USE OF CARDIOPULMONARY BYPASS IN STUDIES OF THE CIRCULATION

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Cardiopulmonary bypass (CPB) provides an important clinical setting to study a complex set of physiological responses to a relatively abnormal state in man. Although CPB from many perspectives represents a controlled form of shock, it nonetheless represents a unique opportunity to study specific human physiological responses to conditions that include constant systemic blood flow, acute haemodilution, hypothermia, exclusion of the lungs from the circulation, regional blood flow abnormalities and protein changes [7]. Considerations that make CPB a useful experimental model to study the effects of anaesthetics on myocardial function will be discussed separately.

CONSTANT FLOW

During CPB, patients receive a continuous flow via a roller pump to provide a specific cardiac output. Arterial pressure changes produced by drugs during constant flow CPB reflect changes in systemic vascular resistance [3,4]. CPB presents a unique opportunity to study the effects of drugs on the peripheral vasculature as well as their ability independently to affect venous capacitance and arterial resistance vessels. Studies of drug effects on vascular resistance in normal (intact) man can be complex and difficult to interpret, since many drugs exhibit diverse effects on both myocardial function and the systemic vasculature. Morphine, for example, may directly dilate the venous capacitance bed producing decreased preload, release histamine from cutaneous mast cells producing arterial and venodilation, slow heart rate, and decrease sympathetic tone [10,15]. The net effects of the administration of morphine on systemic vascular resistance and myocardial function can be unpredictable, depending upon the blood volume, sympathetic tone and ventricular function (fig. 1). For example, studies evaluating the effects of histamine release by opioids as a significant mechanism for hypotension are open to question [6]. In addition, the effects of antihistamine (diphenhydramine or cimetidine) pretreatment, in producing $H_1$- and $H_2$-receptor blockade to attenuate hypotension, have been questioned because these drugs alone may increase heart rate and arterial pressure. Patients undergoing CPB with constant blood flow provide an important experimental model in man to resolve questions concerning the effects of drugs on systemic vascular resistance. Although blood is shunted from the lungs and reduced renal and hepatic blood flow occur during CPB, stable conditions can be achieved and the effects of drugs on the peripheral vasculature determined in man. Few studies have been performed using this model. Existing data suggest both fresh frozen plasma and 5% plasma protein fraction are vasodilators (fig. 2) [3,4].

\[ \text{SVR} = \frac{\text{MAP} - \text{CVP}}{\text{CO}} \]

Fig. 1. Effects of a drug, such as morphine, on calculated systemic vascular resistance (SVR) are complex and depend on multiple factors that vary from patient to patient. MAP = mean arterial pressure; CVP = central venous pressure; CO = cardiac output.

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HAEMODILUTION

Patients undergo rapid haemodilution during the initiation of CPB. A colloid or crystalloid priming solution (or a mixture) is used in the CPB circuit to reduce red blood cell concentration. The net effect is to decrease the blood viscosity rapidly; however, other changes occur, including a 40–50 % dilution of plasma as well as a decrease in total drug concentrations [7]. The net effect may be a new set of equilibria developing between the concentrations of free and bound drug in plasma and in tissues. The concentration of protein-bound drug may decrease in proportion to the degree of haemodilution, while the concentration of the free drug, which is the pharmacologically active drug form, may remain virtually unchanged or may decrease slightly and transiently following rapid haemodilution [8]. At present very few studies have evaluated changes in free drug concentration during CPB. As the total drug concentration decreases with haemodilution, the apparent volume of distribution increases proportionately, but the free drug distribution volume may not change, or may change to a lesser degree. Although most anaesthetists administer additional doses of drugs at the initiation of CPB based on demonstrated decreases in total drug concentration this may, in fact, be unnecessary, because free drug concentrations may be unchanged or only slightly decreased. The acute effects of haemodilution and the resulting changes in drug concentrations, plasma protein binding, extravascular protein binding, pH and temperature changes, as well as changes in plasma oncotic pressure may produce major intercompartmental movements of fluids and drugs [7]. This would provide a unique clinical setting to evaluate the variables affecting pharmacokinetics more or less independently.

