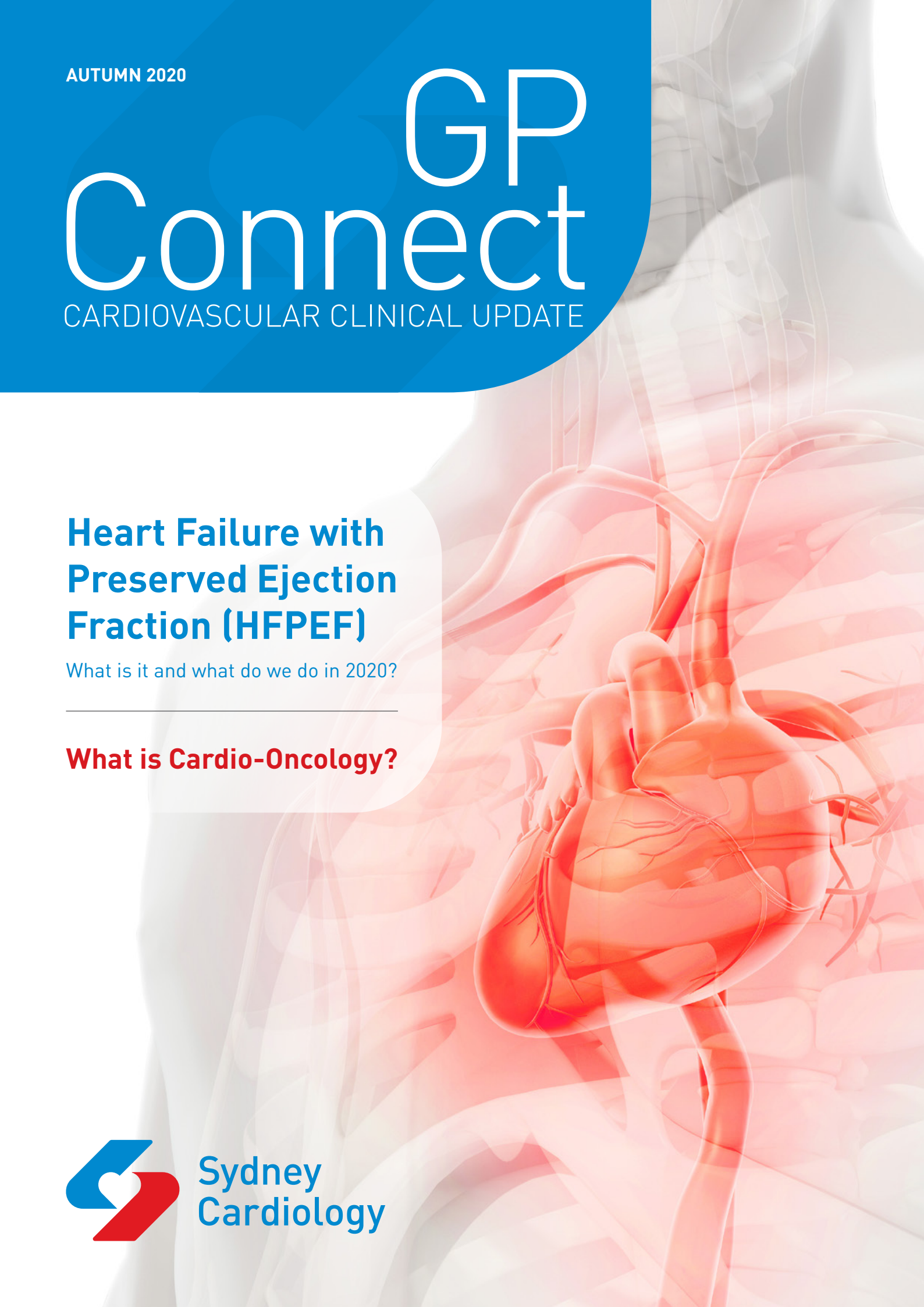
AUTUMN 2020

GP Connect

CARDIOVASCULAR CLINICAL UPDATE



Heart Failure with Preserved Ejection Fraction (HFPEF)

What is it and what do we do in 2020?

What is Cardio-Oncology?

Sydney Cardiology

WELCOME

From the editor – Dr Andrew Terluk

Thank you for reading this edition of GP connect.

During a time of increased telehealth and phone consults it is imperative as health care professionals confronting the pandemic to balance our caution to maintain distance whilst providing optimal care which may include a physical examination and investigations.

In cardiology stress tests, ECG and echocardiography remain pivotal facets of a comprehensive cardiac assessment. We will need to continue to consider vulnerable patients and those who are immunocompromised in our approach to testing.

In this issue I have written a brief overview of 'cardio-oncology' which is another facet of our practice. Associate Professor Martin Brown has also written a detailed piece about diastolic dysfunction which continues to cause significant morbidity.

We sincerely hope you and your families stay well in this trying time.

