TREATMENT OF CARDIORESPIRATORY FAILURE IN THE ELDERLY

F. Rengo, D. Bonaduce, N. Ferrara, V. Canonico,
M. Petretta, P. Abete, C. Vigorito and C. Rengo

Department of Gerontology and Geriatrics
Faculty of Medicine and Surgery
University of Napoli, Italy

INTRODUCTION

A rational approach to the treatment of cardio-respiratory insufficiency must take into account a detailed knowledge of the physiological mechanism underlying chronic cor pulmonale and of the clinical conditions most frequently associated with its acute deterioration.

From a nosographic point of view, it has not been still clearly established whether or not the definition of cardiorespiratory insufficiency should be applied to all patients with associated cardiac and respiratory insufficiency, undependently from temporal sequence or clinical relevance of one of these over the other.

The definition of "cardiorespiratory insufficiency" was also proposed by L. Condorelli about 30 years ago [1] as an alternative to "chronic cor pulmonale" (CCP) defined later by the expert Committee of the W.H.O. as "right ventricular hypertrophy provoked by diseases altering lung function or structure with the exception of congenital heart disease and of those pulmonary abnormalities secondary to pathologic events primarily localized in the left heart". [2]

In this present review we will reserve the definition of cardio-respiratory insufficiency to those acute or subacute clinical pictures characterized by significant anatomic and functional lung impairment with severe respiratory failure and secondary development of cardiac insufficiency. With the exception of severe acute infective and thromboembolic processes and of adult

G. Barbagallo-Sangiorgi et al. (eds.), *Aging and Drug Therapy*

respiratory distress syndrome (ARDS) certainly the "reacutization of CCP", gives the largest contribution to this entity.

CCP is a disease with a high degree of social relevance due to its common occurrence and high mortality and morbity rates. The terminal event is usually represented by a sudden exacerbation of the disease, which terminates a natural history characterized by alternating periods of improvement and deterioration particularly present in advanced decades.

Several diseases may lead to CCP, however, particular clinical and social relevance have diseases primarily compromising air transit to and from alveoli. Particularly important is chronic obstructive airways disease (COAD), an entity with clinical spectrum ranging from panacinous pulmonary emphysema to chronic bronchitis, in which a major role is played, particularly in the asthmatic variety, by the bronchospasm.

Social relevance of COAD can be appreciated by the official mortality tables for 100,000 inhabitants published by the WHO (Europe), based on data obtained in the years 1974/75 from Italian Public Social Service.[3]

The gradual clinical course of CCP can change to a dramatic rapid evolution, as for instance when an acute bronchopulmonary infection complicates the natural history of the disease. In this case there is a sudden worsening of respiratory insufficiency, frequently followed by the development of overt cardiocirculatory failure ("reacutization" of CCP).

This condition can lead to death, or, when treated adequately, can regress to the original clinical state; the reversibility of this syndrome indicates the prevalence in this condition of reversible functional over irreversible anatomic factors.

The reacutization of CCP may have two clinical forms that differ in the time required to develop hypercapnic coma, and are influenced by different therapeutic interventions.

THERAPY OF CARDIO-RESPIRATORY FAILURE

The fundamental aims of therapy cardio-respiratory failure are:[4] prompt removal of hypoxia and hypercapnia by improvement of alveolar ventilation; normalization of acid-base balance; improvement of cardiac performance; improvement of respiratory surface; removal of associated infections; reduction of bronchial obstruction and of the alveolar membrane thickness; reduction of polycythaemia and normalization of the blood viscosity.

TREATMENT OF HYPOXIA AND HYPERCAPNIA

The most important therapeutic measures are represented by oxygen administration, mechanically assisted ventilation, and drugs stimulating the respiratory centres. The treatment of hypoxaemia, which should be imperative whenever arterial pO_2 falls below 50 mmHg, reduces hypoxia induced tissue damage which favours interstitial pulmonary oedema with consequent additional impairment of alveolar capillary diffusion of respiratory gases.[5]

Furthermore, it abolishes pulmonary arteriolar vasoconstriction, improves the metabolic function of important organs such as kidney and brain and allows a good clinical response to cardiac glycosides.

a) Oxygen Therapy

While everybody agrees that O_2 inhalation is a fundamental step in the therapy of cardio-respiratory failure, several controversies exist on its modalities of application. It is well known that pCO_2 levels in the blood tend to rise during O_2 therapy, proportionally to the rise of arterial HbO_2 level.

The rise in pCO_2, whose principal clinical manifestation is progressive drowsiness up to hypercapnic coma, is secondary to many factors: 1) worsening of alveolar hypoventilation due to the decrease of hypoxia-induced stimulation of respiratory centres, which are chronically depressed in the hypercapnic state; 2) impairment of ventilation/perfusion ratio due to reduction of pulmonary arterial vasoconstriction in poorly ventilated alveoli; 3) increased CO_2 production from stimulation of aerobic metabolism. For these reasons, O_2 should be administered at low flow (about 1 lt/min). The aim of this approach is to keep arterial pO_2 within values largely lower than normal (about 60 mmHg), thus maintaining the hypoxia induced stimulation on ventilation.[6]

With the nasal cannula advanced into the pharynx, it is possible to reach very high alveolar O_2 percentage concentration (30-50%), even higher than those obtained with oxygen tent. However, the rise of arterial pO_2 beyond 80 mmHg would only increase the risk of alveolar hypoventilation and of hypercapnic coma with only a slight additional improvement of O_2 availability to tissues, due to the peculiarity of the Hb-O dissociation curve. O_2 administration at high flow could also carry the risk of ARDS. Recently there has been introduced in clinical practice "home O_2 concentration device" and "O_2 bottles for continuous low flow O_2 administration".

b) Central Stimulating Drugs

These drugs are mainly indicated when alveolar hypoventilation is secondary at least in part, to a depression of respiratory centres

by drugs or hypercapnia, particularly in the course of O_2 therapy. Among these drugs, the bulbar analeptics are able to increase the sensitivity of respiratory centres and, in some cases (i.e. Lobeline) also of peripheral chemoreceptors, thus increasing the respiratory work, global and alveolar ventilation, and improving gas exchange.

