PHARMACOLOGICAL SUPPORT OF THE CIRCULATION FOLLOWING CARDIO-PULMONARY BYPASS

Thesis
Submitted in partial fulfillment for
the Master Degree in
Anesthesiology

By
Ali Mohammed Ali Ahmed
M.B. B.Ch.

Supervised By:

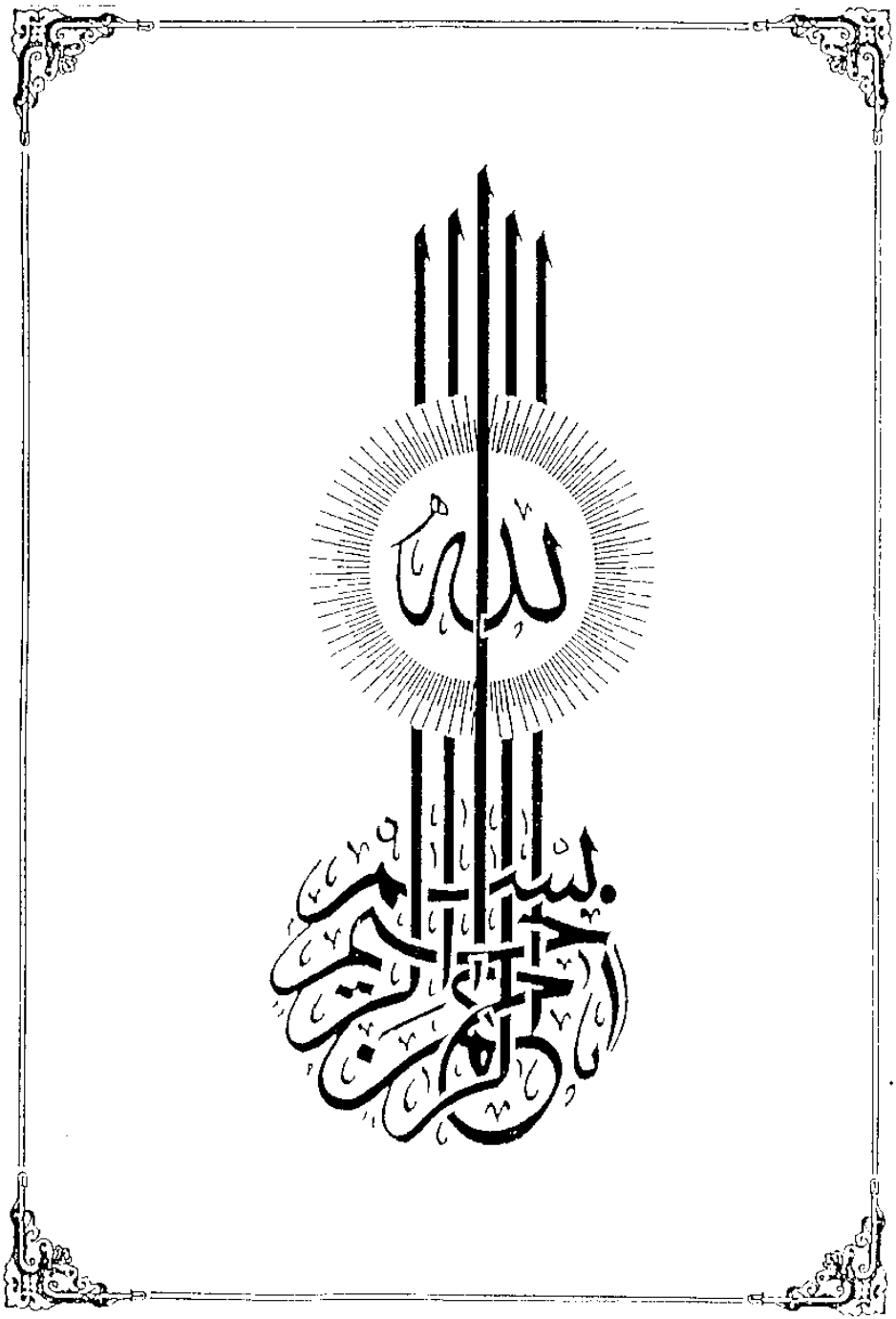
Prof. Dr. Kadry Merhom
Professor and Head of Anesthesia Dept.,
Ain Shams University

Dr. Nahed Effat
Lecturer of Anesthesia,
Ain Shams University

Faculty of Medicine
Ain Shams University

1989

Contents



Acknowledgement

I wish to express my deepest and sincere gratitude to Professor Dr. Kadry Merhom, Head of Anesthesiology Department, Ain Shams University, for his keen supervision, encouragement and support.

I would like also to express my great appreciation to Dr. Nahed Effat, Lecturer of Anesthesiology, Ain Shams University for her generous help and kind care throughout this work.

I should pay much gratitude and respect to all my professors and colleagues, who helped me in this work to see the light.

