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Case Report

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Pharmaceutical Atrial-Ventricular Optimization in Diastolic Dysfunction: A Clinical Concept Application of Materials Engineering To Myocardial Pathophysiology

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Introduction

The cardiac cycle can be divided into two main phases: ventricular contraction (systole) and ventricular relaxation (diastole), at both a macroscopic (Atria and Ventricular) and microscopic level (Actin: Myosin myofilament) [1]. A novel model is elucidated in this paper incorporating the principles of biomechanics, physiology, anatomy and electrophysiology to clinically redefine diastology. The ventricular diastolic phase divided into sub phases. During normal electrophysiological and hemodynamic conditions, the ventricular diastolic phase starts with the closure of the ventricular outflow tract valves (aortic and pulmonic) (S2). One of the three possible intraventricular diastolic vacuum phases follows known as the isovolumic relaxation phase (IVRT). Once the atrio-ventricular valves open, blood flows from the atria to the ventricles passively (producing the e wave) with subsequent active filling of the ventricles with atria contraction (producing the a wave).

Passive myocyte relaxation (micro diastology) is inadequate when the ventricular walls become less compliant (increased modulus). Once the walls become thick and stiff, primarily due to concentric hypertrophy from hypertension or possibly, from infiltrative or valvular conditions, ventricular diastolic volume decreases, thus, causing an increase in ventricular filling pressure and a diminished ventricular output. Cellular and tissue changes can eventually lead to systolic dysfunction likely as a result of chronic, dynamic aberrations (e/a ratio, timing, waveform) of macro and micro myocardial tensile stress and strain at the actin: myosin interface and subsequent atrial: ventricular interface [2]. The degree to which these macro/micro diastolic morphological changes occur with respect to the right and/or left ventricles dictates subsequent up stream repercussions (right heart-JVD, abdominal pain/ bloating, IBS; left heart- PV regurgitation/Afib and downstream repercussions (right heart- decreased RV filling/ output, dyspnea; left heart- decreased cardiac output, increased PCWP, MR), on physiology, symptomatology and pathology.

There are several ways to evaluate myocardial diastolic dysfunction. A traditional methodology uses mitral inflow Doppler echocardiography to evaluate the transmittal flow velocity across the mitral valve, which reflects the pressure gradient between the left atrium and the left ventricle. Normal atria-ventricular flow has two major active filling phases: rapid early filling represented by the e wave and late atrial contraction, represented by a wave, which normally contributes up to 25% of the ventricular end diastolic volume [3]. A normal atria-ventricular flow has an e/a ratio from 0.75 to 1.5, a function of micro diastology [4]. Diastolic dysfunction is presently classified into four grades (pressure: volume/time = velocity) based on the mitral inflow findings using the e and a wave velocities and ratio to evaluate the severity of diastolic dysfunction. Grade 1, mild diastolic dysfunction, referred to as impaired relaxation, has an e/a ratio less than one. This is due to impaired LV micro diastolic relaxation without significant elevated LA pressure. Grade 2, moderate diastolic dysfunction, pseudo normal filling, has a normal e/a ratio appearance because the LA pressure is increased due to impaired LV relaxation and the pressure gradient across the mitral valve is re-established usually as a result of hypertension with increased left sided filling pressure. Grade 3 and 4, severe diastolic dysfunction with restrictive filling, are caused by further increases in ventricular filling pressure indicated by an increased e wave velocity with a peaked appearance and a small a wave. Grade 3 is reversible, (i.e., with respiratory cycle, Valsalva, pharmaceuticals, etc.), while grade 4 has no reversibility of the wave peak velocity with the aforementioned conditions. Both grades are usually symptomatic in patients and are indicative of myocardial creep with loss of actin: myosin cross bridging leading to myocardial fatigue and eventual myocardial failure [5-8].

