The Bundgaard syndrome: Familial persistent ST segment depression syndrome

Acronyms

AF: atrial fibrillation; **BrS:** Brugada syndrome; **CAD:** coronary artery disease; **CHF:** congestive heart failure; **CPVT:** catecholaminergic polymorphic ventricular tachycardia; **ECG:** electrocardiographic/ electrocardiogram; **ICD:** implantable cardioverter defibrillator; **LQTS:** Long QT syndrome; **LMCA:** left main coronary artery; **PVCs:** premature ventricular contractions; **SCD:** sudden cardiac death; **SHD:** structural heart disease; **VF:** ventricular fibrillation; **VT;** ventricular tachycardia;

Description

Henning Bundgaard et al. from The Heart Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark in 2018 described a "Familial ST-segment depression syndrome", considered the newest clinical-electrocardiographic inherited primary arrhythmic syndrome characterized by predisposing to AF, VT/VF, and SCD and a pathognomonic 12-lead ECG pattern. This new inherited arrhythmic syndrome is until now the last 21st century described channelopathy in the same way that BrS was the last channelopathy described in the 20th century (1992). These entities are electrical abnormalities of the heart caused by derangements in the structure and function of the cardiac ion channels or proteins involved in their regulation. These rare diseases are often the underlying cause of syncope and SCD mainly in young individuals and children. Hereditary genetic defects lead to alterations in the ionic currents that determine the morphology and duration of the cardiac action potential, and individuals with these disorders often present with syncope or a life-threatening arrhythmic episode. The

diagnosis is based on clinical presentation and history, the characteristics of the ECG at rest, during exercise and genetic analyses.

The following entities are currently considered the main inherited arrhythmic syndrome or inherited primary arrhythmia syndromes which include:

1. **Hereditary long QT syndrome (LQTS**): The definitive description of LQTS occurred in 1957. Anton Jervell and Fred Lange-Nielsen described a Norwegian family in which 4 of 10 children were deaf and had recurrent syncope during exercise or emotion Three died suddenly, at ages 4, 5 and 9 years. QT prolongation on the ECG was dramatic.[1]
2. **Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)** In 1975, Reid et al. discovered catecholaminergic polymorphic ventricular tachycardia (CPVT) Since it was first discovered in 1975, CPVT has been reported as a cause of syncope, ventricular arrhythmias and SCD. CPVT typically manifests as syncope between 7 and 9 years of age, but SCD may be the first presentation.[2]
3. **Congenital Short QT syndrome (SQTS)** The first report of SQTS to be published was in 2000, describing a family with short QT intervals on the 12-lead ECG, AF occurring at a young age, and an unrelated patient who suffered SCD associated with a short QT interval.[3]
4. **Brugada syndrome (BrS);** In 1986, Prof. Pedro Brugada received his first patient with typical ECG, a Polish Caucasian child, who suffered several episodes of syncope. The boy presented as family background his sister's SCD, even though she had been treated with association of pacemaker implantation and amiodarone. In 1989, a patient with characteristic ECG was described as being a carrier of early repolarization syndrome. In 1991, Pedro and Josep Brugada, with two more cases, presented as an abstract in the NASPE meeting, a new clinical-cardiologic

syndrome, typified by the association of RBBB, persistent ST segment elevation, normal QT interval and SCD. In 1992, the brothers from Catalonia (Spain), Pedro and Josep Brugada, presented the first description of the entity, adding four more patients to the initial description, making a total of eight. This would be the last clinical-cardiologic entity to be identified in the 20th century.

5. **Early repolarization syndrome (ERS):** is diagnosed by the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/ polymorphic VT. Early repolarization pattern was first described in 1936 by Shipley and Hallaran when they performed four-lead ECGs on 200 healthy individuals from 20 to 35-year-old and noticed an elevated ST segment in lead II in 25% of males and 16% of females. Expert consensus recommendations distinguish an early repolarization ECG pattern (ER) and an early repolarization syndrome. The pattern is defined as the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG. The syndrome is said to be present when the pattern is found in (1) a patient resuscitated from otherwise unexplained VF; or (2) an SCD victim with a negative autopsy and medical chart review with a previous ECG. The J-point elevation may be a notch or a slur, with or without elevation of the ST segment**.**
6. **J-Wave Syndrome (JWS):** Among the inherited ion channelopathies associated with potentially life-threatening ventricular arrhythmia syndromes in nominally structurally normal hearts are the J wave syndromes, which encompass BrS and ERS. These ion channelopathies are responsible for SCD, most often in young adults in the third and fourth decade of life. Additionally, J wave syndrome could

be caused by acquired entities such as hypothermia and CAD that represent a continuous spectrum of ventricular arrhythmogenic potential.