CHAPTER ONE
PHYSIOLOGICAL BASIS

Chapter 1

Physiological Basis

* Introduction

The extent of knowledge and expertise required in the management of hemodynamic disturbances depends mainly on proper understanding of the physiological basis which governs these hemodynamic factors. Accordingly, the intervention to reverse the factors which produced these hemodynamic disturbances and to correct their dangerous effects becomes easier. Cardiac output is perhaps the most important single factor that we have to consider in relation to the circulation.

Also, proper understanding of the coronary circulation and regulation of the coronary blood flow is very important for the anesthesiologist not only to avoid impairment of coronary blood flow resulting in ischemia, but also because this myocardial ischemia will result in defective contractility and decreased cardiac output rendering tissue perfusion inadequate all over the body.

Cardiac Output and its Regulation

The cardiac output (C.O.) is the amount of blood pumped to the peripheral circulation per minute. In comparison with blood pressure, C.O. is considered a more useful clinical measure to assess the overall status of the cardiovascular system, but particularly the pumping function of the heart. This is because blood pressure (B.P.) is determined by two factors: C.O. and systemic vascular resistance (S.V.R.)

$$B.P. = C.O. \times S.V.R.$$

i.e. B.P. can be in the normal range even with a low C.O., if S.V.R. is sufficiently high. (Guyton et al., 1972)

Inspite of being controlled by several factors including venous return to the heart (V.R.), peripheral vascular resistance , peripheral tissue oxygen needs, blood volume, body position, and type and pattern of respiration, the two main determinants of C.O. are the heart rate (H.R.) and stroke volume (S.V.). Also, it is to be noted that the peripheral vasculature is affected by a number of intrinsic factors, such as metabolic demand, and extrinsic factors, such as neural and humoral stimuli, all of which produce the appropriate distribution of the C.O. (Braunwald, 1974)

Systemic Factors Determining C.O. - Venous Return

Guyton has analyzed the forces responsible for venous return to the heart (V.R.) and suggested the concept of a "mean circulatory filling pressure" which is the average of the pressure in all segments of the vascular system when each of these pressures is weighed in proportion to the compliance of its respective segment. This average pressure would be a single, integrated, hydrostatic measure of the degree of filling of the circulation and would represent the force tending to propel blood towards the right atrium. He pointed out that without such a filling pressure and return force, the C.O. would be zero no matter how actively the heart would pump. The mean circulatory filling pressure for the systemic system, called the systemic filling pressure (P_{msf}), is about 7 mmHg. in the dog and is believed to be very similar to this in man. The mean pulmonary filling pressure (P_{mpf}), i.e., the comparable figure for the pulmonary circuit, is about 2 mmHg. under circumstances in which nervous and other controls are not operative, the V.R. to the right atrium may be theoretically determined as the balance between the (P_{msf}), i.e., the force tending to return blood to the right atrium and the right atrial pressure (P_{RA}), i.e.,the opposing force. In case of decreased blood volume e.g.hemorrhage or loss of sympathetic tone, which would decrease both arterial

and venous pressure, the P_{mf} will also decrease with a consequent drop in V.R. and C.O. (Guyton, 1973)

* Cardiac Factors Determining C.O.

The basic mechanics of contraction of the heart is regulated by four distinct, although inter-related factors (Braunwald et al., 1976):

1-The preload (Starling's law of the heart).
2-The contractility or inotropic state of the heart.
3-The afterload.
4-The heart rate.

1-Preload

The ventricular preload is the end diastolic volume in each ventricle which determines the resting, initial or end diastolic fibre length. In 1914, Starling (English physiologist) and associates emphasized what is called "The Frank-Starling law" which states that "within physiological limits, the force of ventricular contraction is a direct function of the initial muscle fibre length." (Hurst et al., 1982). These physiological

limits can be explained by Laplace's law, P = T / R where (P) is the pressure developed by a particular level of wall tension (T) and (R) is the radius of the chamber. This formula states that if the diastolic volume is markedly increased a greater myocardial tension is needed to develop a particular level of intraventricular pressure. (Braunwald et al., 1976)

Preload of the left ventricle is determined by the left ventricular end diastolic volume (LVEDV) which represents the initial stretch on the ventricular muscle. LVEDV can be measured in the operating room and intensive care with techniques such as echocardiography, ventriculography, radionucleotide scan and conductance. Left ventricular end diastolic pressure (LVEDP) is usuallly measured clinically as an approximation of the LVEDV so long as the left ventricular compliance is entirely normal. Left ventricular compliance or distensibility decreases due to ischemic heart disease, aortic stenosis and following discontinuation of cardio-pulmonary bypass (C.P.B.). With aortic insufficiency or relief of ischemia with vasodilator drugs, compliance increases i.e. large volumes can be placed in the left ventricle with minimal increases in pressure. Therefore, LVEDP is not always a good reflection of LVEDV. (Kaplan, 1981)

During cardiac surgery, the left ventricular preload is usually measured by inserting a catheter into the left atrium

and measuring left atrial pressure (LAP) which gives a good approximation of LVEDP as long as the mitral valve is completely normal. (Humphery, et al., 1976)

The pulmonary capillary wedge pressure (PCWP) or pulmonary artery occluded pressure (PAOP) is usually a good reflection of the (LAP) provided that the air way pressure is within normal (Lappas, et al., 1973). Measurement of the pulmonary artery diastolic pressure (PAdP) may be used to estimate the (LAP) and is usually quite accurate. However, if the pulmonary vascular resistance is markedly elevated, a large disparity between the (PAdP) and the (LAP) will exist.

