Influence of Blood Temperature on the Pulmonary Circulation

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Innervated, nourished and ventilated dog lungs were perfused in situ with a technic which afforded adequate control of blood flow, pressures, pH and temperature. Variations of the pulmonary (but not of the systemic) blood temperature was followed by pronounced changes of the pulmonary vascular resistance, believed to be attributable to pulmonary vasomotion.

During physiologic studies of total body perfusion we encountered unexpected fluctuations of pulmonary vascular pressures which apparently were related to changes of the blood temperature. The literature does not describe adequately controlled experiments concerned with the effect of blood temperature on pulmonary hemodynamics. We therefore devised and investigated a preparation in which the innervated, ventilated and nourished dog lungs were perfused in situ and in which we analyzed the temperature factor with minimal interference by other major variables affecting the pulmonary circulation (pulmonary and systemic blood flow, ventilatory pressure, composition of alveolar gas, pH of the circulating blood).

Methods

In our preparation blood from one of the several alternative reservoirs was pumped into the pulmonary artery through a cannula; blood collected from another cannula in the apex of the left ventricle was returned to the reservoir. The ascending aorta was clamped off and the root of the pulmonary artery was tied. All systemic venous blood was withdrawn from the right ventricle, arterialized in a heart-lung machine and pumped into a femoral artery. In this preparation the pump-gas exchange machine supplies all systemic blood circuits; the pulmonary circulation is separated from the systemic circulation except for collateral blood flow to the lungs via bronchial vessels.

Pressures were recorded in the abdominal aorta, inferior vena cava, pulmonary artery, pulmonary vein and upper airways with plastic cannulas connected to strain gages, amplifiers and a multichannel direct-writing oscillograph. Flows in both circuits were varied independently by means of calibrated pumps. The temperatures of the gas-exchange unit and of the blood reservoirs were controlled. A mercury thermometer and pH electrodes with automatic temperature compensation were exposed to the blood flowing through a plastic chamber. The pH of the main circulation was monitored and corrected when necessary by infusion of sodium bicarbonate solution. To avoid changes of pH in the pulmonary perfusion blood due to open-circuit ventilation, the lungs were rhythmically inflated under positive pressure with an automatically driven rebreathing bag. Special care was taken to maintain the rectal temperature within the normal range (36 to 38 C.) throughout the experiment. Collateral blood flow to the lungs was measured by a previously described method when steady conditions were reached.

At the beginning of each experiment, the flow-pressure relationships were studied over a wide range of pulmonary blood flows with both circulations at normal temperatures. With constant pulmonary flow, changes of pulmonary blood temperature of a magnitude of 4 to 20 C. were then produced within 20 to 40 sec. by connection of alternative reservoirs with symmetric inflows and outflows while the systemic perfusion system remained at normal temperature. Changes of the pulmonary blood temperature in either direction usually caused acute rises of the pulmonary artery pressure which returned to an intermediate...
value after some minutes. After a new steady state was reached, the flow-pressure relationships were again studied over the same range of flows as before. Hemodynamic studies were usually performed at 4 different temperature levels between 37 and 15°C; the pulmonary blood temperature was then returned to the normal value for control purposes. At the end of some experiments, the effect of hyperthermic blood (40 to 42°C.) was observed; in other experiments the pulmonary perfusion blood was replaced with saline.

In another series of experiments, the pulmonary blood temperature was kept constant at 37°C. While the blood in the systemic circulation was refrigerated. Replacement of the temperature control of the pump-oxygenator with a cooling device resulted in a fall of the blood and the rectal temperatures from 37 to about 28°C. within 10 min. When refrigeration was discontinued and normal conditions were re-established, the rectal temperature returned to normal within 20 to 30 min.

RESULTS

Effect of Sudden Changes of Pulmonary Blood Temperature on Pulmonary Vascular Pressures. During each series of observations in one animal the variables pertaining to the systemic perfusion were kept within a very narrow range of variation. However, the systemic circulation varied between individual animals (flow 60 to 80 ml./min./Kg., mean systemic arterial pressure 60 to 140 mm. Hg, central venous pressure 2 to 6 mm. Hg, systemic arterial pH 7.30 to 7.45, rectal temperature 36 to 38°C.). The pulmonary perfusion pump was set at constant flows ranging from 21 to 73 ml./min./Kg. and the pulmonary vascular pressures were registered for at least 5 min. under constant conditions of pulmonary pH and temperature. The temperature in the pulmonary circulation was then suddenly modified by perfusing the lungs with the blood from a low-temperature reservoir. The maximal change of the pulmonary artery pressure was generally observed within 30 to 45 sec.; it was followed in some instances by stabilization of the pulmonary artery pressure at an intermediate value after 3 to 5 min. perfusion while the increase of the pulmonary venous pressure was inconstant and insignificant (fig. 1). This overshooting effect was more pronounced at higher flows.