7. **Idiopathic Ventricular Fibrillation (IVF):**[4] 2015 ESC guidelines on the management of ventricular arrhythmias consider IVF as an episode of documented VF following which comprehensive clinical evaluation does not identify an underlying cause. The only observed phenotype is short-coupled TdP/PVC triggered VF[5, 6]
8. **Triadin knockout syndrome (TKOS)** It is a potentially lethal disease characterized by T-wave inversions in the precordial leads, transient QT prolongation in some, and recurrent ventricular arrhythmias at a young age despite aggressive treatment. Patients displaying this phenotype should undergo TRDN genetic testing as TKOS may be a cause for otherwise unexplained cardiac arrest in young children. As gene therapy advances, enrollment into the International Triadin Knockout Syndrome Registry is encouraged to better understand TKOS and to ready a well-characterized cohort for future TRDN gene therapy trials. Triadin knockout syndrome.[7] The triadin gene (TRDN) arrhythmia syndrome: TRDN mutations cause CPVT5 but may present with LQTS.
9. **Bundgaard syndrome (described in 2018 and updated in 2021)**[8, 9]

Initially, ECGs reviewed from five unrelated families demonstrated a consistent pattern of widespread, concave-upward ST depression, in the absence of CAD or ischemia. In contrast to other genetic disorders such as BrS and LQTS, these changes remain stable over time, only accentuated by exercise.

Affected individuals had varying time courses of disease, but usually remained asymptomatic until the onset of tachyarrhythmia's, often initially AF with subsequent episodes of VT/VF leading to SCD.

Diagnosing "Familial ST-segment depression syndrome"

Familial unexplained persistent concave-upward ST depression phenotype in at least 7 leads, 90 ms after J point I, II, aVL, aVF, V2-V6. All families had ≥2 members with these characteristics.

ST elevation in lead aVR >0.1 mV. The aVR is a neglected or forgotten lead. It is a unipolar lead facing the RVOT. The lead aVR is a very important lead in localization of CAD. In the presence of anterior ST depression, ST elevation in lead aVR indicates LMCA disease or triple vessel disease where ST elevation is more in aVR than in V1 such as Bundgaard syndrome.

Presence of a notch in the ascending portion of the ST segment most prominent in leads V3-V5.

ECG findings are persistent with time: "static" nature of this pattern. These changes remain stable over time, but accentuated by exercise;

Onset of complications does not appear to correlate with age;

Risk of AF, ventricular arrhythmias, and SCD.

Autosomal dominant pattern of inheritance with high penetrance: 50% of first-degree family members displayed the characteristic ECG phenotype.

The authors proposed the above diagnostic criteria, with "unexplained" highlighting the importance that ischemia's, SHD and metabolic abnormalities have been excluded prior to labelling the condition.

Other secondary diagnostic features were accentuation seen with exercise in some, and the presence of a notch in the ascending part of the ST segment. Note that onset of complications does not appear to correlate with age based on limited observations of affected individuals (Figure 1).

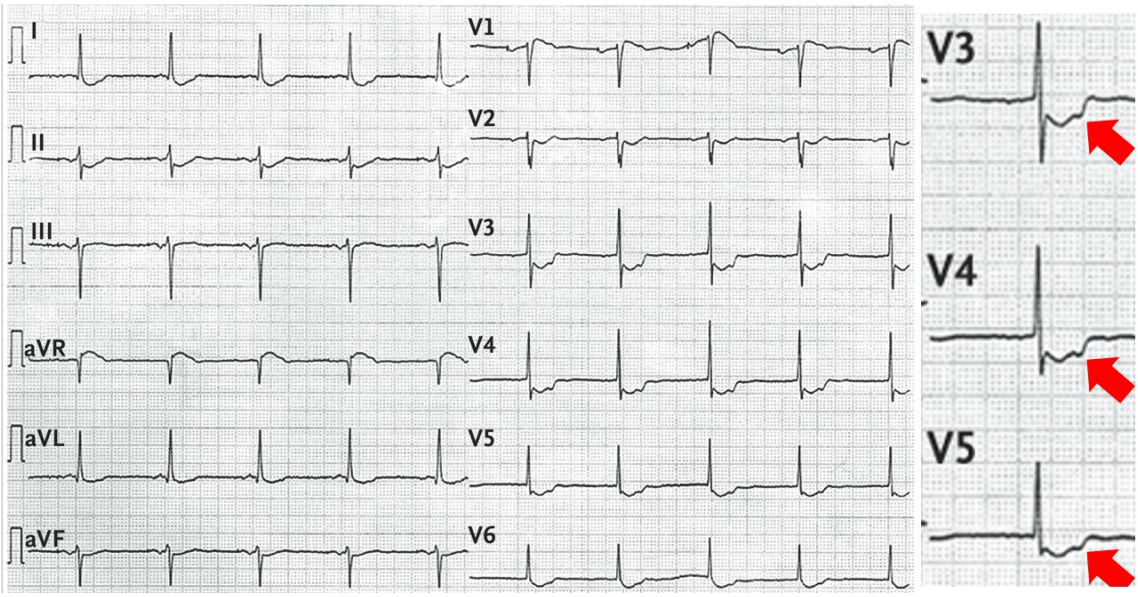


Figure 1: Characteristic ECG of Bundgaard Syndrome: Concave-upward ST-segment depression in leads I, II, aVL, aVF, V2-V6, ST-segment elevation n lead aVR, a notch is visible in the ascending part of the ST segment of the precordial leads, most prominent in leads V3-V5.