HYPOTHERMIA

Various degrees of hypothermia (20–32 °C) may be used during CPB. Hypothermia will decrease metabolic activity and oxygen requirements, alter regional blood flow, decrease enzymatic function and decrease drug metabolism [7]. In addition, hypothermia will produce slowing of the electroencephalogram and potentiate the effects of anaesthetics and other drugs that depress the central nervous system. Decreased metabolism and elimination of drugs may result in more intense and persistent drug effects, during and after CPB. The effects of drugs on systemic vascular resistance may be altered by changes in temperature. Very few studies have focused on the effects of hypothermic conditions on drug effects and drug disposition.

EXCLUSION OF LUNGS FROM THE CIRCULATION

Total cardiopulmonary bypass effectively excludes the lungs from the circulation, by draining venous blood from the inferior and superior venae cavae directly into the oxygenator and returning it to the aorta by the roller pump. This system abolishes the circulation of venous blood to the lungs, but the flow of arterial blood through the bronchial circulation continues to supply the lung’s metabolic needs. Increased blood flow through bronchial and other collateral circulations is often scavenged by a vent placed into the pulmonary vein or into the left ventricle to avoid ventricular distention. Although we consider the lung an organ important for gas exchange, it is a metabolically active organ capable of extensive removal and subsequent enzymatic degradation of endogenous mediators and drugs by endothelial cells. Prostaglandins of the E and F series, 5-hydroxytryptamine, and noradrenaline are rapidly and extensively extracted from blood during their first pass through normal lungs [2,12]. CPB alters the ability of the pulmonary circulation to clear vasoactive amines and may ultimately modify vasoregulation of the peripheral circulation [12]. This may explain why some patients are so vasodilated, with a low systemic vascular resistance after CPB. The lung is also capable of sequestering drugs such as opioids [1] and propranolol [13]. Washout of substances accumulated in lung may occur as perfusion through the pulmonary vasculature is restored during the initial separation from CPB; drug concentrations may increase in the circulating blood [1,13].
USE OF CPB TO STUDY CIRCULATION

REGIONAL BLOOD FLOW ABNORMALITIES

Systemic blood flow during CPB in man is usually non-pulsatile, with flow rates ranging from less than to greater than a normal cardiac index. Hypothermia, often utilized for protection of the isolated organ, together with altered perfusion may profoundly modify blood flow distribution to important organs such as the liver and kidneys. Components of the CPB circuit such as the oxygenator and arterial filter are capable of binding both plasma proteins and drugs (e.g. nitroglycerin and fentanyl) [5, 9, 11, 13, 14]. The net effect on drug concentrations in blood can be expected to be quite variable, depending on the pharmacokinetic characteristics of the drug as well as the physiological changes produced by CPB.

PROTEIN CHANGES

Institution of CPB decreases plasma protein concentrations to affect pharmacokinetics as noted above, but it may also produce significant decreases in other plasma proteins important to normal immune processes. After open heart surgery, patients demonstrate decreased lymphocytic responses to phytohaemagglutinin, concanavalin A, pokeweed mitogens and mixed lymphocyte cultures—indices of depressed immune function [16]. The significance of these changes is unclear. However, the circumstances of CPB provide a unique opportunity to study the effects of immunodeficiency states in man.

SUMMARY

In summary, CPB provides a complex set of physiological circumstances during which the patient is subjected to severe physiological alterations with surprisingly few adverse sequelae. Our ultimate goal in performing medical research is to provide scientific insights that improve patient care. Results of studies of animal models may not always be applicable to man. Although CPB possesses faults inherent to any experimental model, it nonetheless provides a unique opportunity to study safely and effectively a variety of physiological and pharmacological variables that affect cardiovascular functions in man.

REFERENCES