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Could ivabradine challenge be helpful for the diagnosis of intermittent sinoatrial node dysfunction in suspected patients?

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ABSTRACT

Sinoatrial node dysfunction (SND) is an important cause of syncope in the elderly. Though the diagnosis can be relatively straightforward in the persistent form of SND, it can be elusive when the dysfunction is intermittent. For intermittent SND, the diagnosis may require prolonged electrocardiographic recordings with an external or internal loop recorder, or an invasive electrophysiologic study. Ivabradine, an I_f inhibitor that slows sinoatrial discharge rate, is widely used for the treatment of chronic angina or heart failure. Though the drug is contraindicated in patients with known SND as it may exacerbate symptoms, we propose that a simple ivabradine suppression test, followed by a 24-h monitorization of heart rhythm, could be valuable to aid diagnosis of intermittent SND. The test we propose could be used prior to prolonged electrocardiographic monitoring in patients with suspected SND, but both the diagnostic accuracy and the safety should be evaluated with studies prior to implementation.

Introduction

Sinoatrial node dysfunction (SND), also known as sick sinus syndrome, is characterized with persistent or episodic reduction in sinoatrial discharge due to an intrinsic disease of the sinus node, causing a reduction in the heart rate. SND may present with tiredness, fatigue, palpitations, effort intolerance, or with overt heart failure [1,2]. When paroxysmal, the most common mode of presentation is presyncope or syncope, which may or may not be heralded by an aura [3]. Although SND *per se* does not cause an increase in mortality, frequent unheralded syncope attacks could cause substantial physical injury. A permanent pacemaker is indicated if the patient is symptomatic, and an evidence for SND, such as persistent bradycardia, sinoatrial (SA) pause or block, or bradycardia-tachycardia syndrome (BTS), is present [3,4].

A problem with intermittent SND is the difficulty of demonstrating a relationship between symptoms and haemodynamically significant bradycardia or SA pause. When the episodes are infrequent, long term monitoring with an external loop recorder (ELR) or even an implantable loop recorder (ILR) is indicated [5,6]. Demonstration of abnormal SA recovery time with an electrophysiologic study (EPS) is useful in some patients, but a negative EPS does not rule out abnormal SA function due to low sensitivity of this technique [3,7]. In addition, EPS is an invasive technique, which could be inconvenient for some patients. A summary of diagnostic tests currently in use are given in Table 1.

Ivabradine is an inhibitor of "funny" current (I_f), which is the primary current responsible for the spontaneous diastolic depolarization of SA node. I_f current is generated by the inward movement of Na^+ and K^+ ions in phase 4 depolarization, causing a slow but steady increase in resting membrane potential, and subsequently leads to activation of I_{Na} after the threshold potential is reached [8,9]. Hyperpolarization-gated channel (HCN) 4 alpha subunit is the main transmembrane ion channel that carries I_f current, and is targeted by ivabradine [10]. In healthy persons or in patients with underlying chronic cardiac disorders but with normal cardiac conduction, ivabradine produces slowing of sinus rate in a dose-dependent manner, but rarely leads to severe bradycardia as additional ionic channels besides HCN contribute to the normal SA node automaticity [11,12].

Normally, ivabradine is contraindicated in patients with known, advanced sinus node disease as it may produce asystole and syncopal episodes in this setting. However, we consider that the pharmacological properties of ivabradine could be exploited in the presence of suspected but unproven intermittent SND.

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Table 1
Available diagnostic modalities for the diagnosis of sinoatrial nodal disease. SA, sinoatrial node; SND, sinoatrial node dysfunction.

Diagnostic modality	Comment
12-lead electrocardiography	Diagnostic if persistent symptomatic SND. Less valuable in intermittent SND.
24-h Holter monitorization	Valuable in patients with daily symptoms, could refute diagnosis if syncope occurs with another arrythmia.
External loop recorders	Could record ECG up to one month (or longer if needed), valuable in patients with less frequent symptoms.
Implantable loop recorders	Allows prolonged (1 years or more) ECG monitorization, diagnostic in the vast majority of patients. Invasive modality.
Electrophysiologic study	Aids diagnosis in the presence of a prolonged corrected sinoatrial recovery time. Unually inconclusive. Invasive modality.
Exercise electrocardiography	For the diagnosis of chronotropic incompetence.
Pharmacologic challenge with atropine + isoproterenol	Combined parasympatholytic and sympathomimetic challenge to obtain maximal SA discharge rate.
Pharmacologic challenge with atropine + propranolol	Eliminates autonomic influence on SA node for differential diagnosis of extrinsic vs. intrinsic SND.