Clinical significance: does not that look familiar?

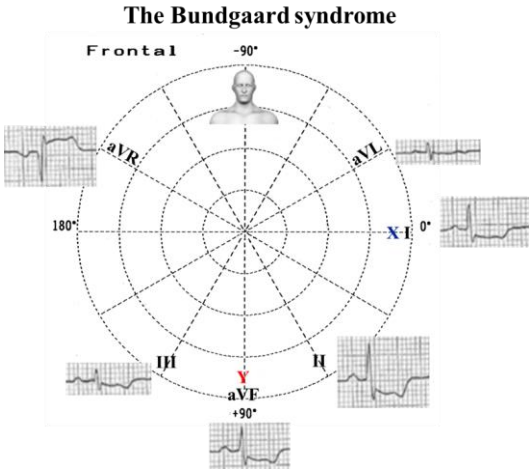
Differential diagnosis

Patients with familial persistent ST-segment depression syndrome presenting with chest pain may be mistakenly identified as suffering from an acute ischemic event consequence of critical obstruction of LMCA. Subsequent unremarkable laboratory and angiography findings, in combination with the "static" nature of this pattern, should raise concern for FSDS and prompt further investigation and screening of family members (Table 1).

	Bundgaard syndrome	**LMCA critical Subocclusion**
Typical precordial pain	No/rare	Yes
Cardiogenic shock.	No	Possible

ST-elevation of lead aVR	Yes	Yes STE in aVR ≥1 mm indicates proximal LAD
Magnitude of ST elevation in aVR ≥1 mm	Yes	Yes, associated with a 6- to 7-fold increase in mortality
Co-existent multi-lead ST depression	Yes. Stable or fixed non- ischemic ST-segment depressions	Yes Dynamic ischemic ST-segment depressions
Static ECG pattern	Yes	No, dynamic
Non-specific interventricular conduction delay	No	Frequent
Notch in the ascending part of the ST segment of the precordial leads V3-5	Characteristic	No
Familial background	Yes, from Eastern Denmark families. Autosomal dominant inheritance	No, acquired.
SHD	without apparent, macroscopic, or subtle	Yes, CAD: subocclusion in LMCA or severe triple vessel disease (3VD)

Table 1



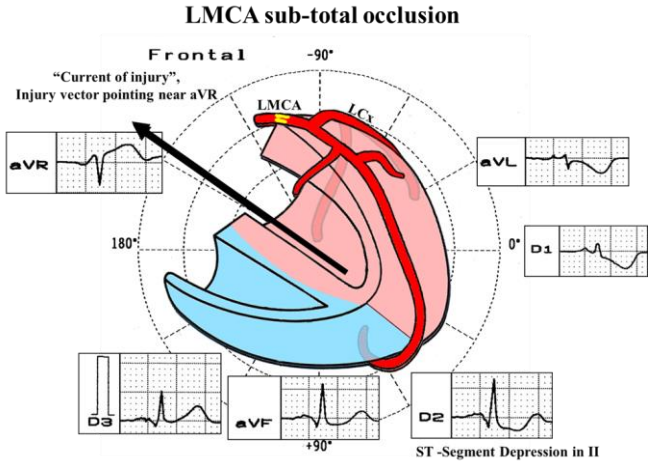


Figure 2. Comparative ECG pattern between the Bundgaard syndrome and LMCA sub-total occlusion in the frontal plane.

