“You don’t really believe that hypoxia causes pulmonary vasoconstriction, do you?” That question was put to me by C. J. Lambertsen while I was a medical student at the University of Pennsylvania. Unanswered and forgotten at the time, it ultimately became the basis of my career as an independent investigator. But before getting to that story and to a review of my experiences with the lung circulation, I will review critical points on the path that led to my career and provided, in no organized way, my training for research.

An early interest in technology and science blossomed after being cultivated by my high school physics teacher, who, remarkably, was a young woman in her first and only year of teaching. She enabled me to see that mathematics could be a useful investigative tool and that I could apply physical principles to gain an understanding of natural phenomena. She recognized my curiosity and encouraged my interest with frequent, often demanding, challenges.

As a teenager I had a consuming interest in electronics, and I read avidly about basic circuitry and radio communication, often to the exclusion of school assignments. Although I maintained an active interest in electronics while in college, my undergraduate education was in chemistry. My introduction to biomedical research came during two summers of my undergraduate years when I was able to combine interests in chemistry and electronics through employment under the direction of Britton Chance at the Johnson Foundation for Biophysics at the University of Pennsylvania. This environment


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provided many lessons on topics in science as well as on the process of scientific investigation. An early lesson about research was that the investigator is obligated to know the characteristics, calibrations, strengths, and weaknesses of his or her instrumentation. Another unforgettable lesson concerned intellectual honesty, and it came about in a painful way. Brit and I were using a hand spectroscope, watching the appearance and disappearance of absorption bands of various cytochromes as oxygen was added to a circulating suspension of yeast. With obvious displeasure at my performance, he insisted that I should be seeing a band at a certain wavelength. I could not see the change and persistently said so. Finally, after inducing considerable discomfort in his employee, he said, “Good. I didn’t see it either. Don’t ever say you do when you don’t.” Then he walked away, leaving me to reflect on the experience.

I finished college unsure of whether I wanted to pursue medicine, chemistry, or biophysics, but an early admission to medical school decided the issue, at least temporarily.

Chris Lambertsen’s laboratory was a popular spot for medical students to experience research, and it was my good fortune to be able to participate in it during one free summer and several months of senior elective time. My assignment was to build apparatus for continuous recording of pH and for controlling alveolar PCO₂ at hypercapnic levels. I also assisted with teaching in the sophomore medical pharmacology laboratory exercises, an experience that gave me a taste of what medical school was like from the “other side.” Chris’s guidance and personal warmth were intangible assets that I recall fondly. I look on my experience in the pharmacology department at Penn as the determining factor in opting for a career in investigative medicine. Lambertsen’s experiments were complicated team efforts in which human subjects were at personal risk. Consequently, experiments were undertaken only after meticulous and detailed planning. I began to appreciate that research must be organized from the start and that inquiry requires an hypothesis and a detailed protocol to test it. Data reduction in Chris’s lab was attended to with great care. One of Chris’s rules was that everything had to be calculated at least twice, preferably by two different people. His rule made a lasting impression of another fundamental requirement for research: one must be confident in the data and their transformations.

The lung was not a subject of much interest in Cleveland while I was there as an intern and medical resident. However, one dedicated pulmonologist (David Gillespie) at what is now Metropolitan General Hospital introduced me to clinical pulmonary physiology. Through this experience I learned that the lung is an organ whose physiology is susceptible to the methods of physics, mathematics, and engineering, in all of which I had an interest (if not an education), so I decided on a career in pulmonary medicine.

At about that time George Wright had left the Trudeau Foundation at Saranac Lake to assume a position in Cleveland as director of medical research at St. Luke’s Hospital, and in 1958 he agreed to serve as my mentor for a fellowship year. I proposed to study the pulmonary circulation, a choice that reflected my interest in both lung and cardiovascular physiology. George apparently believed in the sink-or-swim training method, for he left me on my own to devise and perform my first experiments. His lessons came during the preparations for publication, and he was a stringent editor. One memorable bit of advice he gave me was “to write it as if it was to be published in the Boy Scout Handbook.” Like Wiltz Wagner in recent times, George was critical of my unnecessary obfuscation and my use of mathematical expressions where words were a better choice. His tutoring certainly was help-
ful: my first publication, coauthored with George Wright, was accepted by the Journal of Applied Physiology in its initially submitted form. That publication concerned the shape of the perfusion pressure-flow curves of excised dog lobes and demonstrated the roles of venous and alveolar pressures in determining transmural and longitudinal vascular pressure gradients. It was a satisfying piece of work that, in addition to presenting new material, gave me a start toward understanding the physical properties of lung vessels and their perfusion.

Jerome Kleinerman was associated with the research laboratory at St. Luke's during my fellowship. Jerry became my antagonist, protagonist, colleague, and friend. He taught me to think beyond physiology into the areas of anatomy, pathology, and morphometry, and he caused me to consider the relationships between structure and function. Jerry also taught me a lot about the philosophy and politics of science and about the funding of research.

After fellowship I entered the Public Health Service to study the pulmonary effects of air pollutants. One year of service was spent at St. Bartholomew's Hospital in London, where I came upon Donald McDonald and his important book Blood Flow in Arteries. I spent many hours chewing on the material in that volume and learning more mathematics so that I could understand what McDonald had written.

After two and a half years I left the Public Health Service to study the pulmonary effects of air pollutants. On returning to Cleveland in 1962 I realized that I had a job but that I had not yet established what I was going to do. I needed a project that would be attractive to granting agencies, and I had to develop my first grant. It was then that I remembered Chris Lambertsen's question and the problem of regulation of the pulmonary circulation in response to hypoxia.

In the following description of the experiments that shaped my perception of the pulmonary circulation I will unashamedly stress my own publications, knowing that in many instances my observations were not unique and that references to antecedent and supporting information are provided in the reports that have been cited.

Effect of Hypoxia on the Pulmonary Circulation

In 1962 the phenomenon of hypoxic pulmonary vasoconstriction had been known for at least 15 years, but it was not universally accepted. Some investigators had been unable to demonstrate it, and many were uneasy because constriction was opposite to the effects of hypoxia in other organs. Then as now the basic questions included, is hypoxic pulmonary vasoconstriction a direct response of vascular smooth muscle or is it mediated indirectly, either humorally or reflexly? does it occur in the arterial or in the venous bed, or both? and where is the sensor located? In hopes that I might contribute to the confusion, I undertook my first experiments.

