

# Pulmonary Petechiae: Ventilatory-Circulatory Interactions

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## Summary

Pulmonary petechial hemorrhages are typically observed in sudden infant death syndrome (SIDS), but their cause has not been determined. Some data suggest that SIDS infants die with an obstructed airway. Inspiratory efforts against the closed airway can decrease the efficiency of the cardiac pump by increasing the afterload on the left ventricle and/or by decreasing left ventricular compliance. If these effects are augmented by hypoxia-induced decreases in cardiac contractility as occlusion is maintained, the resultant failure of the left ventricle could produce a large increase in end-diastolic pressure. Increases in left ventricular end-diastolic pressure will then increase pressures in the pulmonary circuit, where rupture of small blood vessels gives rise to petechial hemorrhages.

To evaluate this postulated mechanism of petechiae formation, lightly anesthetized adult rabbits were sacrificed using three 1-min end-expiratory airway occlusions plus a fourth occlusion maintained until death; systemic arterial, intratracheal, and pulmonary wedge pressures (the latter approximating left atrial pressure) were measured during inspiratory efforts and expiratory intervals. Those animals showing minimal evidence of left heart failure, as evidenced by a relatively small difference between wedge and intratracheal pressures during obstructed breathing, showed few pulmonary petechiae. When the above pressure difference was large (greater than 25 mmHg during inspiratory efforts and greater than 10 mmHg during expiratory intervals) numerous pulmonary petechiae (usually  $n > 40$ ) could be observed. Progressive increases in pulmonary wedge pressure and bradycardia during occlusion suggested that direct and/or reflex hypoxic depression of the myocardium contributed to the observed effects. The occlusions produced little change in systemic arterial pressure. These results are consistent with the possibility that mechanical interactions between the heart and lung pumps, along with hypoxia-induced decreases in cardiac contractility accompanying airway obstruction, account for intrathoracic petechiae in SIDS.

## Abbreviations

SIDS, sudden infant death syndrome

The most prominent pathologic finding associated with SIDS is petechiae on the surface of the lungs and other intrathoracic structures (1). The cause of the pulmonary petechiae has not been determined, but postulates have included inspiratory efforts against a closed airway, a reaction to asphyxia (not requiring an obstructed airway), circulatory insults, and the presence of pulmonary infection (2, 5, 7, 8, 9). The proposition that inspiring against a closed airway can result in pulmonary petechiae is of particular interest because it indicates a specific terminal event in the SIDS infant (1, 2, 9). Evidence to support this concept includes morphologic data in humans (1, 2) as well as observations after airway occlusion in animal models (5, 9). From the above studies the suggestion has been made that negative swings in intrapleural

pressure during airway obstruction may be involved in the induction of pulmonary petechiae. It might also be inferred that such effects arise from the systemic circulation because petechiae are observed on the epicardium and thymus as well as the lungs of SIDS infants; however, the bronchial (systemic) circulation does not extend to the lung surface in man (13), suggesting that pulmonary petechiae could be derived instead from the pulmonary circulation. It has also been noted that repetitive airway obstructions in adult men were associated with rises in pulmonary wedge (left atrial) pressure (4). If rises in left atrial pressures were sufficiently large, damage to pulmonary blood vessels could occur with resulting petechial formation. The applicable mechanisms can be inferred from a recent summary by Bromberger-Barnea (3): (1) when the airway is obstructed, inspiratory efforts will cause increasingly negative intrapleural pressures, effectively afterloading the left ventricle; (2) decreases in intrapleural pressure also increase venous return and distend the right heart, resulting in a decreased compliance of the left ventricle; and (3) state of cardiac contractility will determine the effectiveness of the left ventricular pump under the above conditions. If the heart cannot pump effectively, then cardiac failure, as evidence by end-diastolic distension of the left heart, will occur. When failure of the left heart is of sufficient magnitude, transmission of back pressure from the left ventricle to the lungs, via the left atrium and pulmonary veins could cause the rupture of small blood vessel walls and the formation of petechiae.

The present investigation was aimed at evaluating the above mechanism using measured left atrial pressure (approximated by a wedged pulmonary arterial catheter) in spontaneously breathing, lightly anesthetized rabbits during repeated end-expiratory airway occlusion.