In this family of agents, the most largely employed are Prectmamide, Dimefline, Metamivan, Mepixanton, Doxapran etc. In cardio-respiratory failure one or two of these drugs in association are usually administered by i.v. infusion, diluted in 150-250 ml of 5-10 per cent physiologic saline solution, starting with slow infusion rate which is gradually increased until a favourable clinical response or toxicity is observed. Signs of toxicity are: systemic hypertension, bradycardia, nausea and vomiting, due to the stimulating effect of these drugs not only on respiratory centres, but also on bulbar vasomotor and vagal centres. The therapeutic index is very low, and doses of these drugs slightly higher than those necessary to stimulate depressed respiratory centres are able to induce generalized tonico-clonic convulsions and hyperpyrexia. At high doses, malignant hyperkinetic ventricular arrhythmias have also been observed. These drugs should be avoided when diffuse trachiobronchial obstruction or severe impairment of thoracic mechanics due to neuro-muscular diseases prevent the increase of alveolar ventilation; in these patients the stimulation of respiratory centres would only unnecessarily increase the respiratory work.

A very useful drug in the treatment of cardio-respiratory insufficiency, especially in very acute forms, is aminophylline a soluble ethylendiaminic esther of theophylline.[8]

This drug possesses several modalities of action: a) improves the rate and depth of ventilation with a better therapeutic index than other drugs stimulating respiration centres; b) reduces pulmonary arterial pressure by pulmonary arterial vasodilatation; c) has a relaxant effect of bronchial smooth muscle, thus increasing alveolar ventilation.

The frequent disappearance of Cheyne-Stokes respiration with aminophylline seems rather due to the properties of ethylendeamine. Aminophylline should be administered by i.v. infusion diluted in 5 per cent glucose or physiologic saline,the starting infusion rate is usually 6 mg/Kg i.v. in 15 - 20 min. thereafter 1 mg/Kg/h without exceeding 1,5-2 g in 24/h. Plasma blood levels of the drug should be kept between 10 and 20 µ/ml.

c) Mechanical Ventilation

When an intense pharmacological intervention with central stimulating drugs does not succeed in improving alveolar ventilation

and in reducing hypoxaemia, or when hypercapnic coma is impending, it is imperative to start the patient on assisted pulmonary ventilation.[9]

This can be performed with positive or negative pressure, maintaining in either case, continuously or intermittently by a pressure gradient between the pleural cavity and room air. From a practical standpoint, there are two fundamental forms of assisted ventilation, the pressure controlled and the volume controlled ventilation.

In the pressure controlled ventilation, which requires some patient co-operation, the inspiratory flow is triggered by a depression in the system provoked by a spontaneous inspiratory act. This causes a valve opening with consequent respiratory flow at positive pressure, which terminates when pressure in the patient's airways reaches a pre-determined value, usually lower than 30 cm of H_2O.

These systems can allow the patient a spontaneous expiratory phase with or without a negative pressure. Some authors suggest to program, in the course of expiration, progressively increasing resistance (PEEP) or a continuous intrapulmonary positive pressure (CIPP),[10] in order to perform a more complete alveolar distention. With this type of assisted ventilation it is possible to measure the tidal volume and to administer room air or air mixture with 40 per cent O_2. Each course of assisted ventilation should last between 20 and 40 min. and should be repeated several times a day, with frequent determination of arterial blood gases. Pressure controlled ventilation is not indicated in patients with low pulmonary compliance, since in these patients it is very difficult to achieve a satisfactory tidal volume. In these patients, or when the patient is unconscious, it is preferable to adopt a volume controlled assisted ventilation, which allows a pre-established volume of air, or O_2 enriched mixtures, to be administered independently from developed pressure.

In this case, patients should be intubated and one should predetermine respiratory cycle duration and rate, trying to synchronize the activity of the mechanical device with the patient's spontaneous respiration. When this is difficult, drugs stimulating respiratory centres should be discontinued and a short period of 100 per cent O_2 breathing or sedative drugs (morphine, diazepam, barbiturates, meperidine) to depress patient's spontaneous ventilation must be given. It is also important to program the ratio between inspiratory and expiratory time (I/E ratio). The ideal ratio of 1:2 can be changed to 1:4 in patients with COAD; these patients may also benefit from 1:6 ratio. Since PEEP reduces venous return to the heart, it has been suggested that these patients should be monitored by right heart catheterization with determination of right heart

