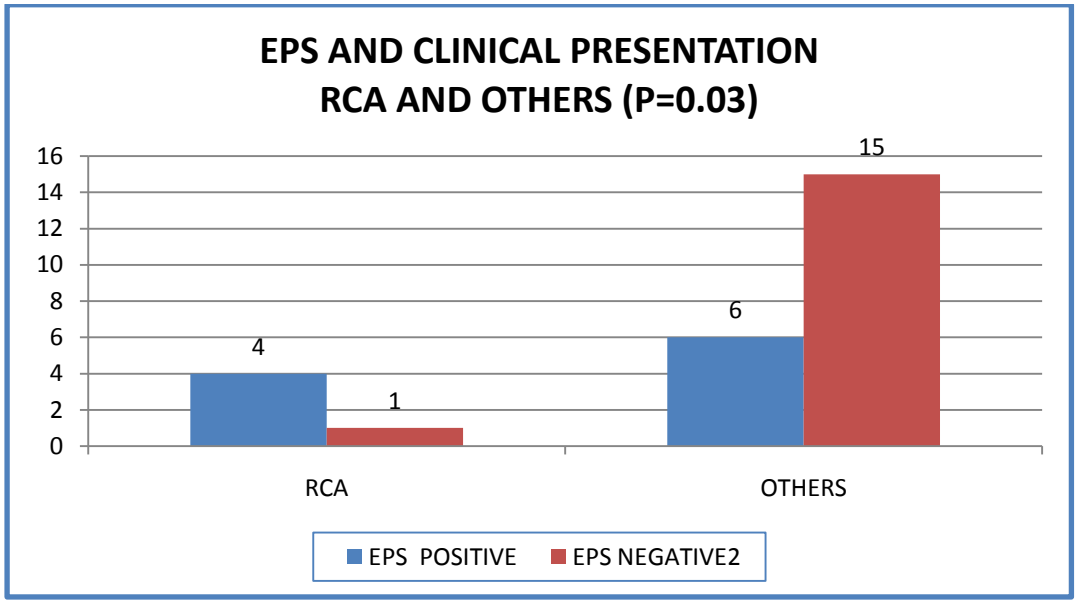
Of other 21 patients 6 (28.57%) had positive VT induction study.

The difference between two groups in terms of VT inducibility was significant (p=0.03)

**Table 7: Clinical Presentation and VT inducibility**

| CLINICALPRESENTATION | EPS POSITIVE | EPS NEGATIVE | P VALUE |
|---|---|---|---|
| RCA | 4 (80%) | 1 (20%) | **0.03** |
| OTHERS | 6 (28.57%) | 15 (71.43%) | |

RCA: Resuscitated cardiac arrest, OTHERS: Syncope, asymptomatic, chest pain, NAB




All patients who underwent EP study were followed for mean period of 27.08 ± 23.56 months. 9 Patients had ICD (6 EPS positive and 3 EPS negative. Those patients who underwent ICD, one patient had inappropriate shock, another had documented VF with aborted shock

both EPS positive. The other 7 ICD patients had no shock. Other 17 patients were asymptomatic on follow up with no significant events.

**Table 8:Follow up of EP studied patients**

| EVENTS | EPS POSITIVE | EPS NEGATIVE | MEAN FOLLOW UP |
|---|---|---|---|
| ICD SHOCKS | 1 INAPRPOPRIATE SHOCK | NIL | 27.08 ± 23.56 months |
| DOC VF | 1 VF | NIL | |
| SCD | NIL | NIL | |
| SYNCOPE | NIL | NIL | |

Total of 14 Brugada syndrome patients underwent ICD implantation. The mean age of patients at ICD implantation was 47.28 ± 11.63 Years. 13 were males, one was female .The indications of ICD included resuscitated cardiac arrest in 7 (50%), Nocturnal agonal breathing in 3 (21.4%) patients, syncope 3 (21.4%) and inducible VT in 1 (7.1%). Family history of SCD was present in 2 (14.28%) patients. 10 (71.42%) patients had spontaneous type 1 ECG while as 4 (28.58%) patients had Type 2 ECG on baseline. Out of 14 patients, 8 (57.14%) patients underwent EP study. Out of 8 patients, 5 (62.5%) patients had EP study positive. Those who had positive EP study, among them 4 (80%)

had VF and one had Sustained Polymorphic VT. Out of three patients who had negative EP study, one had ill sustained polymorphic VT and two had no VT induced.

**Table 9: Baseline Characters Of ICD Patients**

| SNO | AGE/SEX (years) | INDICATION | FHSCD | TYPE | EPS | F/U months |
|---|---|---|---|---|---|---|
| 1 | 46/m | NAB | no | 1 | -ve | 10 |
| 2 | 52/m | RCA | No | 1 | ND | 31 |
| 3 | 32/m | RCA | No | 2 | +ve | 37 |
| 4 | 47/m | RCA | No | 1 | +ve | 39 |
| 5 | 58/m | Syncope | Yes | 2 | -ve | 11 |
| 6 | 49/f | NAB | No | 2 | -ve | 2 |
| 7 | 52/m | EPS positive | No | 1 | +ve | 8 |
| 8 | 69/m | NAB | No | 1 | ND | 38 |
| 9 | 30/m | RCA | No | 1 | ND | 47 |
| 10 | 40/m | RCA | No | 1 | ND | 34 |
| 11 | 43/m | RCA | No | 2 | +ve | 72 |
| 12 | 65/m | RCA | No | 1 | ND | 25 |
| 13 | 46/m | Syncope | Yes | 1 | ND | 29 |
| 14 | 33/m | Syncope | No | 1 | +ve | 90 |

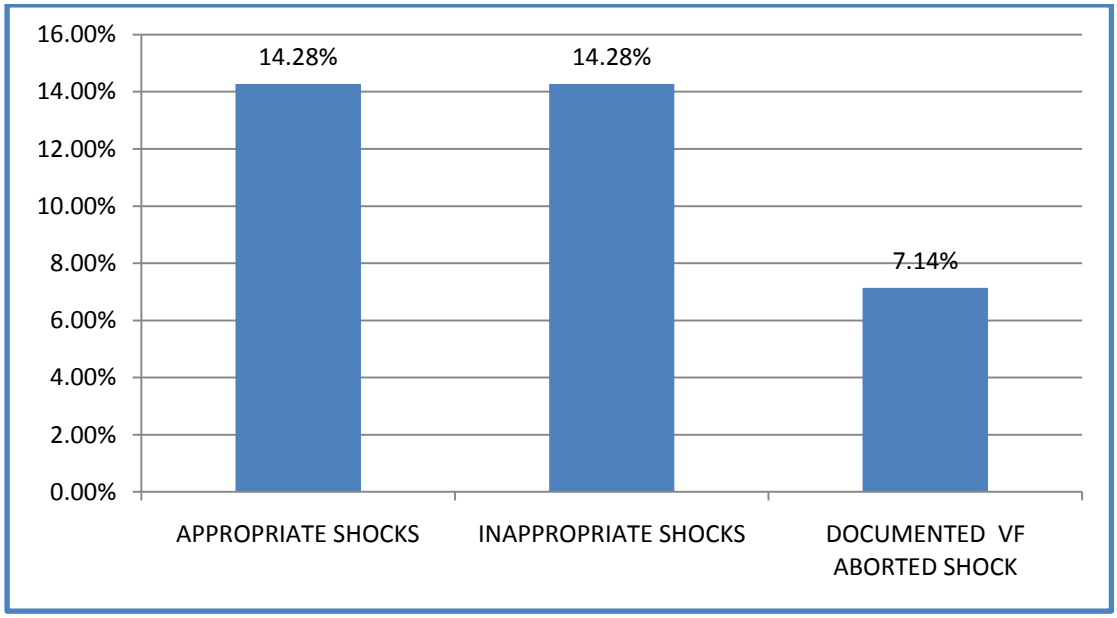
RCA – Resuscitated Cardiac Arrest, NAB – Nocturnal Agonal breathing, ND – Not done

## ICD Follow up and outcomes

The Mean follow up of patients was 33.78±24.36 month appropriate shocks were in **2 (14.28%)** patients, (5 in one patient, 1 in one patient). Inappropriate shocks were in **2 (14.28%)** patients (2 in one patient and one in one patient).One patient had VF with aborted shock. No patient had device related complications. Both patients who had appropriate shocks had history of aborted SCD.

**Table 10: Follow up of ICD patients**

| Appropriate shocks | Inappropriate shocks | Documented VF, aborted shock | Device related Complication | Follow up |
|---|---|---|---|---|
| 14.28%(2/14 | 14.28%(2/14 | 7.14%(1/14) | 0 | 33.78±24.36 months |



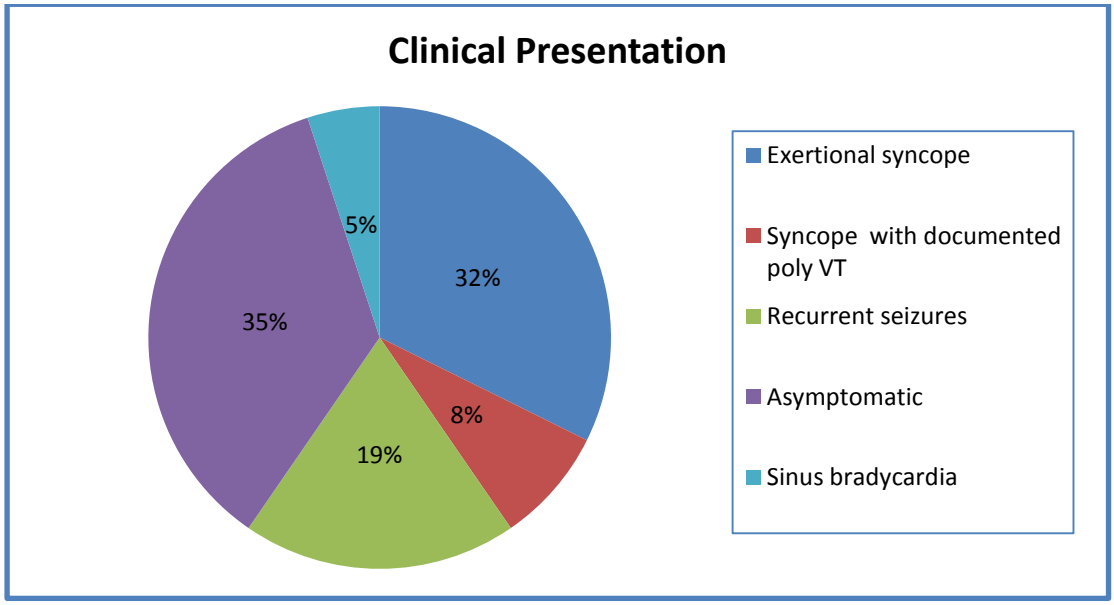
## RESULTS: LQTS Patients

Total of 37 patients were studied, of which 21 were probands and 16 were family members. Mean age of all patients was 16.72±14.31 years. 21 were females and 16 were males. The mean follow up was 4.01±6.44 years.

