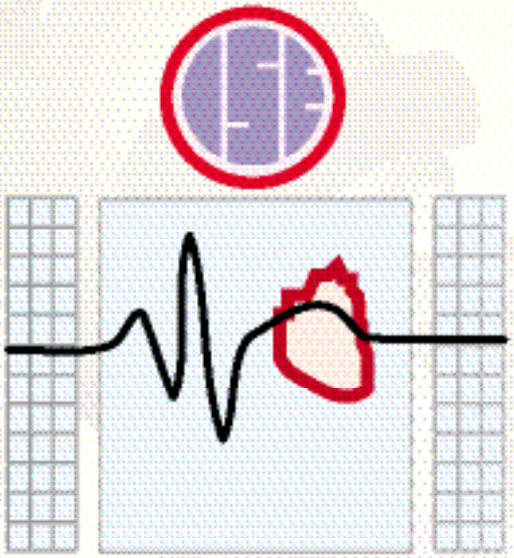
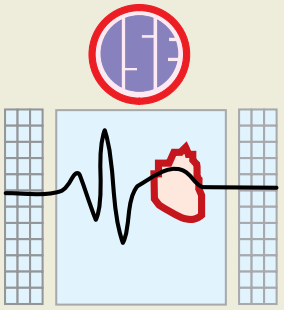
2006 : No. 2



Indian Journal of ELECTROCARDIOLOGY



ISECON 2007

HYDERABAD

24th - 25th February, 2007

CONTACT

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C O N T E N T S

SECRETARIAT
S. B. GUPTA
HON. GENERAL SECRETARY

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Editorial

Dear Colleagues,

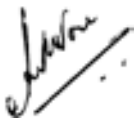
In the midst of chaotic rains in Mumbai and several other parts of the country, we are pleased that we have managed to bring out this issue of the IJE. The journal will be released at the 3rd midterm conference of the ISE. This is being organized by Dr. KK Varshney and his team at Aligarh and has been named AAC- Aligarh Arrhythmia Course. With all-round practically oriented topics, lucid faculty and audience interactive systems, the conference promises to live up to the benchmark set by previous ISECONS.

In this regard we must mention that the last ISECON at Chennai, organized by Dr. Ulhas Pandurangi and his team, was an unqualified success. Even Prof Melvin Scheinmann was appreciative of the professional ambience, the quality of talks, the consumer court sequence and most of all, the level of the audience.

The current issue contains, as always, an ECG quiz. Also, we have 2 articles from the web-based Indian Pacing and EP Journal, on POTS (postural orthostatic tachycardia syndrome) and atrial fibrillation and hyperthyroidism. POTS is a less known enetity. Awareness of this condition is important, to avoid worsening the condition by inappropriate treatment with beta-blockers.

There is a also an ECG vignette, of important clinical relevance, especially with polypharmacy and a plethora of newer drugs.

Yash Lokhandwala
Editor



Amit Vora
Editor

From Hon. Secretary's Desk

Dear Members,

Indian Society of Electrocardiology is on fast track. We have tried to make the programs of ISE, a symbol of academic feasts only.

Dr. K. P. Misra, Dr. Ulhas Pandurangi and their team organized ISECON-2006 at Chennai on 18th and 19th February 2006. There was a Pre-Conference Workshop for paramedics on 17th February 2006; both the events were astounding success. The organizers deserve heartiest congratulations. I feel Pre-Conference Workshops for paramedics shall become a regular feature.

Indian Society of Electrocardiology organized the "2nd ECG Learning Course" for postgraduate students on 22nd and 23rd July 2006 at Mumbai, which was attended by approximately 100 students. Successful candidates were awarded the Certificate of Competence for ECG reading. We would like to make it as a regular feature and would like to rotate to other cities too.

ISECON 2007 will be organized at Hyderabad by Dr. C. Narasimhan and his team in February 2007. Another grand event waits for you!

ISE plans to organize a Satellite Symposium on "Management of Atrial fibrillation" at Goa in February 2007. Keep a check on the announcements at www.iseindia.org.

Now, the Mid-Term CME Course (AAC 2006) is being organized at Aligarh on 2nd and 3rd September 2006 by Dr. K. K. Varshney and his team and cudos to them for bringing another good scientific program.

I look forward to see you all at the above meet, which will be a real treat.

My sincere thanks to Dr. Yash Lokhandwala, Dr. Amit Vora and the Editorial Team for bringing out the 2nd issue of Indian Journal of Electrocardiology – 2006.

Long Live Indian Society of Electrocardiology

Dr S B Gupta
Hon. Secretary
Indian Society of Electrodardiology

Aligarh Arrhythmia Course

2nd - 3rd September, 2006

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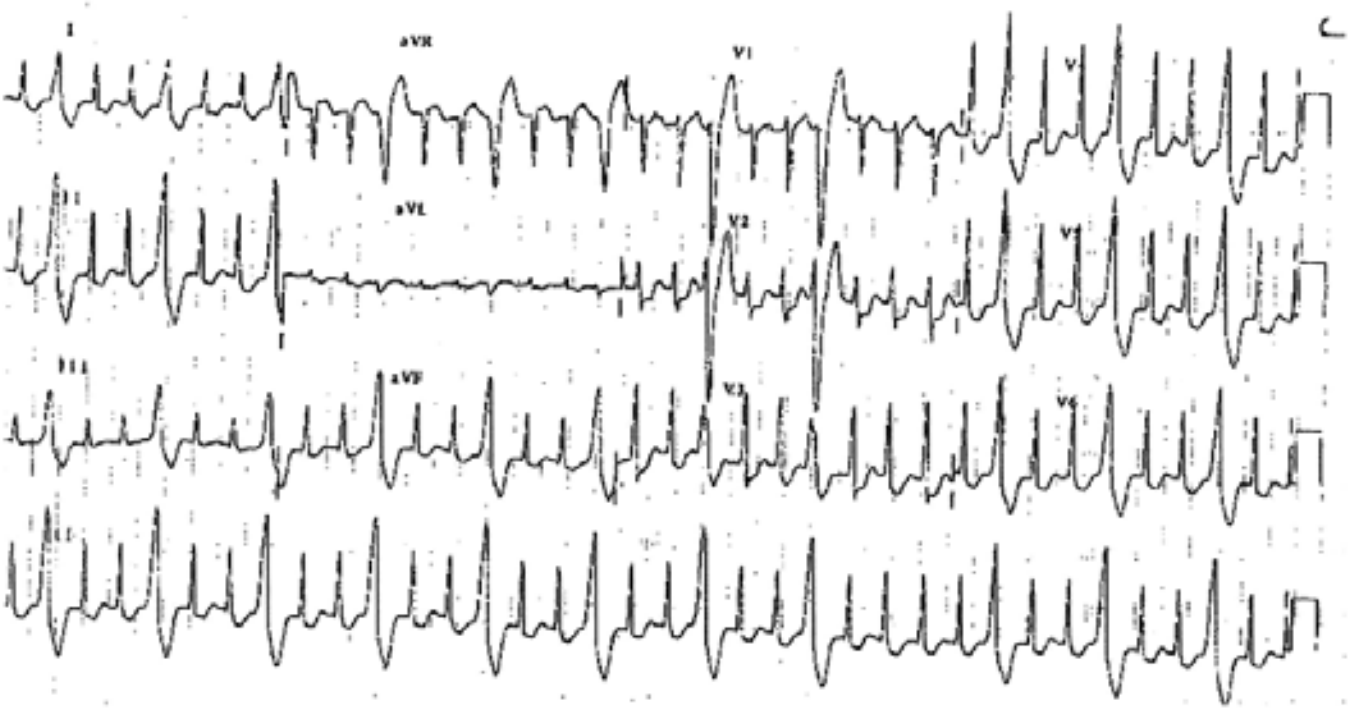
ECG Quiz

ECG - 1

36 yr-old lady c/o paroxysmal palpitations…..



1. This tachycardia ECG shows:

a. SVT with intermittent LBB aberrancy
b. SVT with intermittent preexcitation
c. SVT with PVCs
d. Don't know

For correct answer see overleaf

ECG - 1

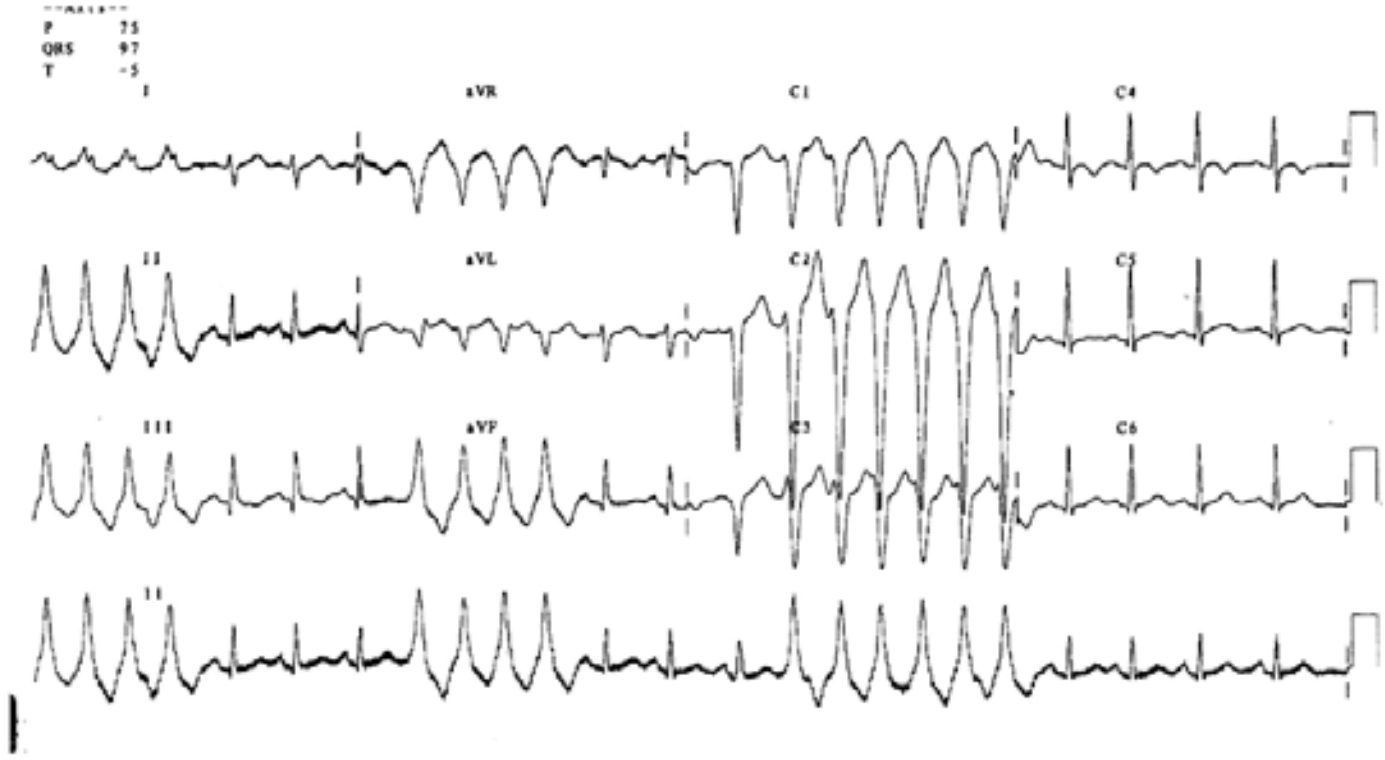
The correct answer is 'a' – SVT with intermittent LBB aberrancy.

The first thing to appreciate in the ECG is that it is very regular. The wide QRS complexes show a typical LBBB morphology, with a sharp downstroke in V1. This morphology and the regular timing rule out PVCs.

Preexcitation will be extremely rare ***during*** a regular narrow QRS tachycardia. This can theoretically occur with multiple accessory pathways, but then the QRS complexes should look like preexcited complexes, which are not seen in this ECG.

ECG - 2

45 yr-old gentleman c/o exertional palpitations…



2. This 12-lead ECG shows:

a. Intermittent SVT with aberrancy
b. Repetitive monomorphic VT
c. Polymorphic VT
d. Ischemia induced VT

For correct answer see overleaf

ECG - 2

The correct answer is 'b' – Repetitive monomorphic VT.

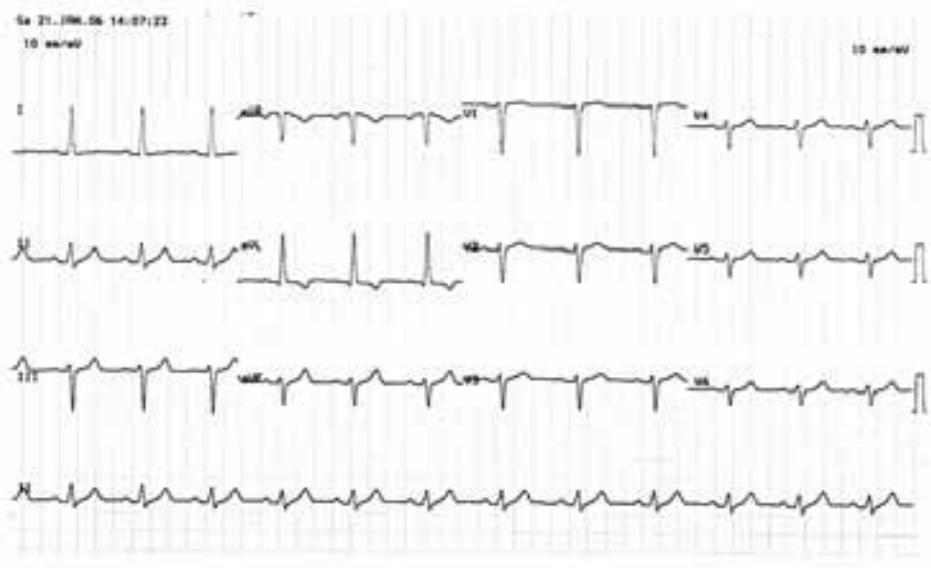
Repetitive short runs of monomorphic wide QRS complex tachycardia are seen. These have a LBBB-like morphology, with a QRS axis of + 60 degrees. The first complex of each run is premature, without a preceding P wave. There is suggestion of AV dissociation, as seen from the changing ST-T complexes. The sinus rhythm portions are normal, without any ST deviation.

Ischemia typically produces polymorphic VT, and there should be other evidence of ischemia; both these features are absent in this ECG.

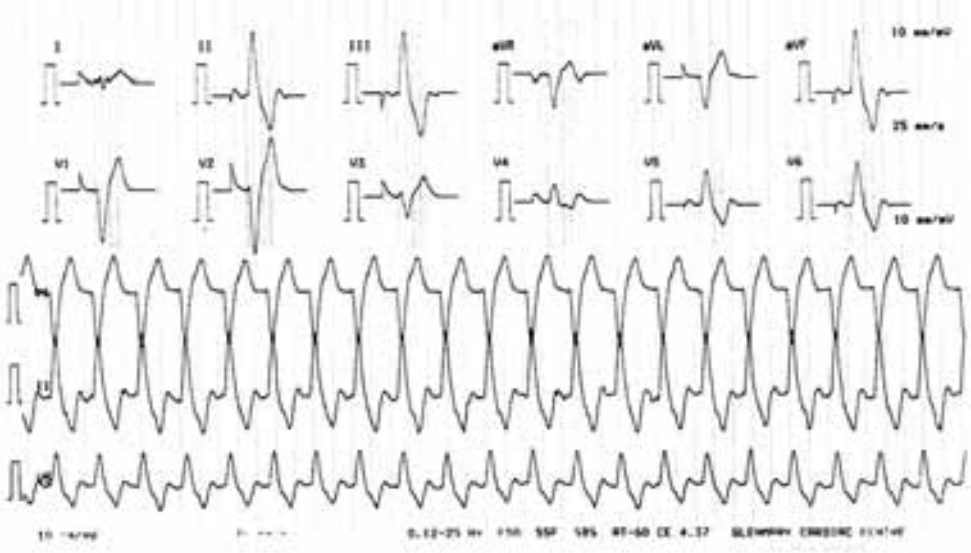
Idiopathic VT, in normal hearts, often arises from the RV outflow tract, which is the site of origin of this VT. Moreover, these VTs are classically repetitive and non-sustained, as seen here.

ECG - 3

35 yrs-old, vague symptoms, PVCs at rest, pre-Stress test ECG



Stage 2 – Bruce protocol…



3. During 2nd stage the ECG shows:

a. Sinus tachycardia with LBBB
b. Atrial tachycardia with LBBB
c. VT
d. Don't know

For correct answer see overleaf

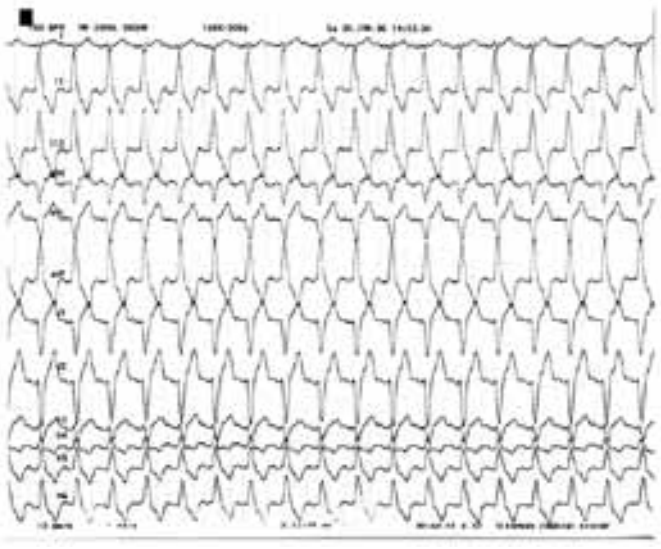
ECG - 3

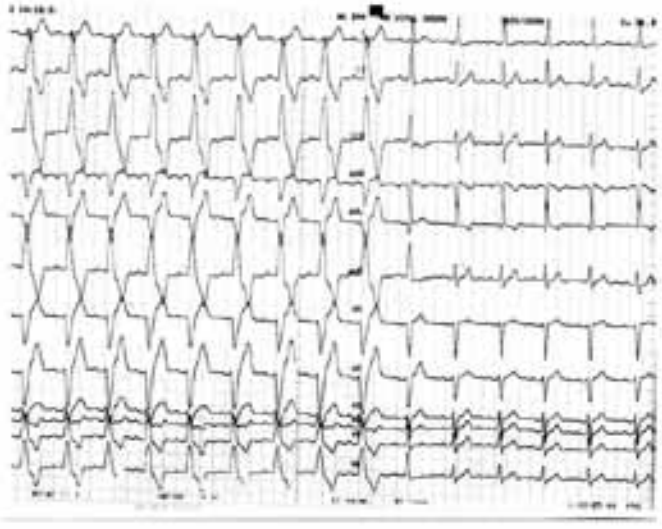
The correct answer is 'a' – Sinus tachycardia with LBBB.

The tachycardia is regular, broad with LBBB morphology. The V1 complex shows a sharp, initial downward complex which is typical for LBBB. Both of these make VT unlikely.