MEET OUR TEAM

We have experienced cardiologists in all major sub specialities to provide the highest quality of patient care. Our Sydney Cardiology team includes:

Dr James Wong

Specialising in general cardiology, prevention of coronary artery disease and hypertension.

Dr Bill Petrellis

Specialising in general adult cardiology and electrophysiology, including atrial fibrillation and device implantation.

Dr Fiona Foo

Specialising in general and interventional cardiology with an interest in heart disease affecting women and sports cardiology.

Dr Gunjan Aggarwal

Specialising in general adult cardiology and non-invasive cardiac imaging, particularly echocardiography and cardiac CT.

Dr Abhinav Luhach

Specialising in general adult cardiology, cardiac CT and preventive cardiology.

A/Prof Martin Brown

Specialising in advanced heart failure, pulmonary hypertension and transplant cardiology.

Dr Ru-Dee Ting

Specialising in general and interventional cardiology, including cardiac haemodynamic studies and complex coronary intervention.

Dr Andrew Terluk

Specialising in general cardiology with an interest in cardiomyopathy in the setting of cancer.

OUR CARDIOLOGISTS PROVIDE ON-CALL SUPPORT 24/7 FOR GPs
PLEASE CALL 02 9966 7700

SAME DAY URGENT APPOINTMENTS

WHAT IS CARDIO-ONCOLOGY?

Dr Andrew Terluk

Cardio-Oncology is a field of interest that pertains to the early detection, surveillance and treatment of cardiovascular conditions occurring in the context of cancer. Most often the negative cardiac effects result from chemotherapy and radiotherapy. There are many uncertain areas in the field not limited to whether certain cancer phenotypes or individual patient genotypes may result in a predisposition for cardiac sequelae.

CARDIAC COMORBIDITIES CAUSED BY CANCER THERAPIES

One major group of at risk individuals are patients who have received anthracyclines and trastuzumab (i.e. monoclonal antibody, Herceptin) for breast cancer. Their effects can be early or late (greater than 5 years after treatment).

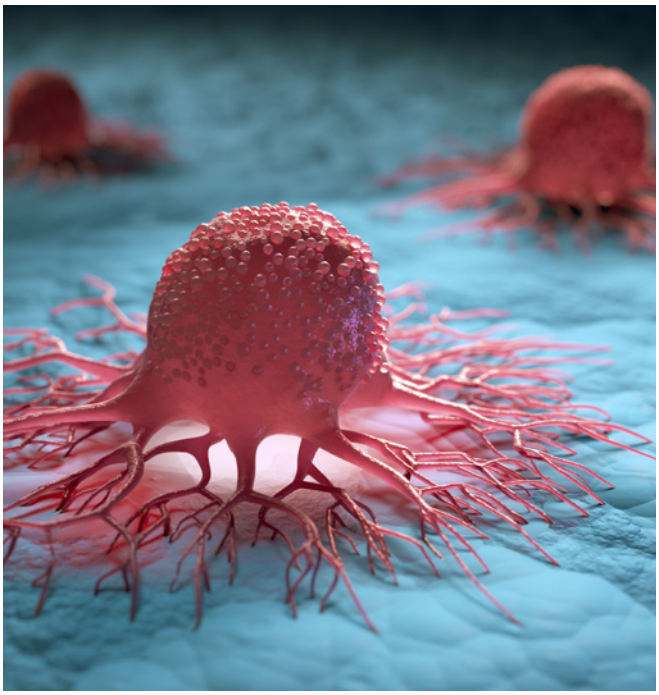
Radiation therapy (in particular in patients with left sided breast cancer) can cause other issues including pericardial damage and coronary disease, in particular the left anterior descending artery which can become selectively atretic.

HOW ARE PATIENTS MANAGED WHO RECEIVE CHEMOTHERAPY?

For many years oncologists have ordered pre-chemotherapy baseline echocardiograms on their patients and have ordered periodic scans throughout a patient's care to help avoid a cardiomyopathy.

Previously the cardiac ejection fraction was recognised as the primary measure of left ventricular function (LVEF). Deriving LVEF is a relative simple process of measuring the internal dimensions of the LV in diastole and systole to determine the percentage of fluid ejected in each cycle (a LVEF of 55% is normal).

In recent years a new technology has emerged which is 'global longitudinal systolic strain' (GLS). This is a semi-autonomous technology that measures the deformation of the myocardium throughout the cardiac cycle by tracking the movement of each speckle. A number is then generated (through the echo software package) which denotes the patient's global myocardial performance (eg. -18%). This number can therefore serve as an ongoing reference for the patient. A perturbation in this number will often denote an adverse chemotherapeutic effect.



One advantage of systolic strain is that it changes prior to any significant change in ejection fraction. Changes in the GLS can therefore 'flag' the patients who are experiencing a toxic chemotherapeutic response. This has led to closer collaboration between cardiologists and oncologists.

