REVIEW ARTICLE

Brugada syndrome

CME

Jessica Jellins
Mitchell Milanovic
David-Joel Taitz
SH Wan 溫兆康
PW Yam 任炳華

As a clinical entity the Brugada syndrome has existed since 1992 and has been associated with a high risk of sudden cardiac death predominately in younger males. Patients can present with symptoms (ie syncope, palpitations, aborted sudden cardiac death) and asymptomatically. Its three characteristic electrocardiographic patterns can occur both spontaneously or after provocation with sodium channel-blocking agents. Risk stratification and the need for treatment depend on the patient's symptoms, electrocardiography, family history, and electrophysiological inducibility to discern if treatment by implantable cardioverter defibrillator, the only effective treatment to date, is appropriate. This review focuses on Brugada syndrome and various aspects of the disease including proposed mechanisms, epidemiology, clinical presentations, genetics, diagnosis, risk stratification, and treatment options.

Introduction

The Brugada syndrome was first described in 1992, and constitutes a new and distinct clinical entity outlined by characteristic electrocardiograms (ECGs) and an associated high risk of sudden cardiac death (SCD). Since the initial description, there have been two consensus conferences to refine understanding about the syndrome, with a published report in 2002 outlining the diagnostic criteria[1] and a subsequent report in 2005 addressing risk stratification guidelines and approaches to therapy.[2] This review provides an overview of the molecular, genetic, epidemiological, and clinical aspects of Brugada syndrome as well as possible approaches to management.

Underlying mechanism

Brugada syndrome as described in 1992[3] was initially thought of as a channelopathy, an exclusively electrophysiological disorder produced by dysfunction of a cardiac ion channel involved in the generation of the action potential (AP) in a structurally normal heart.[3-7] This notion has been challenged and is subject to debate,[5,8] as the first report on Brugada syndrome patients by Corrado et al[9] in 1996 had an underlying structural abnormality. Over time, more studies reported patients with the Brugada ECG patterns showing structural abnormalities of the right ventricle (RV).[10-12] This supports the theory that the pathophysiological mechanism of Brugada syndrome may be due to slowing of conduction in the RV, accompanied by mild structural abnormalities.[8]

Currently, no single causal factor links all patients and thus, the pathophysiological mechanism remains elusive.[8] Two hypotheses have been proposed—the depolarisation theory and the repolarisation theory. To explain the pathophysiology of the type-1 ECG pattern and susceptibility to ventricular arrhythmias (VAs), two hypotheses have been proposed.[5,7,8,13,14] Brugada[15] stated that there are a multitude of possible aetiologies that manifest as the phenotype of the Brugada syndrome ECG. To date, none of these proposed hypotheses have been irrefutably demonstrated.[12]

Key words
Brugada syndrome; Channelopathies; Death, sudden, cardiac

Hong Kong Med J 2013;19:159-67

School of Medicine, Sydney, The University of Notre Dame Australia, 160 Oxford Street, Darlinghurst NSW 2010, Australia
J Jellins, MB, BS, BCom (Liberal Studies)
M Milanovic, BSpExSc
DJ Taitz, BCom/BSc
SH Wan, FHKCP, FHKAM (Medicine)
Department of Medicine and Geriatrics, Tuen Mun Hospital, Tuen Mun, Hong Kong
PW Yam, FHKCP, FHKAM (Medicine)

Correspondence to: Assoc Prof SH Wan
Email: michael.wan@nd.edu.au

Repolarisation (channelopathy) hypothesis

The repolarisation hypothesis was first proposed in 1999,[7] and followed up by a decade of experimental studies. According to this hypothesis, rebalancing of currents at the end of phase 1 of the AP leads to accentuation of the AP notch in the epicardium of the RV. Such accentuation was believed responsible for the characteristic ST-segment elevation (Fig 1).[4-7]

Under normal conditions there is a non-homogeneous expression of the transient outward potassium current (I_{to}) between the epicardium and endocardium, with the epicardium having an increased expression of I_{to} (Fig 1a).[16] In the presence of pathophysiological conditions, such as a *SCN5A* mutation (leading to sodium channel loss-of-function), outward currents overwhelm inward currents, and the epicardium may then exhibit all-or-none repolarisation at the point where the phase-1 AP reaches

布魯格達氏綜合症候群

自從1992年發現布魯格達氏綜合症候群開始，此病便與年青男性高風險的心臟性猝死有關。患者可出現如暈厥、心悸、中止心臟性猝死的症狀，又或者沒有任何症狀。布魯格達氏綜合症候群的三個代表性心電圖模式可以自發性地出現，或受到鈉離子通道阻斷劑的影響。風險分層和治療方法取決於病人症狀、心電圖、家族病史和電誘導性，來辨別唯一有效的治療（自動體外心臟去顫器）是否適當。本文重點討論布魯格達氏綜合症候群以及此病的不同層面，包括建議機制、流行病學、臨床表現、遺傳學、診斷、危險分層和治療方案。

-30 mV.[5] The resulting loss of AP dome at some, but not all, epicardial sites could create marked epicardial dispersion of repolarisation (EDR) [Fig 1d]. This gives rise to a transmural voltage gradient leading to a transmural dispersion of repolarisation (TDR) between the epicardium and endocardium which manifests as the characteristic ST-segment elevation of the ECG.[5,7,12] In addition, the T-wave remains positive when epicardial repolarisation precedes that of myocardial and endocardial regions, resulting in the characteristic type-2 or saddleback ECG (Fig 1b).[5] When sites in the epicardial region exhibit prolongation of the AP, reversed direction of repolarisation across the RV wall may ensue, producing the inverted T-wave and resulting in the type-3 coved-type ECG (Fig 1c).[5]