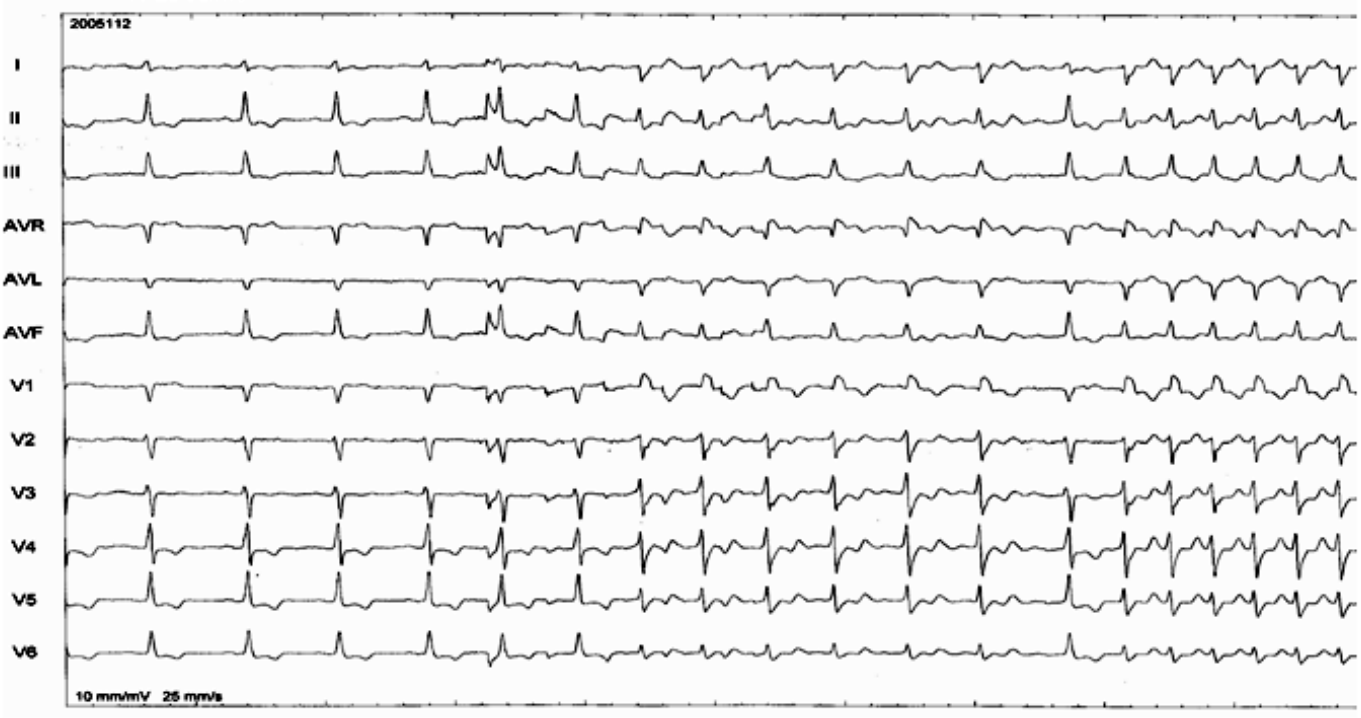
After stopping the exercise test (next figures), as the heart rate slows, the P waves are seen, especially in lead V2.

Isolated rate-related LBBB, especially above heart rates of 120/min, is not indicative of coronary or other heart disease. However, these patients need regular check-ups, clinically and echocardiographically.





ECG - 4



4. This ECG shows:

a. SVT
b. Rate related BBB
c. Artifact
d. All of the above

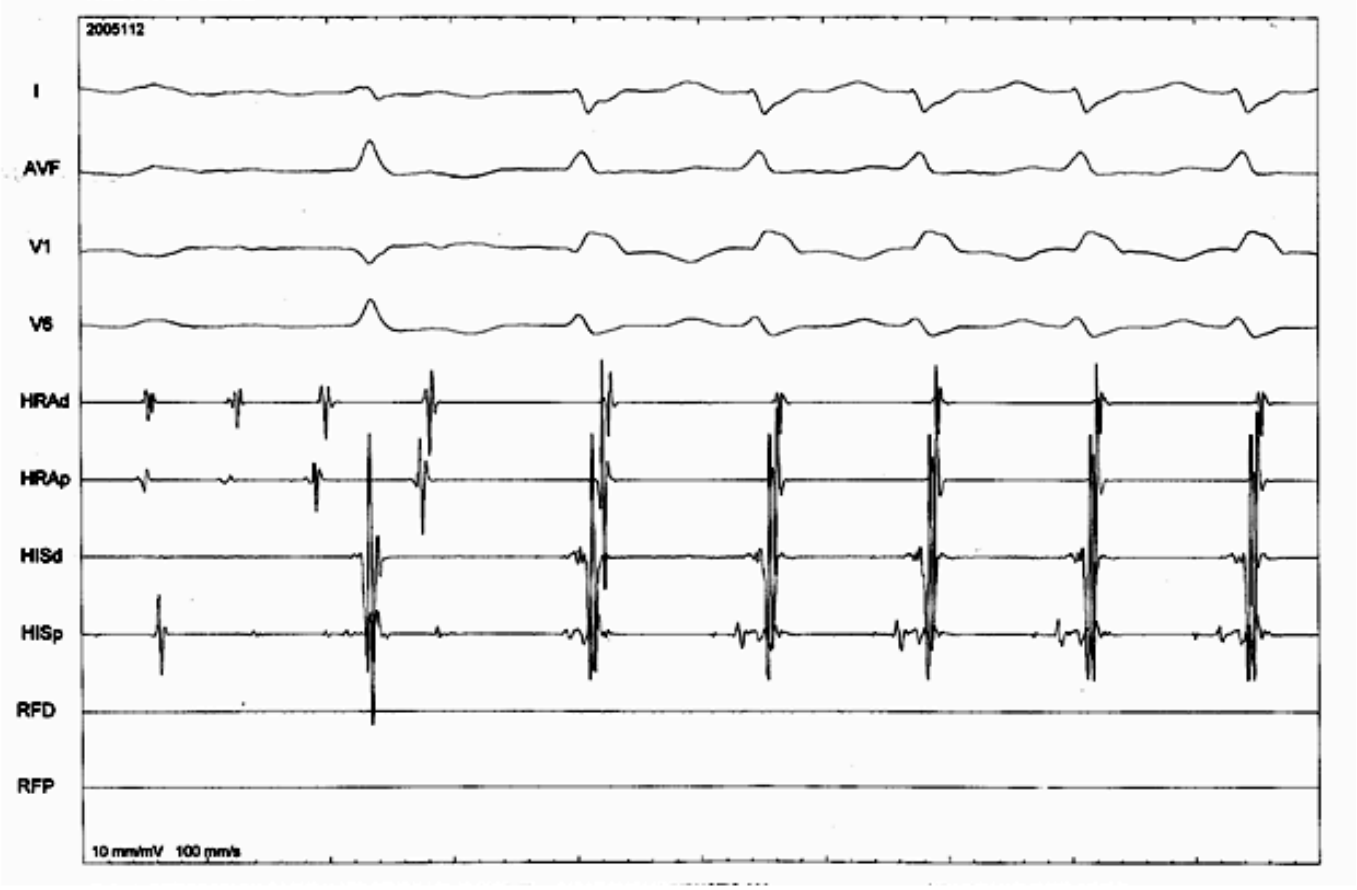
For correct answer see overleaf

ECG - 4

The correct answer is'd' – all of the above.

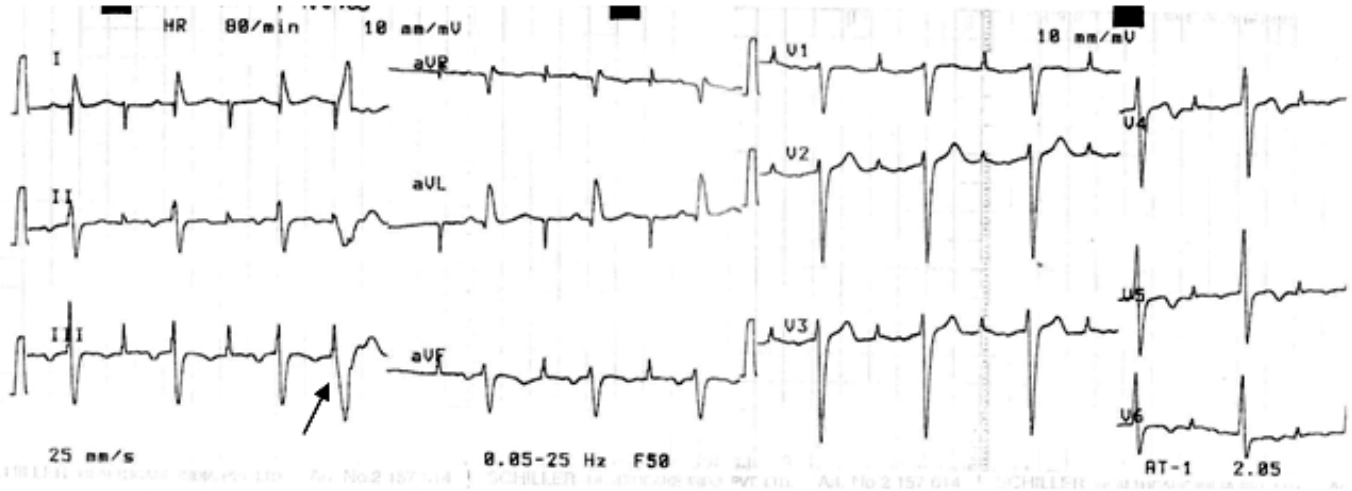
An artifact is seen just before the onset of wide QRS tachycardia. There is RBBB after this. Initially the tachycardia is irregular, with atrial fibrillatory pattern, best seen in lead V2. The last 6 complexes show a regular SVT. Just before this SVT, the QRS complex is narrow due to the relatively long preceding RR interval. This reconfirms that the RBBB is rate-related.

The intracardiac traces (next figure) show the irregular A (atrial) waves during atrial fibrillation, followed by regular A waves during SVT. The QRS complexes and the A waves occur simultaneously during SVT, suggesting that the mechanism of SVT is typical AV nodal reentrant tachycardia.



ECG - 5

Dual chamber pacemaker for SN dysfunction – 10 years ago



5. This pacemaker ECG shows:

a. Capture failure
b. Sensing failure
c. Capture & sensing failure
d. Normal pacing function

For correct answer see overleaf

ECG - 5

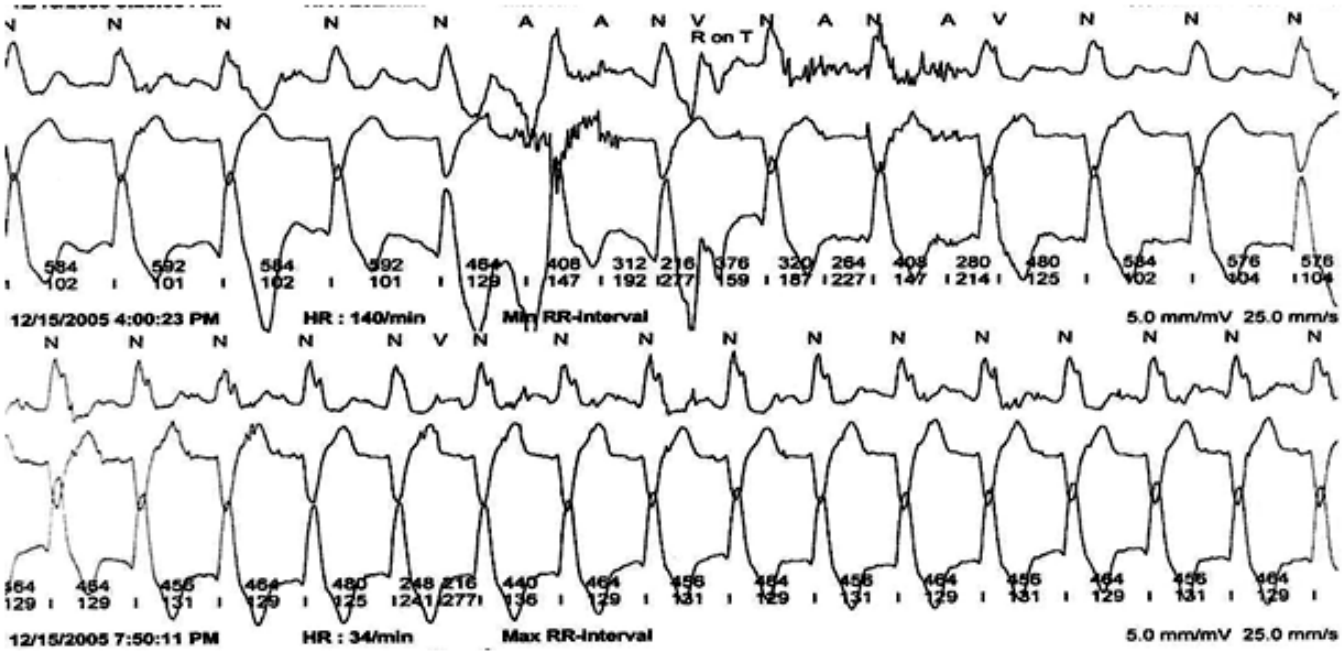
The correct answer is'd' – normal pacing function.

Pacing artifacts are regularly seen, followed after a gap, by P waves. One such pacing stimulus is coincident with a wide QRS complex. The ECG therefore shows atrial pacing. The latency between the stimuli and the P waves is possibly due to atrial myopathy, sometimes the cause of sinus node dysfunction. The long programmed AV delay allows intrinsic AV nodal conduction.

The isolated wide QRS complex is a PVC, occurring coincidentally with the atrial pacing stimulus.

ECG - 6

60 yr-old gentleman with syncope…



6. The likely cause of syncope:

a. AV block
b. VT
c. Postural hypotension
d. TIA

For correct answer see overleaf

ECG - 6

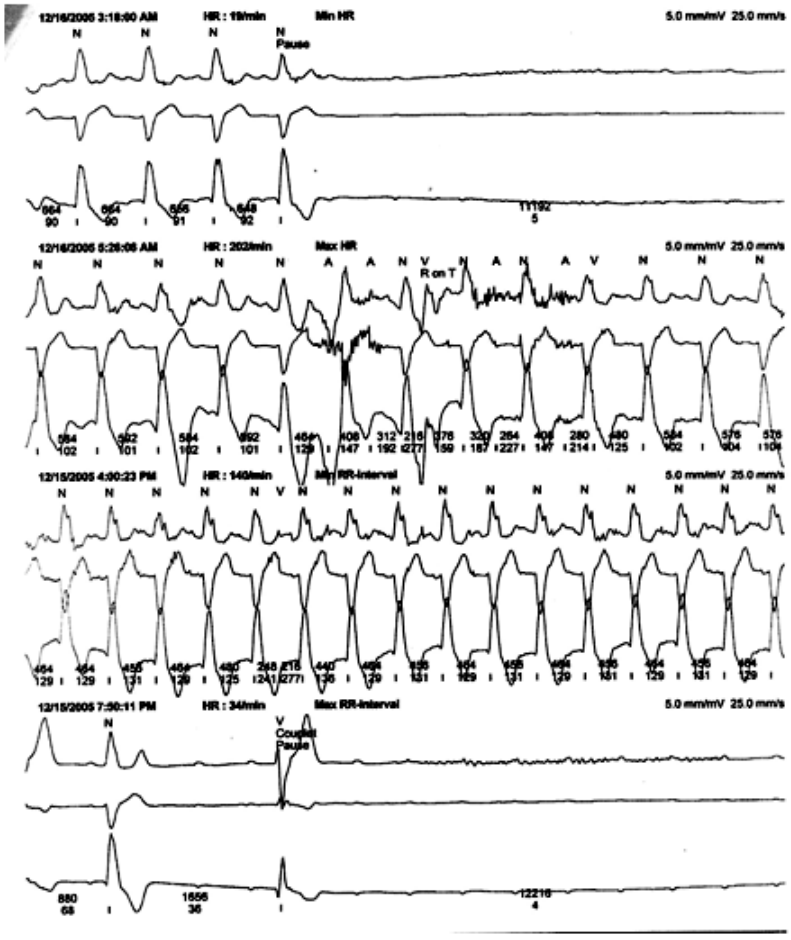
The correct answer is 'a' - AV block.

There are limited channels on this Holter recording. What is obvious is a wide QRS complex (presumably bundle branch block) and possibly a prolonged PR interval. In this setting, it is very important to know the state of the underlying heart and the circumstances preceding the syncope.

With underlying LV dysfunction and bundle branch block (especially LBBB); syncope is often due to VT. Orthostatic hypotension is easily verifiable from the history and examination.

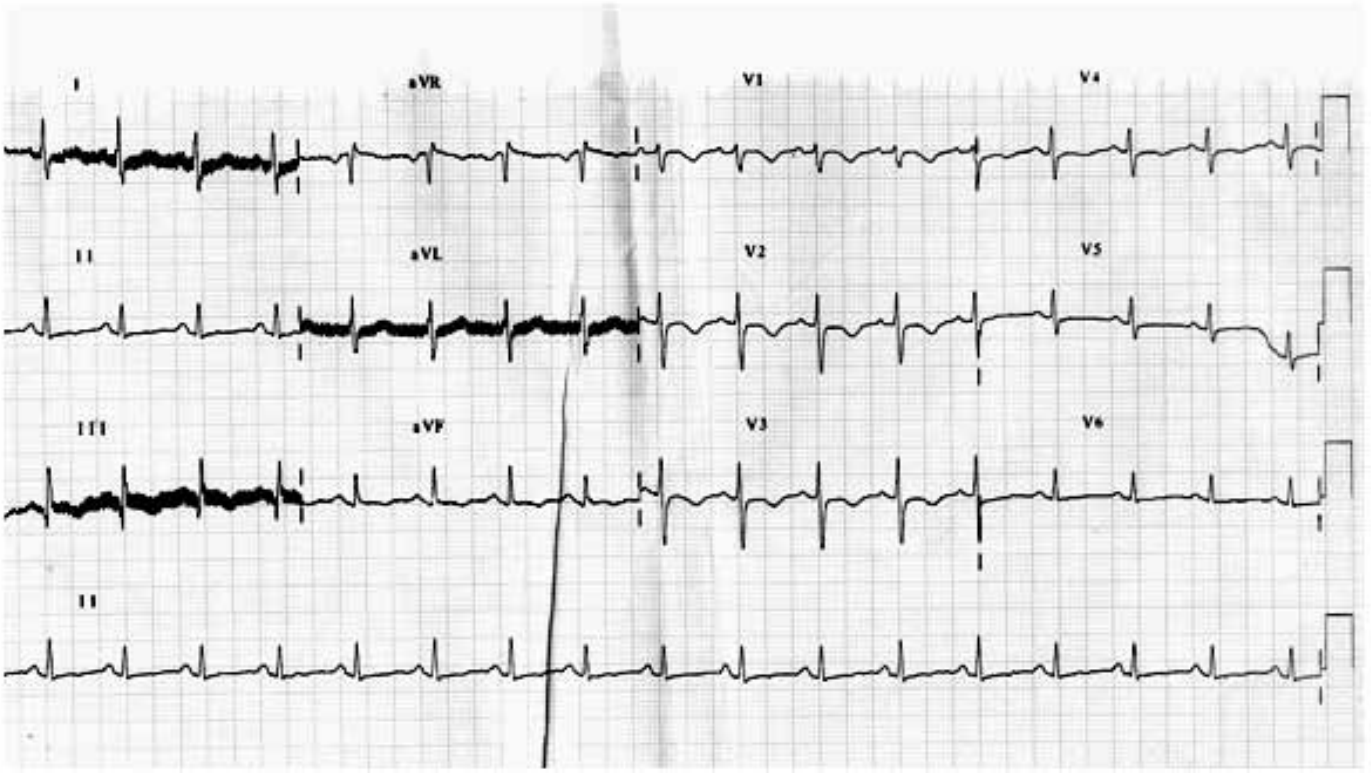
Assuming normal ventricular function, intermittent high-grade AV block as the cause of syncope is therefore the most likely option.

