35-Year-Old Woman With Recurrent Palpitations

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A 35-year-old woman presented to the outpatient clinic with a 2-week history of episodic palpitations. She noted that each episode was abrupt in onset and would last approximately 1 to 2 hours before abating gradually. She denied chest pain, shortness of breath, and light-headedness and had no history of similar symptoms.

The patient's medical and psychiatric history were unremarkable, and her only medication was an oral contraceptive (OC). She had been taking OCs since age 21 years and was currently taking 3 mg of drospirenone and 0.2 mg of ethinyl estradiol (Yasmin 28, Bayer Healthcare Pharmaceuticals, Wayne, NJ). The patient was a smoker and had smoked 1 pack of cigarettes per day since the age of 18 years. She denied alcohol or illegal drug use.

On examination, the patient appeared comfortable and in no distress. Vital signs were as follows: temperature, 36.8ºC; blood pressure, 135/95 mm Hg; heart rate (HR), 102 beats/min and regular; respiratory rate (RR), 18 breaths/min; and oxygen saturation (Spo_2), 91% while breathing room air. Cardiovascular examination revealed tachycardia but no murmurs, S_3, or S_4; jugular venous pressure was normal. Pulmonary examination showed clear lung fields and no signs of effusion. The patient had no goiter, palpable thyroid nodules, or asymmetry. Findings on examination of the skin, eyes, extremities, neurologic system, and peripheral arterial systems were normal.

1. Which <u>one</u> of the following is the <u>most likely</u> etiology for the patient's symptoms of palpitations?

a. *Thyrotoxicosis*
b. *Anemia*
c. *Anxiety disorder*
d. *Nicotine use*
e. *Arrhythmia*

Thyrotoxicosis (hyperthyroidism) will often manifest with alterations in cardiac physiology. Common signs include an increased heart rate, a widened pulse pressure, and an elevated systemic blood pressure. Atrial fibrillation, present in 10% to 20% of hyperthyroid patients, could lead to palpitations.[1] However, in the absence of characteristic skin findings (diaphoretic and warm) and ocular signs (stare and lid lag), overt hyperthyroidism is less likely. In the setting of a significant anemia, palpitations can be perceived secondary to compensatory increases in HR and stroke volume in order to maintain adequate tissue oxygenation. In the absence of risk factors for bleeding, this would be uncommon.

Psychiatric disorders can often coexist with somatic symptoms such as palpitations. In the *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* (*DSM-IV*), palpitations are one of the multiple cardiopulmonary symptoms suggestive of a panic attack. However, in a retrospective study of 107 patients experiencing reentrant paroxysmal supraventricular tachycardia, approximately 70% fulfilled *DSM-IV* criteria for panic disorder as well.[2] Although anxiety-related disorders are in the differential diagnosis for the patient's symptoms, it would be premature to accept this as the sole etiology, especially without the usual accompanying symptoms and before further diagnostics. Although substances such as nicotine that increase adrenergic tone or diminish vagal activity could be a cause of palpitations, such palpitations would not usually present acutely and intermittently if the substances had been used long-term, as they were in this patient.

Arrhythmias are a common cause of palpitations. The etiology can vary from benign premature atrial ectopic activity to more worrisome ventricular arrhythmias. Given the abrupt onset, persistence of symptoms, and the lack of previous psychiatric disease, an underlying cardiac process is the most likely etiology.

A sinus tachycardia of 106 beats/min was evident on electrocardiography. A Holter monitor showed multiple episodes of sinus tachycardia (HR, 100-140 beats/min) of 1 to 2 hours in duration in concordance with palpitations. At follow-up 5 days later, the patient continued to report persistent symptoms. Vital signs were as follows: temperature, 36.7ºC; blood pressure, 130/80 mm Hg; HR, 112 beats/min; RR, 30 breaths/min, and Spo_2, 89% while breathing room air. Examination revealed tachycardia and tachypnea, without accessory muscle use, but findings were otherwise normal. Chest radiographic findings were normal.

Laboratory studies revealed a hemoglobin of 13.3 g/dL (reference ranges provided parenthetically) (12.0-15.5 g/dL) and a thyroid-stimulating hormone level of 1.4 mIU/L (0.3-5.0 mIU/L).

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See end of article for correct answers to questions.