The repolarisation hypothesis could also explain the mechanism of VA initiation. When EDR and TDR occur via all-or-none repolarisation at some epicardial sites, an arrhythmogenic substrate is formed. This creates a vulnerable window when an AP can propagate from sites with normal repolarisation to sites with early repolarisation (Fig 1e). The conduction of an AP dome leads to local re-excitation via a phase 2 re-entry mechanism at sites of early repolarisation, and facilitates the development of extrasystolic beats from these sites.[5,7,17] These extrasystolic beats have been shown to initiate circus movement re-entry[17] and thus give rise to malignant VAs.[7]

Depolarisation (conduction delay and mild structural defects) hypothesis

This hypothesis for the Brugada ECG and susceptibility to VAs proposes a conduction delay in the right ventricular outflow tract (RVOT).[8,18] Accordingly, the AP is not fundamentally altered; rather conduction delay in the RVOT slows AP development in the right ventricle. This pathophysiological mechanism was believed to result in the Brugada ECG pattern and provide an arrhythmogenic substrate via a re-entry circuit.

As described by Meregalli et al,[8] during the initial phase of the cardiac cycle, the RV membrane potential is more positive than in the RVOT, driving

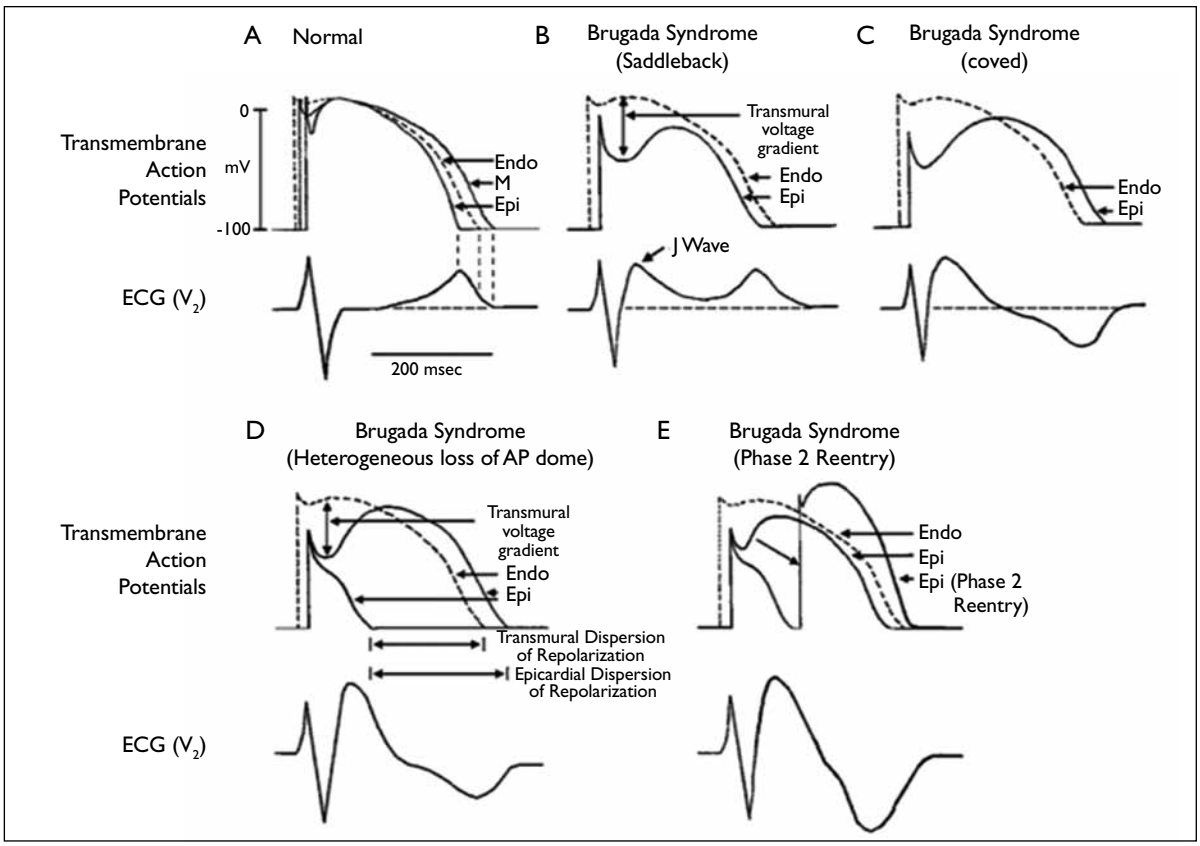

FIG 1. Schematic representation of the repolarisation disorder hypothesis[5*]
Reproduced with permission
* Endo denotes endocardium, M myocardium, Epi epicardium, and ECG electrocardiogram

the intercellular current to the RVOT. The current then passes back from the RVOT to the RV possibly via the extracellular space. During this time, an ECG electrode situated over the RVOT inscribes a positive signal and thus yields the ST-elevation of the Brugada ECG.[8] The membrane potentials are thus more positive in the RVOT than the RV and the potential gradient is reversed. The RVOT then drives the current in the opposite direction, away from the RVOT electrode, resulting in a negative T-wave. Further studies point towards a conduction delay as characteristic of the type-1 ECG.[10,19] The re-entry circuit which leads to a VA is thought to be caused by premature beats originating in the border zone between delayed and early depolarisation,[6] similar to what ensues in the presence of regional transmural ischaemia.[20]

While Brugada syndrome is recognised as a disorder with no gross structural defects,[2] there is some evidence for the involvement of mild structural abnormalities,[9-11,21] which were not previously detectable by conventional cardiac imaging.[3,11] Structural abnormalities found in the Brugada patients include focal fibrosis, myocarditis, apoptosis and fibrofatty replacement of the RV free wall with RV enlargement, dilation and RVOT enlargement.[9,11,13,22] It is suggested that such structural abnormalities play a role in Brugada syndrome[9,21,22] by contributing to slower conduction.[23,24] Other studies have linked structural and functional derangements to Brugada syndrome.[24] As symptomatic arrhythmias in the Brugada syndrome patients generally present around the fourth decade of life,[1,25-27] a time-dependent process of arrhythmogenic substrate generation has been suggested. This may entail development of the structural abnormalities.[14]

Recently it was proposed that the embryological development of the RV can explain the electrophysiological heterogeneity in the ventricular myocardium including the RV outflow tract, which could provide the substrate necessary for arrhythmias.[28] In support of the depolarisation hypothesis, Boukens et al[28] found that heterogeneity in expression of connexins and voltage-gated ion channels as well as tissue architecture may contribute to conduction slowing in the RV. Whether structural alterations in Brugada syndrome are primary or secondary is still unknown.