## MATERIALS AND METHODS

White New Zealand rabbits were anesthetized using a combination of chloralose (40 mg/kg) and diallylbarbituric acid (30-50 mg/kg) administered intravenously. This regimen provided surgically stable anesthesia. The trachea was cannulated and a polyvinyl chloride catheter (0.054 inch OD; 0.034 inch ID) (Norton Plastics; Akron, OH) was inserted into the femoral artery. We found that the above polyvinyl chloride catheter material could be threaded via the right jugular vein through the right heart and into the pulmonary circulation where it was wedged to measure left atrial pressure. Advancement of the catheter was continuously monitored by the changes in intravascular pressure. No special modification of the catheter (*i.e.*, a "floating" tip) was required for this procedure. Both catheters were filled with heparinized saline, and were cleared as necessary during an experiment using small boluses of heparinized saline. Systemic arterial and wedge pressures were measured using Ailtech physiologic transducers (Ailtech; City of Industry, CA). Intratracheal pressure was monitored using a fluid-filled Statham P-23D transducer (Statham Instruments; Hato Rey, Puerto Rico). Transducers were calibrated against mercury manometers and zeroed at heart level. Signals

were processed and recorded on chart paper using a Beckman R-411 Dynograph recorder (Beckman Instruments, Fullerton, CA).

When all catheters were in place, the tracheal cannula was occluded at end-expiration three times for 1-min intervals. Repetitive occlusions of the airway have previously been noted to induce pulmonary petechiae in rabbits (5). The occlusions were separated by 1-min recovery periods. A final end-expiratory occlusion was performed after the third recovery period in order to sacrifice the animal; this occlusion was typically maintained for 2-3 min. Only two 1-min occlusions were performed before sacrifice when it was judged on the basis of prolonged apnea that the animal would not recover from the third occlusion. Intravascular and intratracheal pressures accompanying an occlusion maneuver are illustrated in Figure 1.

Transmural pressure across the left atrium is obtained by subtracting pressure outside the atrium from pulmonary wedge pressure. The former pressure is often assessed using intrapleural pressure or pressure measured from a catheter placed next to the heart (6). During the occlusion maneuvers in the present study, lung volumes were nearly constant (changing only as the result of gas exchange during occlusion) so that a constant pressure difference between intratracheal pressure and any other approximation of pressure outside the heart would be maintained. The use of intratracheal pressure was based on our experience that the position of an intraesophageal catheter (to approximate intrapleural pressure) was sometimes compromised during vigorous respiratory efforts accompanying airway occlusion.

Maximum rises in wedge minus intratracheal pressures always

occurred during the last breaths of an occlusion maneuver (Fig. 1). These effects were assessed by averaging the results over the last 3-4 breaths (13 animals) unless clear breath-by-breath increases in transmural pressure were observed; in that case, only the final breath would be used (two animals). Effects during inspiratory efforts were measured as the difference between the peak decreases in wedge and intratracheal pressure. Loading of the left atrium during each subsequent expiration was measured as the difference between wedge and intratracheal pressure (averaged over approximately 0.5 sec) when intratracheal pressure returned from its inspiratory excursion. For each animal, the three occlusions showing the greatest effects on transmural pressure were averaged to obtain inspiratory and expiratory values. Simultaneously measured heart rates (from the systemic arterial pressure tracing) were also determined and compared with control values before the occlusion maneuver.

Immediately after the final occlusion maneuver, the chest was opened, and the position of the wedge catheter was noted by tracing its course into the pulmonary arterial vasculature. The wedge catheter was then removed, and the lungs and heart were dissected free from the chest. The number of petechiae on each lung, visible to the unaided eye, was counted until a total of 40 was reached; after this point, the number of petechiae was designated as >40. The lungs from all the animals were fixed in 10% buffered formalin. Standard sections from both lower lobes were embedded in paraffin, cut at 5 microns, stained with hematoxylin and eosin, and examined by light microscopy. These sections confirmed the interpretation of surface pulmonary petechiae by