The clinical presentations included exertional syncope in 32.43% (12) patients, seizures in 18.91% (7), Syncope with documented polymorphic VT in 8.1% (3) patients, sinus bradycardia in 5.4% (2) patients, asymptomatic in 35.13% (13). Congenital deafness was present in 13.51% (5) patients. Family history of LQTS was present in 38.09% (8/21) patients. Family history of SCD was present in 5.4% (2) patients.

## Table 11: Clinical characteristics of our population

| Clinical Presentation | Percentage (number) |
|---|---|
| Exertional syncope | 32.43% (12) |
| Syncope with documented polymorphic VT | 8.1% (3) |
| Recurrent seizures | 18.91% (7) |
| Asymptomatic | 35.13% (13) |
| Sinus bradycardia | 5.4% (2) |
| Congenital deafness | 13.51% (5) |
| Family history of LQTS | 38.09% (8/21) |
| Family history of SCD | 5.4% (2) |




ECG of all patients were analyzed and were divided into three types as per T wave morphology. Type 1 LQTS was most common pattern (81.08% 30/37) followed by Type 3 (5.4% 3/37) and LQTS Type 2 was seen only in 2 patients (5.4% 2/30). The mean QTc of the patients

was 531.96± 56.85ms. The mean heart rate was 67.48±11.20. T wave alterans was documented in 2 (5.43%) patients of whom one patient underwent pacemaker due to recurrent syncope. Type 1 ECGs were analyzed and it was found that 3 patients had infantile pattern of Type 1 ECG and rest had broad based T waves.

**Table 12: ECG characteristics of the LQTS patients**

| Parameter | Percentage (Number) |
|---|---|
| Type 1 LQTS | 81.08% (30/37) |
| Type 2LQTS | 5.40 %(2/37) |
| Type 3 LQTS | 13.51% (5/37) |
| T wave alterans | 4. (2/37) |
| Mean QTC (ms) | 531.96 ± 56.85 |
| Mean heart rate | 67.48±11.2 |

7 (18.91%) patients presented with history of recurrent seizures. The mean age at symptom onset was 5.42 ± 5.5 years. Among them 6 were males and 1 was female. The mean delay in diagnosis was 3.07± 3.11 years. Congenital deafness was present in 3(4.85%) patients. Family history of LQTS was present in 14.28% (1/7) of patients. All had Type 1 ECG pattern of LQTS. The mean QTc was 548.57± 59.77 ms. The neurological evaluation of all patients was normal. All patients had poorly controlled seizures and were on multiple antiepileptics. The mean follow up of patients was 9.27±6.4 years.

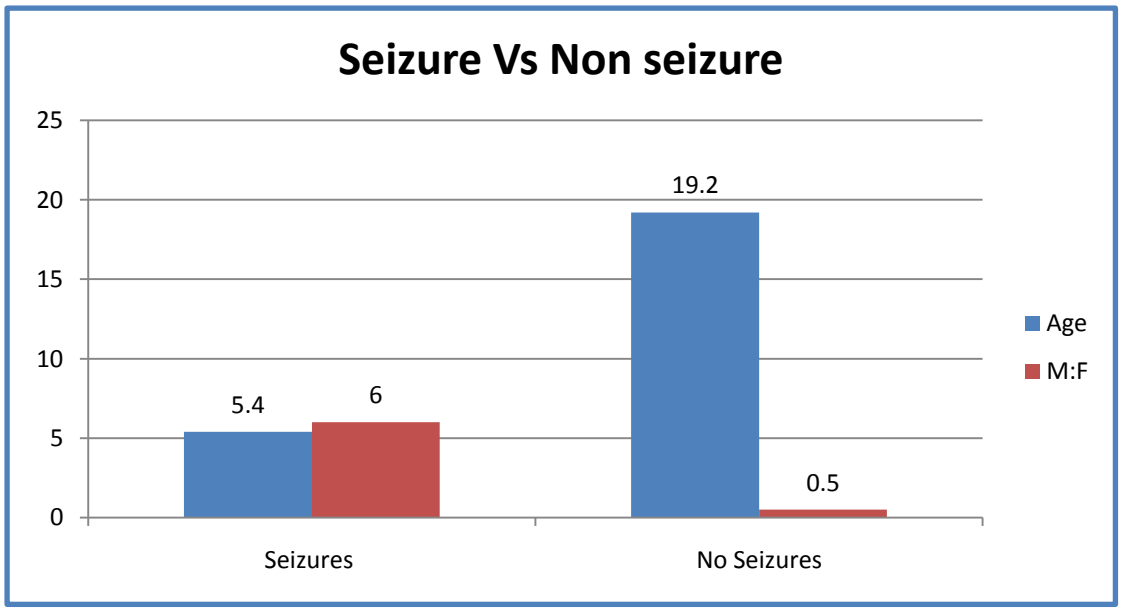
**Table 13 Clinical Characteristics Of Patients Presenting As Seizures**

| | |
|---|---|
| Mean age at presentation(years) | 5.42 ±5.5 years |
| Sex (M:F) | 6:1 |
| Mean delay in diagnosis | 3.07 ± 3.11 years |
| Congenital deafness | 42.85%(3/7) |
| Family history of LQTs | 14.28%(1/7) |
| Type of LQTS (ECG) | Type 1 |
| Mean QTC(ms) | 548.57 ±59.77 |
| T wave abnormalities | 1 patient T wave alterans |
| Neurological evaluation-EEG, CT | Normal |
| Poorly controlled seizures | All |
| Multiple antiepileptics | All |
| Mean follow up | 9.27 ± 6.44 years |

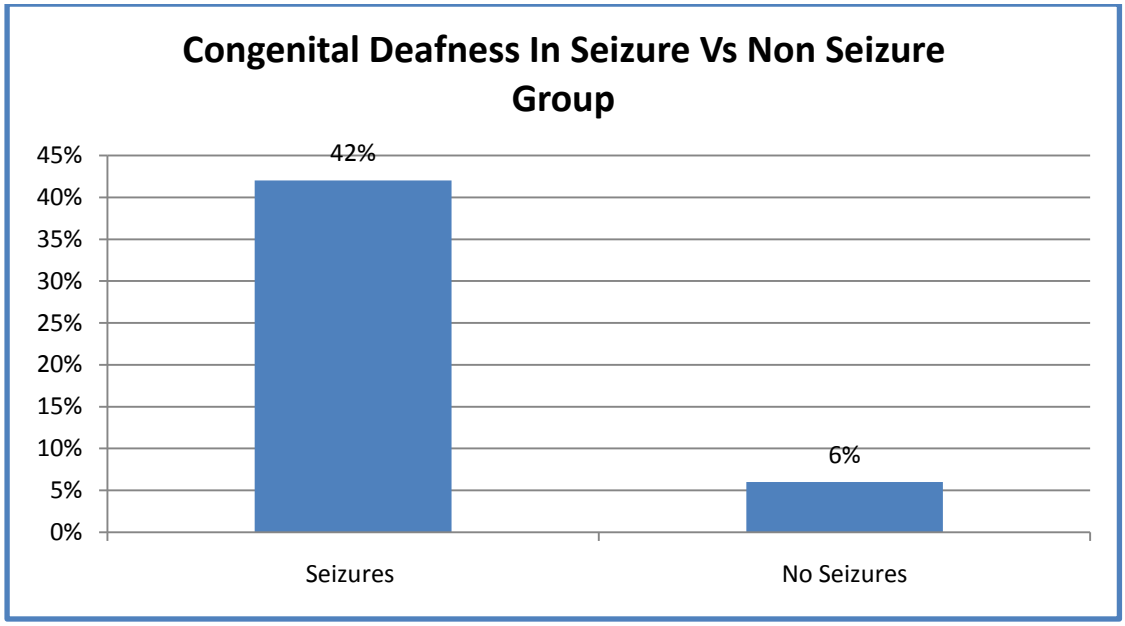
The patients presenting with history of seizures were compared with those presenting without seizures. **The mean age of presentation of patients with seizures was significantly less (5.42 ±5.55 years vs. 19.25±14.20 years) as compared to those without seizures. (p=0.016). Also those presenting with seizures were predominantly males (6:1 vs. 1:2) as compared to other group which had more females (p=0.02). There was significantly greater history of congenital deafness in patients presenting with seizures (42.85% vs. 6.66% p=0.03)**. The mean QTc was also higher in seizure group (548.57 ±59.77 vs. 530.42 ± 57ms p=0.45) however it was not statistically significant. No patient in seizure group had family history of SCD, however in other group 2 patients had family history of SCD (p= 1.0).

**Table 14: Comparison Of Patients Presenting As Seizures Vs Those Without Seizures**

| Clinical parameter | Seizure (7) | Non seizure (30) | P value |
|---|---|---|---|
| Age (years) | 5.42 ±5.55 years | 19.25±14.20 years | **0.016** |
| Sex M:F | 6:1 | 1:2 | **0.02** |
| Congenital deafness | 42.85% (3/7) | 6.66% (2/30) | **0.03** |
| FH SCD | 0 | 6.6% (2/30) | 1.00 |
| Mean QTC(ms) | 548.57 ±59.77 | 530.42 ± 57 | 0.45 |




Age (in years) (p=0.016)