Pulmonary blood temperature was reduced to 3 levels: 30 to 31°C, 24 to 25°C, and 15 to 18°C. Elevation of the pulmonary artery pressure without significant simultaneous increase in pulmonary venous pressure was consistently observed in 29 experiments in 10 dogs. A correlation between the pulmonary artery pressure response and the pulmonary blood flow at the time of the temperature change was not evident.

When the studies at the lowest temperature level were completed (17 to 25°C), the temperature was brought back to about 35°C. The blood reservoir used for rewarming purposes was set at 37°C. and the system returned to normal blood temperature in 6 to 10 min. In all 13 experiments (10 dogs), the pulmonary artery pressure slowly decreased on rewarming while the pulmonary venous pressure fall was inconsistent. The pressure variations were asymptotic in nature and some arbitrary point had to be chosen to characterize the effect of rewarming.
All changes of blood temperature were performed at constant and undisturbed flow and with blood of the same protein content and hematocrit value. The variations of the pulmonary vascular pressures can therefore be expressed in terms of total pulmonary resistance. The results calculated during the peak pressure variation (fig. 2) indicate increased resistance due to lowering the temperature of blood. The decreased resistance values (bottom, fig. 2) refer to conditions 5 min. after the beginning of the perfusion with warm blood; this point was selected because experience had shown that about 90 per cent of the resistance variation is completed at this time.

In 3 dogs, elevation of pulmonary blood temperature (41 to 43 C.) caused a progressive increase of both pulmonary arterial and venous pressures, and pulmonary edema. In 4 dogs, the blood in the pulmonary circuit was washed out and replaced with saline or Ringer solution of the same temperature. Pulmonary artery and venous pressures both fell, thus lowering pulmonary resistance to about 50 per cent of the initial value. Progressive contamination of the pulmonary circulation by the collateral blood flow prevented constant composition of the perfusing fluid.

**Delayed Effects of Changes of Pulmonary Blood Temperature on Pulmonary Vascular Pressures.** The influence of pulmonary blood temperature on flow-pressure relationships was studied in 8 dogs. The pulmonary blood flow was varied between 0 and 120 per cent of the systemic flow (0 to 1500 ml./min.). The highest flows, however, could not always be studied at the lowest temperature because of the high pulmonary artery pressure which might have damaged the preparation. The pressure-flow curves were initiated at the highest possible perfusion rate and subsequent points were obtained with stepwise decreases of flow, each step being maintained 30 sec. Intermittent, positive-pressure ventilation was maintained at constant inflation peaks throughout the experiment.

The shape of the flow-pressure curve obtained (fig. 3) is essentially similar to that described by previous authors for perfused isolated lungs.\(^3\) The curve intercepts the pressure axis at a positive value ranging from 1 to 3 mm. Hg at 37 C. With flows under 200 ml./min. the curve is convex to the pressure axis, with increasing flows it develops a rectilinear portion characterized in the range from 400 to 900 ml./min. by a slope of 1.0 (S.D. 0.16) mm. Hg per 100 ml./min. increase of flow. At the highest flows, the curve sometimes shows a concavity toward the pressure axis, so that the whole curve is S-shaped. When the pulmonary blood temperature is decreased, the pulmonary artery pressure at equivalent flow is increased, thus the pressure-flow curve is displaced to the left. The magnitude of shift is directly related to the decrease of temperature. Below 24 C. the pressure axis intercept (2 to 4 mm. Hg), the convexity toward the pressure axis and the slope of the rectilinear
The pulmonary venous pressure increases slightly from zero mm. Hg at zero flow to 8 mm. Hg at the highest flows. No significant difference related to temperature has been observed in successful experiments when the tone of the preparation after reversal of the temperature conditions was found unchanged.

Variations of pulmonary resistance as a function of the temperature of the perfusing blood under steady conditions may be calculated from the data of the flow-pressure curves. To avoid interference due to the elastic stretch of the vascular bed by the intraluminal pressure, isobaric conditions must be selected. If one starts with the values of flow and pulmonary venous pressure for a pulmonary artery pressure of 15 mm. Hg and takes the resultant pulmonary resistance, at 37 C. = 100 per cent, one finds an average increase in resistance of 61 per cent at 30 C. and 144 per cent at 15 C.

Determination of collateral flow to the lungs showed no consistent correlation with the temperature of the blood perfusing the lungs. In 15 experiments where the temperature was lowered and factors like systemic arterial and venous pressure did not interfere with the experimental conditions, the collateral flow increased in 9, decreased in 3 and remained unchanged in 3.

