Assessment of Diastolic Heart Function – Experience with 16-gated Myocardial Perfusion SPECT

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Abstract
Background: Ischaemic heart disease (IHD) is a major health problem today. However the focus has shifted primarily to angiographically detecting epicardial vessel stenoses, and ways and means of surgically correcting the blocks. Patients are often not fully evaluated for cardiac function, and diastolic dysfunction of heart, which is often an earlier manifestation than systolic dysfunction, goes undetected.

Methods: Recent gamma cameras have better imaging quality due to attenuation correction with SPECT-CT. 121 patients underwent gated myocardial perfusion imaging (MPI) for suspected coronary artery disease (CAD). We studied the diastolic function of these patients by 16-gated SPECT MPI.

Results: 60% patients showed absence of inducible ischaemia on MPI, and hence further invasive procedures like angiography were prevented, 40% showed inducible ischaemia and had to be further evaluated and required intervention. Of all 121 patients, 10% had LV systolic and diastolic dysfunction whereas 66% had isolated diastolic dysfunction. 40% patients had no ischaemia, normal systolic function and only diastolic dysfunction. 40% of these cases had symptoms of chest heaviness/angina equivalent.

Conclusion: Myocardial perfusion imaging is a useful modality for evaluating patients of suspected CAD and in addition to perfusion data, also provides functional assessment of systolic and diastolic function, which provides comprehensive information regarding patients' symptomatology and can guide further management.

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. Nitroglycerine improves systolic and diastolic function by decreasing the preload and afterload.

In heart failure commonly both systolic and diastolic dysfunction are seen. Systolic failure manifestations result from an inadequate cardiac output and tissue 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. It brought into focus the entity of diastolic heart failure with normal systolic function (LVEF ≥ 50%). What is not generally appreciated is the fact that nuclear cardiology techniques viz ECG – gated cardiac blood pool imaging with a gamma camera (1971) and a non-imaging nuclear probe – the nuclear stethoscope (1976) 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 and ischemic heart disease diastolic dysfunction precedes systolic dysfunction by months or years! In a study of 30 patients with hypertension of 5 years duration, with the nuclear stethoscope, diastolic dysfunction (time to peak filling rate more than 180 msec) was seen in all the patients irrespective of the severity (mild, moderate, severe) while systolic function remained normal till late in mild to moderate hypertension. (V.R. Lele, 1990). In this study, Nifedipine was shown to improve diastolic dysfunction.

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, LVFT₁ (early filling time), LVFT₂ (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 same information is obtainable from the nuclear stethoscope (Fig. 2 A+B). An example of increase in LVEF with exercise while decrease in diastolic dysfunction is given in Fig. 3.

**Myocardial perfusion and function imaging**

Radio-tracers like ⁹⁹ᵐTc-Sestamibi or ⁹⁹ᵐTc-Terofosmin are immediately taken up by cardiomyocytes and trapped there, with no washout unlike the earlier generation tracer 201Thallium. The study is conducted in two-parts; one where the tracer is injected in resting condition to assess the baseline cardiac perfusion and second when the patient is injected tracer at the peak of tread-mill/ergometer, or pharmacological stress with Adenosine or Dobutamine. After each injection there is acquisition of SPECT (tomographic) images on the Gamma-camera. The two sets of images are then compared. Basic patterns which are obtained are:

a) Normal perfusion at stress and rest → No old infarct and no inducible ischemia

b) Segmental myocardial perfusion defects on stress, which are not present on resting images → inducible ischemia in the particular coronary territory

c) Myocardial perfusion defect on both rest and stress (fixed defect) old infarct, or hibernating myocardium. The extent of tracer uptake in the infarct zone can be quantified to assess viability in the infarct zone.

Quantitation of ischemic myocardium is made by 19 or 20 segment assessment.

With the introduction of ECG-Gated-SPECT, apart from myocardial perfusion, the cardiac wall motion and thickening are also imaged. The cardiac cycles from one R-wave to the next R-wave are divided into 8 or 16 “bins”. These Gated images provide very dependable and reproducible quantification of left ventricular ejection fraction, end-systolic volume, end-diastolic volume, transient dilatation of LV-cavity during stress (a sign of global ischemia). Segmental wall motion and wall thickening can be visually assessed and quantified by the software. Gated-SPECT improved the diagnostic accuracy of SPECT. This procedure is free from the drawback of subjectivity inherent in echocardiography.

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**Fig. 1**: Computer-derived left ventricular volume curve from which ejection fraction and ejection velocity are calculated.

**Fig. 2**: Nuclear stethoscope generated curves used in deriving the ventricular volumes, ejection fraction and ejection velocity.