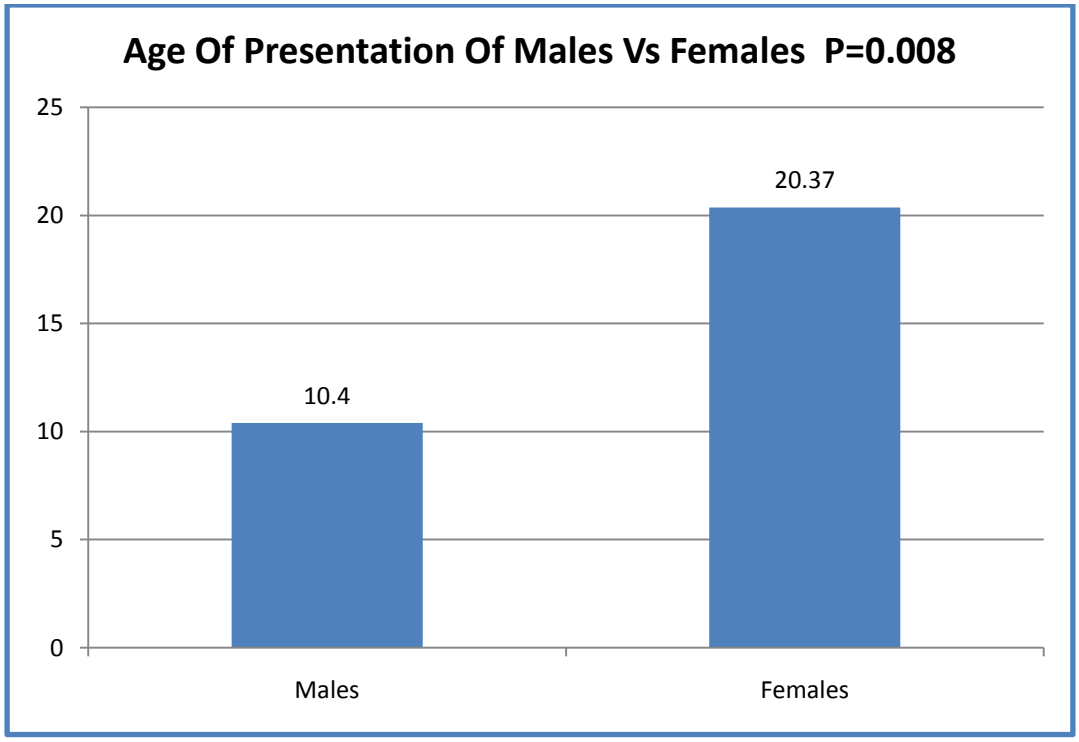


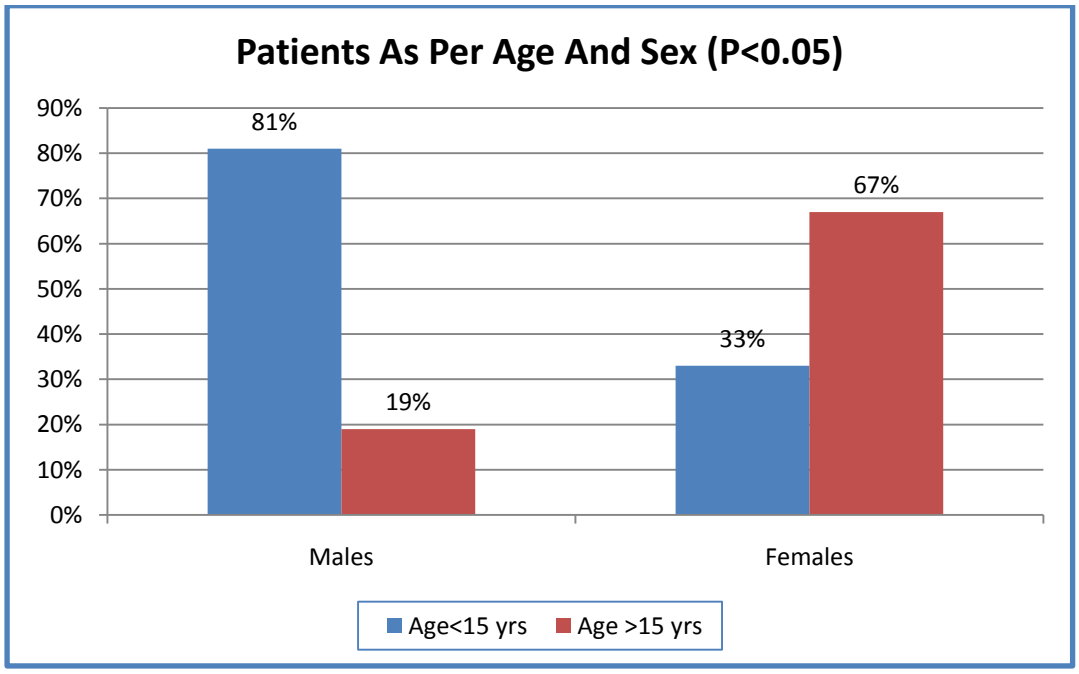

Total number of males were 16 and females were 21. In males probands were 11 (68%) in number while as in females probands were 10 (47.76%) in number (p=0.31). In males family members were 5 (31.25%) while in females family members were 11 (52.38%). (p=0.1). **The mean age of presentation of males was significantly lower as compared to females (10.4±12.94 vs. 20.375±8.66 years p=0.008). In age group less than 15 years, males were significantly more as compared to females (81.25% 13/16 vs. 33.33% 6/21 p=0.002).In age group more than 15 years , females were significantly more than males (66.66% 15/21 vs. 18.5% 3/16; p=0.002).** History of cardiac events between two groups was not statistically significant although it was higher in males as compared to females (75% 12/16 vs. 42.85% 9/21

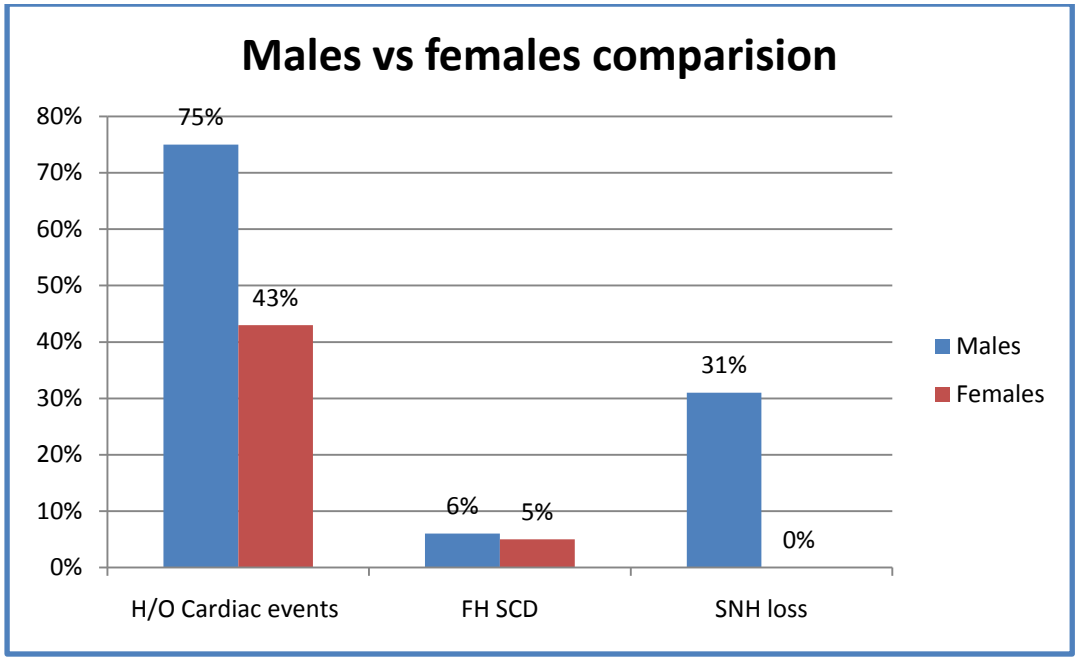
p=0.093). The frequency of family history of sudden cardiac death was similar between two groups (males vs. females 6.25% vs. 4.76% p=1.00). **The mean QTC in males was significantly higher as compared to female patients (556.61± 58.25 vs. 521.11±24.58 ms p=0.016).** The mean heart rate in both groups was similar (males vs. females 68.85±12.40 vs. 66.11 ±10.19 p=0.46). **The incidence of congenital deafness was significantly higher in males as compared to females (31.25% vs. 0% p =0.01)**.The patients having QTc more than 500 ms was similar between the two groups. (Males vs. females 84.6% vs. 66.66% p=0.41).

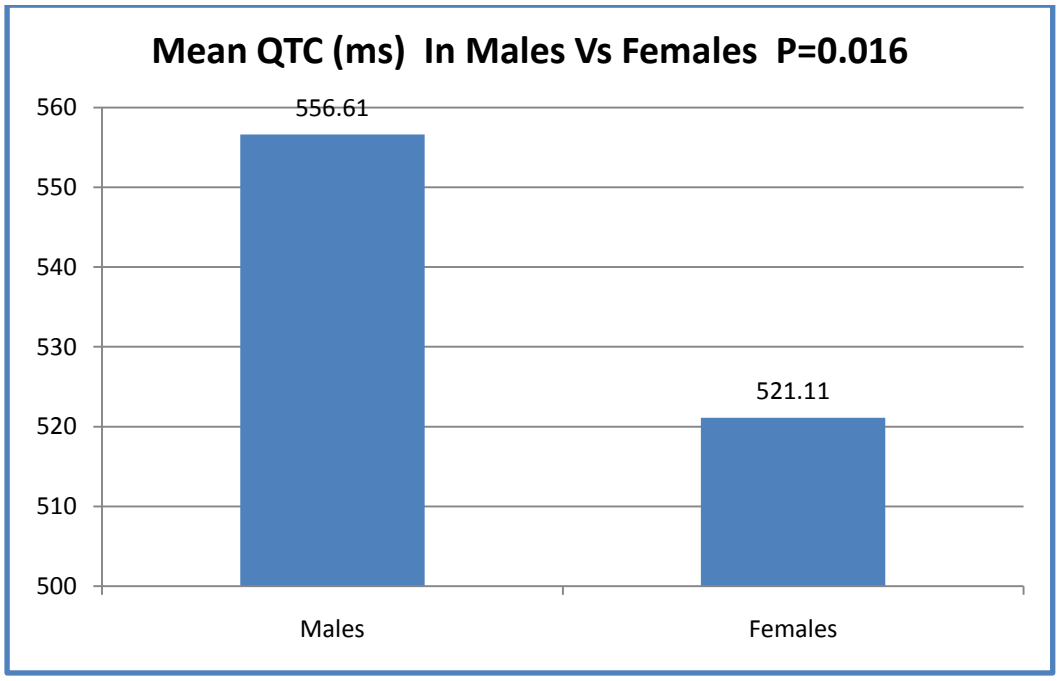
**Table 15: Clinical Features As Per Gender**

| Clinical parameter | Males | Females | P value |
|---|---|---|---|
| Number | 16 | 21 | |
| Index patient | 11 (68.75%) | 10 (47.76%) | 0.31 |
| Family member | 5 (31.25%) | 11 (52.38%) | 0.11 |
| Mean age(years) | 10.4 ± 12.94 | 20.375 ± 8.66 | **0.008** |
| Age<15 | 81.25% (13/16) | 33.33% (6/21) | **0.002** |
| Age >15 | 18.5% (3/16) | 66.66% (15/21) | **0.002** |
| History of cardiac events | 75% (12/16) | 42.85% (9/21) | 0.093 |
| FHSCD | 6.25% (1/16) | 4.76% (1/21) | 1.00 |
| Mean QTc (ms) | 556.61± 58.25 | 521.11 ± 24.58 | **0.016** |
| Heart rate | 68.85± 12.4 | 66.11 ±10.19 | 0.46 |
| SNH loss | 31.25% (5/16) | 0% | **0.01** |
| QTC>500ms | 84.6% (11/13) | 66.66% (12/18) | 0.41 |


Age Of Presentation Of Males Vs Females P=0.008
25
20
15
10
5
0
10.4
20.37
Males
Females


Patients As Per Age And Sex (P<0.05)
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
81%
19%
33%
67%
Males
Females
Age<15 yrs
Age >15 yrs