The next figure shows episodes of complete AV block with prolonged asystole during other times of the Holter recording.



ECG - 7

68 year old lady. Sudden chest uneasiness.



7. This ECG is consistent with:

a. Acute coronary ischemia
b. Acute pulmonary embolism
c. Non-specific T wave inversion
d. Any of the above

For correct answer see overleaf

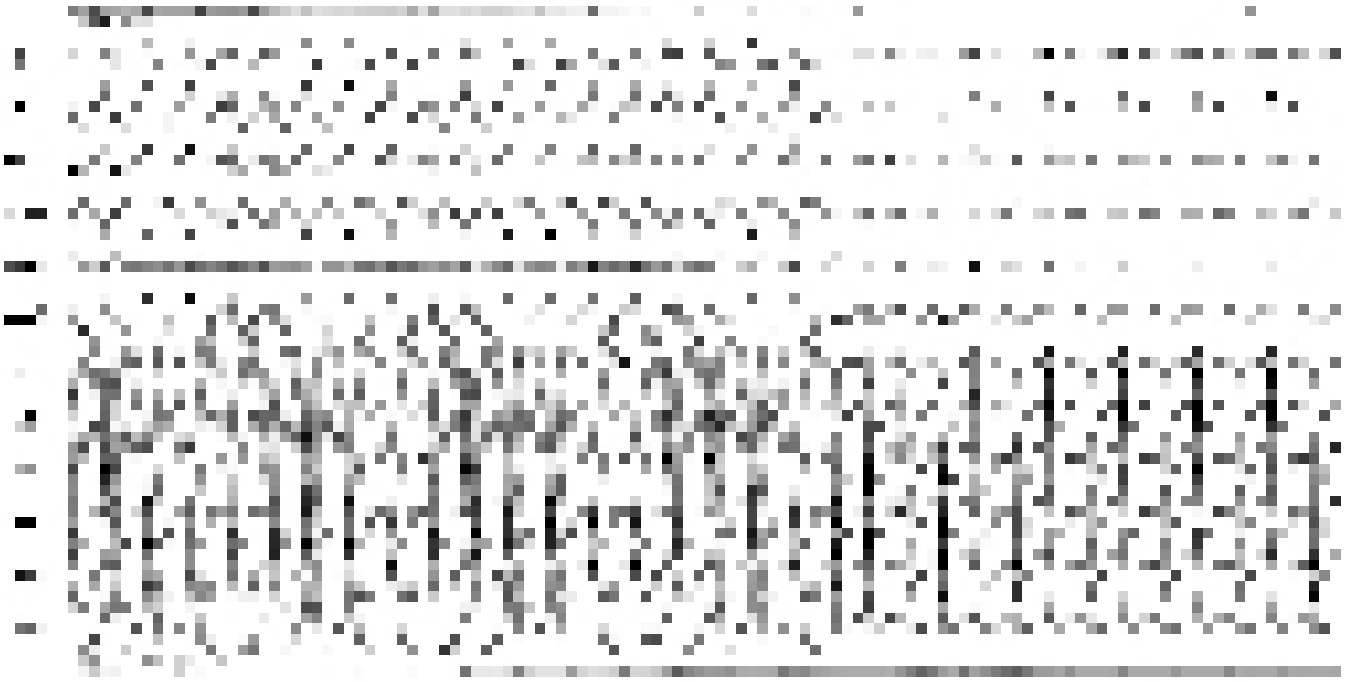
ECG - 7

The correct answer is 'b' – Acute pulmonary embolism.

The ECG shows Sinus Tachycardia and T inversion in V1, V2, and V3. There is also the S1Q3T3 pattern. These findings with the typical history of sudden onset symptoms indicate a high probability of acute pulmonary embolism. A simple confirmatory test would be the arterial oxygen saturation, which was 81% in this case by pulse oximetry. The patient had undergone knee replacement 1 week ago.

ECG - 8

24 yrs-old-man, c/o paroxysmal palpitations…



8. This tachycardia ECG shows:

a. VT & SVT
b. AVNRT with & without LBBB
c. AVRT with & without LBBB
d. Atrial flutter

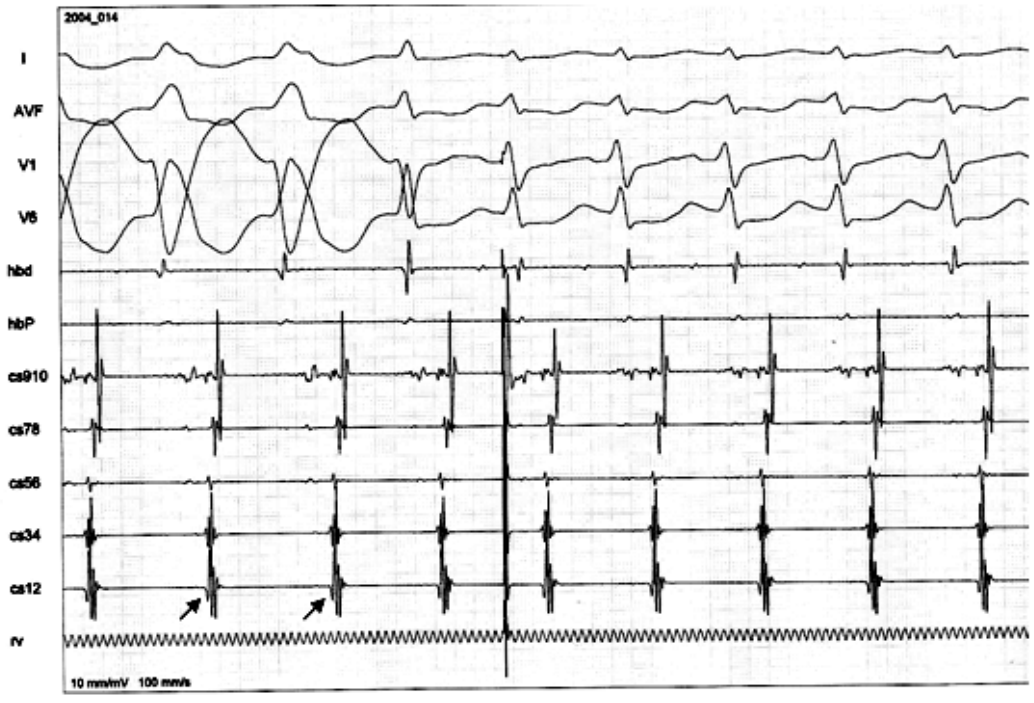
For correct answer see overleaf

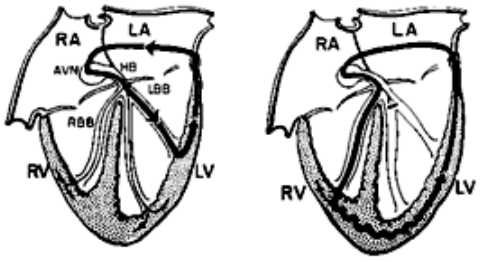
ECG - 8

The correct answer is 'c' – AVRT with and without LBBB.

The tachycardia is ***slower*** when there is LBBB. This clinches the diagnosis of an orthodromic AVRT using a left-sided accessory pathway as the retrograde limb.

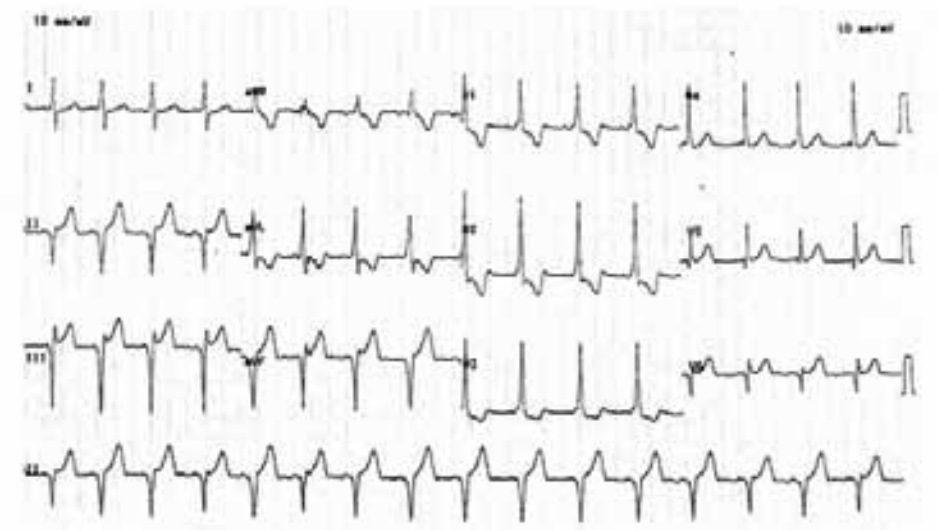
The intracardiac recordings (next figure) show the earliest retrograde atrial activation (arrows) in the channel cs12. This represents the left free wall. The schematic diagram explains why the tachycardia will be slower with LBBB, due to the longer circuit and the extra time taken for transseptal propagation of the impulse.



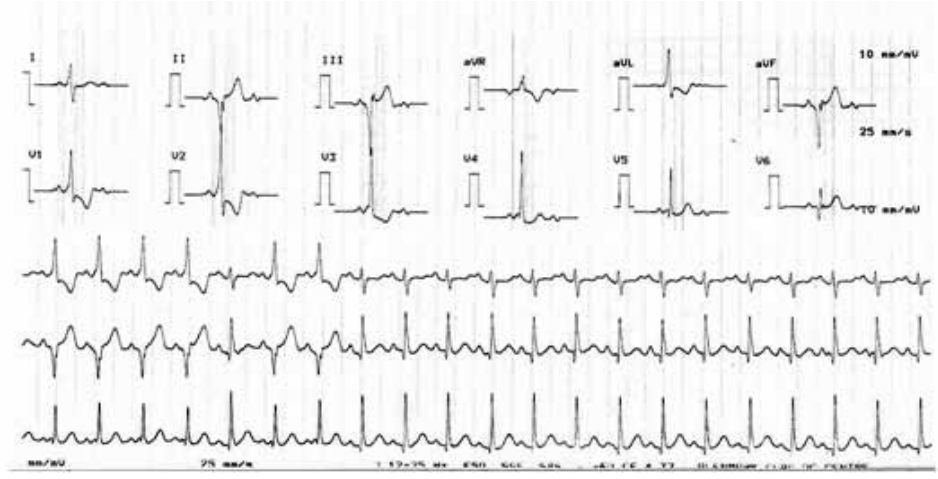


ECG - 9

6 yrs-old-girl, occasional brief lasting palpitations...



on treadmill exercise test….



9. This stress ECG shows:

a. Resolution of BBB
b. Disappearance of preexcitation
c. Intermittent PVCs
d. Don't know

For correct answer see overleaf

ECG - 9

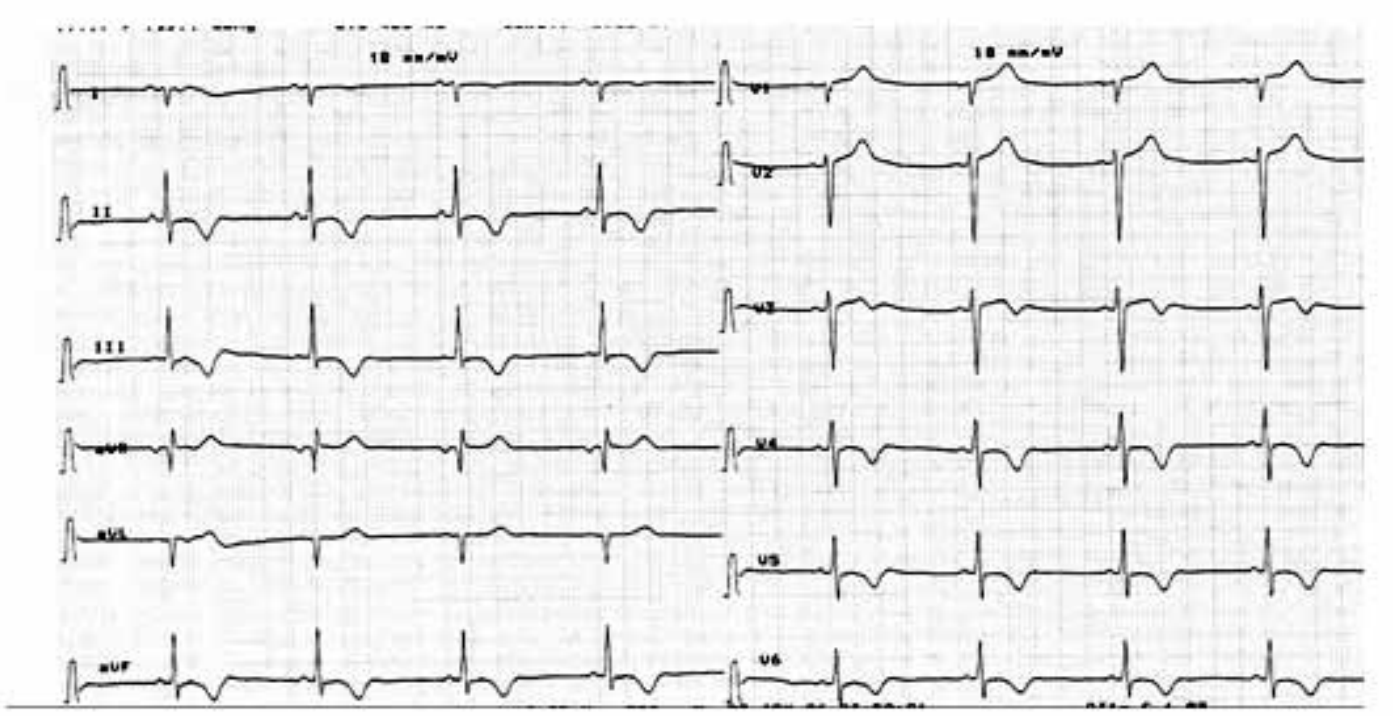
The correct answer is 'b' – Disappearance of preexcitation.

The first ECG shows short PR with QRS widening and delta wave. The delta waves are producing the tall R in V1 and Q waves in II, III and aVF. These suggest a left sided (RBBB pattern in V1) and posterior (Q in II, III, aVF) pathway.

On exercise it is seen that as the rate accelerates the QRS becomes normal and delta disappears. This suggests a long refractory period of the accessory pathway and therefore the patient is at low risk for sudden cardiac death.

ECG - 10

20 year old boy, soon after a prolonged (8 hrs) episode of rapid palpitations



10. The inverted T waves suggest:

a. Ischemia
b. Memory sign of SVT
c. Juvenile T inversion
d. Memory sign of VT

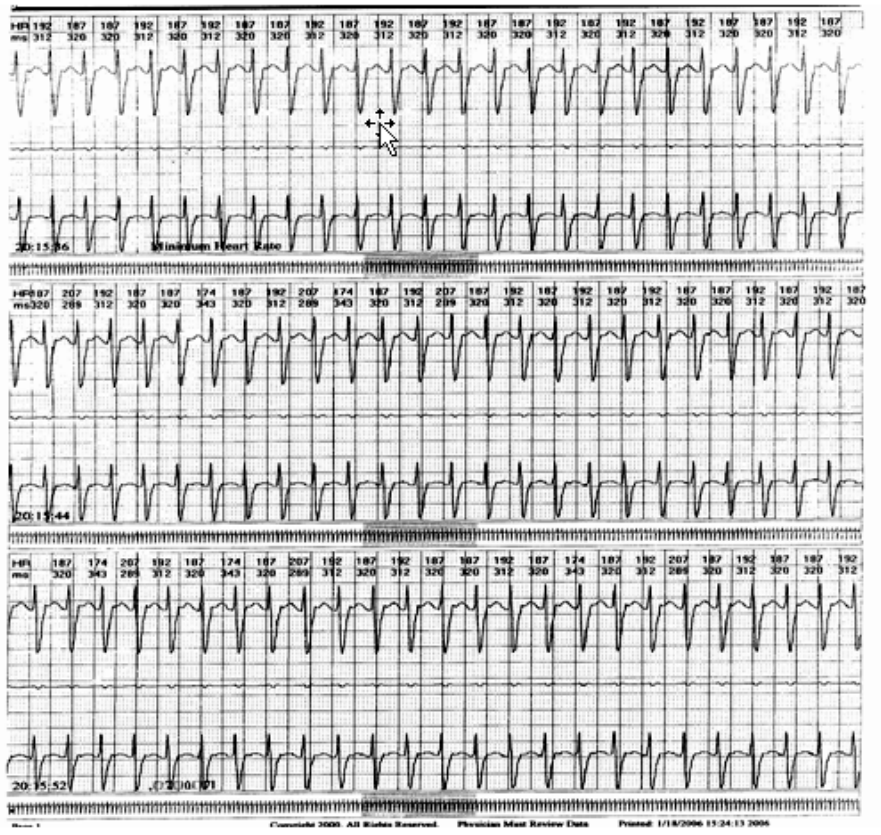
For correct answer see overleaf

ECG - 10

The correct answer is'd' – Memory sign of VT.

