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Recommended Citation
Yap-Hang Will Chan, Unusual Manifestation of Atrioventricular Dissociation in A 63 Year-Old Man and Clinical Insights
Journal of the Hong Kong College of Cardiology 2023;30(5) https://doi.org/10.55503/2790-6744.1515

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CASE REPORT

Unusual Manifestation of Atrioventricular Dissociation in a 63-year-old Man and Clinical Insights

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Abstract

Ivabradine is a specific funny current inhibitor, which blocks Hyperpolarization-activated Cyclic Nucleotide-gated cation channels intra-cellularly and results in delayed diastolic depolarization in a use-dependent manner. Prior-believed to be exclusively expressed within the sinoatrial node, funny channels were recently revealed to be also expressed in the atrioventricular node and throughout the myocardium. These invite a key clinical question as whether pharmacological effects of ivabradine may extend beyond its conventional clinical use.

Here reported is an unusual case of atrioventricular dissociation associated with ivabradine use, dissecting which may lead us to consider broader potential implications of this observation.

Keywords: Atrioventricular dissociation, Isorhythmic dissociation, Ivabradine, Funny current

Introduction

This case report describes the clinical story of a patient who presented with an unusual cardiac rhythm, dissecting which would lead us to consider broader potential implications of the underlying aetiology.

Case report

A 63-year-old man with good past health had recent acute anterior ST segment-elevation myocardial infarction 8 days ago, for which he received primary coronary angioplasty to a thrombotic occlusive lesion of his left anterior descending artery with successful revascularization. He received aspirin, ticagrelor, rosuvastatin, and ramipril, as well as combination anti-anginal therapy comprising bisoprolol (1.25 mg daily), trimetazidine dihydrochloride, and ivabradine (2.5 mg BID). He remained stable until this day, when he developed intermittent bradycardia, hypotension and dyspnea. On examination, there was new-onset epigastric pain with positive Murphy’s sign. A 12-lead electrocardiogram showed an unusual rhythm with variable PR intervals and evidence of accelerated junctional rhythm (Figure 1A). There was pre-existing presence of right bundle branch block. Q waves with some residual ST-segment elevation were evident over leads V1 to V3, with T-wave inversion seen over the precordial and inferior leads. A long tracing was obtained (Figure 1B). Transthoracic echocardiography confirmed static left ventricular ejection fraction of 45% with nil mechanical complication. Subsequent results of serum cardiac troponin were unrevealing. Complete blood counts showed marked neutrophilia. The overall clinical picture was consistent with a primary diagnosis of acute cholecystitis, which was confirmed by a CT scan of the abdomen. He was given...
intravenous antibiotics and underwent successful emergent open cholecystectomy. He subsequently regained normal sinus rhythm, completed a course of antimicrobial treatment and was discharged after rehabilitation. While underlying problems of the patient appeared straightforward, what was the interpretation and cause of the presenting abnormal cardiac rhythm?

Discussion

Here reported is a rare case of atrioventricular (AV) dissociation associated with ivabradine use. Careful analysis of the AV coupling intervals revealed isorhythmic dissociation with triphasic changes (Figure 2). The atrial rhythm was that of a normal sinus rhythm, while accelerated junctional rhythm predominated in the ventricles. The sinus rate could be perceived as “inappropriately normal” in the setting of an active infection. Accelerated junctional rhythm could be due to various causes, such as myocardial ischemia or injury, systemic stressors such as infection, or digitalis toxicity. In this case, sepsis is an apparent trigger. A complete clinical assessment routinely includes assessment of the thyroid function, oxygen level and electrolytes. Notably, there was a period of atrial depolarization faster than but remained dissociated with ventricular depolarization that suggested an element of heart block. The observed isorhythmic dissociation could be a resultant manifestation of sinus node suppression by ivabradine and a relative usurpation by sepsis-triggered accelerated junctional rhythm. While the constituent presence of heart block was at least partially explained by effect of bisoprolol, recent studies uncovered functional expression of Hyperpolarization-activated Cyclic Nucleotide-gated cation channels (HCN) in the AV node [1] and the diseased myocardium [2]. Clinically relevant, extra-sinoatrial node effects of ivabradine in modulating the cardiac rhythm ought to be considered in this context.

Ivabradine is a specific funny current inhibitor, which blocks HCN intra-cellularly and results in delayed diastolic depolarization in a use-dependent manner [3]. Prior-believed to be exclusively expressed within the sinoatrial node, HCN was recently revealed to be also expressed in the atrioventricular (AV) node and throughout the myocardium [4,5]. These invite a key clinical question as whether pharmacological effects of ivabradine may extend beyond its conventional clinical use [6–8].

Ivabradine has been considered and used as a specific inhibitor of the pacemaker current (I_{f}), through targeting the HCN expressed in the sinoatrial node. It is currently FDA-approved for reducing hospitalization in patients with stable, symptomatic heart failure with impaired left ventricular ejection fraction (LVEF) <35% and heart rate ≥70 bpm after maximally tolerated betablocker therapy. It is also
indicated under European Society of Cardiology class IIa recommendation for patients with stable angina who did not respond to first-line therapies [3]. Prior trials demonstrated its good safety profile, with incidence of bradycardia amongst patients administered therapeutic doses of ivabradine ranging between 8% and 18%, the majority being asymptomatic [9,10].

Although in this case, there is an association between ivabradine use and isorhythmic dissociation, causality cannot be readily established. Furthermore, there was co-existing use of a betablocker and ticagrelor, effects of which cannot be excluded. Another important clinical differential diagnosis to consider is the Cope’s sign, a vagally-mediated cardio-biliary reflex that could result in bradycardia and asystole in the presence of abdominal pain. Nevertheless, having considered these study limitations, from the mechanistic perspective a pharmacological effect of ivabradine on the AV node is supported by experimental and recent clinical studies. Furthermore, our recent clinical study also showed that ivabradine may have a potential clinical role in the treatment of patients with permanent atrial fibrillation, based on its effects on the AV node [11]. Thus simple clinical observations as illustrated in this case, re-capitulate mechanistic insights on the effects of ivabradine which may harbor important opportunities for further research and development of cardiac therapeutic frontiers.

**Funding support**

The author’s work was supported by the Sir David Todd Memorial Scholarship 2022/23, and Young Investigator Research Grant 2022, Hong Kong College of Physicians; and Li Shu Pui Medical Foundation Fellowship.

**Conflicts of interest**

None declared.

**Ethical information**

Not applicable.

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