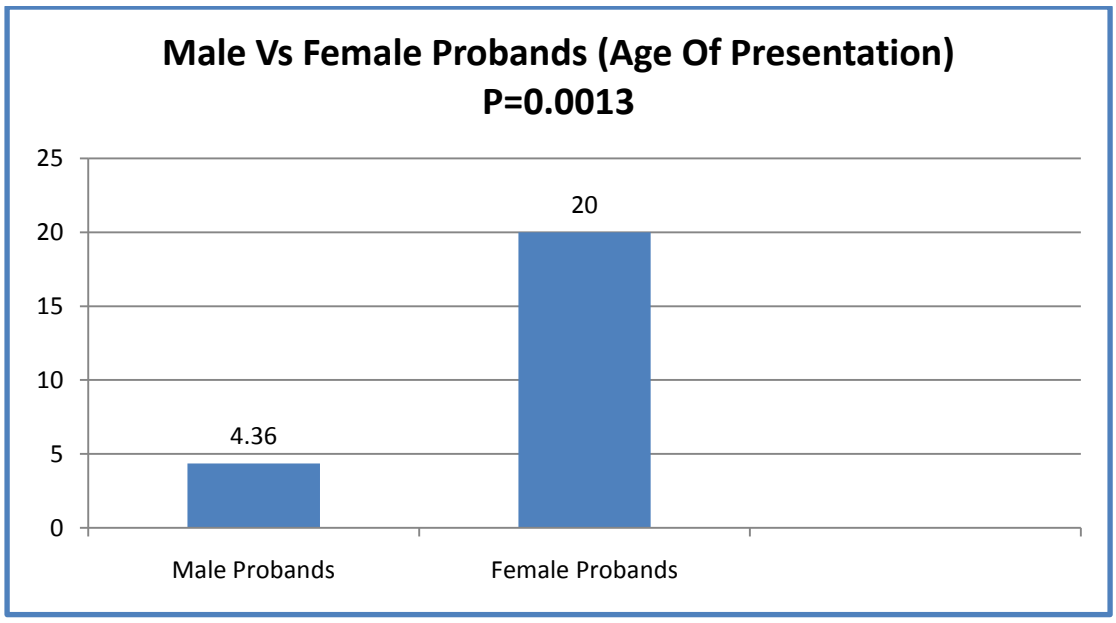

Males vs females comparision
80%
70%
60%
50%
40%
30%
20%
10%
0%
75%
43%
6%
5%
31%
0%
H/O Cardiac events
FH SCD
SNH loss
Males
Females

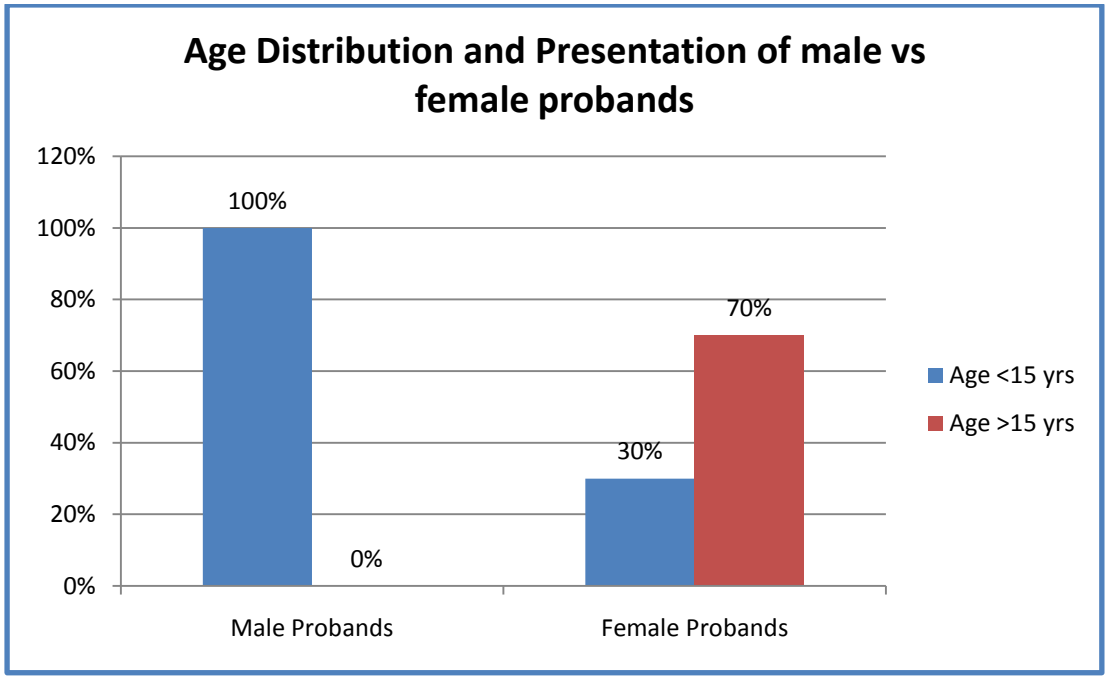

Mean QTC (ms) In Males Vs Females P=0.016
560
550
540
530
520
510
500
556.61
521.11
Males
Females

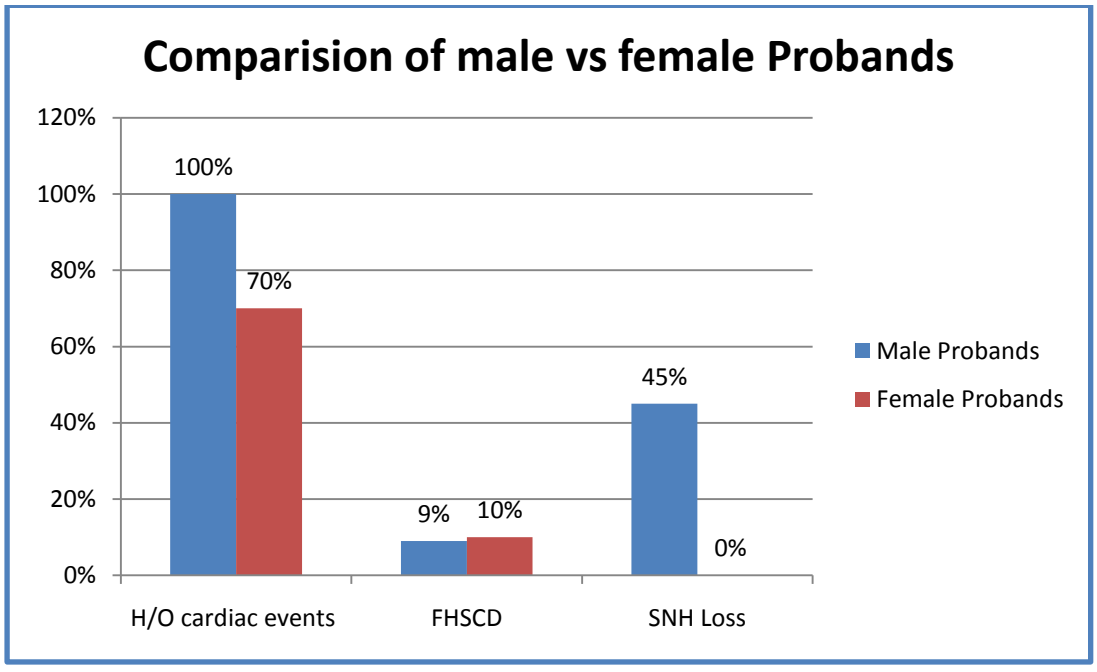
We also compared male probands with female probands. Male probands were 11 in number while as female probands were 10 in number. **The mean age of presentation of male probands was significantly lower as compared to female probands (4.36± 3.88 vs. 20 ±12.52 p=0.0013).** The incidence of cardiac events was more in male probands as compared to female probands, however it did not reach statistical significance. (100%; 11/11 vs 40%; 4/10, p=0.09). **Males were significantly more common in age group less than 15 years as compared to female probands (100% 11/11 vs. 30% 3/10 p=0.003). However in age group more than 15 years, females predominated significantly more than males (70% 7/10 vs. 0% females vs. males p=0.003)**. Family history of sudden cardiac death was similar between the two groups (9.09% vs. 10% male vs. females p= 1.00). **History of congenital deafness was significantly higher in male probands as compared to female probands (45.45% 5/11 vs. 0% males vs. females p=0.03**. The mean QTc although higher in male probands than female (568.66 ± 60.65 ms vs. 529± 28.75 ms p=0.07) did not reach statistical significance.

**Table 16: Comparison of male and female probands**

| Clinical Parameter | Male probands | Female probands | P value |
|---|---|---|---|
| Number | 11 | 10 | |
| Age at presentation (yrs) | 4.36± 3.88 | 20± 12.52 | **0.0013** |
| History of cardiac events | 100% (11/11) | 70% (7/10) | **0.090** |
| Age <15 | 100% (11/11) | 30% (3/10) | **0.003** |
| Age >15 | 0% (0/11) | 70% (7/10) | **0.003** |
| FHSCD | 9.09% (1/11) | 10% (1/10) | 1.00 |
| SNH loss | 45.45% (5/11) | 0% | **0.03** |
| Mean QTC(ms) | 568.66 ±60.65 | 529 ± 28.75 | 0.07 |




Age Distribution and Presentation of male vs female probands
120%
100%
80%
60%
40%
20%
0%
100%
0%
30%
70%
Male Probands
Female Probands
Age <15 yrs
Age >15 yrs


Comparision of male vs female Probands
120%
100%
80%
60%
40%
20%
0%
100%
70%
9%
10%
45%
0%
H/O cardiac events
FHSCD
SNH Loss
Male Probands
Female Probands

We also compared male and female family members with each other. The mean age of diagnosis between two groups was similar (24.79±16.13 vs. 26 ± 18.14 years p=0.89).The incidence of cardiac events between two groups was similar (18.81% vs. 0% p=1.00).The percentage of male and female family members in age group less than and more than 15 yrs was similar (p=1.00).No patient had family history of Sudden cardiac death. The mean QTc between two groups was similar (509.63 ± 22.21 ms vs. 507.36±12.67 p= 0.83)

