Reports of Scientific Meetings

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Airway Dynamics

A Conference on Airway Dynamics was held at Haverford College, Pennsylvania, on August 22 and 23, 1968, as one of the satellite symposia of the Twenty-fourth International Congress of Physiological Sciences.

The principal topics for discussion in the sessions on physical and physiologic characteristics of airways were pressure–flow–volume relationships in the central and peripheral airways. Participants in the discussion included T. A. Wilson (Minneapolis, Minnesota), M. J. Jaeger (Fribourg, Switzerland), P. T. Macklem (Montreal, Canada), R. E. Hyatt (Rochester, Minnesota) and K. P. van de Woestijne (Leuven, Belgium).

Airway resistance can be divided into peripheral and central resistances (R_p and R_c). With a retrograde catheter airway resistance can be studied in up to 10–15 generations of bifurcations within the airways in experimental animals (dogs), as well as in man. The main constituent of airway resistance (R_{aw}) in normal individuals is found in the upper airways between the mouth and major bronchi. Flow resistance in peripheral airways in adults is very small because the total cross-sectional area increases so markedly peripherally. In the presence of high lung volumes (60–80 per cent VC) R_{aw} is low and the contribution of R_p to total lung resistance (R_L) is small. With low lung volumes (25–50 per cent VC), however, airway resistance in relatively small airways (3–8 mm in diameter) constitutes a fairly large proportion of R_L.

In young children, particularly infants, R_p is high and represents a greater proportion of R_L than in adults. The R_p/R_L ratio sharply decreases during growth until the age of 5–6 years, when it reaches the adult level of 5–15 per cent. This agrees with the anatomic fact that in young children peripheral airways are smaller in number and continue to proliferate until 5–8 years of age, when the development of lung tissue is completed. Thus, narrowing of peripheral airways in infants would be expected to produce a proportionately greater increase in airway resistance than it does in adults. This has been found to be the case in infants with severe airway obstruction due to bronchiolitis. In adults, on the other hand, R_p is small and narrowing of peripheral airways may produce only mild airway obstruction.

Airways are under influences of sympathetic and vagal effects which counteract each other. Vagotomy increases lung compliance (C_L) and decreases R_{aw}. Vagal stimulation and sympathectomy increase R_{aw} and thus increase R_L. Propranolol specifically increase R_p but not R_c. The pressure–diameter relationship of the airway is also influenced by vagal stimulation and inhibition (atropine). Changes in the tension of the airway wall, as well as changes in airway volume (the latter constitutes as much as 25–50 per cent of the total lung volume) also influence C_L.

The measurement of dynamic lung compliance (C_{dyn}) is one good indicator of R_L. Normally, C_{dyn} is independent of respiratory frequency. However, in certain pathologic conditions such as bronchitis and bronchial asthma, as well as following injection of propranolol, C_{dyn} becomes frequency-dependent, indicating an increase in R_p.

During forced expiration dynamic compression of airways takes place downstream from the point where airway pressure equals the pleural pressure (equal pressure point). In the presence of lung volumes below 60–70 per cent VC this dynamic compression during forced expiration limits airflow, airflow then becoming independent of the degree of respiratory effort. In higher lung volumes the limiting factor in determining airflow is muscle strength, rather than dynamic compression. In

children dynamic airway compression takes place at much higher lung volumes than in adults. The equal pressure point is closer to the mouth and tends to move upstream as the lung volume decreases.

During inspiration the diameters of the airways are fixed, with a relatively low transmural pressure (4–6 cm H_2O), and additional pressure does not produce further increase in the diameter. This is true regardless of the location of bronchi or bronchioli in relation to the hilus and periphery. Expansion of the lungs with further increase in transmural pressure is associated with elongation of airways. Thus there is a disparity between pressure–diameter and pressure–length relationships of airways. This means that after a certain transmural pressure is achieved, the application of some additional pressure results in force being applied to the wall of the airways (stress magnification). This may be responsible for some of the pulmonary pathology after prolonged IPPB treatment.