Most recently, a third unifying theory combining aspects of the depolarisation and repolarisation hypotheses has been proposed by Hoogendijk et al.[12] However, Brugada[15] suggested that it may be premature to search for a unifying pathophysiological mechanism for this syndrome.

Epidemiology

As the diagnosis of Brugada syndrome relies upon identifying a characteristic ECG pattern, there are inherent difficulties in determining its prevalence. Current prevalence estimates of 5/10 000[29] may underestimate the true prevalence, as many patients present with silent or concealed forms of the disease, without an available characteristic ECG. Brugada syndrome has been estimated to account for 20% of SCDs in the absence of structural heart disease and may be responsible for between 4% and 12% of all patients with SCD.[29]

The prevalence of Brugada syndrome also varies greatly according to location, being higher in East and South-East Asian populations.[2,30-32] A Japanese study reported the prevalence of a type-1 ECG pattern to be 12/10 000.[31] Sudden unexplained nocturnal death syndrome, long identified as endemic to South-East Asian countries,[32] has also been attributed to the Brugada syndrome.[33] Recently, a study of a hospital-based population in Singapore indicated that in those presenting with pre-syncope, syncope and/or palpitations, the prevalence of Brugada syndrome was about 3.1%.[34] In North America and western Europe, the prevalence of the syndrome is relatively lower[35]; one estimate in the US gave a figure of 12/100 000.[36]

Clinical presentation of Brugada syndrome

The clinical manifestations of Brugada syndrome are highly variable; some patients with the syndrome remain asymptomatic while for others endure sudden death. Nevertheless, when symptoms manifest, consistently they do so around the fourth decade of life.[1,25-27] Initial presenting symptoms reported include palpitations, syncope, seizures, and nocturnal agonal respiration.[13] Interestingly, a history of previous syncope was reported in up to 23% of patients presenting with cardiac arrest.[27] Most patients remain asymptomatic, however 17 to 42% of diagnosed patients encountered syncopal episodes or cardiac arrest due to arrhythmic complications, such as polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).[1,26] This might be an overestimate of the real frequency, as asymptomatic patients remain undiagnosed.[29]

Supraventricular tachycardias have been reported in up to 20% of patients with Brugada syndrome.[37] Morita et al[38] noted the frequency of spontaneous atrial fibrillation (AF) to be high (39%), there being increased vulnerability to AF following electrical stimulation. It is unknown, however, as to whether increased susceptibility to VAs correlates with such atrial vulnerability.[29]

Arrhythmias and thus symptoms in Brugada syndrome typically appear when there is a predominance of vagal activity, such as rest or during sleep.[39] According to Takigawa et al,[40] not only do these symptoms occur with a significant circadian peak (midnight to early morning) but there may

also be a significant seasonal peak (spring to early summer).

Gender differences

The Brugada syndrome phenotype is more prevalent in men than in women,[1,25-27,29] with the estimated ratio being up to 8-10:1.[2] Increased manifestations in men has been explained by the presence of significantly higher density of I_{to} currents in males versus females (in canines at least).[41] According to the repolarisation theory, this increases susceptibility to VAs as a more prominent I_{to} in RV epicardium facilitates a loss of the AP dome. A second hypothesis proposes a hormonal effect, with clinical studies suggesting that testosterone may be responsible for gender differences,[42] while experimental studies suggest a hormonal influence on ion currents.[43]

Children

There is little information on Brugada syndrome in the paediatric population,[29] despite the fact that three of the eight affected patients in the initial description of this syndrome were children.[3] Isolated case descriptions exist,[44,45] but large-scale studies are lacking.[46] Benito et al[29] surmise that Brugada syndrome may ensue/manifest in the paediatric age-group as follows:

(1) febrile episodes that frequently trigger for arrhythmias;

(2) symptoms, especially those with a spontaneous type I ECG that have a high risk of VAs; and

(3) having an implantable cardioverter defibrillator (ICD) implantation, benefits having been shown in those with a poor prognosis, though quinidine treatment may be an alternative.

In the paediatric population, Probst et al[46] failed to identify a male predominance, perhaps due to low levels of testosterone in children of both sexes.

Genetics

Brugada syndrome is inherited via autosomal dominant transmission.[2] In 1998, Chen et al[47] identified the first associated mutations in the *SCN5A* gene (locus 3p21), which encodes for the α-subunit of the cardiac sodium channel. In recent years, hundreds of mutations in the *SCN5A* gene have been linked to the syndrome (http://www.fsm.it/cardmoc/). The overall electrophysiological effect[33,48,49] is a reduction of transmembrane sodium current by various mechanisms, including a reduction in current density and gating changes.[50] Mutations in the *SCN5A* gene are currently only found in approximately 18 to 30% of Brugada cases,[2] with a high frequency of mutations in familial rather than sporadic cases,[51] which suggests genetic heterogeneity.[13]

A second locus on chromosome 3, distinct from *SCN5A*, has been linked to Brugada syndrome, and identified as the *GPD1-L* (glyercerol-3-phosphate dehydrogenase 1-like) gene. A mutation in the *GPD1-L* gene results in a reduced inward sodium current.[52] More recently, loss-of-function mutations in genes that encode the cardiac L-type calcium channel have been associated with the Brugada syndrome phenotype.[53] It has also been suggested that the gain-of-function caused by a mutation in the *KCNE3* gene (involved with the β-subunit of the transient outward potassium current) predisposes affected individuals to develop the Brugada syndrome phenotype.[54] Molecular and functional evidence reported in 2011 suggests that a *KCND3* gain-of-function mutation leads to enhanced transient outward current, particularly in the RV (where *KCND3* expression is highest).[55] This latest report provides a basis for the associated pathogenic substrate and phenotypic expression of Brugada syndrome.