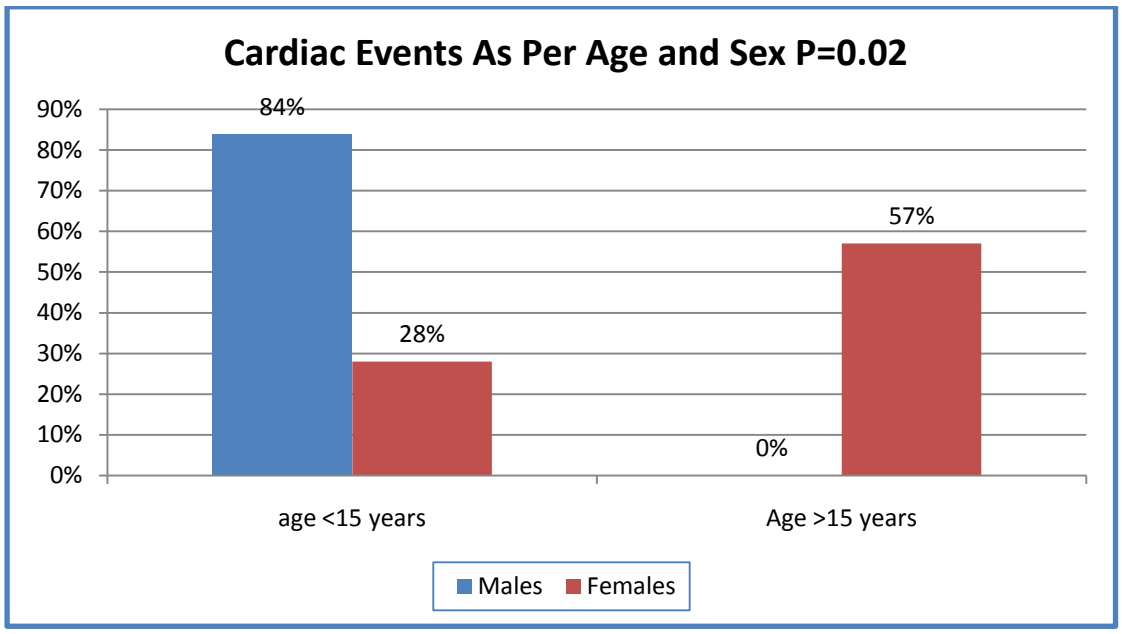
**Table 17: Comparison of male and female family members**

| Clinical Parameter | Female family member | Male family member | P value |
|---|---|---|---|
| Number | 11 | 5 | |
| Age at presentation years | 24.79±16.13 | 26±18.14 | 0.89 |
| History of cardiac events | 18.81 % (2/11) | 0% (0/5) | 1.00 |
| Age<15 | 27.27% (3/11) | 40% (2/5) | 1.00 |
| Age>15 | 72.73% (8/11) | 60% (3/5) | 1.00 |
| FHSCD | 0 | 0 | |
| SNH loss | 0 | 0 | |
| Mean QTC ms | 509.63±22.21 | 507.36±12.67 | 0.83 |

Male and female patients were also divided into two groups to study influence of age in clinical presentation. **In the age group less than 15 years the cardiac events were significantly higher in males as compared to females (males vs. Females 84.61% (11/13) vs. 28.57% (2/7) p=0.02).** In age group more than 15 years of age the cardiac events were higher in females as compared to males, however it did not reach statistical significance (57.14% (8/14) vs. 0/3 (0%) p =0.2).

**Table 18 Clinical events as per age**

| Clinical events | Age <15 years | Age >15 years |
|---|---|---|
| Males | 84.61% (11/13) | 0/3 (0%) |
| Females | 28.57% (2/7) | 57.14% (8/14) |
| **P value** | **0.02** | 0.2 |



**Follow Up of patients**

All symptomatic patients were put on beta blockers. Mean follow up was 4.01 ±6.44 yrs. Last follow up, the mean dose of propranolol was 3.25± 0.94 mg/kg. Six patients underwent PPI (AAI -2, VVI-2, DDD-2). 2 patients were on metoprolol and one patient was also additionally on mexilitine. One patient had stellate ganglion block, however was lost to follow up after that procedure.

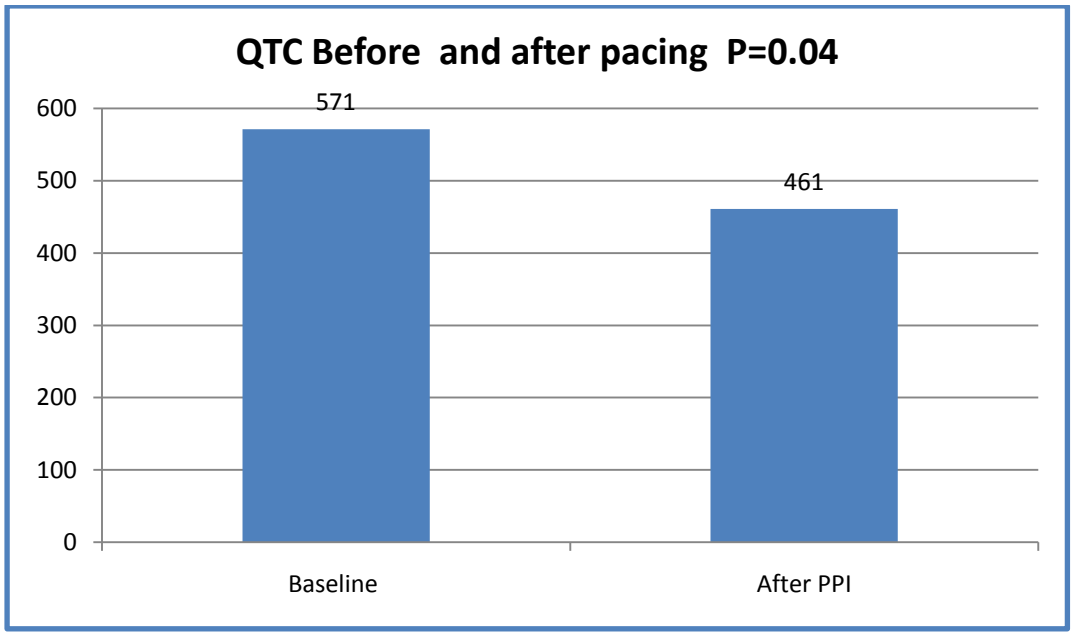
**Table 19: Patients on betablockers**

| **Follow up** | **4.01±6.44 years** |
|---|---|
| Mean dose on last follow up | 3.25±0.94 mg/kg |
| Type | Propanolol |
| Others | 2 patients on metoprolol, 1 on mexilitine |

Total of 6 patients underwent pacemaker implantation. The mean age of pacemaker implantation was 11.4±6.6 years. Three patients were males and three were females. The indications included recurrent syncope despite beta-blocker and conduction system disease. All patients had Type 1 LQTS (ECG, clinically) except one patient who had type 3 LQTS. The mean follow up of pacemaker implanted patients was 7.86± 13.01 years. **The mean QTC before Pacemaker implantation was 571.83± 77.23 ms. After Pacemaker implantation the mean QTc significantly decreased to 461 ± 18.01 ms.(p=0.04)**

**Table 20 : Patients on Pacemaker plus beta blockers**

| **Number** | **6** |
|---|---|
| Age years of implantation | 11.4 ± 6.6 |
| Sex | 3 males 3 females |
| Type | 2DDDR, 2VVI,2AAI |
| Type of LQTS | 5 patients Type 1, one patient type 3 |
| Indications | Recurrent syncope despite beta blockers, conduction system disease |
| Mean follow up years | 7.86 ± 13.01 |
| Events | 2 patients had recurrent syncope despite beta blockers at EOL of pacemaker |
| PG Change | 2 patients had PG change (1 patient twice changed) |
| Baseline QTC | 571.83 ± 77.23 |
| Follow up QTC(post Pacing) | 461 ± 18.01 |
| P value | **0.04** |



One patient died on follow up at age of 13 years (non compliance with medications). Recurrent syncope occurred in two (5.4%) patients who were on pacemaker when end of life of pacemaker had reached despite being on betablockers. 2 patients underwent PG change, one patient had twice PG change. There were no device related complications on follow up. Other patients remained asymptomatic on betablockers.

**Table 21: Events on follow up**

| Event | Number(percentage) |
|---|---|
| Death | 1 (2.70%) |
| Recurrent syncope | 2 (5.4%) |
| Device related complications | 0 |
| PG Change | 3 |
| Mean follow up years | 4.01±6.44 years |

