A. PHARMACOLOGY OF CONGESTIVE HEART FAILURE.

Brief Revision Review - Basic Physiology of the Heart

Cardiac myocytes have:

- well-organized actin/myosin filaments (midway between the highly organized skeletal and the less well-organized smooth muscles). Variates with cardiac muscle type: nodal, atrial, Purkinje, ventricular (epi- to endocardium).
- well-organized sarcoplasmic reticulum which varies with cardiac tissue type – most organised in ventricles.
- contraction requires the entry of calcium through L type channels to trigger release of calcium from sarcoplasmic reticulum and activation of contraction.

Inotropism (contractility status) depends upon resting tension, modulated by the autonomic nervous system, chiefly via sympathetic nerve activity and subsequent β₁ receptor stimulation, as well as by various other hormones and ions. Ionotropism is positive or negative, luseotropism is rate of relaxation - removal of activating Ca++ – again positive or negative.

β₁ receptor stimulation results in positive inotropism via elevation of intracellular cAMP leading to phosphorylation of L type Ca channels and the sarcoplasmic reticulum, resulting in more Ca++ available for contraction but also speeds up relaxation. *(parasympathetics mediate negative inotropism, but only in atria)*

Inotropism in myocytes depends upon initial (resting) tension of the muscle. This relationship is described by the **Frank-Starling** curve thus contractility depends upon pre- and after-load (in situ “venous and arterial” pressures respectively).

Points of Note:

There are a finite number of myocytes in the adult heart - myocytes do not undergo significant mitosis.

Myocytes are lost as a result of: maintained ischaemia which leads to infarction, cardiotoxins, apoptosis, an excessive workload such as occurs with hypertension, cardiac valve defects, blood volume disturbances..

Myocytes respond to a sustained and increased work load with hypertrophy.

Excessive sustained work demand on ventricular myocytes leads to failure of their contractility - heart failure

The weak link in cardiac myocyte contraction is excitation-contraction coupling (the site of cardiac failure).

**Future new drug research directions:** Stem cell research to increase myocyte proliferation, angiogenesis, understanding failure in excitation/contraction coupling, suppressing actions of endogenous cytotoxic substances that exacerbate cardiac injury, and/or are released by ischaemia.
THE PATHOPHYSIOLOGICAL CYCLE OF HEART FAILURE

Heart Failure (insufficient cardiac output) follows:-
Irreversible loss of myocytes – as a result of age, myocardial ischaemia & subsequent infarction, infection, cardiotoxins, various classes of drugs.
The result is excessive chronic demands on the heart due to:-
Excessively high heart rate for too long a period
Excessively high ventricular pressures (pre- and after-load) as induced by hypertension, valvular incompetence.
Excess sympathetic activity (β-agonism) – which is oxygen wasting and can increase intracellular calcium loading

Compensatory responses to inadequate cardiac output (both acute and chronic) include:

- Increased sympathetic activity. Activation of β and α receptors produce the expected effects on the heart (tachycardia, inotropism) and blood vessels (vasoconstriction), respectively, but paradoxically can exacerbate the failure.
- Retention of sodium and water as a result of reduced renal blood flow and release of renin -angiotensin II, vasoconstriction and increased sympathetic nerve actions on blood vessels.
  Angiotensin II – stimulates aldosterone release; it is a direct vasoconstrictor; potentiates sympathetic nervous system, and growth factors.
  Aldosterone mediates retention of sodium (plus water) and increases blood volume
- Other endogenous factors possibly involved in heart failure include atrial naturetic factor, tissue necrosis factor, endothelin, apoptotic factors,

The above are all potential targets for drugs which might ameliorate heart failure. Modulation of the renin/angiotensin/aldosterone, and sympathetic, systems are currently the major therapeutic approaches in the treatment of heart failure.

Cardiodynamic responses to the low cardiac output of heart failure include:-

- Elevated venous pressure: (increased pre-load) via salt and water retention, plus vasoconstriction. Sustained increases in venous pressure cause peripheral and pulmonary oedema.

This increased pre-load utilizes the Frank-Starling relationship to maintain cardiac output via increasing venous filling pressures. However, with heart failure, the position of the Frank-Starling curve falls to the right. The result of the above can create a vicious cycle whereby venous pressure rises and heart failure worsens

Elevated pre-load can be targeted by use of diuretics, ACEIs, veno-dilation, and acute reductions in blood volume

PHARMACOLOGICAL APPROACHES TO TREATING CONGESTIVE HEART FAILURE

The pharmacological approach depends upon whether the failure is acute or chronic, and whether the cause has been identified.

