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Editorial Office
Prof. Dr. Mehdi Zoghi
Ege University, Faculty of Medicine,
Department of Cardiology,
Bornova, 3100, İzmir - Turkey.
Telephone: +90 232 - 3905458
E-mail: mehdi_zoghi@hotmail.com

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Review Article

Brugada Syndrome: A Brief Review on Diagnostic Approach, Risk Stratification, and Management

Raymond Pranata

Department of Cardiology and Vascular Medicine, Siloam Hospitals Lippo Village - Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

ORCID:

Raymond Pranata: https://orcid.org/0000-0003-3998-6551

Abstract

Brugada syndrome is a congenital channelopathy in cardiac ion transmembrane causing an alteration in the electrical conduction of the heart. ST-elevation, as well as right bundle-branch block in anterior precordial electrocardiography (ECG), is pathognomonic in this syndrome. The patient might be asymptomatic or with a history of syncope and prone to develop ventricular tachyarrhythmia which may spontaneously recover or degenerates to ventricular fibrillation, cardiac arrest and even sudden death. Nevertheless, this can be prevented by implantable cardioverter defibrillator implantation. Therefore, it is of paramount importance that clinical suspicion and identification, interpretation of its characteristic ECG pattern and risk stratification to be properly done to diagnose and to manage Brugada syndrome. The author has also done a systematic review (included in the article) for several noninvasive ECG parameters for risk stratification with promising results. Epicardial ablation is an emerging therapy that may "cure" Brugada syndrome.

Keywords: Arrhythmia, Brugada syndrome, risk stratification, sudden cardiac death, syncope

Introduction

Brugada syndrome is a genetically determined channelopathy leading to syncope and ventricular tachyarrhythmia causing sudden death in those without evident structural heart disease. It was first mentioned in 1992.[1,2] Brugada syndrome was commonly considered as an abnormality found commonly in young males (male: female ratio was 9:1) and Southeast Asian. It frequently manifests at the age of 40 years, causing sudden death frequently during sleep.[3-5] Suspicion should arouse when encountering a patient with a history of idiopathic ventricular fibrillation (VF) or polymorphic ventricular tachycardia (VT) that aborts spontaneously and family history of sudden death in young age with or without typical electrocardiography (ECG) findings. The incidence of Brugada syndrome in adults is approximately 0.05%–0.60% and the average age when the diagnosis is established is 41 years old.[6]

Genetic Basis and Pathophysiology

There are 18 genes that are associated with Brugada syndrome from BrS1 to BrS18. Basically, there are abnormalities in sodium, calcium, or potassium ion channels located at heart muscles.[7,8]

Sodium flow

BrS1 gene was the first gene to be discovered which involves SCN5A at chromosome 3p21-23 encodes subunit α of sodium ion channel protein (NaV1.5) which is responsible for depolarization (Phase 0 of action potential). Mutation results in loss-of-function of the sodium channel resulting in less sodium influx into the interior of the cell during depolarization. This mutation was also linked with other cardiac conduction defects (atrioventricular [AV] block, left bundle branch block, and left anterior fascicular block).[9,10] BrS2 is responsible for mutations in glycerol-3-phosphate dehydrogenase 1-like protein reducing both the surface membrane expression and the inward sodium current.[11] SCN1B plays a role in forming subunit β1 of sodium ion

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Address for correspondence: Dr. Raymond Pranata, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia.
E-mail: raymond_pranata@hotmail.com

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which modifies Nav1.5, thus increasing I_{Na} was the cause of BrS5.[12] Meanwhile, BrS7 gene (SCN3B gene) forms subunit β3 of sodium ion channels which alters Nav1.5 trafficking, thereby decreasing I_{Na}.[13]

Calcium flow

CACNA1C mutation results in BrS3 and CACNB2 cause BrS4. They are responsible for a defective unit of the L-type calcium channel. These mutation cause dysfunctions in subunit α and β resulting in loss of function and reduced calcium influx culminating in shortening of the plateau phase of action potential. The *CACNA2D1* gene was reported as responsible for BrS. The α2/δ-subunit of voltage-dependent calcium channels regulates current density and activation/inactivation kinetics of the calcium channel.[7,8]

Potassium flow

KCNE3 gene plays a role in the formation of MiRP2 protein (β-subunit that regulates the potassium channel I_{to}) and modulates some potassium currents in the heart. A recent study revealed that enhanced I_{to} current gradient in the right ventricle was associated with KCND3 gain-of-function mutations (Kir4.3 protein). Another gene associated with BrS is *KCNJ8,* which was previously related to early repolarization syndrome and a marker of gain-of-function in the cardiac K (ATP) Kir6.1 channel. The *KCNE5* gene, which is located in the X chromosome, encodes an auxiliary β-subunit for K channels causing gain-of-function effects on I_{to}.[7,14]

The most prevalent is SCN5A mutation (20% of cases), these dysfunctions resulted in an imbalance between outward and inward positive currents during repolarization causing heterogeneous loss of action potential dome during phase 2. Increased dispersion of repolarization and refractoriness within epicardium and across the wall are associated with phase 2 re-entry mechanism resulting in ventricular arrhythmias.[15] Most of the genetic variants found in Brugada syndrome remain of unknown significance because no comprehensive cellular studies have been performed. Genetic variants other than SCN5A may be responsible for only 2%–5% of diagnostic cases. Recently, there is a notion that Brugada syndrome may not be caused by a single mutation but rather by multiple susceptibility variants [Figure 1].

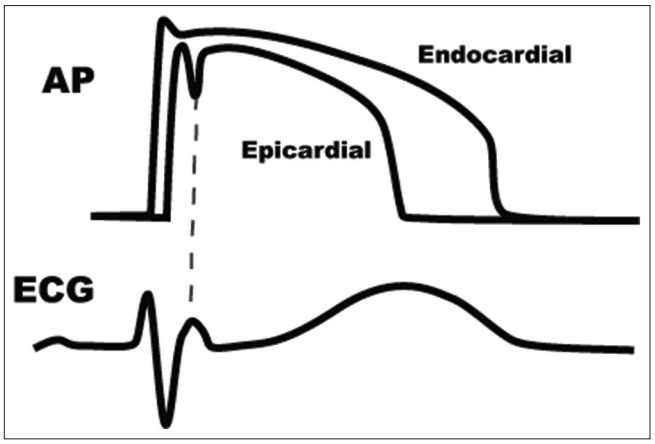


Figure 1: Difference in action potential in epicardial and endocardial myocyte in Brugada syndrome. Repolarization disorder hypothesis stated that the difference between action potential in the epicardial and endocardial myocyte resulted in the typical ST-elevation in Brugada syndrome

Clinical Manifestation and Diagnosis

VF or aborted sudden cardiac death (SCD), syncope, nocturnal agonal respiration, palpitations, and chest discomfort are associated with Brugada syndrome. These symptoms frequently occur during rest or sleep, fever, excess eating or binge drinking resulting in excess vagotonic condition nonetheless they rarely manifest during exercise.[8,16] Symptoms occurring at young age signals an aggressive form of the disease. Overall 20% experienced at least 1 syncope and only 10%–14% suffered cardiac arrest before 60 years old as was shown by international registries and meta-analysis.[6,17] Drugs such as bupivacaine, cocaine, propafenone, methoxamine, β-blocker, potassium channel activator (pinacidil), a tricyclic antidepressant, an opioid analgesic, lithium, and propofol exacerbates ECG pattern and potentially precipitating arrhythmia (visit Brugadadrugs.org). Diagnostic criteria of Brugada syndrome according to 2013 HRS/EHRA/APHRS expert consensus statement is with ST-segment elevation with type I morphology ≥2 mm in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs or in patients with type 2 or type 3 ST-segment elevation in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd, or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology.[16] According to international consensus conference on BrS ST-segment elevation of ≥2 mm in at least two of three precordial leads (V1–V3) with coved morphology associated with complete or incomplete right bundle-branch block was the ECG criteria to fulfill. Other ECG abnormalities that might be found are AV block and atrial fibrillation (10%–25% of patients).[8,18-21] These atrial arrhythmias in Brugada syndrome were associated with genetic variants impairing the sodium channel function along with structural remodeling that promote AF by prolonging refractoriness and slowing conduction velocity which may be heterogeneous and facilitates the development of unidirectional block and re-entry, giving rise to atrial fibrillation, atrial flutter, and AV-nodal re-entry tachycardia.[22]

There are three typical ECG patterns in patients with Brugada syndrome. In type 1 there is a Coved ST-segment elevation ≥2 mm followed by T inversion in >1 precordial leads (V1–V3). ST-T segment saddleback configuration followed by positive or biphasic T wave is seen in type 2 ECG. Meanwhile, type 3 may show coved or saddleback with ST-segment elevation <1 mm [Figure 2]. Typical ST segment changes might be found in patients with concealed form or type 2 or 3 ECG during provocation or fever. Therefore, in

Table 1: Proposed Shanghai Score System for diagnosis of Brugada syndrome

	Points
ECG (12-Lead/Ambulatory)	
Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2
Only award points once for highest score within this category. One item from this category must apply.	
Clinical History*	
Unexplained cardiac arrest or documented VF/ polymorphic VT	3
Nocturnal agonal respirations	2
Suspected arrhythmic syncope	2
Syncope of unclear mechanism/unclear etiology	1
Atrial flutter/fibrillation in patients <30 years without alternative etiology	0.5
Family History*	
First- or second-degree relative with definite BrS	2
Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative	1
Unexplained SCD <45 years in first- or second-degree relative with negative autopsy	0.5
Genetic test result	
Probable pathogenic mutation in BrS susceptibility gene	0.5
Score (requires at least 1 ECG finding). >3.5 points: Probable/definite BrS. 2-3 points: Possible BrS <2 points: Non-diagnostic	

*Only award points once for highest score within this category. BrS=Brugada syndrome; SCD=sudden cardiac death; VF=ventricular fibrillation; VT=ventricular tachycardia. Reproduced from Antzelevitch *et al*.[23]

patients with type 2 or 3 ECG findings, provocation with sodium channels inhibitor.[15] [Figure 2]. There is also new diagnostic criteria of Brugada syndrome (Shanghai score) which was proposed in the consensus statement in 2016 [Table 1].[23] It is important to note in this new consensus, that asymptomatic patients with drug-induced type 1 ECG are considered to be at low risk and need some clinical manifestations to be diagnosed with Brugada syndrome.[23]

Risk Stratification

Almost all studies are in agreement that patient with type 1 baseline ECG and an episode of syncope have a high risk of cardiac arrhythmia in follow-up. The presence of QRS fragmentation and effective refractory period <200 ms were also proposed.[24-26] Risk of lethal or near-lethal arrhythmia episode in previously asymptomatic patient is 8%, event rate at 33 ± 39 months follow-up was reported by Brugada *et al*.; 6% event rate in 34 ± 44 months by Priori *et al*.; 1% event rate was found at 40 ± 50 months and 30 ± 21 months follow-up by Eckardt *et al*. and Giustetto *et al*.[25,27-29] Even though large registries are in agreement that electrophysiological study (EPS) inducibility was most frequently encountered

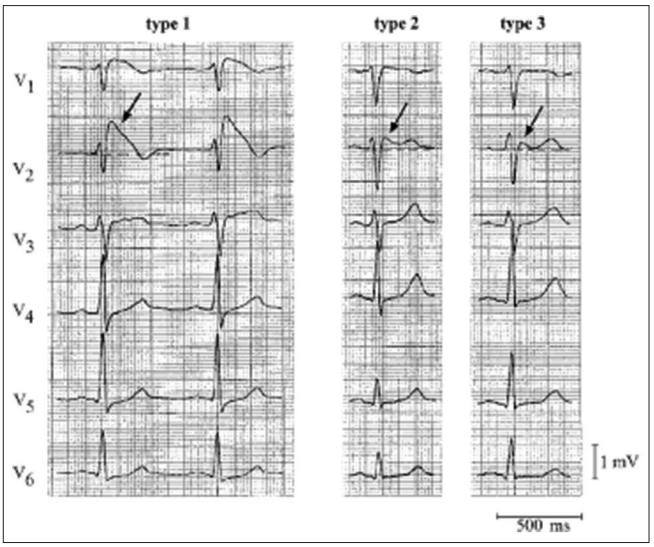


Figure 2: Electrocardiographic characteristics of Brugada pattern in precordial leads. electrocardiography in Brugada Syndrome. Type 1: Coved ST-elevation ≥2 mm followed by T wave deflection. Type 2: Gradually decreasing ST-elevation with saddleback pattern with positive or biphasic T wave and Type 3: coved or saddleback with ≥1 mm ST-elevation.[32] From: Wilde AA, Antzelevitch C, Borggrefe M *et al*.; Study Group on the Molecular basis of arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome. Eur Heart J 2002;23:1648-54

in those who experienced syncope or aborted sudden death, there is no consensus regarding the role of EPS. A study by Siera *et al*. showed 25 ventricular arrhythmia events, which consists of 16 (21.9%) patients in the group that was successfully induced by EPS and 9 (2.7%) patients that are not inducible. The aforementioned arrhythmia resulted in 24 appropriate implantable cardioverter defibrillator (ICD) shocks and 1 resuscitation because of cardiac arrest in those without ICD. The hazard ratio for an arrhythmic event in the future is 8.1 ($P < 0.01$) for those with inducible ventricular arrhythmia during the EPS study.[30] EPS is controversial because the protocols are different between studies, for example; only from RV apex by Brugada group, but other groups from both apex and RVOT, up to double or triple extra stimuli, and minimal coupling interval to 200 ms or to 180 ms, etc.). Recently, VF induction up to two extra stimuli is reported to be useful in the risk stratification of patients with Brugada syndrome.[27,31]

A study showed a Kaplan–Meier curve of 96.8%–99% event-free survival at 1, 5, 10, and 15 years in noninducible ventricular arrhythmia during EPS. It is concluded that in a patient with asymptomatic clinical presentation alone in those with noninducible groups has 99.2% event-free survival at 1, 5, 10, and 15 years.[30,32] Hence, EPS is an excellent predictor in both asymptomatic or those presenting with syncope[2] [Figure 3].

There were also studies that enlist additional tools for the risk stratification mainly Tpeak-end interval (TpTe), Tp-e dispersion, and TpTe/QT ratio [Table 2].[33-41] There were five

Table 2: Role of Tpeak-Tend, Tpeak-Tend/QT ratio, and Tpe dispersion as additional noninvasive electrocardiography parameters for predicting ventricular tachycardia/fibrillation in patients with Brugada Syndrome

Authors	Year	Study design	Samples	Subjects	Outcome of interest	Results
Morita H *et al*.	2018	Case-control study	62	Brugada-type ECG	Initial VF	OR of difference Tpe interval (V1) ≥ +10 ms: 11.0, CI: 2.6-46.1, *P*=0.001
Morita H *et al*.	2018	Retrospective Cohort	471	BrS	VF	TpTe (ms) V2 ≥95 was associated with HR 3.03 1.26-9.01 0.0143
Zumhagen	2016	Case-control study	78	BrS	VT/VF/aborted SCD	TpTe ≥77 ms, 63.6% and 74.1%; AUC 0.675, TpTe/QT ratio ≥0.205, 72.7% and 68.5%; AUC 0.673
Maury P	2015	Case-control study	325	BrS	Sudden death/ appropriate ICD shocks	Maximum Tpe>100 ms OR of 9.61 (95% CI 3.13-9.41) (*P*<0.0001). Sensitivity 84% and Specificity 68%, PPV 19%, NPV 98%
Mugnai	2017	Cohort	448	BrS	VT/VF/SCD/ appropriate ICD shocks	No significant difference was observed in TpTe, TpTe/QT, maximum TpTe, and TpTe dispersion
Kawazoe	2016	Case-control study	143	BrS	VF	Tpe dispersion OR 1.069 (1.03-1.10), *P*: 0.001 independent predictor
Letsas	2010	Case-control study	23	BrS	VT/VF inducibility	TpTe V2 (88.82+15.70 vs. 78.33 + 4.08 ms, *P*=0.02) and V6 (76.33+10.08 vs. 66.66+5.16 ms, *P*=0.04)
						Greater Tpeak-Tend/QT ratio in lead V6 (0.214 + 0.028 vs. 0.180+0.014, *P*=0.009)
Hevia JC	2006	Cohort	29	BrS	VT/VF	QTc >460 ms in V2
						TpTe and Tp-e dispersion were significantly prolonged in patients with recurrences versus patients without events
						TpTe cut-off point >100 ms; Sensitivity 77.8% and specificity 70%; AUC 0.7861
						Tp-e dispersion Cut-off point >20 ms; Sensitivity 66.7% and specificity 90%; AUC 0.7722

TpTe: Tpeak-Tend interval, SCD: Sudden cardiac death, ICD: Implantable cardioverter defibrillator, VF: Ventricular fibrillation, VT: Ventricular tachycardia, ECG: Electrocardiography, OR: Odds ratio, CI: Confidence interval, AUC: Area under the curve, PPE: Positive predictive value, NPE: Negative predictive value, BrS: Brugada Syndrome, HR: Hazard ratio

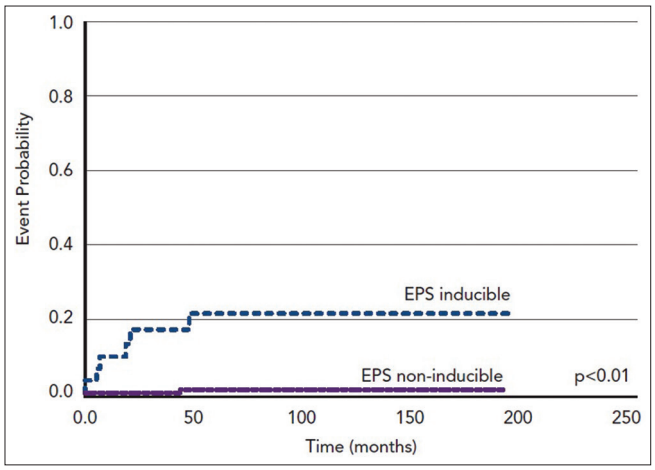


Figure 3: Kaplan–Meier curve showing high event-free survival of EPS noninducible patients. Patients had 96.8%–99% event free survival at 1, 5, 10 and 15 years in non-inducible ventricular arrhythmia during electrophysiological study[32]

studies that showed TpTe was reliable in predicting VT/VF in patient with Brugada syndrome, the cut-off points varied between precordial leads from ≥80 ms to ≥100 ms in which two studies reported a sensitivity 77.8%–84% and specificity 68%–70%; positive predictive value 19%, negative predictive value 98%, odds ratio (OR) 9.61 (95% confidence interval 3.13–9.41) ($P < 0.0001$), area under the curve (AUC) 0.7861 with ≥100 ms. Morita *et al*. indicated TpTe progression of >10 ms on repeat ECG was associated with OR 11.6 ($P = 0.001$). Zumhagen *et al*. showed that TpTe/QT ratio is reliable in predicting VT/VF in which a ratio of ≥0.205 has sensitivity 72.7% and specificity 68.5%; AUC 0.673. Two studies reported that Tp-e dispersion was associated with VT/VF one of which reported Cut-off point >20 ms; sensitivity 66.7% and Specificity 90%; AUC 0.7722. Only Mugnai *et al*. revealed the nonsignificant relation of the aforementioned parameters and VT/VF. Letsas *et al*. indicated that TpTe and greater TpTe/QT ratio in lead V6 are related to VT/VF inducibility, but the latter was not related to the arrhythmic outcome. Spontaneous type 1 ECG, syncope, early repolarization pattern, age (the elderly is at lower risk), and SCN5A mutation (pore lesion) were also associated with higher risk.[42-44]

Management

Drugs that may induce or aggravate ST-segment elevation in the right precordial leads should be avoided (visit Brugadadrugs.org). Excessive alcohol intake should be avoided, and immediate treatment of fever with antipyretic drugs are Class I recommendation [Table 3]. ICD implantation is the only effective modality in Brugada syndrome. Brugada syndrome patients who are survivors of a cardiac arrest and/or have documented spontaneous sustained VT with or without syncope had a Class I recommendation for ICD implantation. Implantation of ICD is recommended (Class IIa) in a patient with syncope (if syncope is suspected as arrhythmic origin)

and spontaneously abnormal ECG (without provocation) because those patients have six times increased risk of cardiac arrest compared to those showing type I ECG after provocation.[2,6] The risk is very low when the diagnosis was

Table 3: Recommendation on therapy and intervention in patient with Brugada Syndrome

Class of Recommendation	Intervention
Class I	The following lifestyle changes are recommended in all patients with diagnosis of BrS
	Avoidance of drugs that may induce or aggravate ST-segment elevation in right precordial leads
	Avoidance of excessive alcohol intake
	Immediate treatment of fever with antipyretic drugs
	ICD implantation is recommended in patients with a diagnosis of BrS who
	Are survivors of a cardiac arrest and/or
	Have documented spontaneous sustained VT with or without syncope
Class IIa	ICD implantation can be useful in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmia
	Quinidine can be useful in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 h
	Quinidine can be useful in patients with a diagnosis of BrS
	Who qualify for an ICD but present a contraindication to the ICD or refuse it and/or
	Have a history of documented supraventricular arrhythmias that require treatment
	Isoproterenol infusion can be useful in suppressing arrhythmic storms in BrS patients
Class IIb	ICD implantation may be considered in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients)
	Quinidine may be considered in asymptomatic patients with a diagnosis of BrS with a spontaneous type 1 ECG
	Catheter ablation may be considered in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks
Class III	ICD implantation is not indicated in asymptomatic BrS patients with a drug-induced type 1 ECG and on the basis of a family history of SCD alone

Expert Consensus Recommendations on BrS Therapeutic Interventions. Priori *et al*. SCD: Sudden cardiac death, ICD: Implantable cardioverter defibrillator, VF: Ventricular fibrillation, VT: Ventricular tachycardia, ECG: Electrocardiography, BrS: Brugada Syndrome

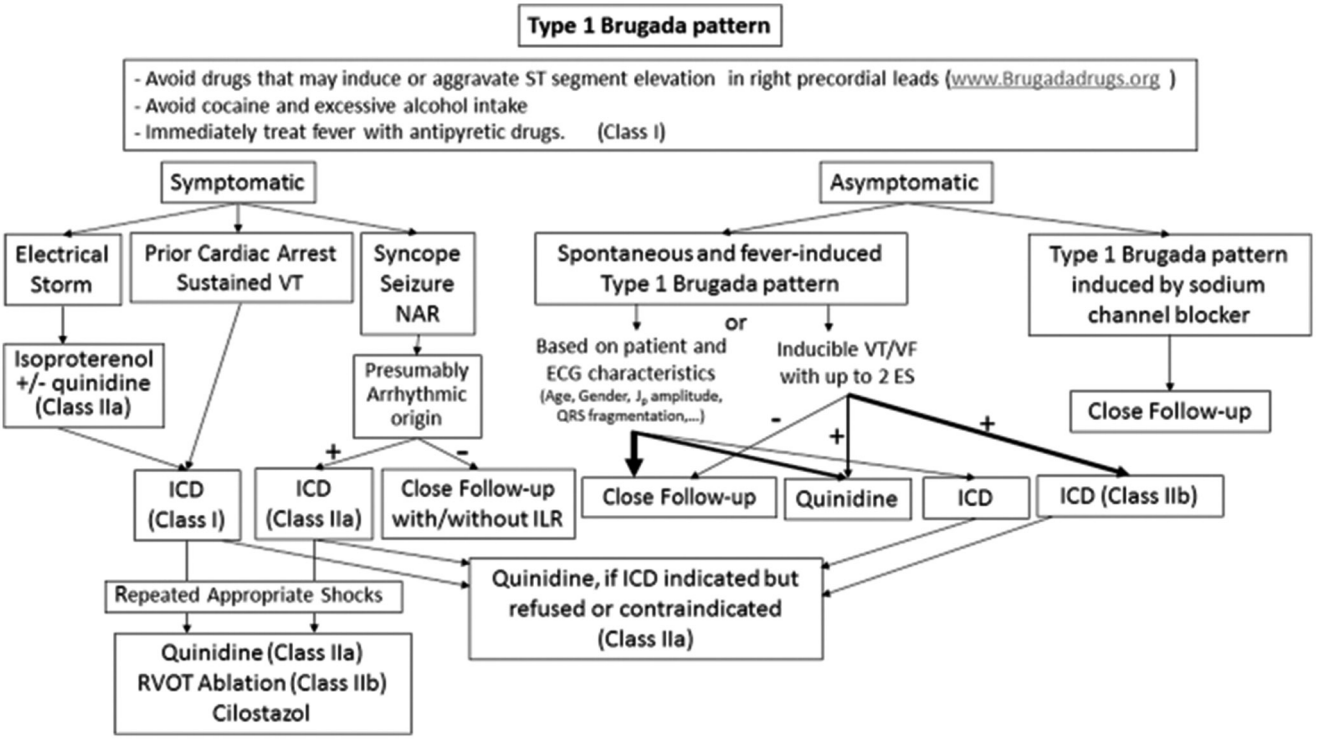


Figure 4: Indications for therapy of patients with Brugada syndrome. The figure above provide flowchart regarding the indications for therapy of patients with Brugada syndrome[23]

made after provocation test with sodium ion channel blockers or by identification of pathogenic mutation only. Follow-up may be needed to observe changes in ECG morphology, from previously requiring provocation to display typical ECG into spontaneously abnormal ECG.[8] Management in a patient with spontaneously abnormal type 1 ECG without a history of syncope is controversial, the risk of life-threatening events in this group is two-fold higher in those without spontaneously ST-segment elevation.[6,17] EPS may be beneficial in this group. However, its role is still controversial, and ICD implantation (Class IIb) may be considered those who develop VF during programmed electrical stimulation (inducible patients) [Figure 4]. QRS fragmentation in these patients was also associated with a worse prognosis.[24] Quinidine, which is the best antiarrhythmic medication available for Brugada syndrome is only used as an adjunct therapy for high-risk patients and to reduce the number of ICD shocks in those with recurrent events.[8] Quinidine may be considered in asymptomatic patients with a diagnosis of Brugada syndrome with a spontaneous type I ECG (Class IIb). Catheter ablation can be considered Brugada syndrome patients with a history of arrhythmic storms or repeated appropriate ICD shocks (Class IIb). Finally, ICD implantation is not indicated in asymptomatic Brugada syndrome patients with a drug-induced type I ECG and on the basis of a family history of SCD alone (Class III).

Epicardial ablation is an emerging treatment in the field of Brugada syndrome. Nademanee *et al*. showed that 9 patients with Brugada syndrome experiencing 2–6 incidence of ventricular arrhythmia per month was arrhythmia free in a follow-up of 2 years after ablation.[41] Brugada *et al*. reported that ablation of the substrate identified in the presence of flecainide could eliminate the Brugada syndrome phenotype.[45] Pappone *et al*. in a study of 50 consecutive patients that underwent ablation showed that ECG pattern normalized in all symptomatic and asymptomatic patients.[46] Follow-up of 3 to 20 months showed that the patients showed no Brugada syndrome phenotype and was not VT/VF inducible seemingly "cured" the Brugada syndrome. Pappone stated that ablation could be useful in those that do not meet the recommendation or refuse ICD implantation. A multicenter randomized trial, ablation in Brugada syndrome for the prevention of VF episodes Study was underway. These findings may usher a new era in treating Brugada syndrome, and the possibility of epicardial ablation being a first-line treatment in the future cannot be overruled.

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Conflicts of interest
There are no conflicts of interest.

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Original Research

Nebivolol Prevents the Increase of Asymmetric Dimethylarginine and Oxidants in Hyperhomocysteinemic Rats

Mustafa Ahmet Huyut

Department of Cardiology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey

ORCID:

Mustafa Ahmet Huyut: https://orcid.org/0000-0001-8740-1429

Abstract

Objective: The objective of this study was to determine nebivolol's inhibitory effect on endothelial dysfunction in hyperhomocysteinemic rats, based on heart pathology and biochemical analysis of serum samples. **Methods:** Male Wistar albino rats weighing between 200 g and 450 g were randomly divided into four groups of equal number (n = 7) as follows: control group, nebivolol group, methionine group, and methionine + nebivolol group. After 28 days, homocysteinemia (Hcy), asymmetric dimethylarginine (ADMA), malondialdehyde (MDA), glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), and catalase (CAT) levels were measured in blood samples and compared between groups. Each rat's hearts were dissected to observe cardiomyocyte degeneration; findings were compared between groups. **Results:** Moderate hyperHcy (hHcy) (Hcy 35.62 ± 7.60 μmol/L) was noted in methionine group ($P < 0.001$). The levels of the antioxidant molecules CAT, GSH, GPx, GR, and SOD were lower, and the levels of the oxidant molecules ADMA, Hcy, and MDA were higher in methionine group ($P < 0.001$). A decrease in antioxidants and also increase in oxidants did not occur in the methionine + nebivolol group ($P < 0.001$). Cardiomyocyte degeneration was more severe in methionine group ($P = 0.01$). **Conclusion:** Endothelial dysfunction induced through short-term hHcy can be prevented through the administration of nebivolol. Nebivolol can prevent elevation of the Hcy levels, and hHcy might cause cardiomyocyte degeneration.

Keywords: Antioxidants, asymmetric dimethylarginin, hyperhomocysteinemia, nebivolol, oxidants

Introduction

Hyperhomocysteinemia (hHcy) is a serious cardiovascular risk factor that occurs due to pharmacological or genetic causes.[1,2] Impaired endothelial function induced by hHcy is a significant cause of morbidity and mortality. Many studies have investigated how to prevent impairment of endothelial function induced by hHcy using vitamins and pharmaceutical agents.

The association between hHcy and cardiovascular diseases was first described by McCully in 1969. McCully observed widespread arterial thrombosis and atherosclerosis.[3,4] A prospective study by Page *et al*.[5] that carried out among women reported that hHcy was an independent risk factor for myocardial infarction.

Healthy endothelial cells detoxify Hcy through the production of nitric oxide (NO). During Hcy metabolism, Hcy combines with adenosine to form S-adenosylhomocysteine while decreasing the adenosine concentration. The decrease in adenosine plasma levels will result in vascular damage.[4,6] Asymmetric dimethylarginine (ADMA) is the endogen inhibitor of the eNOs. Hcy is the most prominent factor that increases the level of ADMA.[7,8] Long-term exposure to ADMA produces hypertensive damage in target organs and accelerates atherogenesis.[9] High ADMA level increased the risk of acute coronary events by 3.9-fold.[10]

Nebivolol is a third-generation, highly selective β1 blocker that promotes vasodilatation through increasing NO in the L-arginine-NO pathway.[11,12] Moreover, unlike other

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Address for correspondence: Dr. Mustafa Ahmet Huyut, Department of Cardiology, Faculty of Medicine, Gaziosmanpasa Hospital, Yeni Yuzyil University, Cukurcesme Caddesi No: 51 Istanbul, Turkey. E-mail: ahuyut@yahoo.com

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beta-blockers, nebivolol increases the NO level by activating eNOs, as it has an agonistic effect on β3 receptors.[13] To prevent hHcy and its harmful effects, Vitamin B12, Vitamin C, Vitamin E, and folic acid have been used in trials with some success.[14-18] The present study was, therefore, conducted to investigate the use of nebivolol for the prevention of hHcy and its harmful effects.