**Fig 1: 24 Hour Holter Recording Of LQTS Patient Showing T Wave Alterans**

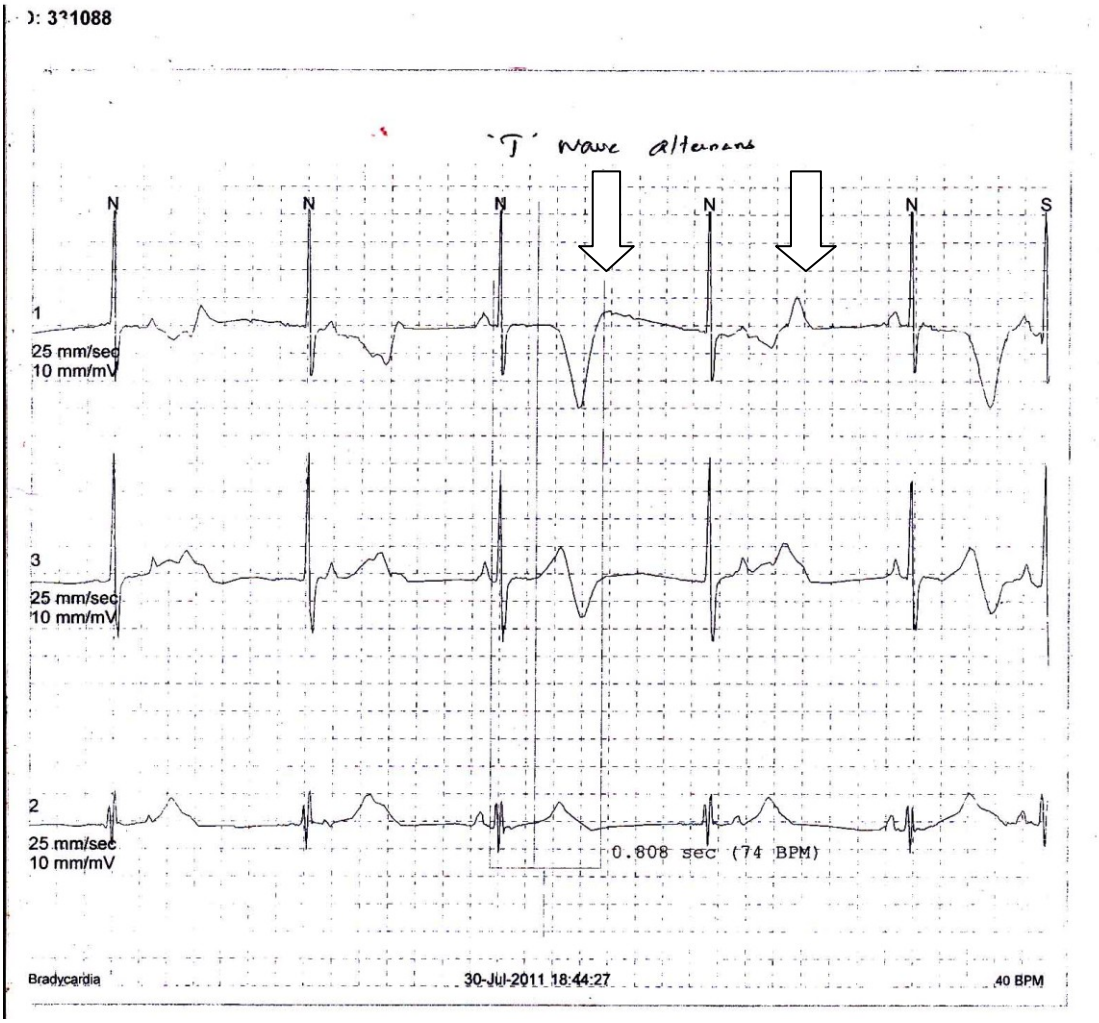


**Fig 2: ECG Showing Type 3 LQTS (Long ST Segment With Peaked T Waves**

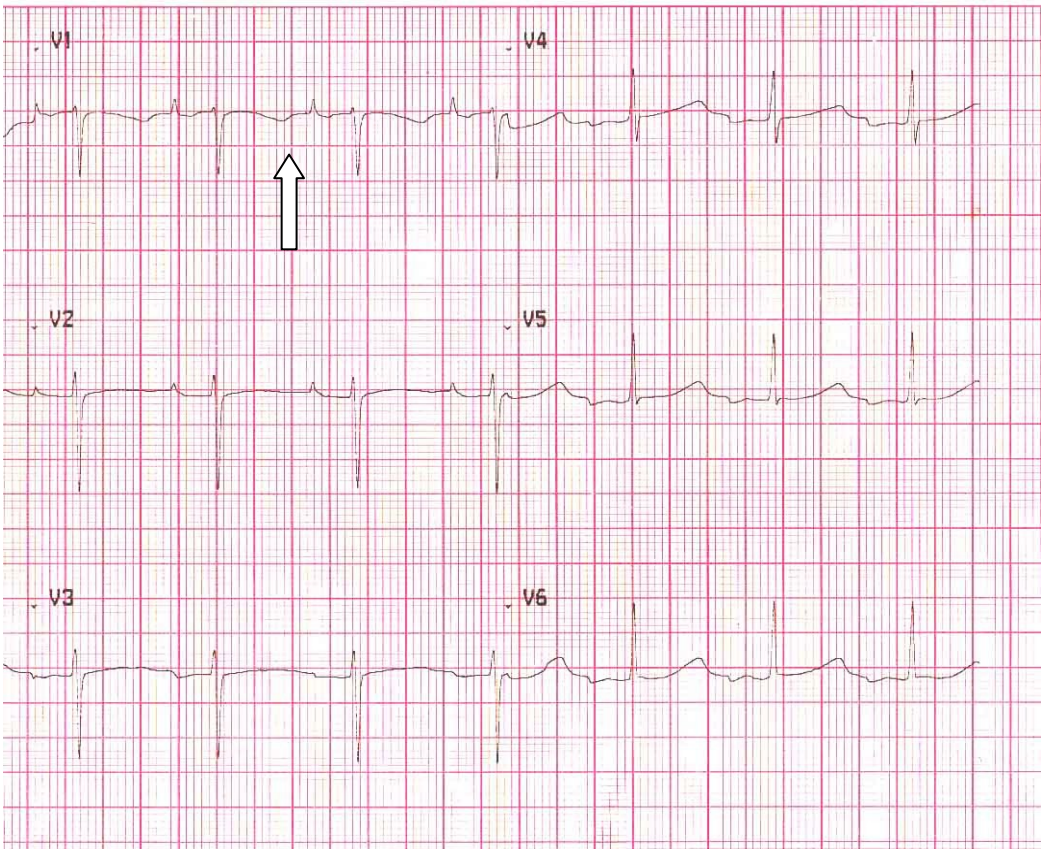



**Fig 3 :ECG showing type 1 LQTS (Infantile pattern)**

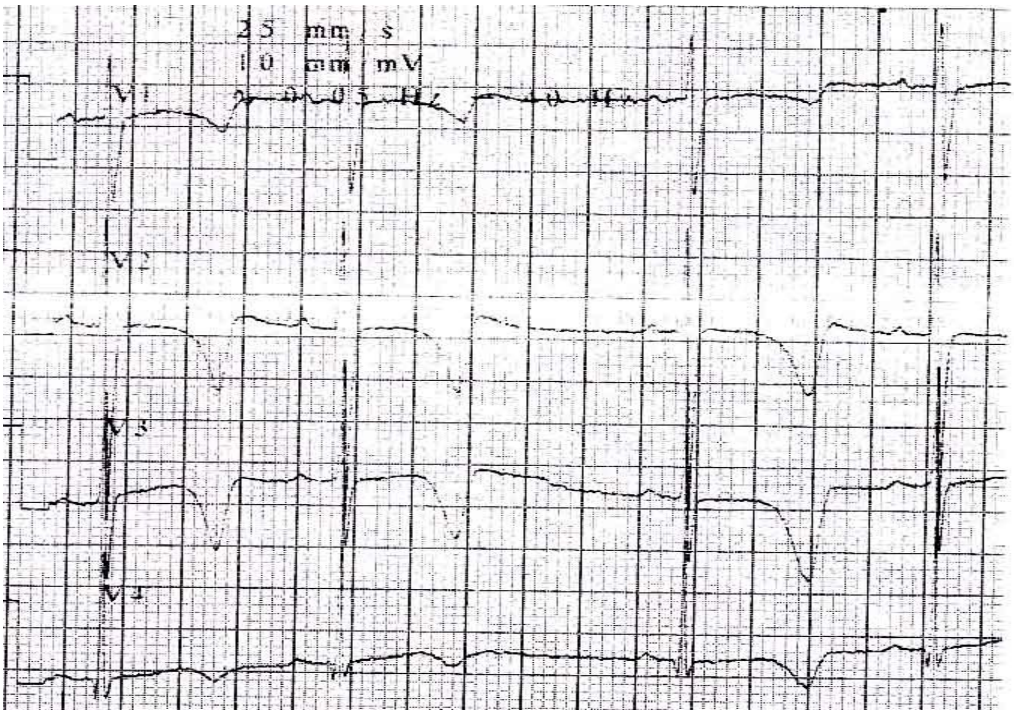


**Fig 4: ECG showing LQTS type 1 (broad based T waves)**

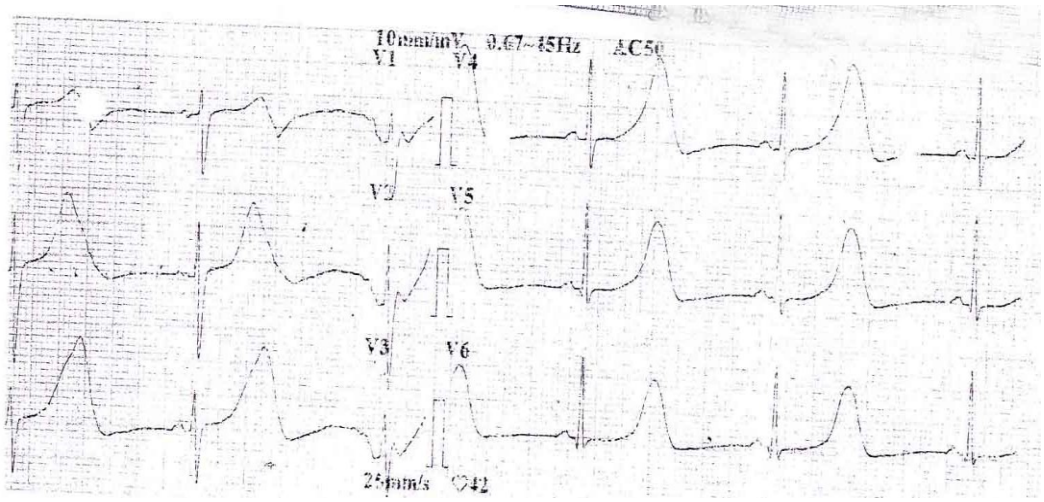



**Fig5: ECG Of Patient Showing Type 1 Brugada Syndrome With Notched QRS Complexes Who Had History Of Aborted Sudden Cardiac Death**