Electrocardiographic and clinical diagnostic criteria

The current consensus[2] on the diagnosis of Brugada syndrome relies on both clinical findings and characteristic ECG patterns that occur spontaneously or are induced by the use of a sodium-channel blocking agents. To date, there are three known ECG subtypes (type-1, type-2, and type-3) that can be detected in more than one of the right precordial leads (V1-V3), and have varying diagnostic value (Fig 2[56]).

The type-1 ECG pattern is diagnostic of Brugada syndrome and is characterised by a coved-shape ST-segment elevation greater than 2 mm (0.2 mV) followed by an inverted T wave in one or more of the right precordial leads (Fig 2a), which occur with or without provocation by a sodium channel-blocking agent.[2] This pattern must ensue alongside one of the following: a history of VF; polymorphic VT; family history of unexplained SCD in persons older than 45 years; family history of coved-type ECGs; inducibility of VT with programmed electrical stimulation, syncopal episodes, or nocturnal agonal respiration.[2]

In the type-2 pattern, the ST-segment resembles a saddleback, with an ST-segment elevation of at least 2 mm (0.2 mV), a trough of the ST-segment elevation of at least 1 mm (0.1 mV) and then either a positive or biphasic T wave (Fig 2b).[2]

The type-3 pattern consists of either a coved (type-1 like) or saddleback (type-2 like) ST-segment elevation between 1 and 2 mm (0.1-0.2 mV) [Fig 2c]. Both type-2 and type-3 ECG findings occur spontaneously, without the use of a sodium channel-blocking agent, but by themselves they are not considered diagnostic. If, however, either the type-2

or type-3 ECG pattern converts to a type-1 ECG pattern after provocation by a sodium channel-blocking agents, and at least one of the aforementioned characteristic clinical findings is present, a diagnosis of Brugada syndrome can be considered.

A high degree of suspicion is warranted if only clinical findings are present. Given the expected variability in ECG recordings in patients with Brugada syndrome, serial recordings are recommended. An individual patient can show either type-1, type-2, or type-3 ECG patterns or even no pathological ECGs.[57]

Diagnostic (electrocardiogram unmasking) agents

The diagnostic type-1 ECG pattern can occur spontaneously or through administration of sodium channel-blocking or Class I anti-arrhythmic agents (Table[19]). Other pharmacological agents which may induce Brugada-like ECG patterns include calcium channel blockers, beta-blockers, anti-anginal drugs, psychotropic drugs (tricyclic and tetracyclic antidepressants, selective serotonin reuptake inhibitors, and phenothiazine) as well as dimenhydrinate, cocaine, bupivacaine, and alcohol.[2,58]

Risk stratification

Risk stratification of Brugada syndrome is aimed at identifying individuals most liable to SCD, so that they can receive appropriate management (Fig 3[2,29]). Individuals with a diagnosis of Brugada syndrome based on a spontaneous or induced type-1 ECG pattern may present with or without symptoms. Symptomatic presentations include aborted SCD, syncope, seizure, and nocturnal agonal respiration. Asymptomatic individuals should be assessed for relevant family history, especially instances of unexplained SCD.

The International Registry of Brugada syndrome reported that 25% (178/724) of this population experienced SCD or VF during their lifetime, at a mean age of 42 (standard deviation, 15) years.[29] Recently, in a larger series of patients, the aborted SCD frequency was estimated to be 7.7%; 1.9% in patients with syncope only, and 0.5% in entirely asymptomatic patients.[59] Other factors denoting increased risk of an adverse cardiac event include aborted SCD, syncope, spontaneous or unmasked type-1 ECG patterns, family history of SCD, and inducibility of VT or VF during an electrophysiological study (EPS).

Among patients presenting with aborted SCD, the risk of its recurrence or VF was 62% (44/71) with a mean follow-up time of 54 months.[24] This cohort is at highest risk for future cardiac events, regardless of other risk factors. These patients have the most compelling indication for treatment with an ICD, the only treatment option demonstrated to be effective to date.[24]

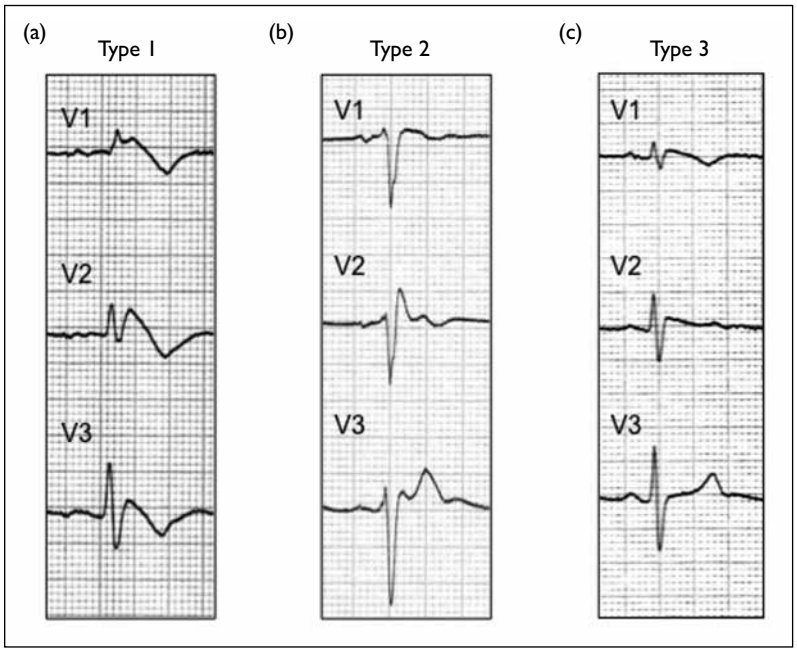

FIG 2. Characteristic electrocardiogram patterns of Brugada syndrome[56]