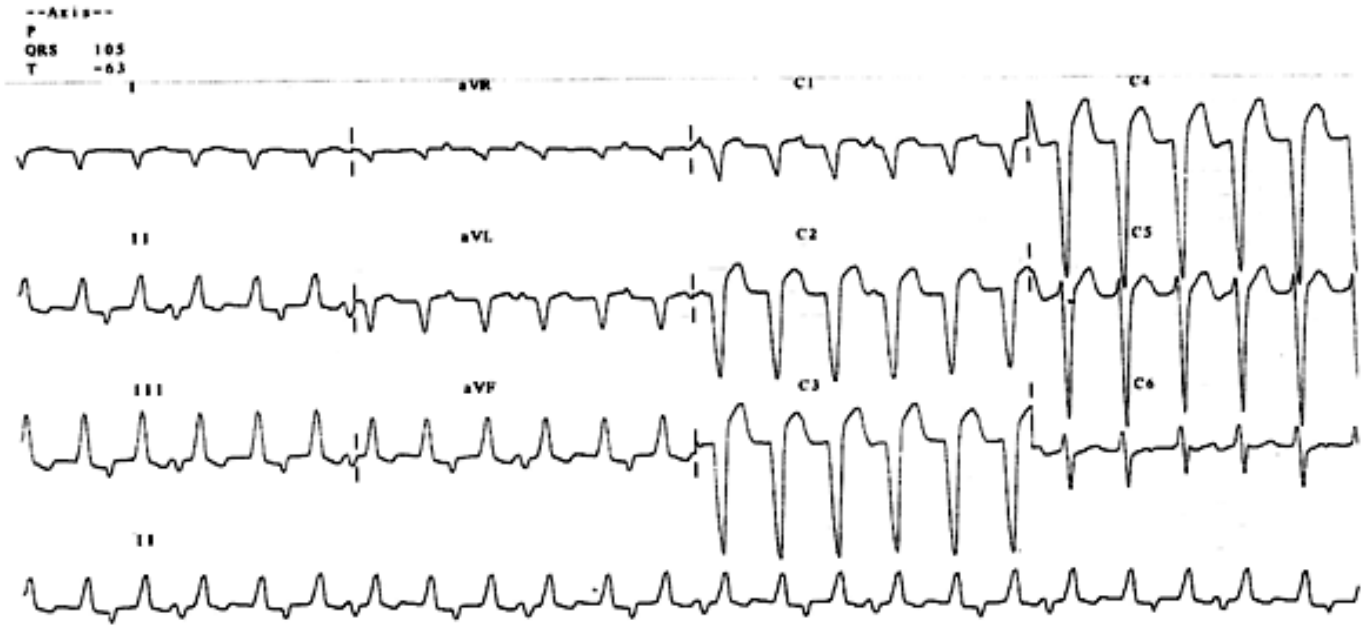
Since the patient is only 20 years old and had palpitations (no angina), there is no basis for ischemia. Juvenile T inversions are typically seen in leads V1-V4, unlike what is seen here.

After any wide QRS tachycardia, transient ST-T changes are seen, which are known as the "memory" sign. T inversions are seen in those leads where the QRS was negative during the tachycardia ***(the T is a memory of the QRS)***. Inferolateral T inversions in young people as a memory sign have been described for "fascicular VT'. This VT occurs in normal hearts and has a typical RBBB pattern with left axis deviation and R/S ratio less than I in the lateral leads. Hence, the T inversion in these leads. The next figure is a Holter recording during palpitations, showing the wide QRS tachycardia.



ECG - 11

40 yrs-old, paroxysmal palpitations….



11. This tachycardia shows:

a. SVT with aberrancy
b. VT with AV dissociation
c. VT with VA conduction
d. VT originating from the LV.

For correct answer see overleaf

ECG - 11

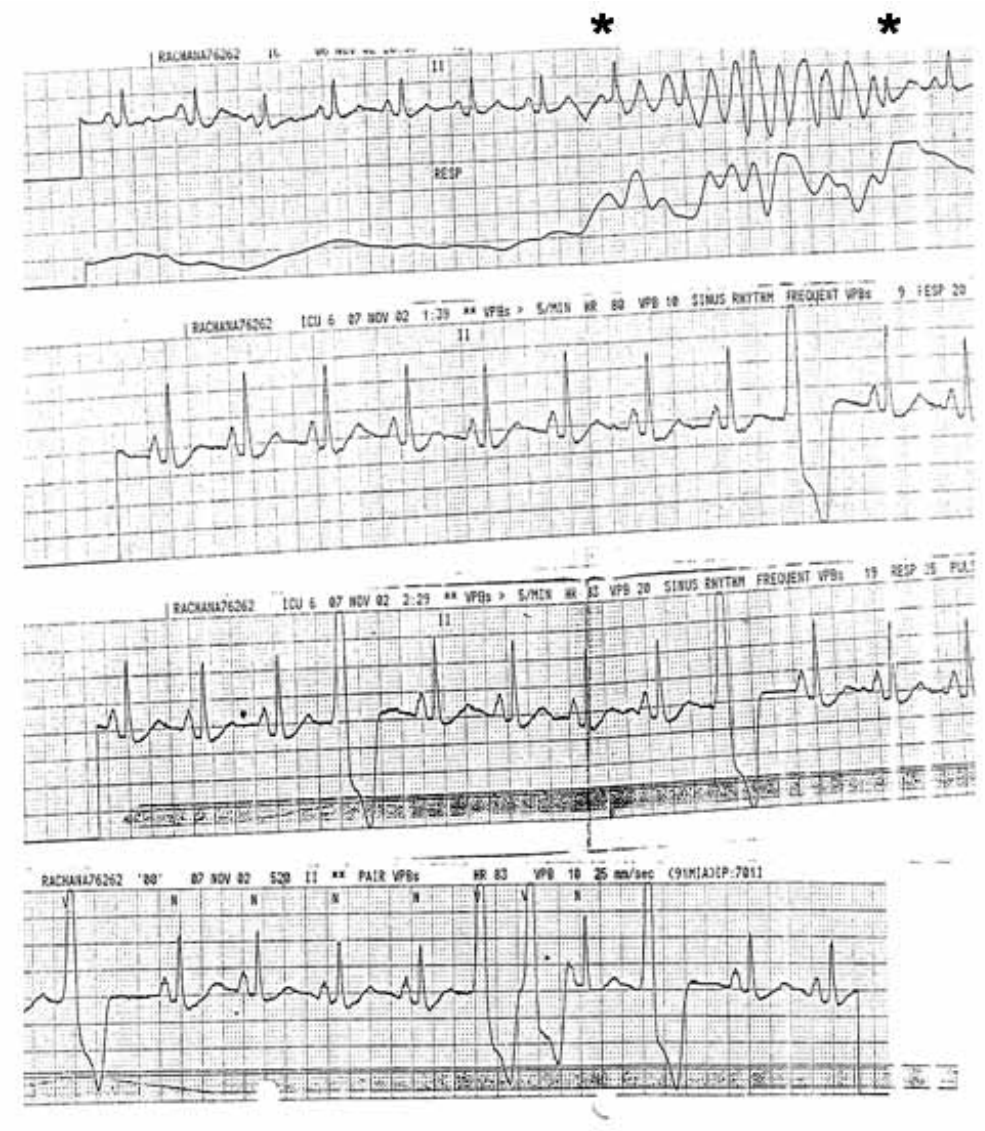
The correct answer is 'c' – VT with VA conduction.

There are more QRS complexes than P waves- this is the strongest reason for diagnosing this as VT. The QRS downstroke in V1 is gradual (contrast with Cases 3 and 8), also consistent with VT. The term AV dissociation implies a separate pacemaker for the atria and the ventricles. This is not the case here.

In long lead II, one can see that every 3rd QRS complex is not followed by a P wave. The P waves are inverted in lead II, with an increase in the R-P time prior to the VA block. This is diagnostic of VT with VA Wenckebach.

ECG - 12

60 yrs-old, post-op. monitoring following Intestinal surgery



12. The monitoring lead shows:

a. PVCs with monomorphic VT
b. PVCs with polymorphic VT
c. Intermittent AF with PVCs
d. None of the above

For correct answer see overleaf

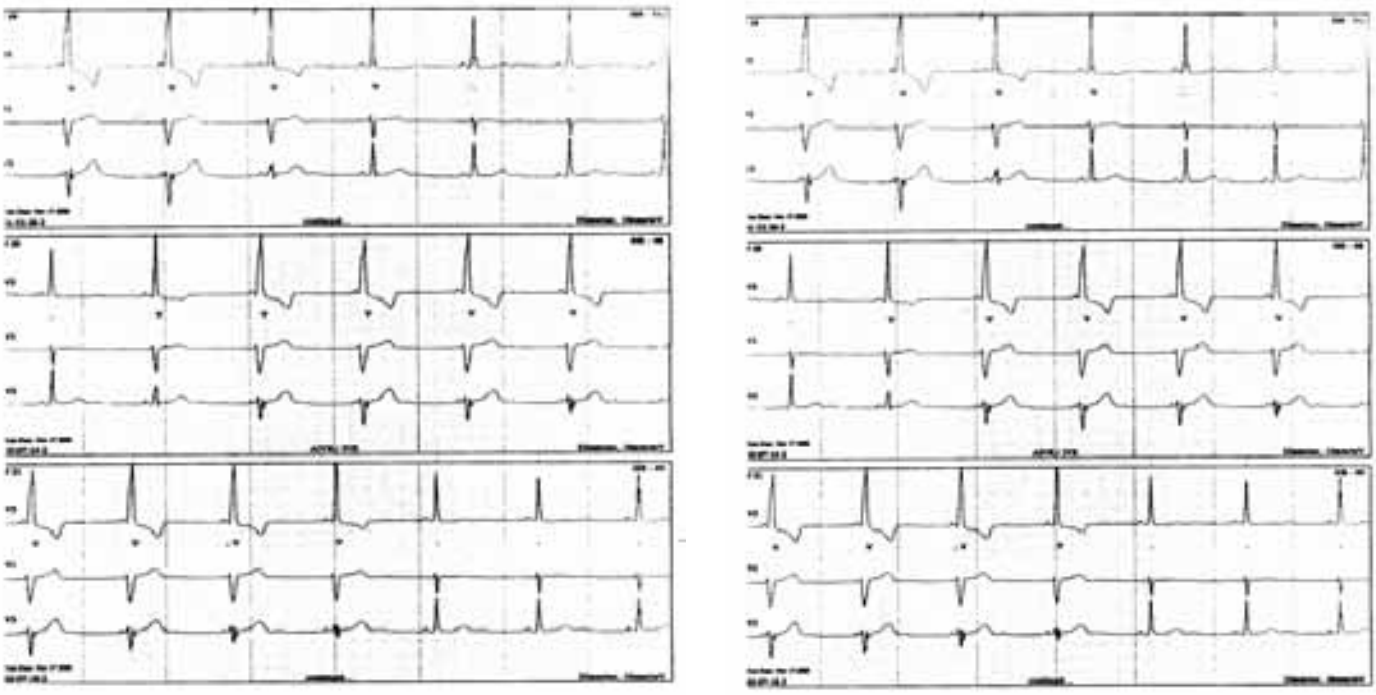
ECG - 12

The correct answer is'd' – none of the above.

The lower 3 strips show unifocal PVCs and a couplet. The top strips show a transient bizarre pattern, in the ECG ***as well as in the respiration monitor***. This suggests an artifact, which is confirmed by careful observation. The RR interval between the 2 QRS complexes marked by asterisks (*) is exactly equal to 4 RR intervals.

ECG - 13

54 year old lady Occasional palpitations



13. This Holter shows:

a. AV block
b. Ventricular escape rhythm
c. Intermittent BBB
d. Intermittent preexcitation

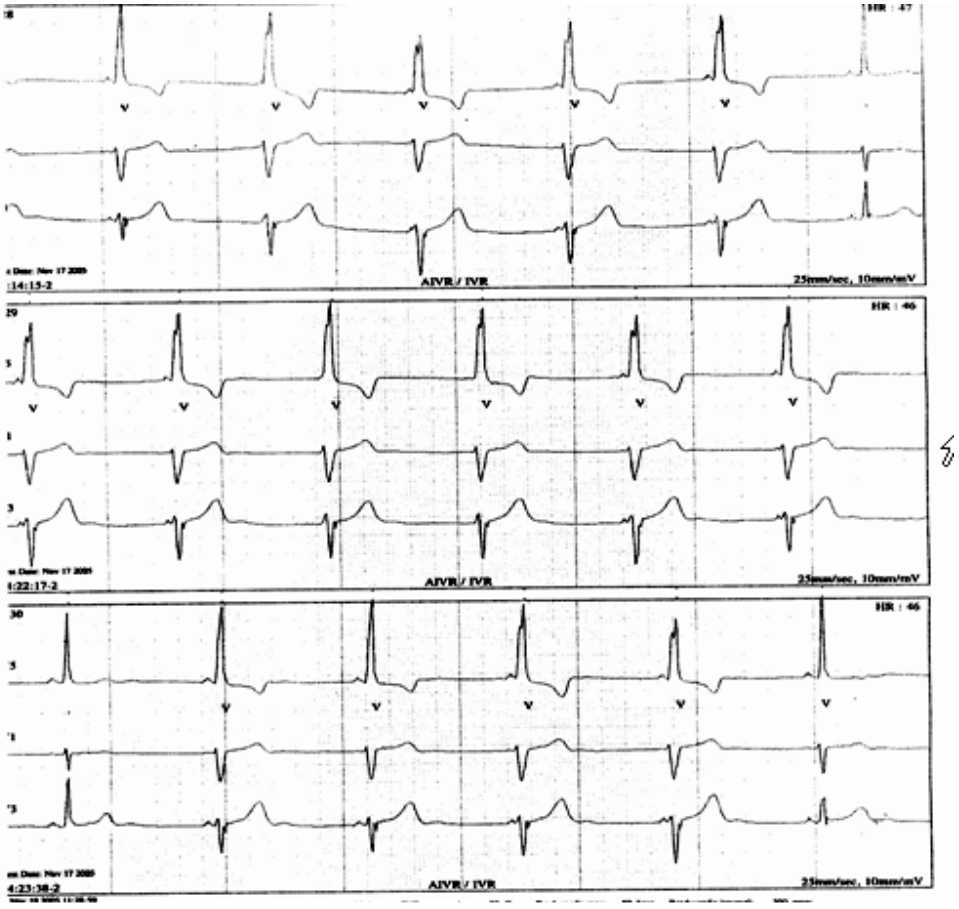
For correct answer see overleaf

ECG - 13

The correct answer is 'b' – Ventricular escape rhythm.

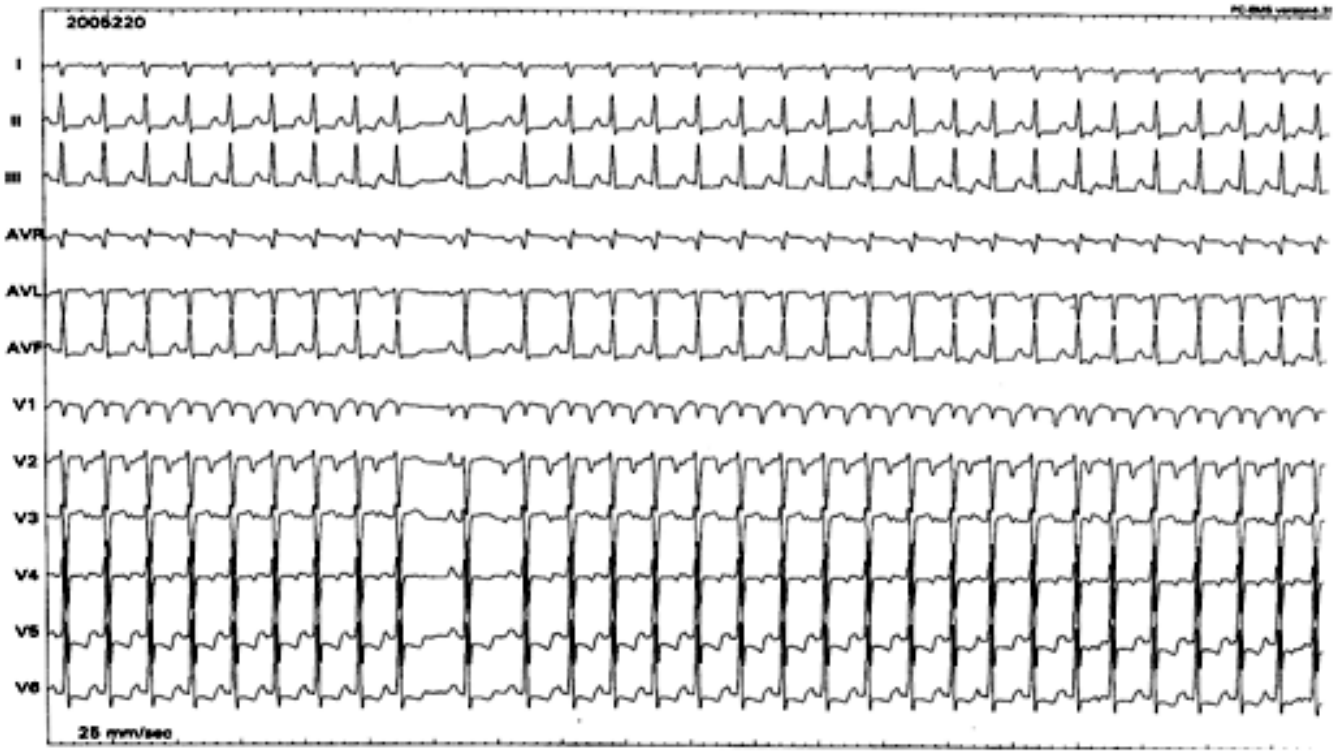
Note the timing of these Holter recordings- all are in the late night/early morning, during sleep ***(even though this patient was a Mumbaikar!)***. Hence the bradycardia is physiological. The sinus bradycardia is associated with varying QRS morphologies; 4 different such morphologies are seen in the top panel. The first complex in the top and bottom panels suggests the P wave "walking into" the QRS complex. This suggests an escape idioventricular rhythm, competing with the slow sinus rate.

The next figure confirms this. The 3rd and 4th QRS complexes in the middle panel are not preceded by P waves.



ECG - 14

8 yrs-old girl, few months of dyspnea & easy fatigue in CHF.



14. This ECG shows:

a. Sinus tachycardia
b. Atrial tachycardia
c. Atrial flutter
d. Atrial fibrillation

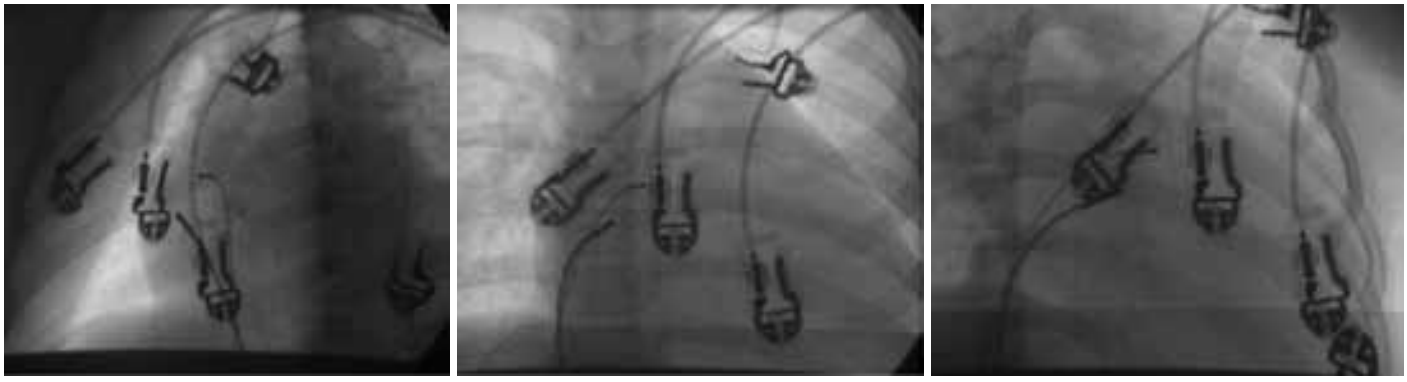
For correct answer see overleaf

ECG - 14

The correct answer is 'b'- atrial tachycardia.

