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CASE REPORT

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Management of Diastolic Dysfunction by Pharmacological Optimization of E-A Wave Synchrony and Morphology

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ABSTRACT

Heart Failure is a major public health problem globally, affecting about 5.1 million patients in the US, almost 40% of whom have predominantly diastolic left ventricular (LV) dysfunction. Pulsed doppler echocardiography of the mitral inflow, in terms of E-A ratio, is used in the assessment of diastolic function. Besides E-A ratio, optimization of E-A wave synchrony and morphology has also been shown to improve diastolic filling and cardiac hemodynamics in patients with cardiac implantable electronic devices (CIED). In this case report, we applied the principles of echocardiographic AV optimization in CIED patients to patients without CIEDs by pharmacological intervention to improve LV diastolic function.

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Heart failure, E-A wave, CIED, Diastolic dysfunction.

Introduction

Diastolic dysfunction, now referred to as heart failure with preserved ejection fraction, is responsible for around 50% of the cases of heart failure [1,2] and the incidence is on the rise over the last few decades [3]. Echocardiography has remained a very rapid, relatively accurate, and noninvasive method to diagnose and follow-up patients with heart failure. Current guidelines include establishing diastolic dysfunction by echocardiography as one of the criteria to diagnose HFpEF [4]. Filling of the ventricle in ventricular diastole occurs in three phases, a rapid early diastolic filling phase driven by the negative pressure from ventricular relaxation where most of the blood enters the ventricle, a mid-diastolic phase where some or no blood enters the ventricle and a late diastolic filling phase with contribution from atrial systole drives the rest of the blood into ventricle. E/A ratio characterizes the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole affected by atrial contraction (the A wave) [5]. Abnormalities in the E/A ratio propose that the left ventricle cannot fill with blood appropriately in the period between contractions. This phenomenon is called diastolic dysfunction and can ultimately cause symptoms of heart failure [6]. Traditionally, diastolic function assessment has been carried out by calculating the parameters of transmittal flow including the early (E) and late (A) diastolic filling velocities, E/A ratio using a conventional pulsed wave Doppler. E/A ratio is also influenced by various compensatory mechanisms, preload, age, afterload, and contractility [7,8]. Therefore, E/A ratio for the diagnosis and grading of diastolic dysfunction is used in conjunction with other parameters like the deceleration time (DT), changes in E/A ratio with Valsalva, E/e' where e' is the early diastole mitral annular tissue velocity measured using tissue doppler, tricuspid regurgitation velocity, and left atrial pressure and volume [9].

Cardiac Implantable Electronic Devices (CIED) are devices capable of performing pacing, defibrillation, and cardioversion of the heart. To ensure effective functioning of the heart, optimizing the CIED is essential and the two main optimization parameters are AV delay (AVD) and VV Offset [10]. The goal of optimizing AVD is to create efficient diastolic dynamics with the help of echocardiography, in turn optimizing the synchrony and temporal morphology of E and A waves in the pulsed doppler of mitral inflow. An efficiently programmed AVD allows the passive diastolic filling (E) and the atrial kick (A) that pushes additional blood into the ventricle to occur synchronously and in optimal proportions [11]. If the AV delay is long, then atrial depolarization starts early, A wave occurs prematurely and fuses with the E wave. If the AV delay is kept too short, then there is E-A diastasis, with the atrial contraction getting interrupted by early contraction of the ventricles resulting in A wave truncation [12]. AVD optimization in patients with pacemakers has been associated with improvement in cardiac hemodynamics and reduction in heart failure symptoms [13]. This principle finds application in cardiac resynchronization therapy (CRT), one of the major types of CIEDs that has revolutionized the treatment of drug-resistant advanced congestive heart failure. The aim of CRT is to achieve mechanical synchrony of the heart via activating electrical impulses in a synchronized fashion [14]. Although CRTs are usually used in the treatment of systolic dysfunction, there has been evidence that they improve the diastolic outcomes of the heart as well [15]. In patients without CIEDs, AVD (PR interval) optimization can instead be done pharmacologically, using drugs that are known to prolong or shorten the PR interval (AVD).

In this case, we demonstrate an 89-year-old woman with multiple comorbidities presented with a malfunctioning Percutaneous

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Endoscopic Gastrostomy (PEG) tube. Echocardiogram revealed a preserved LV ejection fraction, diastolic dysfunction with impaired relaxation pattern, and significant fusion of E-A waves with bilateral pleural effusion. The patient was treated with Ivabradine (IVA).