WHAT IS THE FUTURE OF CARDIO-ONCOLOGY

There are many questions yet to be answered. As the survivorship of oncology patients has increased we are encountering many ongoing challenges. The hard evidence is only beginning to emerge regarding which therapies may be disease modifying.[1] Some smaller studies have suggested that ace inhibitors or angiotensin receptor blockers may have a cardioprotective benefit in this spectrum. It seems likely that close attention to patients' other cardiac comorbidities will also be prudent so as to avoid a 'double hit'.

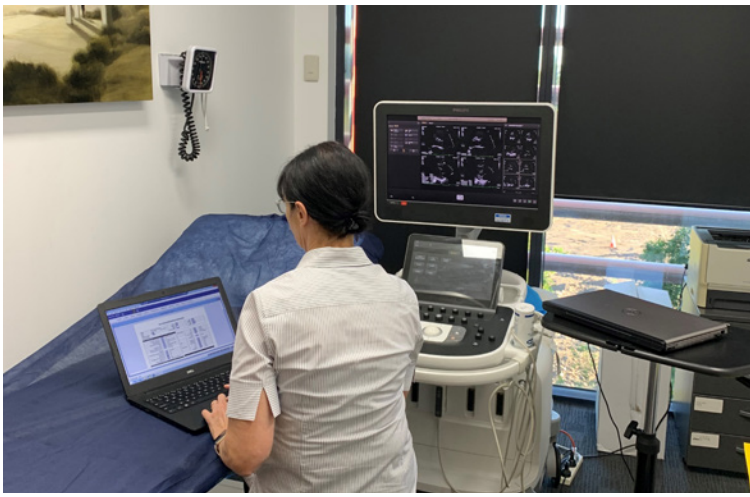
I am sure we will also recognise a range of unforeseen effects as newer agents continue to be applied to a range of patients. We have only scraped the surface in this new, exciting and pivotal cardiac sub-specialty.

1. Cardinale D, Colombo A, Lamantia G et al. Anthracycline-Induced Cardiomyopathy: Clinical relevance and response to pharmacologic therapy. JACC 2010; 55:3. 2013-20.

OUR SERVICES

Sydney Cardiology is a world class comprehensive cardiology service, delivered with expertise and experience.

Using state of the art diagnostic equipment in all five clinic locations, Sydney Cardiology strives to provide exemplary outcomes for long term patient care.



NON-INVASIVE TESTING

Including stress echocardiography, echocardiography, holter monitor studies, ambulatory blood pressure studies, coronary calcium score, dobutamine stress echo, electrocardiogram and event monitor recording.

CARDIAC PROCEDURES

Including coronary angiography, cardiac biopsies, right heart catheterisation, transesophageal echocardiogram and coronary angioplasty.

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Including diagnostic electrophysiology studies, ablation of cardiac arrhythmias, cardiac device implantation, pacemakers and defibrillators, and follow up of implanted cardiac devices.

PERIPHERAL VASCULAR SERVICES

Including renal and lower limb angioplasty, ankle brachial index and SphygmoCorR central blood pressure testing.

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Bella Vista

Macquarie University Hospital
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We provide echo-only, ABP-only and holter monitor-only referral services, with a summary report on any adverse findings.

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF)

A/Prof Martin Brown

GETTING TO KNOW: ASSOCIATE PROFESSOR MARTIN BROWN

Associate Professor Brown joined the Sydney Cardiology team in January 2014 after spending six years caring for heart transplant patients at the Advanced Heart Failure and Transplant Unit of Prince Charles Hospital, Brisbane.

Martin consults at our Chatswood clinic and provides specialist care and management in cases involving high-risk cardiothoracic surgery and severe left and right ventricular failure. Here he discusses heart failure with preserved ejection fraction (HFPEF) with an outline of what is it and what do we do in 2020?

HFPEF – WHAT IS IT AND WHAT DO WE DO IN 2020?

CASE

A 90 year old woman with type 2 diabetes, chronic renal failure and hypertension presents to your practice with pedal oedema and exertional dyspnoea. On examination she has an elevated JVP, normal heart sounds, bibasal crepitations, and pedal oedema. You request a chest x-ray which shows a normal heart size with pulmonary oedema.

Question 1 – What is the most likely diagnosis?

a. Systolic heart failure.
b. Fluid overloaded from renal failure.
c. HFpEF.
d. Pulmonary arterial hypertension.
e. Pulmonary embolus.
Answer: C

Question 2 – What further investigations do you want?

a. ECG.
b. Transthoracic echo.
c. Renal function.
d. NT-proBNP
e. All of the above.
Answer: E

Question 3 – What treatment will you start first?

a. ACE inhibitor.
b. A2RB.
c. Diuretics.
d. Betablocker.
e. Entresto.
Answer: C

INTRODUCTION

Heart failure is one of the commonest medical presentations for General Practitioners and Emergency Departments. 1.3% of all Australians suffer from heart failure with 30,000 new cases per year and 49,000 admissions per year. The in-hospital mortality is high at 8% with a further one year mortality of 8%. Up to 50% of patients with heart failure will have heart failure with preserved ejection fraction (HFPEF), otherwise known as diastolic heart failure. Evidence of diastolic dysfunction is present in 30% of patients greater than 45 years of age.