The goal of those first experiments was to determine if responses to hypoxia could be demonstrated in excised dog lobes under more rigid control of conditions than in prior investigations and, if so, to attempt to define the anatomical location of the response, the relationship to alveolar and perfusate $P_{O_2}$, and the effects of certain pharmacologic blocking agents. The plan was to excise the left lower lobe of an anesthetized dog, enclose it in a humid, warm environment, ventilate it with chosen gas mixtures, and perfuse it at constant flow with systemic venous blood drawn from, and returned to, the donor dog. Although I had had experience perfusing excised lobes under other conditions in the experiments with
Wright, I was not prepared for the problems that arose when perfusing ventilated lobes with blood for extended periods. It was amazing how quickly lobes would become edematous, and for many months we obtained greater flow out the airway than out the vein. Finally, we learned how to minimize the formation of edema and produce preparations that were usable for several hours. We also were able to dispense with the donor dog and use an external reservoir for perfusion with either blood or a physiological salt-colloid solution.

Some of our findings with those lobes are shown in Figure 1. The percentage of O\(_2\) in ventilating gas is indicated above each tracing, but in each case the CO\(_2\) composition was 6.5%. The top left tracing illustrates the pressor response of blood-perfused lobes to a bolus of serotonin (5HT) and to reduction of the inspired %O\(_2\) from the normal control 14 to 6% and then to 0%. Responses to hypoxia were immediately reversed by raising inspired %O\(_2\), as seen in the middle left panel. Responses to 6% O\(_2\) would be sustained, but responses to anoxia would spontaneously recede to baseline within 5–7 min. Thereafter, there would be no response to varying inspired O\(_2\), although the response to 5HT was unchanged (Fig. 1, top right panel). Sometimes the response to hypoxia would return after many minutes of ventilation with the normoxic mixture. A further finding in all preparations was that responses to hypoxia would disappear after 50–60 min of perfusion, whereas responses to 5HT remained unchanged for several hours. The evanescence of the hypoxic response and its depression by severe hypoxia, in contrast to the sustained responses to 5HT, suggested that the hypoxic response might involve some easily impaired process external to the smooth muscle. Several years later we were to find\(^5\) that preparations would respond to hypoxia for a much longer interval if they were cooled to 25–30°C except for brief periods at 37°C, during which the response to hypoxia was tested. This further supported the idea that there was a relatively fragile active metabolic process involved.

The relation between response and O\(_2\) composition of arterial blood and alveolar gas is illustrated in the middle left panel (Fig. 1). Here, the initial ventilating %O\(_2\) has been switched from 94 to 6% and then back to 94%. Note that a pressor response began while arterial Po\(_2\) was 295 mmHg but that it subsided while arterial Po\(_2\) (i.e., Po\(_2\) of blood leaving the reservoir) was still falling. This suggested that the response was sensed at either the alveolar or venous level, but not in the arteries. Later, this was followed up in other lobes that were perfused from vein to artery,\(^3\) and we found that the response to hypoxia was again dissociated from input blood Po\(_2\), suggesting that the sensory site was not in the veins either. Our conclusion, then, was that the sensor lay somewhere in the alveolar gas environment.

When salt solution was substituted for blood in our earliest experiments, hypoxia usually caused a small depressor ef-
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Despite causing constriction, although the responses to 5HT were similar to those seen during blood perfusion. An example of the hypoxic response is shown in the middle right panel of Figure 1. Later, a graduate student, Ben Gorsky, showed that a small amount of plasma potentiates the pressor responses to both hypoxia and serotonin in lobes perfused with artificial perfusates but that small hypoxic responses occurred even in the absence of plasma. Gorsky’s results introduced uncertainty into our earlier conclusion that some component of blood was needed for any hypoxic pressor response to occur.

The bottom panel of Figure 1 shows that potassium cyanide also evokes vasoconstriction and that this can be partially reduced by raising alveolar %O₂ from 14 to 94%. Note that in the presence of cyanide, changing from 94 to 14% O₂ caused constriction, whereas before cyanide this change made no difference. In a later study we found that dinitrophenol caused effects similar to those of cyanide. Thus, a pressor response could be produced by both cytotoxic and hypoxic hypoxia.

Arterial wedge pressures were measured with a 1-mm outside diameter catheter in several lobes of the initial study. Wedge pressure was approximately halfway between arterial and venous pressures and showed characteristics consistent with pressure in small veins. Wedge pressure did not rise during hypoxia, and on a few occasions it fell to zero and lost all responsiveness to alveolar and venous outflow pressures, as though it had been occluded during the pressor response. The wedge pressure measurements were taken as evidence that the pressor response to hypoxia occurred in the arterial bed.

We were unsuccessful in blocking the hypoxic response with hexamethonium, atropine, and brom-lysergic acid diethylamide, thereby provisionally excluding mediation by autonomic ganglia, acetylcholine, or serotonin. Phenoxybenzamine, however, significantly reduced the response. Although this could be interpreted as mediation of the response by alpha adrenergic stimulation, we thought it more likely that phenoxybenzamine had merely left unopposed the dilatory beta-adrenergic effect of catecholamines present in the tissue and perfusate at all oxygen tensions.

Several investigators had found that the hypoxic pressor response could be potentiated by acidosis, but this was not universally agreed on. I thought our approach provided better control of perfusion and ventilation parameters, including gas and blood composition, and we studied this problem. We found that the hypoxic response was progressively depressed by alkalosis, whether caused by hypocapnia or by administration of NaHCO₃ or tris buffer. Sensitivity to pH was marked—a rise from a baseline pH of 7.3 to 7.5 prevented an hypoxic pressor response. The hypoxic response was pH dependent but not specifically PCO₂ dependent. The uppermost trace of Figure 2 shows the arterial pressure response of a perfused lobe when its ventilating gas composition was changed from 6.5% CO₂ in O₂ to 6.5% CO₂ in N₂. The second tracing shows that when the lobe was made hypoxic with 100% N₂, there was no pressor response. When, however, the lobe was ventilated with room air and the pH of the perfusate was adjusted downward with lactic acid (HCl worked equally well), there was a typical pressor response to 100% N₂.

The question of mediation of the hypoxic pressor response by nerve, even in excised lobes, had never been answered. We added the following observations to the controversy. Electrical stimulation at the hilum of the excised perfused lobe caused a pressor response that was somewhat reduced by cooling perfusate from 37 to 25°C. However, raising perfusate pH 0.16 or ventilating without O₂ for 15 min had no significant effect on the response to
Figure 2. Effect of hypocapnic alkalosis on the pressor response to hypoxia in a perfused lung lobe. From reference 4, by permission.

electrical nerve stimulation. Cooling, mild alkalization, and prolonged anoxia, however, all prevented the pressor response to ventilation with 6% O₂. In contrast, procaine at a perfusate concentration of 1 mM or tetracaine at a concentration of 0.1 mM greatly depressed responses to electrical stimulation but had no effect on response to hypoxia. Pressor responses to epinephrine were unaffected by cooling, but the effect of cooling on the serotonin response was interesting. Cooling slightly reduced the serotonin peak response but greatly prolonged the recovery, consistent with temperature sensitivity of the metabolic removal of the agent. Several animals in this series were pretreated with either phenoxybenzamine or reserpine. These treatments did not prevent responses to hypoxia. It was also interesting to note that in lobes from animals given phenoxybenzamine, electrical stimulation during a hypoxic pressor response caused partial reversal that persisted as long as the stimulation was applied. We thought that these findings allowed us to conclude that the responses to hypoxia and to nerve stimulation were independent events.

