Cardiac failure

= failure of the heart to maintain a cardiac output sufficient to meet the metabolic demands of the body

Physiology

Cardiac output = stroke volume * rate

↓

dependent on

Preload

LV end diastolic volume

Volume overload

- High output failure
- Mitral regurgitation
- Cardiac shunts

Contractility

Capacity of myocardium to handle preload and afterload

Myocardial disease

- Ischaemic heart disease
- Cardiomyopathy

Afterload

TPR

Pressure overload

- Systemic HT
- Outflow obstruction, e.g. AS, HOCM

Pathophysiology

A number of responses are associated with the failing myocardium. Initially these improve cardiac output but as the disease progresses, these responses become maladaptive and contribute to a progression of the disease.

Cardiac dilatation

- Cardiac output increases as length of muscle fibre is increased (Frank-Starling Law)

Sympathetic drive

- Increased preload (constriction of capacitance vessels), increased contractility, increased afterload (↑TPR)
- Blood is diverted from liver, kidneys and skin to the heart and brain

Renin-angiotensin system

- Aldosterone causes sodium retention and increased preload
- Angiotensin causes peripheral vasoconstriction (↑TPR)

As ↑preload/contractility/afterload

- ↑oxygen requirement
- Eventual decompensation

Principles of treatment

Reduction of preload

- Diuretics
- Nitrates
- (α-blockers)

Increased capacity of myocardium to contract

- Digoxin

Reduction of afterload

- Hydralazine
- ACE-Is
- α-blockers

Alternatively can consider drugs acting by opposing the maladaptive physiological responses. Such agents are associated with reduced mortality:

Activation of the sympathetic system
- β-blockers

Activation of the renin-angiotensin system
- ACE-Is

Management of chronic cardiac failure

Aim to reduce morbidity (↓symptoms, ↑exercise tolerance) and mortality.

The management of this condition has undergone considerable changes over the last 20 years and is still evolving. The older drugs such as nitrates, hydralazine, α-blockers and digoxin (in sinus rhythm) have been replaced by a combination of diuretic and ACE-I. β-blockade is becoming increasingly important.

Identify cause of failure
- DH – negatively chrono/-inotropic agents
  - E.g. β-blockers, CCBs
- PH – alcoholic cardiomyopathy
  - Important to recognise as may improve considerably with complete abstinence

- Bloods: FBC, UE, TFT
- Imaging: CXR, ideally echo
- Electrical: ECG

Common causes
Low output
- IHD (commonest) – risk factor modification
- Valve lesion – repair
- Arrhythmia – correct or ameliorate
- Drugs – stop/alter

High output
- ATP PPB[1]

Quantify severity of failure
Symptomatic: NYHA classification
- Class I: asymptomatic with ordinary activity
- Class II: slight limitation of physical activity
- Class III: marked limitation of physical activity
- Class IV: dyspnoea at rest

ECG for underlying ischaemia
CXR to confirm fluid congestion
Echo to determine LV function (EF, LV enlargement, paradoxical septal motion)
MUGA for accurate estimate of LV ejection fraction

NB BNP (B-type natriuretic peptide) is a strong prognostic indicator in heart failure, better than NYHA class, creatinine and possibly LVEF[2]; likely to enter clinical use soon

Symptomatic Rx

E.g.
- Loop diuretics, e.g. frusemide 40mg or bumetanide 1mg

[1] Anaemia, thyrotoxicosis, pregnancy, pyrexia, Paget's, beri-beri ☺
[2] DOUST, J.A. ET AL. (2005): How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ* **330**:625-7.

- ± potassium sparing agent, e.g. amiloride 5mg

  (Can be combined: Frumil = frusemide 40mg + amiloride 5mg)

Mechanism
- Inhibit sodium reabsorption from the ascending limb of the Loop of Henle
- Produces a natriuresis with obligatory loss of free water

Adverse effects
- Hyponatraemia
- Hypokalaemia
- Hypomagnesaemia
- Impaired glucose tolerance
- Raised triglycerides and lipids
- Hyperuricaemia

ACE inhibition

Prognostic benefit – reduce mortality

Used in <u>all patients</u> with heart failure unless contraindicated. In practice they are usually given if patients require more than a low dose of diuretic, or post-infarction if any evidence of LV dysfunction.

Mechanism
- Inhibit conversion of angiotensin I to angiotensin II
- Reduction in aldosterone reduces salt and water retention and hence reduces preload
- Reduction of vasoconstrictor angiotensin levels reduces arteriolar tone and hence afterload

Adverse effects
See HT

Specific problems in initiating ACE inhibition in patients with heart failure:
In patients taking large doses of diuretics, the systemic BP may be critically dependent on the renin-angiotensin system; ACE-Is may precipitate a fall in blood pressure

Thus
- Temporary withdrawal of diuretic may be required (48h)
- May need to do this in hospital if high risk of rebound pulmonary oedema
- Test dose of short acting ACE-I e.g. 6.25mg captopril; if tolerated prescribe long acting agent e.g. lisinopril 5mg with lower/same diuretic dose; then up-titrate ACE-I to MTD (dependent on BP)

Important clinical trials
VHeFT 1
- Compared placebo with prazosin (α-blockade) and with hydralazine/ISDN
- Showed that hydralazine/isosorbide dinitrate reduced mortality at 3 years (36%) compared with placebo and prazosin (47%) i.e. a 36% risk reduction
- Established nitrate/hydralazine combination in management of heart failure

VHeFT 2
- Compared hydralazine/ISDN with enalapril in a population comparable to VHeFT1
- Showed benefit of enalapril over hydralazine/ISDN combination

CONSENSUS
- Showed reduced mortality and improved quality of life/exercise tolerance in stage IV heart failure (enalapril)

SAVE
- Showed reduced mortality and reinfarction rates *post MI* for patients with LV EF<40% (captopril)

Beta-blockade

Traditionally, β-blockers have been viewed as deleterious in heart failure in view of their negative inotropic action; however their use is now accepted practice and should be attempted in all patients. Patients that benefit most from β-blockers post MI are those with impaired LV function.