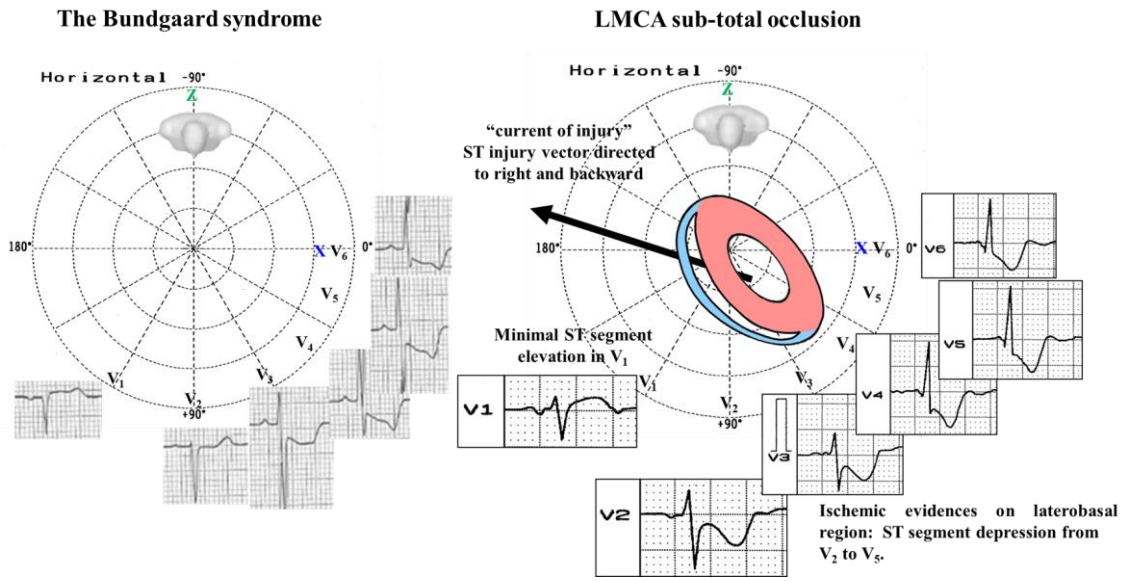


Figure 3. Comparative ECG pattern between the Bundgaard syndrome and LMCA sub-total occlusion in the horizontal plane.

Figure 4. shows a typical ECG pattern of LMCA Sub-Occlusion. Diffuse ST segment depression in the inferolateral leads.

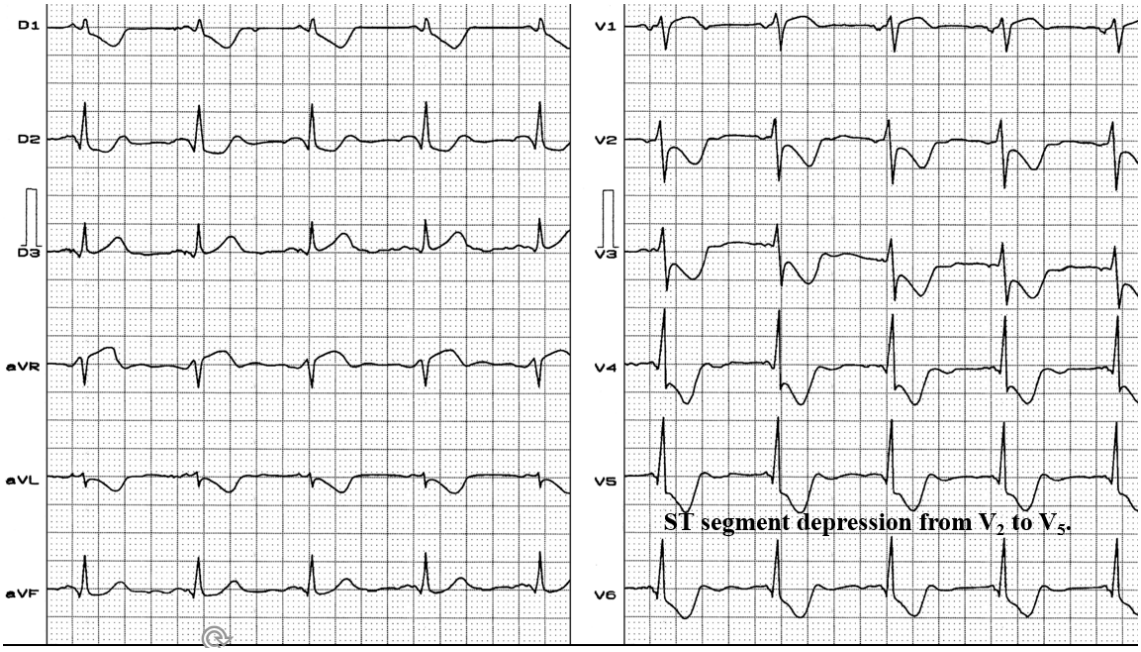


Figure 4. ST segment depression in anterolateral leads and ST segment elevation in aVR >1 mm V_1. Sometimes it is hard to differentiate from the Bundgaard syndrome.

Natural History and Clinical Characteristics of the First 10 Danish Families with Familial ST-Depression Syndrome

Recognition of specific ECG patterns remains a mainspring in the diagnosis of inherited arrhythmia syndromes. Denmark researches in 2018 described a new inherited arrhythmia disease without apparent, macroscopic, or subtle SHD, familial ST-segment depression syndrome, characterized by pronounced ECG changes including persistent, no ischemic ST-segment depressions and risk of AF, ventricular arrhythmias, and SCD. These group proposed diagnostic criteria.[8] They have now identified 7 additional, apparently unrelated, Danish families fulfilling diagnostic criteria resulting in a total of 10 families; all probands were inhabitants of Eastern Denmark.