TABLE. Sodium channel-blocking agents that can unmask Brugada syndrome[19]

Drug	Dosage	Administration
Ajmaline	1 mg/kg over 5 mins	Intravenous
Flecainide	2 mg/kg over 10 mins	Intravenous
Flecainide	400 mg	Oral
Procainamide	10 mg/kg over 10 mins	Intravenous
Pilsicanide	1 mg/kg over 10 mins	Intravenous

Even if there is no history of cardiac arrest, Brugada syndrome is reported to carry an 8.2% (45/547) risk of SCD or VF over 24 months.[25] These individuals experience a type-1 ECG pattern spontaneously or after provocation by a sodium channel-blocking agent. Subjects with spontaneous type-1 ECGs carry a 7.7-fold greater risk of developing an arrhythmic event during their lifetime compared with those with non-spontaneously occurring type-1 ECGs.[2]

In patients with Brugada syndrome, inducibility of VAs by electrophysiological means is a predictor of poorer prognostic outcome. Patients with EPS-inducible VAs reportedly have a hazard ratio of 8.3 (95% confidence interval [CI], 2.8-25.0) for aborted SCD when compared to patients with no inducible VAs.[60] In asymptomatic patients, 6.5% (11/167) developed aborted sudden death, the strongest predictor of VF being inducible arrhythmia following programmed ventricular stimulation ($P<0.008$).[60] Therefore EPS seems to be a useful prognostic tool to complement the risk stratification in patients with no history of aborted SCD. Inducible VT or VF by EPS warrants ICD treatment even for asymptomatic

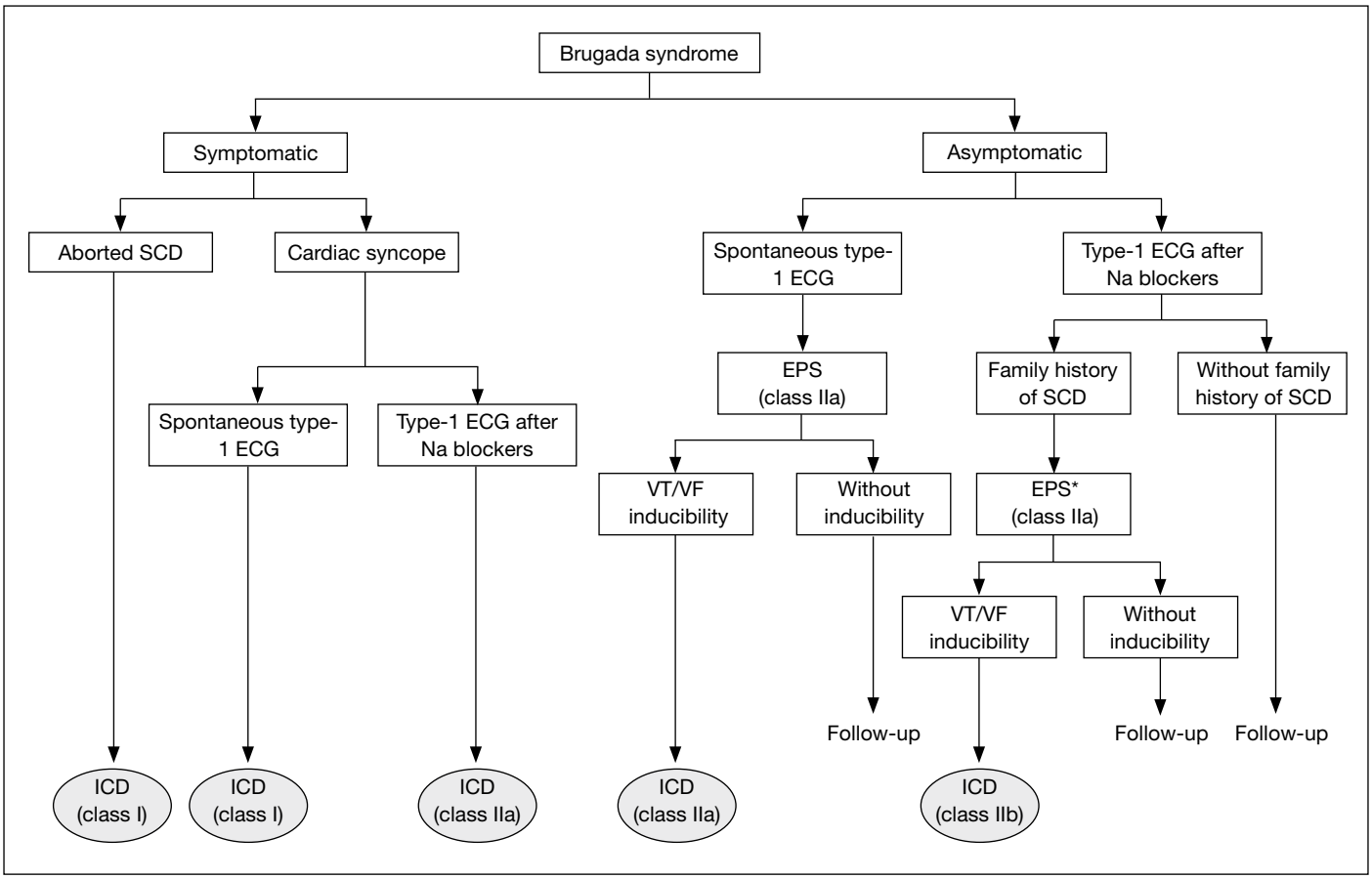

FIG 3. Risk stratification and treatment of the Brugada system[2,29]

SCD denotes sudden cardiac death, ECG electrocardiogram, Na sodium, EPS electrophysiological study, VT/VF ventricular tachycardia/fibrillation, and ICD implantable cardioverter defibrillator

* EPS study is still controversial

patients if they show a spontaneous type-1 ECG or have a family history of sudden death.[29] All other patients warrant close follow-up.