There is a regular narrow QRS tachycardia which terminates just for 1 beat. Lead V1 is misleading during tachycardia, since the P waves here are **more prominent** than the QRS complexes! The abrupt termination and re-initiation of tachycardia suggest a re-entrant mechanism- sinus tachycardia does not behave like this. Also, the P wave during the sinus beat (10^{th} complex) is markedly different from that during tachycardia.

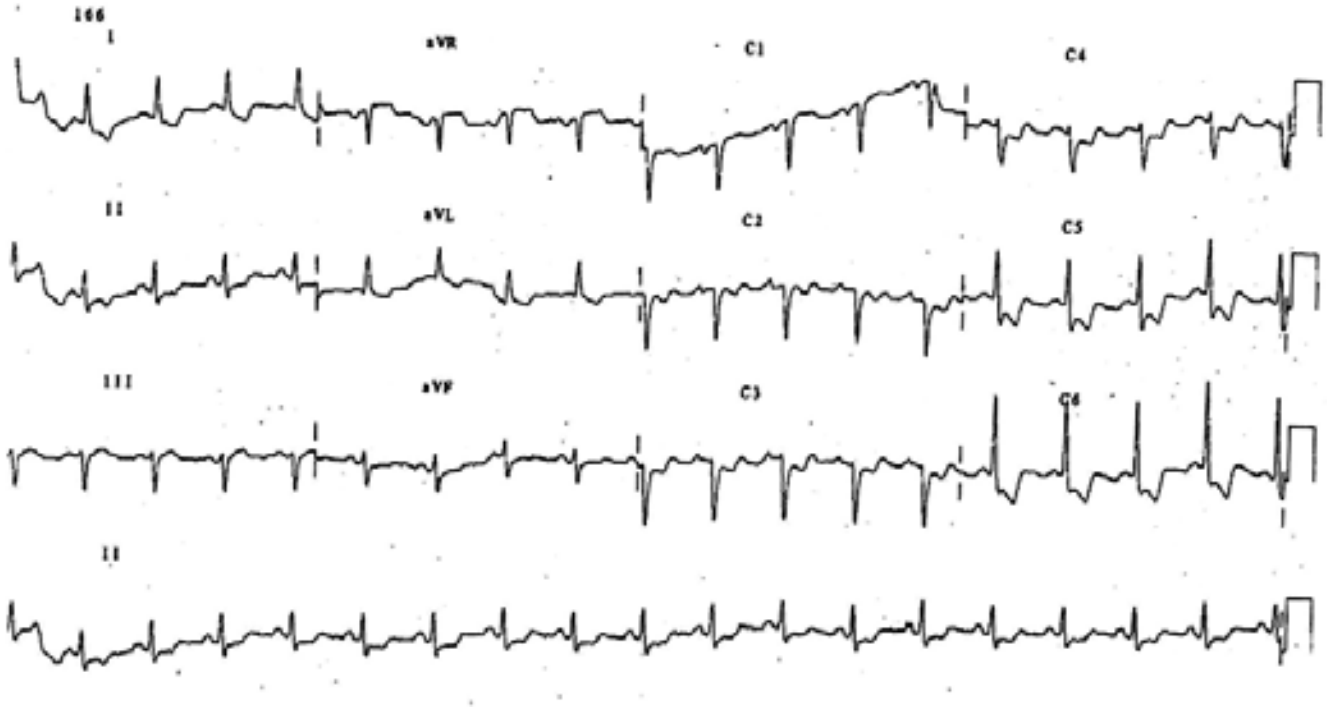
The negative P waves in leads V1-V3 during tachycardia are opposite in polarity to the sinus P wave and suggest origin more anteriorly than the sinus node. The next figure shows the site (arrow) where this tachycardia was found to originate, anteriorly and lower in the RA than the sinus node. A single RF energy here eliminated tachycardia.



40^{o} LAO PA 30^{o} RAO

ECG - 15

72 yr-old, with acute dyspnea & sweating



15. This ECG suggests:

a. Multi-vessel disease
b. Myocarditis
c. Single vessel disease
d. Pulmonary embolism

For correct answer see overleaf

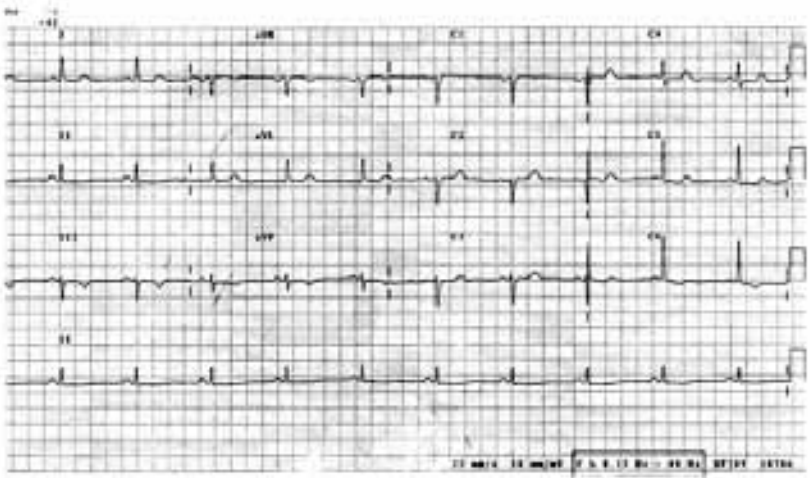
ECG - 15

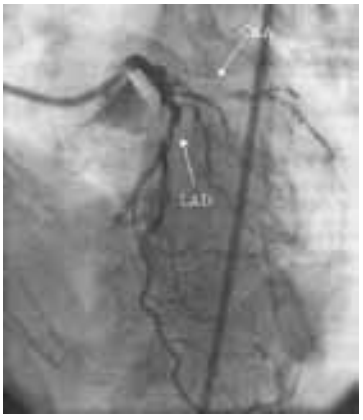
The correct answer is 'a' – Multivessel disease.

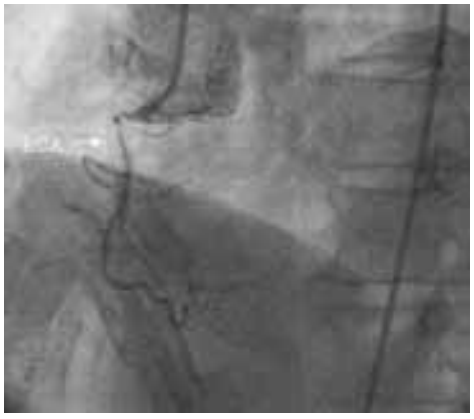
There are widespread ST depressions, horizontal/downsloping in nature. Lead aVR shows ST elevation, the there is some coving of the ST segment in lead V1 as well.

In elderly ladies, sudden dyspnea is a well recognized symptom of ischemia and is called "angina equivalent". Especially with sweating and the ECG changes, the diagnosis of acute, severe ischemia (as with multivessel disease) becomes paramount. The ECG changes reverse as ischemia settles, as seen in the next figure. The coronary angiography (last figure) confirmed the critical triple vessel disease. The patient recovered well after bypass surgery.

After symptoms settled with nitroglycerine







Review Article

Atrial Fibrillation and Hyperthyroidism

This paper has also been published in the ISHNE AF World-Wide Internet Symposium

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ABSTRACT

Atrial fibrillation occurs in 10 – 15% of patients with hyperthyroidism. Low serum thyrotropin concentration is an independent risk factor for atrial fibrillation. Thyroid hormone contributes to arrythmogenic activity by altering the electrophysiological characteristics of atrial myocytes by shortening the action potential duration, enhancing automaticity and triggered activity in the pulmonary vein cardio myocytes. Hyperthyroidism results in excess mortality from increased incidence of circulatory diseases and dysrhythmias. Incidence of cerebral embolism is more in hyperthyroid patients with atrial fibrillation, especially in the elderly and anticoagulation is indicated in them. Treatment of hyperthyroidism results in conversion to sinus rhythm in up to two-third of patients. Beta-blockers reduce left ventricular hypertrophy and atrial and ventricular arrhythmias in patients with hyperthyroidism. Treatment of sub clinical hyperthyroidism is controversial. Optimizing dose of thyroxine treatment in those with replacement therapy and beta-blockers is useful in exogenous subclinical hyperthyroidism.

Key words : Atrial fibrillation; hyperthyroidism; embolism

Introduction

Atrial fibrillation is the most common cardiac arrhythmia other than sinus tachycardia encountered in hyperthyroidism. Atrial fibrillation occurs in 10-15% of patients with hyperthyroidism[1]. It may be the presenting problem in some of them. Higher prevalence occurs in elderly and in those with other coexisting risk factors for atrial fibrillation. Low serum thyroid stimulating hormone is an independent risk factor for development of atrial fibrillation[2]. Atrial fibrillation in thyrotoxicosis is associated with significant mortality and morbidity resulting from embolic events[3].

Thyroid hormones exert their cardiovascular effects either directly through nuclear thyroid receptors or indirectly by influencing sympathoadrenergic system and altering peripheral vascular resistance. Binding of thyroid hormones to nuclear receptors result in increased gene transcription of cardiac myocyte proteins[4]. Thyroid hormones upregulate sarcoplasmic Calcium ATPase, myosin heavy chain alfa, voltage gated K+ channels, Na+ channels and beta1 adrenergic receptors[5-8]. These effects result in increased heart rate, systolic hypertension, increased ventricular contractility and cardiac hypertrophy. Changes in electrophysiological characteristics of atria result in dysrhythmias, especially atrial fibrillation, in patients with hyperthyroidism[9]. Thyroid hormones reduce peripheral vascular resistance[10] and increase oxygen demand of tissues, thus increasing cardiac workload.

Epidemiology

Sinus tachycardia is the most common arrhythmia in hyperthyroidism[11]. Atrial fibrillation is reported in 10 – 15% of patients with hyperthyroidism. Prevalence increases with age. In the study by Agner T et al, 25% of hyperthyroid patients older than 60 years had atrial fibrillation compared to 5% in patients less than 60 years of age[12]. Patients with toxic nodular goiter had an increased incidence of atrial fibrillation compared to younger patients with Grave's disease, probably due to their increased age. (43% versus 10%). Iwasaki T et al reported that 21% of patients with Grave's disease had atrial fibrillation with significant difference between those above and below 40 years of age (31% versus 0%)[13]. In a large study by Krahn et al, overt hyperthyroidism accounted for <1% of cases of new onset atrial fibrillation. According to these investigators, although serum thyrotropin should be measured in all patients with new onset atrial fibrillation to rule out hyperthyroidism, this association is rather uncommon in the absence of additional symptoms and signs of hyperthyroidism[14]. However, 13% of patients with unexplained atrial fibrillation, had biochemical evidence of hyperthyroidism in another report[2].

Lars Frost et al identified that among 40,628 patients with hyperthyroidism from Danish National Registry over a 20 year period, 8.3% had atrial fibrillation or flutter within 30 days from the date of diagnosis. The risk factors for atrial fibrillation in patients with hyperthyroidism were similar to those in general population like age, male sex, ischemic heart disease, congestive heart failure and valvular heart disease[15]. Hyperthyroidism was associated with excess mortality compared to general

population in a cohort of 7209 hyperthyroid subjects, treated with radio iodine. Excess mortality was due to circulatory diseases. Both cardiovascular (Standardized mortality ratio 1.2, 95% CI 1.2 to 1.3; p <0.001) and cerebrovascular (Standardized mortality ratio 1.4, 95% CI 1.2 to 1.5, p <0.001) mortality rates were high in hyperthyroid subjects. The Standardized mortality ratio for dysrhythmia including atrial fibrillation was 1.8 (95% CI 1.5 to 1.9, p value <0.001)[16]. In another study, 1762 hyperthyroid women treated with radio iodine were followed for more than 14 years and there was increased mortality from cardiovascular disease[17]. Cardiac arrhythmias, of which atrial fibrillation is most frequent contribute to excess mortality from cardiovascular and cerebrovascular events by inducing heart failure and predisposing to embolic events.

Subclinical Hyperthyroidism and Atrial Fibrillation

Sub clinical hyperthyroidism is defined as low serum thyrotropin concentration in an asymptomatic patient with normal serum T3 and T4 concentration. It has a prevalence of 0.5% to 3.9% in adults[18] and 11.8% in elderly[19].

Auer J et al, studied 23,638 persons and found that atrial fibrillation occurred in 13.8% patients with overt hyperthyroidism and 12.7% patients with sub clinical hyperthyroidism, compared to 2.3% in euthyroid. The prevalence of atrial fibrillation in patients with low serum thyrotropin concentration was 13.3% compared to 2.3% in persons with normal values. The relative risk of atrial fibrillation in subjects with low serum thyrotropin and normal free T3,T4 values compared to those with normal serum thyrotropin was 5.2. Thus low serum thyrotropin concentration is associated with >5 fold higher likelihood for atrial fibrillation with no significant difference between overt and subclinical hyperthyroidism[20]. Clark T Sawin et al followed 2007 patients from the original cohort of Framingham Heart Study, who were older than 60 years, for 10 years, for development of atrial fibrillation. Subjects with low thyrotropin (<0.1 mU/L) had 28% incidence of atrial fibrillation, compared with 11% in normal subjects. The relative risk for development of atrial fibrillation in patients with low thyrotropin was 3.1[1].

The subjects who had slightly low serum thyrotropin concentrations (0.1 to 0.4mU/L) also had higher risk than those with normal concentrations (relative risk 1.6; p=0.05)

Subclinical hyperthyroidism can be endogenous as occurring in Grave's disease, multinodular goiter or autonomous toxic nodules or exogenous due to thyroxine therapy. Exogenous subclinical hyperthyroidism is the most common cause of subclinical hyperthyroidism[21]. Subclinical hyperthyroidism is also associated with increased cardiovascular morbidity and mortality. 1191 subjects aged over 60 years, when followed up for 10 years, those with low serum thyrotropin (<0.5 mU/L) had higher mortality compared to control population. This excess mortality resulted mainly from circulatory diseases and supraventricular arrhythmias including atrial fibrillation also contributed[22].

Pathogenesis

Effects of thyroid hormones on ion currents of atrial myocytes contribute to genesis of atrial fibrillation. Hyperthyroidism is associated with shortening of action potential duration (APD) resulting in a substrate for atrial fibrillation . A study on the effects of thyroid hormones on mRNA expression and currents of major ionic channels in murine atrium showed that T3 increased expression of the Kv1.5 mRNA and decreased L-type Calcium channel mRNA expression. Action potential duration was shorter in hyperthyroid than in euthyroid myocytes. The ultra-rapid delayed rectifier potassium currents were considerably increased in hyperthyroid than in euthyroid myocytes, whereas the transient outward potassium currents were unchanged. L-type calcium currents were decreased in hyperthyroid than in euthyroid myocytes. T3 increased the outward currents and decreased the inward currents resulting in reduced action potential duration[23]. In another study action potential duration and whole cell currents were studied in myocytes from left and right atria from control and hyperthyroid mice. Hyperthyroidism resulted in more significant APD shortening and greater delayed rectifier potassium current increases in the right atrium than in the left atrium which can contribute to the propensity for atrial arrhythmias[24]. Studies using rabbit pulmonary vein cardiomyocytes have shown that thyroid hormone decreases the APD in pulmonary vein cardiomyocytes which can facilitate the genesis of reentrant circuits. Incubation with thyroid hormone also increased spontaneous activity in the pulmonary vein cardiomyocytes similar to the effect on sinoatrial node cells. Thyroid hormone increased the occurrence of delayed after-depolarisation in pulmonary vein beating and non-beating cardiomyocytes. Incidence of early after-depolarisation was increased in beating cardiomyocytes following incubation with thyroid hormone. Thus thyroid hormone may induce the occurrence of paroxysmal atrial fibrillation through the increase of triggered activity or automaticity in pulmonary veins[25].

ECG may be helpful in identifying hyperthyroid subjects at risk for developing atrial fibrillation. Maximum P wave duration and P wave dispersion were higher in both subclinical and overt hyperthyroidism. P maximum and P wave dispersion were significant predictors of paroxysmal atrial fibrillation[26].

Thyroid hormone potentiates the effect of adrenergic system on heart. Catecholamine levels are either normal or decreased in thyrotoxicosis. Facilitation of action of catecholamines is by increasing tissue sensitivity by increased transcription of beta adrenergic receptors[27] and structural similarity to catecholamines[28]. Hyperthyroidism is associated with reduced vagal activity and reduced heart rate variability which can persist despite restoration of euthyroidism[29].

Embolic Events and Anticoagulation

Thyrotoxicosis is complicated by thromboembolism in approximately 15% of cases[3]. In a retrospective study of 610

patients with hyperthyroidism the risk of cerebrovascular events was greater in those with atrial fibrillation. 15% had atrial fibrillation with the highest frequency in elderly patients. A total of 27 (4.4%) cerebrovascular events occurred, 13% in those having atrial fibrillation and 3% in those with sinus rhythm. Advanced age rather than the presence of atrial fibrillation was the important risk factor for embolism. From this study the indication for prophylactic anticoagulation is doubtful in hyperthyroid patients with atrial fibrillation[30]. In younger patients with hyperthyroidism and atrial fibrillation who do not have other heart disease, hypertension or other risk factors for embolism, the risk of anticoagulant therapy probably outweighs the benefit[31]. The risk of embolism in thyrotoxic atrial fibrillation exceeds that of lone atrial fibrillation. The majority of clinically evident emboli in patients with hyperthyroidism and atrial fibrillation involves central nervous system and occur early in the course of the disease[32]. Elderly patients with thyrotoxicosis and atrial fibrillation and those with other risk factors for thromboembolism have significantly increased risk for arterial thromboembolism and anticoagulant treatment is indicated. Elderly patients are particularly at risk for hemorrhagic complications and hence close monitoring of prothrombin time is required in elderly patients on warfarin. Antiplatelet agents like aspirin may afford some protection against cardioembolic stroke in patients with atrial fibrillation, although these are more effectively prevented by anticoagulation[33].

Treatment

Mainstay of treatment in patients with atrial fibrillation and hyperthyroidism is restoration of euthyroid status. This is by use of antithyroid drugs like carbimazole, propyl thiouracil or radio-iodine . Surgery of thyroid gland is done after achieving euthyroid status by drugs. Beta blockers like propranalol or atenolol are useful in thyrotoxic atrial fibrillation to reduce heart rate and cardiac failure[34,35]. Restoration of euthyroid status is frequently associated with conversion to sinus rhythm . In a study of 163 patients with thyrotoxicosis and atrial fibrillation, 62% were in sinus rhythm within 8-10 weeks after achieving euthyroid state[36]. After 3 months only few will revert spontaneously to sinus rhythm. Electrical or pharmacologic cardioversion may be attempted in patients remaining in atrial fibrillation after achieving euthyroid status. Rate of reversion to sinus rhythm is less in older patients and in those with longer duration of atrial fibrillation and structural heart disease. In another study, of the 256 patients who underwent surgery for thyrotoxicosis 23% had preoperative atrial fibrillation. After surgery 47% of them reverted to sinus rhythm and the rest had better responsiveness to antiarrhythmic drugs. Restoration of sinus rhythm occurred mostly in patients younger than 50 years while in older patients atrial fibrillation persisted[37].

