strips. In general, fluorescence increased 1000-fold, from approximately $2 \times 10^{-3}$ lux (pre-DCFH background radiation) to 2 lux. Distribution of fluorescence within diaphragm appeared heterogeneous. Punctate localizations contrasted with areas of diffuse emission, suggesting compartmentalization either of DCF distribution or of free-radical production. Repetitive twitch or tetanic contractions had no measurable effect on fluorescence.

These observations confirm production of oxygen free-radicals by diaphragm and suggest that oxidants measured under these conditions are not tightly linked to mitochondrial oxidation or excitation-contraction coupling.

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**Session 10**

**Pharmacologic Strategies for Treating Respiratory Failure**

*M. Aubier, M.D.*

The respiratory system consists of a gas-exchanging organ, the lungs, and a pump that ventilates them. The pump consists of the chest wall, which includes the rib cage; the respiratory muscles; and the respiratory centers in the central nervous system, which control the diaphragm and the muscles used to expand the chest wall during breathing.

The pump is the working or active part of the respiratory system, the lungs being merely passively inflated when the respiratory muscles contract. The pump is just as vital as the heart, since without it the lungs would obviously be unable to function, and arterial blood gas homeostasis would not be maintained.

In the past few years, it has been shown that respiratory muscle dysfunction can occur in patients with chronic obstructive respiratory disease, as well as in those with cardiovascular disease. Since respiratory muscle dysfunction can lead to ventilatory failure, its recognition in respiratory diseases will have important therapeutic implications. In some instances, such as acute respiratory failure, the primary goal will be to reduce the load imposed on the respiratory muscles. This can be accomplished by removing the underlying obstruction by using bronchodilators, as in asthma. However, in chronic respiratory system disorders, such as chronic obstructive pulmonary disease (COPD), it may be difficult to reduce the load on the respiratory muscles. Drugs that improve respiratory muscle contractility therefore may prove useful.

This article deals with a new aspect of pharmacologic treatment of respiratory insufficiency, which is represented by respiratory muscle pharmacotherapy. However, respiratory muscle pharmacotherapy is still in its infancy and evolving. We therefore focus on the drugs proved to have a positive effect on respiratory muscles.

**Elements of Respiratory Muscle Contraction**

Respiratory muscle function can be modulated by acting at 2 levels: (1) the excitation-contraction coupling process and (2) the energy supply to the muscles.

**Excitation-Contraction Coupling**

Among the skeletal muscles, the diaphragm presents some unique features. It has to contract physically during life and thus functionally appears to be closer to the myocardium than to limb muscles. In view of this functional similarity between the heart and the diaphragm, there also should be some similarities in their cellular contractile mechanisms, particularly their excitation-contraction coupling processes. This hypothesis has been supported by recent experimental evidence. Indeed, although the central role of calcium in the excitation-contraction coupling of skeletal muscle is well established, the cellular mechanisms by which calcium is made available to the contractile proteins during excitation to elicit contraction of the muscle remain unclear. It generally is thought, however, that the activation of the contractile elements is essentially independent of extracellular calcium, the cyclic nature of Ca2⁺ fluxes in skeletal muscle during excitation-contraction coupling being regarded strictly as intracellular and independent of extracellular calcium. In cardiac muscle, on the contrary, the passage of calcium across the cell membrane is of major importance because without it there would be insufficient calcium from the sarcoplasmic reticulum to initiate contraction.

Recent studies in vivo and in vitro have challenged these classical notions. As shown in Figure 1, it has been found that, in calcium-free medium, isolated diaphragmatic fibers obtained from rats behaved similar to single papillary muscle fibers from the same animal. Indeed, a striking similarity was observed between diaphragmatic and papillary muscle fibers' contractile responses to extracellular calcium deprivation, with complete twitch abolition resulting. On the contrary, no twitch abolition was noted with single soles or extensor digitorum longus fibers, a slow and fast peripheral skeletal muscle, when exposed to 3 h of calcium-free medium. These data also have been confirmed in vivo in the dog when the animal was rendered hypocalcemic by infusion of Ca²⁺ chelator (ethylene-glycolis [β-aminoethy]letter -N,N'-tetra-acetic acid), which led to a decrease in unionized extracellular calcium. In these animals, a marked depression in diaphragmatic contractility was noted with hypocalcemia, whereas the sartorius, a peripheral skeletal muscle of similar histochemical profile, was not affected.