Methods

The study included 28 adult male Wistar albino rats weighed between 250 and 450 g that were obtained from the local University Experimental Animals Laboratory. The rats were randomly divided into four groups of equal number ($n = 7$), and housed in wired cages for 1 month under 12-h circadian rhythm conditions at 22°C –24°C. All the groups were fed standard rat silage and urban drinking water ad libitum. The study protocol was approved by the local University Laboratory Animals Ethics Committee. This study was supported by the local University Scientific Research Projects Unit.

Experimental model

1. The control group ($n = 7$): no medication was administered for 4 weeks. The rats received 1 mL of drinking water od through orogastric gavage to experience the stress of the gavage method.
2. Nebivolol group ($n = 7$): the rats received nebivolol 10 mg/kg/day od through orogastric gavage for 4 weeks
3. Methionine group ($n = 7$): the rats received methionine (M9625 Sigma-Aldrich L-Methionine reagent grade, ≥98% [thin layer chromatography [TLC]) 1 mg/kg/day od through orogastric gavage for 4 weeks
4. Methionine + nebivolol ($n = 7$): the rates received methionine 1 g/kg/day + nebivolol 10 mg/kg/day od through orogastric gavage for 4 weeks. Nebivolol was administered 2 h after the administration of methionine.

Body weight was measured at baseline, and then every week for the adjustment of drug dosage. To achieve hHcy, L-methionine (M9625 Sigma-Aldrich L-Methionine reagent grade, ≥98% [TLC]) was dissolved in phosphate-buffered saline (PBS), pH 7.4, and was given to rats as 1 g/kg/day through oral gavage for 4 weeks. Nebivolol was obtained by crushing 5 mg nexivol (Abdi İbrahim) tablets and dissolving in 10% dimethyl sulfoxide and was given as 10 mg/kg/day through oral gavage for 4 weeks. After 4 weeks, the rats were sacrificed under ether anesthesia, and blood samples were drawn into hemogram tubes with EDTA and standard biochemical tubes. Subsequently, hearts were dissected and immersed in 10% formaldehyde solution for histochemical examination. Blood samples were centrifuged at 4000 rpm at +4°C for 10 min and then stored at − 80°C. Serum was used for the analysis of ADMA, Hcy, malondialdehyde (MDA), NO, catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH), whereas plasma was used for the analysis of glutathione peroxidase (GPx) and glutathione reductase (GR).

Biochemical examination

ADMA (ng/mL) (USCN Life Science Inc., catalog no: E91301Ge) and Hcy (μmol/L) (Cusabio, catalog no. CSB-E13376r) levels were detected through the ELISA method using commercial kits. CAT (U/g) was measured through the ELISA method using a CAT assay kit (Cayman, catalog no. 7070002, USA). GR activity (U/g) was measured through ELISA using a GR assay kit (Cayman, catalog no. 703202, USA). GPx (U/g) was measured through the ELISA method using a GPx assay kit (Cayman, catalog no. 703102, USA). GSH was measured through the ELISA method using a GSH assay kit (Cayman, catalog no. 703002, USA). SOD was measured according to Sun *et al.*[19] The method is based on the reduction of nitroblue tetrazolium through xanthine-xanthine oxidase, which is the producer of superoxide. SOD activity is expressed as U/mg of serum protein. The level of serum protein was determined using the biuret method and an Abbott Architect C 8000 Autoanalyzer (Abbott, Abbott Park, IL, USA). MDA was measured using the Esterbauer method and a lipid peroxidation measurement method.[20] MDA, which reacts with thiobarbituric acid at 90°C –95°C, produces a pink chromogen. After 15 min, the absorbance of the samples that were chilled quickly was read at 532 nm, and the results expressed as nmol/mL.

Pathological examination

Paraffin blocks were prepared from heart tissue samples. Sections 4-μm thick were cut using a microtome. The sections were deparaffinized and collected on glass slides. After staining with H and E (Gul Biology Laboratory, dye for connective and supportive tissue of animals, catalog no. 5089, Istanbul, Turkey), the slides were examined under a light microscope. All samples were evaluated by blinded pathologist. For heart tissue evaluation, myocyte damage was semiquantitatively scored with respect to necrosis, myocyte cell swelling, and detection of fibrosis, according to the scale shown below.

The scoring system scale as follows:

(–): No change
(+): Slight change
(++): Moderate change
(+++): Severe change.

Statistical analysis

Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) version 14.0 for Windows (SPSS, Inc., Chicago. IL, USA). The groups were compared *inter se* and with the control group. The Kolmogorov–Smirnov test was used to assess the compliance of the quantitative values to a normal distribution. Single-direction variance analysis was used to compare normally distributed quantitative data between groups, and Tukey's honestly significant difference or Dunnett's T3 test was used for multiple comparisons between groups, according to the Levene homogeneity test's statistics. Descriptive statistics are shown as mean ± standard deviation. The Kruskal–Wallis

variance analysis was used to compare data not distributed normally between the groups. Descriptive statistics are shown as median (25^{th}–75^{th} percentile). The level of statistical significance was set at $P < 0.05$.

Results

Biochemical findings

Oxidants diagram was showed in Figure 1. The antioxidants diagram was shown in Figures 2 and 3. hHcy was more severe in the methionine group than in the other three groups ($P < 0.001$). The Hcy level was significantly lower in the methionine + nebivolol group than in the methionine group (13.2 ± 2.1 vs. 35.6 ± 7.6 μmol/L) ($P < 0.001$).

The plasma ADMA level was significantly higher in the methionine group than in the other groups ($P < 0.001$). In addition, the ADMA level was significantly lower in the methionine + nebivolol group than in the methionine group (113.2 ± 16.0 vs. 225.7 ± 42.2 ng/mL) ($P < 0.001$).

The plasma CAT level was significantly lower in the methionine group than in the other groups ($P < 0.001$) and was significantly higher in the methionine + nebivolol group than in the methionine group (36.0 ± 3.5 vs. 23.7 ± 6.1 U/g) ($P = 0.006$). In addition, the CAT level was higher in the nebivolol group than in the methionine + nebivolol group (36.0 ± 3.5 vs. 49.0 ± 5.7 U/g) ($P = 0.003$).

The GSH level was significantly lower in the methionine group than in the other groups ($P < 0.001$) and was significantly higher in the methionine + nebivolol group than in the methionine group (1.0 ± 0.1 vs. 0.4 ± 0.1 μmol/L) ($P < 0.001$). In addition, the GSH level was lower in the methionine + nebivolol group than in the control group (1.0 ± 0.1 vs. 1.4 ± 0.3 μmol/L) ($P = 0.03$).

The plasma GPx level was significantly lower in the methionine group than in the other groups ($P < 0.001$) and was significantly higher in the methionine + nebivolol group than in the methionine group (213.20 ± 32.55 vs. 122.54 ± 11.56 U/g) ($P = 0.001$). In addition, the GPx level was lower in the methionine + nebivolol group than in the control group (213.20 ± 32.55 vs. 424.13 ± 38.43 U/g) ($P < 0.001$).

The plasma MDA level was significantly higher in the methionine group than in the other groups ($P < 0.001$) and was significantly lower in the methionine + nebivolol group than in the methionine group (2.18 ± 0.21 nmol/mL vs. 3.02 ± 0.29 nmol/mL) ($P < 0.001$). In addition, the MDA level was higher in the methionine + nebivolol group than in the control group (2.18 ± 0.21 nmol/mL vs. 1.80 ± 0.10 nmol/mL) ($P = 0.015$).

The plasma GR level was significantly lower in the methionine group than in the other groups ($P < 0.001$). In addition, the GR level was lower in the methionine + nebivolol group than in the control group but not significantly (184.56 vs. 273.86 U/g) ($P = 0.081$).

The plasma SOD level was significantly lower in the methionine group than in the other groups ($P = 0.001$). In addition, the SOD level was higher in the methionine + nebivolol group than in the control group but not significantly (1.45 U/mg of

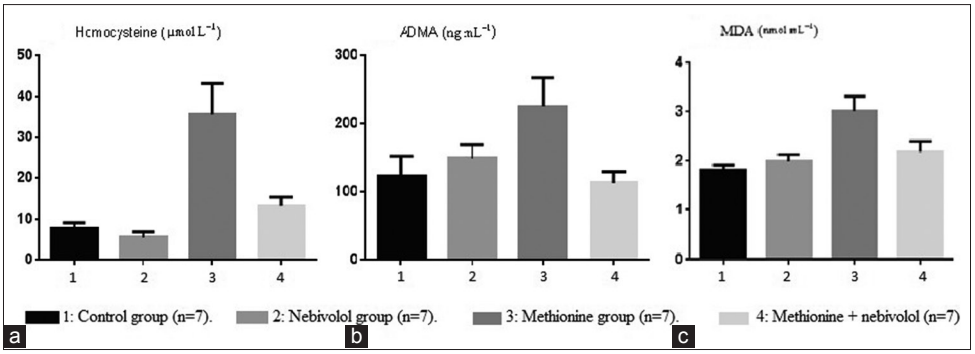


Figure 1: Homocysteinemia and oxidants diagram was showed. (a) Hyperhomocysteinemia, (b) plasma asymmetric dimethyl arginine, (c): and malondialdehyde levels were more severe in the methionine group than in the other groups ($P < 0.001$)

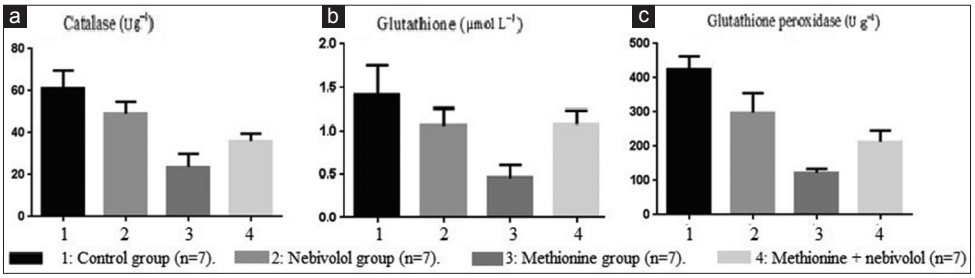


Figure 2: Antioxidants diagram was showed. (a) The plasma catalase, (b) glutathione, (c) and glutathione peroxidase levels were significantly lower in the methionine group than in the other groups ($P < 0.001$)

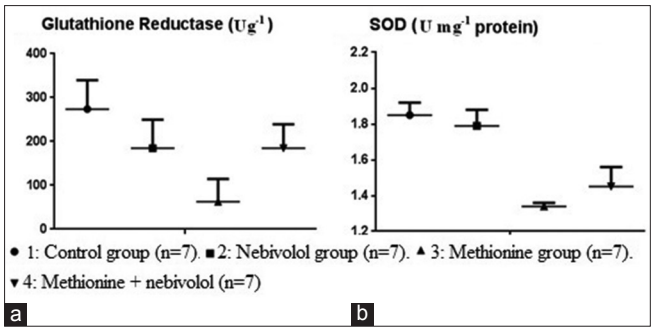


Figure 3: Antioxidants diagram which descriptive statistics for quantitative biochemical data not distributed normally (median given as 25th–75th percentile). (a) The plasma glutathione reductase level was significantly lower in the methionine group than in the other groups ($P < 0.001$). (b) The plasma superoxide dismutase level was significantly lower in the methionine group than in the other groups ($P = 0.001$)

protein vs. 1.34 U/mg of protein) ($P = 1$). Moreover, the SOD level was lower in the methionine + nebivolol group than in the control group (1.34 U/mg of protein vs. 1.85 U/mg of protein) ($P = 0.007$).

Pathological finding

Cardiomyocyte degeneration was significantly more severe in the methionine group than in the other groups ($P = 0.01$) [Figures 4 and 5]. Cardiomyocyte degeneration was less severe in the methionine + nebivolol group than in the control group but not significantly (1.4 ± 0.5 vs. 1.8 ± 1.0 degeneration) ($P = 1$).

Discussion

The present study showed that impaired endothelial function resulted from short-term hHcy could be prevented through the administration of nebivolol. In addition, the administration of nebivolol od 2 h after oral administration of methionine was observed to prevent an increase in the Hcy level. Different data such as tissue oxidant levels from these studies subgroups were published before. In our previous study, GSH, CAT, MDA, and SOD activities in the tissues were determined. The luminal cross-sectional area (LCSA), total cross-sectional area (TCSA), and intima-media thickness (IMT) were measured in the thoracic aorta. Nebivolol treatment decreased high MDA levels in the brain, heart, and liver tissues. The level of GSH was higher in the heart, brain, and kidney tissues of the nebivolol + hHcy group. The activity of CAT increased only in the kidney tissue of the nebivolol + hHcy group, and the activity of SOD was increased in all the tissues in this group. However, serum levels did not measure, and heart tissue did not investigate. Increased IMT and TCSA in the nebivolol + hHcy group were significantly decreased after nebivolol administration. The LCSA was higher in the hHcy group than the control group.[21]

In this study, according to the present biochemical findings, concomitant administration of nebivolol + methionine can prevent impaired endothelial function induced by short-term hHcy. In the present study, cardiomyocyte degeneration was more severe in the methionine group based on histopathological findings.

L-methionine was administered at 1 g/kg/day, as reported by Cao *et al*.[22,23] In the present study, nebivolol was administered at 10 mg/kg/day, as the efficiency and safety of this dose are well known.[24,25] In the difference between groups, hHcy was statistically significant ($P < 0.001$). The Hcy level in methionine + nebivolol group significantly lower than in the methionine group ($P = 0.001$), which indicates that the administration of nebivolol 2 h after the administration of methionine can prevent an increase in the Hcy level.

Nebivolol increases NO through the activation of eNOs and its β3-receptor agonistic effect, which is distinct from other beta-blockers.[13] Nebivolol increases total antioxidant capacity. In the present study, the highest ADMA level was observed in the methionine group, which had a high Hcy level. The ADMA level was 123.8 ± 28.5 ng/mL in the control group versus 225.7 ± 42.2 ng/mL in the methionine group, and the difference was statistically significant ($P < 0.001$).

An elevated ADMA level is an indicator of impaired endothelial function. In addition, the ADMA level can be used for the prediction of cardiovascular morbidity and mortality. The impaired endothelial function is indicative of the early stage of atherosclerosis.[26] Zoccali *et al*.[27] reported that a 2-mmol/L increase in the plasma ADMA level increases the risk of cardiovascular disease by 37%. In a study by Valkonen *et al*.,[10] it was observed that an increase in the ADMA was associated with a 3.9-fold increase in the risk of acute coronary events. In earlier studies, Vitamin B12, Vitamin C, Vitamin E, and folic acid were used to prevent hHcy and these pathologies, and partial success has been achieved.[14-18]

A decrease in ADMA decreases oxidative stress and cellular damage; thus, protein breakdown is prevented and protein synthesis continues. When there is a need for cysteine Hcy is converted to cystathionine with cystathionine beta-synthase through the transsulfuration pathway and is subsequently hydrolyzed to cysteine and excreted in urine or used in protein synthesis.[2] Hcy is metabolized through remethylation and transsulfuration. When remethylation reactions are saturated or there is a need for cysteine Hcy is hydrolyzed to cysteine through the transsulfuration pathway.[2] Cysteine is a rate-limiting substrate; specifically, Hcy breakdowns

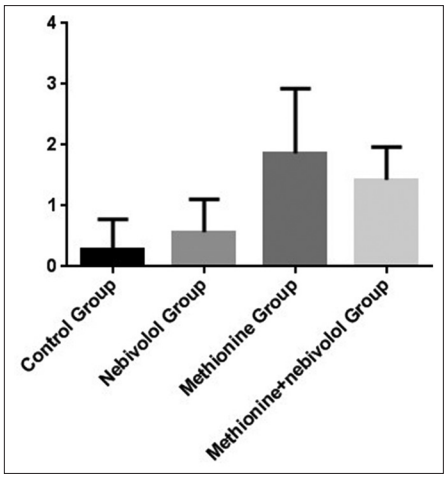


Figure 4: A significant difference in cardiomyocyte degeneration between the methionine group and control group was observed ($P = 0.01$)

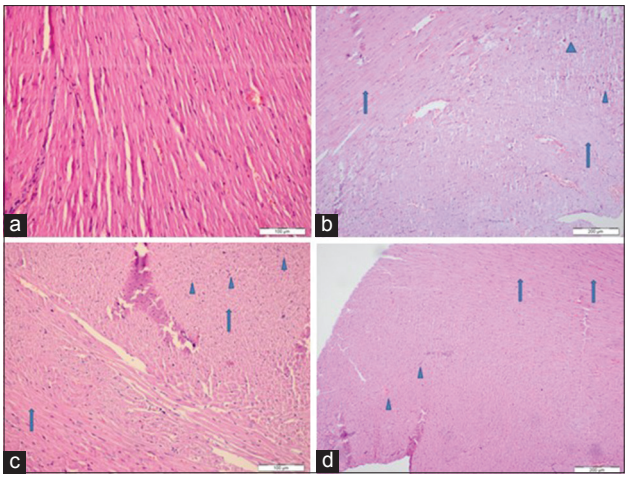


Figure 5: The arrow shows loss of nucleus. The triangle shows degeneration in muscle fiber (a) Control group heart tissue stained with H and E at × 200 (normal). (b) Methionine group heart tissue stained with H and E × 100 (+3 degeneration). (c) Methionine group heart tissue stained with H and E at × 200 (+3 degeneration). (d) Methionine + nebivolol group heart tissue stained with H and E at 100 (+2 degeneration)

to form cysteine and an increase in the serum Hcy level is inhibited. Cysteine formed through transsulfuration of Hcy is used for GSH synthesis; therefore, nebivolol might inhibit an increase in Hcy through these physiologic pathways and others yet to be discerned. The metabolism of ADMA and Hcy shares common pathways. Hcy destabilizes the structure of proteins and increases proteolysis by increasing oxidative stress.[28] On the other hand, the enzyme dimethylarginine dimethylaminohydrolase metabolizes ADMA. Hcy also inhibits this enzyme's activity and causes an increase in the ADMA concentration.[28]

Although the methionine + nebivolol group received methionine, the administration of nebivolol the same day might have inhibited an increase in the ADMA level, which might have been due to the lack of increase in the Hcy level. Nebivolol can prevent methionine-induced elevation of ADMA between the methionine group and the methionine + nebivolol group ($P < 0.001$). There was a positive correlation between oxidative stress and the CAT activity. Wyse *et al*.[18] reported that Hcy administration reduced CAT activity in rats. CAT activity was significantly lower in the methionine group than in the methionine + nebivolol group ($P = 0.006$). Even though the methionine + nebivolol group received methionine, the concomitant administration of nebivolol prevented a decrease in the CAT activity.

Similar to our study, Dimitrova *et al*.[29] reported that the myocardial GSH level was reduced significantly in rats that received Hcy. In the present study, the GSH level was significantly lower in the methionine group than in the other groups, which might indicate that oxidative stress was induced by hHcy in the methionine group. The significant difference in the GSH level was between the present study's methionine group and methionine + nebivolol group ($P < 0.001$).

A significant difference in GPx levels was observed between methionine group and control group ($P < 0.001$) similar to Gilad's study.[30] The significant difference in the GPx level between the methionine group and the methionine + nebivolol group ($P = 0.001$), which might have been associated with the difference in the Hcy level between two groups and the positive effects of nebivolol on total antioxidant capacity.

An elevated MDA level can be considered an indicator of cell damage and lipid peroxidation.[31,32] Yüce and Aksakal[33] examined the effect of Vitamin E in hyperhomocysteinemic rats and reported that the MDA level was higher in hyperhomocysteinemic rats. Similarly, in the present study, the MDA level was significantly higher in the methionine group than in the control group, which might have been an indicator of oxidative stress caused by an elevated Hcy level. Moreover, the MDA level was significantly higher in the methionine group than in the methionine + nebivolol group ($P < 0.001$). The present findings may show that the administration of nebivolol, the same day as the administration of methionine significantly inhibited an increase in the MDA level. Furthermore, in the present study, the GR level was significantly lower in the methionine group than in the control group ($P < 0.001$).

Yamamoto *et al*.[34] observed that Hcy reduced the efficiency of SOD and damaged endothelial heparan sulfate proteoglycan and decrease the defensive ability of endothelial cells against free radicals. In the present study, the SOD level was significantly lower in the methionine group than in the control group ($P = 0.001$), which might have been due to elevated oxidative stress secondary to a high Hcy level.

Zivkovic *et al*. dissected rat hearts and perfused with Hcy in an organ bath, and showed that the left ventricle functions were destroyed.[35] They suggested that the mechanism of action was the toxic effect of the increase in total oxidative capacity

induced by impaired endothelium function and suppressed NO bioactivity that resulted from an elevated Hcy level. There was a significant difference in cardiomyocyte degeneration between the methionine group and control group ($P = 0.01$). hHcy might be caused cardiomyocyte cell degeneration. Chen *et al*.[36] observed a reduction in systolic function in rats with hHcy, and an increased in the size of cardiomyocytes and an increase in intracellular fibrosis in rat heart pathological sections. Although maximum cardiomyocyte degeneration was noted in the methionine group, we could not show any significant protection with nebivolol administration.

The present study's limitations are having a small study population, and time was restricted for 4-week duration. Larger scale and longer durations are required to more clearly observe histopathological and biochemical changes.

Study limitations

To generalize these results and obtain significant histopathological findings, more clinical studies of longer duration and larger scale are necessary to generalize the present findings.

Conclusion

The present findings show that the impairment of endothelial function induced by short-term hHcy can be prevented by the administration of nebivolol. In addition, the administration of nebivolol 2 h after administration of methionine was observed to prevent an increase in the Hcy levels. The present study observes that impaired endothelial function due to short-term hHcy can be prevented by the concomitant administration of nebivolol.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Asymptomatic Pneumothorax Mimicking Pseudoaneurysm after the Implantation of a Dual-Chamber Pacemaker

Tolga Aksu, Tumer Erdem Guler, Serdar Bozyel

Department of Cardiology, University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey

ORCID:

Tolga Aksu: https://orcid.org/0000-0001-8061-9660

Tümer Erdem Güler: https://orcid.org/0000-0003-1349-2123

Serdar Bozyel: https://orcid.org/0000-0002-6582-3660

Abstract

An 80-year-old male, who had undergone dual-chamber pacemaker implantation through left subclavian approach, developed tension pneumothorax of the left side. It caused a pseudoaneurysm-like contracting mass image on the chest X-ray. The diagnosis of pneumothorax was verified by chest computed tomography. Tube thoracostomy drainage was performed immediately without any sequel.

Keywords: Cardiac pacing, cephalic vein cutdown, complication, subclavian puncture, venous access

Introduction

An increase in the frequency of cardiac rhythm management device (CRMD) implantations has also led to an increase in device-related complications, in hospitalization period, and treatment costs.[1-3] Pneumothorax is a relatively mild complication during CRMD implantation using the subclavian puncture technique. However, the incidence of pneumothorax requiring a chest tube may be as high as 0.66% even in experienced centers.[2]

Case Report

An 80-year-old male was referred to our clinic with a 2-month history of progressive fatigue and presyncope episodes. An electrocardiogram showed third-degree heart block with a pulse rate of 36 beats per minute. There was no identifiable and reversible cause of heart block. Thus, he was scheduled for a permanent pacemaker insertion. The atrial and ventricular leads were inserted via the puncture of the left subclavian vein. The right ventricular bipolar screw-in lead (St. Jude Medical Tendril MRI™) was positioned against the right ventricle apex. The right atrial bipolar passive lead (St. Jude Medical Isoflex MRI™) was positioned at the anterolateral wall of the right atrium. Lead sensing, pacing threshold, and pacing impedance of both right atrial and ventricular leads were within the expected normal ranges (the right atrium lead: pacing threshold, 1.5 V/0.4 ms; sensing threshold, 3 mV; lead impedance, 550 Ω and the right ventricle lead: pacing threshold, 0.5 V/0.4 ms; sensing threshold, 13 mV; and lead impedance, 650 Ω). The chest fluoroscopic imaging performed immediately after the procedure revealed pseudoaneurysm-like bulging at the left ventricular apical site [Figure 1]. The site was contracting together with the heart beat. The patient had no chest pain or shortness of breath. A computed tomography scan was scheduled. A left-sided pneumothorax and slight mediastinal shift to the right were detected on the computed tomography [Figures 2 and 3]. A chest tube with underwater seal drainage was inserted according to the recommendation of chest surgeon. Control chest X-ray demonstrated complete resolution of pneumothorax. The chest tube was removed on the 3rd day of hospitalization.

Address for correspondence: Prof. Tolga Aksu, Department of Cardiology, University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey.
E-mail: aksutolga@gmail.com

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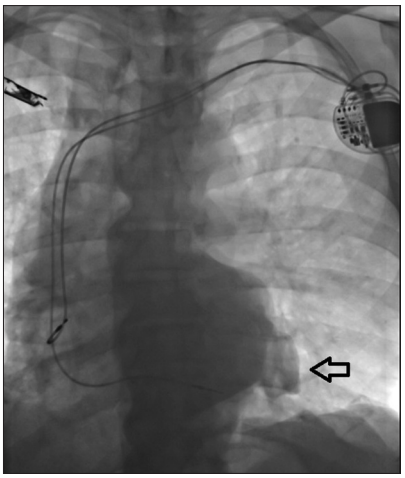


Figure 1: Radiographic findings of a fluoroscopy revealed a left-sided pneumothorax with a pseudoaneurysm-like bulging at the left ventricular apical site (black arrow)

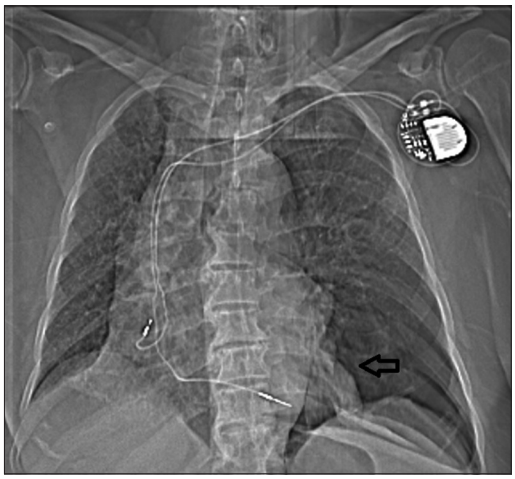


Figure 2: Radiographic findings of a computed tomography in the frontal plane revealed a left-sided pneumothorax with a pseudoaneurysm-like bulging at the left ventricular apical site (black arrow)

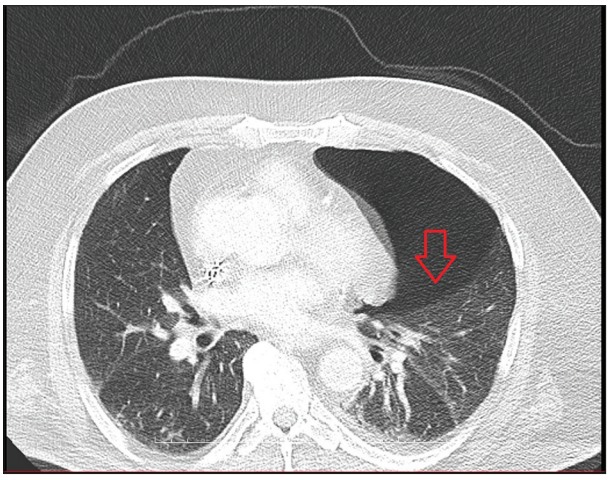


Figure 3: Radiographic findings of a computed tomography in the horizontal plane revealed a left-sided pneumothorax. Please note that the lung tissue is sliding to the posterior side (red arrow)

Discussion

The incidence of pneumothorax after CRMD implantation by using subclavian vein access varies from 0.6% to 5.2% with an average of 2%.[4] The most important precipitating factor is blindly punctured subclavian vein access. A detailed physical examination and anteroposterior chest radiography in standing position should be the first two steps in the assessment of patients demonstrating pneumothorax-related complaints such as chest pain and dyspnea because they are simple, inexpensive, rapid, and noninvasive. However, it should be kept in mind that some forms of pneumothorax may be asymptomatic as in our case. In order to not miss a possible pneumothorax complication in such cases, detailed evaluation of the postprocedural scopical views is of great importance. Chest computed tomography scanning is more sensitive than chest radiography in detecting a small pneumothorax.[5] In addition, computed tomography may be used to differentiate pneumothorax than other possible device-related complications. In the present case, the chest X-ray demonstrated a large left-sided pneumothorax, compressing the left lung and resembling a mass. As a unique nature of the mass, it was contracting together with heart like a pseudoaneurysm. Furthermore, the patient had no complaint of difficulty in breathing after implantation. Hence, we decided to perform chest computed tomography for differential diagnosis.

After proper diagnosis, treatment for pneumothorax varies from simple oxygenation to chest tube drainage. If a tension pneumothorax develops, urgent treatment with a chest tube is necessary. At this point, another important issue is that tension pneumothorax may alter lead-related parameters due to mechanical displacement of the leads by shifting of the mediastinum and may require a lead revision procedure. Thus, to check all lead-related parameters seems as reasonable after such a complication. In our case, there was no change on lead-related parameters. Use of venography or ultrasound to visualize the subclavian veins or the cephalic vein cutdown technique should be considered to avoid this complication in selected patients.

Conclusion

Pneumothorax is a relatively common complication of CRMD implantation using the subclavian puncture technique. Early clinical doubt, well-performed physical examination, and truly used imaging methods are cornerstone for early and true diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Report

Cardioembolic Ischemic Stroke as the Initial Presenting Complaint of a Patient with Acute Infective Endocarditis and Acquired Immunodeficiency Syndrome

Raymond Pranata[1], Veresa Chintya[2], Emir Yonas[3], Vito Damay[1,4]

[1]Faculty of Medicine, Universitas Pelita Harapan, Tangerang, [2]General Practitioner, Sanjiwani General Hospital, Gianyar, [3]Faculty of Medicine, YARSI University, Jakarta, [4]Department of Cardiology and Vascular Medicine, Siloam Hospitals Lippo Village, Tangerang, Indonesia

ORCID:
Raymond Pranata: https://orcid.org/0000-0003-3998-6551
Veresa Chintya: https://orcid.org/0000-0002-7486-1108
Emir Yonas: https://orcid.org/0000-0002-8604-405X
Vito Damay: https://orcid.org/0000-0001-9831-8188

Abstract

Human immunodeficiency virus (HIV) infection is an independent predictor of ischemic stroke, especially in the younger age group. Approximately 1%–5% of HIV/acquired immunodeficiency syndrome patients develop stroke. A 16-year-old male presented with a decreased level of consciousness and a history of right-sided hemiparesis, fever, cough, and dyspnea. The patient was an intravenous drug user (IVDU). Examination revealed the following: blood pressure: 130/70 mmHg, heart rate: 124×/min, temperature 38.5°C, and respiratory rate: 26×/min. Electrocardiographic findings revealed the following: sinus tachycardia: 124×/min, right-axis deviation, incomplete right bundle branch block, and right ventricular hypertrophy. Laboratory findings were as follows: microcytic hypochromic anemia (7.33 g/dL), leukocytosis (32.2 × 10^3/μL) with shift to the left, hyponatremia (122 mmol/L), HIV was positive, and chest X-ray showed pneumonia. Echocardiography showed vegetation in the posterior mitral leaflet, mitral regurgitation, and tricuspid regurgitation with an intact interatrial septum. Computed tomography scan revealed ischemic stroke of the left parieto-occipital lobe. HIV-infected individuals are at 1.5 times increased risk of stroke compared to those without. This case involves an IVDU and a HIV-positive young male presenting with large ischemic stroke in large-vessel territory, suggestive of embolic origin. A part of vegetation on the left side of the heart of this patient dislodged and caused a cerebrovascular accident. There was also unconfirmed suspicion of pulmonary embolism from the right side of the heart. Empiric antibiotics should be started before tailoring to the result of blood culture. Endocarditis conveys a significant risk of cerebral embolism resulting in ischemic stroke and a potentially dismal prognosis.