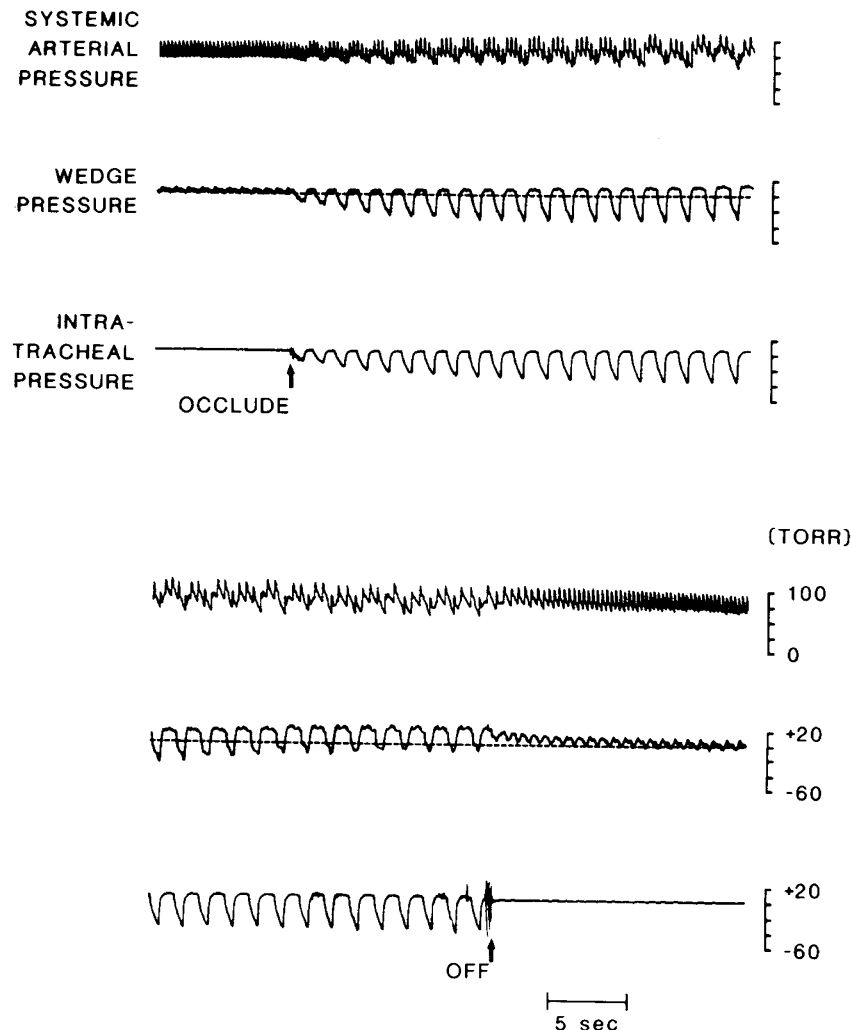


Fig. 1. Effects of end-expiratory airway occlusion on systemic arterial, pulmonary wedge, and intratracheal pressures. The dashed line on the wedge pressure tracing represents a pressure of zero torr. For further explanation, see text.