A. TREATMENT OF ACUTE CONGESTIVE FAILURE: goals of emergency treatment are to prevent death, stabilize the patient, and provide symptomatic relief; it can involve the following:

1. Intravenous furosemide (a high ceiling diuretic to produce marked diuresis (loss of fluid volume) and direct vasodilation
2. Intravenous morphine acting centrally to relieve anxiety: it is also a venodilator.
3. Oxygen (since hypoxia worsens heart failure)
4. Cardiac inotropes given if considered essential: these include:
   Beta1 agonists for immediate inotropism BUT for short term acute use only, since they are oxygen wasting and exacerbate cardiac myocyte damage.
   Digoxin (see later)
5. Nitrovasodilators (nitroglycerin, nitroprusside)
B. **CHRONIC CONGESTIVE FAILURE**: the treatment goals are to provide symptomatic relief, improve life, reduce mortality) with drugs such as:-

1. **Angiotensin converting enzyme inhibitors** - reduce mortality.
   (captopril, enalapril, lisinopril, quinapril, ramipril, and other ***prils) - orally
   **Angiotensin receptor antagonists** - may be equivalent to ACEIs with less side effects
   (losartan, candarsatan, ****tans) - orally

2. **Diuretics**
   (furosemide, thiazides, spironolactone) - orally

3. **Beta blockers.**
   (carvedilol, metoprolol, increasingly others) - orally

4. **Cardiac glycosides** - orally
   (digoxin)

The list of drug types that have been, and are used, to treat heart failure include:-
Aldosterone inhibitors, Angiotensin drugs, Angiotensin Receptor-neprilysin Inhibitors (e.g. valsartan/sacubitril), Beta-blockers, Diuretics, Inotropes including digoxin, Bradycardic drugs, Vasodilators, Calcium channel blockers, Ions (K, Mg), selective Bradycardics.

**Pharmacology of above drugs**

**POSITIVE INOTROPES**

**cAMP DEPENDENT INOTROPES**
All increase cardiac intracellular cAMP leading to phosphorylation of calcium channels, and the sarcoplasmic reticulum, so making more calcium available for contraction at the level of actin and myosin.

**β1 adrenoceptor agonists:**
Endogenous agonists (NE and circulating E) also stimulate other types of adrenoceptors, and their value may be limited. The important point is that the cardiac inotropic actions of β agonists are oxygen wasting, and reduce cardiac efficiency (measured as the ratio of cardiac output to cardiac oxygen use).

- **Dopamine** - also an agonist at dopamine receptors: dilates renal blood vessels to help preserve renal function
- **Dobutamine** is a more β1 selective agonist

*If such drugs are used, it is only for ACUTE SUPPORT of the cardiovascular system since they are oxygen wasting, reduce cardiac efficiency, and promote excessive intracellular accumulation of calcium besides having toxicities and side effects that include tachycardia, arrhythmias, worsening of condition, hypokalaemia*

**Phosphodiesterase inhibitors (elevate tissue cAMP levels)**
- **Aminophylline** - a chemical complex of the xanthine, theophylline, with ethylenediamine. It is a phosphodiesterase inhibitor that also acts on adenosine receptors.
  Can be used in acute situations, and also has bronchodilator actions which helps alleviate any associated cardiac asthma
Orally active cardiac phosphodiesterase (PDE3) inhibitors have been used in the past, but their unfavourable effect of increasing mortality, despite alleviating the cardiac failure, has resulted in their being discontinued or severely limited. Examples include: - amrinone, milrinone, vesarinine.

*If the above are used, it is only for acute support*

**Toxicities and side effects: tachycardia, arrhythmias, nausea, worsening of the condition.***
Cardiac glycosides (for a fuller description of their pharmacology see later)
The same molecular mechanism can be assumed to be responsible for their therapeutic and toxic actions is inhibition of Na/K ATPase. This leads to intracellular accumulation of Na and, therefore, Ca.
Many different cardiac glycosides are found in nature as naturally occurring sugars with a pharmacologically active steroid group – such glycosides occur in plants, and even some animals (e.g. some toads).
Digoxin is used therapeutically in USA & Canada (other glycosides are sometimes used in other countries). For the most part they have been replaced by other drugs.
Plant cardiac glycosides can be ingested accidentally by children, and thereby a cause of poisoning. All cardiac glycosides share the same basic molecular mechanism, but vary in pharmacokinetic characteristics (absorption, metabolism, excretion)

DIGOXIN: given i.v. or oral (70% absorbed, renal excretion). Its therapeutic ratio is close to unity (a dose beneficial for all would be toxic to some), onset of action slow (hours), toxicity common, especially when serum K⁺ is low, including g.i upset and CNS effects. Digoxin-binding antibodies are available for overdose treatment. Digoxin has also been used in ATRIAL FIBRILLATION to reduce ventricular rate.

Toxicities and side effects: Arrhythmias, g.i. upset, CNS disturbance in the elderly, coloured vision, rarely gynaecomastia. Excess toxicity is treated with K⁺, if necessary, and with digoxin antibody fragments

ANGIOTENSIN-RELATED DRUGS AND DIURETICS

ANGIOTENSIN-RELATED DRUGS have a common beneficial mechanism related to increasing excretion of oedema fluid (excess sodium and water), plus ancillary actions.

Angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and renin inhibitors are used. These classes of drug could all be expected to have similar utility in congestive heart failure by reducing the activity of the renin- angiotensin system – RAS activity. However, this may not necessarily be the whole case since renin inhibitors may have lesser utility.

Angiotensin converting enzyme inhibitors (ACEIs): e.g. captopril, lisinopril, enalapril, etc
Reduce symptoms and importantly reduce morbidity and mortality.
Oedema fluid lost - cardiac output rises
Toxicities and side effects:- Cough (10%), rashes, g.i. upset, angioedema

Angiotensin receptor I antagonists: e.g. losartan, candarsatan
May not have complete identity with ACEIs in their actions. They are newer drugs thus less well-known. Do not reduce angiotensin II levels
Reduce symptoms of c.h.f. and reduce morbidity and mortality
Toxicities and side effects:- less than with ACEIs, and no cough

Sacubitril is a pro-drug that is de-ethyated via esterases to neprilysin which blocks deactivating vasoactive peptides thus will increase their to vasodilate and reduce extracellular volumes via sodium excretion.

DIURETICS
Two major types: loop (high ceiling) diuretics (e.g. furosemide) and distal tubule diuretics (e.g. thiazides). Both types cause salt and water loss, and have vasodilator actions. Loop diuretics are more efficacious (higher maximum effect).
Toxicities and side effects:- electrolyte imbalance (especially K⁺ and this is potentially dangerous). With the thiazides, hyperuricaemia, hyperglycaemia, adverse renal effects between furosemide with NSAIDs.
OTHER DRUGS

**Beta blockers**

Appear at first glance to be dangerous since they may exacerbate heart failure by abolishing the acute compensatory reflex increase in cardiac sympathetic drive. This sympathetic activation of the heart might provide acute benefit in the short term but long term beta activation exacerbates failure. Beta blockers are now favoured in chronic and less severe cardiac failure. Expected adverse effects on the heart are not seen when therapy begins with small, but increasing, doses. Beneficial effects were first seen with carvedilol (β1 & β2, α blocker and antioxidant), but benefit is seen with all β blockers.

Toxicities and side effects:- bradycardia, a.v. block, asthma, exacerbated intermittent claudication, hypotension

**Vasodilators**

Given acutely (nitroglycerin or nitroprusside i.v.) can reduce pre- and after-load which provides benefit. Hydralazine, a directly acting vasodilator can be used in conjunction with nitrates.

Toxicities and side effects:- excess hypotension, reflex tachycardia, SLE (systemic lupus systemic lupus erythematosus) with hydralazine

**Morphine (used acutely only)**

Has a very useful anxiolytic action and is a venodilator that reduces pre-load.

Toxicities and side effects: respiratory depression, nausea and vomiting, histamine release

Many of the above drugs have covered in previous lectures but not all of them. In particular the cardiac glycosides are not covered in any depth. Cardiac glycosides have been known for years but are still pharmacologically interesting, not so much for their usefulness in the therapy of congestive heart failure, but more for their rather interesting and unique pharmacology, as well as the relationships between their molecular, cellular, tissue and organ actions which give insights into physiology and pathology.

The main aspects of the pharmacology of cardiac glycosides are outlined below:-

**CARCIC GLYCOSIDES**

**Chemical Structure**

Natural occurring steroids with a lactone ring plus attached sugars.

**SAR**

Overall some degree of structural variation is possible but this does not really influence their basic molecular actions. The effect of molecular changes on their SAR changes is principally upon the pharmacokinetic characteristics in terms of duration of action, bioavailability, metabolism and excretion, etc. Basic pharmacophore is 17C steroid ring coupled to a lactone ring, both of which are essential for action. The attached sugars alter pharmacokinetics.

**Source**

Classically cardiac glycosides are derived from the ‘foxglove’ plant Digitalis lanata, but cardiac glycosides are found in many other plants (e.g. squill, oleander) and are a source of poisoning. They are also found in animals, particularly in cane toads (Bufo marinus) which are toxic if eaten or licked. Pharmaceutical source is still digitalis plants grown specifically for the purpose.

Possibly a cardiac glycoside is an endogenous cardiotropic substance is present in mammalian hearts. The evidence for this is still considered equivocal.

**Molecular Mechanism of action**

The accepted mechanism of action is inhibition of Na/K ATPase, and thereby alteration of the ratio of Na and K in the cell. However some observations may be inconsistent with this mechanism, particularly with respect to speed of onset of action of at least part of the inotropic response to cardiac glycosides in isolated cardiac cells. Cardiac glycosides are not cardiac selective in their action on Na/K ATPases, but the particular ionic status and resulting physiology of cardiac muscle probably makes cardiac tissue more sensitive in a therapeutically useful manner. Thus, inhibition of Na/K ATPase occurs in all tissues and probably accounts for their toxicity.
**Cellular Mechanisms of action**

Inhibition of the Na/K ATPase for sufficient time and duration results in loss of intracellular potassium and an increase in intracellular sodium. As a consequence, there is an increase in calcium available for contraction within the cardiac myocyte. The increasing sodium concentration within the cell is thought to bring in extra calcium (via intracellular sodium being reverse transported in the Ca/Na exchanger for calcium - “pump reversal”).