A number of *small* studies showed mortality reductions
MDC (Metoprolol in Dilated Cardiomyopathy)

- Examined the use of metoprolol in non-ischaemic cardiomyopathy
- 383 patients with NYHA class II-IV heart failure were randomised to metoprolol for one year
- 34% mortality reduction

CIBIS (Cardiac Insufficiency Bisoprolol Study)

- Examined bisoprolol in 641 patients with NYHA class III-IV over 2 years
- Non-significant overall mortality reduction

USCHFTP (US Carvedilol Heart Failure Trials Programme)

- Stratified programme of 4 component protocols showing a 64% risk reduction over 400 treatment days
- Further study with carvedilol showed a less striking benefit

Several *large* scale mortality studies have been undertaken, e.g.
CIBIS II

- Enrolled 2,647 patients with ejection fraction below 35%, equivalent to NYHA class III to IV
- Bisoprolol vs. placebo (plus conventional therapy)
- 32% reduction in all cause mortality

MERIT, COPERNICUS

Note

- Need to start with very small doses, very gradual dose escalation
- Patients may get worse before they get better
- Many patients may not tolerate even a gentle regime

Digoxin

Principal benefit in cardiac failure lies in those patients with associated AF.
Less effective for patients in SR but may have a small benefit due to its +ve inotropic effect (no evidence for doses beyond 62.5μg)

DIG trial: ↓hospitalisation rate, unchanged mortality

Aldosterone antagonists

Spironolactone

RALES[3]: ↓morbidity/mortality in patients with severe heart failure (EF ≤ 0.4) who are already on ACE-I and diuretic, with or without digoxin.

SEs

- Potential problem of severe hyperkalaemia (combined ACE-I and spironolactone) was not seen as a problem in this study
- Men: gynaecomastia, impotence
- Women: menstrual irregularities

Eplerenone

Unlike spironolactone, eplerenone *selectively* blocks the mineralocorticoid receptor

EPHESUS[4]: ↓morbidity/mortality in patients with severe heart failure (EF ≤ 0.4) post MI who are already on standard therapy

[3] PITT, D. (1995): ACE inhibitor co-therapy in patients with heart failure: rationale for the Randomized Aldactone Evaluation Study (RALES). *Eur Heart J* **16** Suppl N:107-10. (NB Aldactone® = spironolactone)

Risk of gynaecomastia is similar to placebo

RALES and EPHESUS cannot be compared directly as they were conducted at different times with different endpoints in different patient populations. For example, 75% of EPHESUS patients were on β-blockers, which was not an established treatment at the time of the RALES study.

Long-term studies directly comparing spironolactone and eplerenone will need to be awaited.

Specific management issues

Patients intolerant of ACE inhibitors

Such patients will benefit from a combination of nitrate and hydralazine that is of less benefit but may be tolerated where ACE inhibitors are not (cf. VHeFT 1/2).

Resistant failure/oedema

Patients who are not controlled on the above regime have a very poor prognosis. Remaining therapeutic options are:

IV diuretics
Presumes poor oral bioavailability due to gut oedema. It is not uncommon to bring such patients into hospital for several days of high dose loop diuretic therapy to try to provoke a diuresis.
NB bumetanide has much better oral absorption from an oedematous gut than frusemide (1mg bumetanide ≈ 40mg frusemide)

Metolazone (thiazide diuretic with some loop diuretic activity)
Can provoke a profound diuresis when combined with a loop diuretic
Patients need to carefully monitor their daily weight and can be educated to take doses as required

Revascularisation
Some patients post MI might benefit from revascularisation to improve function

Transplantation
Predominantly in young patients with non-ischaemic cardiomyopathy

Management of acute pulmonary oedema

- Sit up, 100% oxygen
- IV access
- ECG monitoring, 12-lead ECG
    - ?treatable arrhythmia
    - ?infarction
- 2.5-5mg IV diamorphine
- 40-80mg IV frusemide

Further management (if cardiogenic)

SBP>100mmHg
- Consider further bolus of frusemide
- Start GTN infusion (50mg in 50ml normal saline and titrate up to BP)

SBP 80-100mmHg
- Start a dobutamine infusion (2.5-10μg/kg/min)
- Add nitrate infusion when BP permits

SBP<80mmHg
- Management of cardiogenic shock
- If available measure PCWP

[4] PITT, D. ET AL. (2001): The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. *Cardiovasc Drugs Ther* **15**:79-87.
PITT, D. ET AL. (2003): Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *NEJM* **348**:1309–21.

- If <15mmHg
  - Give plasma expander 100ml every 15min
  - Aim for PCWP 15-20mmHg
- If >15mmHg
  - Inotropic support, e.g. dobutamine infusion
  - Aim for SBP>80mmHg
- Consider ‘renal dose’ dopamine 2-5μg/kg/min (via central line only)
- Consider intra-aortic balloon pump if expecting improvement, or needing to buy time until surgery
- Consider reversible causes