**Fig. 3**: Rise in LV EF on exercise (51% to 61%) but a fall in the diastolic function, indicating that the dyspnoea was due to diastolic dysfunction.

**Fig. 4**: Advantage of SPECT-CT attenuation corrected cardiac imaging: Non-attenuated cardiac slices (upper two rows of each section) show reduced perfusion in inferior wall. Attenuation-corrected images (lower 2 rows) show normal perfusion in the inferior wall, thereby preventing false-interpretation.
for assessment of LV function.

The conventional SPECT images have used 8-bin gating, which gives adequate systolic function but not adequate for diastolic function assessment. It is well known that addition of functional data to perfusion studies provides incremental value at no extra cost. If 16-bin gating techniques are used, systolic as well as diastolic function can be studied – comprising isovolumetric relaxation, rapid ventricular filling and passive ventricular filling (Fig. 5).

Parameters that can be assessed from the above curve are:

a) PER (peak ejection rate) in ml/sec
b) PFR (peak filling rate) (ml/sec) - normal more than or equal to 2.5 times end diastolic volumes per second (may vary according to the system)
c) MFR (mean filling rate)
d) TTPF (time to peak filling) – normally should be less than 180 msec

Fig. 6 illustrates an example of normal systolic function with grossly abnormal diastolic function.

MATERIAL AND METHODS

Since the installation of the new SPECT-CT gamma camera at our institute in December 2006, we started 16-frame gated data acquisition in all MPI studies, along with attenuation and scatter correction. We propose to assess the additional information of diastolic function for assessment of our patients.

We analyzed the data of 121 patients who were referred to the department for the primary diagnosis of IHD. These patients had no history of prior infarcts. They had one or more of cardiac risk factors like hypertension, diabetes, dyslipidemia, family history of IHD, smoking etc.

Patient Selection

- First category of patients were those with risk factors for IHD and a positive treadmill stress test, now referred for stress-MPI to assess the significance of changes on stress ECG, or for risk evaluation prior to insurance.
- Second category of patients had symptoms of atypical angina or angina-equivalent like “breathlessness on exertion”, “tiredness”, vague chest discomfort.
- Some patients with prior myocardial infarction were also studied.

Patient preparation: Patients came with overnight fast. No cardiac medication was taken on the day of the test. Beta-blockers were stopped 48 hours prior to the test. For patients undergoing Adenosine stress test, no tea or coffee was taken 24 hours prior to the study.

Procedure: All patients underwent exercise or Adenosine stress test. Both stress and rest 16-gated images were obtained after injection of 10 mCi and 25 mCi of Tc-Tetrofosmine for stress and rest studies respectively. Images were acquired on a dual head SPECT-CT gamma camera with 180 degree acquisition. CT data was used for attenuation correction.

RESULTS

Total number of patients: 121
Gender distribution: Male: 73 Female: 48

Category 1

- 40 asymptomatic patients with positive stress ECG results: 27 out of 40 (67%) showed normal MPI (no evidence of ischemia) and normal systolic LV function. Of these 27, 16 had isolated diastolic dysfunction. 14 of them were hypertensives (8 males, 6 females)
- 13 out of 40 (33%) showed reversible ischemia but normal LVEF. Of these, 10 showed diastolic dysfunction.

Category 2
Hypertension and Diastolic dysfunction: In our series, we found that 92/121 patients had diastolic dysfunction out of which 80 had isolated diastolic dysfunction. 80% of these patients were hypertensive. The findings of diastolic dysfunction in our studies correlated well with those found on echocardiography of these patients, (though it was observed that some centers did not comment upon this important aspect of cardiac function).

In our series, 11 out of 27 patients with normal stress and rest myocardial perfusion, showed isolated diastolic dysfunction, increased tracer uptake in the apex and septum, ECG patterns of septal hypertrophy (tall R, deep S and inverted T in V3 V4) – these were indicative of hypertrophic cardiomyopathy. These patients showed high LVEF (> 80% as estimated by the gamma camera software). They all showed delayed diastolic relaxation. This was probably the only reason for their symptoms of dyspnoea on exertion or chest heaviness. However, LVH is not a prerequisite for diastolic dysfunction as has been shown in a large study by Zile.9

Diastolic dysfunction in IHD: 38 patients (47.5%) of our series showed reversible ischaemia on stress MPI. Of these, only 8 (21%) showed reduced resting LVEF as well as diastolic dysfunction. 30 (77.8%) cases showed normal systolic function at rest in spite of inducible ischaemia. This shows the inadequacy of a resting echocardiography, so often used for the evaluation of these patients, to detect IHD. Of these, 21 patients had a recent echocardiography which also showed normal LVEF at rest. It was interesting to find that 22 of these patients showed isolated diastolic dysfunction. Hypoxia impairs the rate of ventricular relaxation. Abnormal diastolic performance during ischaemia may occur without any accompanying abnormality of systolic function. Abnormal diastolic function has been noted in 91% of patients with ischemic heart disease and 95% of patients with previous myocardial infarction. It should also be remembered that inducible ischaemia can occur in hypertension with LVH, aortic stenosis with LVH and hypertrophic cardiomyopathy independent of epicardial coronary artery disease.