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2. Given the case information up to this point, which one of the following is the most likely precipitant of this patient's sinus tachycardia?

a. *Chronic nonparoxysmal sinus tachycardia*
b. *Anxiety*
c. *Pulmonary embolism (PE)*
d. *Pheochromocytoma*
e. *Postural orthostatic tachycardia syndrome*

Chronic nonparoxysmal sinus tachycardia is a rare form of supraventricular tachycardia, the mechanism of which is not fully understood. It is a diagnosis of exclusion and is characterized by varying degrees of automaticity and autonomic control. The clinical presentation can range from minimally symptomatic infrequent palpitations to symptomatic chronic tachycardia. However, it would not cause hypoxemia. Anxiety, although associated with sinus tachycardia and tachypnea, would also not cause hypoxemia.

Pulmonary embolism involves obstruction of the pulmonary artery by a thrombus, fat, air, or a tumor that originates from elsewhere in the body. Thromboembolic disease is the most common form and is associated with variable signs and symptoms. Given the presence of tachypnea and hypoxemia, PE is the most likely precipitant of this patient's sinus tachycardia.

Pheochromocytomas are rare catecholamine-secreting tumors that are classically associated with the triad of episodic headaches, diaphoresis, and tachycardia. Hypertension, not present in this patient, is the most common finding. Hypoxemia is not associated with this condition.

Postural orthostatic tachycardia syndrome is an entity characterized by inappropriate tachycardia in response to postural change. It is most prevalent in younger female patients. Symptoms include weakness, dizziness, visual symptoms, palpitations, and (rarely) syncope upon standing. This patient had no postural component to her symptoms.

Because of the concern for PE, spiral computed tomography of the chest with intravenous contrast medium was performed and showed small, acute-appearing, subsegmental PEs in the posterior basal segments of the lower lobes bilaterally with associated peripheral infarction and hemorrhage.

3. Which one of the following is the most appropriate next step in the management of this patient's condition?

a. *Inpatient admission and administration of thrombolytic therapy*
b. *Outpatient administration of low-molecular-weight heparin (LMWH) as bridge to warfarin*
c. *Inpatient admission and administration of intravenous unfractionated heparin (UFH) as bridge to warfarin*
d. *Inpatient admission and administration of LMWH as bridge to warfarin*
e. *Inpatient admission and administration of LMWH without warfarin*

Thrombolytic therapies are potentially life-saving treatments for PE reserved for hemodynamically unstable patients presenting with sustained hypotension and cardiogenic shock. Such was not the case in our patient.

No clear evidence-based guidelines are available for inpatient vs outpatient treatment of acute PE.[3] However, multiple prognostic prediction rules help stratify patients' risk of death, recurrent venous thromboembolism (VTE), and bleeding described in patients with acute symptomatic PE.[4] Common variables to these risk scores are age, comorbid conditions, and hemodynamic abnormalities. The patient's resting hypoxemia (Spo_2, ≤90%), tachycardia (HR, ≥110 beats/min), and tachypnea (RR, ≥30 breaths/min) are suggestive of substantial hemodynamic strain. Therefore, outpatient management of this patient would be less than ideal.

The initial treatment for this patient with objectively confirmed PE is a parenteral antithrombotic agent concomitantly with a vitamin K antagonist. The choice of antithrombotic agent should be individualized. For submassive PE, treatment with LMWH has been shown to be as safe and effective as intravenous UFH.[5] Given its superior convenience and lower risk of heparin-induced thrombocytopenia, LMWH would be favored over UFH for this patient. Intravenous UFH is preferred in morbidly obese patients, in whom inadequate subcutaneous absorption is a concern, and in patients with renal failure, in whom decreased clearance of LMWH can increase the risk of hemorrhage. Unfractionated heparin is also preferred in patients at high risk of hemorrhage or if invasive procedures are likely because intravenous UFH can be stopped more quickly and reversed more reliably with protamine than LMWH.