All families had ≥2 members with unexplained, persistent ST-segment depressions with a characteristic concave appearance; ECG changes were not explained by SHD or CAD. From the 10 Danish families, the authors evaluated 32 individuals (47% men) with the

persistent ST-segment depression phenotype. Mean age at diagnosis was 47 years (range 10 to 79 years). Pedigree analyses were consistent with autosomal dominant inheritance and the penetrance appeared high, as approximately 50% of first-degree family members displayed the ECG phenotype. The ST-segment depressions were most pronounced in leads V4, V5, and II and persisted over time, that is, without episodes of normalization. The mean PR, QRS, and QTc (Bazett)-intervals were 166± 24 ms, 91±12 ms, and 396 ±27 ms, respectively.

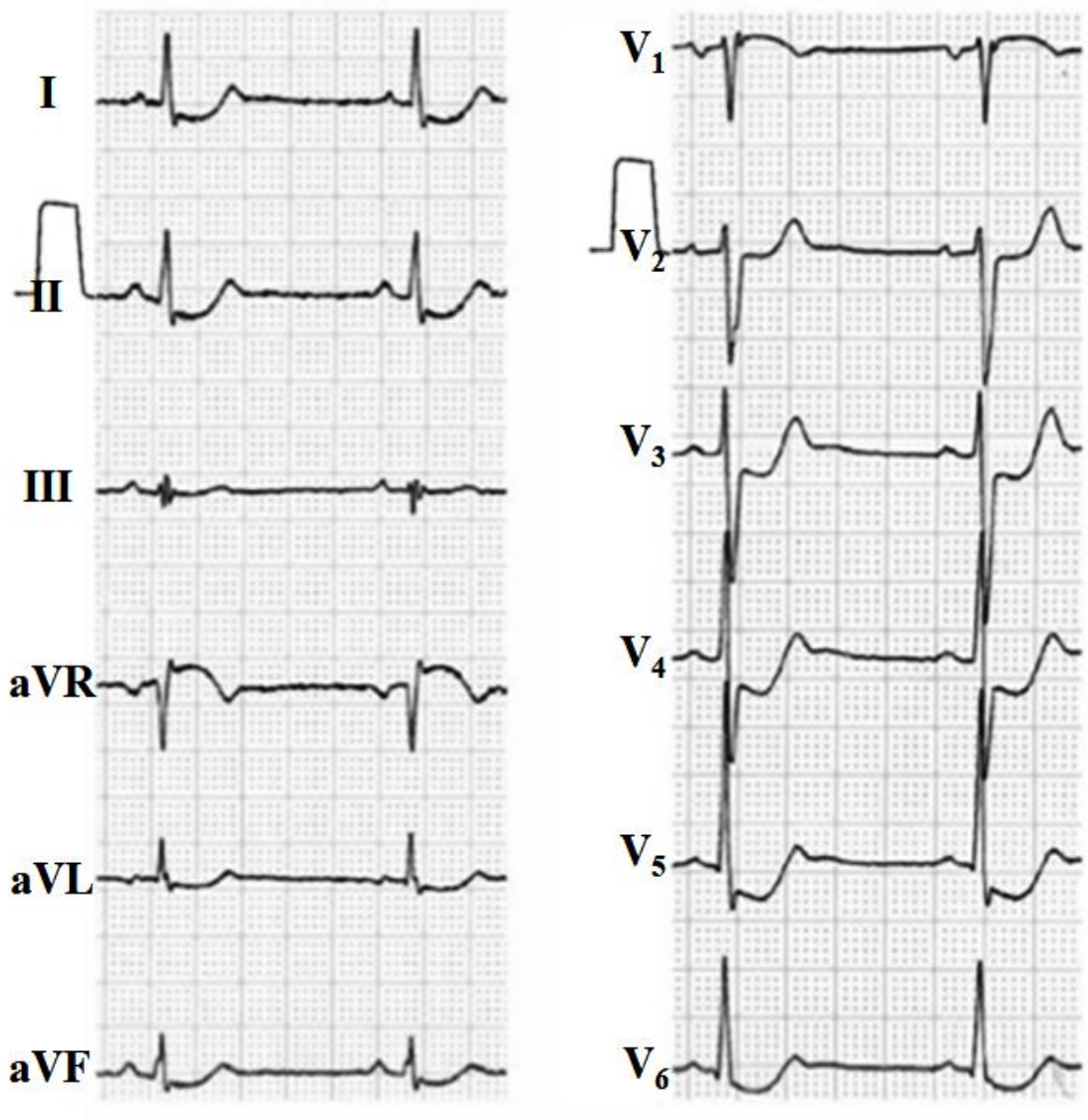
Echocardiography showed a mean left ventricular ejection fraction (LVEF) of 55 ±11% (range 20% to 60%), left ventricular end-diastolic diameter of 52 ± 6 mm (range 44 to 72 mm), and interventricular septal thickness of 9 ±2 mm (range 6 to 12 mm).