pressures and cardiac output. All patients undergoing assisted mechanical ventilation are at risk of the so called "riventilation syndrome".[11] This syndrome, whose main clinical expression is cardiocirculatory collapse, is due to the sudden reduction of arterial pCO_2 with a much slower fall of previously accumulated HCO_3^-, with a consequent metabolic alkalosis, always associated with hypochloraemia. The analysis of arterial blood gases will show an elevated pH, elevated standard HCO_3^- and a total HCO_3^- more or less elevated than standard HCO- according to the values of pCO_2. The treatment of this condition consists of i.v. administration of KCL and NH_4Cl solutions until normal values of serum Cl- ions (100-105 mEq/l) are reached. The preventive administration of small doses of these solutions has been also suggested by some authors in patients with ventilatory insufficiency, since they induce a noticeable improvement of ventilation and reduce hypoxaemia and hypercapnia, despite a transient and mild worsening of acidosis.[12]

d) Bronchodilators

Before discussing bronchodilator drugs a short comment should be made on the regulation of bronchial smooth muscle tone. The nervous regulation of bronchial smooth muscle cell is predominantly under parasympathetic drive, while svmpathetic fibres are scarcely and irregularly distributed. The bronchial smooth muscle cell possesses however beside stimulating parasympathetic receptors for acetylcholine, stimulating alpha-adrenergic receptors and inhibiting beta adrenergic receptors.[13]

These latter seem to have considerable density or sensitivity to circulating catecholamines and to adrenergic drugs, and can be probably identified with the enzyme adenilate-cyclase;[14] the activation of this enzyme leads to the production of cyclic AMP, responsible for the relaxation of bronchial smooth muscle cell. The action of cyclic-AMP is balanced by that of cyclic GMP and vice versa; both nucleotides are metabolized by the enzyme phosphodiesterase. Beside cholinergic and alpha adrenergic stimulation, the contraction of bronchial smooth muslce cells can also be induced by other substances such as histamine, serotonin, SRSA and leukotrienes released locally or systemically in several patho-physiologic conditions. These substances can act directly or through the synthesis, in the (bronchial) tissues, of arachidonic acid metabolites, such as cyclic endoperoxides, thromboxane A_2 (TXA_2) and prostaglandin PGF_2-α.[15]

From the above, it is evident that a bronchodilatation can be obtained, by drugs influencing the neurovegetative regulation of bronchomotor tone, by drugs inhibiting the liberation of chemical mediator- of bronchspasm or by drugs which are competitive or functional antagonists of these mediators.

Among drugs which antagonize the enzyme phospodiesterase, we have already discussed aminophylline. Ephedrine, another drug in the past widely employed in the treatment of bronchospasm has the advantages of a long duration of action and effectiveness by oral route. This drug acts through the liberation of catecholamines from storage sites and through the potentiation of intensity and duration of action of endogenous or exogenous catecholamines, although this mechanism is still unclear and quantitatively less important.[16]

The therapy of bronchospasm is mostly based on drugs directly stimulating beta-adrenergic receptors. The utilization of these drugs, which has received large theoretical recognition, has been limited in clinical practice by adverse secondary cardiovascular effects represented by tachycardia, increase of myocardial work and O_2 consumption and serious cardiac arrhythmias. Since the demonstration of 2 types of beta-adrenergic receptors, beta and beta , the former mainly present in the myocardium, the latter in the bronchial smooth muscle, a new class of therapeutic agents has been introduced, the so called beta stimulating drugs[17] with variable but high ratio of beta$_2$/beta$_1$ receptor stimulating activity. Some of these drugs have not been introduced in clinical practice due to their unfavourable pharmaco-kinetic or toxic properties, while others, such as metaproterenol, fenoterol, trimetochinol, salbutamol, terbutalin, reproterol and carbuterol, are nowadays available commercially and can be administered by oral or parental route, or by aerosol; it is likely that the number of these drugs will increase with the discovery of new similar molecules. In addition the proper adoption of pressurized aerosols with a pre-established single dose has contributed to a reduction of collateral effects, since it permits a topical administration, thus minimizing systemic effects and reducing the risk of overdosage. The efficacy of treatment is maximized by a correct modality of aerosol administration, which should coincide with a slow and maximal inspiration at the end of a complete expiratory act, and be followed by a brief period of post-inspiratory apnea terminated by a slow expiration. However, due to the unhomogeneous alveolar ventilation and to the dead space the drug preferentially diffuses in the most ventilated alveoli; in addition the administration of these drugs by aerosol cannot be utilized in the most serious forms of cardio-respiratory failure. In these patients, broncho-dilator drugs with the best beta$_2$/beta$_1$ activity ratio, such as salbutamol, can be administered by i.m. injection or by slow i.v. infusion. The clinical usefulness of alpha-adrenergic blocking drugs such as inderamine, phentolamine or timoxamine, is only theoretical, due to the prevalence of cholinergic and beta-adrenergic receptors in bronchial walls. Experimentally demonstrated favourable effects of these drugs might be explained by the alpha adrenergic mediated inhibition of purinergic bronchodilatation. Alpha blockers might inhibit the alpha stimulated reduction, through

activation of the enzyme ATP ase, of the amount of ATP available for purinergic transmission; and also inhibit the release, mediated by calcium-dependent ATPase, of chemical mediator of bronchospasm from the mast-cells.[18]

Anticholinergic drugs have well known disadvantages in the therapy of bronchospasm, because of their untoward secondary effects. Two atropine derivatives active by aerosol, ipratropium, an isopropil substitute of atropine, and ossitropium bromide, seem to have overcome these side effects because of a selective effect on bronchial smooth muscle. These drugs have several mechanisms of action: 1) blockade of muscarinic receptors, with reduced formation of cyclic-GMP, both within bronchial smooth muscle, with secondary bronchodilation, and within mast-cells, with reduced release of chemical mediators of bronchospasm; 2) reduced accumulation of arachidonic acid metabolites, particularly $PGF_{2\alpha}$ and TXA_2. The latter is the most powerful constricting agent of bronchial and vascular smooth muscle presently known.