Warfarin decreases carboxylation of factors II, VII, IX, and X as well as proteins C and S by competitively inhibiting vitamin K epoxide reductase. This leads to decreased initiation of the coagulation pathways and aids in preventing further thrombotic events. In patients with acute PE, warfarin should be initiated on the first day of antithrombotic treatment and overlap (bridge) with LMWH or UFH for at least 5 days or until 24 hours after the international normalized ratio (INR) has reached the therapeutic range (INR, 2.0-3.0). The utility of bridging is 3-fold. First, warfarin inhibits only the new synthesis of vitamin K–dependent factors, and therefore preexisting clotting factors require 36 to 72 hours to clear from the circulation. Second, during the first 2 to 3 days of therapy with warfarin, the elevated prothrombin time reflects depletion of factor VII, which has a short half-life (5 to 7 hours); however, it does not reflect adequate anticoagulation because of incomplete suppression of the intrinsic coagulation pathway. Finally, rapid reduction of protein C, an endogenous anticoagulant with a short half-life (6

to 8 hours), can yield a transient hypercoagulable state, potentially leading to increased clot burden and, rarely, warfarin-induced skin necrosis.

In patients with known malignancy and VTE, LMWH alone has been shown to decrease recurrent VTE and potentially improve survival compared with warfarin.[6] This patient had no evidence of malignancy; therefore, monotherapy with LMWH would not be justified.

The patient was admitted to the hospital, and LMWH and warfarin were initiated. On day 3 of the hospitalization, the patient's hemodynamics normalized. Her medications included 10,000 U (200 U/kg) of dalteparin subcutaneously once daily and 5 mg of warfarin orally once daily. Her INR was 2.0 (0.9-1.2).

4. Which one of the following tests would be the least helpful if the patient was evaluated for thrombophilia at this time?

a. *Functional assay of protein C*
b. *Factor V Leiden gene mutation*
c. *Anticardiolipin antibodies, IgG, and IgM*
d. *Prothrombin (G20210A) gene mutation*
e. *Total plasma homocysteine level*

Protein C is a naturally occurring vitamin K–dependent anticoagulant. Deficiency of this protein leads to a hypercoagulable condition that is associated with warfarin-induced skin necrosis. Measurement of protein C activity alone cannot be reliably interpreted in the presence of warfarin or liver disease, both of which lead to decreased hepatic synthesis of protein C. However, protein C activity can be checked concomitantly with factor VII activity, which has a similar half-life. If both are proportionally depressed, then the reduced activity of protein C is attributable to warfarin. If protein C activity is disproportionately reduced, a congenital deficiency cannot be excluded. Checking protein C activity alone would be the least helpful test at this time.

Factor V Leiden is the most common genetic risk factor for VTE and is present in approximately 20% of patients with a first-time thromboembolic event.[7] A point mutation, known as *factor V Leiden*, in the factor V gene results in resistance to degradation by activated protein C and leads to thrombosis. Factor V Leiden testing by polymerase chain reaction is not subject to interference by warfarin. The antiphospholipid syndrome is defined by the presence of at least 1 antiphospholipid antibody in the setting of arterial or venous thrombosis, thrombocytopenia, or recurrent miscarriages. Anticardiolipin or $ß_2$-glycoprotein-I antibodies can be present in the serum of patients with antiphospholipid syndrome and are not affected by the presence of acute thrombosis, warfarin, or LMWH. Hypercoagulability can result from a transition mutation in the prothrombin gene that is associated with increased plasma levels of prothrombin. Prothrombin gene mutation testing via a polymerase chain reaction–based assay is not subject to interference by warfarin. Elevated levels of homocysteine increase (relative risk, 2.5) the risk of arterial and venous thrombosis and are present in approximately 20% of patients with an initial VTE.[7] Hyperhomocysteinemia is heritable but can be secondary to nutritional deficiencies, renal failure, hypothyroidism, and oral contraceptive (OC) use; warfarin does not affect testing.

The patient's PE was thought to be provoked by exogenous estrogen in the setting of tobacco use. Before her presentation, the patient was unaware of the risk of VTE with concomitant use of exogenous estrogen and tobacco. The patient was counseled on these risk factors and was agreeable to cessation of tobacco use but declined alternative contraceptive methods and intended to continue OC pills. It was thought to be appropriate, due to teratogenicity, to continue the OC pills for the duration of warfarin therapy and reconsider their use at follow-up.

The patient was successfully bridged to warfarin. At 3 months follow-up, her palpitations and tachycardia had resolved. Warfarin was discontinued. The patient declined alternative contraceptive methods.