Keywords: Endocarditis, human immunodeficiency virus/acquired immunodeficiency syndrome, immunocompromised, stroke

Introduction

Approximately 1%–5% of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients develop stroke, and ischemic cerebral lesion is found in 4%–34% of autopsies.[1,2] HIV infection is an independent predictor of ischemic stroke, especially in the younger age group.[3] Bacterial endocarditis, marantic endocarditis, HIV-associated cardiac dysfunction, and ischemic heart disease account for 4%–15% of ischemic strokes in people with HIV.[1]

An international prospective cohort study showed that the incidence of stroke in adults with definitive infective endocarditis is 16.9%. A prospective multicentric study in France found that neurological sequelae occurred in 55% of critically ill patients with left-sided infective endocarditis.[4,5]

Address for correspondence: Dr. Raymond Pranata, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia.
E-mail: raymond_pranata@hotmail.com

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Right-sided endocarditis accounts for only 5%–10% of the endocarditis. It mainly involves tricuspid valve in intravenous drug user (IVDU). The incidence of bacterial endocarditis among IVDUs is believed to be 1.5–20/1000 addicts per year.[6]

Case Report

A 16-year-old male presented with a decreased level of consciousness since 1 h before admission and a history of right-sided hemiparesis for 2 h. He had fever since 3 days before admission and a productive cough for 2 weeks. The patient complained of dyspnea for the last 2 days. He had no history of epilepsy or other neurological complaints. There was no family history of stroke or cardiac disease. The patient was a smoker and IVDU.

Upon physical examination, Glasgow Coma Scale was $E_3V_3M_5$, blood pressure was 130/70 mmHg, heart rate was 124×/min, temperature was 38.5°C, and respiratory rate was 26×/min. Cardiorespiratory examination unveiled a Grade IV/VI holosystolic murmur on the apex of the heart radiating to the left axilla and crackles on the lung. Carotid auscultation was within normal limits. Neurological examination showed lateralization of the upper and lower extremities to the right side. Electrocardiography showed sinus tachycardia of 124×/min, right-axis deviation (RAD), incomplete right bundle branch block (RBBB), and right ventricular hypertrophy (RVH) [Figure 1]. Initial laboratory examinations showed microcytic hypochromic anemia (7.33 g/dL), leukocytosis (32.2 × 10^3/μL) with shift to the left, and hyponatremia (122 mmol/L). Coagulation panel was within normal limits. HIV rapid test was ordered and the result was positive. Blood culture was taken. Chest X-ray showed pneumonia [Figure 2]. Echocardiography showed vegetation in the posterior mitral leaflet, mitral regurgitation, and tricuspid regurgitation with an intact interatrial septum [Figure 3]. Computed tomography (CT) scan showed an ischemic stroke of the left parieto-occipital lobe [Figure 4]. The patient was diagnosed with anemia, hyponatremia, sepsis, infective endocarditis, ischemic stroke, and HIV/AIDS. The patient was given levofloxacin 1 × 750 mg IV, ceftriaxone 3 × 2 g IV, methylprednisolone 3 × 62.5 mg IV, aspirin 1 × 80 mg PO, citicoline 2 × 500 mg IV, and ranitidine 2 × 500 mg IV. The patient was admitted to the Intensive Care Unit (ICU), treated to no avail, and passed away on the 3rd day after admission.

Discussion

HIV-infected individuals are at 1.5 times increased risk of stroke compared to those without.[3] This case involves an IVDU and a HIV-positive young male presenting with large ischemic stroke in large-vessel territory suggestive of embolic origin. Stroke risk is directly proportional to the viral load which suggests that the risk may be due to inflammation, endothelial dysfunction, and macrophage activation.[3] A cohort study of 4308 HIV-positive patients showed that bacterial endocarditis was associated with HIV infections;

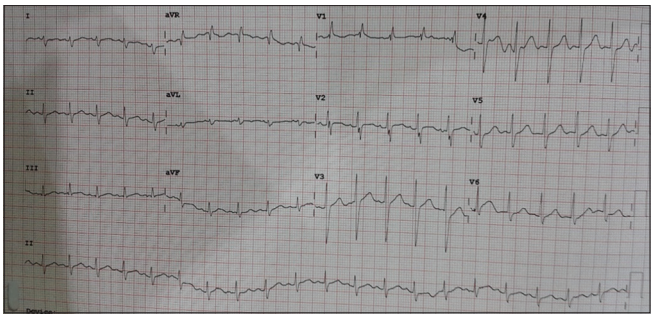


Figure 1: Patient's electrocardiogram

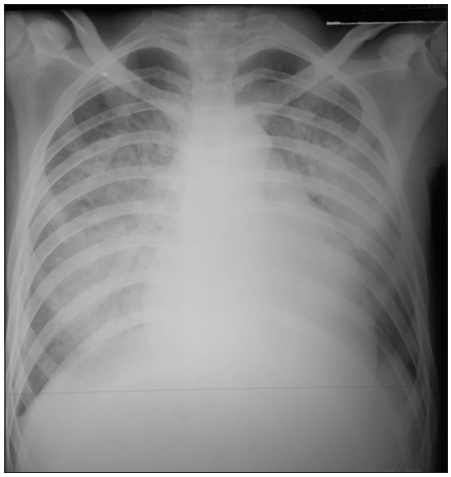


Figure 2: Patient's chest X-ray suggestive of pneumonia

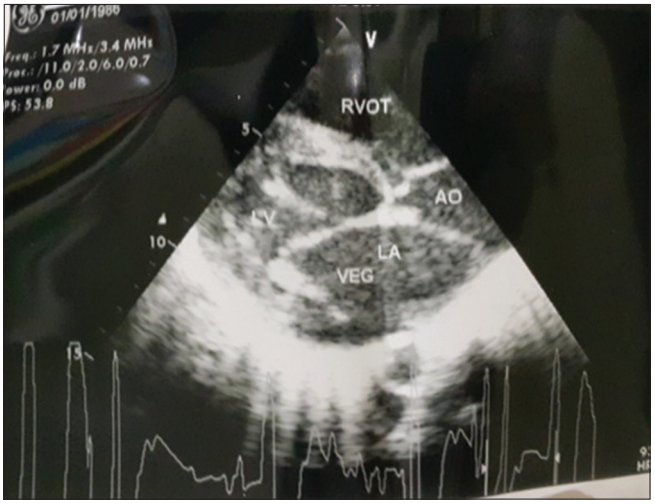


Figure 3: Patient's echocardiography showing vegetation on posterior mitral leaflet

however, some literatures state that endocarditis occurs almost exclusively in IVDU population and the IVDU data were not available in majority of patients in the aforementioned study.[3,7] Thus, the bacterial endocarditis in this patient is a collaboration of both HIV and risk involving IVDU.

IVDUs often inject veins using contaminated needles or without proper antiseptic procedure. Bacteria are introduced

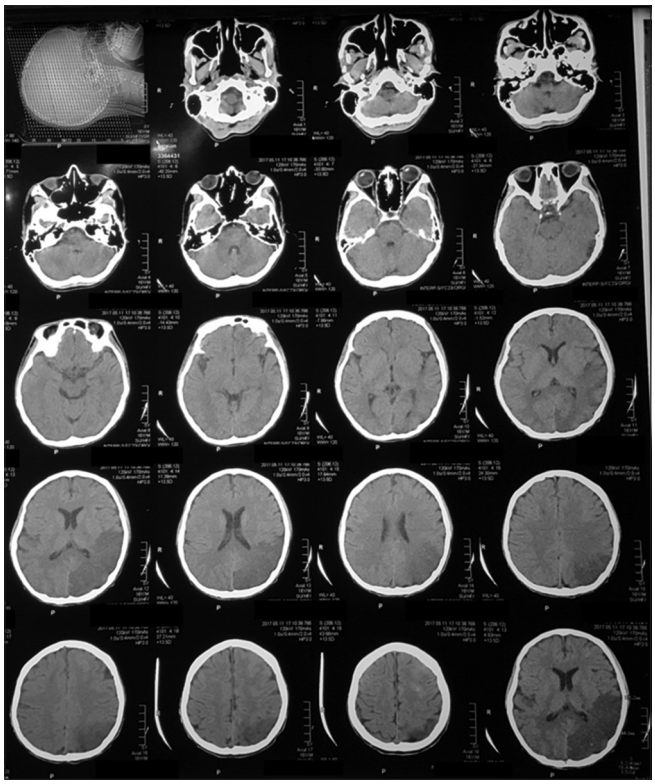


Figure 4: Patient's cranial computed tomography scan

to the right side of the heart via the draining veins. These bacteria may lodge to the heart valves and infect them. The right side of the heart is predominantly affected due to the veins draining to the right side of the heart initially. However, IVDU is associated with not only right-sided valves, but also left-sided valves as shown by three studies demonstrating that the exclusive involvement of right-sided valves was only evident in 46.8%–78% of the patients.[8-10] Involvement of multiple valves (mitral regurgitation + tricuspid regurgitation in this patient) is found in 5%–10% of IVDUs with endocarditis.[5] The valvular damage is usually caused by immunomediated response in patients with bacterial endocarditis; however, HIV-infected patients may have a different course of disease.[11] The damage may be largely caused by bacteremia rather than autoimmune and this causes the patient to be more responsive to antibiotics.

Endothelial injury precedes the formation of platelet fibrin nidus followed by colonization of microorganism and focal adherence of platelet, leading to the formation of vegetation.[12] A part of vegetation on the left side of the heart of this patient dislodged and caused a cerebrovascular accident. Cerebrovascular accidents due to septic embolism are one of the most lethal complications of infective endocarditis, and ischemic stroke is the most common manifestation.[13] Sinus tachycardia, RAD, incomplete RBBB, and RVH upon electrocardiography signify RV strain. Dyspnea and RV strain along with vegetation at the tricuspid valve may suggest pulmonary embolism due to embolization from the tricuspid valve. This requires further investigation such as CT pulmonary angiography which was not possible in our case due to the limited facility.

Empirical antibiotic (ideally vancomycin + gentamycin) should be started before tailoring to the result of blood culture. This patient was given levofloxacin and ceftriaxone due to unavailability of vancomycin. Corticosteroids were given to reduce cerebral edema and inflammation.

Mortality of patients with infective endocarditis who require ICU admission reaches as high as 60% despite advances in medical care.[5]

Conclusion

HIV infection is an independent predictor of ischemic stroke, and one of the pathophysiological mechanisms responsible is through cardioembolism from the affected heart. Infective endocarditis is one of the HIV-associated cardiac dysfunctions, which conveys a significant risk of cerebral embolism culminating into the ischemic stroke and a potentially dismal prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

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Case Report

Painless Aortic Dissection Presented with Acute Paraplegia

Mahmoud Abdelnaby, Mohammed Abada[1], Alyaa Elsayed[2], Moustafa Dawood[2], Yehia Saleh[2], Abdallah Almaghraby[2]

Clinical and Experimental Internal Medicine Department, Cardiology and Angiology Unit, Medical Research Institute, Alexandria University, [1]Department of Critical Care Medicine, Faculty of Medicine, Alexandria University, [2]Department of Cardiology, Faculty of Medicine, Alexandria University, Alexandria, Egypt

ORCID:

Mahmoud Abdelnaby: https://orcid.org/0000-0001-8016-9049
Mohammed Abada: https://orcid.org/0000-0002-2043-2973
Alyaa Elsayed: https://orcid.org/0000-0002-5729-5765
Moustafa Dawood: https://orcid.org/0000-0001-8509-5982
Yehia Saleh: https://orcid.org/0000-0003-3873-5582
Abdallah Almaghraby: https://orcid.org/0000-0001-6541-0850

Abstract

Acute aortic dissection is considered a potentially fatal condition. Neurologic manifestations such as paraplegia are quite rare. We report a case of acute paraplegia in a hypertensive smoker chronic obstructive lung disease patient. Transthoracic echocardiography revealed a dissection flap starting at the aortic annulus and extending to the descending thoracic aorta. Computed tomographic aortography confirmed the diagnosis with a dissection flap extended from the aortic annulus to the entire distal aorta. The patient was referred to another specialized cardiothoracic center, but unfortunately, he died during the surgery.

Keywords: Aortic dissection, computed tomographic aortography, echocardiography, painless paraplegia

Introduction

Acute aortic dissection is the most common cause of death among all aortic pathological conditions. In cases of aortic dissection, the layers of the media are dissected by a column of blood through an intimal tear with variable degrees of proximal and distal extension within the length of the aorta. A wide range of symptoms and signs is linked to either rupture or occlusion of a major vessel.[1]

Pain is the most common classical symptom. Rarely, aortic dissection can be painless. In rare occasions (2%–5% of the patients), acute paraplegia can manifest mainly if the intercostal arteries are involved by the aortic dissection.[1]

Case Report

A 55-year-old hypertensive chronic obstructive lung disease (COPD) heavy smoker male patient, not compliant on his medical therapy, presented with acute exacerbation of COPD. On clinical examination, he was distressed and tachypneic with diffuse expiratory wheezes all over his chest and his blood pressure was 140/90 mmHg. Arterial blood gases revealed hypoxia and severe respiratory acidosis, so he was mechanically ventilated. After 1 day, he started to improve and weaned from mechanical ventilation safely. After weaning, he started to complaint of acute onset of paraplegia without any chest or abdominal or back pain. Clinical examination revealed a motor loss in both lower limbs together with a sensory loss to the level of T9 with loss of bilateral peripheral pulsations from the femoral arteries downward. Electrocardiogram showed 0.5 mm ST elevation in the inferoposterior leads. Laboratory investigations revealed

Address for correspondence: Dr. Mahmoud Abdelnaby, Cardiology and Angiology Unit, Clinical and Experimental Internal Medicine Department, Medical Research Institute, University of Alexandria, Alexandria, Egypt.
E-mail: mahmoud.hassan.abdelnabi@outlook.com

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elevated cardiac enzymes and renal and hepatic functions. His chest X-ray showed a wide mediastinum. Urgent transthoracic echocardiography [Figures 1-4] revealed a dilated aorta with a dissection flap extending from the aortic annulus to the aortic

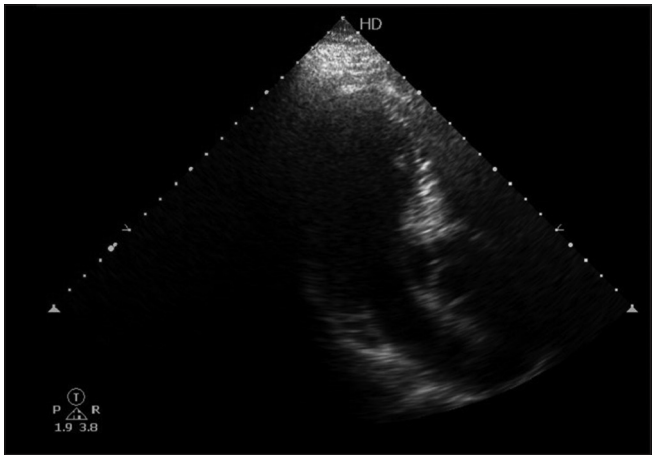


Figure 1: Transthoracic echocardiography apical long view showing a dissection flap extending through ascending aorta

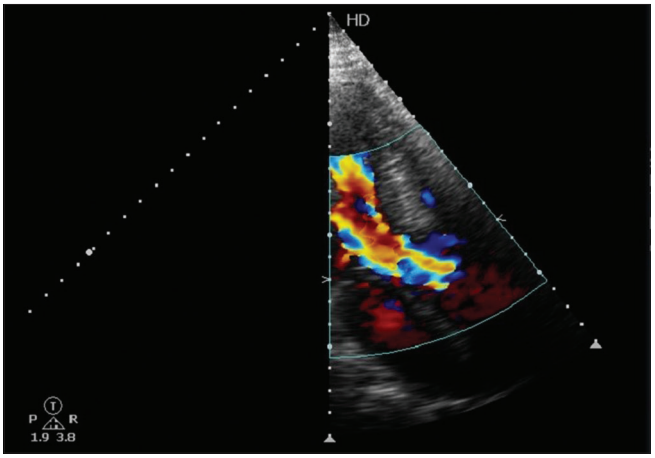


Figure 2: Transthoracic echocardiography color flow in apical long view showing severe aortic regurgitation

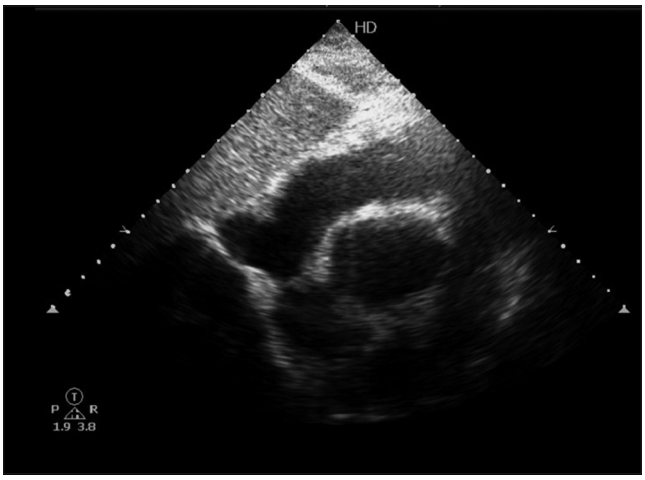


Figure 3: Transthoracic echocardiography subcostal view showing a dissection flap seen at the ascending aorta

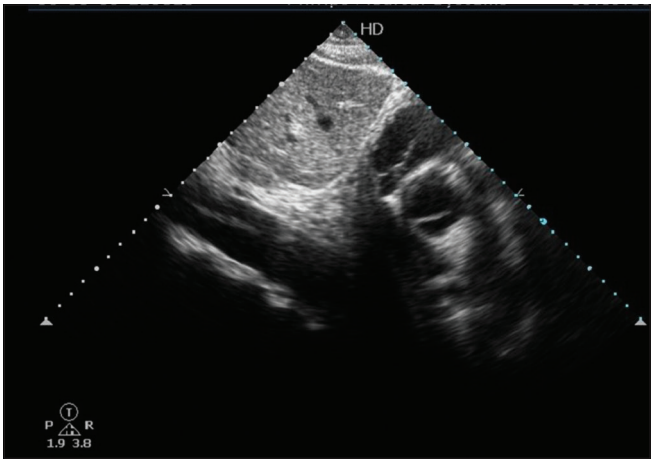


Figure 4: Transthoracic echocardiography subcostal view showing a dissection flap extending through the abdominal aorta

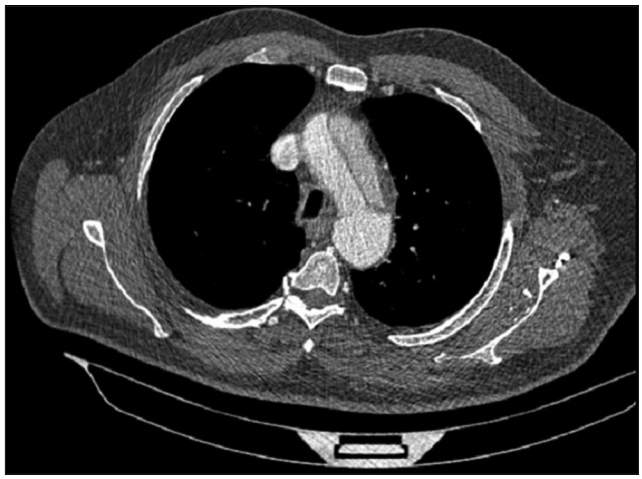


Figure 5: Computed tomographic aortography revealing a dissection flap at the aorta



Figure 6: Computed tomographic aortography revealing a dissection flap in both ascending and descending thoracic aorta



Figure 7: Computed tomographic aortography revealing a dissection flap in descending abdominal aorta

arch, the descending thoracic and the abdominal aorta with severe aortic regurgitation and a preserved left ventricular function with no regional wall motion abnormalities. Urgent computed tomographic aortography [Figures 5-7] showed an intimal tear at aortic arch extending proximally to the aortic annulus and distally to involve the entire aorta up to the left iliac artery affecting several arteries in its course, namely right coronary, innominate, left common carotid, left subclavian, intercostals, superior mesenteric, splenic, hepatic, left renal, left iliac arteries, and partially affecting right renal artery. He was referred for urgent surgery in another highly specialized cardiothoracic center where he, unfortunately, died during the operation.

Discussion

Acute aortic dissection is a sudden pathological aortic condition where blood passes through an intimal tear dissecting the layers of the aortic media, resulting in the formation of a false lumen. A wide variety of symptoms can occur according to the involved branches. A wide range of clinical presentation can be associated with aortic dissection, including confusion or coma from cerebral hypoperfusion or even stroke, electrocardiographic changes, or even elevated cardiac troponin levels, indicating cardiac hypoperfusion and myocardial dysfunction such as inferior ST-elevation myocardial infarction, loss of pulses, sensory function, or motor function due to iliofemoral or brachiocephalic hypoperfusion, creatinine elevation or low urine output due to renal hypoperfusion if the renal vessels were affected by the aortic dissection flap, paraplegia due to spinal hypoperfusion if intercostal blood vessels were affected or mesenteric hypoperfusion resulting in abdominal tenderness, bowel ischemia, or elevated liver enzymes.[2]

In 2%–5% of cases, paraplegia can manifest when intercostal arteries arise from the false lumen of the dissection,[1] resulting in abrupt obstruction of the spinal arteries with interruption of blood flow to the spinal cord, especially to the crucial zones, lower thorax, and lumbar segments.[3] Hence, ischemia of the spinal cord contributes to aortic dissection-related neurological syndromes with a sudden onset of motor weakness and paresthesia (paraplegia)[3] and aortic dissection that presents primarily as paraplegia is rare.[4,5] Painless paraplegia is an extremely rare clinical presentation of aortic dissection with only few case reports in the literature.[6] Aortic dissection is associated with very poor prognosis unless treated promptly.[7] It is very crucial to differentiate between paraplegia caused by aortic dissection from other spinal vascular pathologic conditions that cause painless paraplegia. High index of suspicion, rapid diagnosis, and properly timed intervention are associated with complete recovery from aortic dissection-induced paraplegia.[7]

Conclusion

Acute paraplegia is considered a rare clinical presentation of acute aortic dissection, and it can occur even with no chest or back pain. In patients who have absent bilateral femoral pulse and abrupt onset of paraplegia even if painless, acute aortic dissection must be considered with prompt diagnosis, and urgent intervention is necessary to reduce morbidity and mortality of this fatal condition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Periaortic Abscess Forming Pulsatile Sac around Graft in a Patient with Prosthetic Valve Endocarditis after Bentall Operation

Sinan Varol, Sevgi Özcan[1], Gökmen Kum, Irfan Sahin, Ertugrul Okuyan

Department of Cardiology, Bagcilar Training and Research Hospital, Health Sciences University, [1]Department of Cardiology, Okmeydanı Training and Research Hospital, Health Sciences University, Istanbul, Turkey

ORCID:

Sinan Varol: https://orcid.org/0000-0002-2511-7083
Sevgi Özcan: https://orcid.org/0000-0002-0201-8314
Gökmen Kum: https://orcid.org/0000-0002-6902-1163
İrfan Şahin: https://orcid.org/0000-0001-9165-7566
Ertuğrul Okuyan: https://orcid.org/0000-0002-0626-2939

Abstract

A 62-year-old man with high fever, general fatigue, and history of transient ischemic attack was transferred to our cardiology clinic with high clinic suspicious of endocarditis. He had a history of mitral ring annuloplasty and coronary artery bypass grafting operation before many years ago and reoperation for aortic dissection as Bentall procedure about 3 months ago. Blood tests showed leukocytosis with massive elevation of C-reactive protein, modest elevation of troponin, marked elevation of International Normalized Ratio, mild anemia, and hypoalbuminemia. Transesophageal echocardiogram (TEE) revealed a 4-mm × 15-mm round mobile mass originating from the anterior part of the mitral annular ring. In addition, there were a sac surrounding aortic graft and surrounding aneurismal aorta suggests a separation of graft because of possible aortic perivalvular abscess. There was blood flow into the sac and extensive thrombus with mobile component was seen in it. Blood cultures were positive for *Streptococcus pneumoniae*. Vancomycin, gentamicin, and rifampicin were chosen as antibiotic regimen. Early surgery planned for endocarditis and drained abscess cavity. However, the patient was persistently refused the third heart surgery operation. Repeat TEE showed the absence of vegetation on mitral valve and evident shrinkage of thrombus. Chest X-ray showed large left pleural effusion. Computed tomography with contrast enhancement confirmed this finding and revealed that contrast leak to the periaortic area and spreading a path under pulmonary artery to adjacent of the anterior wall of left ventricle. Thoracentesis was performed. Fistula to left pleura was suspected but not clearly confirmed. At 6 weeks of hospitalization, he clinically deteriorated. Due to confusional state, informed consent was obtained from attending relatives. The patient was transferred to the operating room. Cardiopulmonary resuscitation was initiated and thoracotomy was performed. Dehiscence of the aortic valve was seen. Infected tissues were extracted and repair with new prosthesis aortic valve was performed. Despite all resuscitation efforts, the patient died.

Keywords: Abscess, aortic valve, Bentall, dehiscence, pulsatile sac

Introduction

The Bentall procedure was first described by Bentall and De Bono in 1968. Since then, composite replacement of the aortic valve and ascending aorta has been considered the gold standard for treating ascending aortic dissection complicated by aortic regurgitation.[1] Cardiac surgery is usually required

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Address for correspondence: Dr. Sinan Varol, Department of Cardiology, Bagcilar Training and Research Hospital, Health Sciences University, Istanbul, Turkey.
E-mail: sinanvarol@gmail.com

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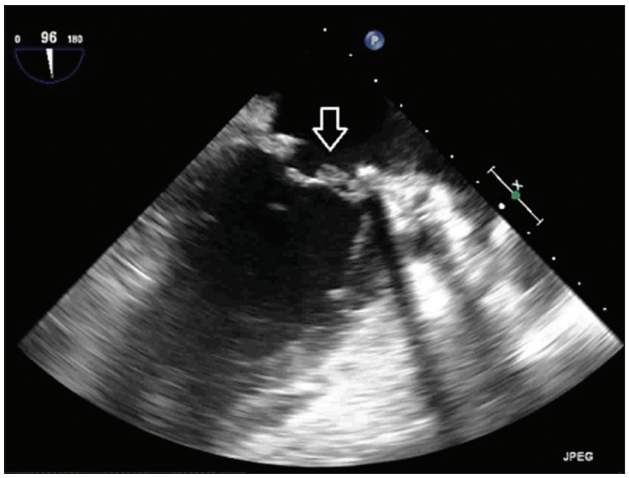


Figure 1: Transesophageal echocardiogram revealed a 4-mm × 15-mm round mobile mass originating from the anterior part of the mitral annular ring

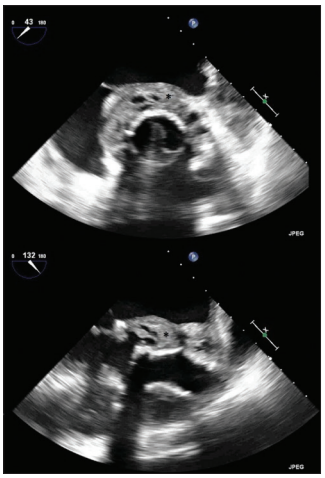


Figure 2: There was a sac surrounding aortic graft and surrounding aneurismal aorta suggests a separation of graft because of possible aortic perivalvular abscess

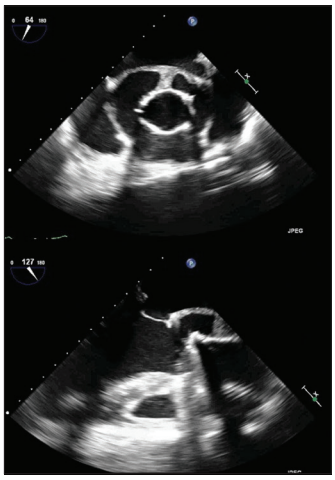


Figure 3: Repeat transesophageal echocardiogram showed the absence of vegetation on mitral valve and evident shrinkage of thrombus

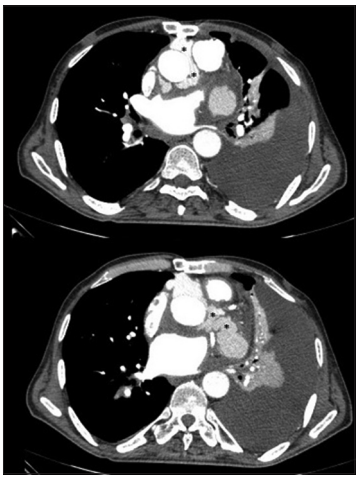


Figure 4: Computed tomography with contrast enhancement confirmed this finding and revealed that contrast leak to the periaortic area and spreading a path under pulmonary artery to adjacent of the anterior wall of the left ventricle

for infections of the mechanical valved conduit because of the high likelihood of resistant organism, and the possibilities of heart failure and embolization. Here, we report a case of early infective endocarditis complicated by periaortic abscess.