HFpEF is caused by left ventricular diastolic dysfunction but can coexist with left and right ventricular systolic dysfunction.

DEFINITION

The definition of heart failure with preserved ejection fraction (HFPEF) has previously been quite nebulous, ranging anywhere from an LVEF of 36% to 55%. Fortunately, the recent Cardiac Society of Australia and New Zealand Guidelines were updated in 2018 which have made the categorisation much simpler with just two cutoffs;

- LVEF < 50% otherwise known as systolic heart failure or heart failure with reduced ejection fraction (HFrEF) &
- LV ejection fraction > 50% is now considered heart failure with preserved ejection fraction (HFpEF).

However other alternative names have been given such as diastolic heart failure, heart failure with preserved systolic function (HFpSF), heart failure with normal ejection fraction (HFnEF), heart failure with normal systolic function (HFnSF) or restrictive cardiomyopathy. All must have evidence of normal systolic function with structural heart disease or elevated left ventricular filling pressures.

Table 1. Updated Australian Guidelines 2018

LVEF >50%	LVEF <50%
• Diastolic heart failure • Heart failure with **preserved** ejection fraction (**HF-PEF**) • Heart failure with **preserved** systolic function (**HF-PSF**) • Heart failure with **normal** ejection fraction (**HF-NEF**) • Heart failure with **normal** systolic function (**HF-NSF**) • Restrictive cardiomyopathy • **Must have evidence of structural heart disease or elevated left filling pressures**	• Systolic Heart Failure • Heart failure with Reduced Ejection Fraction (**HFREF**)

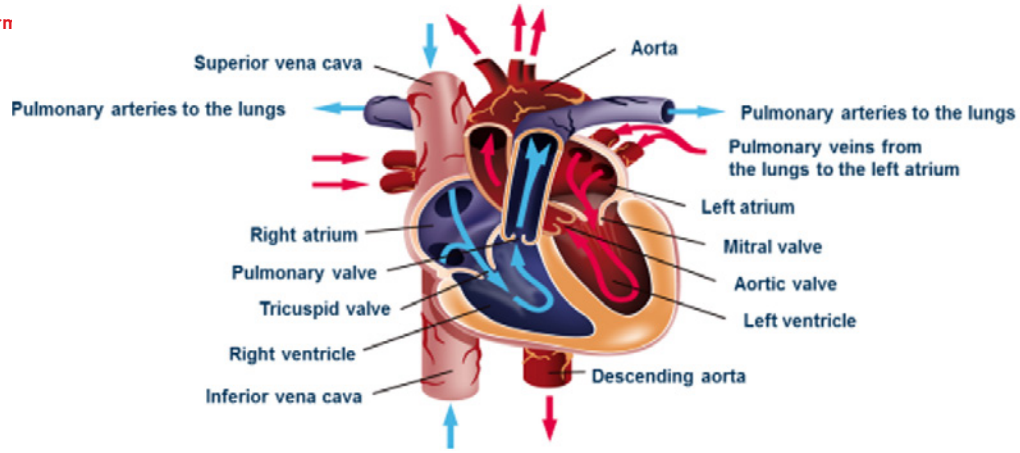
HLC. OCt 2018; 27;10. 1123-1208

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF) (CONTINUED)

PATHOPHYSIOLOGY

Venous deoxygenated blood enters the cardiac circulation through the SVC and IVC into the right atrium, through the tricuspid valve into right ventricle and then passes through the pulmonary valve into pulmonary artery and then to the pulmonary circulation. Oxygenated blood then re-enters the heart through the pulmonary veins into the left atrium, passes through the mitral valve and left ventricle and then passes the aortic valve into the aorta. This requires both active systolic ventricular contraction (pump) and relaxation (suck).

Function of the norn



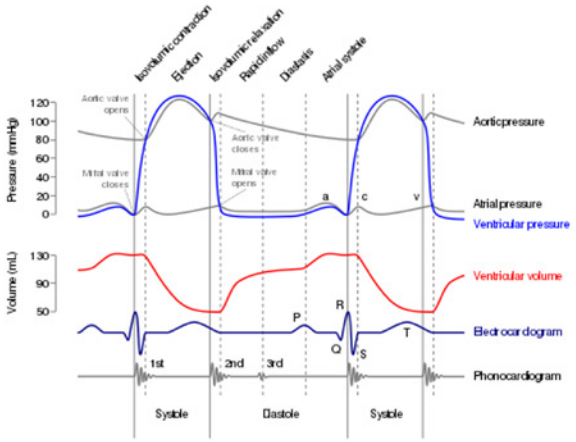
In heart failure with preserved ejection fraction, there is reduced left ventricular relaxation and increased left ventricular stiffness which predominantly affects diastole. The reduced left ventricular relaxation and increased left ventricular stiffness results in increased left ventricular diastolic pressures. This has a subsequent effect of increasing left atrial pressure and resultant left atrial dilation. Eventually, the pressure in the left atrium increases to a point where pulmonary venous return into the left atrium becomes compromised. Increased pulmonary venous pressure then results in extravasation of fluid back into the alveoli from the pulmonary capillaries, causing pulmonary oedema. Eventually, back pressure on the right ventricle can result in right heart failure, elevated jugular venous pressure, hepatomegaly and peripheral oedema.