Glucocorticoid drugs can also be clinically useful in the treatment of cardio-respiratory failure due to their antiphlogistic and bronchodilatating activity.

The antiphlogistic effect is responsible for the reduction of bronchial and interstitial pulmonary oedema with consequent improvement of gas diffusion through the alveolar capillary membranes.

The antiphlogistic effects possessed by glucocorticoids are due to the stabilization of lysosomial membranes, and to the inhibition of leucocytes and mast cells migration. This last effect is, however, potentially unfavourable in patients with infection unless possible complications are prevented bv antibiotic treatment. The glucocorticoid-induced bronchodilatation is mediated by several mechanisms that finally are responible of a potentiation of the catecholamine induced cyclic-AMP production. Glucocorticoids can be administered topically by inhalation, alone or in combination with beta-adrenergic drugs; in the less severe forms of the disease, beclomethasone dipropionate or desamethazone isonicotinate should be preferentially used. Collateral effects with this modality of administration can be represented by dysphonia and oro-pharyngeal candidiasis, which can be treated with topical alkaline solutions containing nystatine. In the most severely compromised patients, i.v. route and steroids with higher antiphlogistic/sodium retentive effect ratio should be preferred, such as prednisone or methyl-prednisolone, since these patients often have a clinically manifest or inapparent retention of salt and water. Other bronchodilator drugs such as disodiocromoglicate, tiaramide, chlorpheniramine, ciproeptadine chlorydrate are preferentially indicated in the chronic stage of COAD rather than in the acute phase of the disease, although they are occasionally useful. Administration by aerosol

route of prostaglandins PGE_1 and PGE_2, of prostacycline PGI and derivatives is still experimental, even though their vasodilator pulmonary effect, by improvine alveolar ventilation without impairment of ventilation/perfusion ratio offers favourable clinical results.

e) Fluidificant and Mucolytic Drugs

These drugs are another fundamental aid in the therapy of cardio-respiratory failure. They are useful for removing viscous bronchial secretions, which contribute to the beginning and maintenance of bacterial infections, reduce the airways lumen and favour bronchial phlogistic processes.

Both quantitative and qualitative abnormalities of bronchial secretions are important factors in sustaining reactive bronchospasm and in impairing muco-ciliar clearance.

Acetylcysteine, a direct mucolytic agent, has still a major role in the treatment of bronchial hypersecretion. The main action of this drug is the disruption of disulphur links of mucoproteins, but it also improves muco-ciliary clearance, reduces the viscosity of secretions and has some antibacterial activity probably through competitive inhibition of cysteine utilization. This drug can be administered by aerosol inhalation or endobronchial instillation, by oral or i.m. injection, with a less immediate effect, and is generally well tolerated.

The drugs with an indirect mucolytic action are not mucolytic in vitro, but interfere with the metabolic processes of the mucus producing cells, possibly through metabolites reaching the airways by the blood. Widely used is bromexine, a benzylaminic derivative of vasicin, an alkaloid extracted from Adathoda vasica, which acts through the decomposition of muco-polysaccarides the activation of lysosomial enzymes of bronchial glands and a modification of carbohydrate metabolism, leading to an incomplete or abnormal synthesis of mucopolysaccarides, can be administered orally by aerosol or by the parenteral route and is well tolerated, with only sporadic reports of mild gastric distress when administered orally. Carboxymethylcysteine can only be given by oral administration, is only active on mucus secretion and has a still unclear mechanism of action, however it is effective and devoid of important side effects. Iodine compounds possess some direct in vitro mucolytic effects, particularly on mucopurulent secretions; however, their main mechanism of action is indirect and are often poorly tolerated.

Sobrerol is the most important of the detergent or tensio/active agents; it has the limitation of being active only on mucus secretions. It can be administered orally, by aerosol, by i.m. injection or rectally, and is usually well tolerated. Other drugs

effective in bronchial hypersecretive states, although not useful in emergencies, are guaifenesin, guacetisal, ipecacuana, and sodium, ammonium and potassium salts, these latter usually given in association with other drugs.

It should be stressed that adequate and cautious hydration, orally or parenterally, is a fundamental part of the mucolytic therapy.

Postural drainage and other physiokinetic therapies are very important in the rehabilitation of patients with chronic obstructive lung disease, but, since these manoeuvres require patient co-operation, they are usually reserved only for patients improving from the acute phase of cardio-respiratory failure. Furthermore it should be remembered that the injudicious use of fluidificant and mucolytic drugs can inadvertently induce particularly in comatose patients or when cough depressant drugs are associated, a massive inundation by the liquefied bronchial secretions, with sudden development of respiratory failure. In this event a prompt endobronchial aspiration is mandatory.

f) The Correction of Acid-base and Electrolyte Abnormalities

This is another fundamental aspect of the treatment of cardio-respiratory failure. Therapy should be monitored by frequent determination arterial blood gases, serum electrolytes total bicarbonates (TB), standard bicarbonates (SB), and excess of deficient base values (positive or negative BE).[20] The most common abnormality of acid base balance in patients with cardio-respiratory failure, is respiratory acidosis, compensated or not compensated. This condition is characterized by a reduced or normal pH, elevated arterial pCO_2, elevated TB, SB normal or increased, according to renal compensation, with TB always higher than SB.