An interesting and, I believe, provocative result occurred when we attempted to stabilize vascular smooth muscle membrane potential using high concentrations of procaine and tetracaine. I had expected that this would impair the response of perfused lobes to hypoxia. Instead procaine at concentrations from 2.5 to 10 mM, or tetracaine at one-tenth those concentrations, had pressor effects of their own that resembled the effects of cyanide and dinitrophenol. That is, when given while ventilating with 14% O₂ they caused a modest vasoconstriction that was reversed by raising inspired O₂ concentration to 94%. In an equivalent fashion, the responses to 6 and 0% O₂ were enhanced. But the most remarkable effect was on the tolerance to anoxia and on the useful life of the preparations. Anoxia, which previously caused unsustained vasoconstriction and subsequent unresponsiveness, now caused sustained vasoconstriction. In addition, the life of the preparation during which responses to hypoxia could be demonstrated was extended by several hours. Furthermore, when a lobe previously unexposed to the anesthetics became incapable of responding to hypoxia after the usual 1 hour of perfusion, addition of procaine would restore and enhance hypoxic responsiveness, which then persisted several more hours. I was unable to find a sufficient explanation for those effects, but it seems to me that there may be an important clue here. On which cells did the effect occur? Perhaps an explanation exists that has not been brought to my attention. Until then, I will contend that this phenomenon merits further study.

In 1966 I turned from studies in perfused lobes to studies of excised vessels. Methods were crude by today’s standards; although vessels were handled with care,
no attempt was made to avoid endothelial injury or to adjust baseline wall stresses to optimum values for development of greatest active changes. In our first study, \(^7\) helical strips were prepared from segmental branches of pulmonary arteries of dogs and rabbits. Strips were immersed in a bath of the same salt solution found earlier to be suitable for perfusion of lobes. Strips were challenged with a number of vasoconstrictor drugs as well as with electrical field stimulation and hyperkalemia. To summarize, no strip, whether precontracted or not, contracted when bath Po\(_2\) was lowered progressively from 600 mmHg to near zero. Tensions of untreated strips were unaffected by even severe hypoxia, but tensions of precontracted vessels fell as O\(_2\) was reduced. Reduction of strip tension required O\(_2\) depletions to near zero, as best shown by responses to electrical stimulation: repeated electrical stimulation caused similar responses when PO\(_2\) was reduced from 600 to 100 mmHg and then 40 mmHg, but further reduction to near zero reduced responses by about 30% within 20 min. Strips prepared from perfused dog lobes that moments before were fully responsive to hypoxia and stabilized with procaine behaved like all other strips. Addition of procaine to the baths of previously untreated vessels did not change their responses to hypoxia. In short, there was nothing to suggest that the hypoxic pressor response of perfused lobes resembled the effects of hypoxia on isolated vessels. Instead, everything pointed to a depressor effect of severe hypoxia, similar to the behavior of systemic vessel strips. In retrospect, there probably was endothelial injury in these preparations because acetylcholine usually caused contraction that could be blocked with atropine. This may be important because some investigators now believe that endothelial factors may play a role in the hypoxic pressor response.

Before undertaking the next experiment with excised vessels, I hypothesized that the hypoxic response depended on something released from lung parenchyma. I expected that such a mediator might be diluted to ineffectiveness if studies were made in an aqueous bath. To reduce that possibility, subsequent studies were made in a water-immiscible fluorocarbon that exhibited high solvation for O\(_2\) and CO\(_2\) but poor solvation of salts and organic chemicals. In the first study, \(^8\) we compared the effects of varying bath PO\(_2\) on responses of rabbit lobar arterial strips with responses of similar strips to which a thin layer of lung parenchyma remained attached and to strips of lung parenchyma of a similar size but as devoid of larger vessels and airways as could be achieved. The bath consisted of two phases: a lower (denser) phase of fluorocarbon on which floated a layer of plasma diluted 50% with physiological salt solution. For the first 60–80 min the tissue strips remained in the fluorocarbon phase and were intermittently challenged by lowering bath Po\(_2\) from 700 to 45 mmHg. We next attempted to enhance any constrictor effect of hypoxia with procaine as we had been able to do with perfused lobes. Procaine was added to the aqueous phase, and the strips were brought into that phase for 10 min before being returned to the fluorocarbon for further challenges. We found that at no time did strips of isolated artery contract in response to oxygen deprivation, although several relaxed with hypoxia after the procaine treatment, and all contracted vigorously with electrical stimulation. In contrast, arterial strips with attached parenchyma at first relaxed during hypoxia, but, toward the end of the first hour and prior to procaine treatment, about half underwent hypoxic contraction. After procaine treatment 9 of 10 strips contracted as PO\(_2\) was lowered. Contraction seemed to begin at a PO\(_2\) near 200 mmHg and reached its maximum near 100 mmHg. After about 4 hours of study a subset of strips of artery with parenchyma were removed from the fluorocarbon and
immersed in a bath of 10% plasma in salt solution (with procaine) where further challenges with PO$_2$ variations were made. All strips removed from fluorocarbon and placed in the aqueous bath continued to display contractile responses to O$_2$ reduction. This suggested that the washout of materials by an aqueous bath may not have been as important as I first thought. To our surprise, all the parenchymal strips in the fluorocarbon bath contracted with O$_2$ depletion both before and after the procaine treatment. The tension change of the parenchymal strips was almost half that of the artery-parenchyma combination. Figure 3 illustrates the effects described above. In each case tension (T) and bath PO$_2$ were simultaneously recorded. The upper left pair show parenchymal contractions obtained after procaine treatment. The upper right panel shows how the parenchyma-covered arterial strips behaved before they began to show contractions, and the lower curves display a response after procaine treatment. These experiments were interpreted as evidence that something from lung parenchyma could evoke contraction in response to hypoxia and indeed was necessary for vessels to contract.