Concentric remodelling of the left ventricle with extracellular matrix deposition and collagen accumulation with coupling limitation result in increased left ventricular thickening and stiffness.

The comorbidities contributing to HFpEF pathophysiology are ageing, hypertension, diabetes, chronic kidney disease, coronary artery disease and atrial fibrillation.

Phases of ventricular diastole

LV Relaxation "LV Suck"



LV Stiffness "Atrial blow"

Lanier et al. Cardiology in review 2012; 20: 230-236

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF) (CONTINUED)

DIASTOLIC HEART FAILURE CRITERIA

There are three main criteria for diagnosing the HFpEF.

1. Symptoms and signs of heart failure with typical symptoms being similar to systolic heart failure; dyspnoea, orthopnoea, PND, fatigue and pedal oedema. Clinical signs include hypervolaemia including raised jugular venous pressure, hepatojugular reflux, third or fourth heart sound, peripheral oedema and pulmonary crepitations.
2. Cardiac investigations show preserved LV ejection fraction without LV dilatation and there must be evidence of LV diastolic dysfunction such as left ventricular hypertrophy, left atrial dilatation, cardiac doppler parameters suggesting raised left ventricular pressures associated and elevated biomarkers such as NT-proBNP or BNP. A high proportion of patients will be in atrial fibrillation.
3. Invasive haemodynamics will show increased left ventricular end diastolic pressure (LVEDP or pulmonary artery occlusion pressure).

Diastolic Heart Failure Criteria

1. Symptoms & Signs Of Heart Failure
- Typical symptoms: breathlessness, orthopnoea, paroxysmal, nocturnal dyspnoea, intolerance, fatigue, swelling
- Typical Signs: raised jugular venous pressure, hepatojugular reflux, third heart sound, oedema, pulmonary crepitations

2. Preserved LV Ejection Fraction
- Currently taken as LV ejection fraction ≥50%
- Without LV dilation

3. LV Diastolic Dysfunction
- Structural: LV hypertrophy, left atrial dilatation
- Doppler: raised E/e' ratio, abnormal mitral inflow, prolonged pulmonary venous A reversal duration
- Biomarkers: raised NT-proBNP, BNP
- Rhythm: atrial fibrillation
- Invasive hemodynamics: increased LV end diastolic pressure, increased LV stiffness

SYMPTOMS AND SIGNS

Excess fluid will present with dyspnoea, oedema, PND, or orthopnoea. Hepatic congestion may present as RUQ pain, bloating or early satiety. The clinical signs will involve atrial fibrillation in 70% of cases. The JVP may be elevated with a right ventricular heave, fourth heart sound and systemic hypertension is often present. There may be subsequent mitral and tricuspid regurgitation as well as bilateral pulmonary crepitations, hepatomegaly and ascites or pedal oedema.

Table 2. Symptoms and signs typical of heart failure

Symptoms	Signs
Typical	**More specific**
• Breathlessness • Orthopnoea • Paroxysmal nocturnal dyspnoea • Reduced exercise tolerance • Fatigue, tiredness, increased time to recover after exercise • Ankle swelling	• Elevated jugular venous pressure • Hepatojugular reflux • Third heart sound (gallop rhythm) • Laterally displaced apical impulse
Less Typical	**Less specific**
• Nocturnal cough • Wheezing • Bloated feeling • Loss of appetite • Confusion (especially in the elderly) • Depression • Palpitations • Dizziness • Syncope • Bendopnea	• Weight gain (>2kg/week) • Weight loss (in advanced HF) • Tissue wasting • Cardiac murmur • Peripheral oedema (ankle, sacral, scrotal) • Pulmonary crepitations • Reduced air entry and dullness to percussion at lung bases (pleural effusion) • Tachycardia • Irregular pulse • Tachypnoea • Cheyne Stokes respiration • Hepatomegaly • Ascites • Cold extremities • Oliguria • Narrow pulse pressure

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF) (CONTINUED)

WHO GETS IT?

This is often a disease of elderly females which accounts for more than 80% of the population.

Clinical clues include a background history of hypertension, diabetes, obesity, coronary artery disease, left ventricular hypertrophy, aortic stenosis, hypertrophic cardiomyopathy, restrictive cardiomyopathy, sleep apnoea, amyloidosis and chronic kidney disease.