It therefore appears that the diaphragm is a unique skeletal muscle that resembles cardiac muscle. These results open new insight into the mechanisms of diaphragmatic contraction, notably by underlining the particularity of the diaphragm among the other striated skeletal muscles. They also will have important pharmacologic implications. Owing to the similarities between diaphragmatic and cardiac muscle fiber's reliance on extracellular Ca²⁺, it is conceivable that drugs or agents that exert a direct inotropic positive or...

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negative effect on the myocardium may have similar action on the diaphragm.

**Energy Supply**

Respiratory muscle dysfunction can result not only when calcium movement at the respiratory muscle cell level is impaired but also when the supply of nutrients is insufficient to meet metabolic demand. During breathing, the oxygen requirements of the respiratory muscles, and especially the diaphragm, are met primarily by increased diaphragmatic blood flow; which is related to cardiac output during unobstructed hyperventilation, hypoxia, and exercise. It seems possible that, when blood flow to the muscle is insufficient, lack of oxygen leads to a shift to anaerobic glycolytic pathways of high-energy phosphate generation. This shift would increase the acid accumulation associated with a given level of ATP turnover, impairing sarcoplasmic reticulum function and reducing the force-generating capability of the diaphragm.

Some evidence suggests also that blood flow may play a role in “washing out” the byproducts of cellular metabolism. Thus it is possible that increased diaphragmatic blood flow may increase the washout of toxic byproducts of cellular metabolism concomitant to an improvement in diaphragmatic energetics.

Whatever the mechanism, because respiratory muscle function, particularly diaphragmatic function, is tightly linked to the level of muscle blood flow, it may be possible to improve diaphragmatic function by administering pharmacologic agents that augment diaphragmatic blood flow in patients in whom it is diminished or not high enough to meet the demands of breathing.

We will first review the drugs that affect the respiratory muscles and essentially the diaphragm, the main inspiratory muscle, by acting on the excitation-contraction coupling process. Then, we will review the drugs that improve diaphragmatic function by acting on its energy supply.

**Drugs Acting at the Level of Excitation-Contraction Coupling**

**Digitalis**

Digitalis preparations are well known for their inotropic effect on cardiac muscle, whereas they have practically no effect on peripheral skeletal muscle. This phenomenon can be accounted for by differences in excitation-contraction coupling in the two types of muscle. Indeed, digitalis inhibits Na⁺ + K⁺ adenosinetriphosphatase at the cell membrane level, which indirectly augments cell entry of calcium. This influx of calcium then increases contraction strength by concentrating this action in the vicinity of the myofibrils. Because the action of digitalis appears to be strongly related to cell membrane transport of calcium, and owing to similarities between the myocardium and the diaphragm concerning the role of extracellular calcium in their contractile processes, recent studies have evaluated the effects of digoxin on diaphragmatic strength generation in dogs and in COPD patients during acute respiratory failure. In both studies, a strong inotropic effect of digoxin was found, occurring without any change in cardiac output or diaphragmatic blood flow, which was measured in the animal study. This suggests that digoxin has a direct inotropic effect on diaphragmatic contractility. Furthermore, in the animal study it was found that, in the same animal, digoxin had no effect on a peripheral skeletal muscle, the sartorius, confirming the differences in the contraction mechanisms of the diaphragm and the peripheral skeletal muscles.

These data strongly suggest that, contrary to that in the hind-limb muscle, extracellular calcium is, as for the heart, necessary for diaphragmatic muscle contraction. This similarity in the importance of extracellular calcium in the diaphragm and the heart's contractile processes probably explains the inotropic effect of digoxin on the diaphragm.