Loss of intracellular potassium and accumulation of intracellular sodium in heart cells also occurs in other tissue and this alters the electrophysiology of all tissues containing Na/K ATPases and is particularly apparent in cardiac and nervous tissue. Such molecular actions may account for toxicity of cardiac glycosides. It is important to recognize that different types of tissues differ in the degree to which they rely on membrane pumps and exchangers such as Na/K ATPase and Na/Ca exchangers, and this may account for some of the apparent selectivity of action of cardiac glycosides for cardiac tissue.

**Tissue Mechanisms of action**

Since the heart is the therapeutic target for cardiac glycosides their actions on cardiac tissue are generally the major focus. On isolated cardiac tissue preparations the main effects are:

- An initial inotropism without effects on the speed of contraction, or on luseotropism.
- Inotropism seen in all cardiac preparations, but most marked in "failing" cardiac tissue.
- Higher doses, or longer exposure, produce arrhythmias as cells begin to depolarize, and cardiac electrophysiology is disturbed enough to precipitate arrhythmias.

Inotropic effects can be seen sometimes in smooth muscle, but not particularly in skeletal muscle. This reflects differences in their cellular ion exchange balance and their excitation-contraction mechanisms.

- Neuronal tissues can show increased excitability when exposed to cardiac glycosides.
- Even erythrocytes will lose K, and gain Na, on exposure to cardiac glycosides.

**Organ Mechanisms of action**

The major therapeutic organ is, of course, the heart where, in addition to positive inotropism, both Direct and Indirect actions are seen on the rate and rhythm of the heart. As an approximation Indirect actions occur at lower doses while Direct actions occur at higher ones, but this is a loose approximation.

Indirect actions are vagotonic inasmuch as there is increased vagal activity on the atria - particularly on the AV and SA nodes. The effect on the AV node is to slow transmission which is why cardiac glycosides were used in the treatment of atrial fibrillation to slow ventricular rate. In untreated atrial fibrillation the ventricular rate can be fast and erratic (due to erratic atrial impulses ‘battering’ the AV node). The aim of digitalis treatment in atrial fibrillation is therefore to control (slow) the ventricular rate.

The interaction between Direct and Indirect effects on the atria are fascinating in terms of cardiac pathophysiology since digoxin can produce atrial arrhythmias and cardiac glycosides can convert atrial flutter to atrial fibrillation. This apparent worsening of an arrhythmia actually makes it easier to control ventricular rate since varying the degree of atrioventricular block in the presence of atrial flutter (a coherent rapid atrial rate) can paradoxically increase ventricular rate to dangerously high levels.

The major toxicities of cardiac glycosides are fatal ventricular arrhythmias due to direct actions on K and Na distributions in cardiac cells, and resulting disturbed electrophysiology. Such arrhythmias account for the fatal effects of cardiac glycoside poisoning.

Other toxicities also can be traced to Na/K ATPase inhibition in:-
- Gastrointestinal tract: nausea, vomiting, diarrhoea
- CNS: coloured vision, anorexia, dizziness, fatigue, hallucinations

All of such actions result in cardiac glycosides having a THERAPEUTIC INDEX close to 1.0 hence the reluctance of physicians to use them (e.g. digoxin in North America).
PHARMACOLOGY OF MYOCARDIAL ISCHAEMIA/INFARCTION.

RELEVANT PHYSIOLOGY OF CORONARY BLOOD FLOW

Cardiac vasculature pharmaco-physiology:

Coronary arteries in humans are usually end arteries BUT collateral arteries may be present but certainly develop over time in the presence of chronic regional myocardial ischaemia – a stimulus that promotes the growth of collaterals. If present, coronary collateral arteries may influence the cardiac vasodilator actions of vasodilators. Different species vary widely in their functional complement of coronary artery collaterals: guinea pigs have many, dogs a moderate amount, rats, pigs and primates few, if any.

Coronary artery tone is mainly independent of the ANS and is usually relatively unresponsive to autonomic drugs, but pathological stimulation of α-receptors can occur. Coronary vessels are highly responsive to local vasodilators such as adenosine whose vasodilator actions usually overwhelm the coronary artery vasodilator actions of exogenous vasodilator drugs.

Coronary Blood Flow:

Is highly and predominantly auto regulated in response to myocardial oxygen requirements hence cardiac vascular tone is relatively independent of exogenous vasodilators. Coronary vasculature is very sensitive to myocardial ischaemia - the most powerful coronary vasodilator drive in the heart. Myocardial ischaemia is the greatest stimulus for increasing blood flow in an ischaemic region of the heart.

Coronary flow occurs during diastole when ventricular wall tension is low (drugs that reduce ventricular wall tension increase coronary flow)

Coronary flow is mostly independent of cardiac nerve activity

Coronary Is REGULATED by:

Cardiac tissue oxygen need since the heart extracts a constant percentage of oxygen from its nutrient blood flow.

