CHAPTER

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Chronic Heart Failure – Newer Diagnostic Modalities

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Chronic heart failure is the end result of cardiac injury from varied etiology. Early diagnosis and proper management can reduce morbidity. Several newer diagnostic modalities have evolved in this field. These modalities are discussed according to their clinical application.

Evaluation of adverse remodeling

Newer Non invasive, imaging modalities[1]

- Sphericity index = $\frac{\text{LVEDV}}{\text{Volume of a sphere having a diameter equal to the ventricular long axis dimension}}$

  It is an earlier and reliable predictor of adverse remodeling

- Left ventricular remodeling index = $\frac{\text{LV mass}}{\text{LV End diastolic volume}}$

  It is extremely useful in differentiating dilated but normally functioning ventricle of "athelete's heart" from dilated cardiomyopathy.[2] Normal values are 1.05 ± 0.15

  Values are decreased in dilated cardiomyopathy.

Histopathologic markers of adverse remodeling[1]

Imaging of fibrosis

- Late Gadolinium enhancement on cardiac MRI. Delayed enhancement is caused by slower washout of gadolinium from regions of myocardial fibrosis.
- Perfusable tissue index measured using PET ratio of perfusable tissue fraction versus anatomic tissue fraction.

Imaging of apoptosis

Phosphatidylserine is a phospholipid that is normally confined to the inner layer of cell membrane. It is externalized during apoptosis. Phospholipid binding protein annexin V is bound to the externalized phosphatidylserine. Labelled annexin V is used as a targeted probe.

Label	Method of detection
Technetium Tc 99m	SPECT/PET
Iron oxide nanoparticles	MRI

Imaging of matrix metalloproteinases

Tracers	Mode of detection
99 m Tc labeled	SPECT
Fluorochrome cy 5.5	Charged couple device camera

Table I : Advantages and limitations of newer non invasive modalities for evaluation of adverse remodeling

	Advantages	Limitations
• Gated SPECT	• No geometric assumptions • Image acquisition independent of patient characteristics and operator expertise • Measurement of EF highly Reproducible	• No geometric assumptions and controlled heart rate • Exposure to ionizing radiation
• Quantitative Gated SPECT Using a software	• - Automatically detects endocardial and epicardial borders	
• Cardiac MRI	• No geometric assumptions • Image acquisition independent of patient characteristics and operator expertise • Useful in characterization of LV geometry-decision regarding reconstructive surgery	• Requires regular rhythm • Not feasible in patients with claustrophobia or implanted metal devices (e.g. pacemakers, AICDs)
• Steady state free precesion cardiac MRI	• Shortened acquisition time • Improved blood – myocardial Contrast	
• 2-D TTE with Harmonic imaging and intravenous ultrasonic contrast	• Inexpensive and portable • Independent of patient characteristics	• Use of geometric assumptions • Operator dependent
• Real time 3-D TEE	• Inexpensive and portable • Independent of patient characteristics • No geometric assumptions Required	• Limited availability • Requires operator expertise • Requires regular heart rhythm

Assessment of myocardial disability [3,4]

Dobutamine Stress Echocardiography

Sustained contractile improvement suggests adequate flow reserve as is seen in the presence of stunning. A biphasic response (initial improvement in contractility followed by reduced contractility) suggests ischemic but viable myocardium (myocardial hibernation).

Nuclear probes for assessment of myocardial viability in heart failure [3,4]

Nuclear probes for myocardial perfusion and cell membrane integrity

Perfusion present at rest	→			Viable		
No perfusion At rest	→	Perfusion after 24 hours	→	Viable		
No perfusion During stress	→	No perfusion at rest	→	Perfusion after reinjection	→	Viable
No perfusion during stress	→	No perfusion at rest	→	No perfusion after reinjection	→	Non viable

Thallium – 201: Viable myocardium concentrates more thallium over time as opposed to scarred myocardium that does not. Enhanced regional concentration of thallium in delayed (24 hours) images as compared to early images reflects viability. Negative predictive value is not high as redistribution may not take place in some patients. Reinjection of Thallium at rest after stress redistribution (stress- redistribution – reinjection protocol)improves sensitivity and has excellent positive and negative predictive values.