Case Report

A 62-year-old man with high fever, general fatigue, and history of transient ischemic attack was transferred to our cardiology clinic with high clinic suspicious of endocarditis. He had a history of mitral ring annuloplasty and coronary artery bypass grafting (CABG) and mitral ring annuloplasty operation 12 years ago and reoperation for aortic dissection as Bentall procedure about 3 months ago. He has diabetes, moderate chronic obstructive pulmonary disease, and right nephrectomy for several years ago. His medication was warfarin, spironolactone plus hydrochlorothiazide, gliclazide, metformin, digoxin, furosemide, and tiotropium. The patient has tachycardia with 2/6 systolic aortic murmur. Bilateral lung sounds were normal. The embolic and rheumatic phenomenon of endocarditis were absent and other findings were normal. Electrocardiogram showed that sinus rhythm with 120 BPM. Blood tests showed leukocytosis with massive elevation of C-reactive protein (CRP), modest elevation of troponin, marked elevation of International Normalized Ratio (INR) value, mild anemia, and hypoalbuminemia [Table 1]. Minimal left pleural effusion was seen on chest X-ray. Transesophageal echocardiogram (TEE) revealed a 4-mm × 15-mm round mobile mass originating from the anterior part of mitral annular ring [Figure 1]. In addition, there were a sac surrounding aortic graft and surrounding aneurismal aorta suggests a separation of graft because of possible aortic perivalvular abscess [Figure 2, Video 1a and b]. There was blood flow into the sac and extensive thrombus with mobile component was seen in it. Blood cultures were positive for *Streptococcus pneumoniae*. Vancomycin, gentamicin, and rifampicin were

Table 1: Blood tests on admission

Parameter	Result	Unit	Reference
Glucose	88	mg/dl	74-106
Urea	34	mg/dL	17-49
Creatinin	0.8	Mg/dl	0.5-0.9
AST	17	U/L	0-32
ALT	7	U/L	17-49
LDH	454	U/L	135-214
Sodium	134	mmol/L	136-145
Potassium	3.99	mmol/L	3.5-5.1
Chloride	96.6	mmol/L	98-107
CK	25	U/L	20-170
CK-MB	20	U/L	<25
Troponin T	0.296	ng/mL	<0.014
WBC	19.720	$10^{-3}/mm^3$	3.9-11.7
Neutrophil	17.060	$10^{-3}/mm^3$	1.9-8
RBC	4.25	$10^{-3}/mm^3$	3.85-5.16
Hb	11.68	gr/dL	12-15
Hct	37.5	RU	34.8-45
PLT	323	$10^{-3}/mm^3$	130-400
Albumin	2.6	g/dL	3.5-5.2
Total protein	6.2	g/dL	6.4-8.3
Prothrombin time	62.6	sec	11-16
INR	6.59		0.8-1.3
aPTT	40.4	sec	30-40
T. Bilirubin	1.21	mg/dl	0.3-1.4
D. Bilirubin	0.65	mg/dl	0.01-0.3
CRP	> 275	mg/dl	0-5

chosen as antibiotic regimen. INR values were high during the 1st week (>5) despite K-vitamin replacement. Leukocytosis and CRP values are gradually decreased with antibiotic regimen and subsequent blood cultures were negative. After clinical stabilization and the fall of INR value to therapeutic range, early surgery planned for endocarditis and drained abscess cavity. The patient informed about his clinical status and requirement of surgical operation. However, the patient was persistently refused third heart surgery operation. At 3rd week of treatment, repeat transesophageal echocardiogram.

TEE showed absence of vegetation on mitral valve and evident shrinkage of thrombus [Figure 3, Video 2a and b]. The leukocyte count was 10900/mm^3 and CRP was 108 mg/L. However, mild-to-moderate dyspnea was developed after a few days. Chest X-ray showed large left pleural effusion. Computed tomography with contrast enhancement confirmed this finding and revealed that contrast leak to the periaortic area and spreading a path under pulmonary artery to adjacent of the anterior wall of left ventricle [Figure 4]. Thoracentesis were performed. Fistula to left pleura was suspected, but not clearly confirmed by noninvasive tests. The patient was continued to refuse a heart operation. At 6 weeks of hospitalization, he suddenly gets hypotensive and clinically deteriorated. Because the patient was in a confusional state, informed consent was obtained from attending relatives. The patient was transferred to the operation room for emergency surgery. Cardiopulmonary resuscitation was initiated and thoracotomy was performed. Dehiscence of the aortic valve was seen. Infected tissues were extracted and repair with new prosthesis aortic valve was performed. However, postoperative myocardial functional recovery could not be achieved. Despite all resuscitation efforts, the patient died.

Discussion

Complications due infection after Bentall procedure are rare (1.4%)[2] but severe and not well documented. Staphylococci, alpha-hemolytic streptococci, and enterococci are the common causative organisms.[3] In a study consists ascending aorta prosthetic graft infections, most common organisms were coagulase-negative staphylococci, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*.[4] Our patient developed infective endocarditis caused by *S. pneumoniae* at 3 months after the procedure. Native valve endocarditis due to *S. pneumoniae* has become rare since the introduction of antibiotics.[5-7] Illicit drug use, altered mental status, and alcohol intake were found as risk factors for endocarditis. For prosthetic valves and graft infections, *S. pneumoniae* is very rare as causative organism.[8]

Austrian syndrome, the combination of meningitis, pneumonia, and infective endocarditis due to *S. pneumoniae* infection, is a rare entity.[9] Given its acute presentation and rapid course, patients should be closely monitored for any complications.

Treatment of pneumococcal endocarditis (PE) includes a prolonged course of intravenous antibiotics and if needed, surgery.[9] Our patient was treated conservatively, and surgical operation cannot be performed because of the refusal by the patient. However, he subsequently developed hemodynamic failure. Surgical evaluation must be pursued in any PE patients with suspicion for complication such as abscess, large vegetation, and valve perforation. The combined medical and surgical approach has improved outcomes, as compared to medical treatment alone in this group of patients.[9]

Conclusion

This case illustrates the need for closer monitoring after surgery. A redo-operation for active prosthetic valve endocarditis after Bentall operation rare in published series is a serious possible complication during follow-up. Its treatment comprises early complete removal of prosthetic material under suitable antibiotic therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Report

High-Grade Atrioventricular Block Requiring Pacemaker Implantation after Cardiac Transplantation: An Unusual Complication

K. K. Talwar, Abhinit Gupta[1], Raghav Bansal[1], Kewal Krishan[2]

Department of Cardiology, Max Healthcare Institute Limited, Departments of [1]Cardiology and [2]CTVS, Max Super Speciality Hospital, New Delhi, India

ORCID:

K. K. Talwar: https://orcid.org/0000-0002-7879-2680
Abhinit Gupta: https://orcid.org/0000-0001-8152-5519
Raghav Bansal: https://orcid.org/0000-0002-1649-8013
Kewal Krishan: https://orcid.org/0000-0001-5321-0958

Abstract

Self-limited bradyarrhythmias are commonly seen in postorthotopic heart transplantation patients. The most common cause of such bradyarrhythmias is sinus node dysfunction. Atrioventricular (AV) nodal blocks requiring pacemaker implantation remain distinctly uncommon. After ruling out reversible causes including dyselectrolytemia and drug toxicity, prolonged ischemia time of donor heart and transplant rejection should be considered as possible causes. The present case describes an uncommon occurrence of persistent high-grade AV block in postheart transplantation period ultimately requiring permanent pacemaker implantation.

Keywords: Brady-arrhythmia, cardiac transplantation, heart transplantation, high grade atrioventricular block, pacemaker implantation

Introduction

Cardiac transplantation remains the treatment of choice for end-stage heart disease. Arrhythmias are common in the orthotopic heart transplant (OHT) recipient, particularly in the early postoperative period, but are usually self-limited. Bradyarrhythmias occur in 8%–23% of patients after OHT depending on the case series and are probably due to sinus node dysfunction, but atrioventricular (AV) conduction disturbances requiring permanent pacemaker implantation are uncommon.[1]

Case Report

A 37-year-old patient underwent bicaval OHT for dilated cardiomyopathy. Pretransplant evaluation of donor heart was negative for any structural heart disease or conduction system disease. Baseline electrocardiogram (ECG) of donor heart was normal. The transplant procedure was uneventful with total ischemia time of <3 h. Immediately after the transplant, the ECG was suggestive of the right bundle branch block (RBBB) with normal PR interval. The posttransplant patient was started on triple immunosuppressive therapy including tacrolimus, mycophenolate mofetil, and prednisolone as per institutional protocol. Epicardial backup pacing was kept in place as a part of the protocol. The patient was noted to have increasing pacing requirements starting from day 7 in postoperative period in view of 2:1 AV block [Figure 1] with intermittent complete heart block. After ruling out reversible causes (hyperkalemia and AV-blocking drugs) and procedural causes (prolonged ischemia time and perioperative injury to AV node), the evaluation for early rejection was planned. Endomyocardial biopsy and electrophysiological (EP) study

Address for correspondence: Dr. K. K. Talwar,
Department of Cardiology, Max Healthcare Institute Limited,
New Delhi, India.
E-mail: kktalwar@hotmail.com

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were done on postoperative day 19. EP study revealed 2:1 AV conduction with prolonged HV interval (130 ms) suggestive of high-grade infra-Hisian AV block [Figure 2]. Histopathological examination and immunohistochemistry of the biopsy specimens were suggestive of mild acute cell-mediated rejection (the International Society for Heart and Lung Transplantation, Grade 1R) and were negative for pathologic antibody-mediated rejection [Figure 3]. Serum tacrolimus levels were found to be low, and with early cell-mediated rejection in consideration, the dose of tacrolimus and steroids was increased. However, the patient continued to have intermittent high-grade AV block. Repeat tacrolimus levels were in range. A permanent pacemaker implantation (single chamber, VVIR) was done on postoperative day 22. The patient was then discharged on immunosuppressive therapy in stable condition. On follow-up after 1 week, the patient was in sinus rhythm with RBBB [Figure 4] and pacemaker interrogation revealed minimal pacing requirement.

Discussion

Bradyarrhythmias after OHT are variably reported, but the most common cause remains sinus node dysfunction. Conduction system abnormalities leading to bradyarrhythmia are distinctly uncommon. Incomplete RBBB is the most common conduction abnormality seen in up to 70% of patients following OHT.[1] The conduction abnormality may persist and may be causally associated with prolonged donor ischemic time and episodes of rejection.[2] However, high-grade AV block remains uncommon, particularly in the early postoperative period. According to a study of 1047 posttransplant patients, first-degree, Mobitz Type I, Mobitz Type II, and complete heart blocks occurred in 8.3%, 0.6%, 0.1%, and 1.8% of patients, respectively.[3]

Whenever AV block occurs after cardiac transplantation, first reversible causes (e.g., hyperkalemia and AV-blocking drugs) should be ruled out and corrected, if any. The preoperative use of amiodarone in the recipient is an important cause of reversible posttransplant bradycardia that should not be missed. Periprocedural injury to AV node and prolonged ischemia time are also associated with postoperative AV node dysfunction and should better be avoided. Rarely, intraoperative coronary air embolism may also cause postoperative conduction disturbances. In a study by Leonelli *et al*., the duration of graft ischemia time and severity of rejection were the major determinants of conduction abnormality after OHT.[4] A total ischemia time >160 min was associated with persistence of conduction abnormality. Ice preservation of donor heart has been proposed as the likely cause of injury to conduction system. However, postoperative AV block is usually transient

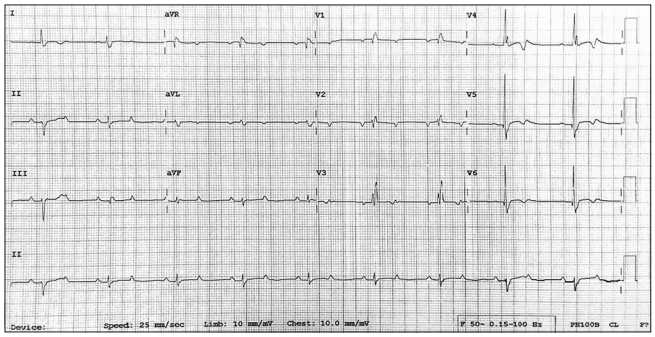


Figure 1: A 12-lead electrocardiogram done on posttransplant day 7 showing 2:1 atrioventricular block with wide QRS complex conduction (left anterior hemiblock and right bundle branch block) suggestive of infra-Hisian block

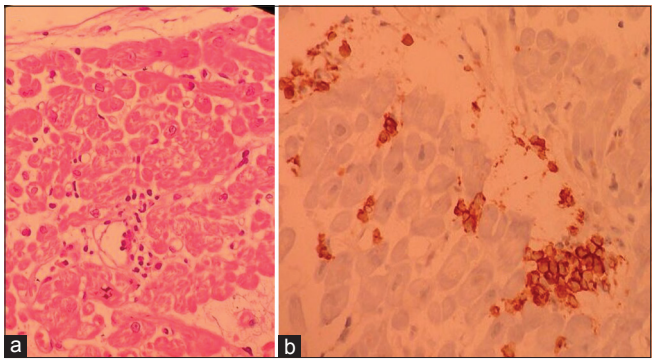


Figure 3: (a) Histopathological examination suggestive of mild acute cellular rejection (International Society for Heart and Lung Transplantation, 2004 Grade 1R) and (b) CD68 positivity on immunohistochemistry

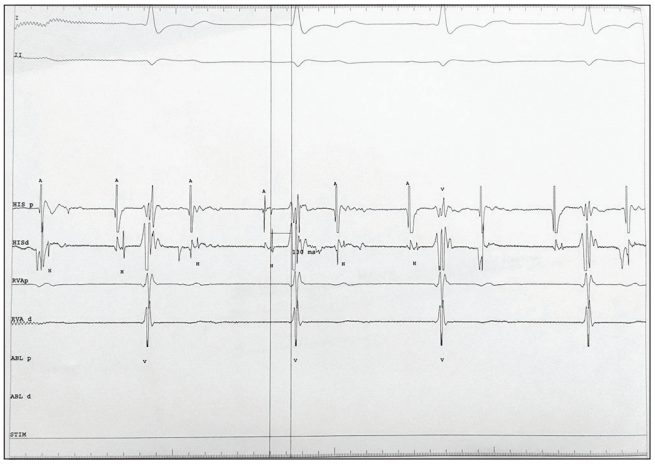


Figure 2: Electrophysiological study trace demonstrating infra-Hisian atrioventricular block (HV interval of 130 ms)

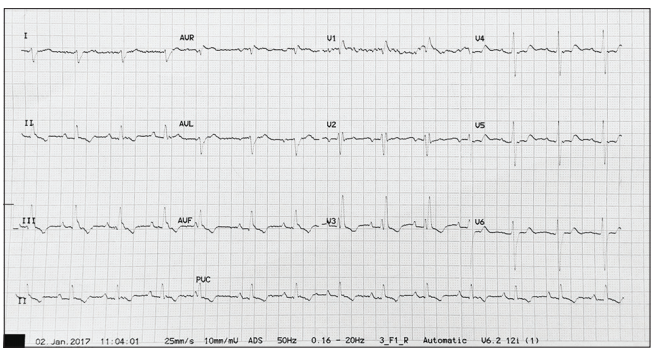


Figure 4: Normal sinus rhythm with right bundle branch block on follow-up

and only rarely requires permanent pacemaker implantation. In a contemporary case series on 1179 transplant patients, prolonged operative time and biatrial anastomosis were identified as independent risk factors for permanent pacemaker implantation.[5] Cardiac conduction tissue is also a specific target related to allograft rejection. The arteries to sinoatrial and AV tissue are frequently involved in both acute cellular reaction and chronic intimal fibrocellular rejection reaction, causing conduction disturbances.[6] Cardiac rejection should be strongly suspected and ruled out with certainty in cases of postoperative AV blocks. Early deceleration of immunosuppressive therapy and underdosing may precipitate early rejection and should be avoided. Cardiac endomyocardial biopsy is the gold standard for diagnosing cardiac rejection and must be done whenever rejection is suspected. If the AV block persists even after treatment of rejection or EP studies are suggestive of high-risk features, implantation of permanent pacemaker may be the right approach. In the present case, EP study helped to guide the approach and tilted the balance toward advocating permanent pacemaker implantation in view of infra-Hisian block.

In a retrospective study of 114 heart transplant recipients, 14 patients (12%) required temporary pacing and 4 patients (3.5%) required permanent pacing.[7] The indication for permanent pacemaker implantation was sinus node dysfunction in 3 patients (75%) and AV block in 1 patient (25%). They observed transplant rejection in 3 patients (21.4%) requiring temporary pacing and in 2 patients (50%) requiring permanent pacing.[7] Although pacemaker implantation is performed in approximately 10%–15% of cardiac transplant recipients, AV block accounts for <20% of these cases.[8,9] Median time to pacemaker implantation is much later for AV block than for sinus node dysfunction (1511 vs. 27 days in a study by Wellmann *et al*.).[5]

To sum up, high-grade AV blocks are uncommon in cardiac transplant recipients (especially in early postoperative period), and if noted, acute rejection and other reversible causes should be carefully ruled before considering for permanent pacemaker implantation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Cor Triatriatum with Mitral Stenosis: A Diagnostic Dilemma

Devvrat Desai, Jignesh Kothari, Parth Solanki, Kinnaresh Baria

Department of Cardiovascular and Thoracic Surgery, U. N. Mehta Institute of Cardiology and Research Center, (Affiliated to B. J. Medical College), Ahmedabad, Gujarat, India

ORCID:

Devvrat Desai: https://orcid.org/0000-0001-7083-9985
Jignesh Kothari: https://orcid.org/0000-0002-7693-2037
Parth Solanki: https://orcid.org/0000-0003-4940-7402
Kinnaresh Baria: https://orcid.org/0000-0001-8380-5514

Abstract

Cor triatriatum sinister is an extremely rare congenital heart defect. Very few cases have been reported for cor triatriatum associated with mitral regurgitation. We are reporting an exceptional case of cor triatriatum associated with calcified mitral valve resulting mitral stenosis. Preoperatively, mitral stenosis was underestimated due to the presence of restricted communication between two chambers of the left atrium. The patient was operated for cor triatriatum repair with mitral valve replacement.

Keywords: Cor triatriatum sinister, mitral valve replacement, posterior annular calcification, rheumatic mitral stenosis

Introduction

Cor triatriatum sinister is an extremely rare congenital heart defect.[1] In classical form of cor triatriatum, there is a division of the left atrium by a fibromuscular membrane, band or tissue, resulting in the development of two distinct chambers, that is, a posterosuperior chamber and anteroinferior chamber. It is even more uncommon in adults and quite exceptional when associated with mitral valve disease.[2] Very few cases have been reported for cor triatriatum associated with mitral regurgitation.

Here, we are reporting an exceptional case of cor triatriatum associated with calcified mitral valve resulting mitral stenosis requiring mitral valve replacement.

Case Report

A 65-year-old female presented with a history of dyspnea and angina on exertion (New York Heart Association Class II) for the past 2 years and progressed to the New York Heart Association Class IV recently. On clinical examination, the patient had a regular heart rate of 80/min with blood pressure of 130/90 mm of mercury (mmHg).

Electrocardiogram confirmed normal sinus rhythm. Chest radiography showed prominent bronchovascular markings [Figure 1].

Transthoracic echocardiography revealed cor triatriatum; a membrane dividing left atrium into posterosuperior venous chamber and anteroinferior mitral chamber. There was a small communication between two chambers. On Doppler flow mapping, mitral valve inflow signal (pg/mg) was 7/3 mmHg. Color and pulse wave Doppler suggested moderate mitral stenosis and mild mitral regurgitation with mild pulmonary arterial hypertension with ejection fraction of 55%. Above findings were confirmed on transesophageal echocardiography.

For further assessment of pulmonary venous anatomy and mitral valve pathology, computerized tomographic pulmonary angiogram was advised. Multislice computed tomography (CT) pulmonary angiography was performed

Address for correspondence: Dr. Devvrat Desai, Department of Cardiovascular and Thoracic Surgery, U. N. Mehta Institute of Cardiology and Research Center, (Affiliated to B. J. Medical College), New Civil Hospital Campus, Asarwa, Ahmedabad - 380 016, Gujarat, India.
E-mail: drdevvratcvts@gmail.com

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after intravenous injection of nonionic contrast which showed the left atrium divided by a thin membrane, suggestive of cor triatriatum. (Loeffler's Type 2 – small restrictive opening with calcification). All pulmonary veins were draining into the posterior chamber of the left atrium [Figure 2a-d]. Mitral posterior annular calcification was found [Figure 3]. Preoperative conventional coronary angiography revealed a right dominant system with no evidence of coronary artery disease. The patient was advised for surgical correction of cor triatriatum.

Surgical technique

The lesion was approached by a midline sternotomy and pericardiotomy. Cardiopulmonary bypass was established using ascending aortic and bicaval cannulation technique. After complete myocardial protection with moderate hypothermia, we approached cor triatriatum through interatrial groove incision.

A large membrane was dividing the left atrium into two compartments posterosuperior and anteroinferior. Both chambers were connected through a restricted, calcified communication across membrane. After complete excision of the membrane, mitral valve was examined. Both mitral commissures were fused. There was a pinhole mitral valve orifice. Posterior annular calcification was present, which was underestimated preoperatively. Subvalvular apparatus was abnormally shortened. Mitral valve was excised and replaced with 25-mm St. Jude Master's series mechanical prosthesis.

Postoperative recovery was uneventful and the patient was discharged after 1 week of postoperative stay. Postoperative transthoracic two-dimensional echocardiography showed satisfactory findings. Follow-up contrast CT thorax, before discharge, showed no residual membrane in the left atrium with normally functioning mitral valve prosthesis [Figure 4a and b].



Figure 1: Preoperative chest radiograph showing prominent bronchovascular markings

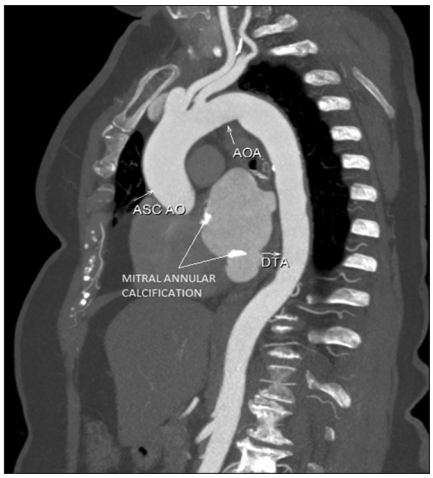


Figure 3: Preoperative computed tomography pulmonary angiogram showing posterior annular calcification of mitral valve

Discussion

Cor triatriatum sinister was first described by Church in 1868. It is found in only 0.1% of cases of congenital heart anomaly. In classical form of cor triatriatum, there is a division of the left atrium by a fibromuscular membrane, band or tissue,

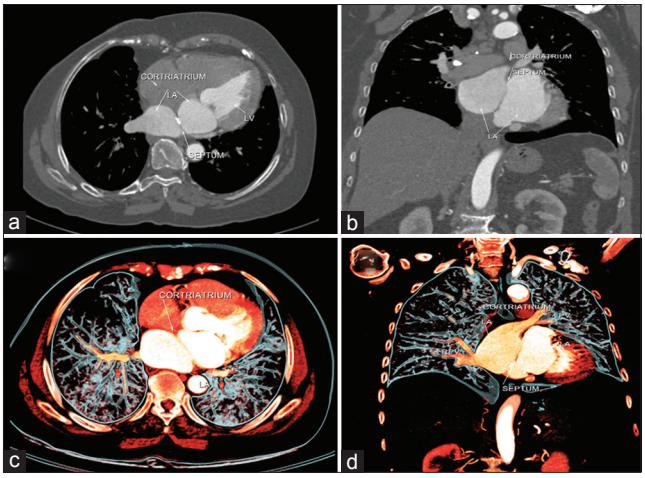


Figure 2: (a-d) Preoperative computed tomography pulmonary angiogram showing cor triatriatum Loeffler's Type 2 – small restrictive opening with calcification

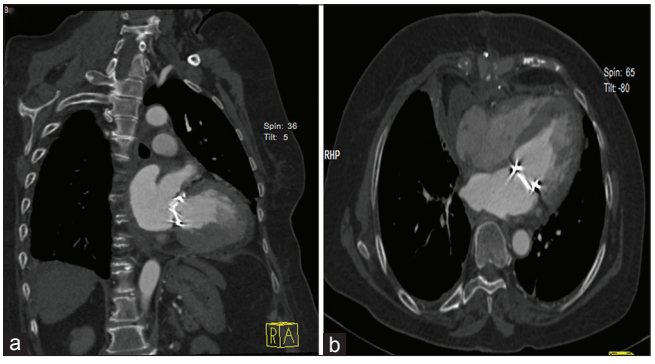


Figure 4: (a and b) Postoperative contrast-enhanced computed tomography thorax showing no residual membrane with mitral valve prosthesis *in situ*

resulting in the development of two distinct chambers, that is, a posterosuperior chamber and anteroinferior chamber. The posterosuperior chamber receives the return of all pulmonary veins. The anteroinferior chamber is a true left atrium which communicates with mitral valve.

Embryological basis for development of cor triatriatum is related with anomalous or failure of inclusion of the pulmonary veins into the posterior left atrial wall.[3] It is usual for patients to present in infancy and early childhood, although some cases remain undetected until adult life.

Natural history depends on the effective aperture size between two chambers of the left atrium. In severely restricted form, presentation occurs in early in infancy. Without surgical intervention, patients die early in infancy.[4,5] Approximately, 75% of persons born with classic cor triatriatum die in infancy.

Pathophysiologically, the obstructive nature of the membrane leads to the creation of a pressure gradient with an associated rise in pulmonary venous and arterial pressures. As a result, clinical presentation often mimics mitral stenosis. At present, the reasons for late presentation are poorly understood. Large unrestricted communication through fossa ovalis between two atria improves the prognosis and delays presentation.

The development of fibrosis and calcification in the opening of the separating diaphragm, mitral insufficiency or mitral stenosis, posterior annular calcification, and the development of atrial fibrillation are some of the various triggers that lead on to the symptoms.

Cor triatriatum sinister remains an uncommon form of congenital heart disease although it is being diagnosed with increasing frequency in adults due to improvements in diagnostic imaging. Wong *et al*.[6] reported, for the first time in 1989, a 49-year-old male patient with the rare combination of cor triatriatum sinister associated with severe mitral regurgitation and abnormal tensor apparatus of the mitral valve with hypoplastic papillary muscle. This diagnosis should be considered in all patients presenting with signs or symptoms of mitral stenosis.

Management in such cases differs from isolated cor triatriatum, in that, in addition to the surgical resection of accessory membrane, the patient requires mitral valve repair or replacement for correction of mitral valve pathology.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Prevalence of Metabolic Syndrome in Young Patients with ST-Elevation Myocardial Infarction

Dear Editor,

I read with interest the outstanding study by Oz *et al*.[1] on the prevalence of metabolic syndrome (MS) in Turkish young patients with ST-elevation myocardial infarction (STEMI). On employing the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III criteria), the authors found a high prevalence of MS (46.8%), and the most frequent component of MS was low high-density lipoprotein level (84.8%) followed by elevated triglycerides (78.1%).[1] I presume that these results ought to be cautiously interpreted. Apart from many limitations addressed by the authors, namely single-center study, not searching to examine the long-term clinical outcomes of all the studied patients, and lack of detailed assessment of vessels lesions, I presume that the following methodological limitation might be further relevant. This limitation is related to the MS definition criteria employed in the study. The impact of this limitation could be addressed in two aspects. On the one hand, there are many definition criteria for MS in the clinical setting and researches. These include the following: NCEP-ATP III; the International Diabetes Federation (IDF); the American Heart Association (AHA), and the World Health Organization (WHO). There is a global confusion on the precision of these criteria to diagnose MS. For instance, in a Turkish study, comparing the prevalence of MS among obese children and adolescents using WHO and NCEP-ATP III guidelines showed that 24% of the subjects were diagnosed as MS according to the NCEP while 38.8% were diagnosed according to the WHO-defined MS. The study recommended using WHO guidelines in the diagnosis of MS as this might detect more patients with MS and lead to better monitoring of them and prevention of their future sequelae.[2] In another Italian study, evaluation of three criteria, namely NCEP-ATP III, IDF, and AHA, showed that the prevalence of MS was significantly estimated higher on employing the AHA and IDF as compared to the ATP III definition and that AHA and IDF definitions were found more sensitive than that of ATP III in diagnosing MS.[3] On the other hand, the ATP III criteria employed in Oz *et al*.'s study[1] are old and are no more worthy as they were set nearly a decade ago.[4] As many national associations have proposed their own diagnostic MS criteria,[5] I presume that constructing national Turkish MS definition criteria could better determine the prevalence of MS in patients with various health disorders. Despite the above-mentioned limitations, the study results urge the need for strict actions to reduce the future risk of cardiovascular consequences in patients with STEMI.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Mahmood Dhahir Al-Mendalawi

Department of Paediatrics, Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq

ORCID:

Mahmood Dhahir Al-Mendalawi: https://orcid.org/0000-0003-2872-453X

Address for correspondence: Prof. Mahmood Dhahir Al-Mendalawi, P.O. Box 55302, Baghdad Post Office, Baghdad, Iraq.
E-mail: mdalmendalawi@yahoo.com

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Authors' Response: Letter to the Editor on Prevalence of Metabolic Syndrome in Young Patients with ST Elevation Myocardial Infarction

We would like to thank Dr. Mahmoud Abdelnabi *et al*. for their valuable comments but according to our opinion, there is confusion about our study design. With regard to the remarks of Dr. Mahmoud Abdelnabi, it should be clear that:

1. The main aim of the study was to determine the prevalence of metabolic syndrome (MS) in patients under 46 years of age who presented with ST elevation myocardial infarction and underwent primary percutaneous coronary intervention and especially this study did not focus on the morphology of coronary lesions
2. The limitations of our study that we mentioned in the limitation part do not affect the prevalence of MS
3. Over the last two decades, various organizations have proposed different definitions, using varying terminologies about MS. There are not just the International Diabetes Federation, the American Heart Association, and the World Health Organization (WHO) but also The European Group for Study of Insulin Resistance proposed a modification of the WHO definition
4. Despite the large number of controversies regarding the nomenclature to be used, this conglomeration of various metabolic abnormalities in NCEP-ATP III criteria has been widely accepted as a screening tool for identifying subjects at high risk of cardiovascular disease and the aim of our study was not to compare these different definitions.

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Conflicts of interest

There are no conflicts of interest.