But my experiences with hypoxia did not end in such a tidy way. There was one more set of experiments.$^9$

I wondered how vessels would respond to variations in environmental PO$_2$ if they were suspended in an even more water-free environment. For this I chose first a bath of a more hydrophobic fluorocarbon and then a "bath" of humidified warm gas. This time we used strips of rabbit aorta as well as parenchyma-free rabbit pulmonary artery. The fluorocarbon bath was used to study only pulmonary artery using the same protocol. However, only one strip was treated with procaine or immersed in the aqueous phase above the fluorocarbon. All strips of pulmonary artery contracted reversibly when bath PO$_2$ was reduced from 700 to 100 mmHg and the procaine-treated strip responded similarly to those not so treated. An example is shown at the top of Figure 4. Contractions were modestly well sustained, but after several hours of study, contractions became less well sustained and there was often a rebound contraction when PO$_2$ was raised. When aorta (AO) and pulmonary artery (PA) were studied in the humid gas environment, each contracted as PO$_2$ was lowered. This is illustrated in the bottom traces of Figure 4. In short here was a dilemma: isolated lengths of both

![Figure 3](image-url)
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• 175

Pulm. Art. Strip in FC 43

250 mg Tension

220

PO2

650

0

Arterial Strips in Wet Gas Chamber

0.0% O2

93.5% O2

PA

AO

40 mg Tension

1 min

Figure 4. Effect of varying bath PO2 on tension of a pulmonary arterial strip immersed in fluorocarbon FC43 and of varying O2 composition of humidified gas in which were suspended strips of aorta and pulmonary artery. From reference 9, by permission.

systemic and pulmonary artery contracted when PO2 was lowered from 700 to 100 mmHg while suspended in humid gas, but both relaxed when PO2 was lowered below 40 mmHg while suspended in an aqueous bath. Note in addition that the in vivo response takes place in the gap between 100 and 20 mmHg PO2, specifically the range found to be without effect on the isolated vessels.

Do my observations with excised vessels provide useful information? I am reluctant to say that I have modeled the in vivo response to hypoxia with any of the isolated vessel techniques. Certainly I am less confident after the second study than I was after the first. Furthermore, I am not convinced that contemporary studies of more carefully prepared smaller pulmonary vessels, which are reported to show hypoxic contraction in aqueous baths, are suitable models of the excised lobe or whole-animal response to alveolar hypoxia. It seems to me that before venturing much further we need as much proof of the equivalence as can be obtained. One way to start might be to list the typical characteristics of the vascular response that most investigators agree are unique to the effects of hypoxia in situ and then to demonstrate that isolated vessels display each of them. These will probably have to be tested for species dependency. Several characteristics immediately come to mind, including sensitivity to cooling and to alkalosis, potentiation by procaine, evocability by both hypoxic and histotoxic hypoxia, suppression following a period of severe hypoxia without loss of pharmacologic responses, and dependence on calcium movement. For now, I will have to rephrase the question first put to me: “You don’t really believe that hypoxia causes pulmonary vasoconstriction as a direct smooth muscle effect, do you?” And it may be my turn to be wrong.

I thought that my studies with hypoxia had come to an impasse and that I was unable to answer the question that bothered me most: is the response a direct muscle effect or is it not? The question of neural control of the pulmonary circulation seemed to offer more opportunities for forward movement.

Reflex Responses of the Pulmonary Vessels

One of the more challenging tasks has been to test the hypothesis that increased pressure in the pulmonary arteries leads to reflex pulmonary arterial constriction. Although it would seem that such a positive
feedback mechanism would lead to a never-demonstrated sustained maximum vasoconstriction, its existence has been postulated, and perhaps demonstrated, several times. The problem lies in the technical difficulty associated with having stimulus and response in the same vessels and in securing certainty that one is in control of the experimental situation. I undertook a study of this problem with Arthur Schneider, an anesthesiology postdoctoral fellow. We believed we had found a way to discriminate between active and passive changes in pulmonary arterial pressure as left atrial pressure was progressively elevated. Experiments were done in anesthetized dogs using biventricular bypass perfusion. We acquired what we thought was convincing evidence that increasing pressure in the pulmonary vascular bed caused pulmonary vasoconstriction and that this was mediated by the sympathetic nerves. We were wrong, as I later showed in a subsequent study. What we had observed was related to a purely mechanical effect in the heart, whose activity was indeed affected by the sympathetic nervous system. (I was later informed by Sol Permutt, who served as journal editor for all three manuscripts, that one reviewer was unhappy when two papers he felt to be less than meritorious were published over his objections. When he had to accept a third that disclosed the error, he was incensed. Apparently the publication and subsequent refutation of errors was not the best way to expand my curriculum vita. Sol periodically reminds me of this.)

Several years later I attempted to reevaluate the problem by using balloons to distend portions of the pulmonary arterial bed while monitoring resistance in other portions. Vasoconstrictor responses had been seen by other investigators with this approach, but there were inconsistencies among the results and questions about the methods. Most important, balloons might have caused unseen or unintended passive changes, and changes in pressure might have been caused by changes in flow. Unlike most others, who had chosen to place balloons under indirect observation with chests closed, we opened chests of anesthetized dogs and attempted to place balloons under direct visual guidance. We found that unless they were constrained, balloons in the left pulmonary artery invariably “popped” retrogradely into the main pulmonary artery when they were inflated sufficiently to exert a force on the arterial wall. Ultimately, we tied all lobar branches of the left pulmonary artery and retrogradely placed a balloon in the parent vessel through an opening in the lower lobe branch. This balloon remained in place. Systemic flow was held constant by a left ventricular bypass pump, and gas exchange was provided externally so that lung volume could be held invariant. We were careful to preserve nerves, and we avoided dissection where they were known to be located. Pressure in the main pulmonary artery was recorded as a reflection of perfusion resistance of the right lung. No amount of distension of the left pulmonary artery influenced perfusion pressure of the right lung, although right lung vasoconstriction could be induced by hypoxic ventilation or by stimulating the right stellate ganglion.

Frustrated, and convinced that pressure changes reported by others represented a passive mechanical effect, I wanted to reproduce the findings of Craig Juratsch and his coworkers, who believed they had evoked vasoconstriction by inflating a balloon placed in the main pulmonary artery. The balloon was said not to have altered cardiac output or occluded major branches but instead to have caused the main artery to be distended in accepting cardiac output. Craig and I had met briefly and discussed his findings some years before, and I wrote to him seeking to borrow his balloon. To my surprise, he not only had balloon catheters but said he
would like to come do the experiments with me. Craig was, and remains, a delightful individual, enjoyable to work with even though he came fully convinced of the existence of reflex vasoconstriction, while I was convinced otherwise. We worked very hard for one week. On the first day, using fluoroscopy, he passed his balloon from a femoral vein of the anesthetized dog into the pulmonary artery. Sure enough, inflation of the balloon was followed by increased pressure downstream to the balloon in the left pulmonary artery where an extension of the catheter lay. But then we opened the chest and placed catheters in apical lobe arterial branches on each side. Pressures recorded from these during inflation of the balloon in the main pulmonary artery revealed that the right pulmonary artery was completely occluded by the inflated balloon. Every inflation and each subsequent experiment provided the same results. An example is shown in Figure 5. From top down are shown aortic pressure, aortic flow, pressure in the left pulmonary artery measured with the balloon (Laks) catheter, and pressures in the left and right pulmonary arteries measured through apical branches. Bursts at higher chart speed show waveforms, whereas intervals of mean pressure recording can be seen as pulse-free plateaus indicated by “M”. The balloon was inflated at the up arrow and deflated at the down arrow. Note that aortic flow and pressure were not significantly changed but that pressure in the left pulmonary artery measured by both devices increased, while pressure in the right fell. Calculated resistance of the left lung actually fell during inflation of the balloon. The changes caused by inflating the balloon were identical to those that followed tightening of a snare around the right pulmonary artery. Throughout this sequence of observations we were careful to test after each step to assure that the original change observed while the chest was closed continued to be present. This experience cast doubt on the interpretation of previous experiments using this particular balloon technique but, of course, did not prove that all prior results were determined entirely passively. We reported the results of this and the preceding study.\textsuperscript{20,26}
After several attempts I had found no support for the hypothesis that pulmonary arterial distension would lead to arterial constriction, and I decided to examine other potential initiators of neurogenic pulmonary vasomotion.