Hypothesis

When a patient presents with episodic syncope and an initial work-up including external loop recorders remains inconclusive, provocation of SA pause or bradycardia with low-dose ivabradine could be attempted prior to more prolonged or invasive procedures are undertaken. Reproduction of syncopal episodes, along with severe sinus bradycardia or SA pauses could be diagnostic in patients with suspected SND. Ideally, the ivabradine challenge should be attempted in a hospital setting with 24-h continuous electrocardiographic monitorization or with telemetry, and facilities for immediate temporary pacing should be available to avoid potential life-threatening prolonged asystole.

Discussion

The etiology of SND is multifactorial, with age-dependent degeneration being the most common cause. Regardless of the underlying etiology, patients with SND exhibit total or subtotal destruction of nodal tissue, and fatty or fibrotic infiltration of the node, as well as areas with nodoatrial discontinuity [13]. It is essential to differentiate external (autonomic) effects on sinus node from intrinsic (structural) SND, as permanent pacing is not indicated in the absence of intrinsic nodal disease. The sole action of ivabradine is on the I_f channels and does not exert any effect on autonomic fibers. Therefore, bradycardia or pauses induced by ivabradine should indicate an intrinsic SND and would allow selection of patients who could benefit from permanent pacemaker implantation.

Pharmacological provocation to assess SA node function is not a new concept and has previously been applied with drugs that affect cardiac autonomic system. The rationale underlying these approaches were either achieving a complete sympathetic and parasympathetic blockade with atropin and propranolol or achieving maximal stimulation of SA node by combining vagolytic effects of atropine with β1-stimulating effects of isoproterenol [14,15]. These approaches, however, have either targeted eliminating autonomic influences on the SA node or achieving maximal stimulation, rather than further suppressing intrinsic SA nodal activity. Even these tests are valuable to negate effects of autonomic system on SA node or to achieve maximal SA discharge rate, these agents are rarely employed in clinical practice. The approach suggested in the present hypothesis is novel as suppression of SA nodal functions, rather than eliminating autonomic influences, is targeted by ivabradine challenge. Projected advantages and disadvantages of the proposed test is summarized in Table 2.

Evidence in favour of hypothesis

Ivabradine causes a dose-dependent reduction in sinus node discharge rate without affecting the atrioventricular node, or other parts of HIS-Purkinje system [16]. As ivabradine dose not block all channels involved in SA automaticity, the drug will not cause profound bradycardia or sinusal arrest in the majority of healthy persons with no known SA node disease. Bradycardia develops in 3–4% of patients on ivabradine therapy, but the majority of these patients are asymptomatic [17]. In SHIFT study, only 1% of patients with congestive heart failure have developed symptomatic bradycardia [12]. In patients with stable angina but no known conduction disease, ivabradine does not cause an increase in conduction disturbances [18]. When interpreting these results, it should be reminded that the majority of patients included in clinical trials received ivabradine on top of β-blockers as the patients evaluated in these studies either had heart failure, coronary artery disease, or both [12,19]. Even when used on top of β-blocker agents, symptomatic or asymptomatic bradycardia rates remained low in subjects with no history of SND. Based on these low rates of symptomatic bradycardia with this agent, we assume that the number of patients with a false positive test would be low after ivabradine challenge if they do not exhibit an intrinsic SND.

On the other hand, the drug is contraindicated in patients with known SND or in those with sinus bradycardia due to the potential of the drug to induce SND or cause an accentuation of bradycardia, pauses, and syncopal episodes. In patients with intermittent SND, in which the symptoms are produced by pauses or short bradycardia episodes, ivabradine could increase the degree of SA dysfunction and therefore reproduce pauses and syncope episodes. Since there is no data regarding to usage of ivabradine in patients with bradycardia, it is not possible to estimate the sensitivity of this "provocation" test at this moment.

An interesting complication in patients using ivabradine is an unexpected increase in paroxysmal atrial fibrillation (PAF) episodes. A meta-analysis of major trials that reported the incidence of AF showed a relative risk of 15% for PAF in patients on ivabradine therapy [20]. The exact cause of this increase in PAF episodes remains unknown, but patients on ivabradine therapy consistently have a lower heart rate compared to control groups in clinical trials. A similar increase in PAF episodes in also observed in patients with SND, which is termed as "tachy-brady" syndrome and is characterized by alternating episodic atrial tachyarrythmias coupled with sinusal bradycardia and prolonged sinus pauses [3,4].

Table 2
Potential advantages and disadvantages of the proposed ivabradine challenge to diagnose intermittent SND. *The test is expected to have a high negative predictive value as the absence of significant bradycardia or pauses should prove adequate sinoatrial function even challenged with a potent I_f blocker.

Potential advantages	Potential disadvantages
Noninvasive	Need for hospitalization.
Eliminates the need for prolonged monitorization	Facilities for temporary pacing should be immediately available if life-threatening bradycardia occurs.
Targets intrinsic node function rather than autonomic influences	False positive tests.
Projected to have a high negative predictive value*	Difficulty in interpretation of asymptomatic episodes.