It depends upon

1) Cardiac work (Blood Pressure* x Heart Rate*)
2) Ventricular wall tension (pre-* and after-load*)

* Factors that can be pharmacologically regulated

ANGINA PECTORIS

Classical angina pectoris is a reversible symptom, usually due to partial regional reversible ischaemia in the heart following an increased cardiac tissue demand resulting from an increased heart rate, usually driven by increased cardiac sympathetic ANS activity. Any increased work demand can result in an ‘at-risk’ area of the myocardium becoming ischaemic. This situation occurs when a need for increased flow in a vessel is limited in one, or more, extramural coronary arteries by atheroma, or inappropriate vasoconstriction.

Partial obstruction (>70%) of a coronary artery limits the extent to which coronary blood flow can increase in response to cardiac work

Partial coronary artery obstruction can be due to:

1) Atheroma* (A large lesion in a major artery limits the increase in coronary blood that is required to meet an increased oxygen demand - due to increased cardiac work.* As a result, limitations to coronary flow occur in the presence of an increased demand for coronary flow; this leads to ischaemia.)
2) Inappropriate coronary artery vasoconstriction*
3) Platelet aggregation can contribute*

* Actions that can be pharmacologically regulated
The pathophysiology of the major types of angina dictate therapeutic objectives.

Fixed Obstruction Angina in which symptoms, and signs (ST segment changes in the ECG), occur predictably for a given amount of physical work, or emotion, via an increase blood pressure and heart rate (Blood Pressure x Heart Rate Product) often predicts symptoms and ECG findings.

Prinzmetal's Angina due to inappropriate coronary artery vasoconstriction requires treatment with exogenous vasodilators.

Crescendo Angina can indicate a high potential for myocardial infarction - involves the above plus inhibition of platelet aggregation. Maintenance of the angina occurs where irreversible ischaemia will lead to infarction.

This above results in the following pharmacological goals:

For treatment of symptoms: reduce cardiac work by reducing heart rate, reducing cardiac work directly, reducing vasoconstriction, while reducing platelet aggregation in the 'at-risk' coronary arteries.

For reduction of causative pathology: reduce blood lipids (e.g. statins); reduce platelet aggregation, control hypertension, provide cardio-protection with a beta blocker

Myocardial Infarction
Myocardial infarction is death of cardiac tissue as a result of long-lasting (not spontaneously reversible or not reversed by treatment) severe regional ischaemia in a part of the heart.

Due to:
- Abrupt and severe permanent obstruction of a coronary artery
- Fibrin/platelet clot
- Regional dissection in an artery

Unless the obstruction is reversed, the cardiac tissue 'down-stream' to an end coronary artery blockage will die.

Pharmacological goals: the immediate goals of treatment in myocardial ischaemia are to prevent or revert to sinus rhythm any potentially lethal arrhythmias, reverse coronary obstruction (fibrinolysis), protect the heart, prevent platelet aggregation and formation of fibrin clots and later to reverse atherogenesis.

Drug Strategies for Treating Angina

Reduce the Oxygen Need of Heart
By blocking the action of cardiac sympathetic nerve stimulation (negative chronotropism and inotropism) with beta blockers; which one? There are “selective” beta blockers, partial agonists (with intrinsic sympathetic activity), or non-selective beta blocker with not much evidence which ones are superior.

Reduce an inappropriately high heart rate due to disease (beta blockers).
Lower blood pressure - acutely with nitrates, chronically with antihypertensive drugs. Lower pre-load (acutely with nitrates)

Vasodilate Constricted Arteries
Use appropriate vasodilators (nitrates or calcium channel blockers with the goal of dilating only the appropriate coronary vessels so as to avoid "coronary steal")
DRUG TREATMENT STRATEGIES FOR MYOCARDIAL INFARCTION

1) ASA or clopidogrel reduce platelet aggregation; a beta blocker reduces possible adverse effects of sympathetic cardiac nerve activity.
2) Prevent arrhythmias - ventricular tachycardia &/or ventricular fibrillation - causing death but antiarrhythmic drugs (lidocaine) are of very limited value
3) Remove the source of the coronary artery obstruction
   By surgery, or other physical techniques
   By fibrinolysis, and clot disruption (fibrinolytic drugs, heparin?)

Ancillary acute and chronic therapy
Acetylsalicylic acid to (ASA) lower potential for platelet aggregation plus beta blockade

DRUGS REDUCING CARDIAC WORK

Beta Blockers
All are effective in the prophylactic treatment of angina by preventing unnecessary $\beta_1$ adrenoceptor stimulation of the heart. The net result is a relative negative chronotropism and inotropism, regardless of sympathetic nervous system activity.