Case Description

An 89-year-old woman with multiple comorbidities presented with a malfunctioning Percutaneous Endoscopic Gastrostomy (PEG) tube. The patient was stuporous, with UTI, elevated leukocytes, and transaminases, and was treated with antibiotics and IV fluids. Echocardiogram revealed a preserved LV ejection fraction, diastolic dysfunction with impaired relaxation pattern, and significant fusion of E-A waves, with bilateral pleural effusion (Figures 1, A and B). Heart rate (HR) ranged from 100-110/min.

Interestingly, a vagal event with decreased HR and shortened PR interval (ectopic junctional beat) was captured in the echo, demonstrating the correction of the E-A wave temporal morphology by de-fusing the waveforms. By CIED echo optimization, prolongation of AV(PR) interval results in E-A wave fusion, while shortening the AV(PR) interval accentuates E-A wave diastasis [4]. Hence a medication that would reduce the sinus rate without PR prolongation will help correct the E-A wave fusion in this patient, and with this rationale, patient was started on ivabradine 5mg BID, which selectively inhibits the inward pacemaker current (If), that controls the spontaneous diastolic depolarization in the sinoatrial node and thus lowers the HR without directly affecting AV conduction [5]. On ivabradine, HR reduced to 70-80/min and a repeat echo demonstrated significant de-fusion of the E-A waveforms. LV diastolic function improved, as evident by the resolution of her pleural effusion (Figure 2 A and B).

Discussion

Ivabradine (IVA) belongs to an HCN (hyperpolarization-activated, cyclic nucleotide-gated) channel blocker family, with a negative chronotropic function. IVA is an orally bioavailable novel medication that selectively binds to and inhibits the HCN channels in the cardiac pacemaker cells of the sinoatrial (SA) node, inhibiting the cardiac pacemaker funny current (I_f) [16]. I_f current allows an influx of sodium-potassium current through HCN channels to cause the diastolic depolarization in the SA node and hence modulate the heart rate [16]. IVA inhibits the influx of I_f current, prolongs diastolic depolarization in the SA node, and slows pacemaker firing. This in turn decreases the heart rate (HR), providing more time for the blood to flow through the heart, and reducing the myocardial oxygen demand without affecting the contractility of the myocardium. Since IVA is specific to the SA nodal activity, it does not affect blood pressure, myocardial contraction, and ventricular repolarization [16].

The HR increases in both systolic and diastolic chronic heart failure (CHF) to maintain the cardiac index. The rise in HR is associated with worsening of coronary artery disease (CAD), cardiac mortality, and increased hospitalization. Thus, a reduction in HR has proven to be beneficial on cardiovascular

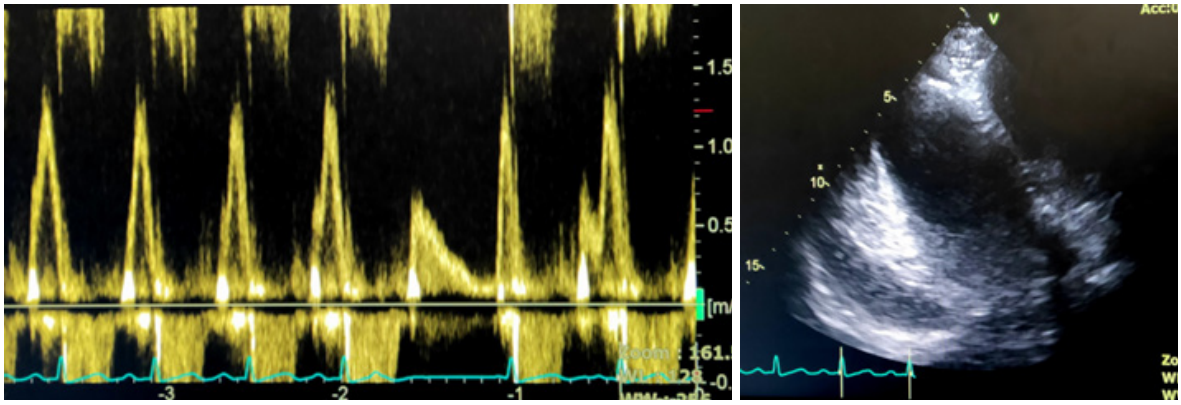

Figure 1: (A) Pulsed doppler echocardiography of the mitral inflow showing E-A wave fusion and a vagal event with decreased HR and shortened PR interval (ectopic junctional beat). **(B)** Pleural effusion seen on echocardiogram.