H. Bachofen (Berne, Switzerland) reported analysis of lung tissue resistance (R_{lt}) which is the difference between the total lung resistance (R_L) and airway resistance R_{aw}: $R_{lt} = R_L - R_{aw}$. R_{lt} is often referred to as tissue viscous resistance, and the inertial frictional force from viscous deformation has been considered to be its primary source. Bachofen's study showed that R_{lt} is volume-dependent but not flow-dependent, indicating that the viscous property of lung tissue is unlikely to be the major factor. The non-flow-resistive retarded elastic response of the lung seems to be important. Mechanical properties of the lung may no longer be considered to be composed of pure viscous and pure elastic factors under either static or dynamic conditions.

J. A. Nadel (San Francisco, California) reported on x-ray visualization of airways using tantalum powder. Tantalum is chemically inert and does not cause undesirable effects on lung compliance, resistance or blood gases. Approximately 0.5 to 1.0 ml of powder (2–4 microns in size) when inhaled in five to six ventilations produces excellent visualization of airways. Clearance takes 12–24 hours. Using this technique constriction of trachea and major bronchi with double folding and constriction of the lower airways have been demonstrated during vagal stimulation, changes which were abolished by inflation of the lungs with a high inflating pressure. This radiologic technique appears quite benign and has considerable potential in research on airway dynamics as well as in clinical studies.

In the session on the pharmacology of airways, A. P. Somlyo (Philadelphia, Pennsylvania) reviewed his recent studies demonstrating that the mechanism by which contraction of striated muscle is produced (a sliding movement of the thin actin and thick myosin filaments relative to each other) is similar in smooth muscles. However, striated muscle function exclusively with a cholinergic effector mechanism, while smooth muscles can be activated by a variety of endogenous and exogenous agents. Responsiveness of smooth muscles to a specific amine or peptide depends on the presence of relatively specific receptors and their arrangement. Interaction of a drug with a receptor, therefore, may lead to contraction or relaxation in different, or even in the same types of smooth muscles. In the case of neurohypophyseal peptides the inhibitory and excitatory effects are mediated by the same receptors, the difference in response being determined by the different secondary messengers released. Cholinergic receptors mediating inhibition (vasodilation) and excitation (constriction) may also be identical, since both effects are blocked by atropine. Relaxation of vascular smooth muscles by acetylcholine is associated with hyperpolarization of membrane and a decrease in spike electrogenesis. Excitation of similar vascular smooth muscles by acetylcholine, on the other hand, is associated with depolarization of membrane and an increase in spike electrogenesis. This difference in response may be due to the difference in ionic equilibrium potentials of various smooth muscles. Variable distributions of receptors within the smooth muscle of homogeneous regions in different species is manifested by the species-specificity of pharmacologic responses. A different regional distribution of receptors within the same species leads to organ specificity and occasionally to radial or axial pharmacologic responsiveness within the same organ or blood vessels.

The contractile response of smooth muscles to drugs can occur in the absence of depolarization and action potential. This effect, pharmacomechanical coupling, operates in polarized as well as in depolarized smooth muscles. The molecular mechanism of pharmacomechanical coupling is not clear, but may be due to the release of calcium ions from a compartment unaffected by depolarization. Certain excitatory drugs may have a secondary relaxant effect which inhibits the maximal contractile response. This mechanism, autoinhibition, is seen in the vascular effects of certain adrenergic agents where the excitatory (α-adrenergic) effects are partially counteracted by inhibitory (β-adrenergic) effects. The degree of inhibition depends on the α/β potency ratio of a given amine and the α/β receptor ratio of a given smooth muscle.

The mechanical consequence of smooth muscle contraction in a tubular structure such as an airway is stiffening (longitudinal fibers) and constriction (circular fibers). In large airways a 30 per cent decrease in circumference is the maximal amount of constriction which can occur, and closing of the airway does not take place. In smaller airways, however, the lumen can be closed by buckled epithelium.