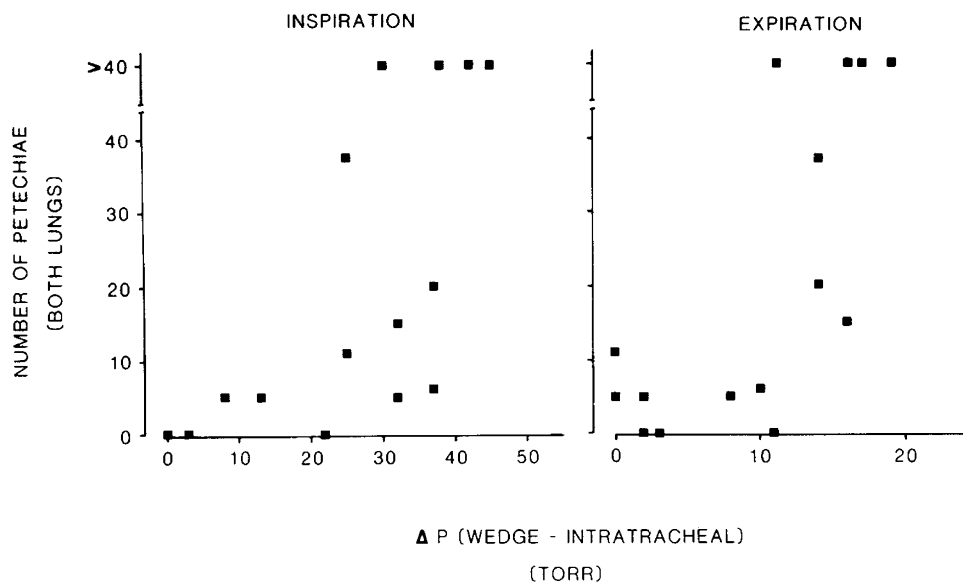


Fig. 2. Pressure differences across the left atrium (approximated using pulmonary wedge and intratracheal pressures) during end-expiratory airway occlusions and the formation of pulmonary petechiae. Number of postmortem pulmonary petechiae is plotted as a function of differences between wedge and intratracheal pressure during end-expiratory airway occlusion maneuvers. Each closed square represents the maximum values averaged for three occlusion maneuvers in a single animal. *Left-hand panel* shows results during inspiratory efforts and *right-hand panel* shows results during expiratory intervals.

gross observation. Inflammatory infiltrates were not found in any lung section.

Statistical treatment of data included the non-parametric Wilcoxon rank sum test, as well as linear regression analysis. A  $P < 0.05$  was considered significant in each case.

#### RESULTS

Relationships between the occurrence of pulmonary petechiae and differences between wedge and intratracheal pressure during airway occlusion are illustrated for both inspiration and expiration in Figure 2. Small pressure differences were always associated with minimal formation of pulmonary petechiae, but large numbers of petechiae were often obtained at higher transmural pressures. For statistical treatment, the above results were divided into nearly equal populations where the inspiratory pressure difference was greater than 25 torr (eight animals) or equal to or less than 25 torr (seven animals). Results during expiration were divided into populations where the pressure differences were greater than 10 torr (eight animals) or equal to or less than 10 torr (seven animals). In both cases, the Wilcoxon rank sum test showed a significantly greater number of pulmonary petechiae in the group with the greatest transmural pressure differences across the left atrium.

It can be observed in Figure 1 that some degree of bradycardia developed during occlusion maneuvers. In general, those animals with the greatest amount of bradycardia also developed the greatest inspiratory differences between wedge and intratracheal pressure during occlusion (Fig. 3). Systemic arterial pressures were little affected by occlusion maneuvers (Fig. 1) except for breath-by-breath variation accompanying respiratory efforts and the terminal fall in pressure when the animal was sacrificed.

In contrast to the large numbers of petechiae that could be observed on the lungs, most rabbits showed no petechiae on either the pericardium or thymus. One animal showed two isolated hemorrhages on the surface of the thymus, but none had epicardial petechiae. No apparent relationship could be seen between this isolated instance of thymic hemorrhage and the occurrence of pulmonary petechiae.

#### DISCUSSION

The observed differences between wedge and intratracheal pressures during inspiratory efforts accompanying airway occlusion

are consistent with the possibility that cardiac function had been impaired by increased afterload on the left heart and/or decreased left heart compliance (3). Some degree of failure can persist into the expiratory phase because the expiratory difference between wedge and intratracheal pressure also rose during occlusion maneuvers. During the course of an occlusion maneuver inspiratory efforts, as noted by negative intratracheal pressure swings, typically reached stable levels whereas wedge pressures continued to increase (Fig. 1). A possible explanation for this effect is that prolonged occlusion results in hypoxia and this could progressively