Clinically, the typical presentation was arrhythmic; AF was the most commonly observed arrhythmia with onset from the fifth decade. During a mean follow-up of 6.5 years, 3 (9%; all men) patients developed ventricular arrhythmias or (aborted) SCD, 4 (13%; all men) had catheter ablations performed (atrial fibrillation [n ¼ 3]; ventricular arrhythmia [n ¼ 1]), 2 (men) received an ICD, 5 (16%; all men) were diagnosed with CHF (LVEF #50%), and 9 (28%; 7 men) developed AF. During follow-up, the ECG pattern remained stable in these patients as well as in those without any events or complications. Importantly, ventricular arrhythmia and reduced systolic function were only seen in men, suggesting a sex-specific natural history. For research purposes, the authors assessed the myocardial architecture in percutaneous septal myocardial biopsies from 3 affected individuals. Findings ranged from near-normal myocardium to variable myocyte/nuclear enlargement, perinuclear loss of myofibrils and vacuolization, and interstitial fibrosis; no pathognomonic findings were identified. Abnormal electro-anatomic mapping was revealed in two investigated patients performed due to a large burden of premature ventricular contractions.

Screening of large gene panels was negative, and whole exome sequencing of 4 affected individuals from the index family was performed. Sequencing, alignment, and variant calling were performed using Broad Institute best practices, and filtering was performed for protein-altering heterozygous variants with a minor allele frequency <0.1%. No disease-causing variant was identified. Strikingly, some of the affected individuals tolerated the severely abnormal repolarization pattern for decades before arrhythmias occurred. It is a hallmark and a clinical challenge that pathognomonic ECG changes associated with other inherited arrhythmia syndromes such as LQTS and BrS syndrome are dynamic over time.[10, 11] This is in contrast with familial ST-segment depression syndrome in which all affected individuals showed persistent ECG changes, except from aggravated but reversible ST-segment deviations during exercise. In idiopathic VT, no SHDs are generally identified, but recently a mosaic of subclinical findings on detailed electrophysiological investigations were reported.[12] This seems to resemble findings in familial Bundgaard syndrome. The optimal clinical management of patients with familial Bundgaard syndrome is unknown, and signs and symptoms should be treated according to general recommendations. However, it seems prudent to take the observed increased risk of sudden cardiac death into consideration; for example, when considering ICD implantation in affected patients with documented ventricular arrhythmias and/or syncopal attacks. In conclusion, the authors have identified 10 Danish families fulfilling criteria for the novel familial Bundgaard syndrome consistently showing autosomal dominant inheritance; the genetic cause remains elusive. The phenotype was associated with arrhythmias, aborted SCD, or CHF in almost one-half of the cases. The findings warrant follow-up and cascade screening of relatives to patients with familial Bundgaard syndrome like in other inherited arrhythmia syndromes.

ECG examples of a typical the Bundgaard syndrome

Example 1

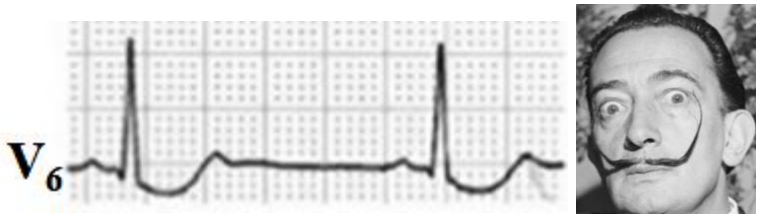


12-lead ECG: Sinus bradycardia (55 bpm), P axis +57°, P duration 100 ms, PR interval 155 ms, QRS axis +30°, ST segment depression concave upward in I, II, aVF, and from V2 to V6, ST segment elevation >1 mm in aVR.

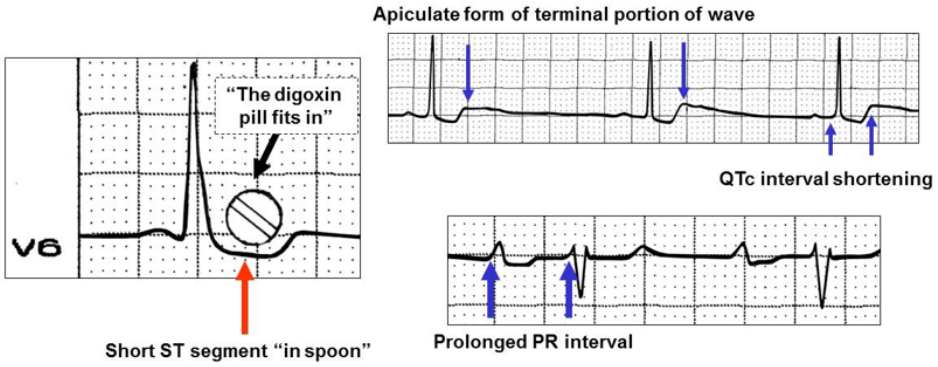
Clinical diagnosis: Bundgaard syndrome.