Histamine plays a significant role in airway constriction in allergic disorders. H. J. H. Colebatch (Sydney, Australia) investigated the histamine effect in conducting airways and terminal airways (alveolar ducts and alveoli) in cat preparations. In the presence of pre-existing airway constriction, the injection of histamine into the pulmonary artery in experimental animals produces a transient decrease in C_{dyn} and a decrease in R_L. When histamine is injected in the aorta, R_L decreases without changes in C_{dyn}. After bilateral adrenalectomy or injection of propranolol, histamine increases R_L. In both intact and vagotomized animals injection of histamine into the right side of the heart or into the aorta decreases C_{dyn} with frequency dependency and increases R_L. These changes are more marked and prolonged after adrenalectomy and are reversible only by injection of epinephrine. These findings indicate that the effect of histamine is influenced by the initial state of airway constriction and that histamine releases an adrenalin-like substance from adrenal glands which counteracts its airway-constrictive effect. Bronchoconstriction is also enhanced by a reflex mediated by the vagal nerve. "Alveolar-duct" constriction seems to occur independently of bronchoconstriction and may be produced by direct contact with circulating histamine in the pulmonary circulation.

In investigations of pressure–flow–volume relationships in humans, A. Bouhuys (New Haven, Connecticut) demonstrated that variable parts of airways responded differently to bronchodilators and constrictors. In asthmatic patients a bronchodilator (isoproterenol) significantly increases total airway conductance, G_{aw} (reciprocal of resistance). Maximum expiratory flow at low lung volume, an index of conductance of the segment upstream from the equal pressure point, also increases. In normal individuals a similar increase in G_{aw} is observed. Interestingly, however, maximum expiratory flow does not change, or even decreases, at lower lung volumes. These findings indicate that isoproterenol dilates large airways and thereby increases total airway conductance. Smaller airways may be dilated, but at the same time become less stiff or even flabby and are subjected to dynamic compression during forced expiration. A bronchoconstrictor such as histamine decreases maximum expiratory flow rate at low lung volumes, indicating constriction of small airways. The large airways are more rigid and their response to a bronchoconstrictor may be less. G_{aw} is, however, decreased only in some subjects by histamine. Similar findings have been observed among hemp and cotton workers who exhibit asthma-like bronchospasm upon dust exposure: some of these patients show decreases in both G_{aw} and maximum expiratory flow rate, while others show only a reduction in maximum expiratory flow rate.

Under normal circumstances serotonin is concentrated within platelets. When platelets are aggregated by thrombin and other agents, serotonin is released into circulation and activated. M. Stein and his associates (Providence, Rhode Island) showed that pulmonary thromboembolism in dogs produced a decrease

in C_{dyn}, an increase in R_L, a widening of A–a P_{CO_2} gradient, and tachypnea. Certain substances known to produce platelet aggregation and serotonin release produced similar changes. Heparinized dogs, for example, are protected from changes in C_{dyn} and R_L following pulmonary embolism. A similar protection is seen in dogs following administration of methysergide (antiserotonin) or glyceryl guaiacolate (a platelet aggregation inhibitor) and in the presence of thrombocytopenia. On the basis of these findings, together with results of electron-microscopic studies of thromboemboli, these authors speculate that the observed changes in pulmonary functions are produced by the direct effect of serotonin on terminal airways. Further studies are needed to see if these findings are applicable in patients with pulmonary embolism, since platelet serotonin contents may be different in dogs and humans.

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Australian Society of Anaesthetists

The Australian Society of Anaesthetists held its annual meeting at the Queen's Lodge Motor Inn, Melbourne, Australia, October 5–9, 1968. One of the highlights of the three-day meeting was a symposium on renal failure and renal transplantation.

Mr. Vernon Marshall, a surgeon from Melbourne, discussed the differential diagnosis and treatment of acute renal failure. He pointed out that oliguria could be pathologic when urinary volume fell to less than 500 ml per 24 hours. This must be differentiated from oliguria resulting from a depletion of the body fluids, leading to renal ischemia. The latter will respond to fluid and electrolyte administration. On the other hand, established intrinsic renal failure, probably due to acute tubular necrosis, will not respond to fluids and electrolytes, which are, in fact, contraindicated and predispose to pulmonary edema. However, since the diagnosis is usually in doubt, a trial fluid load can and must be given for differentiation. Five hundred ml of blood, plasma expander, or electrolyte solution is infused along with mannitol during measurement of central venous pressure. If diuresis does not appear, the diagnosis of acute tubular necrosis is established. Mr. Marshall mentioned, in passing, that he believed mannitol is more than an osmotic diuretic in that it also increases renal blood flow.