5. Which one of the following oral contraceptives would be most reasonable to consider in the long-term management of this patient?

a. *Norethindrone (1 mg) plus mestranol (0.05 mg) (Ortho Novum 28, Ortho-McNeil Pharmaceuticals, Raritan, NJ)*
b. *Levonorgestrel (0.1 mg) plus ethinyl estradiol (0.02 mg) (Aviane21, Duramed Pharmaceuticals, Cincinnati, OH)*
c. *Drospirenone (3 mg) plus ethinyl estradiol (0.02 mg) (Yaz, Bayer Healthcare Pharmaceuticals, Wayne, NJ)*
d. *Norethindrone (0.5 mg) plus ethinyl estradiol (0.035 mg) (Brevicon, Watson Pharmaceuticals, Salt Lake City, UT)*
e. *Norethindrone (0.35 mg) (Micronor/Nor-QD, Watson Pharmaceuticals, Salt Lake City, UT)*

Mestranol, the 3-methyl ether of ethinyl estradiol, is used in first-generation formulations of combination (estrogen-progestogen) OC pills. The dose of estrogen as well as the type of progestogen influences the rate of VTE. However, absolute contraindications to any OC containing estrogen (eg, mestranol or ethinyl estradiol) include a previous thromboembolic event, undiagnosed uterine bleeding, active liver disease, and a history of an estrogen-dependent tumor. Therefore, a combination OC pill containing mestranol would not be appropriate in this patient with a history of VTE.

Levonorgestrel is a second-generation progestogen used in combination OC pills as well as in the progestogen-releasing intrauterine device, Mirena (Bayer Healthcare Pharmaceuticals, Wayne, NJ). Because of the presence of

ethinyl estradiol, this combination OC pill would be inappropriate. Drospirenone is a spironolactone analogue that has progestogenic, antimineralocorticoid, and antiandrogenic activity. Because of the latter 2 properties, it is associated with less weight gain and reduced hirsutism, respectively. However, the presence of ethinyl estradiol precludes its use in this patient.

Norethindrone is a progestogen used in combination OC pills as well as in progestogen-only contraceptive pills. Although this remains controversial, progestogen-only contraceptive pills have not convincingly been shown to be an independent risk factor for VTE.[8-11] Therefore, norethindrone without ethinyl estradiol would be the preferred OC pill in this patient.

The patient returned to the clinic 1 year after the completion of her anticoagulation. She had discontinued tobacco use and had experienced no episodes of recurrent VTE.

DISCUSSION

Acute PE is a common and potentially fatal disease. Symptoms and signs of PE are variable. In PIOPED II (Prospective Investigation of Pulmonary Embolism Diagnosis), a large national collaborative study, tachycardia was noted in 25% of patients with no previous cardiopulmonary disease. Dyspnea was the most common symptom overall.[12] The criterion standard for diagnosis is pulmonary angiography; however, spiral computed tomography with intravenous contrast medium has become increasingly used because of its availability and ability to detect alternative pulmonary abnormalities. Once the diagnosis is established, the clinician's goal is to identify thrombotic risk factors in order to guide appropriate management.

Risk factors that predispose patients to VTE can be classified as acquired or inherited. Common acquired risk factors include age, malignancy, surgery, immobilization, smoking, pregnancy, puerperium, and exogenous female hormones. Evidence suggests that risk factors for atherosclerotic disease are linked to VTE, but further elucidation is needed. Substantial evidence points to 2 of these risk factors, smoking and exogenous estrogen use, as predisposing conditions.[7,13]

Smoking is an independent risk factor with a dose-dependent and reversible association with VTE.[14] The risk of VTE in those taking combination OC pills depends on the dose of estrogen, type of progestogen, and length of use. The mechanism of estrogen-induced VTE is not completely known but is thought to be related to increased thrombin generation. The second-generation progestogen, levonorgestrel, is currently thought to have a decreased incidence of VTE compared with newer third-generation progestogens (eg, desogestrel or gestodene).[10]

No strict guidelines have been published about whom to screen for thrombophilias. Patients with an inherited thrombophilia with 1 provoked VTE have no higher risk of spontaneous recurrence than patients with a normal genotype.[15]

The management of PE provoked by an acquired risk factor, such as tobacco smoking or OC use, should consist of 3 months of vitamin K antagonist therapy and elimination of the risk factor (ie, smoking cessation). Screening for an inherited thrombophilia after a first VTE event in all patients is not currently recommended and should be individualized. After VTE, patients insistent on continuing OC use should be offered progestogen-only formulations, albeit with caution.

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Correct answers: 1. *e*, 2. *c*, 3. *d*, 4. *a*, 5. *e*