The description of novel and conventional principles by which ventricular diastole, diastology, are herein described. The e and a wave are "normally" minimally separated during right/left ventricular diastole, producing a second intracardiac diastolic vacuum effect, and their distance inversely reflects the AV node/PR interval delay at the macro diastolic level. If the AV node delay is shorter than normal, as represented by the PR interval on EKG, then diastasis (de-fusion) may occur between the e and a waves with possible a wave truncation, resulting in premature closure of the tricuspid/ mitral valves. This produces a possible caval/ pulmonary vein regurgitation downstream effect. If there is a long AV node delay/PR interval, the e and a waves are described as fused with a possible early relaxation abnormality producing completion of atrial contraction before the AV valve is completely closed resulting in a prolonged isovolumetric contraction time (IVCT), the generation of a third intracardiac diastolic vacuum effect [9]. These intracardiac vacuums may be minimal or in excess of >50% of the cardiac cycle, i.e., >50% of life, thereby demarcating this effect as a major potential upstream and/ or downstream anatomical, electrophysiological and / or physiological process which must be considered when assessing etiologies of symptoms and pathological processes.

In addition to the macro diastolic component, the micro diastolic element must be considered when assessing symptoms, conditions and/or diseases possibly due to diastology derangement. Microdiastology refers to the microscopic processes which occur during ventricular diastole, i.e., any process, physiological (acidosis, hypocalcaemia, etc.) and/or pathological (fibrosis, elastosis, etc.) at the actin/myosin interface level. The three potential intracardiac vacuum periods, IVRT, e-a diastasis, IVCT, must be considered in assessing symptoms, pathologies and/potential treatments for cardiac and systemic conditions so as to treat and/or prevent diastolic related symptoms/pathologies by eliminating these periods of intracardiac vacuum. The downstream vacuum effects may potentially lead to inadequate ventricular preload, as an example, while the upstream vacuum effect could produce gastrointestinal symptoms possibly misconstrued as irritable bowel syndrome as one of multiple such consequences due to this diastolic aberration.

The AV node delays the electrical impulse as it travels from the atria to the ventricles resulting in the macro diastolic feature of the novel diastology concept described herein. This delay allows for adequate ventricular filling during diastole. There is also a significant influence of the autonomic nervous system and/ or aging/pathological processes on the AV node. Sympathetic stimulation allows for shortening of the conduction time and the refractoriness of the impulse via the fast pathway [10]. However, it must remember that as the AV node becomes diseased, decrement and prolongation of AV conduction occurs at lower sinus rates and, therefore, fusion of e-a waveforms occurs. Alternatively, with enhanced AV conduction, e-a diastasis occurs with the generation of an intracardiac vacuum being produced. AV nodal decremental conduction is a protective feature of the heart that does not allow rapid atrial signals, i.e., atrial fibrillation/ flutter, to transmit to the ventricles through the HIS bundle. Pathological, iatrogenic, pharmaceutical and/or certain cardiac conduction processes can be used to prolong or shorten the AV interval allowing for optimization/normalization of diastolic filling physiology.

The methodology discussed is based on published CIED* optimization techniques and applied standard electrophysiological and echocardiographic principles to individuals without CIEDs using chronotropic and dromotropic pharmacotherapies while assessing cardiac function using echocardiography to primarily optimize diastolic cardiac function based on previously described, novel parameters of diastology characterization [9-12]. This was assessed by improvement in AV valve inflow physiology and e-a wave morphology and timing. This case and the applied echocardiographic principles described aim to use accepted timing intervals in current echocardiographic CIED optimization techniques to normalize inherent cardiac physiology to modify and prevent future cardiac decompensation in diastolic and systolic disease and heart failure states [9-11]. A case illustrating pharmacotherapy optimization of both systolic and diastolic function in various states of diastolic dysfunction will be presented.