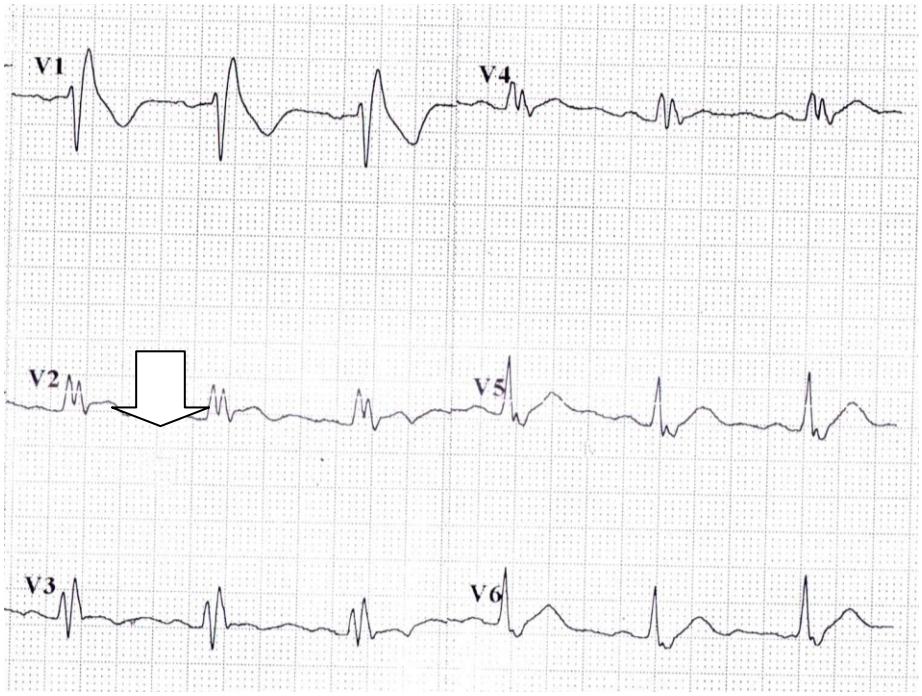


**Fig 6: ECG Showing Type 1 Brugada Syndrome With Notched Complexes**

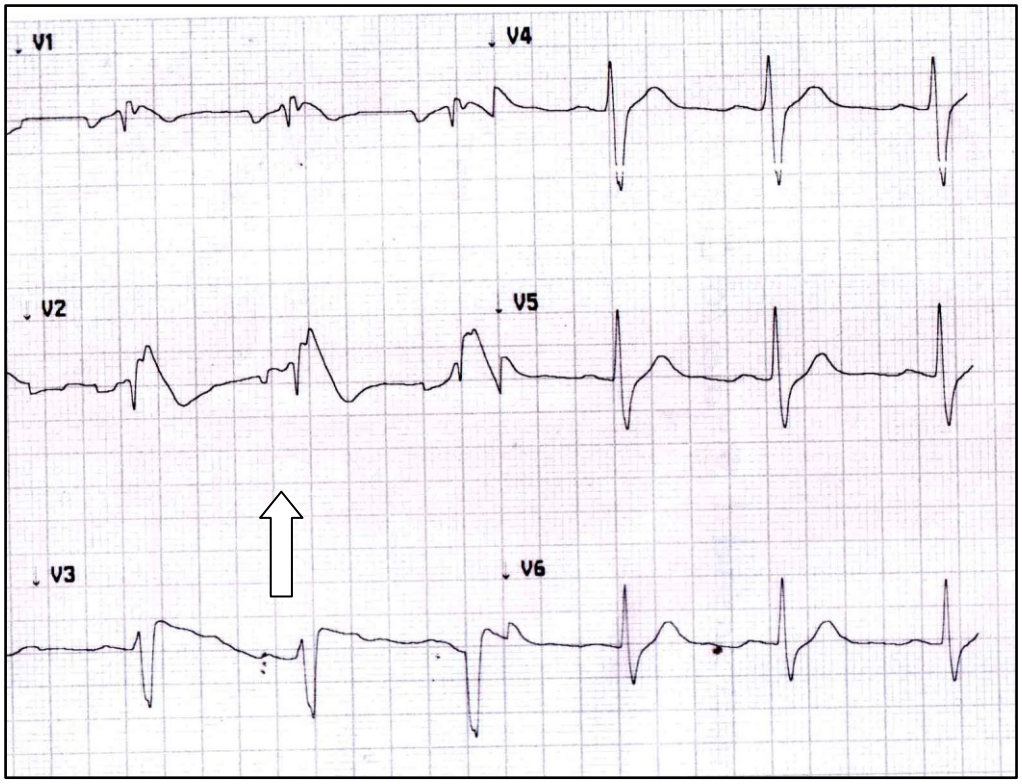



**Fig 7: ECG Showing Positive Flecainide Response**

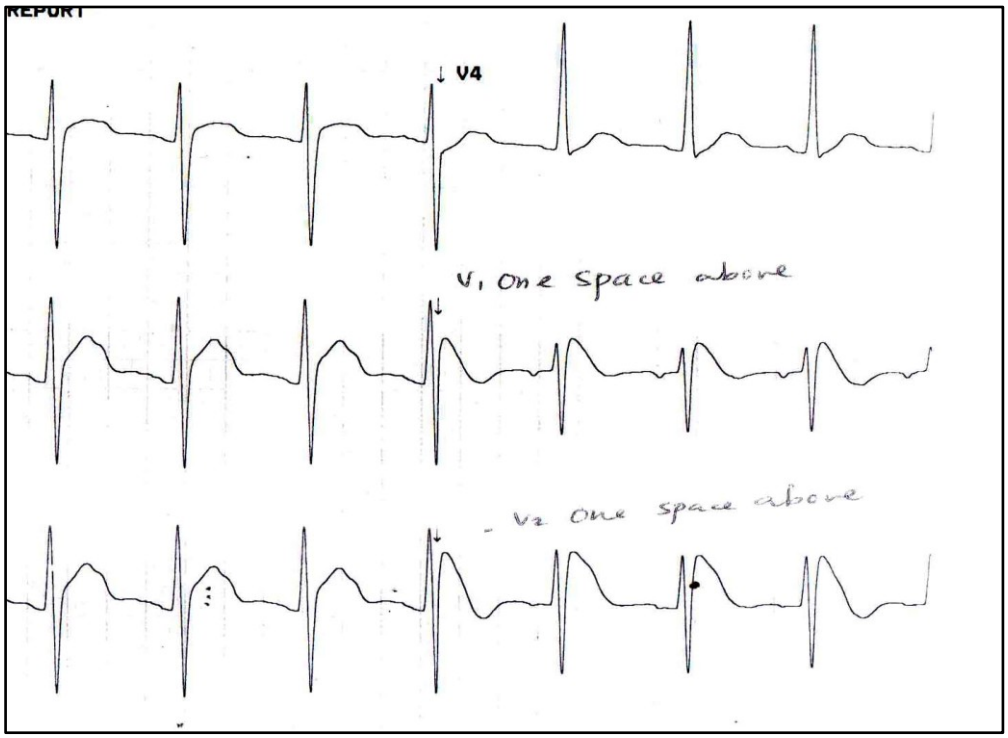


**Fig 8: Polymorphic VT In Brugada Patient**

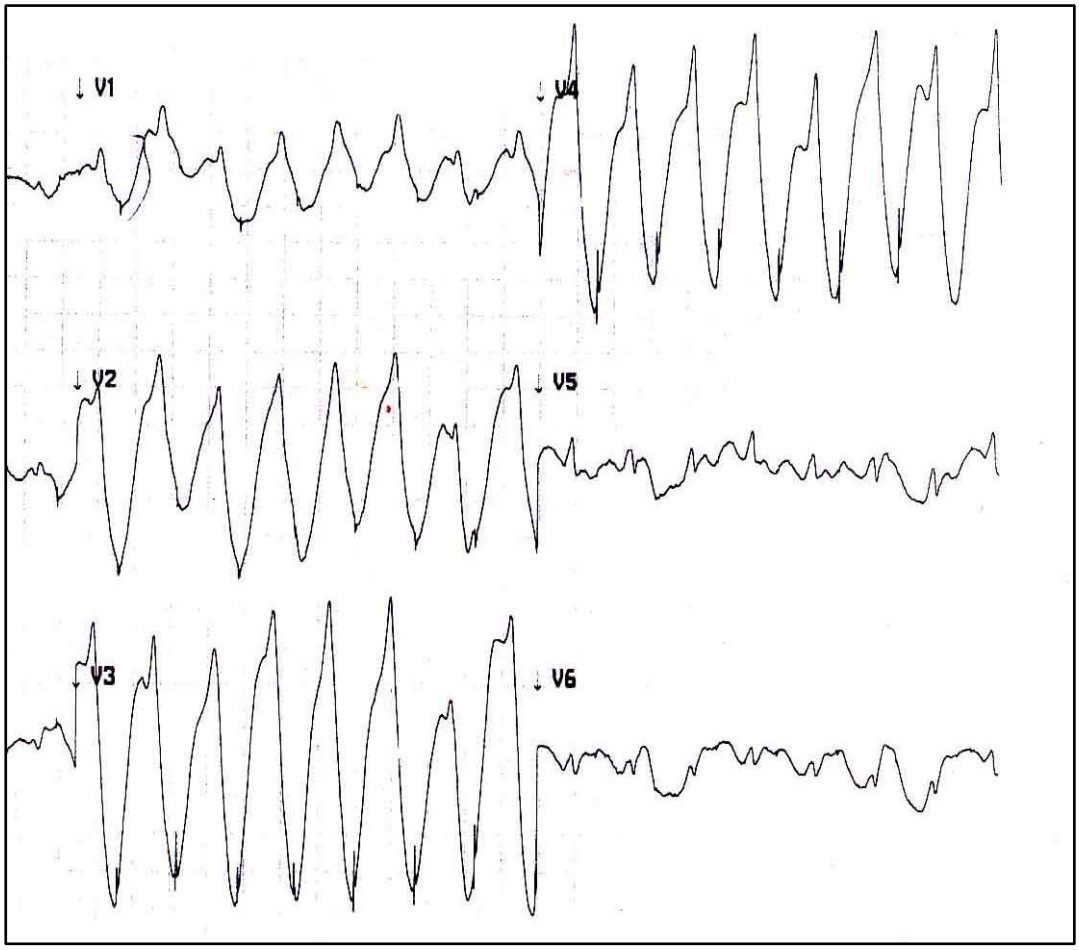
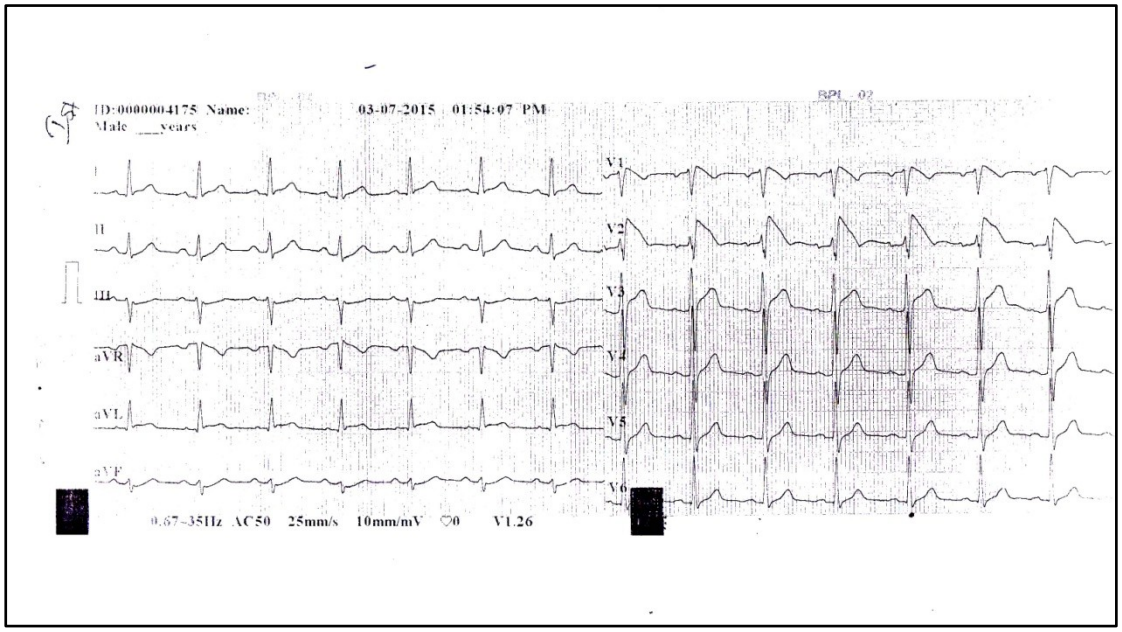
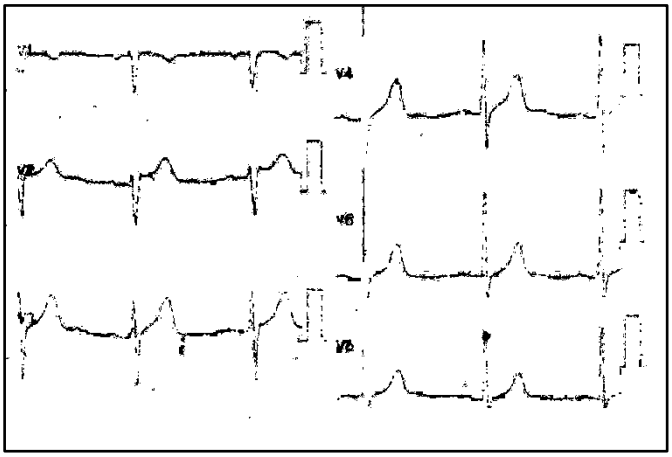


**Fig 9: ECG showing the type 1 brugada pattern in a patient with fever**




**ECG of same patient in Afebrile state**



# Discussion

Brugada and Long QT syndrome are cardiac channelopathies characterized by repolarization and depolarization abnormalities. Very little data is available regarding these disorders in our population. Whether our patients present with similar or different patterns as compared to other populations is not known. The aim of our study was to analyze the clinical presentation, risk factors and treatment outcomes of our patients. This has important implications in treatment and management of our patients.