Left ventricular systolic performance, function and contractility at rest in patients with diastolic heart failure (DHF) 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. They suggest possible changes in molecular and biochemical properties of cardiomyocytes and extracellular matrix proteins such as fibrillar collagen, underlying DHF.

Proliferation of extracellular matrix occurs in myocardial infarction, long-standing hypertension and a variety of cardiomyopathic disorders especially hypertrophic cardiomyopathy. Many signaling molecules such as endothelin, matrix metalloproteins, TNFα, TGFβ and angiotensin cause maladaptive hypertrophy, proliferation of collagen, fibrosis and apoptosis especially under conditions of left ventricular pressure overload. The interstitial connective tissue is rich in type I and type III fibrillar collagen, whose quantity is determined by the balance between synthesis and degradation via matrix metalloproteinases (MMPs) which degrade matrix proteins and tissue inhibitors of metalloproteinases (TIMPs). Excess collagen & fibrosis interfere with both systolic shortening and diastolic lengthening. This fibrosis has successfully been demonstrated by Gadolinium-DTPA delayed enhancement MRI in patients with hypertrophic cardiomyopathy.12 We urgently need a radionuclide tracer for in-voiv assessment of fibrosis. At present, MRI seems to be the only tool for assessing it. 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. In all our 80/121 patients with isolated diastolic dysfunction, we found that the size of LV cavity was not dilated with normal ESV and EDV. Patients with diastolic heart failure (DHF) tend to be older, more of them are females, 75% with DHF are hypertensive and have normal EDV. Increase in passive stiffness along with decrease in active relaxation explain diastolic HF. 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 Ca2+ 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.

Forskolin (active principle of an Ayurvedic herb Mainmool) has unique action of activating membrane-bound adenyl cyclase to produce cAMP which causes improvement in inotropic and lusitropic function in patients with congestive heart failure. This was shown by a study of 30 patients with congestive heart failure given IV infusion of Forskolin under the nuclear stethoscope (RD Lele, KG Nair 1982).13 A comparison was made with the effect of sublingual nitroglycerine. While NG improved systolic and diastolic function by decreasing preload and afterload, Forskolin showed improvement at constant preload and afterload – true inotropic and lusitropic action. Unfortunately, no oral preparation of Forskolin is available.

No current therapy has been shown to improve survival in diastolic HF with a normal LVEF > 50%. This includes ACE inhibitors, AT1 receptor blockers, b 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 admissions for heart failure compared to 1509 patients who received placebo. Cardiovascular death did not differ between groups (170 vs 170).14

In one study of 137 patients with diastolic HF (which included hypertensive, diabetic & IHD patients) statin therapy was associated with improved survival.15

We suggest that recognition of diastolic dysfunction, especially in hypertensive patients, provides a window of opportunity to prevent progression to heart failure.

**References**


13. Lele RD, Nair KG. Personal communication.


Announcement

3rd WINTER
INDO-AMERICAN CME

Jointly held by API-TNSC (Association of Physicians of India - Tamil Nadu State Chapter) ATMA (American Tamil Medical Association, USA).

Venue : Hotel Savera, Chennai
Date : On 3rd and 4th January’2009 at Hotel Savera Chennai.

For further information, registration and for sending abstract, please contact : Hi-Tours, #83, Pantheon road, Sri Kalyan Square, Egmore, Chennai - 600 008.
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Announcement

2nd National Conference on Infectious Diseases

Infectious Diseases Society of India (IDSI) is organising a second national conference on Infectious Diseases. The highlights of the conference are:
Emerging new infections, changing face of old infections, XDR TB, nosocomial infections, immuno nutrition and newer diagnostic techniques.
Renowned international and national faculty has consented to share their experiences.
Venue : YB Chavan Center, Mumbai.
Date : 27th-28th Feb & 1st Mar. 2009
Registration fees: Rs. 2,000/- upto 15th Nov. 2008
Chairperson: Prof. Alaka Deshpande
Organising Secretary: Dr. Om Srivastav
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