Diastolic Dysfunction and Diastolic Heart Failure (DHF)

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Introduction :

Analysis of the pump function of the heart viz. systolic shortening (inotropic function) and diastolic lengthening (lusitropic function) has classically centered on the relation between the end-diastolic volume (EDV) of the ventricle (which is related to the length of the muscle fibre) and its stroke volume (SV) (the Frank Starling relation). Inotropic & lusitropic function along with heart rate and rhythm, preload & after load determine the overall cardiac function.

In heart failure commonly both systolic and diastolic dysfunction are seen. Systolic failure manifestations result from an inadequate cardiac output and hypoperfusion – weakness, fatigue, reduced exercise tolerance. Diastolic dysfunction manifestations relate to elevation of filling pressure in the left and / or right ventricle (dyspnoea, orthopnea, pulmonary congestion, peripheral edema). In 1997 Doppler echocardiography was acclaimed as the clinician's Rosetta stone for evaluation of diastolic filling of left ventricle in health and disease (Nishimura RA, Tajik AJ)[1]. It brought into focus the entity of diastolic heart failure with normal systolic function (LVEF $\geq$ 50%) (Vasan and Levy 2000)[2]. What is not generally appreciated is the fact that nuclear cardiology techniques viz ECG – gated cardiac blood pool imaging with a gamma camera (1971)[3] and a non-imaging nuclear probe – the nuclear stethoscope (1976)[4] had clearly shown the ability to non-invasively measure both systolic and diastolic dysfunction and also established the fact that in many cardiac diseases especially Hypertensive heart disease diastolic dysfunction precedes systolic dysfunction by months or years !

Radionuclide Ventriculography (RNV) :

The ECG gated cardiac blood pool imaging (described as radionuclide ventriculography – RNV, or multigated acquisition – MUGA) provides a computer-derived time –activity curve over the left ventricle which looks like a map of south India (Fig. 1); It shows various phases of the cardiac cycle – PEP

(Pre-ejection period; LVET (ejection time), ER (ejection rate) ; ejection velocity (rate of change of volume expressed as dV/dT max, $LVFT_1$ (early filling time), $LVFT_2$ (late filling time), filling rate (FR) and time to peak filling (TPF). By using the area –length method of Sandler and Dodge (or count based methods not dependent on geometric assumptions) the computer gives end-diastolic volume (EDV), end systolic volume (ESV), stroke volume (SV) and ejection fraction (EF). Stroke volume multiplied by heart rate gives cardiac output (CO). In addition, phase and amplitude images give regional ejection fraction and regional wall motion histogram.

The study is done at rest, and at various levels of supine bicycle exercise, followed by sublingual nitroglycerine. Changes in the pulmonary blood volume with exercise are detected by exercise RNV[6]. A typical normal response is given by the following values :

Normal LVEDV : 75 ± 20 ml/m^2 Normal LVESV 25 ± 7 ml/m^2

Systolic function:LVEF Normal Rest 58 ± 8 Exercise >5-10% rise over resting EF.

ER 2.23

dV/dT max 3.8

Diastolic function : Filling rate > 2.6

TPF – Time to peak filling < 150 ms

Exercise / Rest pulmonary blood volume ratio : Normal 0.94 ± 0.6 Abnormal $\geq$ 1.06.

The Nuclear Stethoscope (a sodium iodide scintillation probe coupled to a high temporal resolution digital rate meter) allows measurements of changes in radioactivity every 10 milliseconds and displays a beat–to-beat left ventricular blood pool radioactivity curve as well as a composite beat LV time activity curve (Fig. 2 a and b) which gives all parameters of systolic & diastolic function, at rest, during exercise and after drug intervention eg.. sublingual nitroglycerine[7].

In our extensive experience of over 5000 exercise RNV studies we showed that sublingual nitroglycerine improves both systolic and diastolic dysfunction by causing decrease in the pre-load as well as after load, in patients with CAD[8].