Beta blockers vary in their:
Pharmacokinetic characteristics
(Lipid solubility, pharmacokinetic half-life, metabolism, excretion)
Selectivity of blocker for $\beta_1$ adrenoceptors (but potency of $\beta_1$: $\beta_2$ may be limited <10)
Partial agonist action (stimulate $\beta$ receptors when sympathetic nerve activity is low, but block when sympathetic activity is high – intrinsic sympathetic activity-ISI)

Beta blockers also reduce blood pressure, hence their use as antihypertensive drugs. Reduce mortality is associated when used in myocardial infarction.

Calcium Channel Blockers?
Reduce both pre- and after-load
Reduce cardiac work and relax vaso-constricted coronary arteries
In healthy hearts only verapamil and diltiazem exert negative inotropic actions. Dihydropyridines (nifedipine and other "ipines") may, however, have negative inotropic actions in severely compromised hearts. All of the available calcium channel blockers cause vasodilation in veins and arteries, but vary in their selectivity for different blood vessels.

Other vasodilators (nitrates)
Drugs that are vasodilators include nitrates, antihypertensive drugs.
Nitrates in particular dilate large veins and thereby reduce pre-load while also dilating collaterals.
Reduce wall tension (reducing pre- and/or after-load). Various vasodilators will do this, and therefore reduce cardiac work as well as oxygen demand.

PHARMACOLOGY OF NITRITES AND NITRATES.
NITRATES IN GENERAL
Nitrates that release NO are capable of relaxing most contracted smooth muscle, but the smooth muscles of blood vessels are particularly sensitive to their actions. They will relax gut smooth muscle, but are less active on airway smooth muscle - hence not bronchodilators.

NO is a ubiquitous endogenous vasodilator - nitregic nerves, and other stimuli, release endogenous NO. NO nerves have varying role in different arteries and veins.
Many organic nitrites/nitrates have been synthesized, all act at a molecular level by generating nitric oxide (NO), the ubiquitous endogenous vasodilator.
Actions of NO include:
- Relax most contracted smooth muscles. In blood vessels this results in vasodilation – reduction of pre- (veins) and after- (arterioles) load.
- Nitrates have some degree of selectively for different types of vessel beds – especially capacitance vessels.
- Produce excellent venodilation as well as dilation of coronary collaterals.
- Dilation of collateral arteries in coronary beds can specifically prevent coronary "steal" with the nitrates. However, general and unselective coronary artery vasodilation can result in blood flow being "stolen" from an ischaemic area, hence not all vasodilators are useful.

**NITROGLYCERIN**
Nitroglycerin taken sublingually is the nitrate used acutely to terminate an on-going ANGINA attack, or is taken for acute prophylaxis to prevent an expected attack. Its half-life is very short. Usually given sublingually (as tablet or aerosol) where absorption is good. Nitroglycerin can be applied to the skin in the form of a cream, or a paste. However tolerance rapidly develops with chronic exposure to nitrates; it can also be given intravenously for limited periods.

**OTHER NITRATES**
A variety of other organic nitrates have been used some are orally active (e.g. isosorbide dinitrate).

**Adverse effects of nitrates**
- Headache/hypotension, but tolerance to the headache in particular develops rapidly. However tolerance to beneficial effects of nitrates can occur with the long acting nitrates, or nitrate patches.
- Methaemoglobinaemia – occurrence is rare when treating angina.

**TREATMENT OF MYOCARDIAL INFARCTION**

**Two distinct therapeutic goals:**
1. Prevent a first attack, or the re-occurrence of an attack
2. Ensure survival from the attack and reverse occlusive process so as to restore blood flow to the cardiac tissue at risk.

**Prevention of myocardial infarction:**
- Treat causative conditions: change behaviour (hypertension, elevated cholesterol, tobacco, weight, physical activity)
- Protective drug therapy: (beta blockers, statins, ACE inhibitors, acetylsalicylic acid)

**Surviving a myocardial infarct and reversing the causative blockade:**
- Morphine; for pain and anxiety
- **Ensure survival:** VF is major cause of death, heart failure is another cause of death. Use of antiarrhythmic drugs are of little use, but electrical defibrillation is vital to terminate sustained ventricular tachycardia, essential for ventricular fibrillation.
- Reversal of occlusion: reverse occlusive process with fibrinolytic drugs/anticoagulants and initiate preventive therapy.
Mechanisms of action/side effects/toxicity

Acetylsalicylic acid (aspirin): a small daily dose selectively co-valently binds to and blocks platelet COX and production of TXA2 – a pro-aggregatory eicosanoid – while and avoids excess gastric toxicity due to COX block in the stomach. Other antiplatelet drugs include dipyridamole, ticlopidine, clopedigrol.

ACE inhibitors (***prils, ***artans): Block the function of the renin-angiotensin system. ACEIs are anti-hypertensive drugs shown to reduce mortality in cardiovascular disease. Angiotensin antagonists (losartan) are similar.

Antiarrhythmics: Atropine for bradycardia. Lidocaine is of limited value in preventing ventricular tachycardias. After MI there are very few antiarrhythmic drugs of real preventive value, and their danger is worsening of arrhythmias.