**Xanthines—Mechanism of Action**

A recent study demonstrated in dogs in vivo that although theophylline, at therapeutic doses, increased the force of contraction of the diaphragm, its action was affected by prior administration of verapamil. This substance blocked the potentiating effect of theophylline, suggesting that theophylline may affect calcium channels at the cell membrane level, because verapamil is believed to inhibit the slow inward calcium currents. How this increased calcium influx produced by theophylline may increase muscle contraction is not known, but there are two possible explanations: Because the quantity of calcium entering the cell during a
normal action potential is insufficient to activate the contractile proteins directly, a theory of calcium-induced calcium release has been proposed. The theory proposes that the small amount of calcium crossing the sarcolemma during an action potential does not activate the myofilaments directly but induces a release of calcium from the sarcoplasmic reticulum that is sufficient for activation. Alternatively, under some circumstances, the magnitude of calcium influx might be increased such that the sarcoplasmic reticulum could be bypassed and the contractile proteins activated directly. The mechanism by which theophylline affects the cell membrane to increase the influx of calcium is not elucidated fully. Theophylline, which potentiates muscle contractility only in the presence of calcium in the medium, is a potent antagonist of adenosine; adenosine, however, has been shown to decrease calcium influx in frog skeletal muscle. It therefore is possible that theophylline might block adenosine receptors. Convincing support for this hypothesis comes from a study that found that the concentration of theophylline required to show antagonism to adenosine was substantially lower than that required to demonstrate other effects (for example, phosphodiesterase inhibition and intracellular Ca2+ translocation) that have been suggested to explain the drug’s actions. Furthermore, it has been shown that the effects of theophylline and enprofylline, a xanthine derivative with no antiadenosine effect, had different actions on the human diaphragm, no inotropic effect being observed with enprofylline44 (Fig 2).

**Effects of Theophylline on Respiratory Muscle**

**In vitro studies:** In isolated preparations, theophylline has been shown to strengthen the contractions of skeletal muscle elicited by direct and indirect electrical stimulation, an action caused by a potentiation of twitch tension. This effect also has been well documented in isolated phrenic nerve diaphragm preparation of rats. Indeed, theophylline, in concentrations ranging from 25 to 100 μg/ml, was found to increase both tension development and the maximum rate of rise of tension during electrical stimulation of the diaphragm. This increased tension of the nerve-stimulated preparation observed with theophylline was not significantly different from that observed when the diaphragm was stimulated directly. This suggests that theophylline has a direct inotropic effect on the diaphragmatic fiber.

All the experiments that demonstrated an inotropic effect of theophylline on skeletal muscle or isolated diaphragm tissue were performed with doses of the drug much higher than therapeutic doses used in humans. It therefore has been argued that theophylline had no effect on the diaphragm at therapeutic doses in humans or that the effects observed in vivo result primarily from a secondary action of the drug, such as an increased muscle blood flow by metabolic effects or both. One of the major problems with the in vitro preparations used for the experiments in this study is that large strips of muscle devoid of blood supply are used. This inherently limits drug’s diffusion into the tissues and could explain the lack of sensitivity of these preparations to a therapeutic dose of theophylline.

Recently, using an in vitro model of isolated diaphragmatic fibers, we demonstrated that theophylline produced a dose-dependent increase in peak-twitch tension,19 which, at a concentration equivalent to a therapeutic dose of 15 mg/L, amounted to 111±1.5% of control (p<0.05). On the other hand, theophylline had no effect on a hemidiaphragm preparation until a dose of 250 mg/L was given. These findings demonstrate, therefore, that theophylline has an inotropic effect on isolated diaphragmatic fibers at therapeutic dose levels and also suggest that the effects of theophylline on diaphragmatic contractility are caused by direct action of the drug on the contractile properties of the diaphragmatic fibers. It also should be noted that theophylline has been shown in vitro to improve the contractility in fatigued skeletal muscles in a fashion similar to that in fresh muscles.