The central venous pressure (CVP) is the poorest approximation of the LVEDP, but is often used to estimate the LVEDP in patients with good and parallel function of both the right and left ventricles. The (CVP) can be higher or lower than the LVEDP depending on the underlying pathology (Sarnoff and Berglund, 1954).

Preload of the right ventricle is determined by the (CVP) which accurately reflects the right ventricular end diastolic volume in most cases, unless a change in right ventricular compliance occurs e.g. in right ventricular infarction.

Factors affecting the preload of the heart include the total blood volume, body position, intrathoracic pressure, intrapericardial pressure, venous tone, pumping action of skeletal muscles and the atrial contribution to ventricular filling. (Ross, 1972)

2-Contractility and the inotropic state

Contractility is the capabilty of the cardiac muscle to shorten in response to a stimulus. It is the most difficult factor to quantitate individually due to its dependence on preload and afterload, but it can be examined quantitatively using ventriculography techniques. Further quantitative data can be attained by calculation of ejection fractions (EF) (Cohn, et al., 1974)

$$EF = EDV - ESV/EDV$$

where EDV is end-diastolic volume and ESV is end systolic volume. The normal level of 0.70 declines to 0.40 with moderate hypocontractility and below 0.20 with severe dysfunction.

The relationship between myocardial activation and contraction depends on the presence of calcium. Excitation of the cell

membrane and depolarization lead to a rapid influx of extracellular calcium, and the spread of electrical activity via the sarcoplasmic tubules causes the release of intracellular calcium and activation of contraction. Myocardial contraction is initiated when ionic calcium released from the sarcoplasmic reticulum reaches the reactive sites on myofilaments producing a conformational change in the troponin-tropomyosin complex so that it no longer inhibits the actin-myosin interaction. (Langer, 1971)

* Factors influencing contractility:

When sympathetic stimulation causes the heart to beat with increased contractility and at a faster rate, not only is the contraction more forceful and faster, but the relaxation and elastic recoil of the ventricular musculature are also more rapid which lowers the ventricular diastolic pressure and increases the pressure gradient between the atrium and ventricle and consequently ventricular filling. (Sonnenblick, 1980). Of course, parasympathetic stimulation produces reciprocal effects.

Myocardial contractility is increased by increased activation of the myocardium which is mediated in one form or another by an enhanced availability of calcium ions inside the cell (Fabiato and Fabiato, 1979). Catecholamines including

norepinephrine, epinephrine and isoproterenol, act through beta receptors on the myocardial cell that activate the adenyl cyclase system, which ultimately affects membrane systems within the cells that deliver calcium to the contractile proteins. Phosphorylation of these membranes also enhances relaxation. (Katz, 1977)

Digitalis glycosides also enhance contractility, but act by inhibiting the Na^{+}-K^{+} ATPase stimulant pump mechanism in the cell surface membrane, which appear to leave larger amounts of Ca^{++} within the fibre. (Langer, 1977)

Contractility is also increased to some degree by corticosteroids, aldactone, angiotensin, serotonin and glucagon (Glick, 1972). The physiological role of other substances such as prostaglandins and polypeptide systems such as kinekard and cardioglobulin in the regulation of myocardial contractility is unclear (Hurst et al., 1982). The effects of thyroxine on myocardial contractility are to increase contraction and relaxation rate. (Skelton et al., 1976)

Myocardial contractility is diminished by hypoxia and many drugs e.g. barbiturates, quinidine, propranolol, procainamide, lidocaine and calcium channel blockers. Acidosis also depresses myocardial contractility, particularly if the sympathoadrenal

system is impaired.(Rocamora and Downing, 1969). Morphine produces a negative inotropic effect on isolated myocardial strips, but in the conscious dog it produces a beta-adrenergic mediated increase in myocardial contractility and alpha-adrenergic mediated coronary vasoconstriction. (Vatner et al., 1975)

Most of inhalational and I.V. anesthetics depress myocardial contractility significantly (Vatner and Braunwald, 1975). In addition, the reflex control mechanisms influencing heart rate may be altered by anesthesia. The reflex bradycardia of acute hypertension is caused mainly by withdrawal of sympathetic stimulation under anesthesia, while in the conscious state it is caused by increased parasympathetic restraint (Higgins et al., 1973). In anesthesized animals, the increase in heart rate produced by acute volume loading and presumed stimulation of low pressure receptors in the atria (The Bainbridge reflex) is erratic; on the other hand the reflex is consistently found in conscious animals and can be blocked by the combination of atropine and propranolol. (Horwitz and Bishop, 1972). In contrast, the "Anrep effect" or the positive inotropic effect of an acute increase in afterload has been demonstrated in the anesthetized animal, but is difficult to demonstrate in the conscious subject with low spontaneous heart rate. (Vatner and Braunwald, 1975)