Influence of Systemic Blood Temperature on the Pulmonary Vascular Pressures. In 5 dogs the systemic blood temperature was lowered while the pulmonary circulation was perfused at normal temperature. The rectal temperature fell about 10 C. in 10 min. while the pulmonary blood temperature usually fell about 1 C. The pulmonary arterial and venous pressures showed no significant changes related to temperature variation of the systemic blood (lowest rectal temperature 26 C.) when both systemic and pulmonary flows were maintained constant. After observations were made at the lowest temperature in a steady state, the systemic circulation was slowly rewarmed. No noteworthy changes in pulmonary arterial or venous pressures were observed during rewarming.

The systemic arterial pressure fell 10 to 30 mm. Hg almost immediately after starting the systemic perfusion with cool blood; it then rose slowly to a higher value than before hypothermia. During rewarming a diphasic change of the systemic arterial pressure opposite in direction occurred. The systemic arterial pressure at the end of the experiment was almost the same as at the beginning. The systemic venous pressure did not show noteworthy changes. No attention was given to possible changes in collateral blood flow to the lungs.
DISCUSSION

Any attempt to identify mechanisms of pulmonary vascular pressure changes must distinguish between (a) active vasomotion and (b) passive hemodynamic changes (redistribution of blood between systemic and pulmonary circulation, back pressure from the left atrium, altered bronchomotor tone, change of physicochemical properties of the blood). Our preparation excludes blood shifts from the systemic circulation and changes in ventilatory or gas exchange patterns. However, the changes of blood viscosity with temperature are expected to cause variations of the pulmonary vascular pressures; this passive effect must be differentiated from active pulmonary vasomotion.

Among previous authors Fühner and Starling did not find any change of the pulmonary arterial or venous pressures in a heart-lung preparation after lowering the temperature by 11.5°C, but this observation was made in only 1 dog which had received pulmonary vasoconstrictor agents. Similarly Sarnoff and Berglund found no change in the distensibility of the pulmonary vascular bed when the temperature of the perfusing blood was decreased. Their lung preparation, however, was not considered to be living. None of the numerous published investigations of hemodynamics during hypothermia or fever permit deductions concerning the tonus of pulmonary blood vessels, because far too few variables were controlled and any given result can be interpreted in many different ways. For instance, Nahas et al. reported a fall of pulmonary arterial pressure in hypothermia, but the pulmonary blood flow and the left atrial pressure were not measured in their experiments, which therefore do not permit conclusions about the effect of temperature on pulmonary resistance.

In our experiments the systemic or pulmonary blood temperatures were varied independently of each other while other factors which might influence pulmonary vascular pressures (systemic and pulmonary blood flow, pulmonary blood protein content, hematocrit, ventilatory pressure, alveolar gas composition) were kept constant. Cooling the blood at constant carbon dioxide content necessarily increases its pH. With relation to the pulmonary circulation, this means that we have to deal not only with the direct effect of temperature change on blood viscosity and possibly pulmonary vasomotion, but that the direct effect of pH changes on blood viscosity and hindrance of the pulmonary vascular bed has to be considered.

There is no convincing evidence in the literature that the pH is an important factor of blood viscosity within the physiologic range. An increase in carbon dioxide content by bubbling gas through the blood, which would scarcely fail to produce a pH drop, has been associated with an increase of the blood viscosity.

On the other hand, changes in the viscosity of whole blood following venous stasis bear no demonstrable relation to the carbon dioxide or oxygen content. Far more important is the direct effect of blood pH on the hindrance of pulmonary blood vessels. It has been shown previously that an increase in pH is constantly associated with a decrease of pulmonary vascular resistance. This effect far outweighs the change in blood viscosity (if any) due to the pH variation. Since cooling the blood increases the pH, the effect of temperature decrease through pH displacement at constant carbon dioxide content, as realized in our experiments, will tend to dampen the increase in pulmonary vascular resistance observed and will in no case exert an additive effect to the phenomenon. The aging of the preparation did not introduce an error since the initial and final flow-resistance curves taken at the same temperature were indistinguishable in successful experiments (fig. 4). The remarkable stability of the pulmonary vasomotor tone despite severe experimental interference with pulmonary perfusion rates may be due to the separation of the functional and the nutritive circulation in the lungs.

The different effects of cooling of the systemic and of the lesser circulation show that the action of blood temperature on the pulmonary vascular pressures is local.
FIG. 5. Data of figure 3. Relationship of pulmonary arterial pressure (PAP) to flow in the pulmonary vascular bed. Note the linear relationship between log PAP and log F and the parallelism of the functions at different temperatures and viscosity of the perfusate.