Head injury and/or increased intracranial pressure may be associated with pulmonary hypertension and pulmonary edema, and some have proposed that there may be a neurogenic pulmonary vasomotor component. Harvey Cushing had demonstrated that increased intracranial pressure caused proportional systemic arterial vasoconstriction sufficient to raise arterial pressure above intracranial pressure and thereby restore cerebral blood flow. This vasoconstriction was shown to depend on sympathetic efferent activation. Extension of the Cushing experiment to include pulmonary vascular pressures could be expected to provide observations that would bear not only on pulmonary responses to intracranial misadventures but also on the general problem of the role of the sympathetic nerves in control of the pulmonary circulation. Others had used it for that purpose, but results were controversial because it was unclear whether pulmonary vascular pressure changes were determined actively or as a result of changes in the heart and systemic vessels. I believed we had techniques that could better exclude the secondary consequences.

We opened the chests of anesthetized dogs, collected venous systemic and pulmonary venous blood into external reservoirs, and substituted two pulsatile-flow pumps for the ventricles. This allowed control of flow and left atrial pressure while we observed changes in systemic and pulmonary arterial pressures in response to brief intervals of increased intracranial pressure. Intracranial pressure was varied by forcing physiological salt solution into the subarachnoid space through a hollow plug screwed into the skull. Figure 6 shows a typical response. When intracranial pressure (Pic) was increased, systemic arterial pressure (Pao) increased. Heart rate (HR) rose transiently with increased Pic but then fell. Atropine eliminated the bradycardia but not the tachycardia. There were very small but statistically significant changes in pulmonary arterial pressure (Ppa), which as a group did not differ significantly from the small changes in left atrial pressure (Pla) that also occurred. The atrial pressure rise probably occurred as a result of a mechanical effect of the bradycardia on discharge rate through the atrial cannula because it was reduced or eliminated by atropine. In spite of the similarity of average arterial and atrial pressure changes, the Ppa-Pla gradient rose an average of 0.36 cmH₂O which, though small, was statistically significant. We were unable to find a significant change in pulmonary arterial pulse pressure during the time of increased Pic, suggesting arterial wall stiffness did not change. There was a graded relationship between the magnitude of the imposed increase in Pic and the increase in Pao. During increased Pic we also noted a rise...
in levels of the external reservoirs. This was not quantified but was believed to reflect the considerable systemic vasoconstriction that was induced. We briefly ventilated the lungs with $N_2$ and found a reversible pulmonary pressor response. This was taken as evidence that pulmonary vessels were capable of constricting under the experimental conditions. These experiments were interpreted as showing that even massive activation of sympathetic efferent activity was incapable of evoking a physiologically significant pulmonary vasomotor response, although there was evidence of a small but statistically significant effect. The systemic vascular changes and the changes in heart rate were in keeping with prior observations.

I was not encouraged by any of the foregoing experiments to believe that there is significant neural control of the adult canine pulmonary vascular bed. My attention was then directed to the possibility that the lung vessels may be an important starting point for reflexes, rather than an important destination.

**Systemic Vasomotor Changes Initiated by High Pulmonary Vascular Pressure**

My curiosity was initially drawn to reflex cardiovascular changes that might occur in response to increased left ventricular end-diastolic pressure. There was abundant evidence that reflexes might arise from distension of the left atrium and ventricle, from intraparenchymal pulmonary vessels, and from the major pulmonary arteries. Most information, however, was either in the form of afferent nervous activity in response to pressure changes or hemodynamic variables measured under conditions where primary changes were insufficiently separated from secondary phenomena. I wanted to isolate stimuli and to control secondary events. Secondary events were to include not only other reflexes, but also changes in systemic flow, lung mechanics, and gas exchange. Furthermore, our efforts were to be directed toward measuring outcome in terms of physiological sequelae rather than as changes in afferent neural activity, for we contended that the former best represents the reflex whereas the latter only represents one form of the input to the controller.

Most work prior to ours had implied that distension of components of the left heart and pulmonary circulation would cause systemic vasodilation and cardiac slowing. Controversy existed. Some investigators were unable to find vasomotor effects of left atrial and/or pulmonary vein distension while others found reflex tachycardia. In other hands distension of the pulmonary arteries had been found to cause systemic vasoconstriction. The hypothesis of our first study was that retrograde pulmonary hypertension brought about by increasing left atrial pressure would cause systemic vasodilation and a fall in heart rate and that these responses would be eliminated by vagotomy and partially suppressed by interaction of systemic arterial baroreflexes. We used biventricular bypass to isolate the stimulus to the left heart and pulmonary vessels and to isolate the response from interacting or secondary effects. This was achieved in anesthetized dogs by opening the chest, stopping the ventricular beat by inducing ventricular fibrillation, draining systemic and pulmonary venous blood from the right ventricle and left atrium, and perfusing the systemic and pulmonary circulations through cannulas in the aorta and left lower lobe pulmonary artery. Pressure in the left heart was controlled by a Starling resistor in the left atrial drain line. The pulmonary perfusion pump ran at constant rate, but provision was made to servocontrol the systemic pump so that blood pressure could be held.
constant. We measured left atrial pressure, pulmonary and systemic arterial pressures, and systemic arterial flow. Heart rate was acquired from the left atrial pressure pulse. Systemic vascular resistance was continuously computed and recorded. All illustration of effects with (P = C) and without (Q = C) servocontrol of arterial pressure is shown in Figure 7. When left atrial pressure (Pla) was raised abruptly from 0 to 20–25 cmH₂O the typical response was a transient fall of systemic vascular resistance (SVR) averaging 35% that gave way over a period of 40–60 s to a plateau decline of 21%. When systemic arterial pressure (Pao) was not servocontrolled, the respective changes were declines of 26 and 12%, significantly less than with servocontrol. Fall of resistance was accompanied by a fall in heart rate (HR) from tachycardic baseline rates of 150–200 beats/min. In a few instances, increased left atrial pressure brought about a rise in systemic vascular resistance and heart rate. That outcome seemed to occur most often when baseline resistance and blood pressure were unusually and abnormally low. Bilateral cervical vagotomy eliminated all effects of increased left atrial pressure. Use of pulsatile, rather than continuous, pulmonary perfusion did not alter response, although it might have been expected to increase a response if mediated by pulmonary arterial baroreceptors with properties similar to the systemic arterial baroreceptor. We also tested the hypothesis that a change in lung volume would alter the response to increased left atrial pressure. There were three reasons for this hypothesis: (1) lung volume changes can change the effective perivascular pressure and perhaps the vascular strain imposed by a change in intravascular pressure, (2) slowly adapting pulmonary receptors reflexly alter systemic vasomotor tone and may have an influence on further neural modulation, and (3) greater lung volumes may mechanically limit enlargement of the heart and any reflex dependent on that strain. And indeed we found that an increase of end-expiratory pressure from 5 to 12 cmH₂O significantly reduced the response to increased left atrial pressure.