Treatment of subclinical hyperthyroidism is controversial. Some authors advocate careful follow up of these patients for development of overt hypothyroidism, cardiac dysrhythmias and other circulatory complications[38]. But others have suggested routine treatment for subclinical hyperthyroidism as it is associated with adverse cardiac events. Antithyroid drugs or radio-iodine may be useful especially in those with nodular goiter and cardiac risk factors[39]. Treatment of subclinical hyperthyroidism with antithyroid drugs was shown to reduce left ventricular mass index, heart rate, atrial and ventricular premature beats and atrial fibrillation. Many patients in this group with subclinical hyperthyroidism had symptoms, high Wayne clinical index and echocardiographic abnormalities which reduced with treatment[40]. Biondi et al observed that treatment with selective beta1 blocker bisoprolol reduces left ventricular mass index and atrial arrhythmias in patients taking long term thyrotropin suppressive therapy with thyroxine[41]. Dosage of thyroxine in patients receiving replacement therapy should be adjusted to a normal and not suppressed thyrotropin level[42].

Conclusion

Atrial fibrillation is a major cause of morbidity and mortality in overt as well as subclinical hyperthyroidism. It is associated with cerebral embolic events, especially in elderly and those with co-morbid risk factors. Treatment with anti-thyroid drugs and beta-blockers is indicated in most of the cases.

References

1. Sawin CT, Geller A, Wolf P, Belanger A, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'agostino RB . Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med.1994; 331:1249–1252.
2. Forfar JC, Miller HC, Toft AD. Occult thyrotoxicosis: a reversible cause of "idiopathic" atrial fibrillation. Am J Cardiol. 1979;44:9-12.
3. Staffurth JS, Gibberd JS, Tang FS. Arterial embolism in thyrotoxicosis with atrial fibrillation. Br Med J.1977; 2:688–690.
4. Lazar MA . Thyroid hormone receptors: multiple forms, multiple possibilities. Endocr Rev . 1993;24:184–193.
5. Rohrer D, Dillmann WH. Thyroid hormone markedly increases the mRNA coding for sarcoplasmic reticulum Ca2+-ATPase in the rat heart. J Biol Chem.1988; 263:6941–6944.
6. Arai M, Otsu K, MacLennan DH, Alpert NR, Periasamy M Effect of thyroid hormone on the expression of mRNA encoding sarcoplasmic reticulum proteins. Circ Res.1991; 69:266–276.
7. Dudley SC, Baumgarten CM. Bursting of cardiac sodium channels after acute exposure to 3,5,3_-triiodo-L-thyronine. Circ Res. 1993; 73:301–313.
8. Shimoni Y, Severson DL.Thyroid status and potassium currents in rat ventricular myocytes. Am J Physiol.1995; 268:H576–H583.
9. Klein I, Ojamaa K .Thyroid hormone and the cardiovascular system. N Engl J Med . 2001;344:501–509.
10. Ojamaa K, Klemperer JD, Klein I . Acute effects of thyroid hormone on vascular smooth muscle. Thyroid.1996; 6:505–512.
11. Polikar R, Feld GK, Dittrich HC, Smith J, Nicod P .Effect of thyroid replacement therapy on the frequency of benign atrial and ventricular arrhythmias. J Am Coll Cardiol.1989; 14:999– 1002.

12. Agner T, Almdal T, Thorsteinsson B, Agner E . A reevaluation of atrial fibrillation in thyrotoxicosis. Dan Med Bull .1984;31:157–159.

13. Iwasaki T, Naka M, Hiramatsu K, Yamada T, Niwa A, Aizawa T, Murakami M, Ishihara M, Miyahara Y . Echocardiographic studies on the relationship between atrial fibrillation and atrial enlargement in patients with hyperthyroidism of Graves' disease. Cardiology.1989; 76:10–17.

14. Krahn AD, Klein GJ, Kerr CR, et al. How useful is thyroid function testing in patients with recent-onset atrial fibrillation? Arch Intern Med.1996;156:2221-4.

15. Lars Frost, Peter Vestergaard, Leif Mosekilde . Hyperthyroidism and Risk of Atrial Fibrillation or Flutter -A Population-Based Study. Arch Intern Med. 2004;164:1675-1678.

16. Franklyn J, Maisonneuve P, Sheppard M, Betteridge J, Boyle P . Mortality after treatment of hyperthyroidism with radioactive iodine. N Engl J Med. 1998; 338:712–718

17. Goldman MB, Maloof F, Monson RR, Aschengrau A, Cooper DS, Ridgway EC Radioactive iodine therapy and breast cancer. A follow-up study of hyperthyroid women. Am J Epidemiol.1988; 127:969–980.

18. Bagchi N, Brown T, Parish R . Thyroid dysfunction in adults over age 55 years. A study in an urban US community. Arch Intern Med .1990; 150:785–787.

19. Parle J, Franklyn J, Cross K, Jones C . Prevalence and follow-up of abnormal thyrotropin concentrations in the elderly in the United Kingdom. Clin Endocrinol .1991;34:77–83.

20. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. Am Heart J .2001;142:838–842.

21. Biondi B, Fazio S, Carella C, Amato G, Cittadini A, Lupoli G, et al. Cardiac effects of long term thyrotropin-suppressive therapy with levothyroxine. J Clin Endocrinol Metab. 1993;77:334-8.

22. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA Prediction of all cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Lancet.2001; 358:861–865.

23. Watanabe H, Ma M, Washizuka T, Komura S, Yoshida T, Hosaka Y, Hatada K, Chinushi M, Yamamoto T, Watanabe K, Aizawa Y. Thyroid hormone regulates mRNA expression and currents of ion channels in rat atrium. Biochem Biophys Res Commun. 2003;308(3):439-44.

24. Hu Y, Jones SV, Dillmann WH.Effects of Hyperthyroidism on Delayed Rectifier Potassium Currents in Left and Right Murine Atrium. Am J Physiol Heart Circ Physiol. 2005 ;May 13. [Epub ahead of print]

25. Yao-Chang Chen, Shih-Ann Chen, Yi-Jen Chen, Mau-Song Chang, Paul Chan,Cheng-I. Lin. Effects of thyroid hormone on the arrhythmogenic activity of pulmonary vein cardiomyocytes Effects of thyroid hormone on the arrhythmogenic activity of pulmonary vein cardiomyocytes J Am Coll Cardiol, 2002; 39:366-372.

26. Aras D, Maden O, Ozdemir O, Aras S, Topaloglu S, Yetkin E, Demir AD, Soylu MO, Erdogan MF, Kisacik HL, Korkmaz S. Simple electrocardiographic markers for the prediction of paroxysmal atrial fibrillation in hyperthyroidism . Int J Cardiol. 2005; 99(1):59-64.

27. Maciel B, Gallo L, Marin Neto J, Maciel L, Martins L . Autonomic control of heart rate during dynamic exercise in human hyperthyroidism. Clin Sci.1988; 75:209–215.

28. Dratman M, Goldman M, Crutchfield F, Gordon J . Nervous system role of iodocompounds in blood pressure regulation. Life Sci .1982;30:611–622.

29. Osman F, Daykin J, Sheppard M, Franklyn J, Gammage M. Cardiac rhythm abnormalities in thyrotoxicosis—the explanation for excess vascular mortality. J Endocrinol. 2000; 164:P321.

30. Petersen P, Hansen JM. Stroke in thyrotoxicosis with atrial fibrillation. Stroke 1988;19:15-8.

31. Presti C, Hart R. Thyrotoxicosis, atrial fibrillation, and embolism, revisited. Am Heart J.1989; 117:976–977.

32. Gilligan DM, Ellenbogen KA, Epstein AE. The management of atrial fibrillation. Am J Med 1996;101:413-21.

33. Miller V, Pearce L, Feinberg W, Rothrock J, Anderson D, Hart R . Differential effect of aspirin versus warfarin on clinical stroke types in patients with atrial fibrillation. Neurology.1996; 46:238–240.

34. Mintz G, Pizzarello R, Klein I. Enhanced left ventricular diastolic function in hyperthyroidism: noninvasive assessment and response to treatment. J Clin Endocrinol Metab . 1991;73:146-50.

35. Klein I, Becker DV, Levey GS. Treatment of hyperthyroid disease. Ann Intern Med 1994;121:281-8.

36. Nakazawa HK, Sakurai K, Hamada N, Momotani N, Ito K. Management of atrial fibrillation in the post-thyrotoxic state. Am J Med 1982;72: 903-6.

37. Fierro N, Gonnella C, Pietropaolo L, Morelli A, Di Cola G, D'Ermo G, Galassi G Jr, Galassi G. Atrial fibrillation and hyperthyroidism: results after thyroidectomy. G Chir. 2002;23(11-12): 431-3.

38. Koutras D . Subclinical hyperthyroidism. Thyroid .1999; 9:311–315

39. Toft AD. Clinical practice. Subclinical hyperthyroidism. N Engl J Med . 2001; 345:512–516.

40. Sgarbi JA, Villaca FG, Garbeline B, Villar HE, Romaldini JH. The effects of early antithyroid therapy for endogenous subclinical hyperthyroidism in clinical and heart abnormalities. J Clin Endocrinol Metab. 2003 Apr;88(4):1672-7.

41. Biondi B, Fazio S, Carella C, Sabatini D, Amato G, Cittadini A, Bellastella A, Lombardi G, Sacca L. Control of adrenergic overactivity by beta blockade improves quality of life in patients on long-term suppressive therapy with levothyroxine. J Clin Endocrinol Metab.1994; 78:1028– 1033.

42. Mercuro G, Panzuto MG, Bina A, Leo M, Cabula R, Petrini L, Pigliaru F, Mariotti S. Cardiac function, physical exercise capacity, and quality of life during long-term thyrotropin-suppressive therapy with levothyroxine: effect of individual dose tailoring. J Clin Endocrinol Metab .2000;85:159–164.

Review Article

The Postural Tachycardia Syndrome (POTS): Pathophysiology, Diagnosis & Management

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ABSTRACT

Postural tachycardia syndrome (POTS), characterized by orthostatic tachycardia in the absence of orthostatic hypotension, has been the focus of increasing clinical interest over the last 15 years 1. Patients with POTS complain of symptoms of tachycardia, exercise intolerance, lightheadedness, extreme fatigue, headache and mental clouding. Patients with POTS demonstrate a heart rate increase of ≥30 bpm with prolonged standing (5-30 minutes), often have high levels of upright plasma norepinephrine (reflecting sympathetic nervous system activation), and many patients have a low blood volume. POTS can be associated with a high degree of functional disability. Therapies aimed at correcting the hypovolemia and the autonomic imbalance may help relieve the severity of the symptoms. This review outlines the present understanding of the pathophysiology, diagnosis, and management of POTS.

Key Words: Postural Tachycardia Syndrome; Pathophysiology; Diagnosis; Management

Introduction

Postural tachycardia syndrome (POTS), characterized by orthostatic tachycardia in the absence of orthostatic hypotension, has been the focus of increasing clinical interest over the last 15 years[1]. Patients with POTS complain of symptoms of tachycardia, exercise intolerance, lightheadedness, extreme fatigue, headache and mental clouding. This disorder is not new[2], but has gone by many different names over the last 150 years, including mitral valve prolapse syndrome, neurocirculatory asthenia, orthostatic tachycardia, and orthostatic intolerance[3,4]. An advantage of the name postural tachycardia syndrome (POTS) is that it focuses attention on the sympathetic activation which characterizes the disorder. This review outlines the present understanding of the pathophysiology, diagnosis, and management of POTS.

Physiology of Upright Posture

Assumption of the upright posture requires prompt physiological adaptation to gravity. There is an instantaneous descent of ~500ml of blood from the thorax to the lower abdomen, buttocks, and legs. In addition, there is a 10-25% shift of plasma volume out of the vasculature and into the interstitial tissue[5]. This shift decreases venous return to the heart, resulting in a transient decline in both arterial pressure and cardiac filling. This has the effect of reducing the pressure on the baroreceptors, triggering a compensatory sympathetic activation that results in an increase in heart rate and systemic vasoconstriction (countering the initial decline in blood pressure). Hence, assumption of upright posture results in a 10-20 beat per minute increase in heart rate, a negligible change in systolic blood pressure, and a ~5 mmHg increase in diastolic blood pressure.

Pathophysiology of Orthostatic Dysregulation

Failure of the regulatory mechanism to respond properly may lead to either ***orthostatic hypotension***, as is seen in autonomic failure, or ***orthostatic tachycardia***, as is seen in POTS. Orthostatic hypotension is defined as a fall in pressure on standing of more than 20/10 mmHg. However, it is common in patients with autonomic failure for the decline to be much greater than this, which may result in loss of consciousness soon after standing. On the other hand, in POTS, blood pressure is typically maintained on standing or may even increase. Heart rate rises more than 30 bpm and symptoms reminiscent of impaired cerebral perfusion may develop.

Clinical Presentation of Postural Tachycardia Syndrome (POTS)

Diagnostic Criteria & Common Clinical Features

POTS is defined (**Table 1**) as the presence of symptoms of orthostatic intolerance for at least 6 months accompanied by a heart rate increase of at least 30 beats/min within 5-30 minutes of assuming an upright posture. This should occur in the absence of orthostatic hypotension (a fall in blood pressure >20/10 mmHg). The syndrome must occur in the absence of prolonged bed rest, medications that impair autonomic regulation (such as vasodilators, diuretics, antidepressants or anxiolytic agents), or any other chronic debilitating disorders that might cause tachycardia (such as dehydration, anemia or hyperthyroidism).

It is important to recognize that this syndrome is typically disabling. Hence, the mere observation of orthostatic tachycardia is not, by itself, sufficient to make the diagnosis of POTS.

Table 1: Criteria for the Postural Tachycardia Syndrome

1. Heart rate increase ≥30 beats per minute from supine to standing (5-30 min)
2. Symptoms get worse with standing and better with recumbence.
3. Symptoms lasting ≥6 months
4. Standing plasma norepinephrine ≥600 pg/ml (≥3.5 nM)
5. Absence of other overt cause of orthostatic symptoms or tachycardia (e.g. active bleeding, acute dehydration, medications).

Symptoms include mental clouding ("brain fog"), blurred or tunneled vision, shortness of breath, palpitation, tremulousness, chest discomfort, headache, lightheadedness and nausea. While pre-syncope is common in these patients, only a minority (~30%) actually pass out. The chest pains are almost never due to coronary artery obstruction, but are sometimes associated with electrocardiographic changes in the inferior leads, particularly when upright[6].

Many patients complain of significant exercise intolerance and extreme fatigue. Even activities of daily living, such as bathing or housework, may greatly exacerbate symptoms with resultant fatigue. This can pose significant limitations on their functional capacity.

The disorder primarily affects women of child-bearing age. The female:male ratio is 4:1. The reason for the strong female predominance is not known, but it should be noted that orthostatic tolerance is reduced in normal healthy females[7]. Others disorders such as autoimmune diseases and irritable bowel syndrome are seen commonly in patients with POTS, and also have higher prevalence in women.

Patients frequently report that their symptoms began following acute stressors such as pregnancy, major surgery, or a presumed viral illness, but in others cases, symptoms develop more insidiously. About 80% of female patients report an exacerbation of symptoms in the premenstrual phase of their ovulatory cycle (unpublished data). Gazit et al. have also reported an association between joint hypermobility and POTS[8]. Many patients have bowel irregularities and have been co-diagnosed with irritable bowel syndrome, and some have abnormalities of sudomotor regulation[9].

Psychological Profile in POTS

Patients with POTS are sometimes clinically diagnosed as having anxiety disorders such as panic disorder. Indeed, patients demonstrate elevated scores on the Beck Anxiety Inventory[10] (23±10 vs. 7±8; P<0.001), a commonly used instrument that quantifies the magnitude of anxiety symptoms[11]. Unfortunately, this questionnaire includes somatic anxiety symptoms (such as palpitation) which can result from a hyperadrenergic state such as is seen in POTS. When a newer, cognitive-based measure of anxiety (the Anxiety Sensitivity Index[12]) is used, there was a trend toward less anxiety in the patients with POTS than the general population (15±10 vs. 19±9; P=0.063)[11]. Thus, much of the anxiety attributed to patients with POTS might be due to a misinterpretation of their physical symptoms.

We did find that patients with POTS often have diminished attention and concentration compared to matched healthy volunteers[11]. Using the Inattention score from the Connors Adult ADHD Rating Scale[13], the patients with POTS scored significantly higher than did the normal control subjects.

Physical Findings in POTS

The most striking physical feature of POTS is the severe tachycardia that develops on standing from a supine position. Blood pressure and heart rate must be measured in both postures and should be taken not only immediately after standing but also at 2, 5 and 10 minutes as occasional patients have a delayed tachycardia[14]. Normal subjects commonly develop a transient tachycardia within the 1st minute of standing that should not be mistaken for POTS. A sustained heart rate increase ≥30 beats per minute is considered diagnostic of orthostatic tachycardia (**Figure 1**). The systolic blood pressure should not fall by more than 20 mmHg, and in many cases it will actually increase with standing. Recent data suggests that there may be a significant circadian variability in the orthostatic tachycardia seen in patients with POTS[15]. In a cohort of 17 patients with POTS, the orthostatic tachycardia was greater in the morning than in the evening (38±4 bpm vs. 27±3 bpm; P<0.001), while there was no diurnal difference in the orthostatic change in blood pressure. These data suggest that to optimize diagnostic sensitivity, postural vital signs should be performed in the morning.

Cardiac auscultation may reveal a murmur of mitral valve prolapse, but significant mitral regurgitation is unusual. A striking physical feature of POTS is the dependant acrocyanosis that occurs in 40-50% of patients with POTS (**Figure 2**). These patients experience a dark red-blue discoloration of their legs, which are cold to the touch. This can extend from the feet to above the level of the knees. The reasons underlying this phenomenon are not clear. The current data suggest that the problem is not due to increased pooling in the venous capacitance vessels, but rather due to decreased blood flow in the skin[16,17].