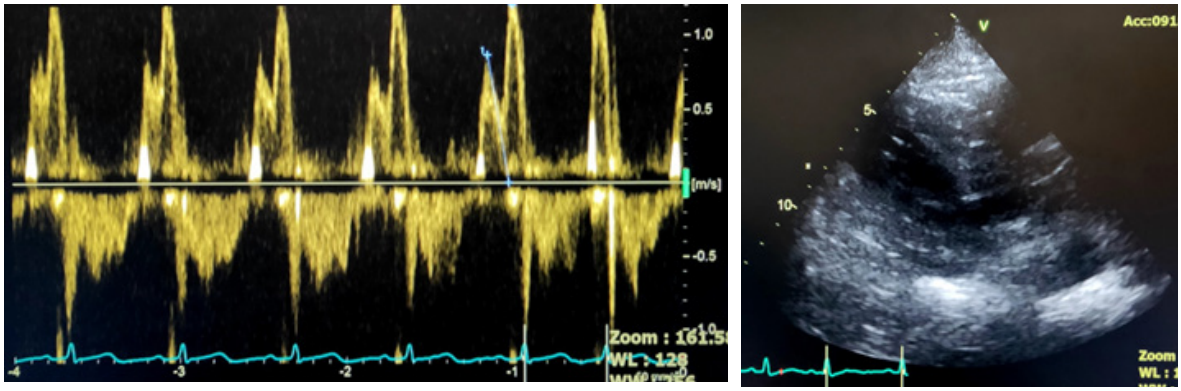

Figure 2: (A) Pulsed doppler echocardiography of the mitral inflow showing significant E-A wave de-fusion post treatment with ivabradine. **(B)** Pleural effusion resolved post treatment with ivabradine.

mortality, morbidity, and decreased rate of hospitalization in heart failure patients [17]. Several studies have testified that the heart rate lowering property of IVA is beneficial in patients with symptomatic and CHF with a reduced ejection fraction (HFrEF) of less than 40% and who have heart rate above 70 bpm despite receiving optimal doses and/or intolerance of beta-blocker medication [16]. However, its effect on improvement in heart failure patients with preserved ejection fraction (HFpEF) of more than 50% or slightly reduced ejection fraction (EF between 40% and 50%) is not well described. Thus, this study aims to evaluate the effects of Ivabradine (IVA) on patients with diastolic heart failure and preserved ejection fraction (HFpEF).

Cacciapuoti, F., et al. (2017) studied the role of IVA in 25 patients with diastolic heart failure (HF) who belonged to NYHA (New York Heart Association) Class II and III. IVA (5 mg/twice daily) was added to their conventional HF medical regiment for 3 months. Patients underwent two-dimensional (2D) echocardiographic evaluation (for pulmonary venous flow and diastolic mitral flow) and tissue Doppler imaging (TDI) (for diastolic mitral flow) at the mitral annulus immediately before the start of and at the end of 3 months IVA therapy. It was noted that the HR was significantly reduced from baseline in those on IVA therapy. The improved patterns of LV diastolic function seen on 2D echocardiography and TDI of the HFpEF patients upon the administration of IVA to the conventional HF regimen matched with the clinical improvement of these patients [17]. The baseline diastolic mitral Doppler flow findings of HFpEF patients in NYHA class II showed an impaired LV diastolic function with E/A ratio < 1, while there was a significant increase in E velocity and a reduction of A wave velocity after 3 months (12 weeks) of IVA therapy [17]. Additionally, IVA causes a reduction in oxidative stress, circulating angiotensin II-aldosterone levels, cardiac fibrosis and remodeling, and ventricular collagen Type I improving diastolic function [17]. IVA stabilizes proinflammatory cytokines, tumor necrosis factor (TNF)-α, and IL-6. These effects of IVA on HF patients cause ventricular relaxation, increased myocardial compliance, LV remodeling, and improvement of endothelial function. These factors are crucial in reducing all-cause mortality and readmission for worsening HF symptoms in patients with HFpEF [17].

Conclusion

The principles of AV optimization in patients with CIEDs can thus be applied to pharmacologically optimize E-A wave synchrony and morphology in patients with diastolic dysfunction to help improve their cardiac hemodynamics. This concept could potentially be applied to patients with silent diastolic dysfunction, to prevent their downstream cardiopulmonary decompensation.

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