15% of patients less than 50 years will have evidence of diastolic dysfunction and this increases with age to 50% in patients aged over 70 years.

DIFFERENTIALS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

Other alternative diagnoses are restrictive cardiomyopathy such as due to myocardial infarction, cardiac sarcoid, haemochromatosis or amyloid. Valvular disorders may mimic HFpEF e.g mitral stenosis, mitral regurgitation, aortic regurgitation, aortic stenosis and tricuspid regurgitation. Right ventricular heart failure such as is found in pulmonary arterial hypertension, right ventricular infarct or arrhythmogenic right ventricular dysplasia may present with similar sypmtoms and signs. Pericardial disease can often also present with similar symptoms as can obstructive lesions in the left atrium such as atrial myxoma. High output cardiac failure with anaemia, thyrotoxicosis and vitamin deficiency may present with symptoms of heart failure.

DIFFERENTIALS OF HEART FAILURE WITH PRESERVED EF

- **Restrictive cardiomyopathy** – Amyloid, Sarcoid, Haemochromatosis, Fabrys
- **Valvular** – MS, MR, AR, AS, TR
- **Right Heart Failure** – PAH, RV Infarct, ARVD
- **Pericardial Disease**
- **Obstructive Lesions** – Atrial Myxoma
- **High Output Heart Failure** – Anaemia, thyrotoxicosis, Beri Beri

INVESTIGATIONS AND ASSESSMENT

When assessing a patient with symptoms suggestive of HFPEF, a chest x-ray will often show normal cardiac size (no left ventricular dilatation) with pulmonary oedema. The ECG will often show atrial fibrillation in 70% of cases, left ventricular hypertrophy or left atrial enlargement. Biomarkers such as NT-proBNP or BNP will be elevated but the normal ranges are often age related.

The transthoracic echo will often show left ventricular hypertrophy, dilated left atrium or increased left atrial volume. Mitral inflow and annular velocities (E/a ratio and E/e prime > 15). Left ventricular mass may be increased. The echo may show evidence of pulmonary hypertension which is related to the increased left sided venous pressure. The RV may be dilated and subsequent to that tricuspid regurgitation may develop.

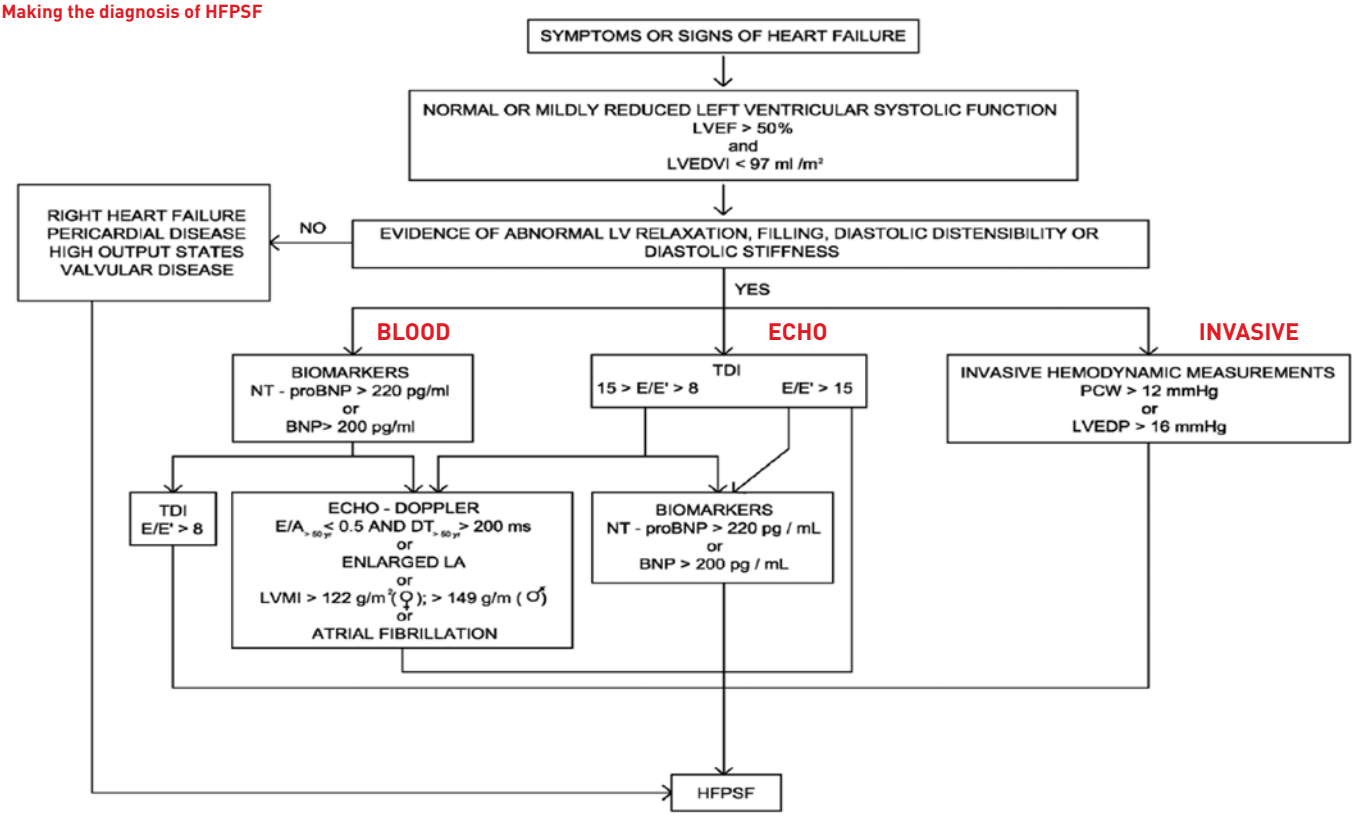
Invasive tests to confirm diagnosis include right heart catheterisation which will show an elevated pulmonary artery occlusion pressure ("wedge") although often a saline challenge will need to be performed to assess patient's response to fluid. A left heart catheter, such as performed during a coronary angiogram, may show elevated left ventricular end diastolic pressure (LVEDP) greater than 16mmHg.