In the next study of the cardiopulmonary baroreflex, we acquired stimulus-response relationships using both step and sinusoidal input pressures of variable magnitude. In addition we examined the relationship between sinusoidal forcing frequency and response, while using a constant stimulus amplitude. The preparation was the same as that used earlier, although systemic arterial pressure was not servocontrolled. Step pressure changes were applied from a baseline left atrial pressure of 0 cmH₂O. The magnitudes of both the transient and sustained falls of systemic vascular resistance were essentially linearly related to left atrial step pressure magnitude over the range 10 to 35 cmH₂O. For phasic pressure forcing, we servocontrolled left atrial pressure using a low frequency signal generator and a third pump to impose a back pressure on atrial drainage such that left atrial pressure varied sinusoidally. At frequencies below 0.03 Hz, the systemic arterial pres-
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sure output waveform was cyclic but not sinusoidal, whereas from 0.03 Hz to 0.08 Hz the output waveform appeared to be an undistorted sinusoid whose amplitude became progressively less as forcing frequency was raised. Above 0.08 Hz, the response was too small to be detectably cyclic. Over the frequency range 0.03 to 0.08 Hz the input-output characteristics resembled those of a linear second-order system, and on that basis we determined stability characteristics. We found that the system behaved with a natural frequency of 0.05 Hz and that its gain and phase margins assured stability. When left atrial pressure was forced to vary sinusoidally at 0.03 Hz using a range of amplitudes from 5 to 30 cmH$_2$O, the induced systemic arterial pressure variations were linearly related to the magnitudes of the forcing pressure.

In all preceding experiments with the cardiopulmonary baroreflex the stimulus pressure was imposed equally throughout the lung vessels and left heart chambers. Our next goal was to determine the roles of individual subcompartments. The first of those studies$^{14}$ demonstrated responses to pressurization of the pulmonary arterial compartment and pressurization of the left atrium-pulmonary vein compartment. Open-chest anesthetized dogs were provided with external gas exchange and systemic vascular perfusion by draining systemic venous blood from the right atrium and, after gas exchange, returning it to the aorta by a continuous-flow pump. Systemic arterial pressure was sevocontrolled. Valve orifices at the base of the heart were occluded by clamping the fibrillating ventricles with a single large clamp placed just below the atriovenous groove. A small drain was placed in the left ventricular cavity. Recalling that gas does not traverse capillaries except at high pressure, we were able to distend the arterial and veno-atrial compartments selectively by admitting 5% CO$_2$ in O$_2$ through catheters in the pulmonary artery and atrial appendage. While one compartment was gas pressurized, we opened a drain from the other so that any transcapillary gas passage would not cause a pressure change in the second compartment. Step changes of pressure of various magnitudes were used to determine pressure-response curves. We found that pressurization of the veno-atrial compartment caused systemic vascular resistance to fall in amounts that were essentially linearly proportional to forcing pressure over the range 10 to 30 cmH$_2$O but that, on average, a plateau was achieved at about 30 cmH$_2$O. Those results were indistinguishable from the earlier experiments in which the entire cardiopulmonary compartment was pressurized as a unit. A similar linear response and plateau were found when pressurizing the pulmonary arterial compartment, but responses were about one-third those obtained from the vein-atrium, and the plateau occurred at 60 cmH$_2$O. The vein-atrial reflex was further characterized to show that responses varied in proportion to rate of rise of pressure if a ramp stimulus was used and that greatest responses would follow a uniform 5 cmH$_2$O step change if that step was introduced from a baseline pressure of 15 cmH$_2$O.

The gas insufflation experiments did not include pressurization of the pulmonary capillary bed, nor did they separate pulmonary veins from left atrium. Further discrimination was made in preparations using the same basic bypass perfusion technique but in which all pulmonary veins were tied at their atrial junctions so that the pulmonary and left heart chambers could be individually pressurized with blood. Responses to pulmonary vascular pressurization was essentially the same as that found with isolated arterial distension, whereas the response to left heart distension was similar to vein-atrial pressurization.$^{16}$ Mild pulmonary edema was induced with sustained pressure in a subset of this study, and more severe
Edema was caused by alloxan in another subgroup. Edema per se had no detectable effect on systemic vascular resistance or on subsequent responses to pulmonary vascular pressurization.

The experiences with control of systemic vascular resistance by a cardiopulmonary baroreflex indicated that, although vasodilatory responses could occur consequent to increased pressure in the pulmonary arteries, a much larger response followed distension of the left atrium. (We had also shown that distension of the fibrillating ventricle was ineffective over the pressure range used to evoke the atrial response.15) I had anticipated that pulmonary congestion would play a bigger role and, anticipating a role for C-fiber reflexes, that capillary congestion would show itself to be important. But this was not so. Furthermore, atrial and pulmonary arterial baroreflexes did not seem to summate when induced together. Although it was apparent that the greatest effect on resistance was transient, this was not detectably different from the time course of the systemic arterial baroreflex, which we often displayed by abruptly increasing set point pressure of the servocontroller. In what seemed appropriate, the optimum baseline pressure from which to acquire the left atrial baroreflex corresponded rather closely with normal transmural pressure and the threshold, and plateau pressures of the pulmonary artery response curve exceeded those of the atrial response by an amount roughly in proportion to the normal mean pressures of those compartments. Teleologically (and to address utility is not without merit), the vasodilatory cardiopulmonary baroreflex would seem destined to respond to acutely higher left ventricular end-diastolic pressures in a way that, at least temporarily, reduces ventricular load and promotes stability. In my experience it has been a robust and reproducible reflex observable under a wide range of conditions. Its effects are dramatically large, most easily appreciated during servocontrol of systemic arterial pressure wherein it was often necessary to quickly double systemic flow to maintain pressure. One thing not disclosed is whether the left atrium ever "sees" the necessary transmural pressure: in the intact animal, restraints by the pericardium or by mechanical cardiopulmonary interaction may significantly reduce the strain in response to any given change in intraatrial pressure.