Beta blockers (***olols): Nullify the adverse effects of the sympathetic nervous system on the heart - precipitation of myocardial ischaemia/infarction and lethal arrhythmias.

Fibrinolytics (***ases): Tissue plasminogen activator (TPA) and derivatives (alteplase), streptokinase and its derivative (anistreplase). Activate plasminogen to produce plasmin (lysis fibrin).

Heparin (**parins): Blocks the fibrin cascade. Heparin derivatives (low molecular weight heparins such as enoxaprin, dalteparin).

DRUGS AND CARDIOTOXICITY

Many drugs are capable of exhibiting what might loosely be called “cardiotoxicity” in that they adversely influence the performance of the heart (rate, rhythm and force), directly or indirectly, acutely or chronically. Some of these actions are a direct result of the over-expression of the basic pharmacological action of a drug, whereas others arise independent of any basic pharmacology and have cardiotoxic actions that were unexpected. Examples of the former, include drugs blocking ion channels for sodium, calcium and potassium ions, i.e. ion channel blocking drugs, and examples of the latter include anthracycline anticancer drugs. Common cardiotoxic drugs include cocaine, methamphetamine, cyclic antidepressants, sodium, calcium and potassium channel blockers, beta-blockers, and digoxin.

Recognition of the possible ancillary arrhythmogenic actions of drugs is of concern to safety pharmacology. Thus, a drug that has actions on cardiac ion channels are viewed with suspicion because of excess of deaths due to cardiac arrhythmias associated with such drugs. Drugs which have blocking actions on sodium, potassium or calcium channels are always viewed with suspicion. The classic examples are drugs with cardiac sodium channel blocking actions, such as certain Class I antiarrhythmic drugs which caused an increase in death, rather than a decrease, in those considered at risk of arrhythmias (the CAST trial) and treated with such drugs. Another classic case was with drugs which blocked iKr (a repolarizing K channel) and caused the potentially fatal arrhythmia of Torsade de Pointes. A variety of different drugs from various pharmacological classes were found to be pharmacologically tainted in this way, not just antiarrhythmic drugs. Thus testing for such cardiac ion channel blocking actions is now compulsory.

Cardotoxicity resulting from an excess of basic pharmacological actions.
The most obvious examples of this type of drug are:

Ion channel blockers
Sodium channel blockers. Calcium channel blockers, potassium channel blockers

The most obvious examples of this type of drug are:

Sodium channel blockers e.g. Class I antiarrhythmics, and other drugs with sodium channel blocking actions, such as local anaesthetics, plus many other examples of individual drugs from other drug classes. Many different drugs at very high concentrations will block sodium channels.

Block of gNa in cardiac cells disturbs normal electrophysiology, and has a negative inotropic (cardio-depressant) action.

Expected actions:
1) **Electrophysiological effects** seen as a widening of the QRS of ECG, prolonged PR and bradycardia.

Arrhythmias: bradycardia, A-V block, ventricular tachycardia, and even ventricular fibrillation (such actions can be worsened by other concomitant pharmacological actions such drugs may have).

2) Also, depresses contractility – presumably related to sodium channel blockade.

3) Other pharmacological actions, e.g. atropinic actions seen with some sodium channel blocking antiarrhythmics (VW Class I).

Can produce death, via arrhythmias and/or cardiovascular depression due to reduced cardiac output.

**Sodium channel blockers**, e.g. Class I antiarrhythmics, other sodium channel blockers such as local anaesthetics and examples from other drug classes

**Calcium channel blockers.**

1) Main ECG effect is seen on AV node as PR prolongation, atrioventricular block and bradycardia.

2) Main cardiac effect is to depress contractility, via blockade of $I_{si}$

None of the calcium channels blockers are truly cardiac selective and do not relax blood vessels but some (verapamil and diltiazem) are less selective for vascular tissue than the dihydropyridines. However, at lower plasma concentrations all calcium channel blockers will vasodilate blood vessels and thus cause hypotension.

Most noticeable ECG effect of those directly acting on the AV node is PR prolongation (blockade of $I_{si}$ in AV node)

Also they have potential bradycardic effects and can disrupt sinus node function. $I_{si}$ is responsible for the action potential in SA node, but actual pacing is dependent upon the pacing current $I_f$ which is not blocked by calcium channel blockers.

Toxicity presents as AV block (of varying degrees), and as cardiac failure. In the presence of a reduced cardiac reserve (incipient heart failure) such toxicity is much more likely to occur.

**Potassium channel blockers.**

There many different types of potassium channels found in the various types of cardiac tissue. The most important with respect to dangerous cardiac actions, is probably the $I_{kr}$ (hERG) channel. Blockade of this channel delays repolarisation, thereby increasing the QT interval of the ECG. Prolongation of the QT and QTc (QT corrected for rate) is associated with Torsade de Pointes as a consequence of after-potentials, or the induction of re-entry circuits. There are many mutations of ion channels (potassium in particular) that moderately, or markedly, prolong QTc and this effect can combine with drug effects to cause even more prolongation of QTc, or reveal a latent tendency for QTc widening.