Case Report

We need to create a patient life scenario from a healthy youth to a teenager with mild symptoms of chest pressure at rest brushed off as atypical chest pain due to costchondritis with subsequent development of dyspnea with exertion in his 20-40's. In his 50s, he developed palpitations with paroxysms of "SVT" treated with the addition of a calcium channel blocker to his ACE inhibitor for hypertension. At 58yrs old, he began developing scotomas and fleeting memory loss with EKG (SR with fractionated p wave). At 60yrs., he had his first CVA "due to hypertensive crisis". At 62yrs., he developed a cold left leg with gangrenous changes requiring a left BKA. At 64yrs, he had documented atrial flutter with spontaneous contrast and significant MR noted on TEE with preserved EF, was placed on a NOAC, and subsequently underwent a cardioversion and ablation. At 66-year-old, this Hispanic male with diabetes mellitus and hypertension presented to the hospital emergency room with dry gangrene of the right foot in sinus rhythm. A surgical debridement of the wound was planned and cardiology clearance was requested.

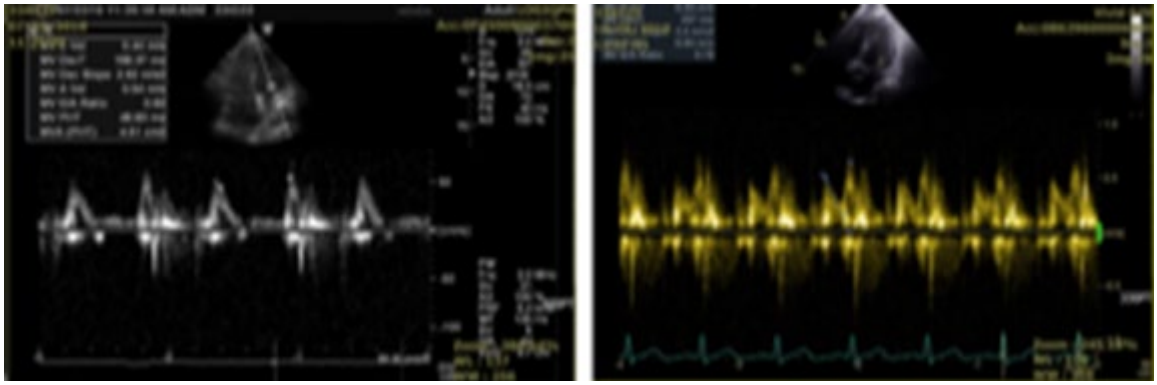

Figure 1: Pulse Doppler of the mitral valve from 2016 (left) and 2019 (right) in a patient without a CIED* on metoprolol.

A preop 2016 2D-echo Doppler revealed trace mitral regurgitation with mild diastolic dysfunction with an e/a ratio < 1 (Type 1) by conventional definition, significant e-a diastasis with minimal a wave truncation by Doppler on no dromotropic agents. LVEF was greater than 55%. In 2019, Figure 1, right image, while treated with metoprolol 50mg BID, the pulse Doppler of the mitral valve revealed an e/a ratio slightly less than 1 and a normalized e-a waveform morphology and timing with no e-a diastasis. The ejection fraction remained preserved with only mild mitral regurgitation.

Discussion

The patient presents a unique case of corrected e-a diastasis pharmaceutically based on echocardiographic CIED optimization principles [9,11]. In Figure 1, the 2016 echo showed diastasis of the e and a waves with the e wave taller than the a wave conventional as Type 2 diastolic dysfunction, pseudo normal pattern (e/a 0.8-1.5, MV DecT 160-200ms) [8]. Three years later, the patient exhibited a taller a wave than e wave (Type 1 diastolic dysfunction by current definition, e/a <1.0, DecT >200ms). The patient's diastolic dysfunction "regressed" by the conventional definition of diastolic dysfunction utilizing e/a ratios with increased ventricular stiffness or modulus, however there was no further evidence of diastasis, fusion, truncation or early relaxation, a primary function of macro diastology, purportedly as a result of the dromotrophic effect of metoprolol normalizing waveform, morphology and timing evidenced by fusion of the e-a waveforms [13]. The addition of a dromotroph, metoprolol, a selective Beta 1 antagonist, slowed fast pathway conduction of the AV node, resulting in diminution of the e-a diastatic period and a more physiologically normal diastology waveform with loss of the a wave truncation.