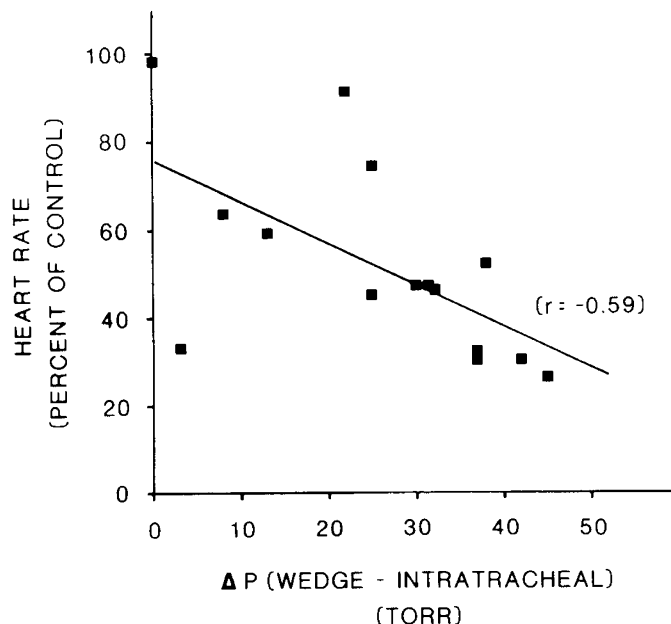


Fig. 3. Effects of end-expiratory airway occlusion on heart rate. Heart rate during end-expiratory airway occlusions (% of pre-occlusion values) is plotted as a function of maximum inspiratory difference between wedge and intratracheal pressures during the occlusion maneuvers. Heart rates were measured simultaneously with pressures. Each point represents the average of three occlusions in a single animal. The regression is significant ( $P < 0.05$ ).

decrease myocardial contractility. The occurrence of bradycardia during occlusion, whether as a direct effect of hypoxia on the myocardium or, more likely, as a hypoxia-induced reflex (11) would tend to preload the left ventricle at any given cardiac output (*i.e.*, for any given cardiac output, more diastolic filling time is available). A hypoxia-induced reflex decrease in inotropy of the heart is also possible, but such an effect cannot be extrapolated from available data in the rabbit (11). It can be suggested that a combination of the above mechanisms might "back up" sufficient pressure into the pulmonary microcirculation to cause rupture of small blood vessels, thus inducing a petechial pattern of hemorrhage. It is unlikely that the observed pulmonary petechiae were derived from the bronchial circulation because other intrathoracic structures with a systemic blood supply (thymus and epicardium) showed essentially no evidence of surface hemorrhage.

Another possible mechanism, whereby intravascular pressure could be increased in the left atrium and pulmonary circulation, is a rising afterload to the left heart accompanying systemic hypertension induced by large increases in systemic vascular resistance. Systemic hypoxia during occlusion could induce a release of endogenous catecholamines (10, 12), which might produce such a response. Indeed, studies from our laboratory using norepinephrine infusion in anesthetized open-chested rats indicated that rises in left atrial pressure accompanying severe systemic hypertension were associated with a petechial pattern of hemorrhage in the lungs (unpublished results). In the anesthetized rabbit, norepinephrine infusion also elicited severe systemic hypertension and pulmonary petechiae (5). The above mechanism was not crucial in the present study, however, because systemic arterial pressure was minimally affected during occlusion maneuvers. The example of Figure 1 is typical of the small effects on systemic arterial pressure we observed. Even if sympathetic activation did occur, as might be inferred from increases in peripheral resistance observed at the initiation of hypoxia in the rabbit (11), the lack of a notable systemic pressor response indicates that the heart itself was compromised, presumably due to the mechanical mechanisms previously discussed.

A third possibility, that right heart hypertension due to pulmonary venous constriction induced pulmonary petechiae, is an unlikely mechanism for the effects we observed. In our preliminary studies, some catheters were allowed to remain in the pulmonary artery rather than advanced to the wedge position. It was noted that rises in pulmonary arterial pressure were generally smaller than those obtained from the wedged catheter, and large numbers of petechiae could occur, even with minimal elevations in pulmonary arterial pressure; therefore, pulmonary venous constriction was negligible or was associated with a decrease in contractility of the right ventricle.

The present study cannot be extrapolated to conclude that airway obstruction is the cause of petechiae in SIDS; nevertheless, our data suggest a reasonable mechanism whereby such a terminal event could induce this pathologic change. Our data do not consider petechiae observed on the heart and thymus of SIDS

infants. It is important to note that such hemorrhages must occur by a different mechanism than described here. Possibly, airway obstruction is again involved because decreases in intrathoracic pressures could produce large transmural pressure difference at the surface of intrathoracic structures with a systemic blood supply. In the present study using the rabbit, petechiae were not typically observed on the epicardium or thymus. Further, we estimated the effective arterial pressure in intrathoracic structures with a systemic blood supply during inspiratory efforts accompanying airway occlusion (systolic pressure minus intratracheal pressure). The maximum values among the four rabbits showing the greatest number of pulmonary petechiae (>40) averaged 143 mmHg (range 131–155 mmHg). Such values do not seem to be excessive for the systemic vasculature and would not be expected to induce hemorrhage.

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