**K⁺ ions**

An appropriate ratio of intracellular to extracellular K ions is essential for stable cardiac rhythm. Changes in the extracellular concentration of K⁺ can be arrhythmogenic, or paradoxically, antiarrhythmic. Various classes of drugs (particularly diuretics and cardiac glycosides) can decrease extracellular K⁺ concentrations.

Both low and high concentrations of K⁺ can initiate and sustain cardiac arrhythmias. The most dramatic is where a high extracellular K⁺ concentration precipitates ventricular fibrillation by varying degrees of partial depolarization and the resulting heterogeneity of depolarization and repolarization that gives rise to the induction of multiple fractionating re-entry circuits – to VT and/or VF. Low extracellular K is also arrhythmogenic by also apparently paradoxically increasing excitability. Within limits (>4 and <7mM) a relatively higher K⁺ might protect against some arrhythmias. This has been demonstrated experimentally. Thus, there is a range of possible K⁺ concentrations that are safe while outside that range falls or rises in extracellular potassium are dangerous.
Other cardio-toxicities

While inappropriate cardiac ion channel blockade can produce arrhythmias, as described above, various other classes of drugs, toxins and venoms can also produce arrhythmias.

The classic example of such cardiotoxicity is excessive sympathetic activity which can result in both atrial, and potentially lethal, ventricular arrhythmias. This is most obvious with endogenous norepinephrine and epinephrine, whether induced by sympathetic autonomic activation, or by indirectly acting sympathomimetic drugs, including cocaine and amphetamine, and its derivatives, as well as other drugs that release or potentiate the actions of norepinephrine (tricyclic antidepressants).

Negative inotropes

One can distinguish between negative inotropes that produce negative inotropy acutely, and those that do so chronically. The latter often produced their adverse chronic effects as a result of the death of cardiac myocytes.

Acutely acting

There are a number of negative inotropes that can reduce cardiac contractility, including the ion channel blockers listed above. Since acute blockade of cardiac sympathetic activity in a cardiac-compromised animal can result in a pathological reduction in cardiac output, drugs that compromise such increases can have this adverse effect. Beta blockers are the most obvious examples.

Chronically acting

A variety of drugs and toxins can chronically damage the heart. This can be of a specific nature or generalized to all types of cardiac myocytes.

Arrhythmogens

Ion channel blockers of the important ion channels in the heart are all potential arrhythmogens. Sodium channel blockers at sufficiently high concentrations will disturb conductions and give rise to arrhythmias, L type calcium channel blockers will reduce transmission through the AV node and at high enough concentrations block the sinus node.

Sympathomimetics

Excessive cardiac sympathetic activity, by a variety of mechanisms, can results in calcium overload and subsequent apoptosis. Patchy necrosis can follow excessive beta agonism and this may be arrhythmogenic. Both directly and indirectly acting sympathomimetics can also have such an action.

Cardiotoxic drugs that directly damage cardiac myocytes

A variety of anticancer drugs can adversely affect cardiac function by killing individual cardiac cells. It is this aspect of their pharmacology this limits their usefulness as anticancer drugs. The classic example is doxorubicin, and its congeners. It has to be remembered that one starts out with a given number of cardiac cells, and that these cannot be replaced.

Late onset cardiotoxic effects of doxorubicin are increasingly a problem for patients who survive childhood cancer and have been treated with the drug. Such cardiotoxicity is often progressive, and in some patients produces disabling symptoms. The cardiotoxicity is often progressive, leading ultimately to congestive heart failure in some subjects.

Cardiotoxicity of several cytotoxic drugs, especially the anthracyclines, leads to long term morbidity. The mechanism for anthracycline induced cardiotoxicity may involve the formation of free radicals and oxidative stress resulting in cardiac cell apoptosis and/or immunologic reactions. Cardiac toxic effects are very dose dependent. Antioxidants, and use of iron chelators such as dexrazoxane given with anthracycline therapy, lowers the incidence of such cardiotoxicity. Other cytotoxic drugs (5-fluorouracil, cyclophosphamide and the taxoids) can be cardiotoxic by unknown mechanisms. Novel
cytotoxic drugs (e.g. trastuzumab and cyclopentenyl cytosine) also appear to be cardiotoxic as does the tyrosine kinase inhibitor sunitinib.

**Cardiotoxic venoms**

Certain toxic proteins in snake, jellyfish and other venoms are to an extent selectively cardiotoxic in their actions. The mechanism of action of some is a result of their insertion into the plasma membrane to form an ion pore resulting in the rundown of ion concentrations plus calcium overload which can result in the death of cardiac myocytes.

**Non-specific cardiac related toxicities**

Meta analyses of large scale clinical trials suggests an increased mortality with particular drugs. The increased deaths are often described as being cardiac-related, but regardless of cause, drugs have been removed from the market as a consequence. Such drugs include some COX2 inhibitors, appetite suppressants, anti-diabetic drugs. In some cases the drug was linked being linked to pathology of cardiac valves.

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