In Grade 2 diastolic dysfunction, pseudo normalization, the pressure between the ventricles and the atria is re-established, although, the intracardiac pressure is increased initially due to decreased left ventricular relaxation (decreased elasticity/ increased modulus), occurring at a micro diastolic level, i.e., between the actin and myosin interface [14,15]. After the patient started metoprolol, his echocardiogram showed a reversible conventional pattern to grade 1 diastolic dysfunction, but with complete loss of the diastasis/intracardiac vacuum effect due in part to effects on macro diastolic properties. It is also hypothesized that the loss of the elastic recoil mechanism of the ventricles at a micro diastolic level causes a decrease in the force of blood into the ventricles without changes in the left atrium pressure. Physiologically, a delay of the IVRT is seen which is responsible for the delay in the atria-ventricular valves opening potentially producing upstream (pulmonary vein, caval) regurgitation/ volume/pressure overload. The rate of the blood flow into the ventricles fall so the slope of the e wave decreases. The taller a wave in grade 1 dysfunction can be attributed to the abnormally high atrial filling pressures generated with atrial contraction into a downstream volume/pressure overloaded right/left ventricle.

Beta-blockers, such as metoprolol, if titrated correctly, can cause normalization of the e-a waveform without excessive fusion. Metoprolol has beta 1 receptor blockade activity with minimal beta 2 receptor blockade effect. It has negative inotropic and chronotropic activity thus resulting in potentially decreased cardiac output [16]. Metoprolol also has a direct effect of slowing the AV nodal fast pathway electrophysiology conduction properties. As seen in Figure 1, it is evident that beta-blockers can potentially normalize both micro and macro diastolic dysfunction. While it is unknown when this patient was placed on a beta-blocker during the three years between the two echocardiograms, it is evident there was improvement in diastasis and waveform morphology/timing eliminating the intracardiac vacuum effect on upstream structures. This finding provides evidence of the benefits of using a beta-blocker and other dromotrophs in the normalization of diastolic function and atria-ventricular inflow physiology. (This reasoning process, i.e., at both a macro and micro diastolic level, should be clinically applied to all cases where chronotropic and dromotropic pharmaceuticals are used and/or where certain symptoms/ conditions go unexplained) [17].