DIAGNOSIS

For patients with symptoms and signs of heart failure, a chest x-ray and echo are normally the first test of choice and must show normal left ventricular systolic function LVEF (>50%). Left ventricular and diastolic volume must be normal (<97ml/m2). Echo parameters may show evidence of abnormal left ventricular relaxation or elevated filling pressure. A measurement of left ventricular stiffening called E/e prime is helpful. Result less than 8 is suggestive of normal LV diastolic function. However an E/e prime of 8-15 is borderline and E/e prime > 15 is confirmatory for diastolic dysfunction. An elevated NT-proBNP or BNP will assist in confirming the diagnosis.

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF) (CONTINUED)

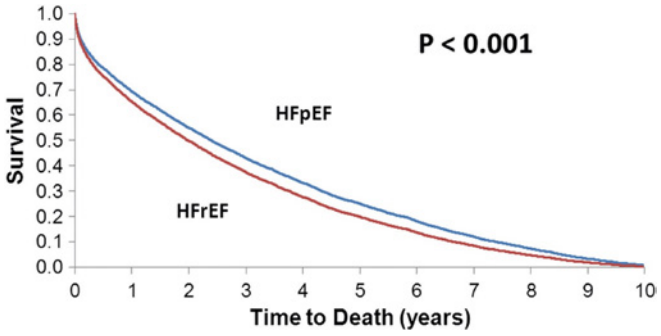
Making the diagnosis of HFPSF



PROGNOSIS

One year survival for HFpEF is marginally better than that for heart failure with reduced ejection fraction at approximately 80%.