The increase in blood viscosity has been said to range from 0.8 per cent\(^8\) to 2 per cent\(^13\) and even 3 per cent\(^8\) per degree centigrade of cooling. The effect of pseudoplasticity of blood in the narrow vessels on the temperature-viscosity function has not yet been investigated, but it is probably of little importance.\(^14\) In our experiments the increase of pulmonary resistance per degree of decrease in temperature averaged 5.2 per cent\(^\) in acute temperature variations. A change of this magnitude cannot be explained by an alteration of the viscosity factor alone, although viscosity contributes to the observed phenomenon. Even under steady temperature conditions, the increase in pulmonary resistance with decreased temperature cannot be explained in terms of viscosity changes. This observation is not felt to contradict previous studies of isolated denervated vascular beds\(^15\) where resistance changes were completely explained by considerations of viscosity: our lung preparation was not deprived of its nervous connections. Furthermore, considerations of blood viscosity could not explain the changes of the pulmonary artery pressure after sudden temperature reductions where a pressure peak is followed by stabilization of the pulmonary artery pressure at an intermediate value, a response which almost mimics intrapulmonary injection of a vasoconstrictor drug. Since we did not attempt to measure the blood temperature at the precapillary level, it is impossible to exclude that the pulmonary artery pressure peak was due to an "overshooting" of the temperature change. On the other hand, such a biphasic response to a unidirectional temperature change has been observed on isolated arteries.\(^16\) We believe that the decrease of the temperature of the blood perfusing the lungs causes pulmonary vasoconstriction.

Pulmonary artery pressure responses to increase of the blood temperature from hypothermic values to normal can be explained by changes in viscosity alone. The slow, regular fall of the pulmonary artery pressure with increasing temperature and also the effect on resistance of 2.1 per cent per degree rise, are arguments for a physical mechanism rather than for a biologic one, although a combination of both is possible. The slower rate of temperature variation while rewarming could have lessened the vasomotor response, since it has been shown\(^16\) that vasomotion is not manifest when the rate of temperature change is above or below a critical value.

Hydrodynamic considerations on perfusions in vivo and limitations of Poiseuille's law when applied to blood flowing through small vessels have been discussed extensively in the last years.\(^18\)-\(^21\) The effect of temperature on the pressure-flow relationship which is described here is similar to changes seen in other vascular beds after increasing the hematocrit,\(^22\) after adding increasing amounts of a vasoconstrictor drug,\(^23\) or after exciting the sympathetic fibers with stimuli of increasing intensity.\(^20\) The positive-pressure intercept with its arteriovenous pressure gradient at zero-flow corresponds to a very low "critical closing pressure."\(^11\) The convexity of the curve in the low flow range is not explained by considerations of apparent viscosity and pseudoplastic flow because it was observed to the same extent while perfusing with saline or hemolyzed blood. The slope
of the linear part of the function is in good agreement with estimates derived from similar preparations by other authors. This slope increases when temperature decreases, but remains far less steep than in systemic vascular beds. In some experiments where the flow was increased above 1500 ml./min., the pulmonary artery pressure rose rapidly, thereby giving to the upper part of the curve a curvature opposite in direction to the one observed in the low flow range. In our preparation the tip of the registration cannula in a lobar branch of the left pulmonary artery pointed "upstream." It is therefore not excluded that at very high flows some of the kinetic energy of the blood could be converted back into potential energy, added to the "ideal" lateral pressure reading and explaining the "S" shape. A relative "stenosis" of our left ventricular outflow would also cause a rise of the pulmonary venous pressure and secondarily of the pulmonary artery pressure.

Our pressure-flow data are well described by the empirical formula proposed by Green et al.\textsuperscript{24} \(P = k \cdot PAP^n\) where \(k\) and \(n\) are constants for a particular hindrance and blood (fig. 5). Considering that temperature influences both vasomotor tone (hindrance) and viscosity, it appears not possible at the present time to decide whether this parallelism is significant or only the result of opposing factors. Our data on the pulmonary circulation are still too scarce to describe the pressure-flow relationship in terms of physical principles. The rapidly expanding knowledge of non-Newtonian flow will contribute to future understanding of this problem.

**Summary**

Pulmonary arterial and venous pressures were recorded in dog preparations in which the systemic and pulmonary circulations were perfused separately and which afforded complete control of variables which are known to influence pulmonary hemodynamics. With constant pulmonary blood flow, variations of the pulmonary (but not of the systemic) blood temperature were followed by pronounced changes of the pulmonary arterial pressure, believed to be attributable to pulmonary vasmotion.

**SUMMARY IN INTERLINGUA**

Le pressiones pulmono-arterial e venose esseva registrate in preparatos cauin in que le circulationes systemic e pulmonar esseva perfundite separatamente e in que omne le variabiles que exerce cognoscimente un influentia super le hemodynamica poteva esser regulata con complete libertate. In le presentia de un constante fluxo de sanguine pulmonar, variationes in le temperatura del sanguine pulmonar—sed non in le temperatura del sanguine systemic—esseva sequite per pronunciaste alteraciones del pression pulmono-arterial. Es postulate que iste phenomeno es attribuibile a vasmotion pulmonar.

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