Therapy in these patients should be addressed toward the improvement of respiratory failure. Alkaline solutions should be reserved for patients with more severe acidosis, progressive hypoxaemia or signs of impending renal failure.

Small amounts of isotonic (1/6 molar) sodium bicarbonate solution, containing about 170 mEq/l of anions and equivalent sodium amounts should be administered. In some patients, a metabolic acidosis is superimposed on the respiratory acidosis; in these cases TB are reduced, but always higher than SB because of hypercapnia, and lactic acid levels are increased over the normal range of 1.2 mEq/l. In these patients alkaline solutions are indicated such as 1/6M bicarbonate or lactate, with the aim of keeping TB levels above 18 mEq/l.

From a practical standpoint, the following formula can be used to calculate the amount of bicarbonate to be administered: BE x 0.3 x kg. only 1/2 of the value obtained in this fashion is usually given in the first 24 hours; the remaining amount should be administered according to the results of blood gas and analytic determinations. In these patients the diuretic of choice is ethacrynic acid, which is more effective than other diuretics in patients with acidosis. When a powerful and rapid effect is required in patients with respiratory acidosis, THAM or 8.4 per cent sodium bicarbonate solutions containing 1 mEq of HCO_3^-/ml should be used. However, careful attention should be given to avoid post-hypercapnic metabolic alkalosis, usually a consequence of an incongruous therapeutic regime and often not recognized by clinicians, who focus their attention on the treatment of acidosis. This condition usually intervenes when arterial pCO_2 levels tend to normalize, but HCO_3^- values are still elevated, because of the slow kidney compensatory mechanism and of excessive administration alkaline solutions or alkalinizing diuretics. These latter drugs can favour metabolic alkalosis also by the production of hypo-kalaemia or hypochloraemia.

Post-hypercapnic metabolic alkalosis is characterized by normal or elevated pH, elevated SB, TB more elevated than SB because of hypercapnia, and frequently by hypochloraemia and hypo-kalaemia. The therapy in this condition consists first of all in the removal of the determining causes. In addition, chloride deficiency should be corrected by NH_4Cl or lysine monochloride administration with the aim of raising chloride plasma levels not above 95 mEq/l.

In the correction of metabolic alkalosis the diuretic of choice is acetazolamide which favours the loss of HCO- at the level of renal tubules, through the inhibition of the enzyme carbonic anhydrase. However, this drug also increases renal elimination of potassium ion, by reducing the availability of hydrogen ion to be exchanged with sodium at the level of the distal tubules. Potassium deficit can be corrected by KCl solutions, but this therapy should be conducted cautiously, because the physiological extracellular concentration of K^+ is very small, and because hypokalaemia can mask high K^+ intracellular concentrations; in this case severe complications may arise when acidosis is corrected and intracellular potassium ion is exchanged with hydrogen ions.

g) Cardiokinetic Drugs

These drugs play a fundamental role in the therapy of cardio-respiratory failure, even though their use has been challenged by some authors in the stable stage of chronic obstructive lung disease because of a possible increase in pulmonary arterial pressure, due to improved right ventricular output against a restricted pulmonary

arterial bed. A contemporaneous removal of hypoxia is always necessary, since the hypoxic myocardial fibre is unable to respond to cardiokinetic drugs.[21] In these patients the risk of toxicity is particularly present due to the frequently associated hypokalaemia, which lowers the therapeutic index of digitalis. Furthermore, since the tachycardia in these patients is mainly secondary to hypoxaemia and hypercapnia, the dose of cardiokinetic drugs to be administered cannot be determined by the usual heart rate criterion.

h) Diuretic Drugs

Ethacrynic acid should be reserved for patients with a tendency to metabolic acidosis, since this drug, compared to other diuretics, has more powerful hydrogen, chloride and potassium depleting properties. However, ethacrynic acid can precipitate metabolic alkalosis, with consequent reflex hypoventilation and worsening of respiratory acidosis up to hypercapnic coma.

Carbonico-anhydrase inhibiting diuretic drugs are only indicated in the condition of respiratory acidosis associated with post-hypercapnic metabolic alkalosis. Usually other potassium depleting diuretics are used, such as thiazides, xipamide, fenquizone, which can be given only orally, and particularly furosemide and bumetanide, generally given in association with potassium sparing drugs such as spironolactone, triamterene, amiloride, or potassium canreonate an active spironolactone derivative. Patients should also be kept on a Na restricted diet (for example, fresh fruit and boiled rice) until the chloride eliminated with the urine is less than 2 g/day; thereafter, the Na intake can be raised up to 20 mEq/day until clinical improvement occurs. The Na depletion improves cardio-respiratory conditions and the general clinical state; furthermore, it enhances alveolar ventilation and gas diffusion through the alveolar capillary membranes by the reduction of oedema at the level of bronchial mucosa and alveolar capillary interstitial tissue, respectively. However, body weight, electrolyte and acid base balance should be constantly monitored, and dehydration which would preclude the efficacy of mucolytic drugs should be avoided.

i) Increase of the Respiratory Surface

This is another important aim of therapy of cardio-respiratory failure, particularly in the reacutization phase of the disease and is accomplished by modification of pulmonary hemodymics.