Technetium 99 m labeled sestamibi and tetrofosmin advantages over thallium

- Shorter half life
- Less radiation exposure

Table 2

Perfusion	FDG uptake	Interpretation	
Normal	Present	• Normal wall motion • Regional wall motion Abnormality	• Normal • Stunning – viable
Reduced	Present	Mismatch pattern	• Hibernation – viable
Reduced	Absent	Matched pattern	• Scar

- Improved quality of gated images

  Nitrate: enhanced rest imaging and low dose dobutamine gated SPECT improve accuracy of assessment of myocardial viability

Nuclear probes for assessment of myocardial metabolism

Hypoperfused but viable tissue is metabolically active whereas scarred tissue is metabolically inactive

- 18 F-2 Fluoro-2deoxyglucose (FDG)

  It is a glucose analog. Myocardial uptake of this tracer parallels glucose uptake. This test is, therefore, performed in a 'fed' or 'glucose loaded' state. Uptake is strongly influenced by plasma levels of insulin and free fatty acids. Insulin stimulates uptake and free fatty acids inhibit uptake. Therefore, image quality is poor in patients with impaired glucose tolerance or overt diabetes. Hyperinsulinemic euglycemic clamping can overcome this problem but it is time consuming and laborious. Use of nicotinic acid derivatives can also improve image quality in these cases.

- β Methyl-(p^{123} I)- iodophenyl – pentadecanoic acid

  It is a fatty acid analog and is used for fatty acid imaging. Reduced uptake relative to perfusion is due to delayed recovery of myocardial metabolism after ischemic injury

Nuclear probes for imaging the tissue angiotensin–converting enzyme receptor system

Radiolabeled captopril or lisinopril

Cardiovascular magnetic resonance assessment[5]

Differentiation of ischemic and non-ischemic cardiomyopathies:-

- Delayed contrast enhancement after Gadolinium administration is very effective in tissue characterization. This modality can identify microscars that can not be detected by other imaging techniques. Gadolinium is an inert substance and is not nephrotoxic.
- "Ischemic type" hyperenhancement may be transmural but always involves subendocardium and correlates with area of vascular distribution.
- "Non ischemic type" hyperenhancement
- Dilated cardiomyopathy either shows no hyperenhancement or shows patchy or linear striae of hyperenhancement limited to mid myocardium.
- In myocarditis, enhancement is nodular or diffuse and located primarily subepicardially. It does not correlate with vascular territories.

Early diagnosis of infiltrative cardiomyopathies:

- Sarcoidosis – Cardiac magnetic resonance can detect early and small lesions before they are detectable on ECG, Echo or PET.
- Hemosiderosis – MRI can identify iron-laden tissue through the loss of signals created by the presence of iron.
- Arrhythmogenic RV cardiomyopathy – Areas of fibropathy infiltration show delayed hyperenhancement after gadolinium.

Diagnosis of hypertrophic cardiomyopathy:

- Cardiac MRI is superior to echo in diagnosis

of apical hypertrophic cardiomyopathy

- This modality is also useful in differentiating hypertrophic cardiomyopathy from Amyloidosis. Hypertrophic cardiomyopathy does not show subendocardial enhancement. Amyloidosis shows subendocardial and global involvement that does not follow any specific coronary artery territory.

Assessment of myocardial viability

- Cardiac MRI is more accurate than radionuclide scintigraphy and dobutamine stress echocardiography in predicting viable myocardium in patients with severe LV dysfunction. Gadolinium enhanced MRI studies do not require administration of agents to provoke ischemia. This approach is, therefore, safer in patients who have severe coronary artery disease and active myocardial ischemia or angina. Reliably detects thickening of pericardium

Assessment of diastolic function [6]

Pulsed Doppler indices of left ventricular filling are influenced by several variables such as relaxation, compliance, heart rate, arrhythmia, age and filling pressure.

Color M-mode Doppler echocardiography

Slope of the color wave front (Vp)correlates with the velocity at which the blood flow propagates within the ventricle. Vp in superior to conventional pulse doppler as it is not influenced by alterations in preload. In patients who have impaired relaxation but elevated preload, E wave of pulse Doppler is prominent (pseudonormal)but Vp is reduced.

Pulmonary venous inflow Doppler pattern

Pulmonary venous inflow atrial reversal duration exceeding 30 milliseconds above mitral inflow A wave duration also identifies pseudonormal pattern and LV end diastolic pressure of more than 15 mmHg.

Systolic flow is more than diastolic flow in normal adults. Reversal of flow pattern (diastolic more than systolic) is seen in restrictive pattern of diastolic dysfunction.

Hepatic vein flow demonstrates similar changes. In advanced stages reversed flow during atrial or ventricular contraction are increased during inspiration.