Prognosis – 1 year survival

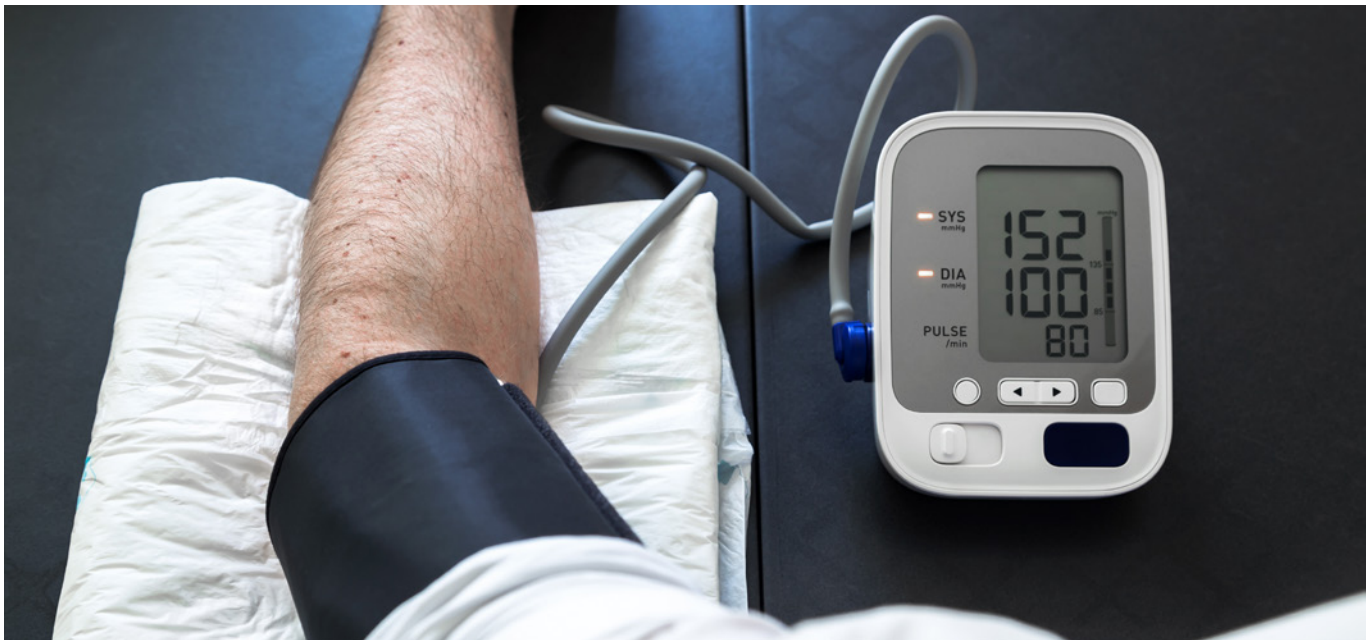


TREATMENT

Currently all trials for medical therapy of diastolic dysfunction have been disappointing and do not increase survival. Negative trials so far have studied ACE inhibitors, A2RB, digoxin, sildenafil, calcium channel blocker, Entresto and betablockers. The mineralcorticoid receptor antagonist spironolactone has been shown to reduce left ventricular diastolic dysfunction in terms of echo derived E/e prime and left atrial size (aldo-HF study) and reduced hospital admissions for heart failure (TOPCAT study) but there was but no effect on exercise capacity, patient's symptoms or quality of life.

The main aims of management are to control the blood pressure and maintain sinus rhythm or rate control. If there is obstruction from hypertrophic obstructive cardiomyopathy or aortic stenosis then these obstructions should be relieved surgically or percutaneously. Alternative causes of dyspnoea must be excluded and the congestion should be treated with diuretics such as frusemide and spironolactone. Weight loss and exercise in obese patients with HFpEF

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF) (CONTINUED)



has shown an increase in exercise capacity (peak VO2) of 10%. Coronary revascularisation should be considered in patients with coronary artery disease with demonstrable myocardial ischaemia and atrial fibrillation should be managed according to the published clinical guidelines. ACE inhibitors, calcium channel blockers, betablockers and A2RBs may be used for management of hypertension in patients with HFpEF but have no effect on the long term outcome of HFpEF beyond blood pressure control. There is no benefit of nutritional supplementation.

MANAGEMENT

- Control BP
- Maintain sinus rhythm or rate control
- Relieve obstruction if present (HOCM, AS)
- Exclude other causes of symptoms
- Treat congestion > **Diuretics**
- **Cardiac Rehabilitation**
- **No role for ACEi, A2RB, Digoxin, sildenafil, CCB, Entresto, B-blockers**
- **Spironolactone (ALDO-HF and TOPCAT)**
  - » Improved left ventricular diastolic function
  - » No effect on excercise capacity, patient symptoms, or quality of life
  - » Reduced HF hospitalisations

CONCLUSION

HFpEF or diastolic heart failure presents with symptoms and signs of congestion similar to systolic heart failure but the left ventricular size and ejection fraction are normal (LVEF>50%) with echo parameters suggest increased left ventricular filling pressures with elevated biochemical markers such as natriuretic peptides. Investigations include chest x-ray, echo, ECG, NT-proBNP, haemoglobin, thyroid function, renal function and glucose. The disease is common in elderly, particularly females with a history of hypertension, diabetes, and renal impairment. Differentials as listed above should be excluded and treatment consist of fluid restriction, daily weights, low salt diet, diuretics, spironolactone, maintaining sinus rhythm and good blood pressure control with exercise and weight loss for obese patients. Unfortunately, there is currently no cure or medication shown to prolong survival for this disease but clinical trials are ongoing.

References

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. European Heart Journal, Volume 37, Issue 39, 14 October 2016, Pages 2999–3058, https://doi.org/10.1093/eurheartj/ehw272

CSANZ Heart Failure Guidelines. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018

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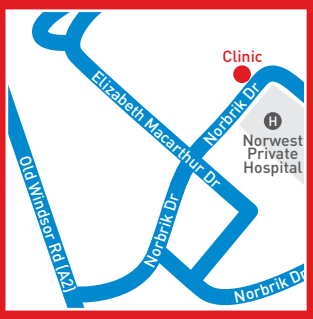

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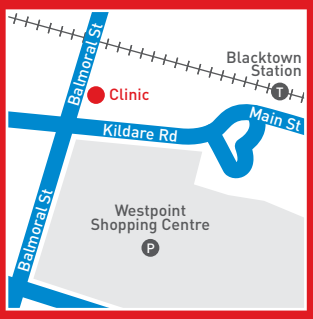

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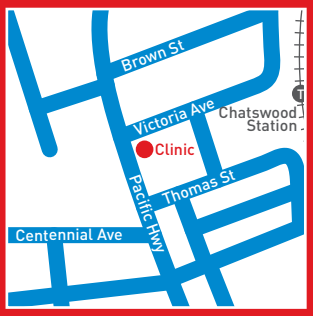

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Sydney Cardiology

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