**Effects of Cardiac and Pulmonary Vascular Pressures on Breathing**

Inspired by reports of cardiodynamic hyperpnea and of the effects of congestion on slowly and rapidly adapting pulmonary receptors and on C-fiber afferent activity, I next addressed the question of the role of cardiac and pulmonary vascular pressures in the control of breathing.

Our first effort made use of the methods described above in which ligation of pulmonary veins and cross-clamping of the ventricles of dogs on cardiopulmonary bypass perfusion enabled independent distension of pulmonary vascular and left atrial compartments. In addition to recording cardiovascular pressures, breathing was monitored by recording the diaphragm electromyogram. Note that in these preparations in which external gas exchange was provided there was no need for lung ventilation. Consequently, lungs were held at a single baseline transpulmonary pressure during the period of perfusion. This approach decoupled breathing activity from lung volume movements and gas exchange and was an important aspect of our experiments on the control of breathing because many secondary effects were prevented in this way. Based on observations of others, I had anticipated that lung congestion would cause tachypnea, but I had no firm preconvictions regarding the effect of atrial disten-
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We were surprised to find that lung congestion decreased breathing frequency through prolongation of expiratory time. Changes appeared and disappeared immediately on change in vascular pressure. We used vascular pressures ranging from 20 to 70 cmH₂O and found that there was a threshold near 30 cmH₂O. Prolongation of expiration varied directly with pressure above that threshold. There were no significant effects on inspiratory time, peak inspiratory magnitude, or the rate of inspiratory activity. An example is shown in Figure 8. Although in 6 of 15 experiments expiration time shortened for two or three breaths at the onset of vascular pressurization, the respiroinhibitory effect of congestion that prevailed in all experiments resembled that of lung inflation, considered to be a response to stimulation of slowly adapting airway receptors. Congestion did not influence breathing after bilateral cervical vagotomy.

The effect of left atrial distension on breathing was inconstant and inconclusive in that early study. However, when there was an effect on breathing it seemed to be weakly excitatory. Subsequent studies using similar but improved methods have shown that breathing frequency can be stimulated by distension of the left atrium. Shortening of both expiration and inspiration contribute to this change, and, in addition, there may be a small reduction in depth of inspiration. Breathing frequency was, by inspection, a linear function of left atrial pressure above a threshold of 8 cmH₂O. An atrial pressure of 30 cmH₂O caused an average change in frequency of 20%. Although the changes were not large, the reflex was robust: it could be demonstrated under a wide range of conditions, it was reproducible, and it could be evoked by changes in left heart loading or by the increased pressure consequent to induction of atrial fibrillation. I concluded that this left atrial reflex could play a role in tachypnea of exercise or left ventricular failure, but it was not clear how this would interact with the respiroinhibitory effect of lung congestion, which should be simultaneously active under most conditions in the intact animal. We undertook further investigations of the effects of lung vascular congestion and of interaction between lung and cardiac reflexes.

As noted earlier, the anticipated response to lung congestion was tachypnea secondary to stimulation of juxtaglomerular C-fiber endings (sometimes referred to as type J receptors). In contrast, our results suggested that slowly adapting receptors had been stimulated. Recall that in those experiments lung volume did not change throughout the breathing cycle. If congestion stimulated or “sensitized” the slowly adapting receptors under normal conditions, where lung volume varies with breathing, congestion may result in
tachypnea. The reasoning behind this is that because the slowly adapting receptors may activate the inspiratory off switch, enhancement of their activity will lead to shallow tachypnea if minute ventilation is to be preserved (for example, by the CO₂-related chemoreflex). This suggested an experiment to test the hypothesis that congestion enhances the sensitivity of the Hering-Breuer reflex, a reflex attributed to slowly adapting airway receptors.

Anesthetized dogs were prepared by draining systemic venous blood from the right atrium to an external gas exchanger and perfusion pump that returned it to the aorta at constant flow. Ventricular fibrillation was induced, and drains were placed in the right and left ventricular cavities. A second pump perfused the lungs and left heart chambers with blood from the external reservoir admitted through a cannula in the main pulmonary artery. Perfusion flow rate of this second system was intentionally low—about 500 ml/min. Pressure within the lung-heart compartment was adjusted by regulating the resistance of outflow from the left ventricle. During baseline conditions, pressure in the pulmonary artery was approximately 0 cmH₂O. Breathing movements of the diaphragm were monitored. The Hering-Breuer reflex was characterized by the relationship between breathing frequency and transpulmonary pressure. Transpulmonary pressure was increased from 2 cmH₂O to 20 cmH₂O, or to the point of apnea if that occurred first. Each step was held for 20 s while breathing movements stabilized. After making observations under baseline vascular conditions, the effect of congestion was tested by raising pressure in the pulmonary artery to 60 cmH₂O. About 1 min was allowed for stabilization before a Hering-Breuer reflex response relationship was obtained as before. Vascular pressure was then returned to baseline, and another response to inflation was obtained. An example of the results is provided in Figure 9. Note that breathing frequency fell in a nearly linear way as airway pressure (Paw) was raised. Note also that congestion had no significant effect on frequency of respiration (fr) at low airway pressure but that as Paw rose, frequency did not decrease as much as it had while lung vessels and left heart were not distended. Those characteristics pertained to the group as a whole. The failure of frequency to fall as much during congestion implied that the Hering-Breuer reflex was less rather than more effective during congestion. In each of these experiments we also infused a small amount of oleic acid into the lung vessels to cause an acute chemical injury. This was associated with an increased frequency of breathing at low airway pressures, which fell readily with inflation such that at higher airway pressures there was no apparent effect of the acid. The result could be interpreted as enhancement of the Hering-Breuer reflex by lung vascular injury.

In the experiments with the Hering-Breuer reflex we noted that congestion of lungs and left heart did not cause a sustained fall in breathing frequency as it had in the earlier experience with isolated lung vascular congestion, although there

![Figure 9. Relationship between transpulmonary pressure and breathing frequency before, during, and after congesting the lung vascular bed. From reference 22, by permission.](image-url)
was usually a transient dip at the onset of the vascular pressure rise. I wondered if this reflected the combined effects of the depressor pulmonary reflex and the excitor cardiac reflex. Two groups of dogs were prepared using methods for perfusion and stimulus isolation already described. In one group we looked for the effects of isolated pulmonary vascular congestion and in the other the effects of combined lung vessel and left heart distension. In both groups we also attempted to block conduction of myelinated vagal afferent fibers by nerve cooling in an attempt to bring out C-fiber afferent effects. As predicted, congestion of isolated vessels caused marked initial transient depression of breathing followed by a sustained plateau at an intermediate level. Pressurization of combined vessels and left heart, however, caused an initial transient depression followed by an increased frequency significantly above the prestimulus baseline. During vagal block, pressurization of isolated lung vascular or combined lung-heart compartments caused stimulation of breathing. An example of each of these effects is shown in Figure 10.