Laboratory Abnormalities in POTS

Some authors advocate the use head-up tilt table testing as a standardized method to assess an individual's response to a change in posture[1]. The patient is positioned on a standard tilt table and following baseline measurements of blood pressure and heart rate, the patient is inclined to a 70-

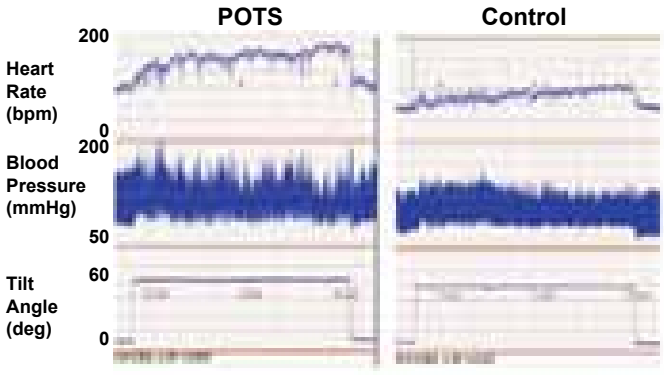

Figure 1 – Hemodynamics with Upright Posture in POTS

The tracings for heart rate, blood pressure, and tilt table angle are shown for a patient with the postural tachycardia syndrome (POTS; **left**) and for a healthy control subject (**right**) during a 30 minute tilt head-up test. With head-up tilt, the heart rte immediately increases in POTS and peaks at over 170 bpm prior to the end of the tilt. In contrast the heart rate of the healthy control subject rises to just over 100 bpm. The patient with POTS does not experience a reduction in blood pressure during the tilt test. It is largely unchanged during the test.

degree head-up angle. Blood pressure and heart rate are then measured either continuously or at least every 12 minutes. The orthostatic tachycardia is often measured in a similar fashion to the standing test, with a similar threshold used to diagnose orthostatic tachycardia (an increase of ≥30 bpm)[1]. However, the physiology in response to passive standing on a tilt table (with the legs still) is not the same as "active standing" where the patient must support their own weight and maintain their balance. The latter requires use of the "skeletal muscle pump" and mimics real life, while the tilt table does not. For this reason Streeten et al. use similar criteria for orthostatic tachycardia (>27 bpm), but only with active standing[18]. In a recent study, we compared the orthostatic heart rate response of these 2 methods, and found that the tilt table test was associated with an increased orthostatic tachycardia in both patients with POTS and control subjects[19]. While both tests were sensitive for the diagnosis of POTS with a 30 bpm threshold for orthostatic tachycardia, the stand test had a specificity of 79% compared to only 23% for the tilt table test.

POTS patients should have only sinus tachycardia. An electrocardiogram should be done routinely to rule out the presence of an accessory bypass tract or any abnormalities of cardiac conduction. A Holter monitor might prove useful to exclude a re-entrant dysrhythmia, especially if the patient gives a history of paroxysmal tachycardia with a sudden onset and sudden offset. Other tests such as echocardiograms are only required in individual cases when there is doubt about the structural integrity of the heart.

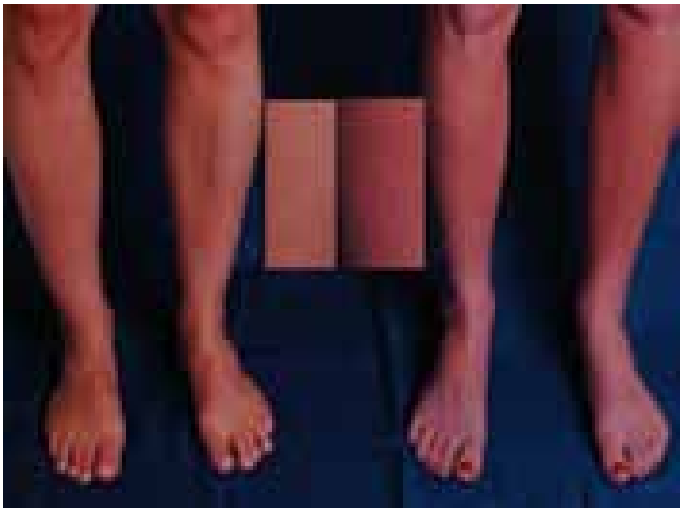

Figure 2 – Acrocyanosis in POTS

One of the more striking physical features in the postural tachycardia syndrome (POTS) is the gross change in dependent skin color that can occur with standing. The panel shows the legs of 2 people who have been standing for 5 minutes, a healthy control subject (**left**) and a patient with POTS (**right**). The patient with POTS (right) has significant dark red mottling of her legs extending up to the knees while standing, while the control subject does not have a similar discoloration.

We often measure plasma norepinephrine levels in both a supine and standing position (at least 15 minutes in each position prior to blood sampling). The supine norepinephrine is often high normal in patients with POTS, while the upright norepinephrine is usually elevated (>600 pg/ml), a reflection of the exaggerated neural sympathetic tone that is present in these patients while upright.

Tests of autonomic nervous system function typically show intact or exaggerated autonomic reflex responses. These patients often have preserved vagal function as reflected by their sinus arrhythmia ratio in response to deep breathing. They often have a vigorous pressor response to the Valsalva maneuver, with an exaggerated blood pressure recovery and overshoot both before and after release[20].

The blood volume is low in many patients with POTS[5]. This can be objectively assessed with nuclear medicine tests to directly measure either the plasma volume or the red cell volume. This knowledge may help to focus the treatment plan.

Some patients with POTS have co-existent complaints of episodic flushing. In about half of these cases there is an associated mast cell activation disorder[20]. This can be diagnosed by collecting urine from individual 2-4 hour voids following a severe flushing spell for determination of methylhistamines.

Differential Diagnosis

The clinical picture of POTS can be confused with pheochromocytoma because of the paroxysms of hyperadrenergic symptoms. Patients with pheochromocytoma are more likely to have symptoms while lying down than POTS patients, and often have much higher plasma norepinephrine levels. The diagnosis of pheochromocytoma is made by assessment of plasma or urinary metanephrines[21].

There is commonly some confusion between neurally mediated syncope and POTS. There is a clinical overlap between the 2 disorders, such that about 30% of patients with POTS also have neurally mediated syncope. Nonetheless, most patients with POTS do not faint.

Almost all patients with POTS also have associated fatigue. The reasons are not entirely clear. In some patients, but not all, the fatigue improves with pharmacological control of the orthostatic tachycardia. Some patients with POTS have symptomatic overlap with chronic fatigue syndrome.

Pathophysiology of POTS

Tachycardia and asthenia on standing is a final common pathway of many pathophysiological processes. POTS is therefore best viewed as a syndrome rather than a disease. Many disorders with a common key clinical presentation (the orthostatic tachycardia) have been described. Over the last decade, much has been learned about specific forms or subtypes within POTS, although a simple test to categorize the individual patient remains elusive. We discuss here the common POTS phenotypes including neuropathic POTS and central hyperadrenergic POTS (**Figure 3**).

There are multiple distinct pathophysiological subtypes within the postural tachycardia syndrome (POTS). The **top panel** (**3a**) shows a basal situation with a normal amount of sympathetic nervous system outflow from the brain that activates receptors in the blood vessels (vascular tone & venous return), heart (heart rate & contractility) and kidney (blood volume regulation through renin). **Panel 3b** shows a schematic of Neuropathic POTS. There is patchy denervation of the sympathetic innervation of the blood vessels in the extremities (especially the legs) and the kidney with subsequent hypovolemia and increased orthostatic venous pooling. This feeds back to the brain to increase sympathetic nervous system outflow in a compensatory effort. This increased sympathoneural flow is sensed most in the heart where there is no denervation. **Panel 3c** shows a schematic of Central Hyperadrenergic POTS. In this case, the underlying problem is excessive sympathetic nervous outflow from the brain that affects the blood vessels, kidneys and the heart. In addition to tachycardia, this form of POTS is often associated with orthostatic hypertension.

Neuropathic POTS

Considering that POTS patients have high plasma NE levels, it would seem paradoxical that a neuropathy is proposed as an underlying process. Yet some of them have a form of dysautonomia, with preferential denervation of sympathetic nerves innvervating the lower limbs[22-24]. There have been several findings consistent with this hypothesis. The results of sudomotor axon reflex testing[22] and galvanic skin stimulation[23] support this as well as skin biopsy results[25]. Further, these patients have been found to be hypersensitive to infusions of norepinephrine and phenylephrine into veins of the foot, despite high circulating plasma norepinephrine concentrations[24]. This suggests that there is a denervation hypersensitivity of the leg veins. Using a segmental norepinephrine spillover approach, Jacob et al.[26] demonstrated that patients with POTS had normal sympathetic neuronal norepinephrine release in their arms, but less norepinephrine release (and thus less sympathetic activation) in their lower body.

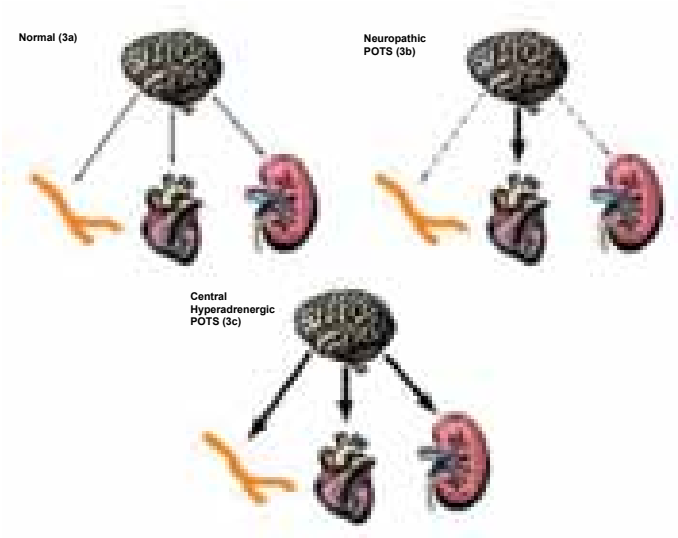

Figure 3 – Pathophysiological Schema in POTS

Hypovolemia & Blood Volume Regulation

Many patients with POTS have low plasma volumes[27,28], but not all[29]. To determine if hypovolemia existed in an unselected group of POTS patients, we studied 15 patients with POTS (not selected for blood volume) and 14 control subjects[5]. Plasma volume was measured using ^{131}I labeled human serum albumin using a dye dilution technique, and compared to the predicted blood volume for each individual, based upon their height, weight, and gender. As can be seen in **Figure 4**, the control subjects did not have a significant plasma volume deficit (0.8±2.5%). In contrast, the patients with POTS had a plasma volume deficit of 12.8±2.0% ($P<0.001$).

The renin-angiotensin-aldosterone system plays a key role in the neurohormonal regulation of plasma volume in humans. Plasma

renin activity and angiotensin II would be expected to increase in response to hypovolemia in order to promote blood volume expansion. Angiotensin II promotes sodium and water retention directly by stimulating sodium resorption in the proximal tubules, and indirectly by stimulating aldosterone secretion.

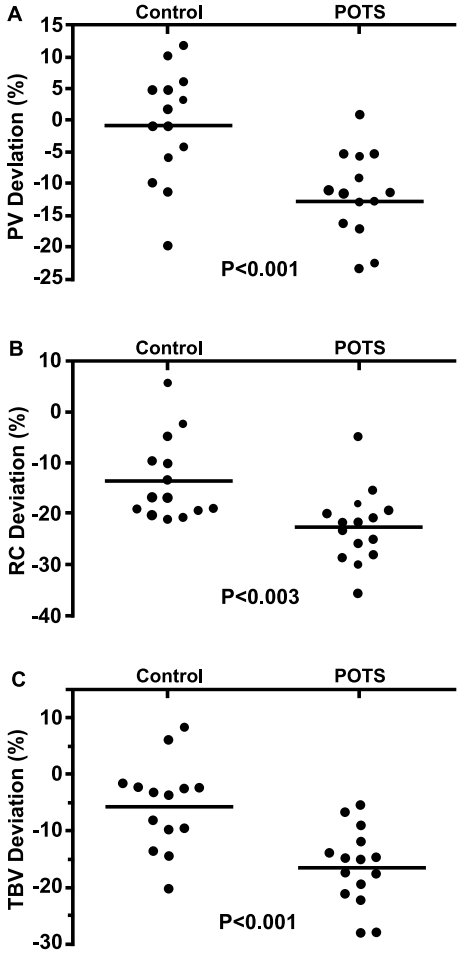

Figure 4 – Blood Volume Deviation in POTS

The 3 panels show the blood volumes of control subjects and patients with POTS compared to hat expected based on their individual height, weight and gender. Data are shown for plasma volume (**PV; Panel A**), red cell volume (**RC; Panel B**) and total blood volume (**TBV; Panel C**). The plasma volume and total blood volume of the control subjects was similar to their expected values. The patients with POT had a deficit of their plasma volume (**Panel A**), red cell volume (**Panel B**) and total blood volume (**Panel C**) compared to the control group. Figures adapted with data from Raj SR, Biaggioni I, Yamhure PC, Black BK, Paranjape SY, Byrne D, Robertson D. The Renin-Aldosterone Paradox and Perturbed Blood Volume Regulation Underlying the Postural Tachycardia Syndrome. Circulation 2005; 111:1574-1582.

Patients with orthostatic tachycardia who were also hypovolemic have low levels of standing plasma renin activity and aldosterone compared to normovolemic patients[21,2]. This is true in both supine (190±140 pM vs. 380±230 pM; P=0.017) and upright posture (480±290 pM vs. 810±370 pM; P=0.019). One would have expected a compensatory increase in both plasma renin activity and aldosterone given the hypovolemia in these patients. This low level of plasma renin activity and aldosterone is a paradox that remains unexplained. These data suggest that abnormalities in the renin-angiotensin-aldosterone axis might have a role in the pathophysiology of POTS by contributing to hypovolemia and impaired sodium retention. Such hypovolemia could be accounted for by a neuropathic process involving the kidney. A significant modulator of renin release is the sympathetic nervous system. Thus perturbations in the renin-aldosterone system might result from partial sympathetic denervation involving the kidney.

Central Hyperadrenergic POTS

As a part of the definition, POTS is associated with a hyperadrenergic state (**Table 1**). In many such cases, the hyperadrenergic state is secondary to a partial dysautonomia or hypovolemia. There are some cases, however, in which the primary underlying problem seems to be excessive sympathetic discharge. These patients often have extremely high levels of upright norepinephrine. While we require the upright norepinephrine level to be >600 pg/ml for the diagnosis of POTS, the hyperadrenergic subgroup often has upright norepinephrine level >1000 pg/ml and it is occasionally >2000 pg/ml. These patients sometimes have large increases in blood pressure on standing, indicating that baroreflex buffering is somehow impaired.

Central hyperadrenergic POTS in its most florid form is much less common than neuropathic POTS, comprising only ~10% of patients. Thus therapy in these cases usually targets a decrease in sympathetic tone both centrally and peripherally.

Central sympatholytics such as methyldopa or clonidine can be used. Peripheral beta-adrenergic blockade may be better tolerated by these patients than by those with neuropathic POTS.

Norepinephrine Transporter Deficiency

A specific genetic abnormality has been identified in a kindred with hyperadrenergic POTS[30]. These individuals have a single point mutation in the norepinephrine transporter (NET). The resultant inability to adequately clear norepinephrine produces a state of excessive sympathetic activation in response to a variety of sympathetic stimuli. While rare, this mutation has taught us much about the importance of a functional NET.

Although functional NET mutations might be infrequent, pharmacological NET inhibition is very common. Many antidepressant and attention deficit medications work at least in

part through inhibition of NET. This includes traditional drugs such as tricyclic antidepressants, and newer medications which are pure NET inhibitors (e.g. atomoxetine or reboxetine). Both we[31] and others[32] have found that pharmacological NET inhibition can recreate an orthostatic tachycardia phenotype in susceptible healthy volunteer subjects. Yohimbine, a central alpha-2 antagonist that will also increase synaptic norepinephrine, can also cause orthostatic tachycardia[33].

Mast Cell Activation

Some patients with POTS have co-existent mast cell activation. These patients have episodic flushing and abnormal increases in urine methylhistamine (the primary urinary metabolite of histamine)[20]. Methylhistamine should ideally be measured in 2 hour aliquots at the time of a flushing episode and not just in a random 24 hour period. Other associated symptoms include shortness of breath, headache, lightheadedness, excessive diuresis, and gastrointestinal symptoms such as diarrhea, nausea, and vomiting. Flushing can be triggered by long-term standing, exercise, premenstrual cycle, meals, and sexual intercourse. These patients often have a hyperadrenergic response to posture, with both orthostatic tachycardia and hypertension. They demonstrate a vigorous sympathetic vasopressor response during the Valsalva maneuver with a blood pressure overshoot in late phase II and an exaggerated phase IV blood pressure overshoot. It is not clear if mast cell activation, releasing vasoactive mediators, represents the primary event in these patients or if sympathetic activation, through release of norepinephrine, neuropeptide Y and ATP, is the cause of mast cell activation[34].

In these patients, beta-adrenergic antagonists can actually trigger an episode and worsen symptoms. Centrally acting agents to decrease the sympathetic nervous system discharge (e.g. methyldopa or clonidine) may prove effective. Alternatively, treatment could target mast cell mediators with a combination of antihistamines (H1-and H2-antagonists) and with the cautious use of non-steroidal agents (high dose aspirin) in refractory cases.

Non-Pharmacological Treatment of POTS

No therapy is successful for all patients with POTS. Initial efforts should focus on identifying and treating any reversible causes. Potentially contributory medications (especially vasodilators, diuretics, and drugs that inhibit NET) should be withdrawn. If a patient has been through prolonged bedrest, their symptoms will gradually improve as they recondition themselves to upright posture. Treatment should be optimized for any chronic disease that is present. If there is clear evidence of a re-entrant supraventricular arrhythmia, then this should be treated, including with radiofrequency ablation as appropriate. However, radiofrequency sinus node modification for the sinus tachycardia of POTS is not recommended. This often makes the patient's symptoms worse (and occasionally the patient becomes pacemaker dependent). Specific therapies are summarized in **Table 2**.

It is important to educate the patient about the nature of the disorder. The patient should avoid aggravating factors such as dehydration, and extreme heat. In order to ensure adequate hydration, we ask our patients to consume 8-10 cups of water daily and to rapidly drink 16 fl oz of water to lower their heart rates[35]. In addition, they are asked to aggressively increase their sodium intake up to 200 mEq/day. This is often hard to achieve without NaCl tablets 1 gm/tablet TID with meals. Elastic support hose can help to minimize the degree of peripheral venous pooling and enhance venous return. We recommend 30-40 mmHg of counter-pressure and they should come up to the waist. If the stockings are only knee-high, a line of edema can form just above the stockings. Their use can be limited by their tolerability as the stockings can be hot, itchy and uncomfortable. Exercise (both aerobic and resistance training) is also encouraged and has been shown to be beneficial[36]. In addition to reversing any "deconditioning", this intervention can also increase blood volume. Vigorous exercise may acutely worsen symptoms and may even result in prolonged fatigue. It is important that patients start slowly and remain within range of their "target heart rate" in the early stages to avoid symptoms that might discourage further exercise.

