C 3. Determinants and control of cardiac output

a. Explain Starling’s law of the heart and its relation to excitation-contraction coupling.

The Frank-Starling mechanism is the rise in developed force of contraction with increasing stretch of the myocardium with the result that within physiological limits, stroke volume rises with end diastolic volume: the heart pumps out as much blood as comes in. This mechanism is produced by the increased force of contraction developed by cardiac muscle with increasing distension of the heart producing both an increased passive tension and active contraction as the interdigitation of actin and myosin fibres is optimized up to a point by increased stretch. Stretch on the right atrial wall also produces a small direct chronotropic effect.

The pressure-volume relation was originally described in vitro as a length-energy relationship for isolated myofibrils. The energy term is interpreted as force, tension, work, pressure or cardiac output with decreasing reliability. The length term is measured as LVEDV, LVEDP, LAP, PCWP, RAP or CVP with decreasing reliability.

b. Define preload, afterload and myocardial contractility.

**preload**
- the wall-stress of the ventricle in diastole
- a description of the filling pressure of the heart
  - increased by systemic filling pressure
  - intravascular volume, vascular compliance
  - posture, activity, atrial contraction
  - decreased by gravity, PEEP, IPPV, tamponade, mitral stenosis
  - resistance to venous return (SVR)

**afterload**
- the wall stress of the ventricle in systole
- a description of the resistance against which the heart ejects blood
  - increased by diastolic pressure, SVR (major determinant normally)
  - aortic valve impedance
  - circulatory impedance: elastic vessels, blood flow characteristics
  - ventricular inertia
  - decreased by wall thickness (T = Pr/2h)

**contractility**
- the force of contraction of the ventricle independent of preload and afterload
- measured as dP/dt or systolic pressure curve over a range of preloads
- increased by intracellular Ca²⁺ (digoxin, Treppe & Bainbridge effects)
intracellular cAMP (β₁ stimulation, glucagon, phosphodiesterase inh.)
thyroid hormones, histamine (minor effect)
afterload (Anrep effect)
decreased by
ischaemia

c. Describe the factors that control preload, afterload and myocardial contractility.

The stroke volume of the ventricles depends on end diastolic and end systolic volumes. EDV ranges typically from 120 ml to 180 ml and ESV from 10 ml to 50 ml. Thus cardiac output can be at least doubled by increases in stroke volume. Increases in rate can increase cardiac output by a factor of about 3 to 4 depending on fitness.

Cardiac output is determined largely by systemic factors as the Frank-Starling mechanism ensures that in most circumstances cardiac output equals venous return. Preload is determined by total venous return (in turn determined by the autoregulation of components of the systemic circulation and dependent on metabolic activity). It is also dependent upon effective function of the atria and upon the duration of diastole to allow adequate ventricular filling.

Afterload is a function of total peripheral resistance, provided there is no local problem such as aortic valve disease. Peripheral resistance is determined by arteriolar tone, much of which is autoregulated in the splanchnic circulation under resting conditions. In exercise, a substantial fall in resistance of the circulation to skeletal muscle and in hyperthermia dilatation of skin circulation can result in a big fall in TPR and consequent rise in cardiac output in order to maintain blood pressure.

Myocardial contractility is increased by preload, heart rate (force-frequency relation), circulating catecholamines acting at cardiac β₁-receptors and inotropic agents such as digoxin and phosphodiesterase inhibitors. It is reduced by parasympathetic tone, hypoxia, hypercapnia, acidosis, myocardial depressants and loss of myocardium.

d. Describe myocardial oxygen demand and supply.

Myocardial contraction is around 20% efficient in producing physical work in pumping blood, the remainder of energy used being liberated as heat. Metabolism in cardiac muscle is almost exclusively aerobic, oxygen demand being directly related to work. The oxygen requirement is proportional to the tension-time product. Wall tension is equal to Pr/2h (proportional to pressure and radius and inversely to wall thickness). Thus afterload is a major determinant of oxygen requirement as it increases the pressure derived in systole and heart rate and stroke volume are not major elements in oxygen demand.

Oxygen supply to cardiac muscle is via the coronary arteries. There is significant anatomical variation in their distribution. The usual pattern is of a right coronary supplying the right ventricle and extending around to the posterior aspect of the left ventricle and a left coronary dividing into LAD supplying the anterior of the left ventricle and a circumflex artery extending to the apex and posterior of the heart, anastomosing with the RCA territory. There is significant anastomosis of the arterial supply, allowing for retrograde perfusion in some cases of coronary stenosis or occlusion.

Resting flow is about 225 ml/min with a 70% efficiency at extracting O₂, increasing up to about 800 ml/min in exercise. Perfusion is best in diastole, especially in the subendocardial region of the LV, where there is very little perfusion during systole.
e. Describe Guyton’s cardiac output curves and explain the factors that affect them.

These are the curves for cardiac output and venous return as related to right atrial pressure. Two curves for a particular situation intersect at the cardiac output, assuming that the Frank-Starling mechanism is operating. This enables easy analysis of the effects of physiological changes which affect either curve.

The cardiac output curve shows a progressive rise in output as filling pressure rises up to a maximum level. Changes in intrathoracic pressure shift the whole curve left or right as the right atrial pressure is shifted relative to systemic venous pressure. Changes in contractility shift the maximum level of the output curve. Cardiac tamponade flattens the curve as the non-compressible fluid in the pericardial cavity makes diastolic filling unresponsive to rises in filling pressure.

The venous return curve runs from zero where right atrial pressure is equal to systemic filling pressure back to a maximum level. Further reduction in right atrial pressure well below atmospheric pressure causes collapse of extrathoracic veins rather than any further increase in venous return. Reduced resistance to venous return, from shunting or dilatation of arteriolar or venous circulation, increases the slope of the curve. A rise in systemic filling pressure, from infusion of fluid or effective autotransfusion from vasoconstriction in response to sympathetic activity, shifts the curve up and to the right. Vasoconstriction will also increase resistance and reduce the slope of the curve.

As the cardiac output curve has quite a steep section, manipulating venous return to shift the intersection of the curves to the right can produce a very marked increase in cardiac output in the short term. Examples include transfusion, sympathomimetics and A-V shunting.

g. Describe the pressure-volume relationship of the ventricle and its clinical applications.

Acute cardiac damage from infarction or other injury results in a marked reduction in the effectiveness of contraction, with a resultant rise in right atrial pressure and fall in CO (1→2). Reflex sympathetic discharge followed by recovery (if any) and fluid retention produces a rise in contractility and in systemic filling pressure, leading to a recovery of CO at a higher right atrial (and systemic filling) pressure (2→3).

Thus a certain amount of fluid retention is adaptive in cardiac failure and is a normal response to
a fall in cardiac output. However excess fluid retention becomes maladaptive as the volume-pressure curve of the ventricle shows a fall in effectiveness of contraction at very high filling pressures, presumably as a result of distraction of actin and myosin filaments beyond their optimal interdigitation. Increased ventricular radius and wall tension also directly increases myocardial oxygen demand, further compromising the heart. Rising filling pressures lead to systemic and pulmonary oedema.

This example illustrated both the clinical usefulness of increasing circulating volume in circumstances of reduced effectiveness of contraction (AMI or spinal anaesthesia) and also of limiting circulating volume with diuretics in chronic cardiac failure.