Tugba Kemaloglu Öz, Nazmiye Özbilgin[1], Aylin Sungur[1], Elif Gülsah Bas, Ahmet Zengin[1], Tayfun Gürol, Özer Soylu, Bahadir Dagdeviren

Department of Cardiology, Faculty of Medicine, Bahcesehir University, [1]Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Center, Istanbul, Turkey

ORCID:
Tugba Kemaloglu Öz: https://orcid.org/0000-0003-1168-8237
Nazmiye Özbilgin: https://orcid.org/0000-0002-3334-8359
Aylin Sungur: https://orcid.org/0000-0001-1904-4906
Elif Gülsah Bas: https://orcid.org/0000-0003-0193-6495
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Tayfun Gürol: https://orcid.org/0000-0001-8200-3747
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Bahadir Dagdeviren: https://orcid.org/0000-0001-6945-0745

Address for correspondence: Dr. Tugba Kemaloglu Öz, E5 Üzeri 23, Nisan Sok Merdivenköy No: 17, 34732, Kadiköy, Istanbul, Turkey.
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Addresses

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Prof. Dr. Mehdi Zoghi
Ege University, Faculty of Medicine,
Department of Cardiology,
Bornova, 3100, İzmir - Turkey.
Telephone: +90 232 - 3905458
E-mail: mehdi_zoghi@hotmail.com

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Review Article

Brugada Syndrome: A Brief Review on Diagnostic Approach, Risk Stratification, and Management

Raymond Pranata

Department of Cardiology and Vascular Medicine, Siloam Hospitals Lippo Village - Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

ORCID:

Raymond Pranata: https://orcid.org/0000-0003-3998-6551

Abstract

Brugada syndrome is a congenital channelopathy in cardiac ion transmembrane causing an alteration in the electrical conduction of the heart. ST-elevation, as well as right bundle-branch block in anterior precordial electrocardiography (ECG), is pathognomonic in this syndrome. The patient might be asymptomatic or with a history of syncope and prone to develop ventricular tachyarrhythmia which may spontaneously recover or degenerates to ventricular fibrillation, cardiac arrest and even sudden death. Nevertheless, this can be prevented by implantable cardioverter defibrillator implantation. Therefore, it is of paramount importance that clinical suspicion and identification, interpretation of its characteristic ECG pattern and risk stratification to be properly done to diagnose and to manage Brugada syndrome. The author has also done a systematic review (included in the article) for several noninvasive ECG parameters for risk stratification with promising results. Epicardial ablation is an emerging therapy that may "cure" Brugada syndrome.

Keywords: Arrhythmia, Brugada syndrome, risk stratification, sudden cardiac death, syncope

Introduction

Brugada syndrome is a genetically determined channelopathy leading to syncope and ventricular tachyarrhythmia causing sudden death in those without evident structural heart disease. It was first mentioned in 1992.[1,2] Brugada syndrome was commonly considered as an abnormality found commonly in young males (male: female ratio was 9:1) and Southeast Asian. It frequently manifests at the age of 40 years, causing sudden death frequently during sleep.[3-5] Suspicion should arouse when encountering a patient with a history of idiopathic ventricular fibrillation (VF) or polymorphic ventricular tachycardia (VT) that aborts spontaneously and family history of sudden death in young age with or without typical electrocardiography (ECG) findings. The incidence of Brugada syndrome in adults is approximately 0.05%–0.60% and the average age when the diagnosis is established is 41 years old.[6]

Genetic Basis and Pathophysiology

There are 18 genes that are associated with Brugada syndrome from BrS1 to BrS18. Basically, there are abnormalities in sodium, calcium, or potassium ion channels located at heart muscles.[7,8]

Sodium flow

BrS1 gene was the first gene to be discovered which involves SCN5A at chromosome 3p21-23 encodes subunit α of sodium ion channel protein (NaV1.5) which is responsible for depolarization (Phase 0 of action potential). Mutation results in loss-of-function of the sodium channel resulting in less sodium influx into the interior of the cell during depolarization. This mutation was also linked with other cardiac conduction defects (atrioventricular [AV] block, left bundle branch block, and left anterior fascicular block).[9,10] BrS2 is responsible for mutations in glycerol-3-phosphate dehydrogenase 1-like protein reducing both the surface membrane expression and the inward sodium current.[11] SCN1B plays a role in forming subunit β1 of sodium ion

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Address for correspondence: Dr. Raymond Pranata, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia.
E-mail: raymond_pranata@hotmail.com

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which modifies Nav1.5, thus increasing I_{Na} was the cause of BrS5.[12] Meanwhile, BrS7 gene (SCN3B gene) forms subunit β3 of sodium ion channels which alters Nav1.5 trafficking, thereby decreasing I_{Na}.[13]

Calcium flow

CACNA1C mutation results in BrS3 and CACNB2 cause BrS4. They are responsible for a defective unit of the L-type calcium channel. These mutation cause dysfunctions in subunit α and β resulting in loss of function and reduced calcium influx culminating in shortening of the plateau phase of action potential. The *CACNA2D1* gene was reported as responsible for BrS. The α2/δ-subunit of voltage-dependent calcium channels regulates current density and activation/inactivation kinetics of the calcium channel.[7,8]

Potassium flow

KCNE3 gene plays a role in the formation of MiRP2 protein (β-subunit that regulates the potassium channel I_{to}) and modulates some potassium currents in the heart. A recent study revealed that enhanced I_{to} current gradient in the right ventricle was associated with KCND3 gain-of-function mutations (Kir4.3 protein). Another gene associated with BrS is *KCNJ8,* which was previously related to early repolarization syndrome and a marker of gain-of-function in the cardiac K (ATP) Kir6.1 channel. The *KCNE5* gene, which is located in the X chromosome, encodes an auxiliary β-subunit for K channels causing gain-of-function effects on I_{to}.[7,14]

The most prevalent is SCN5A mutation (20% of cases), these dysfunctions resulted in an imbalance between outward and inward positive currents during repolarization causing heterogeneous loss of action potential dome during phase 2. Increased dispersion of repolarization and refractoriness within epicardium and across the wall are associated with phase 2 re-entry mechanism resulting in ventricular arrhythmias.[15] Most of the genetic variants found in Brugada syndrome remain of unknown significance because no comprehensive cellular studies have been performed. Genetic variants other than SCN5A may be responsible for only 2%–5% of diagnostic cases. Recently, there is a notion that Brugada syndrome may not be caused by a single mutation but rather by multiple susceptibility variants [Figure 1].

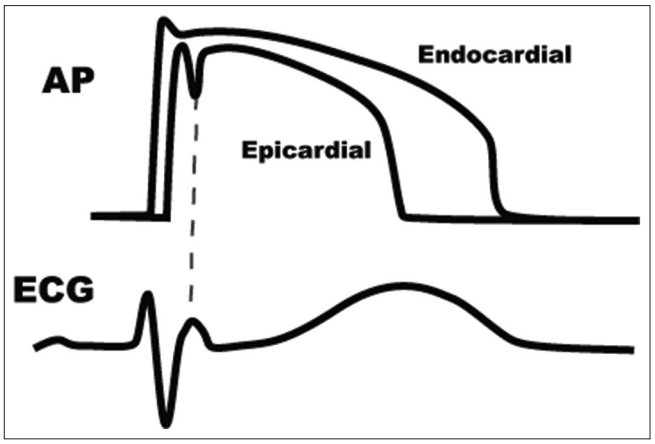


Figure 1: Difference in action potential in epicardial and endocardial myocyte in Brugada syndrome. Repolarization disorder hypothesis stated that the difference between action potential in the epicardial and endocardial myocyte resulted in the typical ST-elevation in Brugada syndrome

Clinical Manifestation and Diagnosis

VF or aborted sudden cardiac death (SCD), syncope, nocturnal agonal respiration, palpitations, and chest discomfort are associated with Brugada syndrome. These symptoms frequently occur during rest or sleep, fever, excess eating or binge drinking resulting in excess vagotonic condition nonetheless they rarely manifest during exercise.[8,16] Symptoms occurring at young age signals an aggressive form of the disease. Overall 20% experienced at least 1 syncope and only 10%–14% suffered cardiac arrest before 60 years old as was shown by international registries and meta-analysis.[6,17] Drugs such as bupivacaine, cocaine, propafenone, methoxamine, β-blocker, potassium channel activator (pinacidil), a tricyclic antidepressant, an opioid analgesic, lithium, and propofol exacerbates ECG pattern and potentially precipitating arrhythmia (visit Brugadadrugs.org). Diagnostic criteria of Brugada syndrome according to 2013 HRS/EHRA/APHRS expert consensus statement is with ST-segment elevation with type I morphology ≥2 mm in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs or in patients with type 2 or type 3 ST-segment elevation in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd, or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology.[16] According to international consensus conference on BrS ST-segment elevation of ≥2 mm in at least two of three precordial leads (V1–V3) with coved morphology associated with complete or incomplete right bundle-branch block was the ECG criteria to fulfill. Other ECG abnormalities that might be found are AV block and atrial fibrillation (10%–25% of patients).[8,18-21] These atrial arrhythmias in Brugada syndrome were associated with genetic variants impairing the sodium channel function along with structural remodeling that promote AF by prolonging refractoriness and slowing conduction velocity which may be heterogeneous and facilitates the development of unidirectional block and re-entry, giving rise to atrial fibrillation, atrial flutter, and AV-nodal re-entry tachycardia.[22]

There are three typical ECG patterns in patients with Brugada syndrome. In type 1 there is a Coved ST-segment elevation ≥2 mm followed by T inversion in >1 precordial leads (V1–V3). ST-T segment saddleback configuration followed by positive or biphasic T wave is seen in type 2 ECG. Meanwhile, type 3 may show coved or saddleback with ST-segment elevation <1 mm [Figure 2]. Typical ST segment changes might be found in patients with concealed form or type 2 or 3 ECG during provocation or fever. Therefore, in

Table 1: Proposed Shanghai Score System for diagnosis of Brugada syndrome

	Points
ECG (12-Lead/Ambulatory)	
Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2
Only award points once for highest score within this category. One item from this category must apply.	
Clinical History*	
Unexplained cardiac arrest or documented VF/ polymorphic VT	3
Nocturnal agonal respirations	2
Suspected arrhythmic syncope	2
Syncope of unclear mechanism/unclear etiology	1
Atrial flutter/fibrillation in patients <30 years without alternative etiology	0.5
Family History*	
First- or second-degree relative with definite BrS	2
Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative	1
Unexplained SCD <45 years in first- or second-degree relative with negative autopsy	0.5
Genetic test result	
Probable pathogenic mutation in BrS susceptibility gene	0.5
Score (requires at least 1 ECG finding). >3.5 points: Probable/definite BrS. 2-3 points: Possible BrS <2 points: Non-diagnostic	

*Only award points once for highest score within this category. BrS=Brugada syndrome; SCD=sudden cardiac death; VF=ventricular fibrillation; VT=ventricular tachycardia. Reproduced from Antzelevitch *et al*.[23]

patients with type 2 or 3 ECG findings, provocation with sodium channels inhibitor.[15] [Figure 2]. There is also new diagnostic criteria of Brugada syndrome (Shanghai score) which was proposed in the consensus statement in 2016 [Table 1].[23] It is important to note in this new consensus, that asymptomatic patients with drug-induced type 1 ECG are considered to be at low risk and need some clinical manifestations to be diagnosed with Brugada syndrome.[23]

Risk Stratification

Almost all studies are in agreement that patient with type 1 baseline ECG and an episode of syncope have a high risk of cardiac arrhythmia in follow-up. The presence of QRS fragmentation and effective refractory period <200 ms were also proposed.[24-26] Risk of lethal or near-lethal arrhythmia episode in previously asymptomatic patient is 8%, event rate at 33 ± 39 months follow-up was reported by Brugada *et al*.; 6% event rate in 34 ± 44 months by Priori *et al*.; 1% event rate was found at 40 ± 50 months and 30 ± 21 months follow-up by Eckardt *et al*. and Giustetto *et al*.[25,27-29] Even though large registries are in agreement that electrophysiological study (EPS) inducibility was most frequently encountered

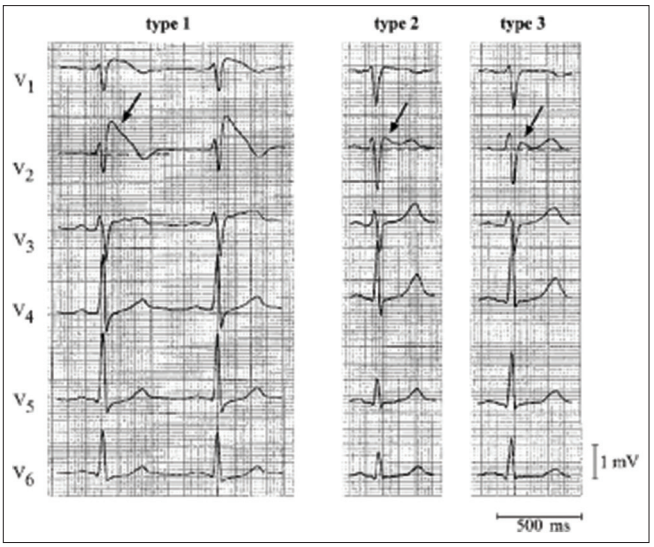


Figure 2: Electrocardiographic characteristics of Brugada pattern in precordial leads. electrocardiography in Brugada Syndrome. Type 1: Coved ST-elevation ≥2 mm followed by T wave deflection. Type 2: Gradually decreasing ST-elevation with saddleback pattern with positive or biphasic T wave and Type 3: coved or saddleback with ≥1 mm ST-elevation.[32] From: Wilde AA, Antzelevitch C, Borggrefe M *et al*.; Study Group on the Molecular basis of arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome. Eur Heart J 2002;23:1648-54

in those who experienced syncope or aborted sudden death, there is no consensus regarding the role of EPS. A study by Siera *et al*. showed 25 ventricular arrhythmia events, which consists of 16 (21.9%) patients in the group that was successfully induced by EPS and 9 (2.7%) patients that are not inducible. The aforementioned arrhythmia resulted in 24 appropriate implantable cardioverter defibrillator (ICD) shocks and 1 resuscitation because of cardiac arrest in those without ICD. The hazard ratio for an arrhythmic event in the future is 8.1 ($P < 0.01$) for those with inducible ventricular arrhythmia during the EPS study.[30] EPS is controversial because the protocols are different between studies, for example; only from RV apex by Brugada group, but other groups from both apex and RVOT, up to double or triple extra stimuli, and minimal coupling interval to 200 ms or to 180 ms, etc.). Recently, VF induction up to two extra stimuli is reported to be useful in the risk stratification of patients with Brugada syndrome.[27,31]

A study showed a Kaplan–Meier curve of 96.8%–99% event-free survival at 1, 5, 10, and 15 years in noninducible ventricular arrhythmia during EPS. It is concluded that in a patient with asymptomatic clinical presentation alone in those with noninducible groups has 99.2% event-free survival at 1, 5, 10, and 15 years.[30,32] Hence, EPS is an excellent predictor in both asymptomatic or those presenting with syncope[2] [Figure 3].

There were also studies that enlist additional tools for the risk stratification mainly Tpeak-end interval (TpTe), Tp-e dispersion, and TpTe/QT ratio [Table 2].[33-41] There were five

Table 2: Role of Tpeak-Tend, Tpeak-Tend/QT ratio, and Tpe dispersion as additional noninvasive electrocardiography parameters for predicting ventricular tachycardia/fibrillation in patients with Brugada Syndrome

Authors	Year	Study design	Samples	Subjects	Outcome of interest	Results
Morita H *et al*.	2018	Case-control study	62	Brugada-type ECG	Initial VF	OR of difference Tpe interval (V1) ≥ +10 ms: 11.0, CI: 2.6-46.1, *P*=0.001
Morita H *et al*.	2018	Retrospective Cohort	471	BrS	VF	TpTe (ms) V2 ≥95 was associated with HR 3.03 1.26-9.01 0.0143
Zumhagen	2016	Case-control study	78	BrS	VT/VF/aborted SCD	TpTe ≥77 ms, 63.6% and 74.1%; AUC 0.675, TpTe/QT ratio ≥0.205, 72.7% and 68.5%; AUC 0.673
Maury P	2015	Case-control study	325	BrS	Sudden death/ appropriate ICD shocks	Maximum Tpe>100 ms OR of 9.61 (95% CI 3.13-9.41) (*P*<0.0001). Sensitivity 84% and Specificity 68%, PPV 19%, NPV 98%
Mugnai	2017	Cohort	448	BrS	VT/VF/SCD/ appropriate ICD shocks	No significant difference was observed in TpTe, TpTe/QT, maximum TpTe, and TpTe dispersion
Kawazoe	2016	Case-control study	143	BrS	VF	Tpe dispersion OR 1.069 (1.03-1.10), *P*: 0.001 independent predictor
Letsas	2010	Case-control study	23	BrS	VT/VF inducibility	TpTe V2 (88.82+15.70 vs. 78.33 + 4.08 ms, *P*=0.02) and V6 (76.33+10.08 vs. 66.66+5.16 ms, *P*=0.04)
						Greater Tpeak-Tend/QT ratio in lead V6 (0.214 + 0.028 vs. 0.180+0.014, *P*=0.009)
Hevia JC	2006	Cohort	29	BrS	VT/VF	QTc >460 ms in V2
						TpTe and Tp-e dispersion were significantly prolonged in patients with recurrences versus patients without events
						TpTe cut-off point >100 ms; Sensitivity 77.8% and specificity 70%; AUC 0.7861
						Tp-e dispersion Cut-off point >20 ms; Sensitivity 66.7% and specificity 90%; AUC 0.7722

TpTe: Tpeak-Tend interval, SCD: Sudden cardiac death, ICD: Implantable cardioverter defibrillator, VF: Ventricular fibrillation, VT: Ventricular tachycardia, ECG: Electrocardiography, OR: Odds ratio, CI: Confidence interval, AUC: Area under the curve, PPE: Positive predictive value, NPE: Negative predictive value, BrS: Brugada Syndrome, HR: Hazard ratio

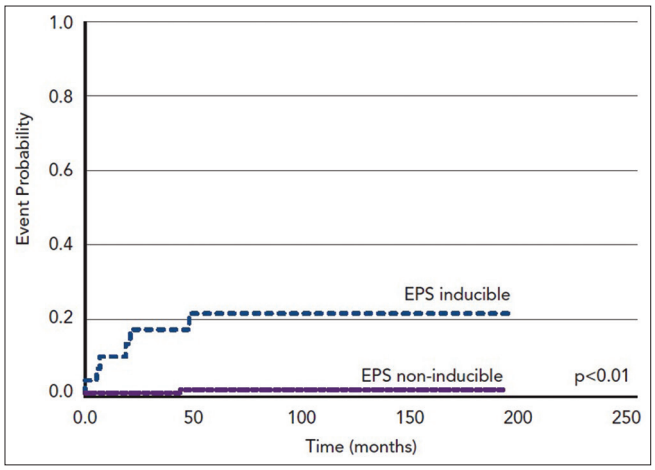


Figure 3: Kaplan–Meier curve showing high event-free survival of EPS noninducible patients. Patients had 96.8%–99% event free survival at 1, 5, 10 and 15 years in non-inducible ventricular arrhythmia during electrophysiological study[32]

studies that showed TpTe was reliable in predicting VT/VF in patient with Brugada syndrome, the cut-off points varied between precordial leads from ≥80 ms to ≥100 ms in which two studies reported a sensitivity 77.8%–84% and specificity 68%–70%; positive predictive value 19%, negative predictive value 98%, odds ratio (OR) 9.61 (95% confidence interval 3.13–9.41) ($P < 0.0001$), area under the curve (AUC) 0.7861 with ≥100 ms. Morita *et al*. indicated TpTe progression of >10 ms on repeat ECG was associated with OR 11.6 ($P = 0.001$). Zumhagen *et al*. showed that TpTe/QT ratio is reliable in predicting VT/VF in which a ratio of ≥0.205 has sensitivity 72.7% and specificity 68.5%; AUC 0.673. Two studies reported that Tp-e dispersion was associated with VT/VF one of which reported Cut-off point >20 ms; sensitivity 66.7% and Specificity 90%; AUC 0.7722. Only Mugnai *et al*. revealed the nonsignificant relation of the aforementioned parameters and VT/VF. Letsas *et al*. indicated that TpTe and greater TpTe/QT ratio in lead V6 are related to VT/VF inducibility, but the latter was not related to the arrhythmic outcome. Spontaneous type 1 ECG, syncope, early repolarization pattern, age (the elderly is at lower risk), and SCN5A mutation (pore lesion) were also associated with higher risk.[42-44]

Management

Drugs that may induce or aggravate ST-segment elevation in the right precordial leads should be avoided (visit Brugadadrugs.org). Excessive alcohol intake should be avoided, and immediate treatment of fever with antipyretic drugs are Class I recommendation [Table 3]. ICD implantation is the only effective modality in Brugada syndrome. Brugada syndrome patients who are survivors of a cardiac arrest and/or have documented spontaneous sustained VT with or without syncope had a Class I recommendation for ICD implantation. Implantation of ICD is recommended (Class IIa) in a patient with syncope (if syncope is suspected as arrhythmic origin)

and spontaneously abnormal ECG (without provocation) because those patients have six times increased risk of cardiac arrest compared to those showing type I ECG after provocation.[2,6] The risk is very low when the diagnosis was

Table 3: Recommendation on therapy and intervention in patient with Brugada Syndrome

Class of Recommendation	Intervention
Class I	The following lifestyle changes are recommended in all patients with diagnosis of BrS
	Avoidance of drugs that may induce or aggravate ST-segment elevation in right precordial leads
	Avoidance of excessive alcohol intake
	Immediate treatment of fever with antipyretic drugs
	ICD implantation is recommended in patients with a diagnosis of BrS who
	Are survivors of a cardiac arrest and/or
	Have documented spontaneous sustained VT with or without syncope
Class IIa	ICD implantation can be useful in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmia
	Quinidine can be useful in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 h
	Quinidine can be useful in patients with a diagnosis of BrS
	Who qualify for an ICD but present a contraindication to the ICD or refuse it and/or
	Have a history of documented supraventricular arrhythmias that require treatment
	Isoproterenol infusion can be useful in suppressing arrhythmic storms in BrS patients
Class IIb	ICD implantation may be considered in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients)
	Quinidine may be considered in asymptomatic patients with a diagnosis of BrS with a spontaneous type 1 ECG
	Catheter ablation may be considered in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks
Class III	ICD implantation is not indicated in asymptomatic BrS patients with a drug-induced type 1 ECG and on the basis of a family history of SCD alone

Expert Consensus Recommendations on BrS Therapeutic Interventions. Priori *et al*. SCD: Sudden cardiac death, ICD: Implantable cardioverter defibrillator, VF: Ventricular fibrillation, VT: Ventricular tachycardia, ECG: Electrocardiography, BrS: Brugada Syndrome

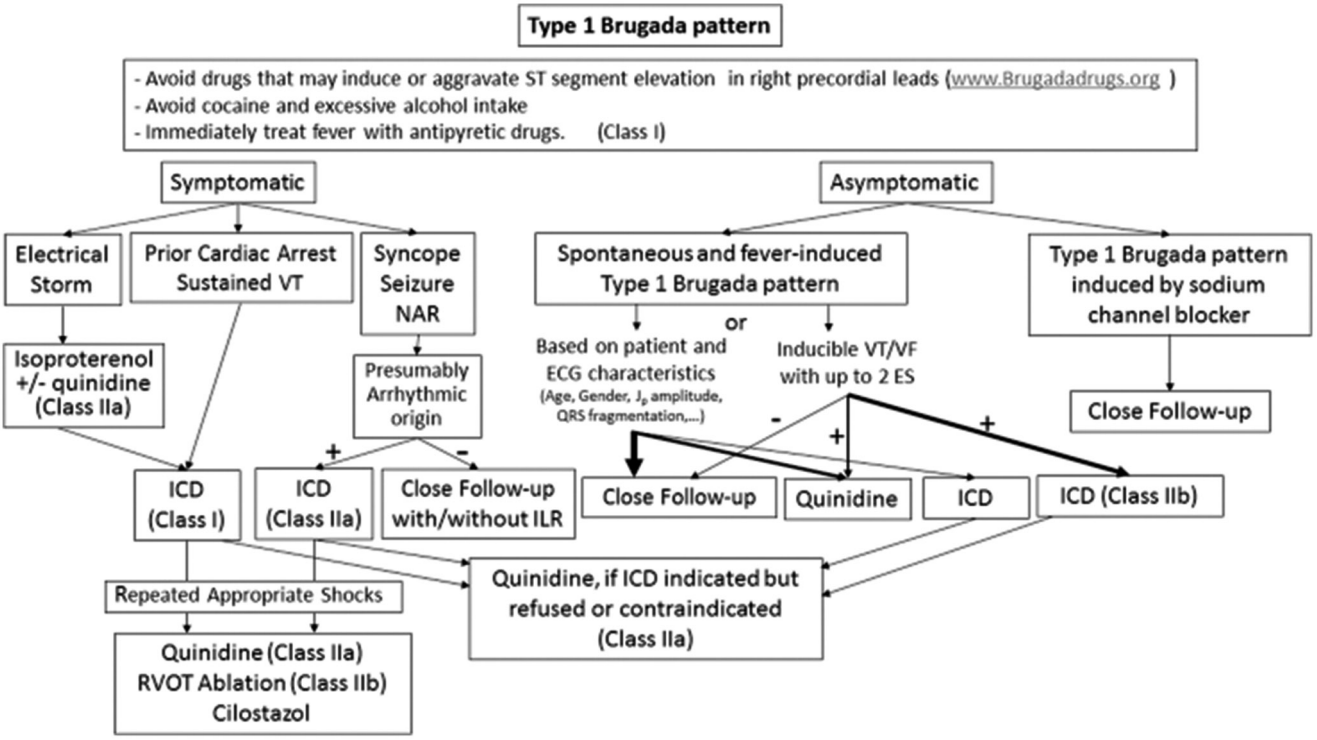


Figure 4: Indications for therapy of patients with Brugada syndrome. The figure above provide flowchart regarding the indications for therapy of patients with Brugada syndrome[23]

made after provocation test with sodium ion channel blockers or by identification of pathogenic mutation only. Follow-up may be needed to observe changes in ECG morphology, from previously requiring provocation to display typical ECG into spontaneously abnormal ECG.[8] Management in a patient with spontaneously abnormal type 1 ECG without a history of syncope is controversial, the risk of life-threatening events in this group is two-fold higher in those without spontaneously ST-segment elevation.[6,17] EPS may be beneficial in this group. However, its role is still controversial, and ICD implantation (Class IIb) may be considered those who develop VF during programmed electrical stimulation (inducible patients) [Figure 4]. QRS fragmentation in these patients was also associated with a worse prognosis.[24] Quinidine, which is the best antiarrhythmic medication available for Brugada syndrome is only used as an adjunct therapy for high-risk patients and to reduce the number of ICD shocks in those with recurrent events.[8] Quinidine may be considered in asymptomatic patients with a diagnosis of Brugada syndrome with a spontaneous type I ECG (Class IIb). Catheter ablation can be considered Brugada syndrome patients with a history of arrhythmic storms or repeated appropriate ICD shocks (Class IIb). Finally, ICD implantation is not indicated in asymptomatic Brugada syndrome patients with a drug-induced type I ECG and on the basis of a family history of SCD alone (Class III).

Epicardial ablation is an emerging treatment in the field of Brugada syndrome. Nademanee *et al*. showed that 9 patients with Brugada syndrome experiencing 2–6 incidence of ventricular arrhythmia per month was arrhythmia free in a follow-up of 2 years after ablation.[41] Brugada *et al*. reported that ablation of the substrate identified in the presence of flecainide could eliminate the Brugada syndrome phenotype.[45] Pappone *et al*. in a study of 50 consecutive patients that underwent ablation showed that ECG pattern normalized in all symptomatic and asymptomatic patients.[46] Follow-up of 3 to 20 months showed that the patients showed no Brugada syndrome phenotype and was not VT/VF inducible seemingly "cured" the Brugada syndrome. Pappone stated that ablation could be useful in those that do not meet the recommendation or refuse ICD implantation. A multicenter randomized trial, ablation in Brugada syndrome for the prevention of VF episodes Study was underway. These findings may usher a new era in treating Brugada syndrome, and the possibility of epicardial ablation being a first-line treatment in the future cannot be overruled.

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Conflicts of interest
There are no conflicts of interest.

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Original Research

Nebivolol Prevents the Increase of Asymmetric Dimethylarginine and Oxidants in Hyperhomocysteinemic Rats

Mustafa Ahmet Huyut

Department of Cardiology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey

ORCID:

Mustafa Ahmet Huyut: https://orcid.org/0000-0001-8740-1429

Abstract

Objective: The objective of this study was to determine nebivolol's inhibitory effect on endothelial dysfunction in hyperhomocysteinemic rats, based on heart pathology and biochemical analysis of serum samples. **Methods:** Male Wistar albino rats weighing between 200 g and 450 g were randomly divided into four groups of equal number (n = 7) as follows: control group, nebivolol group, methionine group, and methionine + nebivolol group. After 28 days, homocysteinemia (Hcy), asymmetric dimethylarginine (ADMA), malondialdehyde (MDA), glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), and catalase (CAT) levels were measured in blood samples and compared between groups. Each rat's hearts were dissected to observe cardiomyocyte degeneration; findings were compared between groups. **Results:** Moderate hyperHcy (hHcy) (Hcy 35.62 ± 7.60 μmol/L) was noted in methionine group ($P < 0.001$). The levels of the antioxidant molecules CAT, GSH, GPx, GR, and SOD were lower, and the levels of the oxidant molecules ADMA, Hcy, and MDA were higher in methionine group ($P < 0.001$). A decrease in antioxidants and also increase in oxidants did not occur in the methionine + nebivolol group ($P < 0.001$). Cardiomyocyte degeneration was more severe in methionine group ($P = 0.01$). **Conclusion:** Endothelial dysfunction induced through short-term hHcy can be prevented through the administration of nebivolol. Nebivolol can prevent elevation of the Hcy levels, and hHcy might cause cardiomyocyte degeneration.

Keywords: Antioxidants, asymmetric dimethylarginin, hyperhomocysteinemia, nebivolol, oxidants

Introduction

Hyperhomocysteinemia (hHcy) is a serious cardiovascular risk factor that occurs due to pharmacological or genetic causes.[1,2] Impaired endothelial function induced by hHcy is a significant cause of morbidity and mortality. Many studies have investigated how to prevent impairment of endothelial function induced by hHcy using vitamins and pharmaceutical agents.

The association between hHcy and cardiovascular diseases was first described by McCully in 1969. McCully observed widespread arterial thrombosis and atherosclerosis.[3,4] A prospective study by Page *et al*.[5] that carried out among women reported that hHcy was an independent risk factor for myocardial infarction.

Healthy endothelial cells detoxify Hcy through the production of nitric oxide (NO). During Hcy metabolism, Hcy combines with adenosine to form S-adenosylhomocysteine while decreasing the adenosine concentration. The decrease in adenosine plasma levels will result in vascular damage.[4,6] Asymmetric dimethylarginine (ADMA) is the endogen inhibitor of the eNOs. Hcy is the most prominent factor that increases the level of ADMA.[7,8] Long-term exposure to ADMA produces hypertensive damage in target organs and accelerates atherogenesis.[9] High ADMA level increased the risk of acute coronary events by 3.9-fold.[10]

Nebivolol is a third-generation, highly selective β1 blocker that promotes vasodilatation through increasing NO in the L-arginine-NO pathway.[11,12] Moreover, unlike other

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Address for correspondence: Dr. Mustafa Ahmet Huyut, Department of Cardiology, Faculty of Medicine, Gaziosmanpasa Hospital, Yeni Yuzyil University, Cukurcesme Caddesi No: 51 Istanbul, Turkey. E-mail: ahuyut@yahoo.com

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beta-blockers, nebivolol increases the NO level by activating eNOs, as it has an agonistic effect on β3 receptors.[13] To prevent hHcy and its harmful effects, Vitamin B12, Vitamin C, Vitamin E, and folic acid have been used in trials with some success.[14-18] The present study was, therefore, conducted to investigate the use of nebivolol for the prevention of hHcy and its harmful effects.