There have been so far no studies on Brugada syndrome from our country. We analyzed 46 Brugada syndrome patients presenting to us in a single centre. Our patients were mostly males with male to female ratio of about 14:1. Other populations also have male preponderance, with males being 8-10 times more common than females (3). Male predominance has been explained by some because of increased transient outward current in males while others have suggested that it is because of increased testosterone levels (6,7). The mean age of presentation of our patients was 38.97±15.40 years which is comparable with other studies (3). Our patients commonly presented with syncope (40%) while 18% had history of sudden cardiac death and 4% presented with Nocturnal agonal breathing. The initial clinical presentation has

important role in risk stratifying individuals, as we found that those patients who had presented with history of aborted sudden cardiac death had higher event rate on follow up as compared to others (p=0.02). This is in accordance with other studies that have shown high event rate in patients who had presented with history of aborted sudden cardiac death.(16,17,18). However cardiac event rate in our population was low as compared to other studies. The annual event rate in our patients who had history of sudden cardiac death was 1% as compared to event rates of 10 % in Japanese registry, 7 % in FINGER registry and 69% in Brugada registry. There were no events in our population who presented with syncope or who were asymptomatic, however event rate in patients with syncope or asymptomatic presentation have been 0.6%, 0.5% in Japanese Registry, 1.9% and 0.5 % in FINGER registry and 19%, 8% respectively in Brugada registry. The difference can be explained by different populations studied however, our study had less number of patients with less follow up which can account for the apparent differences observed. In our patients fever precipitated cardiac events occurred in 26% of cases, which has been well described in other studies(11). About 4% of our cases had history of nocturnal agonal breathing and many patients had history of sudden cardiac death of

family member during sleep. This Circadian pattern has been studied previously also (12,13). Interestingly we also found in our study that around 6% of our Brugada patients were misdiagnosed as acute Myocardial Infarction and underwent emergency CAG which showed normal coronaries. Brugada syndrome masquerading as MI has been described before (52). Our patients who had presented with history of aborted sudden cardiac death or nocturnal agonal breathing had significantly higher ST elevation as compared to those who presented with syncope or were asymptomatic (4.22±1.2 mm vs 3.34± 0.97mm) (p=0.04). Degree of ST elevation can be used as marker for more severe presentation and can help in predicting future cardiac events. Mizumaki et al demonstrated Spontaneous augmentation of ST elevation occurred more frequently in patients who had history of VF as compared to those who were asymptomatic (14).

Major issue in Brugada syndrome is to assess the role of PES in predicting future events. In our study 26 patients underwent VT induction for prognostication. Our overall VT inducibility rate was 38%. All patients were divided into two groups, those who presented with history of resuscitated cardiac arrest and those with other presentations (syncope, nocturnal agonal breathing, asymptomatic). In the former

group VT inducibility rate was significantly higher as compared to later (80% vs 28%) (p=0.03). However on follow up there was no significant difference of cardiac events. There have been plenty of studies which have supported the role of VT induction in prognostication (24,25,26,27) while many others have reported that VT induction is of no use in predicting cardiac events (10,17,29,30,31,32). The latest study from Brugada et al which had long follow up of large number of patients has shown VT induction to be useful parameter in predicting event recurrence in future (26). This variability can be explained by the different populations studied, as Brugada registry included patients who had high event rates as compared to other studies. Many others have proposed that uniform protocol of PES can lead to uniformity of results. Makimoto et al tried to analyse this concept and found that Single or double extra stimuli at PES were found out to be adequate as a prognostic indicator in Brugada syndrome and stimulation site and coupling interval of extras had no prognostic value as indicator in Brugada patients (33). However there is need of further research and studies to arrive at definite conclusion.

We also found that patients who had presented with history of sudden cardiac death or nocturnal agonal breathing had higher

percentage of Spontaneous type 1 Brugada pattern and abnormal ECG patterns like notched complex, wide QRS duration and early repolarization abnormalities as compared to those who had more benign presentation, however because of small sample size it did not reach statistical significance. This concept that actually both repolarization and depolarization abnormalities are important in BRS has been well documented in various studies. (22, 23)

Among our patients 14 had ICD implantation. The most common indication for ICD implantation in our population was history of aborted sudden cardiac death (50%). The mean age of patients at ICD implantation was 47.28±11.63 Years. The Mean follow up of patients was 33.78 ± 24.36 months. On follow up we found that appropriate shocks occurred in 14% of Patients while as inappropriate shocks also occurred in 14% of patients. This is comparable to other studies (38, 39, 40, and 41) although inappropriate shocks were more in some studies. No patient had any device related complications on follow up, this is different from other studies where device complications and failure rates have been major concern with lead failure rates of as high as 29% (41). This difference could be due to younger age of ICD implantation in other studies as compared to our cases where mean age of ICD

implantation was 47.28±11.63 years, besides our follow up was less as compared to other studies, more events can be expected on longer follow up.

Long QT syndrome was first described in 1957 in a family of deaf children with history of sudden cardiac deaths in the siblings (44). International LQTS registry was established as main source of information regarding LQTS patients worldwide and has significantly contributed in understanding of the natural history, clinical course and treatment outcomes of these patients worldwide. The first publication from this registry came in 1985 and since then it has contributed in understanding of LQTS in many studies (42,43,53). However despite this world wide registry there is very scant data about the natural history, clinical course and efficacy of various treatment modalities in our population. We attempted to study LQTS in our population in order to give better insight into the natural history of our patients which would in turn help in their better management.

We studied total of 37 patients of which 21 were probands and 16 were family members and our mean follow up was 4.01±6.44 years. Our patients were younger at diagnosis. Mean age of all patients was 16.72±14.31 yrs which is less as compared to other studies. (42,43,50).

The mean age of presentation of males was significantly lower as compared to females (10.4±12.94 vs 20.375±8.66; p=0.008) in our population which has usually been seen in other studies (50). The age and sex related differences in LQTS presentation have been well studied and described, we also found in our patients that these differences are common. The mean age of presentation of male probands was also significantly lower as compared to female probands (4.36± 3.88 vs 20 ±12.52; p=0.0013) in our population which is consistent with other studies (43,50). We also noted significant difference in gender in presentation of patients below 15 years of age which were predominantly males. (81.25%; 13/16 vs 33.33%; 6/21, p=0.002). Our male patients had significantly higher history of congenital deafness as compared to females. (31.25% vs. 0%) (p =0.01). The mean QTC was longer in males as compared females (556.61± 58.25 vs 521.11±24.58 ms; p=0.016), however this difference was not significant when we compared male with female probands (568.66 ± 60.65 ms vs 529± 28.75 ms p=0.07). The earlier difference was probably because overall greater percentage of male patients presented as probands as compared to females in our population and probands are known to have longer QTc than family members. However we continued to observe significant difference in age of onset, incidence of congenital deafness and presentation in age less than 15 years between male and female probands also.{Age of onset (M:F 4.36± 3.88 vs 20 ±12.52) (p=0.0013)

Incidence of congenital deafness (45% 5/11 vs. 0% males vs. females) (p=0.03) and age of onset less than 15 years (M:F 100% 11/11 vs 40% 4/10) (p=0.003)}. However we did not observe this difference in these parameters when we compared male and female family members .In the age group less than 15 years the cardiac events were significantly higher in males as compared to females [males vs females 84.61% (11/13) vs 28.57% (2/7)] (p=0.02). Females continued to have cardiac events in adolescence and adulthood also while as we did not observe any events in adult males (57 % vs 0%). This is in accordance with other studies which have shown that males are susceptible to cardiac events in the prepubertal group while as females continue to be symptomatic throughout adulthood. It is not clear as to why there are differences in QTc duration and clinical manifestations with age and sex (54, 55). It has been proposed that testosterone may cause shortening of QT interval in males or lack or absence of this sex hormone may actual prevent QTc shortening in females. Animal studies have shown that QT prolongation to Quinidine may be blunted by androgen (56). Boyle et al has shown in animal studies that estrogen modifies expression of ion channels and potassium currents (57). Females undergo various hormonal changes in pregnancy and menses which can lead to QTc prolongation and arrhythmia susceptibility (54). Some studies have also shown that males having LQTS3 have lower heart rate as compared to females with LQTS3 thus it may lead to increased QTc in males despite similar QT in both

males and females (50). We also noted that all our patients who presented with torsade de pointes were females. This is in agreement with other studies which have shown that females usually predominate in presentations of torsade de pointes due to any cause of QT prolongation (58,59,60). Unknown differences in electrophysiological substrates result in lethal ventricular arrhythmias and VF in males and self limiting torsade in females (58). About 19% of our patients presented with history of recurrent seizures. We noted a male preponderance and early age of onset in this group of patients. The mean delay in diagnosis was 3.07±3.11 years. These patients were younger as compared to others and also frequently had congenital deafness (42.85% vs. 6.66% p=0.03). Their misdiagnosis as seizures led to their unnecessary treatment with multiple antiepileptic drugs with poorly controlled seizures. These patients dramatically improved with betablockers and had no recurrence of seizures thereafter. LQTS presenting and getting misdiagnosed as seizures is well reported in other studies. (61, 62)

The mean follow up of patents was 4.01±6.44 years. All symptomatic patients were on betablockers, most of them were on propanolol with average dose of 3.25±0.94 mg/kg. Six of our patients underwent pacemaker implantation and indications included recurrent syncope despite beta blockers and conduction system disease.

Propanolol was effective in majority of our patients in controlling symptoms with little side effects. No patient had any arrhythmic syncope on beta blocker, however one patient died on follow up (non compliance of medications). Six patients underwent pacemaker. We observed that mean QTc before Pacemaker implantation was 571.83± 77.23 ms and it significantly decreased to 461±18.01 ms after pacemaker on follow up. (p=0.04), There were no significant cardiac events on follow up except in two patients who developed recurrent syncope at End of life of pacemaker and needed PG change and became asymptomatic thereafter. There were no device related complications in our patients. Combination of pacemaker and beta blockers was effective in controlling cardiac events in our patients with no significant complications. The effectiveness of propanolol and pacemaker in treating patients of LQTS has been shown in multiple studies (51,63,64).

# Conclusion

The present study is the first study on Brugada syndrome and LQT syndrome in Indian population designed to give insight into the clinical presentation, risk stratification and treatment outcomes of these two cardiac channelopathies.

We found that in our population of BRS, aborted sudden cardiac death to be most important prognostic factor for future cardiac events. The overall event rate was low in our population. Although VT inducibility did not predict future events, a positive VT induction study was more common in those who had history of aborted SCD. ICD is effective in treating lethal arrhythmias although it is associated with some risk of inappropriate therapy.

There are significant age and gender related differences in presentation of LQTS in our population. LQTS can mimic refractory seizure disorder in paediatric population. Beta-blockers and Pacemaker implantation are effective in controlling symptoms in our patients of LQTS

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