In discussing the current therapy of acute renal failure, Mr. Marshall thought more attention should be paid to certain advantages peritoneal dialysis has over the artificial kidney. It is simple, safer, more economic both in cost and in need for constant supervision, and hypotension is no bar to its use. On the other hand, peritoneal dialysis is slower to correct the blood changes of acute renal failure. Mr. Marshall also noted that most institutions have mortality rates of 30 to 40 per cent in acute renal failure. In considering the prophylaxis of acute renal failure in the surgical patient, Mr. Marshall suggested that all patients undergoing major surgical procedures should have the central venous pressure monitored to make certain that the circulating blood volume is within normal limits, and that mannitol should routinely be administered prophylactically.

Dr. Priscilla Kincaid-Smith, an internist from Melbourne, discussed the management of chronic renal failure. She said that the number of patients with chronic renal failure alive at the end of ten years of therapy with either chronic dialysis or renal transplantation is small. Before embarking on more radical therapy, one must be certain that the patient would not recover with conservative treatment. Two conservative methods were discussed: the first was to make certain that the patient did not have salt depletion, often true in patients with polycystic kidneys. These patients do not need renal transplants but should have their salt intake increased and regulated appropriately. The second was dietary manipulation, which Dr. Kincaid-Smith found effective in many patients with high levels of blood urea nitrogen. The basic principles of dietary therapy include restriction of carbohydrate and the use of either of several different newer diuretics to prevent the formation of edema. She has lowered BUN's from levels as high as 400–500 mg down to 80 mg with

this regime. Some patients treated in this manner have gone for as long as 2½ years; the symptoms of uremia have disappeared, and if death did occur it was often due to heart disease rather than to kidney disease. It is essential that blood transfusions be used sparingly in these patients, because they may be followed by oliguria from which the patient does not recover.

If conservative methods fail, resort must be to dialysis or transplant. With chronic dialysis, about 90 per cent of the patients can be treated successfully for the first year, but the success rate diminishes an additional 10 per cent each year thereafter. Patients on chronic dialysis are always anemic and, in the opinion of Doctor Kincaid-Smith, dialysis is too complicated and too expensive. She believes grafting of cadaver kidneys is more promising; so far, she has had approximately 50 per cent success with this therapy. However, one cannot accommodate all patients requiring transplants and many patients must be kept on dialysis. In comparing the availability of renal transplantation in the United Kingdom and in Australia, she noted that the British program is heavily financed, and that although 1,300 patients per year require transplant, only 6 per cent can be so treated. In Australia, on the other hand, the transplantation program is operating on a shoestring budget, with a demand of 300 patients for transplantation each year, one-third of which can be accommodated.

Doctor J. Knight, anesthetist from Melbourne, discussed technical aspects of renal transplantation. He noted that recipients are often unprepared for the procedure and two or three may be brought in to the hospital on an emergency basis when a potential donor becomes available. The patients often do not have the advantage of premedication, and all have been on dialysis so that their veins are in poor condition. Most of the patients are hypotensive as well as anemic and hyponatremic, and all have clotting defects. The latter can be overcome by the use of fresh blood and fresh frozen plasma. If the recipient has been dialyzed recently, he may be dehydrated. All of the recipients have vascular shunts in place which they are very protective of. All are apprehensive, as well as usually cold and with marked vasoconstriction. The surgical problems of transplantation include removal of the kidney from the donor with a sufficient segment of the ureter and vessels intact. If adequate segments are not obtained, the transplantation usually is a failure. Technically speaking, the operation is a straightforward vascular anastomosis. Often clotting defects lead to excessive bleeding during or following operation, with the infection which then so frequently follows resulting in failure of the grafted kidney to function. While Dr. Knight thought that this was the most common cause of failure of the operation, some from the audience disagreed and believed that immunologic problems leading to rejection of the transplanted kidney constitute the most frequent cause for failure. It has also been found that if the donor has been well hydrated at the time of death, renal ischemia, which otherwise may preclude a successful transplantation, may be avoided. If the kidney wasn't secreting before death of the donor, it won't secrete after transplantation.