However, some have questioned whether inducibility on EPS is associated with increased risk of adverse cardiac events. A meta-analysis that included 1500 patients concluded that an inducible EPS carried a relative risk of only 1.88 (95% CI, 0.62-5.73, P=0.27).[61] Priori et al[27] also failed to find a relationship between recurrences of VAs and EPS inducibility or non-inducibility.

In one of the largest series of Brugada syndrome patients to date (n=1029), it was shown that predictors of arrhythmic events were spontaneous type-1 ECGs and symptoms.[59] Apparently a familial history of SCD, male gender, presence of an *SCN5A* mutation, and inducibility of VAs during EPS were not predictive. Other studies, however, have found that male gender per se carries a poorer prognosis for adverse cardiac events (hazard ratio=5.3; 95% CI, 1.6-16.6).[25]

In contrast to the recommendations of the Second Consensus on Brugada syndrome the ACC/AHA/HRS 2008 Practice Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities,[62] the following differences in the levels of evidence for ICD implantation in patients with Brugada syndrome are shown:

- For cardiac syncope, the level is Class IIa;
- For documented VT not resulting in cardiac arrest, the level is Class IIa;
- In asymptomatic patients with a spontaneous type-1 ECG pattern and EPS inducibility, there is currently no evidence.

Treatment

To date treatment options for Brugada syndrome have been limited to device-related and pharmacological therapies. However, education and prevention of arrhythmias via lifestyle awareness should also be considered in line with broader recommendations for other cardiac conditions about which more is known.

Management of acute malignant arrhythmias or electrical storms includes early defibrillation and resuscitation of the patient, followed by admission to a specialised cardiac care facility. Any provocative circumstances such as fever should be treated with antipyretics and/or cooling. Any

intake of arrhythmogenic drugs/substances should be discontinued. Pharmacological treatment with isoprenaline (1-2 μg bolus intravenously followed by continuous infusion of 0.15-2.0 μg/min) and/or quinidine (300-1500 mg/day) has been used for electrical storms. In children, dosing is often tailored to bodyweight. The suggested quinidine dosage for children is 30 to 60 mg/kg/day given in four divided doses.[46,63,64]

Device treatment

For Brugada syndrome, the most recent Consensus Report[2] regards ICDs as the only established form of effective treatment. Best practice entails ICD implantation according to the aforementioned risk stratification outline. In summary, an ICD should be offered to all symptomatic patients presenting with Brugada syndrome. All asymptomatic patients should undergo further risk stratification to assess their indication for an ICD.

In symptomatic patients treated with an ICD, the average annual shock rate was reported to be 2.6% and for asymptomatic patients it was 1.5%.[65] Thus far, data on cryosurgical ablation in Brugada syndrome have been limited.[2]

Complications of implantable cardioverter defibrillator

Although ICDs are very effective in treating VF and the implantation procedure is usually very safe, there may be surgical complications. These include bleeding, pneumothorax, perforation of vascular structures, cardiac tamponade, and infections. Post-implantation issues include displacement or fracture of leads, false shocks (eg inappropriately shocking a patient with fast AF or exercise-related sinus tachycardia), and the need to replace the device because of battery depletion.

Role of drugs as long-term treatment

Relatively small case series describe the use of drugs as potentially beneficial in Brugada syndrome patients, though none of these agents are proven to completely prevent arrhythmias. Moreover, some of these drugs have not been tested to an appreciable extent in Brugada syndrome patients; others may have unacceptable side-effects. In the absence of provoking drugs, only severely symptomatic or high-risk patients may be candidates for long-term pharmacological treatment, preferably in a medical centre with suitable expertise and experience. Currently, quinidine seems to be the treatment of choice for such therapy.[66]

Pharmacological therapies are directed at rebalancing the ion channel currents. These are active for the duration of phase 1 of the epicardial AP in the RV, and thereby minimise the magnitude of the notch, and restore the normal dome of the AP or both.[2,29]

Irrespective of the ion channel involved, a prominent I_{to} (transient outward potassium current) seems to play a predominant role in arrhythmogenesis. Consequently, blocking the I_{to} channel is a logical approach and this can be done with quinidine.[67] Quinidine, a class Ia anti-arrhythmic, is the most studied pharmacological treatment in Brugada syndrome. Its mechanism of action relies on its I_{to} blocking properties.[2] More specifically, Benito et al[29] state that quinidine is effective in the suppression of phase-2 re-entry in experimental models, and has demonstrable clinical efficacy (decreasing inducibile VF and spontaneous VF during follow-up). It is also used as adjunctive therapy with ICD implants to control electrical storms and as a viable treatment option in children.[29] Clinical evidence also demonstrates that it can normalise ST-segment elevation in patients with Brugada syndrome.[19]

Belhassen et al[66] claimed to have used quinidine effectively as the sole therapy (without ICD back-up) for patients with symptomatic Brugada syndrome, including those with prior spontaneous VF. In a recent study, none of the 50 patients with symptomatic or asymptomatic Brugada syndrome developed symptomatic VAs while on quinidine therapy during follow-up periods ranging from 3 months to more than 10 years.[68] However, quinidine often causes side-effects (diarrhoea, thrombocytopenia, hepatitis) that resolve after drug discontinuation. The main concern relates to the potential pro-arrhythmic activity of quinidine, there being an estimated 2 to 8% risk for torsades de pointes in treated patients. Most instances of quinidine-induced torsades de pointes occur soon after initiation of therapy, which therefore warrants close monitoring during the first few days of therapy. Torsades de pointes ensuing long after the onset of therapy is often caused by drug interactions or hypokalaemia,[69] for which meticulous avoidance of risk factors may reduce the likelihood.