Methods

The study included 28 adult male Wistar albino rats weighed between 250 and 450 g that were obtained from the local University Experimental Animals Laboratory. The rats were randomly divided into four groups of equal number ($n = 7$), and housed in wired cages for 1 month under 12-h circadian rhythm conditions at 22°C –24°C. All the groups were fed standard rat silage and urban drinking water ad libitum. The study protocol was approved by the local University Laboratory Animals Ethics Committee. This study was supported by the local University Scientific Research Projects Unit.

Experimental model

1. The control group ($n = 7$): no medication was administered for 4 weeks. The rats received 1 mL of drinking water od through orogastric gavage to experience the stress of the gavage method.
2. Nebivolol group ($n = 7$): the rats received nebivolol 10 mg/kg/day od through orogastric gavage for 4 weeks
3. Methionine group ($n = 7$): the rats received methionine (M9625 Sigma-Aldrich L-Methionine reagent grade, ≥98% [thin layer chromatography [TLC]) 1 mg/kg/day od through orogastric gavage for 4 weeks
4. Methionine + nebivolol ($n = 7$): the rates received methionine 1 g/kg/day + nebivolol 10 mg/kg/day od through orogastric gavage for 4 weeks. Nebivolol was administered 2 h after the administration of methionine.

Body weight was measured at baseline, and then every week for the adjustment of drug dosage. To achieve hHcy, L-methionine (M9625 Sigma-Aldrich L-Methionine reagent grade, ≥98% [TLC]) was dissolved in phosphate-buffered saline (PBS), pH 7.4, and was given to rats as 1 g/kg/day through oral gavage for 4 weeks. Nebivolol was obtained by crushing 5 mg nexivol (Abdi İbrahim) tablets and dissolving in 10% dimethyl sulfoxide and was given as 10 mg/kg/day through oral gavage for 4 weeks. After 4 weeks, the rats were sacrificed under ether anesthesia, and blood samples were drawn into hemogram tubes with EDTA and standard biochemical tubes. Subsequently, hearts were dissected and immersed in 10% formaldehyde solution for histochemical examination. Blood samples were centrifuged at 4000 rpm at +4°C for 10 min and then stored at − 80°C. Serum was used for the analysis of ADMA, Hcy, malondialdehyde (MDA), NO, catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH), whereas plasma was used for the analysis of glutathione peroxidase (GPx) and glutathione reductase (GR).

Biochemical examination

ADMA (ng/mL) (USCN Life Science Inc., catalog no: E91301Ge) and Hcy (μmol/L) (Cusabio, catalog no. CSB-E13376r) levels were detected through the ELISA method using commercial kits. CAT (U/g) was measured through the ELISA method using a CAT assay kit (Cayman, catalog no. 7070002, USA). GR activity (U/g) was measured through ELISA using a GR assay kit (Cayman, catalog no. 703202, USA). GPx (U/g) was measured through the ELISA method using a GPx assay kit (Cayman, catalog no. 703102, USA). GSH was measured through the ELISA method using a GSH assay kit (Cayman, catalog no. 703002, USA). SOD was measured according to Sun *et al.*[19] The method is based on the reduction of nitroblue tetrazolium through xanthine-xanthine oxidase, which is the producer of superoxide. SOD activity is expressed as U/mg of serum protein. The level of serum protein was determined using the biuret method and an Abbott Architect C 8000 Autoanalyzer (Abbott, Abbott Park, IL, USA). MDA was measured using the Esterbauer method and a lipid peroxidation measurement method.[20] MDA, which reacts with thiobarbituric acid at 90°C –95°C, produces a pink chromogen. After 15 min, the absorbance of the samples that were chilled quickly was read at 532 nm, and the results expressed as nmol/mL.

Pathological examination

Paraffin blocks were prepared from heart tissue samples. Sections 4-μm thick were cut using a microtome. The sections were deparaffinized and collected on glass slides. After staining with H and E (Gul Biology Laboratory, dye for connective and supportive tissue of animals, catalog no. 5089, Istanbul, Turkey), the slides were examined under a light microscope. All samples were evaluated by blinded pathologist. For heart tissue evaluation, myocyte damage was semiquantitatively scored with respect to necrosis, myocyte cell swelling, and detection of fibrosis, according to the scale shown below.

The scoring system scale as follows:

(–): No change
(+): Slight change
(++): Moderate change
(+++): Severe change.

Statistical analysis

Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) version 14.0 for Windows (SPSS, Inc., Chicago. IL, USA). The groups were compared *inter se* and with the control group. The Kolmogorov–Smirnov test was used to assess the compliance of the quantitative values to a normal distribution. Single-direction variance analysis was used to compare normally distributed quantitative data between groups, and Tukey's honestly significant difference or Dunnett's T3 test was used for multiple comparisons between groups, according to the Levene homogeneity test's statistics. Descriptive statistics are shown as mean ± standard deviation. The Kruskal–Wallis

variance analysis was used to compare data not distributed normally between the groups. Descriptive statistics are shown as median (25^{th}–75^{th} percentile). The level of statistical significance was set at $P < 0.05$.

Results

Biochemical findings

Oxidants diagram was showed in Figure 1. The antioxidants diagram was shown in Figures 2 and 3. hHcy was more severe in the methionine group than in the other three groups ($P < 0.001$). The Hcy level was significantly lower in the methionine + nebivolol group than in the methionine group (13.2 ± 2.1 vs. 35.6 ± 7.6 μmol/L) ($P < 0.001$).

The plasma ADMA level was significantly higher in the methionine group than in the other groups ($P < 0.001$). In addition, the ADMA level was significantly lower in the methionine + nebivolol group than in the methionine group (113.2 ± 16.0 vs. 225.7 ± 42.2 ng/mL) ($P < 0.001$).

The plasma CAT level was significantly lower in the methionine group than in the other groups ($P < 0.001$) and was significantly higher in the methionine + nebivolol group than in the methionine group (36.0 ± 3.5 vs. 23.7 ± 6.1 U/g) ($P = 0.006$). In addition, the CAT level was higher in the nebivolol group than in the methionine + nebivolol group (36.0 ± 3.5 vs. 49.0 ± 5.7 U/g) ($P = 0.003$).

The GSH level was significantly lower in the methionine group than in the other groups ($P < 0.001$) and was significantly higher in the methionine + nebivolol group than in the methionine group (1.0 ± 0.1 vs. 0.4 ± 0.1 μmol/L) ($P < 0.001$). In addition, the GSH level was lower in the methionine + nebivolol group than in the control group (1.0 ± 0.1 vs. 1.4 ± 0.3 μmol/L) ($P = 0.03$).

The plasma GPx level was significantly lower in the methionine group than in the other groups ($P < 0.001$) and was significantly higher in the methionine + nebivolol group than in the methionine group (213.20 ± 32.55 vs. 122.54 ± 11.56 U/g) ($P = 0.001$). In addition, the GPx level was lower in the methionine + nebivolol group than in the control group (213.20 ± 32.55 vs. 424.13 ± 38.43 U/g) ($P < 0.001$).

The plasma MDA level was significantly higher in the methionine group than in the other groups ($P < 0.001$) and was significantly lower in the methionine + nebivolol group than in the methionine group (2.18 ± 0.21 nmol/mL vs. 3.02 ± 0.29 nmol/mL) ($P < 0.001$). In addition, the MDA level was higher in the methionine + nebivolol group than in the control group (2.18 ± 0.21 nmol/mL vs. 1.80 ± 0.10 nmol/mL) ($P = 0.015$).

The plasma GR level was significantly lower in the methionine group than in the other groups ($P < 0.001$). In addition, the GR level was lower in the methionine + nebivolol group than in the control group but not significantly (184.56 vs. 273.86 U/g) ($P = 0.081$).

The plasma SOD level was significantly lower in the methionine group than in the other groups ($P = 0.001$). In addition, the SOD level was higher in the methionine + nebivolol group than in the control group but not significantly (1.45 U/mg of

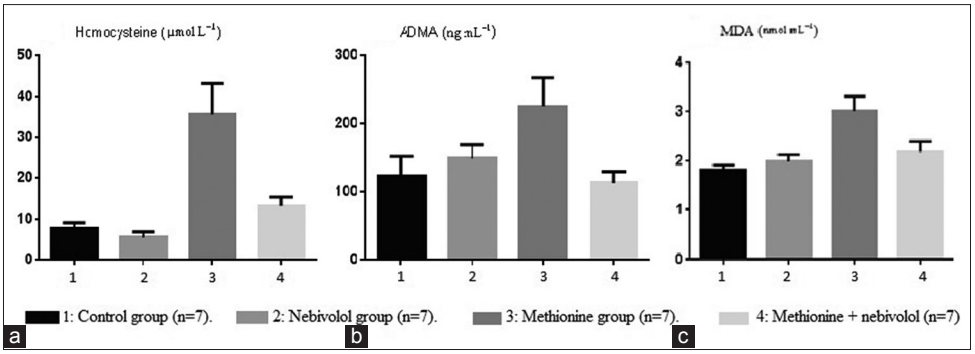


Figure 1: Homocysteinemia and oxidants diagram was showed. (a) Hyperhomocysteinemia, (b) plasma asymmetric dimethyl arginine, (c): and malondialdehyde levels were more severe in the methionine group than in the other groups ($P < 0.001$)

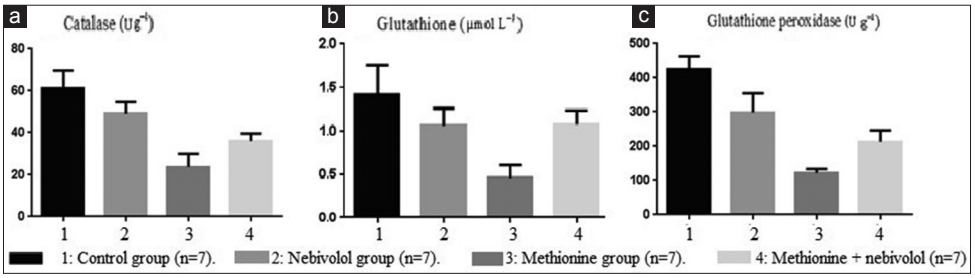


Figure 2: Antioxidants diagram was showed. (a) The plasma catalase, (b) glutathione, (c) and glutathione peroxidase levels were significantly lower in the methionine group than in the other groups ($P < 0.001$)

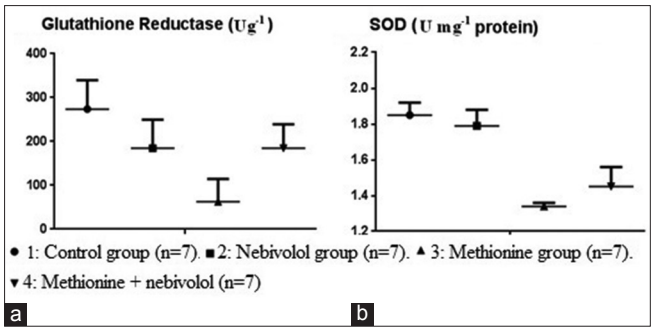


Figure 3: Antioxidants diagram which descriptive statistics for quantitative biochemical data not distributed normally (median given as 25th–75th percentile). (a) The plasma glutathione reductase level was significantly lower in the methionine group than in the other groups ($P < 0.001$). (b) The plasma superoxide dismutase level was significantly lower in the methionine group than in the other groups ($P = 0.001$)

protein vs. 1.34 U/mg of protein) ($P = 1$). Moreover, the SOD level was lower in the methionine + nebivolol group than in the control group (1.34 U/mg of protein vs. 1.85 U/mg of protein) ($P = 0.007$).

Pathological finding

Cardiomyocyte degeneration was significantly more severe in the methionine group than in the other groups ($P = 0.01$) [Figures 4 and 5]. Cardiomyocyte degeneration was less severe in the methionine + nebivolol group than in the control group but not significantly (1.4 ± 0.5 vs. 1.8 ± 1.0 degeneration) ($P = 1$).

Discussion

The present study showed that impaired endothelial function resulted from short-term hHcy could be prevented through the administration of nebivolol. In addition, the administration of nebivolol od 2 h after oral administration of methionine was observed to prevent an increase in the Hcy level. Different data such as tissue oxidant levels from these studies subgroups were published before. In our previous study, GSH, CAT, MDA, and SOD activities in the tissues were determined. The luminal cross-sectional area (LCSA), total cross-sectional area (TCSA), and intima-media thickness (IMT) were measured in the thoracic aorta. Nebivolol treatment decreased high MDA levels in the brain, heart, and liver tissues. The level of GSH was higher in the heart, brain, and kidney tissues of the nebivolol + hHcy group. The activity of CAT increased only in the kidney tissue of the nebivolol + hHcy group, and the activity of SOD was increased in all the tissues in this group. However, serum levels did not measure, and heart tissue did not investigate. Increased IMT and TCSA in the nebivolol + hHcy group were significantly decreased after nebivolol administration. The LCSA was higher in the hHcy group than the control group.[21]

In this study, according to the present biochemical findings, concomitant administration of nebivolol + methionine can prevent impaired endothelial function induced by short-term hHcy. In the present study, cardiomyocyte degeneration was more severe in the methionine group based on histopathological findings.

L-methionine was administered at 1 g/kg/day, as reported by Cao *et al*.[22,23] In the present study, nebivolol was administered at 10 mg/kg/day, as the efficiency and safety of this dose are well known.[24,25] In the difference between groups, hHcy was statistically significant ($P < 0.001$). The Hcy level in methionine + nebivolol group significantly lower than in the methionine group ($P = 0.001$), which indicates that the administration of nebivolol 2 h after the administration of methionine can prevent an increase in the Hcy level.

Nebivolol increases NO through the activation of eNOs and its β3-receptor agonistic effect, which is distinct from other beta-blockers.[13] Nebivolol increases total antioxidant capacity. In the present study, the highest ADMA level was observed in the methionine group, which had a high Hcy level. The ADMA level was 123.8 ± 28.5 ng/mL in the control group versus 225.7 ± 42.2 ng/mL in the methionine group, and the difference was statistically significant ($P < 0.001$).

An elevated ADMA level is an indicator of impaired endothelial function. In addition, the ADMA level can be used for the prediction of cardiovascular morbidity and mortality. The impaired endothelial function is indicative of the early stage of atherosclerosis.[26] Zoccali *et al*.[27] reported that a 2-mmol/L increase in the plasma ADMA level increases the risk of cardiovascular disease by 37%. In a study by Valkonen *et al*.,[10] it was observed that an increase in the ADMA was associated with a 3.9-fold increase in the risk of acute coronary events. In earlier studies, Vitamin B12, Vitamin C, Vitamin E, and folic acid were used to prevent hHcy and these pathologies, and partial success has been achieved.[14-18]

A decrease in ADMA decreases oxidative stress and cellular damage; thus, protein breakdown is prevented and protein synthesis continues. When there is a need for cysteine Hcy is converted to cystathionine with cystathionine beta-synthase through the transsulfuration pathway and is subsequently hydrolyzed to cysteine and excreted in urine or used in protein synthesis.[2] Hcy is metabolized through remethylation and transsulfuration. When remethylation reactions are saturated or there is a need for cysteine Hcy is hydrolyzed to cysteine through the transsulfuration pathway.[2] Cysteine is a rate-limiting substrate; specifically, Hcy breakdowns

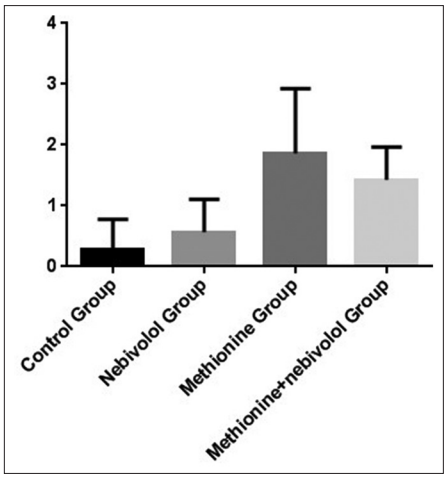


Figure 4: A significant difference in cardiomyocyte degeneration between the methionine group and control group was observed ($P = 0.01$)

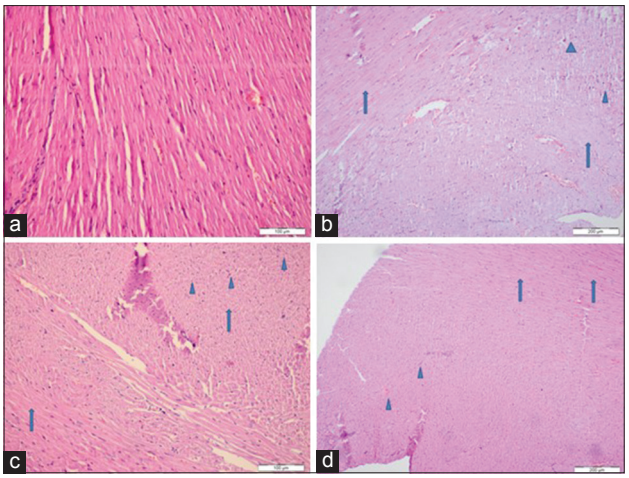


Figure 5: The arrow shows loss of nucleus. The triangle shows degeneration in muscle fiber (a) Control group heart tissue stained with H and E at × 200 (normal). (b) Methionine group heart tissue stained with H and E × 100 (+3 degeneration). (c) Methionine group heart tissue stained with H and E at × 200 (+3 degeneration). (d) Methionine + nebivolol group heart tissue stained with H and E at 100 (+2 degeneration)

to form cysteine and an increase in the serum Hcy level is inhibited. Cysteine formed through transsulfuration of Hcy is used for GSH synthesis; therefore, nebivolol might inhibit an increase in Hcy through these physiologic pathways and others yet to be discerned. The metabolism of ADMA and Hcy shares common pathways. Hcy destabilizes the structure of proteins and increases proteolysis by increasing oxidative stress.[28] On the other hand, the enzyme dimethylarginine dimethylaminohydrolase metabolizes ADMA. Hcy also inhibits this enzyme's activity and causes an increase in the ADMA concentration.[28]

Although the methionine + nebivolol group received methionine, the administration of nebivolol the same day might have inhibited an increase in the ADMA level, which might have been due to the lack of increase in the Hcy level. Nebivolol can prevent methionine-induced elevation of ADMA between the methionine group and the methionine + nebivolol group ($P < 0.001$). There was a positive correlation between oxidative stress and the CAT activity. Wyse *et al*.[18] reported that Hcy administration reduced CAT activity in rats. CAT activity was significantly lower in the methionine group than in the methionine + nebivolol group ($P = 0.006$). Even though the methionine + nebivolol group received methionine, the concomitant administration of nebivolol prevented a decrease in the CAT activity.

Similar to our study, Dimitrova *et al*.[29] reported that the myocardial GSH level was reduced significantly in rats that received Hcy. In the present study, the GSH level was significantly lower in the methionine group than in the other groups, which might indicate that oxidative stress was induced by hHcy in the methionine group. The significant difference in the GSH level was between the present study's methionine group and methionine + nebivolol group ($P < 0.001$).

A significant difference in GPx levels was observed between methionine group and control group ($P < 0.001$) similar to Gilad's study.[30] The significant difference in the GPx level between the methionine group and the methionine + nebivolol group ($P = 0.001$), which might have been associated with the difference in the Hcy level between two groups and the positive effects of nebivolol on total antioxidant capacity.

An elevated MDA level can be considered an indicator of cell damage and lipid peroxidation.[31,32] Yüce and Aksakal[33] examined the effect of Vitamin E in hyperhomocysteinemic rats and reported that the MDA level was higher in hyperhomocysteinemic rats. Similarly, in the present study, the MDA level was significantly higher in the methionine group than in the control group, which might have been an indicator of oxidative stress caused by an elevated Hcy level. Moreover, the MDA level was significantly higher in the methionine group than in the methionine + nebivolol group ($P < 0.001$). The present findings may show that the administration of nebivolol, the same day as the administration of methionine significantly inhibited an increase in the MDA level. Furthermore, in the present study, the GR level was significantly lower in the methionine group than in the control group ($P < 0.001$).

Yamamoto *et al*.[34] observed that Hcy reduced the efficiency of SOD and damaged endothelial heparan sulfate proteoglycan and decrease the defensive ability of endothelial cells against free radicals. In the present study, the SOD level was significantly lower in the methionine group than in the control group ($P = 0.001$), which might have been due to elevated oxidative stress secondary to a high Hcy level.

Zivkovic *et al*. dissected rat hearts and perfused with Hcy in an organ bath, and showed that the left ventricle functions were destroyed.[35] They suggested that the mechanism of action was the toxic effect of the increase in total oxidative capacity

induced by impaired endothelium function and suppressed NO bioactivity that resulted from an elevated Hcy level. There was a significant difference in cardiomyocyte degeneration between the methionine group and control group ($P = 0.01$). hHcy might be caused cardiomyocyte cell degeneration. Chen *et al*.[36] observed a reduction in systolic function in rats with hHcy, and an increased in the size of cardiomyocytes and an increase in intracellular fibrosis in rat heart pathological sections. Although maximum cardiomyocyte degeneration was noted in the methionine group, we could not show any significant protection with nebivolol administration.

The present study's limitations are having a small study population, and time was restricted for 4-week duration. Larger scale and longer durations are required to more clearly observe histopathological and biochemical changes.

Study limitations

To generalize these results and obtain significant histopathological findings, more clinical studies of longer duration and larger scale are necessary to generalize the present findings.

Conclusion

The present findings show that the impairment of endothelial function induced by short-term hHcy can be prevented by the administration of nebivolol. In addition, the administration of nebivolol 2 h after administration of methionine was observed to prevent an increase in the Hcy levels. The present study observes that impaired endothelial function due to short-term hHcy can be prevented by the concomitant administration of nebivolol.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Asymptomatic Pneumothorax Mimicking Pseudoaneurysm after the Implantation of a Dual-Chamber Pacemaker

Tolga Aksu, Tumer Erdem Guler, Serdar Bozyel

Department of Cardiology, University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey

ORCID:

Tolga Aksu: https://orcid.org/0000-0001-8061-9660

Tümer Erdem Güler: https://orcid.org/0000-0003-1349-2123

Serdar Bozyel: https://orcid.org/0000-0002-6582-3660

Abstract

An 80-year-old male, who had undergone dual-chamber pacemaker implantation through left subclavian approach, developed tension pneumothorax of the left side. It caused a pseudoaneurysm-like contracting mass image on the chest X-ray. The diagnosis of pneumothorax was verified by chest computed tomography. Tube thoracostomy drainage was performed immediately without any sequel.

Keywords: Cardiac pacing, cephalic vein cutdown, complication, subclavian puncture, venous access

Introduction

An increase in the frequency of cardiac rhythm management device (CRMD) implantations has also led to an increase in device-related complications, in hospitalization period, and treatment costs.[1-3] Pneumothorax is a relatively mild complication during CRMD implantation using the subclavian puncture technique. However, the incidence of pneumothorax requiring a chest tube may be as high as 0.66% even in experienced centers.[2]

Case Report

An 80-year-old male was referred to our clinic with a 2-month history of progressive fatigue and presyncope episodes. An electrocardiogram showed third-degree heart block with a pulse rate of 36 beats per minute. There was no identifiable and reversible cause of heart block. Thus, he was scheduled for a permanent pacemaker insertion. The atrial and ventricular leads were inserted via the puncture of the left subclavian vein. The right ventricular bipolar screw-in lead (St. Jude Medical Tendril MRI™) was positioned against the right ventricle apex. The right atrial bipolar passive lead (St. Jude Medical Isoflex MRI™) was positioned at the anterolateral wall of the right atrium. Lead sensing, pacing threshold, and pacing impedance of both right atrial and ventricular leads were within the expected normal ranges (the right atrium lead: pacing threshold, 1.5 V/0.4 ms; sensing threshold, 3 mV; lead impedance, 550 Ω and the right ventricle lead: pacing threshold, 0.5 V/0.4 ms; sensing threshold, 13 mV; and lead impedance, 650 Ω). The chest fluoroscopic imaging performed immediately after the procedure revealed pseudoaneurysm-like bulging at the left ventricular apical site [Figure 1]. The site was contracting together with the heart beat. The patient had no chest pain or shortness of breath. A computed tomography scan was scheduled. A left-sided pneumothorax and slight mediastinal shift to the right were detected on the computed tomography [Figures 2 and 3]. A chest tube with underwater seal drainage was inserted according to the recommendation of chest surgeon. Control chest X-ray demonstrated complete resolution of pneumothorax. The chest tube was removed on the 3rd day of hospitalization.

Address for correspondence: Prof. Tolga Aksu, Department of Cardiology, University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkey.
E-mail: aksutolga@gmail.com

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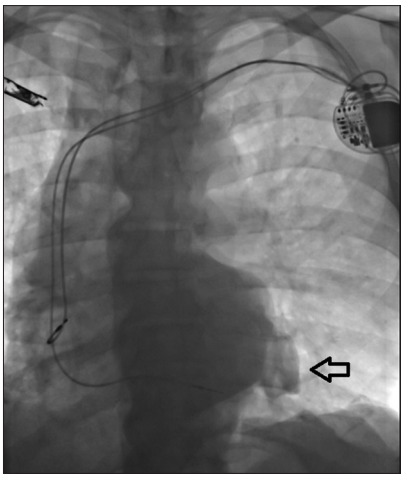


Figure 1: Radiographic findings of a fluoroscopy revealed a left-sided pneumothorax with a pseudoaneurysm-like bulging at the left ventricular apical site (black arrow)

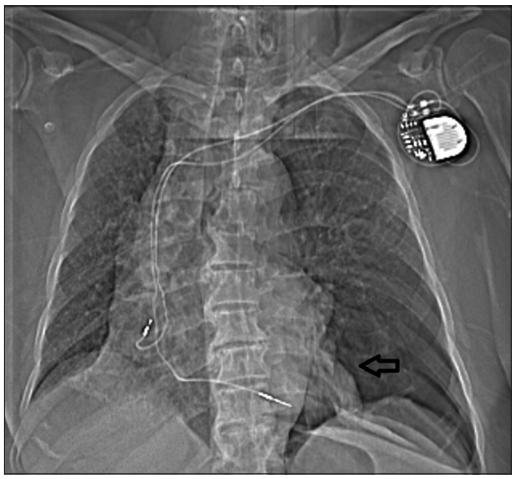


Figure 2: Radiographic findings of a computed tomography in the frontal plane revealed a left-sided pneumothorax with a pseudoaneurysm-like bulging at the left ventricular apical site (black arrow)

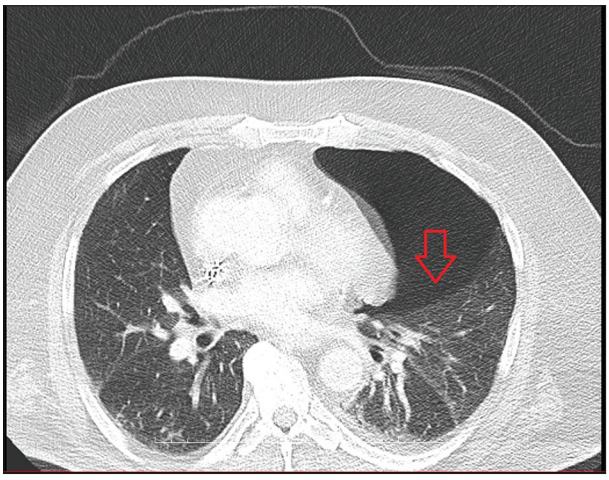


Figure 3: Radiographic findings of a computed tomography in the horizontal plane revealed a left-sided pneumothorax. Please note that the lung tissue is sliding to the posterior side (red arrow)

Discussion

The incidence of pneumothorax after CRMD implantation by using subclavian vein access varies from 0.6% to 5.2% with an average of 2%.[4] The most important precipitating factor is blindly punctured subclavian vein access. A detailed physical examination and anteroposterior chest radiography in standing position should be the first two steps in the assessment of patients demonstrating pneumothorax-related complaints such as chest pain and dyspnea because they are simple, inexpensive, rapid, and noninvasive. However, it should be kept in mind that some forms of pneumothorax may be asymptomatic as in our case. In order to not miss a possible pneumothorax complication in such cases, detailed evaluation of the postprocedural scopical views is of great importance. Chest computed tomography scanning is more sensitive than chest radiography in detecting a small pneumothorax.[5] In addition, computed tomography may be used to differentiate pneumothorax than other possible device-related complications. In the present case, the chest X-ray demonstrated a large left-sided pneumothorax, compressing the left lung and resembling a mass. As a unique nature of the mass, it was contracting together with heart like a pseudoaneurysm. Furthermore, the patient had no complaint of difficulty in breathing after implantation. Hence, we decided to perform chest computed tomography for differential diagnosis.

After proper diagnosis, treatment for pneumothorax varies from simple oxygenation to chest tube drainage. If a tension pneumothorax develops, urgent treatment with a chest tube is necessary. At this point, another important issue is that tension pneumothorax may alter lead-related parameters due to mechanical displacement of the leads by shifting of the mediastinum and may require a lead revision procedure. Thus, to check all lead-related parameters seems as reasonable after such a complication. In our case, there was no change on lead-related parameters. Use of venography or ultrasound to visualize the subclavian veins or the cephalic vein cutdown technique should be considered to avoid this complication in selected patients.

Conclusion

Pneumothorax is a relatively common complication of CRMD implantation using the subclavian puncture technique. Early clinical doubt, well-performed physical examination, and truly used imaging methods are cornerstone for early and true diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Report

Cardioembolic Ischemic Stroke as the Initial Presenting Complaint of a Patient with Acute Infective Endocarditis and Acquired Immunodeficiency Syndrome

Raymond Pranata[1], Veresa Chintya[2], Emir Yonas[3], Vito Damay[1,4]

[1]Faculty of Medicine, Universitas Pelita Harapan, Tangerang, [2]General Practitioner, Sanjiwani General Hospital, Gianyar, [3]Faculty of Medicine, YARSI University, Jakarta, [4]Department of Cardiology and Vascular Medicine, Siloam Hospitals Lippo Village, Tangerang, Indonesia

ORCID:
Raymond Pranata: https://orcid.org/0000-0003-3998-6551
Veresa Chintya: https://orcid.org/0000-0002-7486-1108
Emir Yonas: https://orcid.org/0000-0002-8604-405X
Vito Damay: https://orcid.org/0000-0001-9831-8188

Abstract

Human immunodeficiency virus (HIV) infection is an independent predictor of ischemic stroke, especially in the younger age group. Approximately 1%–5% of HIV/acquired immunodeficiency syndrome patients develop stroke. A 16-year-old male presented with a decreased level of consciousness and a history of right-sided hemiparesis, fever, cough, and dyspnea. The patient was an intravenous drug user (IVDU). Examination revealed the following: blood pressure: 130/70 mmHg, heart rate: 124×/min, temperature 38.5°C, and respiratory rate: 26×/min. Electrocardiographic findings revealed the following: sinus tachycardia: 124×/min, right-axis deviation, incomplete right bundle branch block, and right ventricular hypertrophy. Laboratory findings were as follows: microcytic hypochromic anemia (7.33 g/dL), leukocytosis (32.2 × 10^3/μL) with shift to the left, hyponatremia (122 mmol/L), HIV was positive, and chest X-ray showed pneumonia. Echocardiography showed vegetation in the posterior mitral leaflet, mitral regurgitation, and tricuspid regurgitation with an intact interatrial septum. Computed tomography scan revealed ischemic stroke of the left parieto-occipital lobe. HIV-infected individuals are at 1.5 times increased risk of stroke compared to those without. This case involves an IVDU and a HIV-positive young male presenting with large ischemic stroke in large-vessel territory, suggestive of embolic origin. A part of vegetation on the left side of the heart of this patient dislodged and caused a cerebrovascular accident. There was also unconfirmed suspicion of pulmonary embolism from the right side of the heart. Empiric antibiotics should be started before tailoring to the result of blood culture. Endocarditis conveys a significant risk of cerebral embolism resulting in ischemic stroke and a potentially dismal prognosis.