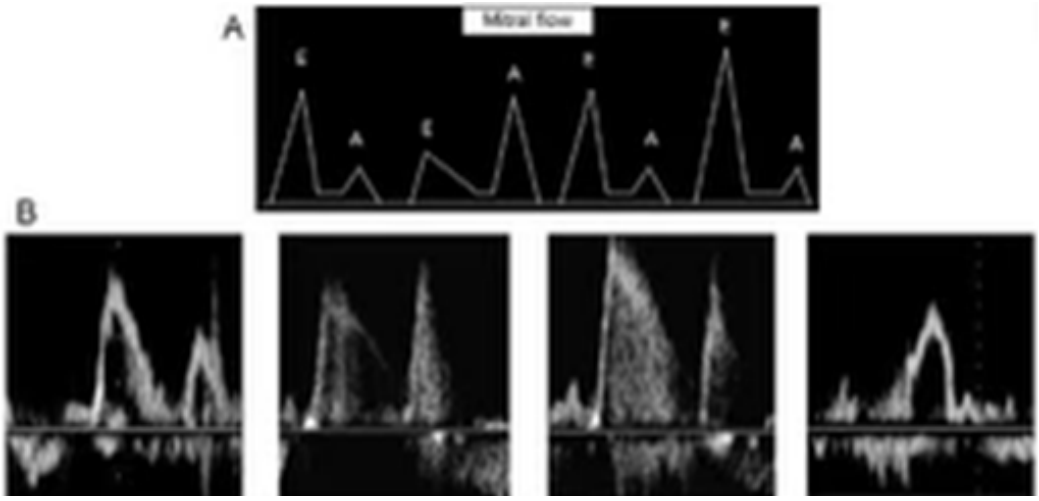

Figure 2: Drawn image (A) An Actual Image (B) Showing the e and a Doppler waves and their variations according to diastolic dysfunction grades. This schema shows the different grades of DD (normal DF, grade 1 DD, grade 2 DD, and grade 3 DD from left to right) as initially suggested by Appleton et al.10 DD, diastolic dysfunction; DF, diastolic function.
CIED- Cardiovascular Implantable Electronic Device

Conclusion

Based on the above description and redefinition of ventricular diastolic filling waveforms, patterns, timing and ratios, the accepted CIED timing intervals for echocardiographic AV optimization can be applied to patients without CIEDs using pharmaceuticals and their known effects on AV conduction with correlation simultaneously to the ventricular filling patterns, morphologies and timing by Doppler of the AV valves. The pharmaceutical effects of dromotropic agents can be used, directly and/or indirectly, to alter the AV nodal conduction system. Negative dromotropic drugs, such as non-dihydropyridine calcium channel blockers, beta-blockers and digoxin, can be used to increase the AV node delay. Positive dromotrophs, dihydropyridine calcium channel blockers, such as nifedipine or amlodipine, can be used to shorten AV nodal conduction, directly or indirectly. Studies need to be performed to evaluate the changes in micro/macro diastolic function of patients without CIEDs using echocardiographic optimization techniques with various dromotrophic drugs. For instance, if fusion of the e/a waves is seen on the echocardiogram shortening the AV delay by either adding a medical therapy that enhances the AV conduction or eliminating medical therapy that prolongs AV conduction would benefit diastolic filling parameters/patterns. It is even hypothesized that the application of ablative therapies of the periAV nodal structures be further studied and characterized with enhanced mapping techniques so as to apply micro-ablation to the periAV nodal tissues to either shorten or length AV conduction to correct macro diastolic fusion or diastasis of the e-a waveforms, respectively. If such interventions fail to normalize the Doppler AV valve waveforms, it is proposed that an "Ablate and Pace" approach be utilized whereby the AV node would be ablated and a dual pacemaker implanted and paced AV delays would be programmed so as to provide AV valve normal inflow waveforms and physiology. From a micro diastolic standpoint, if after attempting correction of e-a morphology, waveform, morphology and timing is not successful as described above, consideration for evaluating the myocardial substrate for micro diastolic processes, i.e., inflammation and/ or fibrosis from rheumatologic/immunologic and/ or infectious processes should be undertaken with endo myocardial biopsy. Today, this tool of EchoOp and PharmOp may prove to identify processes such as infiltrative amyloidosis, hemochromatosis, etc. or other genetic abnormalities such as familial hypertrophic cardiomyopathy. Etc. and to better provide more discrete treatment options to improve clinical outcomes and downstream risks of heart failure and secondary conditions.

Hence, by normalization of diastolic patterns, timing, morphology and ratios echocardiographic and clinical outcomes, may be improved utilizing the EchoOp and PharmOp principles described. The above proposed concept and protocol of altering the timing interval of the cardiac cycle to optimize the macro diastolic cardiac function has significant potential in which diastolic dysfunction and disease should be evaluated and treated. In addition, micro diastolic parameters must be considered as well so that any given treatment provides for optimization of both the macro and micro components of the myocardium in diastole. Given that ventricular diastole accounts for nearly 2/3s of one's life, it is paramount that the timing, waveform and morphology of macro diastole be optimized, while concomitantly considering micro diastolic aberrations utilizing pacemaker optimization principles and endo myocardial biopsies with pharmaceuticals to diagnose, treat and prevent the acute and chronic downstream and upstream pathologies of abnormal diastology.

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