In view of the limited evidence base for the use of pharmacotherapies such as quinidine, the mainstay of treatment continues to be ICD implantation. Quinidine therapy may be an alternative in those who are ineligible or persons refusing such an intervention.

Miscellaneous

It is recommended that patients diagnosed with Brugada syndrome are counselled, such that they and their relatives are informed. Patient education should include advice on avoidance of provoking agents, as well as cardiopulmonary resuscitation training for family members.

References

1. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 2002;105:73-8.
2. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005;111:659-70.
3. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol 1992;20:1391-6.
4. Link MS, Antzelevitch C, Waldo AL, et al. Clinical cardiac electrophysiology fellowship teaching objectives for the new millennium. J Cardiovasc Electrophysiol 2001;12:1433-43.
5. Antzelevitch C. Brugada syndrome. Pacing Clin Electrophysiol 2006;29:1130-59.
6. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. Circulation 1996;93:372-9.
7. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999;100:1660-6.
8. Meregalli PG, Wilde AA, Tan HL. Pathophysiological mechanisms of Brugada syndrome: depolarization disorder, repolarization disorder, or more? Cardiovasc Res 2005;67:367-78.
9. Corrado D, Nava A, Buja G, et al. Familial cardiomyopathy underlies syndrome of right bundle branch block, ST segment elevation and sudden death. J Am Coll Cardiol 1996;27:443-8.
10. Coronel R, Casini S, Koopmann TT, et al. Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: a combined electrophysiological, genetic, histopathologic, and computational study. Circulation 2005;112:2769-77.
11. Frustaci A, Priori SG, Pieroni M, et al. Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. Circulation 2005;112:3680-7.
12. Hoogendijk MG, Opthof T, Postema PG, Wilde AA, de Bakker JM, Coronel R. The Brugada ECG pattern: a marker of channelopathy, structural heart disease, or neither? Toward a unifying mechanism of the Brugada syndrome. Circ Arrhythm Electrophysiol 2010;3:283-90.
13. Capulzini L, Brugada P, Brugada J, Brugada R. Arrhythmia and right heart disease: from genetic basis to clinical practice. Rev Esp Cardiol 2010;63:963-83.
14. Wilde AA, Postema PG, Di Diego JM, et al. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. J Mol Cell Cardiol 2010;49:543-53.
15. Brugada P. Commentary on the Brugada ECG pattern: a marker of channelopathy, structural heart disease, or neither? Toward a unifying mechanism of the Brugada syndrome. Circ Arrhythm Electrophysiol 2010;3:280-2.
16. Näbauer M, Beuckelmann DJ, Uberfuhr P, Steinbeck G. Regional differences in current density and rate-dependent properties of the transient outward current in subepicardial and subendocardial myocytes of human left ventricle. Circulation 1996;93:168-77.
17. Lukas A, Antzelevitch C. Phase 2 reentry as a mechanism of initiation of circus movement reentry in canine epicardium exposed to simulated ischemia. Cardiovasc Res 1996;32:593-603.
18. Tukkie R, Sogaard P, Vleugels J, de Groot IK, Wilde AA, Tan HL. Delay in right ventricular activation contributes to Brugada syndrome. Circulation 2004;109:1272-7.
19. Postema PG, van Dessel PF, de Bakker JM, et al. Slow and discontinuous conduction conspire in Brugada syndrome: a right ventricular mapping and stimulation study. Circ Arrhythm Electrophysiol 2008;1:379-86.
20. Janse MJ, Kléber AG. Electrophysiological changes and ventricular arrhythmias in the early phase of regional myocardial ischemia. Circ Res 1981;49:1069-81.
21. Takagi M, Aihara N, Kuribayashi S, et al. Localized right ventricular morphological abnormalities detected by electron-beam computed tomography represent arrhythmogenic substrates in patients with the Brugada syndrome. Eur Heart J 2001;22:1032-41.
22. Tada H, Aihara N, Ohe T, et al. Arrhythmogenic right ventricular cardiomyopathy underlies syndrome of right bundle branch block, ST-segment elevation, and sudden death. Am J Cardiol 1998;81:519-22.
23. Furushima H, Chinushi M, Okamura K, et al. Comparison of conduction delay in the right ventricular outflow tract between Brugada syndrome and right ventricular cardiomyopathy: investigation of signal average ECG in the precordial leads. Europace 2007;9:951-6.
24. Takagi M, Aihara N, Kuribayashi S, et al. Abnormal response to sodium channel blockers in patients with Brugada syndrome: augmented localised wall motion abnormalities in the right ventricular outflow tract region detected by electron beam computed tomography. Heart 2003;89:169-74.
25. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation 2003;108:3092-6.
26. Eckardt L, Probst V, Smits JP, et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. Circulation 2005;111:257-63.
27. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105:1342-7.
28. Boukens BJ, Christoffels VM, Coronel R, Moorman AF. Developmental basis for electrophysiological heterogeneity in the ventricular and outflow tract myocardium as a substrate for life-threatening ventricular arrhythmias. Circ Res 2009;104:19-31.
29. Benito B, Brugada J, Brugada R, Brugada P. Brugada syndrome. Rev Esp Cardiol 2009;62:1297-315.
30. Matsuo K, Akahoshi M, Nakashima E, et al. The prevalence, incidence and prognostic value of the Brugada-type electrocardiogram: a population-based study of four decades. J Am Coll Cardiol 2001;38:765-70.
31. Miyasaka Y, Tsuji H, Yamada K, et al. Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. J Am Coll Cardiol 2001;38:771-4.
32. Tungsanga K, Sriboonlue P. Sudden unexplained death syndrome in north-east Thailand. Int J Epidemiol 1993;22:81-7.
33. Vatta M, Dumaine R, Varghese G, et al. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. Hum Mol Genet 2002;11:337-45.