Keywords: Endocarditis, human immunodeficiency virus/acquired immunodeficiency syndrome, immunocompromised, stroke

Introduction

Approximately 1%–5% of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients develop stroke, and ischemic cerebral lesion is found in 4%–34% of autopsies.[1,2] HIV infection is an independent predictor of ischemic stroke, especially in the younger age group.[3] Bacterial endocarditis, marantic endocarditis, HIV-associated cardiac dysfunction, and ischemic heart disease account for 4%–15% of ischemic strokes in people with HIV.[1]

An international prospective cohort study showed that the incidence of stroke in adults with definitive infective endocarditis is 16.9%. A prospective multicentric study in France found that neurological sequelae occurred in 55% of critically ill patients with left-sided infective endocarditis.[4,5]

Address for correspondence: Dr. Raymond Pranata, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia.
E-mail: raymond_pranata@hotmail.com

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Right-sided endocarditis accounts for only 5%–10% of the endocarditis. It mainly involves tricuspid valve in intravenous drug user (IVDU). The incidence of bacterial endocarditis among IVDUs is believed to be 1.5–20/1000 addicts per year.[6]

Case Report

A 16-year-old male presented with a decreased level of consciousness since 1 h before admission and a history of right-sided hemiparesis for 2 h. He had fever since 3 days before admission and a productive cough for 2 weeks. The patient complained of dyspnea for the last 2 days. He had no history of epilepsy or other neurological complaints. There was no family history of stroke or cardiac disease. The patient was a smoker and IVDU.

Upon physical examination, Glasgow Coma Scale was $E_3V_3M_5$, blood pressure was 130/70 mmHg, heart rate was 124×/min, temperature was 38.5°C, and respiratory rate was 26×/min. Cardiorespiratory examination unveiled a Grade IV/VI holosystolic murmur on the apex of the heart radiating to the left axilla and crackles on the lung. Carotid auscultation was within normal limits. Neurological examination showed lateralization of the upper and lower extremities to the right side. Electrocardiography showed sinus tachycardia of 124×/min, right-axis deviation (RAD), incomplete right bundle branch block (RBBB), and right ventricular hypertrophy (RVH) [Figure 1]. Initial laboratory examinations showed microcytic hypochromic anemia (7.33 g/dL), leukocytosis (32.2 × 10^3/μL) with shift to the left, and hyponatremia (122 mmol/L). Coagulation panel was within normal limits. HIV rapid test was ordered and the result was positive. Blood culture was taken. Chest X-ray showed pneumonia [Figure 2]. Echocardiography showed vegetation in the posterior mitral leaflet, mitral regurgitation, and tricuspid regurgitation with an intact interatrial septum [Figure 3]. Computed tomography (CT) scan showed an ischemic stroke of the left parieto-occipital lobe [Figure 4]. The patient was diagnosed with anemia, hyponatremia, sepsis, infective endocarditis, ischemic stroke, and HIV/AIDS. The patient was given levofloxacin 1 × 750 mg IV, ceftriaxone 3 × 2 g IV, methylprednisolone 3 × 62.5 mg IV, aspirin 1 × 80 mg PO, citicoline 2 × 500 mg IV, and ranitidine 2 × 500 mg IV. The patient was admitted to the Intensive Care Unit (ICU), treated to no avail, and passed away on the 3rd day after admission.

Discussion

HIV-infected individuals are at 1.5 times increased risk of stroke compared to those without.[3] This case involves an IVDU and a HIV-positive young male presenting with large ischemic stroke in large-vessel territory suggestive of embolic origin. Stroke risk is directly proportional to the viral load which suggests that the risk may be due to inflammation, endothelial dysfunction, and macrophage activation.[3] A cohort study of 4308 HIV-positive patients showed that bacterial endocarditis was associated with HIV infections;

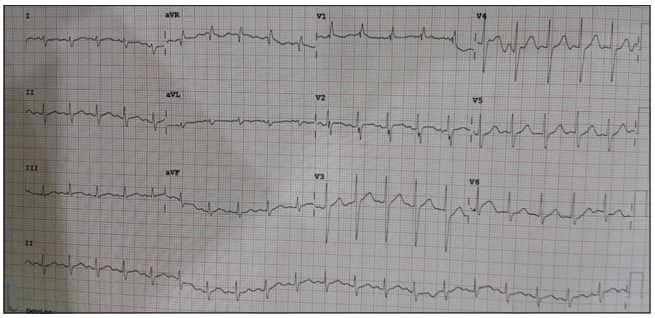


Figure 1: Patient's electrocardiogram

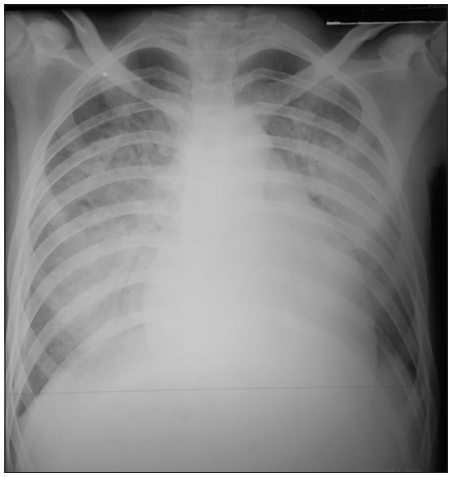


Figure 2: Patient's chest X-ray suggestive of pneumonia

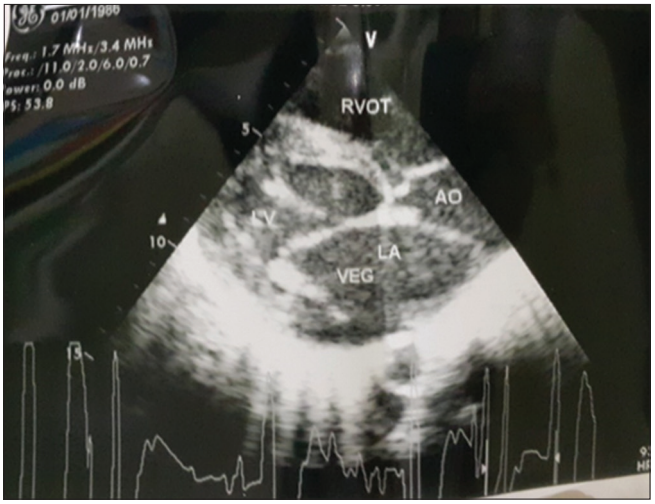


Figure 3: Patient's echocardiography showing vegetation on posterior mitral leaflet

however, some literatures state that endocarditis occurs almost exclusively in IVDU population and the IVDU data were not available in majority of patients in the aforementioned study.[3,7] Thus, the bacterial endocarditis in this patient is a collaboration of both HIV and risk involving IVDU.

IVDUs often inject veins using contaminated needles or without proper antiseptic procedure. Bacteria are introduced

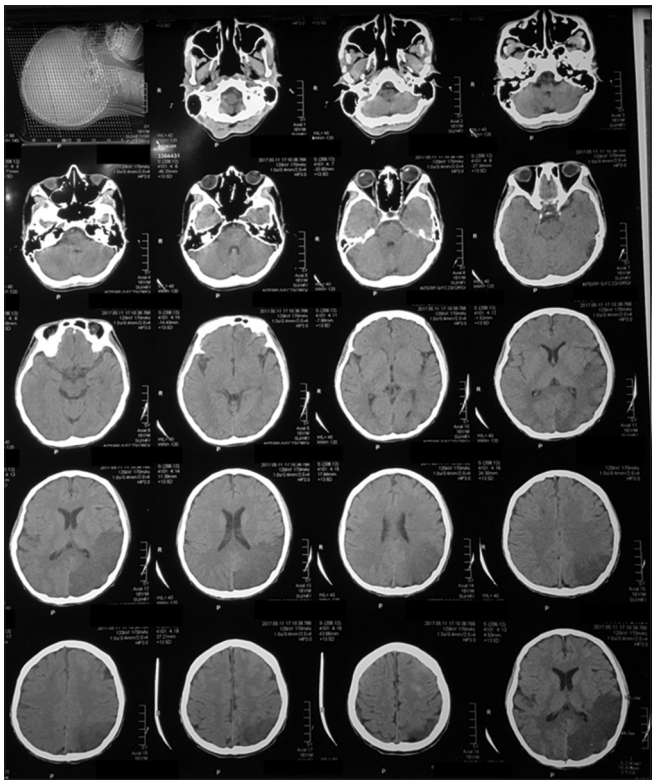


Figure 4: Patient's cranial computed tomography scan

to the right side of the heart via the draining veins. These bacteria may lodge to the heart valves and infect them. The right side of the heart is predominantly affected due to the veins draining to the right side of the heart initially. However, IVDU is associated with not only right-sided valves, but also left-sided valves as shown by three studies demonstrating that the exclusive involvement of right-sided valves was only evident in 46.8%–78% of the patients.[8-10] Involvement of multiple valves (mitral regurgitation + tricuspid regurgitation in this patient) is found in 5%–10% of IVDUs with endocarditis.[5] The valvular damage is usually caused by immunomediated response in patients with bacterial endocarditis; however, HIV-infected patients may have a different course of disease.[11] The damage may be largely caused by bacteremia rather than autoimmune and this causes the patient to be more responsive to antibiotics.

Endothelial injury precedes the formation of platelet fibrin nidus followed by colonization of microorganism and focal adherence of platelet, leading to the formation of vegetation.[12] A part of vegetation on the left side of the heart of this patient dislodged and caused a cerebrovascular accident. Cerebrovascular accidents due to septic embolism are one of the most lethal complications of infective endocarditis, and ischemic stroke is the most common manifestation.[13] Sinus tachycardia, RAD, incomplete RBBB, and RVH upon electrocardiography signify RV strain. Dyspnea and RV strain along with vegetation at the tricuspid valve may suggest pulmonary embolism due to embolization from the tricuspid valve. This requires further investigation such as CT pulmonary angiography which was not possible in our case due to the limited facility.

Empirical antibiotic (ideally vancomycin + gentamycin) should be started before tailoring to the result of blood culture. This patient was given levofloxacin and ceftriaxone due to unavailability of vancomycin. Corticosteroids were given to reduce cerebral edema and inflammation.

Mortality of patients with infective endocarditis who require ICU admission reaches as high as 60% despite advances in medical care.[5]

Conclusion

HIV infection is an independent predictor of ischemic stroke, and one of the pathophysiological mechanisms responsible is through cardioembolism from the affected heart. Infective endocarditis is one of the HIV-associated cardiac dysfunctions, which conveys a significant risk of cerebral embolism culminating into the ischemic stroke and a potentially dismal prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Painless Aortic Dissection Presented with Acute Paraplegia

Mahmoud Abdelnaby, Mohammed Abada[1], Alyaa Elsayed[2], Moustafa Dawood[2], Yehia Saleh[2], Abdallah Almaghraby[2]

Clinical and Experimental Internal Medicine Department, Cardiology and Angiology Unit, Medical Research Institute, Alexandria University, [1]Department of Critical Care Medicine, Faculty of Medicine, Alexandria University, [2]Department of Cardiology, Faculty of Medicine, Alexandria University, Alexandria, Egypt

ORCID:

Mahmoud Abdelnaby: https://orcid.org/0000-0001-8016-9049
Mohammed Abada: https://orcid.org/0000-0002-2043-2973
Alyaa Elsayed: https://orcid.org/0000-0002-5729-5765
Moustafa Dawood: https://orcid.org/0000-0001-8509-5982
Yehia Saleh: https://orcid.org/0000-0003-3873-5582
Abdallah Almaghraby: https://orcid.org/0000-0001-6541-0850

Abstract

Acute aortic dissection is considered a potentially fatal condition. Neurologic manifestations such as paraplegia are quite rare. We report a case of acute paraplegia in a hypertensive smoker chronic obstructive lung disease patient. Transthoracic echocardiography revealed a dissection flap starting at the aortic annulus and extending to the descending thoracic aorta. Computed tomographic aortography confirmed the diagnosis with a dissection flap extended from the aortic annulus to the entire distal aorta. The patient was referred to another specialized cardiothoracic center, but unfortunately, he died during the surgery.

Keywords: Aortic dissection, computed tomographic aortography, echocardiography, painless paraplegia

Introduction

Acute aortic dissection is the most common cause of death among all aortic pathological conditions. In cases of aortic dissection, the layers of the media are dissected by a column of blood through an intimal tear with variable degrees of proximal and distal extension within the length of the aorta. A wide range of symptoms and signs is linked to either rupture or occlusion of a major vessel.[1]

Pain is the most common classical symptom. Rarely, aortic dissection can be painless. In rare occasions (2%–5% of the patients), acute paraplegia can manifest mainly if the intercostal arteries are involved by the aortic dissection.[1]

Case Report

A 55-year-old hypertensive chronic obstructive lung disease (COPD) heavy smoker male patient, not compliant on his medical therapy, presented with acute exacerbation of COPD. On clinical examination, he was distressed and tachypneic with diffuse expiratory wheezes all over his chest and his blood pressure was 140/90 mmHg. Arterial blood gases revealed hypoxia and severe respiratory acidosis, so he was mechanically ventilated. After 1 day, he started to improve and weaned from mechanical ventilation safely. After weaning, he started to complaint of acute onset of paraplegia without any chest or abdominal or back pain. Clinical examination revealed a motor loss in both lower limbs together with a sensory loss to the level of T9 with loss of bilateral peripheral pulsations from the femoral arteries downward. Electrocardiogram showed 0.5 mm ST elevation in the inferoposterior leads. Laboratory investigations revealed

Address for correspondence: Dr. Mahmoud Abdelnaby, Cardiology and Angiology Unit, Clinical and Experimental Internal Medicine Department, Medical Research Institute, University of Alexandria, Alexandria, Egypt.
E-mail: mahmoud.hassan.abdelnabi@outlook.com

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elevated cardiac enzymes and renal and hepatic functions. His chest X-ray showed a wide mediastinum. Urgent transthoracic echocardiography [Figures 1-4] revealed a dilated aorta with a dissection flap extending from the aortic annulus to the aortic

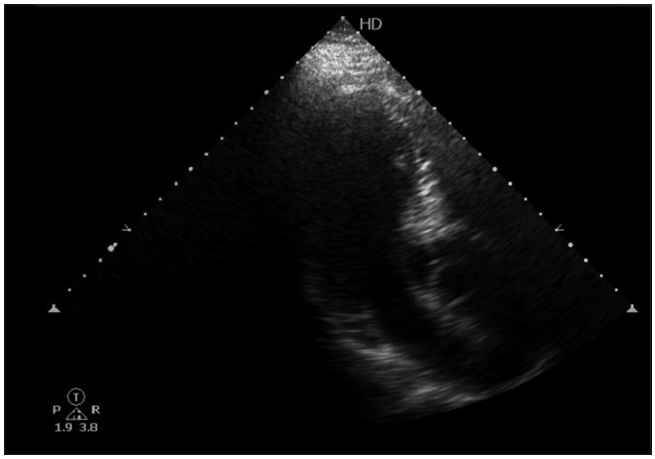


Figure 1: Transthoracic echocardiography apical long view showing a dissection flap extending through ascending aorta

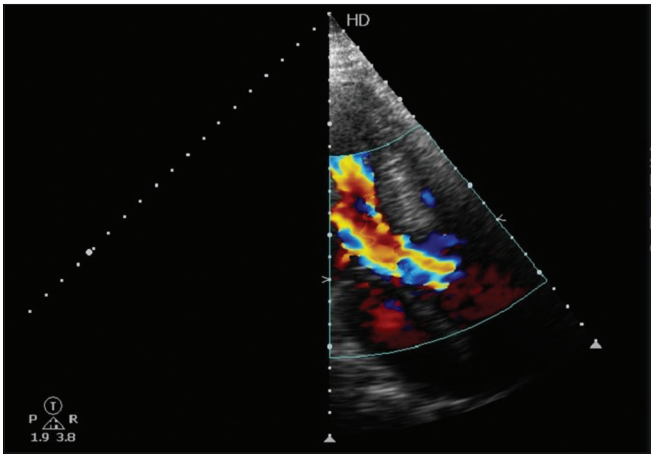


Figure 2: Transthoracic echocardiography color flow in apical long view showing severe aortic regurgitation

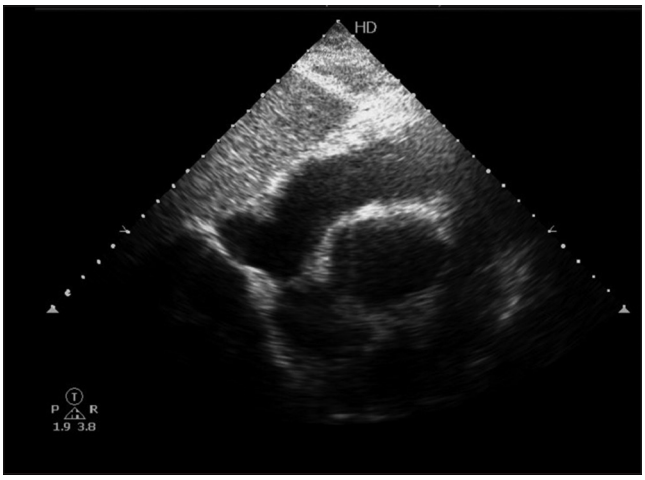


Figure 3: Transthoracic echocardiography subcostal view showing a dissection flap seen at the ascending aorta

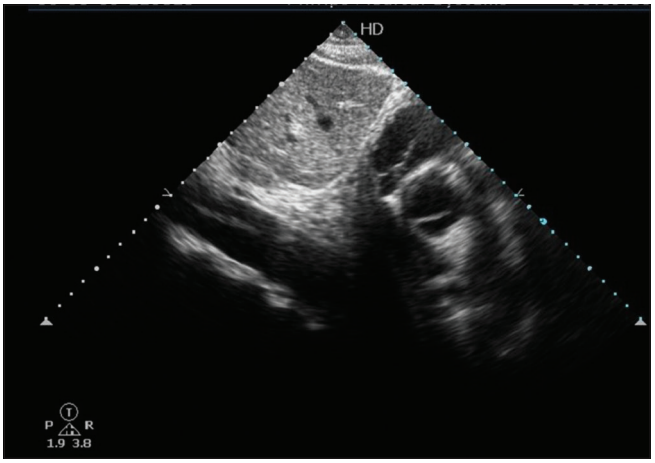


Figure 4: Transthoracic echocardiography subcostal view showing a dissection flap extending through the abdominal aorta

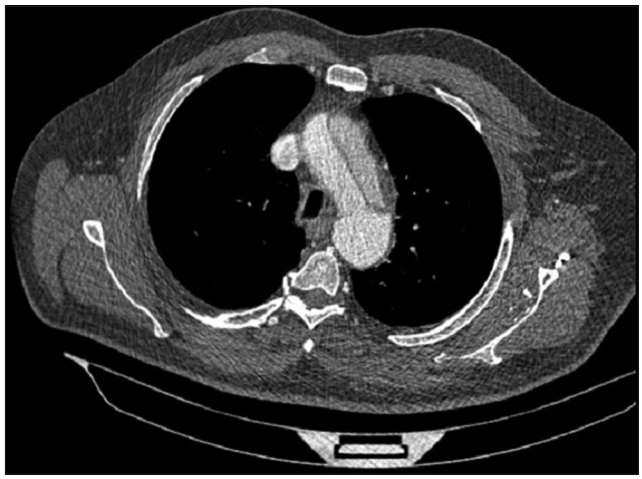


Figure 5: Computed tomographic aortography revealing a dissection flap at the aorta



Figure 6: Computed tomographic aortography revealing a dissection flap in both ascending and descending thoracic aorta



Figure 7: Computed tomographic aortography revealing a dissection flap in descending abdominal aorta

arch, the descending thoracic and the abdominal aorta with severe aortic regurgitation and a preserved left ventricular function with no regional wall motion abnormalities. Urgent computed tomographic aortography [Figures 5-7] showed an intimal tear at aortic arch extending proximally to the aortic annulus and distally to involve the entire aorta up to the left iliac artery affecting several arteries in its course, namely right coronary, innominate, left common carotid, left subclavian, intercostals, superior mesenteric, splenic, hepatic, left renal, left iliac arteries, and partially affecting right renal artery. He was referred for urgent surgery in another highly specialized cardiothoracic center where he, unfortunately, died during the operation.

Discussion

Acute aortic dissection is a sudden pathological aortic condition where blood passes through an intimal tear dissecting the layers of the aortic media, resulting in the formation of a false lumen. A wide variety of symptoms can occur according to the involved branches. A wide range of clinical presentation can be associated with aortic dissection, including confusion or coma from cerebral hypoperfusion or even stroke, electrocardiographic changes, or even elevated cardiac troponin levels, indicating cardiac hypoperfusion and myocardial dysfunction such as inferior ST-elevation myocardial infarction, loss of pulses, sensory function, or motor function due to iliofemoral or brachiocephalic hypoperfusion, creatinine elevation or low urine output due to renal hypoperfusion if the renal vessels were affected by the aortic dissection flap, paraplegia due to spinal hypoperfusion if intercostal blood vessels were affected or mesenteric hypoperfusion resulting in abdominal tenderness, bowel ischemia, or elevated liver enzymes.[2]

In 2%–5% of cases, paraplegia can manifest when intercostal arteries arise from the false lumen of the dissection,[1] resulting in abrupt obstruction of the spinal arteries with interruption of blood flow to the spinal cord, especially to the crucial zones, lower thorax, and lumbar segments.[3] Hence, ischemia of the spinal cord contributes to aortic dissection-related neurological syndromes with a sudden onset of motor weakness and paresthesia (paraplegia)[3] and aortic dissection that presents primarily as paraplegia is rare.[4,5] Painless paraplegia is an extremely rare clinical presentation of aortic dissection with only few case reports in the literature.[6] Aortic dissection is associated with very poor prognosis unless treated promptly.[7] It is very crucial to differentiate between paraplegia caused by aortic dissection from other spinal vascular pathologic conditions that cause painless paraplegia. High index of suspicion, rapid diagnosis, and properly timed intervention are associated with complete recovery from aortic dissection-induced paraplegia.[7]

Conclusion

Acute paraplegia is considered a rare clinical presentation of acute aortic dissection, and it can occur even with no chest or back pain. In patients who have absent bilateral femoral pulse and abrupt onset of paraplegia even if painless, acute aortic dissection must be considered with prompt diagnosis, and urgent intervention is necessary to reduce morbidity and mortality of this fatal condition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Periaortic Abscess Forming Pulsatile Sac around Graft in a Patient with Prosthetic Valve Endocarditis after Bentall Operation

Sinan Varol, Sevgi Özcan[1], Gökmen Kum, Irfan Sahin, Ertugrul Okuyan

Department of Cardiology, Bagcilar Training and Research Hospital, Health Sciences University, [1]Department of Cardiology, Okmeydanı Training and Research Hospital, Health Sciences University, Istanbul, Turkey

ORCID:

Sinan Varol: https://orcid.org/0000-0002-2511-7083
Sevgi Özcan: https://orcid.org/0000-0002-0201-8314
Gökmen Kum: https://orcid.org/0000-0002-6902-1163
İrfan Şahin: https://orcid.org/0000-0001-9165-7566
Ertuğrul Okuyan: https://orcid.org/0000-0002-0626-2939

Abstract

A 62-year-old man with high fever, general fatigue, and history of transient ischemic attack was transferred to our cardiology clinic with high clinic suspicious of endocarditis. He had a history of mitral ring annuloplasty and coronary artery bypass grafting operation before many years ago and reoperation for aortic dissection as Bentall procedure about 3 months ago. Blood tests showed leukocytosis with massive elevation of C-reactive protein, modest elevation of troponin, marked elevation of International Normalized Ratio, mild anemia, and hypoalbuminemia. Transesophageal echocardiogram (TEE) revealed a 4-mm × 15-mm round mobile mass originating from the anterior part of the mitral annular ring. In addition, there were a sac surrounding aortic graft and surrounding aneurismal aorta suggests a separation of graft because of possible aortic perivalvular abscess. There was blood flow into the sac and extensive thrombus with mobile component was seen in it. Blood cultures were positive for *Streptococcus pneumoniae*. Vancomycin, gentamicin, and rifampicin were chosen as antibiotic regimen. Early surgery planned for endocarditis and drained abscess cavity. However, the patient was persistently refused the third heart surgery operation. Repeat TEE showed the absence of vegetation on mitral valve and evident shrinkage of thrombus. Chest X-ray showed large left pleural effusion. Computed tomography with contrast enhancement confirmed this finding and revealed that contrast leak to the periaortic area and spreading a path under pulmonary artery to adjacent of the anterior wall of left ventricle. Thoracentesis was performed. Fistula to left pleura was suspected but not clearly confirmed. At 6 weeks of hospitalization, he clinically deteriorated. Due to confusional state, informed consent was obtained from attending relatives. The patient was transferred to the operating room. Cardiopulmonary resuscitation was initiated and thoracotomy was performed. Dehiscence of the aortic valve was seen. Infected tissues were extracted and repair with new prosthesis aortic valve was performed. Despite all resuscitation efforts, the patient died.

Keywords: Abscess, aortic valve, Bentall, dehiscence, pulsatile sac

Introduction

The Bentall procedure was first described by Bentall and De Bono in 1968. Since then, composite replacement of the aortic valve and ascending aorta has been considered the gold standard for treating ascending aortic dissection complicated by aortic regurgitation.[1] Cardiac surgery is usually required

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Address for correspondence: Dr. Sinan Varol, Department of Cardiology, Bagcilar Training and Research Hospital, Health Sciences University, Istanbul, Turkey.
E-mail: sinanvarol@gmail.com

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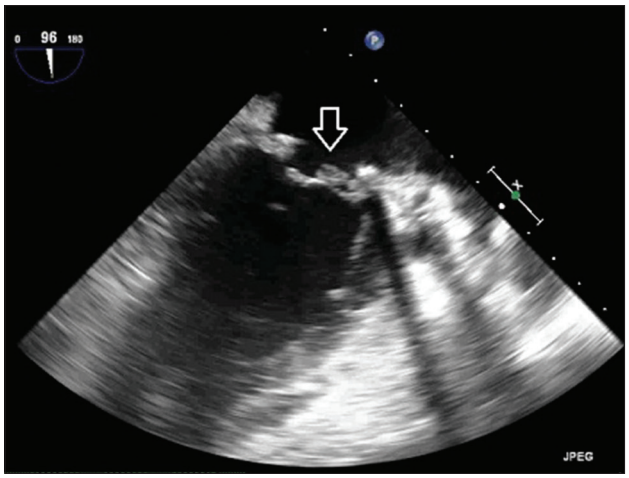


Figure 1: Transesophageal echocardiogram revealed a 4-mm × 15-mm round mobile mass originating from the anterior part of the mitral annular ring

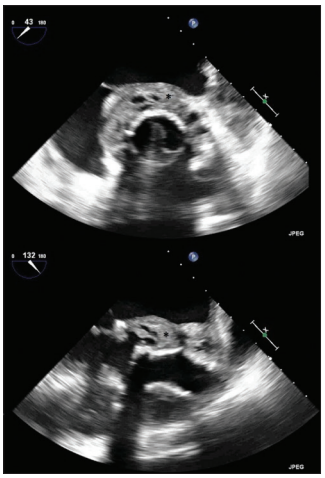


Figure 2: There was a sac surrounding aortic graft and surrounding aneurismal aorta suggests a separation of graft because of possible aortic perivalvular abscess

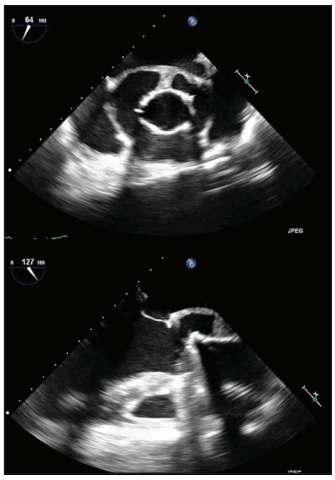


Figure 3: Repeat transesophageal echocardiogram showed the absence of vegetation on mitral valve and evident shrinkage of thrombus

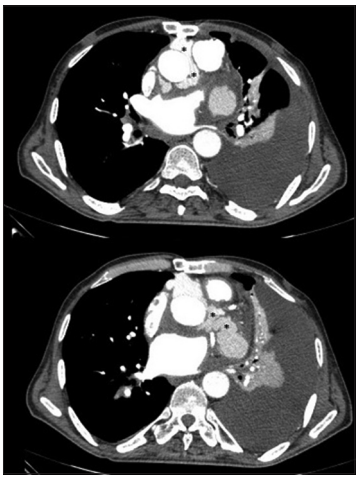


Figure 4: Computed tomography with contrast enhancement confirmed this finding and revealed that contrast leak to the periaortic area and spreading a path under pulmonary artery to adjacent of the anterior wall of the left ventricle

for infections of the mechanical valved conduit because of the high likelihood of resistant organism, and the possibilities of heart failure and embolization. Here, we report a case of early infective endocarditis complicated by periaortic abscess.