Many of the therapeutic interventions discussed increase the capillary respiratory surface and the alveolar-capillary diffusion (aminophylline, nicotinic acid).

Vasodilators should be employed in patients with more advanced right ventricular overload. Preference should be given to i.v. or sublingual nitrates, which by reducing venous return, right atrial and pulmonary pressures, decrease right ventricular overload. It is fundamental in these patients to try to improve with vasodilator drugs, the capacity of pulmonary vascular bed, especially when this is severely reduced such as in patients with primary pulmonary hypertension. Unfortunately, the drugs proposed in this condition, such as phentolamine, acetylcholine, tolazoline, hydrallazine, reserpine, isoprenaline, and ganglioplegics even though effective in single patients, especially when infused directly into the pulmonary artery, in the long term lose efficacy in most cases.[22] Despite these limitations, these drugs can be tried in cardiorespiratory failure, particularly in order to reduce the functional pulmonary vasoconstriction; venesection can also be employed when hematocrit is over 60 per cent. This is usually accomplished by withdrawing 250-300 ml of blood every 2 - 3 days until lowering the haematocrit to 48 - 50 per cent, always trying to keep Hb values over 12 g%. An equivalent amount of plasma expanders should always be infused, in order to avoid dangerous reduction of blood volume and of cardiac output.

Venesection, by reducing polycythaemia, increases O_2 disposal to tissues at the same level of O_2 content, thus decreasing tissue hypoxia, and reduces blood viscosity, which contributes to pulmonary arterial hypertension and to the decreased blood flow velocity, and predisposes to thrombo-embolic phenomena. Prevention of thromboembolic episodes should be accomplished either with heparin, oral anticoagulants or platelet anti-aggregating drugs (such as aspirin, dipyridamole, sulphynpirazone) in those patients in whom repeated unrecognized pulmonary microemboli may represent an aetiologic factor in chronic cor pulmonale or of its reacutization. However, thromboembolic phenomena are frequent, although often clinically silent, also in chronic cor pulmonale secondary to chronic obstructive lung disease.

For these reasons, and when absolute contraindications are not present, it is advisable to give anticoagulants in the reacutization of cor pulmonale particularly in patients with severe pulmonary arterial hypertension and polycythaemia reserving thrombolytic therapy only to those in whom an active thromboembolic episode is demonstrated. When acute pulmonary thromboembolism is demonstrated, streptokinase or, preferentially, urokinase should be administered by continuous i.v. infusion or by direct infusion in the pulmonary artery; heparin should also be given in association, followed by oral anticoagulants by the second day. Dosage of these drugs has to be regulated on thrombin time, which should be maintained around values twice normal. Later, with the patients on oral anticoagulants, prothrombin time should be kept between 15 and 35 per cent of normal.

j) Antimicrobic Drugs

They play a major role in the therapy of cardio-respiratory failure. Acute infections are the most frequent cause of reacutization of CCP patients.

The use of these drugs should be based on the identification of the aetiologic agent of the infection, its sensitivity to antibiotics, therapeutic range, pharmacokinetic characteristics, preferential route of administration and adequate dosages. The choice of the appropriate antibiotic agent, its dosage and route of administration should be individualized to the need of the single patient.

Particular attention should be given to the factors regulating the diffusion of the drug into the bronchial secretions and exudates. At the level of bronchopulmonary perfusion, and to the ability of the drug to pass the haematobronchial barrier, the so called "pneumotropism" and its modification by bronchopulmonary infection.[23]

In patients with acute bronchopulmonary infection a bacteriologic analysis of bronchial secretions should always be undertaken in order to identify the aetiologic agent or agents and to test their sensitivity to several antibiotics. This practice is particularly important, since with increasing frequency bronchopulmonary infections are sustained by so called opportunistic aetiologic agents, often in multiple association, such as anaerobic agents resistant to the usual chemio-antibiotics particularly in hospitalized, cachectic and older patients.[24]

Sputum cultures should be repeated in case of persistence or recurrence of symptoms since in the course of the infection the development of bacterial "step resistance" or virulentation of saprophitic bacteria by antibiotics is frequent.

Considerable controversies have arisen on the modalities of obtaining samples of bronchopulmonary secretions for diagnostic purposes. Subglottid sampling is being more widely performed especially when the choice of the adequate antibiotic is critical. A useful criterion for differentiating a true superinfection from the non causal mere presence of germs in the secretions is the quantitative evaluation of the number of such micro-organisms: a number over 10^6/ml probably indicates an aetiologic role.

However in ambulatory practice, a differential diagnosis between bacterial and viral or mycoplasm bronchopneumonia infection can be easily made on clinical grounds and with simple laboratory test. In fact the usual aetiologic agents in ambulatory patients with acute bronchopneumonia complicating CCP are Diplococcus pneumoniae, Staphylococcus aureus, Streptococcus pyogenes,

Haemophylus influenzae and Klebsiella pneumoniae which with rare exceptions respond to the most wide spectrum bactericidal antibiotics, and particularly to cephalosporin.

In acute cardio-respiratory failure with rapid clinical course the antibiotic of choice should have a wide spectrum and should be given parenterally at high dosages. [25]

In patients with more rapid evolution, it is mandatory to immediately administer parenteral antibiotics, also of different types in association, giving the preference to those with broad spectrum and bactericidal action, without waiting for the results of cultures; these however will be required subsequently in order to control the results of therapy or to readjust the therapy, if unsuccessful. In such cases hospitalization is also required, and the antibiotics of choice are usually the aminoglycosides and parenteral cephalosporins, (cephamicines, metoximines).