Tissue Doppler echocardiography

It evaluates velocity of myocardial movement during systole and diastole. Ventricular systole produces a positive wave. During diastole, there are two negative waves – first corresponding to early ventricular filling and second corresponding to atrial systole. Early ventricular filling velocity correlates inversely with left ventricular relaxation. This parameter is also not affected by preload. Tissue Doppler velocities are also helpful in differentiating pericardial constriction from restrictive cardiomyopathy. Early diastolic velocity is normal (> 8 cm/sec.)in pericardial constriction whereas it is reduced in restrictive cardiomyopathy.

Combining various parameters allows better evaluation of diastolic function.

Evaluation of myocardial dyssynchrony[7]

- Time delay between onset of flow in right and left ventricular outflow tracts by pulse wave doppler. Delay of more than 45 seconds denotes significant dyssynchrony.
- Delay between posterior and septal inward motion on m-mode echocardiography delay of more than 130 milliseconds is considered significant.
- Tissue Doppler echocardiography – time delay between systolic peaks at septal and lateral walls. Delay of more than 65 milliseconds is significant.
- Strain-encoded MRI – Provides three dimensional information an regional mechanics and may emerge as an important technique.

	Adult	Elderly	Impaired Relaxation	Pseudo normal pattern	Restriction
Atrial Size	N	N	↑	↑	↑
E/A	> 1		< 1	> 1	> 2
IVRT	< 100 msec.		> 100 msec.	< 100	< 60
DT	< 220 msec.		> 220 msec.	150-220	< 150
PV S/D		S > D	S > D	S > D or equal	S < D
AR			N or ↑	> 35 cm/sec.	> 35 cm/sec.
Color M mode Vp	> 55 cm/sec.	> 45 cm/sec.	< 45 cm/sec.	< 45 cm/sec.	< 45 cm/sec.
TD Em	> 10 cm/sec.	> 8 cm/sec.	< 8 cm/sec.	< 8 cm/sec.	< 8 cm/sec.

Abbrevation:- E- Mitral flow Doppler E wave velocity, A- Mitral flow Doppler A wave velocity, IVRT – Isovolumic Relaxation Time, DT- Deceleration time, PV- Pulmonary vein doppler flow, S-Systolic, D-Diastolic, AR- Atrial Reversal velocity in pulmonary vein flow, Vp- Velocity of propagation, TDEm – Tissue Doppler E wave velocity Reversibility with a valsalva or other pre load reducing maneuvers differentiates reversible from irreversible stage.

Imaging of cardiac autonomic nervous system[8]

Tracer	Use for
Nor epinephrine analogs	
• Tc 99m metaiodobenzylguanidine (MIBG)	myocardial sympathetic innervation imaging at presynaptic level
• C-11 metahydroxyephedrine (HED)	
• C-11 CGP 12177 C-11 CGP 12388	used for post-synaptic adreno receptor imaging
• F-18 fluroethoxybenzovesamical (FEOBU)	for imaging acetylcholine transperters

Heart to mediastinum uptake ratio of MIBG less than 1.75 correlates with poor prognosis.

Direct visualization of coronary arteries [9]

Electron beam CT (EBCT)

- Requires a breathhold of 30-40 seconds depending on heart rate.
- Specificity of 91% and sensitivity of 87%.
- Approximately 20% uninterpretable segments.
- Overestimation of luminal narrowing by coronary calcification
- Motion artifacts

Multislice CT – using 64 slice scanners

- Sensitivity – 99% specificity – 95%
- High radiation exposure
- Need for low heart rate
- Reduced imaging quality in patients with severe coronary calcification.

Endomyocardial biopsy

Indications:

- Selected patients with unexplained (myocardial ischemia excluded) heart failure.
- Differentiation between constrictive and restrictive etiology

To "rule out" heart failure in patients with confusing symptoms and signs

- Estimation of plasma natriuretic peptide level
- N terminal atrial natriuretic peptide
- Brain natriuretic peptide

Other test of neuroendocrine evaluation

Circulating levels of noradrenaline, renin, angiotensin II, aldosterone, endothelin-1, and adrenomedullin

Limitations : Inaccurate and difficult to interpret in individual patient. Diuretics, vasodilators, ACE inhibitors and betablockers affect the plasma concentration of endocrine substances.

- Plasma levels of noradrenaline rise with age and healthy subjects over the age of 75 yrs may have plasma concentration in heart failure range.

Conclusion

Although several advances have occurred in evaluation of chronic heart failure, they have not made any significant impact on mortality. Modalities that can detect subclinical myocardial damage and its precise etiology need to be evolved. Technical advances in the field of nuclear probes and cardiac MRI may solve the problem.

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