To complete our studies of the effects on breathing of pressures in the pulmonary circulation, we confined pressure changes to the beating right ventricle and the extraparenchymal pulmonary arteries. Again, bypass perfusion and gas exchange provided control of secondary variables. We found that if outflow resistance from the pulmonary arterial component was raised sufficient to increase arterial pressure to about 65 cmH₂O, there would be a small increase in breathing frequency.¹⁹ This result was not seen in all experiments and was not as repeatable as were changes caused by congestion of intraparenchymal vessels or the left heart. Our results conflicted with those of others who have suggested that breathing may be importantly modulated by right heart loading but confirmed studies that showed only a small effect of high arterial pressures that were confined to the closed extraparenchymal arterial compartment.

My experiences with reflex effects on breathing that arise from the heart and pulmonary vessels have shown that small (5–25%) upward changes in breathing frequency can be generated by increased pressure in the extraparenchymal arterial portion but more particularly by increased pressure in the left atrium. Similar increases can be caused by lung congestion if a dominant and much larger depressor effect is prevented by blocking myelinated afferent fibers. The pressures shown to be effective are within the range of expected pressures in the intact animal, at least at times of stress, and this is particularly true for the left atrial reflex. The lack of uniform direction of change makes it impossible to anticipate the combined effects of these reflexes in the intact situation. Our demonstrations only provide evidence that certain things may happen. They could not test the hypothesis that cardiopulmonary pressure variations are effective in the control of breathing in the intact animal. If nothing else, these experiments
serve as useful reminders of the complexity of reflex control systems and the near-futility of creating a valid large-system model without more sophisticated and extensive information. In that regard, performance of these experiments was a rewarding but at the same time a cautionary experience.

**Effect of Lung Vessel and Left Heart Pressures on Airways**

Although well established in the experiences of clinicians, cardiac asthma had not been well documented in the physiology laboratory, and I couldn’t resist a look to see if left heart and/or lung vascular congestion caused reflex changes in lung mechanics. This was done in two series of experiments, both of which used the now-familiar technique of cardiopulmonary bypass perfusion and external gas exchange. Both studies were combined in a single report. In one study we looked at changes in lung compliance and resistance brought about by increased pressure in the combined chambers of the left heart and pulmonary circulation. In this study, after establishing cardiopulmonary bypass perfusion, the lungs and left heart were perfused with a second pump at low flow admitted through a cannula in one pulmonary arterial branch and drained from cannulas in atrium and ventricle. The lungs were ventilated with 5% CO₂ in O₂ by a piston respirator connected through a dead space that exceeded tidal volume, incorporated to minimize gas exchange and drying. Airway pressure and flow were continuously monitored, while pressure in the left heart and lung vessels was raised from zero to 45 cmH₂O by partially occluding the outflow of blood. Dynamic lung compliance and resistance were calculated from the airway pressure and flow records. We found that compliance fell and resistance rose whenever pressure was raised in the lung vessels and left heart but that changes of the same direction and size were present after bilateral cervical vagotomy. Induced changes were approximately 20% of baseline values. The effect of vagotomy itself was to increase compliance and reduce resistance. In each experiment we were able to find the expected vagally-mediated change in systemic arterial pressure, confirming the presence of reflex activity secondary to congestion. I inferred from these observations that the changes in lung mechanics brought about by congestion were, in this case, passive and not by reflex.

Because others had found the trachea to undergo reflex contraction typical of smaller airways, I speculated that this may be a more sensitive site from which to detect changes. In a second series of experiments, dogs were once again prepared with cardiopulmonary bypass, but in this group all pulmonary veins were tied at the atrium so that the pulmonary vessels and left heart could be individually pressurized with blood drawn from the external reservoir. Lung ventilation was stopped and an endotracheal tube was passed that had a long compliant cuff. The cuff was inflated to exert a small force on the trachea. Changes in cuff pressure were used to detect changes in tracheal muscle tone. We recorded cuff pressure while pressurizing the left heart and the pulmonary vessels and while imposing different transpulmonary pressures through the endotracheal tube. We found that distension of the left heart consistently caused tracheal contraction. Pulmonary vascular congestion caused contraction in 6 animals but relaxation in 4 others. Lung inflation caused tracheal relaxation in 8 animals but relaxation in 2. Bilateral cervical vagotomy led to tracheal relaxation and loss of changes during lung inflation, vascular congestion, or left heart distension. An example of tracheal contractions with left heart and pulmonary vascular congestion is shown in Figure 11. In this record-
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Figure 11. Variations in pressure in an endotracheal tube cuff caused by lung inflation and deflation and by distension of the left heart chambers or lung vessels. From reference 18, by permission.

Intriguing the same transducer was used to acquire both the left heart (Plh) and the pulmonary vascular (Pves) pressure by switching from one catheter to the other in the interval between the two episodes of pressurization. Tracheal activity, reflected in the tracheal cuff pressure (Pcuff), can also be seen to vary with lung inflation (i) and deflation (d). Small changes in aortic pressure (Pao) are also apparent.

Unlike the first study, the second provided evidence in support of reflex increase in airway tone consequent to left heart or lung vascular distension. However, we also saw evidence of reflex airway relaxation with lung congestion. This should come as no surprise because congestion has been documented to cause stimulation of each of the several afferent receptor types in the lung. Typically, stimulation of slowly adapting receptors leads to airway relaxation, whereas rapidly adapting receptor or C-fiber ending stimulation results in bronchoconstriction. Note that lung inflation, which also stimulates each receptor group, had a similar divergent effect among the experiments, although the dominant effect seemed to be that attributable to slowly adapting receptors. The appearance of reflex effects of congestion on airways that were apparently dominated by slowly adapting receptors was reminiscent of the effect of congestion on breathing frequency.

Epilogue

It has been my pleasure for over more than 30 years to explore the lung circulation, lung mechanics, lung-heart interactions, and the control of breathing. Whereas some have preferred to focus more narrowly and to greater depth, I have found satisfaction in covering a range of topics in lung physiology. I am somewhat concerned that a narrow path is treads at some peril, at least to one’s students, who may not appreciate the whole from a few of its parts. The whole is too fascinating to let pass by.

Looking back over my experiences, I see the lung circulation as a largely passive system, albeit with complicated physical properties, whose most prominent active regulation comes in response to regional oxygen composition. The lung vessels seem able to play an interesting but as yet uncertain role as the afferent site in several reflexes. None of the above is without controversy, and I am left with more questions than when I began. Looking forward to other topics of personal interest, I see the prospect for demonstrations of control of vascular smooth muscle by a wide range of local and circulating compounds, the regulations of which remain to be explored. I also envision greater interest in an immense vascular surface area that exchanges more with blood than just the respiratory gases and that must be understood in those terms. I look forward to better understanding lung microvascular mechanics and the rheology of pulmonary blood flow, topics about which our knowledge is sketchy and which are in urgent need of further study.

The universe, at least this little part of it, is still expanding.
References