Aminoglycosides are a group of parenterally active drugs similar to streptomycin. The number of these drugs has progressively increased in the last few years, however their major pharmacological properties are similar, with some difference concerning the activity against myobacteria and Pseudomonas aeruginosa. These antibiotics are active on both gram + and gram - bacteria, such as Enterobacter, Brucella, Haemophilus and sometimes Pyocianeus; they are relatively less active against streptococcus and pneumococcus. Their side effects are represented by frequent ototoxicity and nephrotoxicity, and by the poor therapeutic index in presence of renal insufficiency. Caution is particularly required in patients over 60 years, and in those with pre-existing renal disease; in these cases one should avoid treatment over 10 days and maintain adequate hydration in order to preserve renal perfusion.

Cephalosporins are also parenterally active broad spectrum antibiotics. They have the potential disadvantages (particularly cephaloridine) of possible nephrotic acute tubular necrosis with elevated doses; furthermore, they are sensitive to the action of endo-betalactamasis (cephalosporinasis) produced by some gram- bacteria. However, second and third generation cephalosporin, (cephamycins and metoximins) are resistant to beta-lactamasis. Among cephamicines the only utilized compound is cephoxitin, while cephuroxim and cephotaxime are the most widely used among metoximin group. These new drugs, resistant to both eso- and endo- beta lactamasis produced by gram + and gram- bacteria, respectively should be reserved only for the most compromised patients, in order to avoid the selection and the diffusion of resistant groups. Psudomonas is, however, resistant to both cephamycine and metoximine. In infections sustained by this agent, carbenicillin should be given by i.v. infusion at doses up to 20 - 30 g/day, in association with gentamicin, tobramicin, amikacin or sisomicin.

Compared to these wide spectrum bactericidal antibiotics, tetracyclins, which are only bacteriostatic are of second choice. However, they are first choice antibiotics in infections sustained by Rickettsiae.

Fosphomicin can also be useful in the most severe cases of cardio-respiratory failure, alone or in association with aminoglycosides; however, large i.v. doses must be given because of the unfavourable pharmacokinetic characteristics of this drug in broncho-pneumonic disease.

Particularly important are infections caused by anaerobic microorganisms, which can be the primary cause of acute deterioration of broncho-pulmonary diseases, or rather can superimpose, by development of bacterial resistance, during the hospitalization of cachectic patients. Anaerobic germs form an heterogeneous group (Bacteroides, Fusobacter, Clostridia, Propionibacter, Peptococchi, Peptostreptococchi, Enbacter, Bifidobacter) generally resistant to the usual chemio-antibiotic agents. For these reasons, whenever the presence of fetid sputum and of predisposing factors suggest an aetiological role of anaerobic germs, it is mandatory, before starting antibiotic therapy, to obtain repeated cultures during febrile spells; samples should be taken in absolute anaerobiosis and cultured on specific media.

The antibiotics of choice in these patients are wide spectrum penicillins or an injectable cephalosporin at high doses, in association with gentamicin and chloramphenicol, or tiamphenicol or lincomicin; therapy should be readjusted according to the clinical course and to the results of repeated cultures with antibiograms.

In the most severe cases, when multiple microrganisms are involved, non specific human immunoglobulins given i.v. at adequate dose are also indicated.

The forms of cardio-respiratory failure with slow clinical evolution, also require prompt antibiotic treatment preceded by sputum cultures with antibiogram, giving the preference to wide spectrum bactericidal antibiotics and the oral route.

In these patients, the drugs of choice are the oral penicillins similar to Penicillin G, which are however ineffective against most gram -ve bacteria and are inactivated by beta-lactamases, the isossazolil-penicillins, which are resistant to eso-beta-lactamases but have a spectrum of action limited to gram + bacteria, or ampicillin and derivated, which have a wider spectrum but are inactivated by eso-beta-lactamases. Particularly indicated in these patients are the orally active cephalosporins, which have the advantage of being resistant to eso-beta-lactamases, and of being

active against both gram + and - bacteria; they are however inactive against Pseudomonas and, at least the classic cephalosporins, are inactivated by endo-betalactamases.

The most widely used oral cephalosporins are cephalexin, cephadrin and cefadroxil. The oral administration of these drugs yields effective blood concentrations equivalent to those obtained by parenteral cephalosporins.

Tetracyclins possess the above indicated limitations in most seriously ill patients; in addition, generally it is preferable to avoid the association of a bactericidal with a bacteriostatic antibiotic; although this rule has several exceptions and favourable results have been obtained with the combination tetracycline-amoxicillin.

Rifampicin, a well known antibiotic active against mycobacterium tuberculosis, can be employed in association with other drugs for its capacity for reaching high concentration in the secretions; however its indiscriminate use should be avoided for the risk of selecting resistant strains of mycobacteria. In addition, the drug is not without serious side effects.

Extremely important and of difficult solution is the problem of prophylaxis of infective recurrences in chronic cor pulmonale. The administration of short cycles of antibiotics in patients with non specific chronic bronchopneumonic disease has been widely used. However, several controlled studies have shed considerable doubt on the validity of this chemioprophylaxis, particularly for the risk of favouring bacterial resistance to the most widely used antibiotics. Parenteral or local (by aerosol) administration of antimicrobial vaccines although empirically used, does not usually give favourable results.