34. Sidik NP, Quay CN, Loh FC, Chen LY. Prevalence of Brugada sign and syndrome in patients presenting with arrhythmic symptoms at a Heart Rhythm Clinic in Singapore. Europace 2009;11:650-6.
35. Gallagher MM, Forleo GB, Behr ER, et al. Prevalence and significance of Brugada-type ECG in 12,012 apparently healthy European subjects. Int J Cardiol 2008;130:44-8.
36. Patel SS, Anees S, Ferrick KJ. Prevalence of a Brugada pattern electrocardiogram in an urban population in the United States. Pacing Clin Electrophysiol 2009;32:704-8.
37. Eckardt L, Kirchhof P, Loh P, et al. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? J Cardiovasc Electrophysiol 2001;12:680-5.
38. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. J Am Coll Cardiol 2002;40:1437-44.
39. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol 1996;27:1061-70.
40. Takigawa M, Noda T, Shimizu W, et al. Seasonal and circadian distributions of ventricular fibrillation in patients with Brugada syndrome. Heart Rhythm 2008;5:1523-7.
41. Di Diego JM, Cordeiro JM, Goodrow RJ, et al. Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. Circulation 2002;106:2004-11.
42. Shimizu W, Matsuo K, Kokubo Y, et al. Sex hormone and gender difference—role of testosterone on male predominance in Brugada syndrome. J Cardiovasc Electrophysiol 2007;18:415-21.
43. Bai CX, Kurokawa J, Tamagawa M, Nakaya H, Furukawa T. Nontranscriptional regulation of cardiac repolarization currents by testosterone. Circulation 2005;112:1701-10.
44. Priori SG, Napolitano C, Giordano U, Collisani G, Memmi M. Brugada syndrome and sudden cardiac death in children. Lancet 2000;355:808-9.
45. Sanatani S, Mahkseed N, Vallance H, Brugada R. The Brugada ECG pattern in a neonate. J Cardiovasc Electrophysiol 2005;16:342-4.
46. Probst V, Denjoy I, Meregalli PG, et al. Clinical aspects and prognosis of Brugada syndrome in children. Circulation 2007;115:2042-8.
47. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998;392:293-6.
48. Rook MB, Bezzina Alshinawi C, Groenewegen WA, et al. Human SCN5A gene mutations alter cardiac sodium channel kinetics and are associated with the Brugada syndrome. Cardiovasc Res 1999;44:507-17.
49. Vatta M, Dumaine R, Antzelevitch C, et al. Novel mutations in domain I of SCN5A cause Brugada syndrome. Mol Genet Metab 2002;75:317-24.
50. Tan HL. Sodium channel variants in heart disease: expanding horizons. J Cardiovasc Electrophysiol 2006;17(Suppl 1):151S-157S.
51. Schulze-Bahr E, Eckardt L, Breithardt G, et al. Sodium channel gene (SCN5A) mutations in 44 index patients with Brugada syndrome: different incidences in familial and sporadic disease. Hum Mutat 2003;21:651-2.
52. London B, Michalec M, Mehdi H, et al. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. Circulation 2007;116:2260-8.
53. Antzelevitch C, Pollevick GD, Cordeiro JM, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. Circulation 2007;115:442-9.
54. Delpón E, Cordeiro JM, Núñez L, et al. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. Circ Arrhythm Electrophysiol 2008;1:209-18.
55. Giudicessi JR, Ye D, Tester DJ, Crotti L, Mugione A, Nesterenko VV, et al. Transient outward Current (I(to)) gain-of-function mutations in the KCND3-encoded Kv4.3 potassium channel and Brugada syndrome. Heart Rhythm 2011;8:1024-32.
56. Napolitano C, Priori SG. Brugada syndrome. Orphanet J Rare Dis 2006;1:35.
57. Veltmann C, Schimpf R, Echternach C, et al. A prospective study on spontaneous fluctuations between diagnostic and non-diagnostic ECGs in Brugada syndrome: implications for correct phenotyping and risk stratification. Eur Heart J 2006;27:2544-52.
58. Yap YG, Behr ER, Camm AJ. Drug-induced Brugada syndrome. Europace 2009;11:989-94.
59. Probst V, Veltmann C, Eckardt L, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. Circulation 2010;121:635-43.
60. Brugada P, Brugada R, Brugada J. Should patients with an asymptomatic Brugada electrocardiogram undergo pharmacological and electrophysiological testing? Circulation 2005;112:279-92;discussion 279-92.
61. Gehi AK, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. J Cardiovasc Electrophysiol 2006;17:577-83.
62. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;51:e1-62.
63. Ohgo T, Okamura H, Noda T, et al. Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. Heart Rhythm 2007;4:695-700.
64. Watanabe A, Fukushima Kusano K, Morita H, et al. Low-dose isoproterenol for repetitive ventricular arrhythmia in patients with Brugada syndrome. Eur Heart J 2006;27:1579-83.
65. Sacher F, Probst V, Iesaka Y, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. Circulation 2006;114:2317-24.
66. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. Circulation 2004;110:1731-7.
67. Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. J Cardiovasc Electrophysiol 2001;12:268-72.
68. Rosso R, Glick A, Glikson M, et al. Outcome after implantation of cardioverter defibrillator [corrected] in patients with Brugada syndrome: a multicenter Israeli study (ISRABRU). Isr Med Assoc 2008;10:435-9.
69. Viskin S, Fish R, Roden DM. Drug induced torsade de pointes. In: Baunwald E, Fauci SA, Isselbacher KJ, editors, et al. Harrison's principles of internal medicine. Harrison's online. 14th ed; 2000: 231.