Case Report

A 62-year-old man with high fever, general fatigue, and history of transient ischemic attack was transferred to our cardiology clinic with high clinic suspicious of endocarditis. He had a history of mitral ring annuloplasty and coronary artery bypass grafting (CABG) and mitral ring annuloplasty operation 12 years ago and reoperation for aortic dissection as Bentall procedure about 3 months ago. He has diabetes, moderate chronic obstructive pulmonary disease, and right nephrectomy for several years ago. His medication was warfarin, spironolactone plus hydrochlorothiazide, gliclazide, metformin, digoxin, furosemide, and tiotropium. The patient has tachycardia with 2/6 systolic aortic murmur. Bilateral lung sounds were normal. The embolic and rheumatic phenomenon of endocarditis were absent and other findings were normal. Electrocardiogram showed that sinus rhythm with 120 BPM. Blood tests showed leukocytosis with massive elevation of C-reactive protein (CRP), modest elevation of troponin, marked elevation of International Normalized Ratio (INR) value, mild anemia, and hypoalbuminemia [Table 1]. Minimal left pleural effusion was seen on chest X-ray. Transesophageal echocardiogram (TEE) revealed a 4-mm × 15-mm round mobile mass originating from the anterior part of mitral annular ring [Figure 1]. In addition, there were a sac surrounding aortic graft and surrounding aneurismal aorta suggests a separation of graft because of possible aortic perivalvular abscess [Figure 2, Video 1a and b]. There was blood flow into the sac and extensive thrombus with mobile component was seen in it. Blood cultures were positive for *Streptococcus pneumoniae*. Vancomycin, gentamicin, and rifampicin were

Table 1: Blood tests on admission

Parameter	Result	Unit	Reference
Glucose	88	mg/dl	74-106
Urea	34	mg/dL	17-49
Creatinin	0.8	Mg/dl	0.5-0.9
AST	17	U/L	0-32
ALT	7	U/L	17-49
LDH	454	U/L	135-214
Sodium	134	mmol/L	136-145
Potassium	3.99	mmol/L	3.5-5.1
Chloride	96.6	mmol/L	98-107
CK	25	U/L	20-170
CK-MB	20	U/L	<25
Troponin T	0.296	ng/mL	<0.014
WBC	19.720	$10^{-3}/mm^3$	3.9-11.7
Neutrophil	17.060	$10^{-3}/mm^3$	1.9-8
RBC	4.25	$10^{-3}/mm^3$	3.85-5.16
Hb	11.68	gr/dL	12-15
Hct	37.5	RU	34.8-45
PLT	323	$10^{-3}/mm^3$	130-400
Albumin	2.6	g/dL	3.5-5.2
Total protein	6.2	g/dL	6.4-8.3
Prothrombin time	62.6	sec	11-16
INR	6.59		0.8-1.3
aPTT	40.4	sec	30-40
T. Bilirubin	1.21	mg/dl	0.3-1.4
D. Bilirubin	0.65	mg/dl	0.01-0.3
CRP	> 275	mg/dl	0-5

chosen as antibiotic regimen. INR values were high during the 1st week (>5) despite K-vitamin replacement. Leukocytosis and CRP values are gradually decreased with antibiotic regimen and subsequent blood cultures were negative. After clinical stabilization and the fall of INR value to therapeutic range, early surgery planned for endocarditis and drained abscess cavity. The patient informed about his clinical status and requirement of surgical operation. However, the patient was persistently refused third heart surgery operation. At 3rd week of treatment, repeat transesophageal echocardiogram.

TEE showed absence of vegetation on mitral valve and evident shrinkage of thrombus [Figure 3, Video 2a and b]. The leukocyte count was 10900/mm^3 and CRP was 108 mg/L. However, mild-to-moderate dyspnea was developed after a few days. Chest X-ray showed large left pleural effusion. Computed tomography with contrast enhancement confirmed this finding and revealed that contrast leak to the periaortic area and spreading a path under pulmonary artery to adjacent of the anterior wall of left ventricle [Figure 4]. Thoracentesis were performed. Fistula to left pleura was suspected, but not clearly confirmed by noninvasive tests. The patient was continued to refuse a heart operation. At 6 weeks of hospitalization, he suddenly gets hypotensive and clinically deteriorated. Because the patient was in a confusional state, informed consent was obtained from attending relatives. The patient was transferred to the operation room for emergency surgery. Cardiopulmonary resuscitation was initiated and thoracotomy was performed. Dehiscence of the aortic valve was seen. Infected tissues were extracted and repair with new prosthesis aortic valve was performed. However, postoperative myocardial functional recovery could not be achieved. Despite all resuscitation efforts, the patient died.

Discussion

Complications due infection after Bentall procedure are rare (1.4%)[2] but severe and not well documented. Staphylococci, alpha-hemolytic streptococci, and enterococci are the common causative organisms.[3] In a study consists ascending aorta prosthetic graft infections, most common organisms were coagulase-negative staphylococci, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*.[4] Our patient developed infective endocarditis caused by *S. pneumoniae* at 3 months after the procedure. Native valve endocarditis due to *S. pneumoniae* has become rare since the introduction of antibiotics.[5-7] Illicit drug use, altered mental status, and alcohol intake were found as risk factors for endocarditis. For prosthetic valves and graft infections, *S. pneumoniae* is very rare as causative organism.[8]

Austrian syndrome, the combination of meningitis, pneumonia, and infective endocarditis due to *S. pneumoniae* infection, is a rare entity.[9] Given its acute presentation and rapid course, patients should be closely monitored for any complications.

Treatment of pneumococcal endocarditis (PE) includes a prolonged course of intravenous antibiotics and if needed, surgery.[9] Our patient was treated conservatively, and surgical operation cannot be performed because of the refusal by the patient. However, he subsequently developed hemodynamic failure. Surgical evaluation must be pursued in any PE patients with suspicion for complication such as abscess, large vegetation, and valve perforation. The combined medical and surgical approach has improved outcomes, as compared to medical treatment alone in this group of patients.[9]

Conclusion

This case illustrates the need for closer monitoring after surgery. A redo-operation for active prosthetic valve endocarditis after Bentall operation rare in published series is a serious possible complication during follow-up. Its treatment comprises early complete removal of prosthetic material under suitable antibiotic therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Report

High-Grade Atrioventricular Block Requiring Pacemaker Implantation after Cardiac Transplantation: An Unusual Complication

K. K. Talwar, Abhinit Gupta[1], Raghav Bansal[1], Kewal Krishan[2]

Department of Cardiology, Max Healthcare Institute Limited, Departments of [1]Cardiology and [2]CTVS, Max Super Speciality Hospital, New Delhi, India

ORCID:

K. K. Talwar: https://orcid.org/0000-0002-7879-2680
Abhinit Gupta: https://orcid.org/0000-0001-8152-5519
Raghav Bansal: https://orcid.org/0000-0002-1649-8013
Kewal Krishan: https://orcid.org/0000-0001-5321-0958

Abstract

Self-limited bradyarrhythmias are commonly seen in postorthotopic heart transplantation patients. The most common cause of such bradyarrhythmias is sinus node dysfunction. Atrioventricular (AV) nodal blocks requiring pacemaker implantation remain distinctly uncommon. After ruling out reversible causes including dyselectrolytemia and drug toxicity, prolonged ischemia time of donor heart and transplant rejection should be considered as possible causes. The present case describes an uncommon occurrence of persistent high-grade AV block in postheart transplantation period ultimately requiring permanent pacemaker implantation.

Keywords: Brady-arrhythmia, cardiac transplantation, heart transplantation, high grade atrioventricular block, pacemaker implantation

Introduction

Cardiac transplantation remains the treatment of choice for end-stage heart disease. Arrhythmias are common in the orthotopic heart transplant (OHT) recipient, particularly in the early postoperative period, but are usually self-limited. Bradyarrhythmias occur in 8%–23% of patients after OHT depending on the case series and are probably due to sinus node dysfunction, but atrioventricular (AV) conduction disturbances requiring permanent pacemaker implantation are uncommon.[1]

Case Report

A 37-year-old patient underwent bicaval OHT for dilated cardiomyopathy. Pretransplant evaluation of donor heart was negative for any structural heart disease or conduction system disease. Baseline electrocardiogram (ECG) of donor heart was normal. The transplant procedure was uneventful with total ischemia time of <3 h. Immediately after the transplant, the ECG was suggestive of the right bundle branch block (RBBB) with normal PR interval. The posttransplant patient was started on triple immunosuppressive therapy including tacrolimus, mycophenolate mofetil, and prednisolone as per institutional protocol. Epicardial backup pacing was kept in place as a part of the protocol. The patient was noted to have increasing pacing requirements starting from day 7 in postoperative period in view of 2:1 AV block [Figure 1] with intermittent complete heart block. After ruling out reversible causes (hyperkalemia and AV-blocking drugs) and procedural causes (prolonged ischemia time and perioperative injury to AV node), the evaluation for early rejection was planned. Endomyocardial biopsy and electrophysiological (EP) study

Address for correspondence: Dr. K. K. Talwar,
Department of Cardiology, Max Healthcare Institute Limited,
New Delhi, India.
E-mail: kktalwar@hotmail.com

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were done on postoperative day 19. EP study revealed 2:1 AV conduction with prolonged HV interval (130 ms) suggestive of high-grade infra-Hisian AV block [Figure 2]. Histopathological examination and immunohistochemistry of the biopsy specimens were suggestive of mild acute cell-mediated rejection (the International Society for Heart and Lung Transplantation, Grade 1R) and were negative for pathologic antibody-mediated rejection [Figure 3]. Serum tacrolimus levels were found to be low, and with early cell-mediated rejection in consideration, the dose of tacrolimus and steroids was increased. However, the patient continued to have intermittent high-grade AV block. Repeat tacrolimus levels were in range. A permanent pacemaker implantation (single chamber, VVIR) was done on postoperative day 22. The patient was then discharged on immunosuppressive therapy in stable condition. On follow-up after 1 week, the patient was in sinus rhythm with RBBB [Figure 4] and pacemaker interrogation revealed minimal pacing requirement.

Discussion

Bradyarrhythmias after OHT are variably reported, but the most common cause remains sinus node dysfunction. Conduction system abnormalities leading to bradyarrhythmia are distinctly uncommon. Incomplete RBBB is the most common conduction abnormality seen in up to 70% of patients following OHT.[1] The conduction abnormality may persist and may be causally associated with prolonged donor ischemic time and episodes of rejection.[2] However, high-grade AV block remains uncommon, particularly in the early postoperative period. According to a study of 1047 posttransplant patients, first-degree, Mobitz Type I, Mobitz Type II, and complete heart blocks occurred in 8.3%, 0.6%, 0.1%, and 1.8% of patients, respectively.[3]

Whenever AV block occurs after cardiac transplantation, first reversible causes (e.g., hyperkalemia and AV-blocking drugs) should be ruled out and corrected, if any. The preoperative use of amiodarone in the recipient is an important cause of reversible posttransplant bradycardia that should not be missed. Periprocedural injury to AV node and prolonged ischemia time are also associated with postoperative AV node dysfunction and should better be avoided. Rarely, intraoperative coronary air embolism may also cause postoperative conduction disturbances. In a study by Leonelli *et al*., the duration of graft ischemia time and severity of rejection were the major determinants of conduction abnormality after OHT.[4] A total ischemia time >160 min was associated with persistence of conduction abnormality. Ice preservation of donor heart has been proposed as the likely cause of injury to conduction system. However, postoperative AV block is usually transient

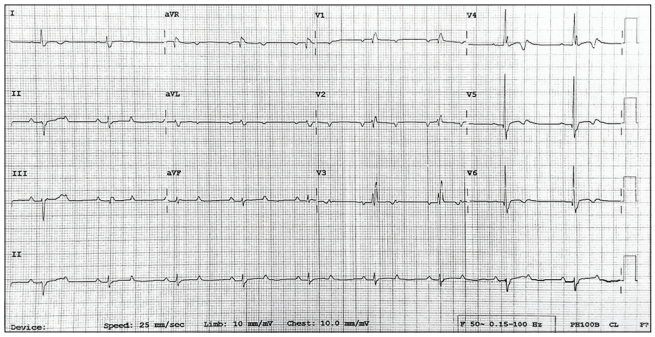


Figure 1: A 12-lead electrocardiogram done on posttransplant day 7 showing 2:1 atrioventricular block with wide QRS complex conduction (left anterior hemiblock and right bundle branch block) suggestive of infra-Hisian block

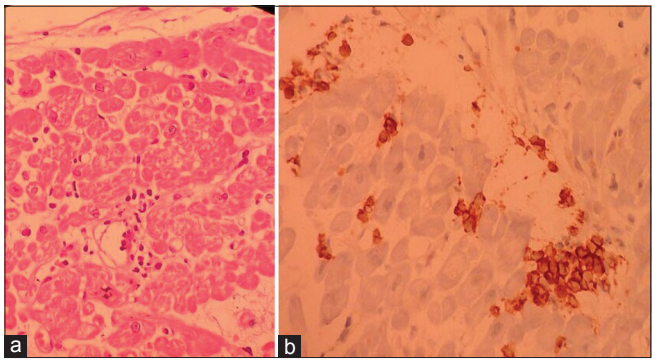


Figure 3: (a) Histopathological examination suggestive of mild acute cellular rejection (International Society for Heart and Lung Transplantation, 2004 Grade 1R) and (b) CD68 positivity on immunohistochemistry

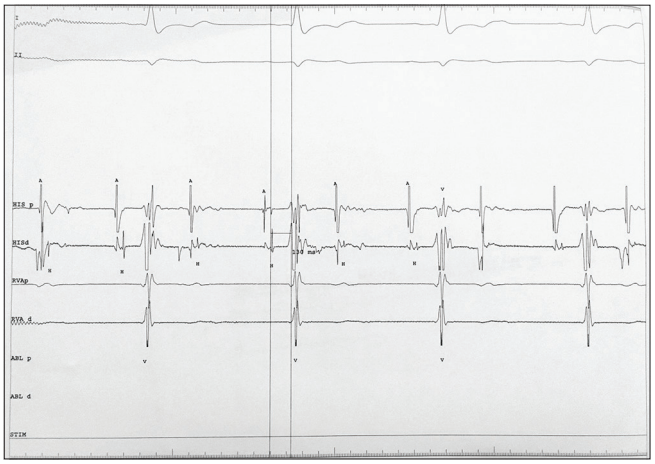


Figure 2: Electrophysiological study trace demonstrating infra-Hisian atrioventricular block (HV interval of 130 ms)

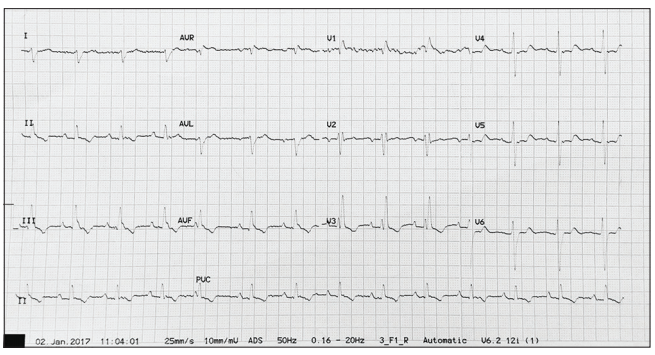


Figure 4: Normal sinus rhythm with right bundle branch block on follow-up

and only rarely requires permanent pacemaker implantation. In a contemporary case series on 1179 transplant patients, prolonged operative time and biatrial anastomosis were identified as independent risk factors for permanent pacemaker implantation.[5] Cardiac conduction tissue is also a specific target related to allograft rejection. The arteries to sinoatrial and AV tissue are frequently involved in both acute cellular reaction and chronic intimal fibrocellular rejection reaction, causing conduction disturbances.[6] Cardiac rejection should be strongly suspected and ruled out with certainty in cases of postoperative AV blocks. Early deceleration of immunosuppressive therapy and underdosing may precipitate early rejection and should be avoided. Cardiac endomyocardial biopsy is the gold standard for diagnosing cardiac rejection and must be done whenever rejection is suspected. If the AV block persists even after treatment of rejection or EP studies are suggestive of high-risk features, implantation of permanent pacemaker may be the right approach. In the present case, EP study helped to guide the approach and tilted the balance toward advocating permanent pacemaker implantation in view of infra-Hisian block.

In a retrospective study of 114 heart transplant recipients, 14 patients (12%) required temporary pacing and 4 patients (3.5%) required permanent pacing.[7] The indication for permanent pacemaker implantation was sinus node dysfunction in 3 patients (75%) and AV block in 1 patient (25%). They observed transplant rejection in 3 patients (21.4%) requiring temporary pacing and in 2 patients (50%) requiring permanent pacing.[7] Although pacemaker implantation is performed in approximately 10%–15% of cardiac transplant recipients, AV block accounts for <20% of these cases.[8,9] Median time to pacemaker implantation is much later for AV block than for sinus node dysfunction (1511 vs. 27 days in a study by Wellmann *et al*.).[5]

To sum up, high-grade AV blocks are uncommon in cardiac transplant recipients (especially in early postoperative period), and if noted, acute rejection and other reversible causes should be carefully ruled before considering for permanent pacemaker implantation.

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Conflicts of interest

There are no conflicts of interest.

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Cor Triatriatum with Mitral Stenosis: A Diagnostic Dilemma

Devvrat Desai, Jignesh Kothari, Parth Solanki, Kinnaresh Baria

Department of Cardiovascular and Thoracic Surgery, U. N. Mehta Institute of Cardiology and Research Center, (Affiliated to B. J. Medical College), Ahmedabad, Gujarat, India

ORCID:

Devvrat Desai: https://orcid.org/0000-0001-7083-9985
Jignesh Kothari: https://orcid.org/0000-0002-7693-2037
Parth Solanki: https://orcid.org/0000-0003-4940-7402
Kinnaresh Baria: https://orcid.org/0000-0001-8380-5514

Abstract

Cor triatriatum sinister is an extremely rare congenital heart defect. Very few cases have been reported for cor triatriatum associated with mitral regurgitation. We are reporting an exceptional case of cor triatriatum associated with calcified mitral valve resulting mitral stenosis. Preoperatively, mitral stenosis was underestimated due to the presence of restricted communication between two chambers of the left atrium. The patient was operated for cor triatriatum repair with mitral valve replacement.

Keywords: Cor triatriatum sinister, mitral valve replacement, posterior annular calcification, rheumatic mitral stenosis

Introduction

Cor triatriatum sinister is an extremely rare congenital heart defect.[1] In classical form of cor triatriatum, there is a division of the left atrium by a fibromuscular membrane, band or tissue, resulting in the development of two distinct chambers, that is, a posterosuperior chamber and anteroinferior chamber. It is even more uncommon in adults and quite exceptional when associated with mitral valve disease.[2] Very few cases have been reported for cor triatriatum associated with mitral regurgitation.

Here, we are reporting an exceptional case of cor triatriatum associated with calcified mitral valve resulting mitral stenosis requiring mitral valve replacement.

Case Report

A 65-year-old female presented with a history of dyspnea and angina on exertion (New York Heart Association Class II) for the past 2 years and progressed to the New York Heart Association Class IV recently. On clinical examination, the patient had a regular heart rate of 80/min with blood pressure of 130/90 mm of mercury (mmHg).

Electrocardiogram confirmed normal sinus rhythm. Chest radiography showed prominent bronchovascular markings [Figure 1].

Transthoracic echocardiography revealed cor triatriatum; a membrane dividing left atrium into posterosuperior venous chamber and anteroinferior mitral chamber. There was a small communication between two chambers. On Doppler flow mapping, mitral valve inflow signal (pg/mg) was 7/3 mmHg. Color and pulse wave Doppler suggested moderate mitral stenosis and mild mitral regurgitation with mild pulmonary arterial hypertension with ejection fraction of 55%. Above findings were confirmed on transesophageal echocardiography.

For further assessment of pulmonary venous anatomy and mitral valve pathology, computerized tomographic pulmonary angiogram was advised. Multislice computed tomography (CT) pulmonary angiography was performed

Address for correspondence: Dr. Devvrat Desai, Department of Cardiovascular and Thoracic Surgery, U. N. Mehta Institute of Cardiology and Research Center, (Affiliated to B. J. Medical College), New Civil Hospital Campus, Asarwa, Ahmedabad - 380 016, Gujarat, India.
E-mail: drdevvratcvts@gmail.com

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after intravenous injection of nonionic contrast which showed the left atrium divided by a thin membrane, suggestive of cor triatriatum. (Loeffler's Type 2 – small restrictive opening with calcification). All pulmonary veins were draining into the posterior chamber of the left atrium [Figure 2a-d]. Mitral posterior annular calcification was found [Figure 3]. Preoperative conventional coronary angiography revealed a right dominant system with no evidence of coronary artery disease. The patient was advised for surgical correction of cor triatriatum.

Surgical technique

The lesion was approached by a midline sternotomy and pericardiotomy. Cardiopulmonary bypass was established using ascending aortic and bicaval cannulation technique. After complete myocardial protection with moderate hypothermia, we approached cor triatriatum through interatrial groove incision.

A large membrane was dividing the left atrium into two compartments posterosuperior and anteroinferior. Both chambers were connected through a restricted, calcified communication across membrane. After complete excision of the membrane, mitral valve was examined. Both mitral commissures were fused. There was a pinhole mitral valve orifice. Posterior annular calcification was present, which was underestimated preoperatively. Subvalvular apparatus was abnormally shortened. Mitral valve was excised and replaced with 25-mm St. Jude Master's series mechanical prosthesis.

Postoperative recovery was uneventful and the patient was discharged after 1 week of postoperative stay. Postoperative transthoracic two-dimensional echocardiography showed satisfactory findings. Follow-up contrast CT thorax, before discharge, showed no residual membrane in the left atrium with normally functioning mitral valve prosthesis [Figure 4a and b].



Figure 1: Preoperative chest radiograph showing prominent bronchovascular markings

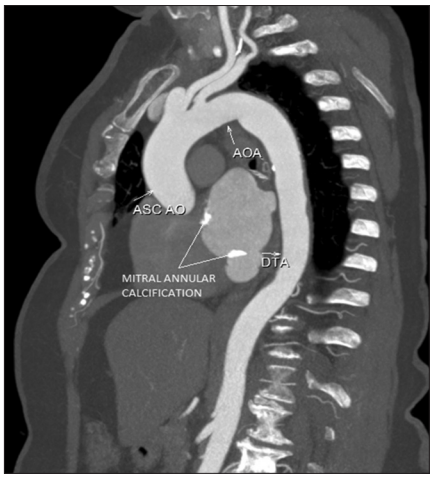


Figure 3: Preoperative computed tomography pulmonary angiogram showing posterior annular calcification of mitral valve

Discussion

Cor triatriatum sinister was first described by Church in 1868. It is found in only 0.1% of cases of congenital heart anomaly. In classical form of cor triatriatum, there is a division of the left atrium by a fibromuscular membrane, band or tissue,

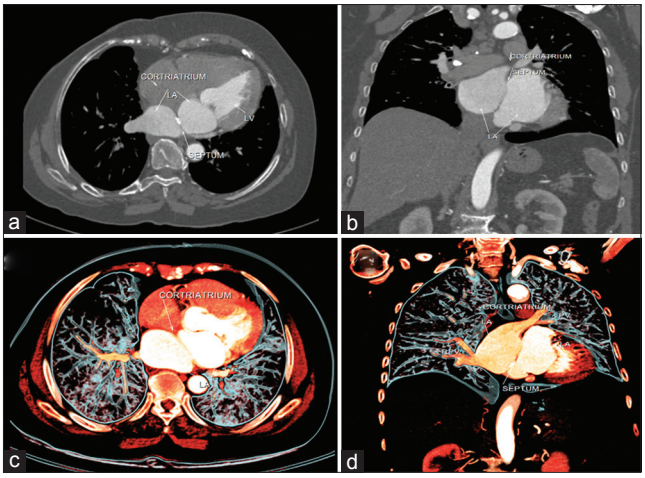


Figure 2: (a-d) Preoperative computed tomography pulmonary angiogram showing cor triatriatum Loeffler's Type 2 – small restrictive opening with calcification

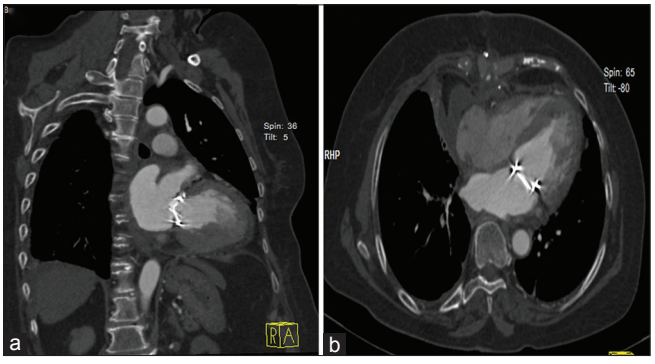


Figure 4: (a and b) Postoperative contrast-enhanced computed tomography thorax showing no residual membrane with mitral valve prosthesis *in situ*

resulting in the development of two distinct chambers, that is, a posterosuperior chamber and anteroinferior chamber. The posterosuperior chamber receives the return of all pulmonary veins. The anteroinferior chamber is a true left atrium which communicates with mitral valve.

Embryological basis for development of cor triatriatum is related with anomalous or failure of inclusion of the pulmonary veins into the posterior left atrial wall.[3] It is usual for patients to present in infancy and early childhood, although some cases remain undetected until adult life.

Natural history depends on the effective aperture size between two chambers of the left atrium. In severely restricted form, presentation occurs in early in infancy. Without surgical intervention, patients die early in infancy.[4,5] Approximately, 75% of persons born with classic cor triatriatum die in infancy.

Pathophysiologically, the obstructive nature of the membrane leads to the creation of a pressure gradient with an associated rise in pulmonary venous and arterial pressures. As a result, clinical presentation often mimics mitral stenosis. At present, the reasons for late presentation are poorly understood. Large unrestricted communication through fossa ovalis between two atria improves the prognosis and delays presentation.

The development of fibrosis and calcification in the opening of the separating diaphragm, mitral insufficiency or mitral stenosis, posterior annular calcification, and the development of atrial fibrillation are some of the various triggers that lead on to the symptoms.

Cor triatriatum sinister remains an uncommon form of congenital heart disease although it is being diagnosed with increasing frequency in adults due to improvements in diagnostic imaging. Wong *et al*.[6] reported, for the first time in 1989, a 49-year-old male patient with the rare combination of cor triatriatum sinister associated with severe mitral regurgitation and abnormal tensor apparatus of the mitral valve with hypoplastic papillary muscle. This diagnosis should be considered in all patients presenting with signs or symptoms of mitral stenosis.

Management in such cases differs from isolated cor triatriatum, in that, in addition to the surgical resection of accessory membrane, the patient requires mitral valve repair or replacement for correction of mitral valve pathology.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Prevalence of Metabolic Syndrome in Young Patients with ST-Elevation Myocardial Infarction

Dear Editor,

I read with interest the outstanding study by Oz *et al*.[1] on the prevalence of metabolic syndrome (MS) in Turkish young patients with ST-elevation myocardial infarction (STEMI). On employing the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III criteria), the authors found a high prevalence of MS (46.8%), and the most frequent component of MS was low high-density lipoprotein level (84.8%) followed by elevated triglycerides (78.1%).[1] I presume that these results ought to be cautiously interpreted. Apart from many limitations addressed by the authors, namely single-center study, not searching to examine the long-term clinical outcomes of all the studied patients, and lack of detailed assessment of vessels lesions, I presume that the following methodological limitation might be further relevant. This limitation is related to the MS definition criteria employed in the study. The impact of this limitation could be addressed in two aspects. On the one hand, there are many definition criteria for MS in the clinical setting and researches. These include the following: NCEP-ATP III; the International Diabetes Federation (IDF); the American Heart Association (AHA), and the World Health Organization (WHO). There is a global confusion on the precision of these criteria to diagnose MS. For instance, in a Turkish study, comparing the prevalence of MS among obese children and adolescents using WHO and NCEP-ATP III guidelines showed that 24% of the subjects were diagnosed as MS according to the NCEP while 38.8% were diagnosed according to the WHO-defined MS. The study recommended using WHO guidelines in the diagnosis of MS as this might detect more patients with MS and lead to better monitoring of them and prevention of their future sequelae.[2] In another Italian study, evaluation of three criteria, namely NCEP-ATP III, IDF, and AHA, showed that the prevalence of MS was significantly estimated higher on employing the AHA and IDF as compared to the ATP III definition and that AHA and IDF definitions were found more sensitive than that of ATP III in diagnosing MS.[3] On the other hand, the ATP III criteria employed in Oz *et al*.'s study[1] are old and are no more worthy as they were set nearly a decade ago.[4] As many national associations have proposed their own diagnostic MS criteria,[5] I presume that constructing national Turkish MS definition criteria could better determine the prevalence of MS in patients with various health disorders. Despite the above-mentioned limitations, the study results urge the need for strict actions to reduce the future risk of cardiovascular consequences in patients with STEMI.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Mahmood Dhahir Al-Mendalawi

Department of Paediatrics, Al-Kindy College of Medicine, University of Baghdad, Baghdad, Iraq

ORCID:

Mahmood Dhahir Al-Mendalawi: https://orcid.org/0000-0003-2872-453X

Address for correspondence: Prof. Mahmood Dhahir Al-Mendalawi, P.O. Box 55302, Baghdad Post Office, Baghdad, Iraq.
E-mail: mdalmendalawi@yahoo.com

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Authors' Response: Letter to the Editor on Prevalence of Metabolic Syndrome in Young Patients with ST Elevation Myocardial Infarction

We would like to thank Dr. Mahmoud Abdelnabi *et al*. for their valuable comments but according to our opinion, there is confusion about our study design. With regard to the remarks of Dr. Mahmoud Abdelnabi, it should be clear that:

1. The main aim of the study was to determine the prevalence of metabolic syndrome (MS) in patients under 46 years of age who presented with ST elevation myocardial infarction and underwent primary percutaneous coronary intervention and especially this study did not focus on the morphology of coronary lesions
2. The limitations of our study that we mentioned in the limitation part do not affect the prevalence of MS
3. Over the last two decades, various organizations have proposed different definitions, using varying terminologies about MS. There are not just the International Diabetes Federation, the American Heart Association, and the World Health Organization (WHO) but also The European Group for Study of Insulin Resistance proposed a modification of the WHO definition
4. Despite the large number of controversies regarding the nomenclature to be used, this conglomeration of various metabolic abnormalities in NCEP-ATP III criteria has been widely accepted as a screening tool for identifying subjects at high risk of cardiovascular disease and the aim of our study was not to compare these different definitions.

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Conflicts of interest

There are no conflicts of interest.

Tugba Kemaloglu Öz, Nazmiye Özbilgin[1], Aylin Sungur[1], Elif Gülsah Bas, Ahmet Zengin[1], Tayfun Gürol, Özer Soylu, Bahadir Dagdeviren

Department of Cardiology, Faculty of Medicine, Bahcesehir University, [1]Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Center, Istanbul, Turkey

ORCID:
Tugba Kemaloglu Öz: https://orcid.org/0000-0003-1168-8237
Nazmiye Özbilgin: https://orcid.org/0000-0002-3334-8359
Aylin Sungur: https://orcid.org/0000-0001-1904-4906
Elif Gülsah Bas: https://orcid.org/0000-0003-0193-6495
Ahmet Zengin: https://orcid.org/0000-0002-6823-2305
Tayfun Gürol: https://orcid.org/0000-0001-8200-3747
Özer Soylu: https://orcid.org/0000-0003-4983-8755
Bahadir Dagdeviren: https://orcid.org/0000-0001-6945-0745

Address for correspondence: Dr. Tugba Kemaloglu Öz, E5 Üzeri 23, Nisan Sok Merdivenköy No: 17, 34732, Kadiköy, Istanbul, Turkey.
E-mail: tugbakemalogluoz@gmail.com

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