The superior convexity shape of the ST segment resembles the spoon-like appearance of the digitalis effect or Salvador Dali's mustache.

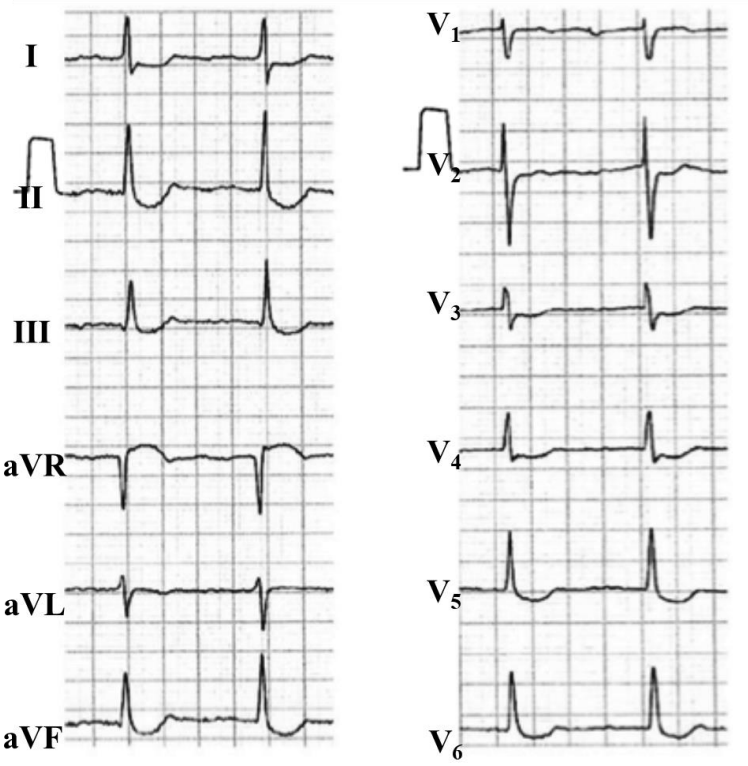
A) The superior convexity shape of the ST segment in the Bundgaard syndrome



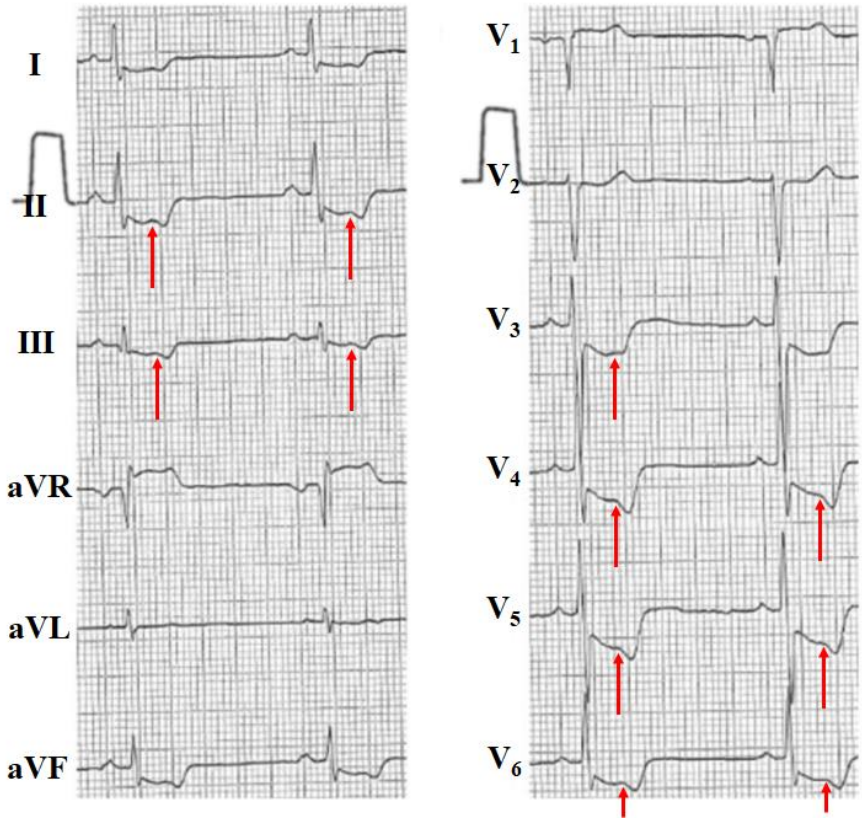
B) The superior convexity shape of the ST segment in the digitalis effect



Example 2



Example 3



Presence of a notch in the ascending portion of the ST segment most prominent in leads V3-V6, and II-III (red arrows). ST segment depression in the anterolateral wall and inferior leads, and ST segment elevation in aVR >1 mm.