Acute blood volume expansion is effective at controlling the heart rate and acutely improving symptoms. Jacob et al.[37] found that 1 liter of physiological saline infused intravenously over 1 hour decreased the orthostatic tachycardia from 33±5 bpm before the infusion to 15±3 bpm immediately following the infusion. The physiological saline was more effective at heart rate control than were treatments with either an alpha-1 agonist or an alpha-2 agonist. This treatment is not practical on a day to day basis as a medical setting is required to insert the intravenous catheter and infuse the saline. Recently, there have been reports of patients having regular saline infusions, typically 1 liter of normal saline every other day or every day. Many report an improvement in symptoms. However, there are not yet objective data to substantiate such benefit. Further, there is a risk of vascular access complications or infection. At this time, such therapy for patients with POTS should be considered cautiously.

Pharmacological Treatment of POTS

No medicines are approved by the United States Food and Drug Administration for the treatment of POTS. Thus all agents are used for this disorder are "off label". Furthermore, there are no pharmacological agents that have been tested in a long-term properly powered randomized clinical trial.

In patients in whom the presence of hypovolemia is either known or strongly suspected, fludrocortisone (an aldosterone analogue) is often used. Through enhanced sodium retention, it should expand the plasma volume, although there is a paucity

Table 2: Treatments for the Postural Tachycardia Syndrome

Ser Num	Therapy	Dosage	Mechanism	Drawbacks
Non-Pharmacological Approaches				
1	Water	8-10 cups/day (2-2.5 L/day)	Blood volume expansion	?Hyponatremia
2	Increase Dietary Salt	200-300 mEq Na^+/day	Blood volume expansion	Difficult to augment sufficiently without supplements
3	Nacl tablets	1 gm tablet PO TID	Blood volume expansion	Poor taste; nausea & dyspepsi (take after meals)
4	Elastic support hose	30-40 mmHg counter-pressure; waist high	Enhanced venous return	Hot, itchy & uncomfortable; edema above stocking if only knee high
5	Exercise	30 min x 3+ times per week; both aerobic & resistance	Blood volume expansion; reverse deconditioning	Vigorous exercise may worsen symptoms and result in prolonged fatigue
6	Acute IV saline	IL N/S over 1-3 hours IV	Blood volume expansion	Effective at acute heart rate control; inconvenient; medical setting needed
7	Chronic IV Saline	IL N/S IV q2 days-qdaily	Blood volume expansion	Anecdotal benefit only; requires central line; risks of access complications & infection; logistically difficult
Medications to Augment Blood Volume				
8	Fludocortisone	0.05-0.1 mg PO OD-BID	Blood volume expansion	Edema; fluid retention; hypokalemia; headache; hypertension
9	Desmopressin (DDAVP)	0.1-0.2 mg PO OD-BID	Blood volume expansion	Hyponatremia; headache; edema
10	Erythropoietin	2000-3000 IU SQ 1-3/week	Blood volume expansion	Expensive; requires injection
Medications to Decrease Sympathetic Tone				
11	Clonidine	0.05-0.2 mg PO BID	Agoinist of presynaptic alpha-2 receptor; decreases SNS traffic	Mental clouding; fatigue; drowsiness; constipation; dry mouth
12	Methyldopa	125-250 mg PO TID	False neurotransmitter; decreases SNS traffic	Hypotension; headache; constipation; drowsiness
Other Medications				
13	Propranolol	10-20 mg PO BID-QID	Beta-adrenergic receptor antagonist	Hypotension; drowsiness; fatigue; wheezing; nightmares
14	Midodrine	2.5-10 mg PO TID	Alpha-1 adrenergic receptor agonist	Hypertension; goose bumps; urinary retention; pins & needles sensation
15	Pyridostigmine	30-60 mg PO TID	Acetylcholinesterase inhibitor	Abdominal cramping; diarrhea; increased sweating; increased secretions / tearing
16	Modafinil	100 mg PO BID	Stimulat; mechanism unclear	May reduce mental clouding; increase in heart rate

NaCl – Table salt; PO – by mouth; OD – once daily; BID – twice daily; TID – three times daily; QID – four times daily; IV – intravenous;

of data regarding the exact mechanisms of action. Although fairly well tolerated, side effects can include hypokalemia, hypomagnesemia, worsening headaches, acne, and fluid retention with edema. Another volume expanding agent that may be helpful for short-term use is oral vasopressin (DDAVP). This agent causes the kidney to retain free water, but not sodium. Potential side effects include hyponatremia, edema and headache. Erythropoietin has occasionally proven useful in patients with POTS who are refractory to other forms of therapy. While the primary mode of action is likely an increase in intravascular volume via its increase in red cell mass, erythropoietin also

appears to have a direct vasoconstrictive effect, possibly through enhanced red cell mediated nitric oxide scavenging[38]. Treatment with erythropoietin has many drawbacks including the significant expense and the need for subcutaneous administration.

Central sympatholytic medications are often useful and well tolerated in patients with the central hyperadrenergic form of POTS, but may not be as well tolerated in neuropathic POTS. Clonidine is an alpha 2 agonist that acts centrally to decrease sympathetic nervous system tone. Clonidine, at doses of 0.05 mg to 0.2 mg PO BID, can stabilize heart rate and blood pressure in patients with a large amount of postganglionic sympathetic involvement. Unfortunately, it can also cause drowsiness, fatigue and worsen the mental clouding of some patients. Methyldopa, a false neurotransmitter, is sometimes more successful in controlling symptoms in these patients at doses of 125 mg to 250 mg PO TID[39].

When used in low doses, beta-adrenergic antagonists can be useful. We typical use propranolol 10-20 mg PO BID-QID. While this dose range is small, such doses can often have a significant impact on heart rate control, and higher doses are often not tolerated due to hypotension and fatigue.

Since a failure of vascular resistance may be an integral part of neuropathic POTS, vasoconstrictors such as midodrine (an alpha-1 agonist) can be employed[40]. Some patients cannot tolerate this agent due to the unpleasant sensation of scalp tingling or goosebumps. Midodrine can also cause hypertension.

We recently reported that an unselected group of patients seen in our inpatient research unit were given a trial of the acetylcholinesterase inhibitor pyridostigmine. By increasing the levels of synaptic acetylcholine at both the autonomic ganglia and the peripheral muscarinic parasympathetic receptors, pyridostigmine significantly restrained the heart rate in response to standing in our patients with POTS. We prescribe pyridostigmine 30mg to 60 mg PO TID alone or in combination with low dose propranolol. Pyridostigmine can enhance bowel motility, so it is not always well tolerated in patients with diarrhea-predominant irritable bowel syndrome symptoms.

While most of the treatments discussed above have focused on the control of heart rate, many patients are also greatly troubled by mental clouding. Modafinil, a stimulant whose mechanism is not yet clear, has been used in some patients with resulting improvement in alertness. However, caution is advised as it may aggravate the orthostatic tachycardia[41].

Conclusions

POTS is a disorder of the autonomic nervous system in which many symptoms can be treated. The cardinal manifestation is symptomatic orthostatic tachycardia. The disorder can produce substantial disability among otherwise healthy people. Patients with POTS demonstrate a heart rate increase of ≥30 bpm with prolonged standing (5-30 minutes), often have high levels of upright plasma norepinephrine, and many patients have a low blood volume. Therapies aimed at correcting the hypovolemia and the autonomic imbalance may help relieve the severity of the symptoms. Continued research is vital to better understand this disorder and to differentiate its various subtypes.

References

1. Low PA, Opfer-Gehrking TL, Textor SC, Benarroch EE, Shen WK, Schondorf R, Suarez GA, Rummans TA. Postural tachycardia syndrome (POTS). Neurology. 1995;45:S19-S25.
2. Wooley CF. Where are the diseases of yesteryear? DaCosta's syndrome, soldiers heart, the effort syndrome, neurocirculatory asthenia--and the mitral valve prolapse syndrome. Circulation. 1976;53:749-751.
3. Miller JW, Streeten DH. Vascular responsiveness to norepinephrine in sympathicotonic orthostatic intolerance. J Lab Clin Med. 1990;115:549-558.
4. Wieling W, Shepherd JT. Initial and delayed circulatory responses to orthostatic stress in normal humans and in subjects with orthostatic intolerance. Int Angiol. 1992;11:69-82.
5. Raj SR, Biaggioni I, Yamhure PC, Black BK, Paranjape SY, Byrne DW, Robertson D. Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. Circulation. 2005;111:1574-1582.
6. Friesinger GC, Biern RO, Likar I, Mason RE. Exercise electrocardiography and vasoregulatory abnormalities. Am J Cardiol. 1972;30:733-740.
7. Fu Q, Witkowski S, Okazaki K, Levine BD. Effects of gender and hypovolemia on sympathetic neural responses to orthostatic stress. Am J Physiol Regul Integr Comp Physiol. 2005;289:R109-R116.
8. Gazit Y, Nahir AM, Grahame R, Jacob G. Dysautonomia in the joint hypermobility syndrome. Am J Med. 2003;115:33-40.
9. Khurana RK. Orthostatic intolerance and orthostatic tachycardia: a heterogeneous disorder. Clin Auton Res. 1995;5:12-18.
10. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56:893-897.
11. Raj, V., Haman, K., Raj, S., Blakely, R., Robertson, D., and Shelton, R. Psychiatric profile and attention deficits in the postural tachycardia syndrome. Clin Auton Res 14(5), 309. 2004.
12. Peterson RA, Reiss S. Anxiety Sensitivity Index Manual. 1992. International Diagnostic Systems, Worthington, OH.
13. Conners CK, Erhardt D, Sparrow E. Conner's adult ADHD rating scales (CAARS) technical manual. 1999. Multi-Health System, Inc.
14. Streeten DH, Anderson GH, Jr. Delayed orthostatic intolerance. Arch Intern Med. 1992;152:1066-1072.
15. Raj, S. R., Garland, E. M., Biaggioni, I., Black, B. K., and Robertson, D. Morning heart rate surge in postural tachycardia syndrome. Circulation 112, U810, 2005.
16. Freeman R, Lirofonis V, Farquhar WB, Risk M. Limb venous compliance in patients with idiopathic orthostatic intolerance and postural tachycardia. J Appl Physiol. 2002;93:636-644.
17. Stewart JM. Pooling in chronic orthostatic intolerance: arterial vasoconstrictive but not venous compliance defects. Circulation. 2002;105:2274-2281.
18. Streeten DH. Orthostatic disorders of the circulation: Mechanisms, manifestations and treatment. 1987. Plenum Medical Book Publishing, New York.

19. Raj, S. R., Dzurik, M. V., Biaggioni, I., Black, B. K., Paranjape, S. Y., and Robertson, D. Diagnosing postural tachycardia syndrome: comparison of tilt versus standing. Circulation 112, U765, 2005.

20. Shibao C, Arzubiaga C, Roberts LJ, Raj S, Black B, Harris P, Biaggioni I. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. Hypertension. 2005;45:385-390.

21. Manger WM, Eisenhofer G. Pheochromocytoma: diagnosis and management update. Curr Hypertens Rep. 2004;6:477-484.

22. Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? Neurology. 1993;43:132-137.

23. Hoeldtke RD, Davis KM. The orthostatic tachycardia syndrome: evaluation of autonomic function and treatment with octreotide and ergot alkaloids. J Clin Endocrinol Metab. 1991;73:132-139.

24. Streeten DH. Pathogenesis of hyperadrenergic orthostatic hypotension. Evidence of disordered venous innervation exclusively in the lower limbs. J Clin Invest. 1990;86:1582-1588.

25. Singer W, Spies JM, McArthur J, Low J, Griffin JW, Nickander KK, Gordon V, Low PA. Prospective evaluation of somatic and autonomic small fibers in selected autonomic neuropathies. Neurology. 2004;62:612-618.

26. Jacob G, Costa F, Shannon JR, Robertson RM, Wathen M, Stein M, Biaggioni I, Ertl A, Black B, Robertson D. The neuropathic postural tachycardia syndrome. N Engl J Med. 2000;343:1008-1014.

27. Jacob G, Robertson D, Mosqueda-Garcia R, Ertl AC, Robertson RM, Biaggioni I. Hypovolemia in syncope and orthostatic intolerance role of the renin-angiotensin system. Am J Med. 1997;103:128-133.

28. Fouad FM, Tadena-Thome L, Bravo EL, Tarazi RC. Idiopathic hypovolemia. Ann Intern Med. 1986;104:298-303.

29. Streeten DH, Thomas D, Bell DS. The roles of orthostatic hypotension, orthostatic tachycardia, and subnormal erythrocyte volume in the pathogenesis of the chronic fatigue syndrome. Am J Med Sci. 2000;320:1-8.

30. Shannon JR, Flattem NL, Jordan J, Jacob G, Black BK, Biaggioni I, Blakely RD, Robertson D. Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. N Engl J Med. 2000;342:541-549.

31. Vincent S, Bieck PR, Garland EM, Loghin C, Bymaster FP, Black BK, Gonzales C, Potter WZ, Robertson D. Clinical assessment of norepinephrine transporter blockade through biochemical and pharmacological profiles. Circulation. 2004;109:3202-3207.

32. Schroeder C, Tank J, Boschmann M, Diedrich A, Sharma AM, Biaggioni I, Luft FC, Jordan J. Selective norepinephrine reuptake inhibition as a human model of orthostatic intolerance. Circulation. 2002;105:347-353.

33. Raj, S. R., Vincent, S., Black, B. K., Paranjape, S. Y., Taneja, I., and Robertson, D. Postural tachycardia syndrome: 2 contrasting pharmacological models. Heart Rhythm 1, S101. 2004.

34. Arzubiaga C, Morrow J, Roberts LJ, Biaggioni I. Neuropeptide Y, a putative cotransmitter in noradrenergic neurons, induces mast cell degranulation but not prostaglandin D2 release. J Allergy Clin Immunol. 1991;87:88-93.

35. Shannon JR, Diedrich A, Biaggioni I, Tank J, Robertson RM, Robertson D, Jordan J. Water drinking as a treatment for orthostatic syndromes. Am J Med. 2002;112:355-360.

36. Winker R, Barth A, Bidmon D, Ponocny I, Weber M, Mayr O, Robertson D, Diedrich A, Maier R, Pilger A, Haber P, Rudiger HW. Endurance exercise training in orthostatic intolerance: a randomized, controlled trial. Hypertension. 2005;45:391-398.

37. Jacob G, Shannon JR, Black B, Biaggioni I, Mosqueda-Garcia R, Robertson RM, Robertson D. Effects of volume loading and pressor agents in idiopathic orthostatic tachycardia. Circulation. 1997;96:575-580.

38. Biaggioni I, Robertson D, Krantz S, Jones M, Haile V. The anemia of primary autonomic failure and its reversal with recombinant erythropoietin. Ann Intern Med. 1994;121:181-186.

39. Jacob G, Biaggioni I. Idiopathic orthostatic intolerance and postural tachycardia syndromes. Am J Med Sci. 1999;317:88-101.

40. Grubb BP, Karas B, Kosinski D, Boehm K. Preliminary observations on the use of midodrine hydrochloride in the treatment of refractory neurocardiogenic syncope. J Interv Card Electrophysiol. 1999;3:139-143.

41. Taneja I, Diedrich A, Black BK, Byrne DW, Paranjape SY, Robertson D. Modafinil elicits sympathomedullary activation. Hypertension. 2005;45:612-618.

Case - 1

Drug Induced Long QT Syndrome

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A 25-yr-old lady was posted for surgery for bifid uvula and cleft palate. She had no prior cardiac symptoms of dyspnea, fatigue, chest pain, palpitations or syncope. She gave no history of allergy to drugs. Her clinical examination revealed normal cardiovascular findings. She was given fitness for surgery, which was performed under general anesthesia. The surgery was uneventful and after a few hours of observation in the recovery, having completely regained consciousness was shifted to the ward. Suddenly she complained of palpitations, giddy feeling and vomited. On noticing irregular and rapid pulse was shifted to the intensive care unit. A 12 lead ECG (figure 1) revealed a markedly prolonged QT interval. The QT interval was 0.58 seconds and the QTc was 0.64 seconds. There was associated global giant T wave inversion. She was empirically given 2 gms of magnesium and her serum potassium was 4.8 meq/l. She did not have any repeat symptoms of palpitation and there was no further vomiting, headache and neurologic examination was normal. She was receiving ciprofloxacin antibiotic pre-operatively. This was immediately withheld. Gradually over the next few days her QT interval normalized and 7 days later ECG showed QT interval of 0.38 seconds and QTc was 0.44s (figure 2). A family screening of first-degree relatives with clinical history and ECG has been scheduled.

Acquired, drug-induced long QT is a menace and there is no foolproof manner in which this could be predicted and prevented. One needs to have a high index of suspicion and the immediate treatment would be to withhold the offending agent, correct hypokalemia and empirically use magnesium. Isoprenaline and temporary pacing may have to be used in case of significant bradycardia. These patients need to be intensively monitored till the offending drug wears-off. A family screening to identify form-fruste of congenital long QT syndrome should be performed. In absence of any evidence of congenital long QT syndrome the only precaution would be to give the list of medication known to prolong QT interval and they need to be avoided in the future.

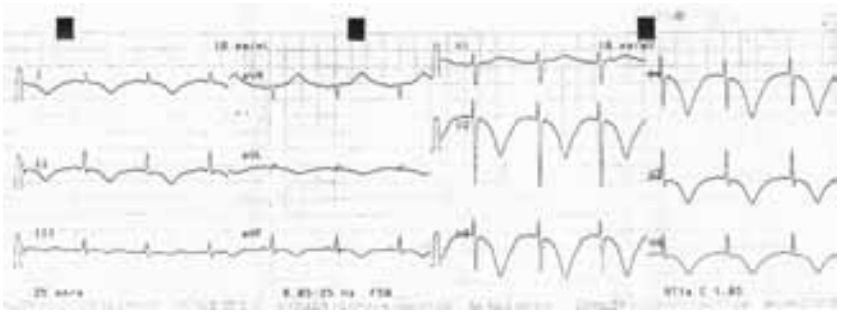

Figure 1 : 12 lead ECG showing markedly prolonged QT : 0.58 s (QTc : 0.64 s) with global T wave inversion

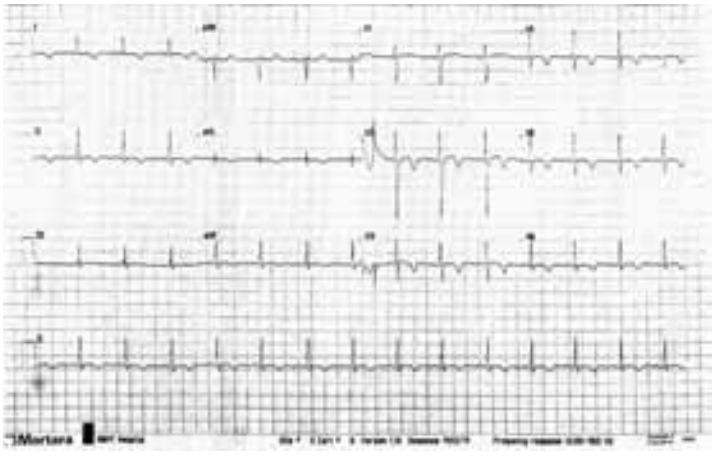

Figure 2 : 12 lead ECG after 7 days showing a normal QT : 0.38 s (QTc : 0.44 s)