The anesthetic technique recommended is basically nitrous oxide–curare. Extracellular fluid deficits in the recipient should be made up with Ringer's lactate solution and a sufficient quantity of fresh blood must be available—up to 6 liters. Two intravenous infusions should be available, one for the electrolyte solution, the other for blood utilizing a blood warmer. A pulmonary ventilator is invaluable to keep hands free for monitoring and regulation of infusions. Dr. Knight monitors the pulse with a finger monitor because he believes that if there is a good pulse there, then there is probably a good pulse everywhere. Pethidine (Demerol) or morphine is used to control pain and to suppress output of antidiuretic hormone. Blood *p*H is monitored and sodium bicarbonate used to reverse acidosis. *d*-Tubocurarine is preferred as the relaxant, and no problems have appeared with reversal at the end of the procedure. Dr. Knight has upon occasion failed to be able to reverse gallamine. Mannitol is injected intravenously after the completion of the venous and before completion of the arterial anastomosis. As soon as the clamps are removed

from the anastomosed vessels, 200 mg of hydrocortisone are given.

Complications encountered include hypotension due to extensive oozing of blood and failure of adequate replacement. The anesthetist must be cautioned against the use of vasoconstrictors, since an untoward response is often seen. Hypothermia is another common complication, usually resulting from the large incision and failure to keep the patient adequately warm.

Mr. Peter Morris, a surgeon from Melbourne, discussed immunologic aspects of transplantation. A cadaver kidney seldom survives more than five years. The cause of the death of the kidney is usually a cellular immuno-response, although a humoral response is not to be discounted. Nine patients subjected to second renal transplants were studied, all of whom had demonstrated cytotoxic antibodies. In three of these there was hyperacute rejection; four of the kidneys failed within one to six months, and an additional one failed in eight months. Mr. Morris noted that all patients who had had a cardiac transplantation were showing evidence of rejection. Patients develop antibodies against leukocytes through transfusions, pregnancies, skin grafting and the like. Leukocytes can be typed; if the projected recipient and donor have their leukocytes typed and evidence of rejection by the recipient appears, the chances of organ rejection are better than 85 per cent. Immunosuppression can be accomplished to some extent with azothioprine or corticosteroids. Antilymphocyte suppression has been tried in 80 patients, but the results are equivocal. Mr. Morris predicts that by 1975 all donors and recipients will first be subjected to tissue typing; there will be long-term storage of organs to be transplanted, there will be better immunosuppressive techniques, there will be international shipping of organs for transplantation, and the transplantation of animal organs into the human being will be established.

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Drugs

SUBCUTANEOUS HEPARIN Prolonged treatment with subcutaneous calcium heparinate is superior to treatment with dicumarol derivatives. With dicumarol derivatives, the mortality rate due to pulmonary embolus was 2.2 per cent in 1,000 patients, whereas in 500 patients treated with calcium heparinate it was only 0.6 per cent. Calcium heparinate is injected into the iliac fossa by means of a graduated tuberculin syringe with an intradermal needle. The starting dosage is 0.1 ml/10 kg. A biologic test for clotting (Howell's test) is performed after six hours. If clotting is prolonged by 1.5 to 2 times, the starting dosage is maintained. Otherwise the dosage is raised or lowered accordingly. The injections are administered every 12 hours. The biological tests (Howell's and Quick's) are performed twice weekly for the first two weeks and weekly thereafter. Subcutaneous nodules at the injection site can be avoided if the injections are administered perpendicularly and not tangentially. Hemorrhage may occur spontaneously or following trauma. Hematomas of the abdominal wall were common, but internal bleeding occurred very rarely. Epistaxis following insertion of a nasogastric tube may necessitate a temporary decrease in the subcutaneous heparin injections. Hematuria occurred once following bladder catheterization and on another occasion revealed the presence of a bladder stone. Accidental overdosage of heparin may be treated quickly with protamine sulfate. (*Amstutz, P., Szekely, A. M., and Pocidalo, J. J.: Les Traitements Anticoagulants Prolonges Par L'Heparine Sous-Cutanee, Anesth. Analg. 30: 203 (March) 1968.*)