Who is Prof Henning Bundgaard?

Professor of Cardiology and Professor, Senior Consultant in Cardiology, DMSc

Affiliated to Department of Cardiology, Heart Centre and University of Copenhagen

His research areas include Personal medicine, inherited cardiac disease, including cardiomyopathies, ion channel diseases, non-syndromic aorta-diseases, Fabry disease, storage diseases, Heart failure, Endocarditis, Structural and functional heart diseases in children

Professional address: The Heart Center, Department of Cardiology, B2141, Rigshospitalet, Blegdamsvej9, DK-2100 Copenhagen Ø. The Faculty of Health and Medical Sciences, University of Copenhagen, DK-2200 Copenhagen N. Email: henning.bundgaard@regionh.dk Telephone: +45 3545 0512. Personal information: Born September 27, 1961. Telephone +45 2611 2290 Education: MD (1988), PhD (1997), internal medicine (2003), cardiology (2004), Dr.Med. (2005). Fellowship in Cardiology in Sydney, Australia 2002-2004. ½ time employment in The National Board of Health 1996-2002. Position: Professor (2015), consultant in cardiology (2007), the Heart Center,

Rigshospitalet, University of Copenhagen. • Head, Capital Region's Unit for Inherited Cardiovascular Disease. • Head, Clinical Academic Group "Precision diagnostics in cardiology", 2017.

• Head, NordForsk project, 2019 Scientific focus areas:

• Cardio-genetics, inherited cardiac diseases, hypertrophic cardiomyopathy, heart failure, sudden cardiac death.

• Personalised medicine in cardiology, focusing on precision diagnostics.

• PI of RCTs of beta III adrenoceptor agonist treatment in heart failure. • PI of RCT of treatment of patients with infectious endocarditis (n=400) (NEJMx2).

• Co-PI of the Copenhagen Baby Heart study, which aims to include 25.000 newborns in Copenhagen (2016-2018) assessed by ECG and echocardiography, with blood samples and data on family, pregnancy and delivery + prenatal scanning data.

• PhD and doctoral thesis: Na,K-pump regulations in muscles and heart. International relations: • PI of the Nordic PerMed collaboration project: Precision Diagnostics and Predictions in Ischemic Heart Disease including Identification of Over-Treated Patients. Granted dkr 29 mio.

• Head of H2020 consortium; Personalized medicine in ischemic heart disease. Stage 1 application submitted; obtained score 3.5 (threshold ≥4). 8 countries involved. Alternative calls searched.

• Initiator of the web-based "Scandinavian PTSMA-database", now extended to include Germany, the Czech Republic and the Netherlands.

• Co-chair, Nordic HCM registry. • Participant, Nordic ARVC Registry.

• Active participant, EU programme (ERN) on inherited cardiac diseases.

• Professor Rasmussen H, Sydney: Na,K-pump regulation in heart diseases .

• Professor Ho C, Brigham and Women's Hospital, Boston,: RCTs in hypertrophic cardiomyopathy in children and adolescents. Additional work on animal HCM models.

2 Supervision of PhD and Medical Students:

• Past supervisor for 10 Ph.D. projects.

• Current supervisor for 8 Ph.D. students.

• Current supervisor for 6 medical students.

Management Experience: • Head, Clinical Academic Group: Precision diagnostics in cardiology, 2017.

• Lead position in establishing the sub-speciality "inherited cardiac diseases" in cardiology in Denmark and in establishing and currently heading the Unit for Inherited Cardiac Diseases, Rigshospitalet (now REAH for The Capital Region).

• Danish Board of Health, 7 years' part-time: development and organisation of physician postgraduate training and specialisation.

• Organiser of scientific meetings and conferences.

• Chair/participant in development of several cardiology guidelines.

• Member, Danish Heart Foundation research council.

• Member, Academic Council of Copenhagen University and Copenhagen University Hospital Board.

• Member of working group on establishment of the knowledge database (chair of the sub-group The Danish Clinical Genomic Database (Mid 2018 to 2019))

, The Danish National Genome Center. Press relations

• Multiple interviews and press releases related to cardio-genetics, sudden cardiac death, ethics related to genetics, endocarditis, etc. in all major Danish newspaper, radio and TV (DR, TV2) and in several international press media related to oral presentations of four international late breaking clinical trials.

Bibliographic overview: No. of publications (WoS): 205.

First authorships: 23

Corresponding authorships: 26

Citations: 2044.

H-index: 32.

Patent: Treatment of heart failure in humans with beta 3 AR agonists.

Link to complete list of publications: https://orcid.org/0000-0002-0563-7049

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