Chemio-antibiotic prophylaxis in the course of influenza virus infections is advantageous in patients with chronic cor pulmonale, due to the potential risk of bacterial infections in these patients, compared to the relatively minor risk of selecting resistant bacterial strains.

However, these situations should be prevented by the wide application, particularly in older patients, of the anti-influenzal vaccines. An alternative to such prophylaxis can be represented by amantadine in short courses (100 mg b.i.d. by mouth). Whenever the typical symptoms of influenza occur a trial with isoprinosin 4 g/day p.o. in divided doses, can also be attempted.

In order to prevent infection recurrences, in most recent years courses of therapy with mucolytic or antisecretory drugs have often been used, considering the lack of unfavourable side effects as is the case with cycles of chemio-antibiotics.

Rehabilitation is another important aspect of prevention, but this is outside the scope of the present review. However, cardio-respiratory rehabilitation has to be reserved for qualified centres, provided with adequate instrumentation, and with intensive care units. These may be necessary for possible deterioration of cardio-pulmonary status during the course of the rehabilitation program in those patients with more severe anatomo-functional impairment.

In these centres adequage hygienic rules, such as elimination of tobacco smoke, and also cycles of physiokinetic and inhalation therapy can be applied, together with attempts at respiratory reduction with periods of intermitent positive pressure respiration.

REFERENCES

1. L. Condorelli, Il Cuore polmonare cronico, Rif.Med. 73:1393 (1979).
2. Organition Mondial de la Sante': Le coeur pulmonaire chronique. Rapport d'un Comite d'esperts. Series des rappotrs technique. Geneve, 213 (1961).
3. A. Blasi, D. Olivieri, Secrezione bronchiale ed aspetti fisiopatologici dell'ipersecrezione. Il Pensiero Scientifico, Ed. Roma, 107 (1980).
4. M. Condorelli, F. Rengo, D. Bonaduce, Fisiopatologia e clinica del cuore polmonare cronico, in: "Medicina Clinica-Diagnostica e terapia," A. Beretta Anguissola, ed., Ed. Medico Scientif-iche, Torino (1979).
5. P. J. Cohen, The metabolic function of oxygen and biochemical lesion of hypoxia, Anesthesiology 37:148 (1972).
6. E. J. Campbell, The management of acute respiratory failure in chronic bronchitis and emphysema, in: "The J. Burns Amberson Lecture" Am.Rev.Resp.Dis. 96:626 (1967)
7. S. C. Wang, J. W. Ward, Analeptics, Pharmacol.Ther. 3:123 (1977).
8. D. C. Webb, J. L. Andrews, Bronchodilator Therapy, N.Engl.J.Med. 297:476 (1977).
9. J. F. Nunn, Applied/Respiratory Physiology, 2nd ed. Butterworths, London (1977).
10. R. R. Kirby, Intermittent mandatory ventilation, Curr.Probl. Anesth.Crit.Care Med. 5:18 (1977).
11. M. Pasargiklian, G. Fumagalli, A. Ferrara, La terapia del disequilibrio acidobase nel trattamento intensivo della patologia respiratoria, Min.Med. 70:1 (1979).
12. G. Giuntini, A. Santolicandro, Insufficient respiratoria, in: "Terapia Medica Moderna," Vol. 1. L. Baschieri, ed., Ed. Ambrosiana, Torino, (1979).
13. J. B. Richardson, C. C. Ferguson, Neuromuscular structure and function in the airways, Fed.Proc.38:202 (1979).

14. G. A. Robinson, R. W. Butcher, E. W. Sutherland, Cyclic AMP, Academic Press, Inc. New York (1971).
15. B. Samuelsson, G. Folco, E. Granstrom, H. Kindhal, C. Malmsten, Prostaglandins and thromboxanes: biochemical and physiological considerations. Adv.Prostaglandins and Thromboxanes 4:1 (1978).
16. D. M. Aviado Jr.,"Sympathomimetic drugs," Charles C. Thomas, Springfield, Ill, (1970).
17. A. M. Lands, A. Arnold, J. F. McAuliff, F. P. Luduena, T. G. Brown, Differentiation of receptor systems activated by sympathomimetic amines, Nature 214:597 (1967).
18. C. G. Irvin, R. Boileau, J. Tremlay, R. R. Martin, P. T. Macklem, Bronchodilatation: noncholinergic, nonadrenergic mediation demonstrated in vivo in the cat, Science 207:791 (1980).
19. L. Reid,"Mucus in health and disease," New York Plenum Press, New York (1977).
20. H. W. Davemport, "The ABC of acid-base chemistry," The University of Chicago Press, Chicago, (1970).
21. F. Rengo, M. Condorelli, D. Nonaduce, Mechanism of pulmonary hypertension by hypoxemia. 2nd Europ.Symp.Coagulation platelet fibrinolysis and vascular diseases, Palermo (1980).
22. R. P. Gatewood, P. N. Yu, Primary pulmonary hypertension in: "Progress in Cardiology, P. N. Yu, J. F. Goodwin, eds., Vol. III, Lea and Febiger, Philadelphia (1979).
23. J. E. Pennington, Immunological and infections in the lung, C. H. Kirkpatrick, H. Y. Reynolds, Dekker, New York (1977).
24. W. B. Pratt,"Chemotherapy of Infection," Oxford University Press, New York (1977).
25. G. L. Mandell, R. G. Douglas Jr., J. E. Bennett, "Principles and Practice of Infectious Disease," John Wiley and Sons, New York (1979).