We also showed that Forskolin, active principle of an Indian herb Mainmool, given as I. V. infusion in 30 cases of heart failure improved both systolic and diastolic function at constant preload and after load – hence it is a truly inotropic and lusitropic agent which acts by directly activating membrane – bound adenylate cyclase and increase CAMP in the myocardium[9]. There is sufficient published literature documenting the fact that in asymptomatic hypertensive patients diastolic dysfunction precedes systolic dysfunction by several months or years. The same observation applied to most other types of heart disease as well **:** Valvular disease (aortic stenosis, aortic regurgitation) ischemic heart disease; hypertrophic cardiomyopathy, myocarditis, etc. in which diastolic dysfunction precedes systolic dysfunction.

It is noteworthy that 40 – 50 percent of patients with heart failure have a normal rest LVEF $\geq$ 50%, a criterion for diastolic HF. Patients with DHF tend to be older, more of them are females and 75% patients with diastolic heart failure are hypertensive, (40% of whom have LV hypertrophy LV mass > 125 g/m^2). All have a normal EDV. (Redfield 2004)[10]. Fig. 3 illustrates an Ex RNV study of DHF, in a patient who complained of dyspnoea on exertion..

2D Echocardiography :

When suitable and good windows are obtainable, echocardiography is superbly well suited for the evaluation of global and regional ventricular systolic function, wall motion and thickening. It allows simultaneous assessment of valvular, pericardial, intra-myocardial and extra cardiac abnormalities. It is portable and can be performed at the bedside of the critically ill patient. Its major limitation is an inability to visualise all regions of LV in every patient. Image quality is poor in obese patients and patients with COPD. Unlike nuclear medicine quantitation of regional LV dysfunction is not possible so far. Exercise studies are not possible. It

is worth noting that till the advent of Doppler Echo-cardiography, "diastolic dysfunction" was not in the vocabulary of echocardiographers, as well as cardiologists wedded to echocardiography (demonstrating a tubular vision which ignores the many valuable new insights about diastolic dysfunction provided by nuclear cardiology since 1977).

Doppler echocardiography :

Doppler echocardiography allows non-invasive evaluation of ventricular diastolic filling. The transmitral velocity curves reflect the relative pressure gradients between the left atrium (LA) and left ventricle (LV) throughout the diastolic filling period. The progression of diastolic dysfunction in disease states can be assessed by the Doppler flow velocity curves. In early stages of diastolic dysfunction there is an abnormality of relaxation with a decrease in early filling and a compensatory increase in filling at atrial contraction, resulting in a low E : A ratio of 0.5 and deceleration time (DT) of 280 ms. In this instance the LVEDP is low at 6 mm Hg. As diastolic dysfunction progresses, there is a restriction to filling, a high early diastolic velocity and low velocity at atrial contraction resulting in high E. A ratio of 3, and DT 120 ms. In this instance the LVEDP is markedly elevated to 34 mm Hg. The DT reflects the rate of decline of early velocity and is a measure of the effective operative compliance of the LV.

These trans-mitral flow curves can be used to estimate LV filling pressure and to determine prognosis in certain disease entities. The addition of Doppler interrogation of pulmonary venous flow, analysis of Doppler tissue velocities of annular motion and right sided chamber flow velocities provide further information concerning the diastolic properties**.** Grading of the severity of diastolic dysfunction (Grades I – IV) is now possible based on Doppler velocities.

RV cavity enlargement, RV wall thickness, RV systolic pressure and pulmonary artery pressure can be estimated with Doppler echocardiography.

Left ventricular systolic performance, function and contractility at rest in patients with diastolic heart failure have been extensively studied in 75 patients with DHF

and found to be normal compared to 75 normal subjects under basal conditions using cardiac catheterization as well as echocardiography (Baicu et al 2005)[11]. They suggest possible changes in molecular and biochemical properties in cardiomyocytes and extracellular matrix proteins such as fibrillar collagen, underlying DHF.

Molecular mechanisms in DHF:

A recent editorial concluded that "there exsits no consistent abnormality of intrinsic diastolic properties that can explain the occurrence of heart failure in patients with a normal systolic function" (Burkhoff, Maurer, Packer, 2003)[12].

Myocardial relaxation during diastole is not a passive process but an active energy-dependent process using ATP and cAMP, activation of the protein phospholamban and Ca^{2+} uptake into the sarcoplasmic reticulum (SR) via the calcium pump SERCA 2a. Both haemodynamic pressure overload and mutations of the genes encoding specific cytoskeletal proteins in the SR, ryanodyne receptor, calcium uptake pump and phospholamban interfere with relaxation.

Proliferation of extracellular matrix occurs in myocardial infarction, long-standing hypertension and a variety of cardiomyopathic disorders. Many signaling molecules such as endothelin, TNFα, TGFβ and angiotensin cause maladaptive hypertrophy, proliferation of collagen, fibrosis and apoptosis especially under conditions of left ventricular pressure overload. Excess collagen & fibrosis interfere with both systolic shortening and diastolic lengthening. The stiff non-compliant LV has a normal EDV and a limited ability to use the Frank-Starling mechanism. Hence there is no increase in stroke volume during exercise leading to symptoms of effort intolerance. EDV is lower and ED pressure is higher in patients with diastolic HF. Increase in passive stiffness along with decrease in active relaxation explain diastolic HF. Left ventricular hypertrophy is not a prerequisite for diastolic dysfunction to occur (Zile, Baieu, Gaasch 2004)[13]. Chronic maladaptive signals can be inhibited by ACE inhibitors, AT_1, receptor blockers, 3rd generation β blockers such as nebivolol (which also increases NO

production. thereby inhibiting endothelial inflammation and proliferation triggered by NFKB)> These are essentially preventive approaches to halt progression. .

Imaging Myocardial Fibrosis :

Can molecular nuclear medicine imaging detect myocardial collagen deposition and fibrosis ? Here one can draw on the anology of hepatic fibrosis, which in animal models is reversible in earlier stages. By complexing cyclic peptides binding PDGF or TGFα receptors with Indium-111, high uptake was seen post-injection in the cirrhotic liver and retained at 72 hours in an experimental rat model (Zang et al 2001 Chinese literature). The possibility of directly blocking the synthesis of matrix proteins by somatic gene therapy remains for the future.

Gadolinium-DTPA delayed enhancement magnetic resonance imaging (deMRI) has successfully demonstrated the interstitial fibrosis routinely observed in patients with hypertrophic cardiomyopathy (HCM).

Management of DHF :

Major goal in management of diastolic HF is to reduce ischemia, hypertrophy and fibrosis (which caused the dysfunction) and to reduce pulmonary and / or systemic venous congestion, a major consequence of diastolic dysfunction. Pulmonary edema in diastolic HF is often the result of sodium retention and expansion of central blood volume. Dietary sodium restriction and diuretics are useful for this purpose. Slowing the heart rate provides more time for ventricular filling; for this beta blockers or non-dihydropyridine calcium antagonists are useful.

No current therapy has been shown to improve survival in diastolic HF with a normal LVEF > 50%. This includes ACE inhibitors, AT_1 receptor blockers, β blockers or calcium channel blockers. Their role is mainly secondary prevention. The effect of angiotensin 1-receptor blocker condesartan was studied in a placebo-controlled trial in 3023 patients. 1509 patients who received 32 mg. Once a day had fewer hospital admission for heart failure compared to 1509 patients who received placebo. Cardiovascular death did not differ between groups (170 vs 170). (Charm Preserved Trial) (Yusuf S et al 2003)[14].

In one study of 137 patients with diastolic HF (which included hypertensive, diabetic & IHD patients) statin therapy was associated with improved survival (Fukuta H et al 2005)[15].

New opportunities for Nuclear Cardiology :

The inability to augment LV diastolic performance and function during exercise has been a notable feature of DHF, hence I suggest that exercise RNV is an appropriate and cost-effective approach. More than 150 Nuclear Medicine centres in India can offer to the cardiologists the facility of exercise RNV (MUGA) and Gated SPECT myocardial perfusion and function (MPF). Current Gamma cameras do provide the option of acquiring ECG gated SPECT perfusion images with 16 (rather than the usual 8) frames and software is available to derive all systolic and diastolic function parameters at rest and after exercise (Fig. 4) similar to MUGA. An ExRNV study showing a normal LVEDV and normal LVEF, PFR < 2 and tPFR > 150 ms. along with increase in pulmonary blood volume on exercise (thereby explaining the symptom of effort intolerance), establish the diagnosis DHF, and allows serial studies to monitor response to therapy.

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