**Human studies—normal subjects:** In normal human subjects, theophylline at the usual therapeutic dose (the dose used for a bronchodilator effect) has a potent effect on diaphragmatic contractility, confirming in vitro findings. During voluntary graded inspiratory efforts, the transdiaphragmatic pressure following aminophylline infusion increases significantly, with an average of 15% at any given electrical activity.18

Theophylline has been known for many years to be effective against skeletal muscle fatigue. We recently extended this observation to the fatigued diaphragm.18 Fatigue was produced in 2 groups of subjects by resistive loaded breathing. Aminophylline was infused either before the fatigue run and maintained throughout the recovery period or injected intravenously after the fatiguing procedure. When aminophylline was injected before the fatigue run, transdiaphragmatic pressure recovered rapidly after fatigue at all frequencies of stimulation. When aminophylline was administered after the production of fatigue, the transdiaphragmatic pressure after drug infusion exceeded preinfusion values.

**Patients:** Although theophylline has a potent action on the
fatigued diaphragm in normal subjects, the paramount question is whether it has a similar effect in patients with severe COPD, in whom hypoxia and hypercapnia may influence respiratory muscle contractility. In a study of theophylline’s effects on diaphragm contractility, 15 patients with COPD, whose conditions were stable, were observed.17 All had hypoxia and hypercapnia (mean PaO2 57±8 mm Hg and mean PaCO2 53±3 mm Hg), severe obstruction (mean FEV1 27% of predicted), and overinflation (mean total lung capacity 135% of predicted). Diaphragmatic strength was assessed by measuring the Pdi generated at functional residual capacity during a maximal inspiratory effort against closed airway (Pdi max). Diaphragmatic fatigue was induced by resistive loaded breathing, the subjects developing 60% of their Pdi maximum at each inspiration until exhaustion. Pdi maximum and the time course of the fatigue runs were performed before and after 7 days and 30 days of aminophylline administration. A control group that received a placebo instead of aminophylline was studied with the same protocol. No significant change in the mechanical properties of the respiratory system was noted after administration of theophylline or placebo. Theophylline (mean plasma level 14±2 mg/L) significantly increased Pdi maximum (p<0.01) by 20% after 7 days of administration, and this increase persisted after 30 days. No significant change in Pdi maximum was observed in the group that received the placebo. The clinical benefit of theophylline in COPD patients is not clear-cut, however. Indeed, conflicting data are reported in the literature. Eaton and colleagues18 reported that aminophylline did not affect dyspnea at rest and that it did not significantly improve 12-minute walk or progressive cycle ergometry performance of COPD patients. By contrast, Neitrzeba and coworkers19 found that aminophylline improved maximal inspiratory pressure and peak inspiratory flow rate as well as exercise performance in COPD patients; and Mahler and coworkers20 found that it had a beneficial effect on the sensation of dyspnea. In acute exacerbations of COPD patients, no significant additional benefits were observed when theophylline was added to an otherwise standard treatment (inhaled metaproterenol, ampicillin, and supplemental oxygen). However, these studies generally were performed on a few patients and over a relatively short time. To solve that problem, Murciano and colleagues21 conducted a study on 60 patients with severe COPD. All were studied in stable state and were severely obstructive, with a mean FEV1 amounting to 29±10% of predicted and mean PaO2 and PaCO2 of 61±10 mm Hg and 51±8 mm Hg, respectively, while breathing room air. Dyspnea was evaluated by a visual analog scale. Respiratory muscle performance was evaluated by the ratio of pleural pressure (Ppl) over minimal pleural pressure (Pplmin) at functional residual capacity. The patients received sustained release theophylline or placebo during a 2-month period. This was a randomized crossover single-blind study with a wash-out period of 15 days between the theophylline and placebo periods. After 2 months of theophylline administration (mean plasmatic level ±15 mm Hg ±3 mm Hg/ml), minute ventilation (Ve) increased from 10±2.5 to 12±2.5 L/min (p<0.001). This increase in Ve was secondary to a significant increase in tidal volume, whereas respiratory frequency was not affected significantly. These changes were accompanied by a significant improvement in arterial blood gases, with

![FIGURE 3. Individual and mean changes in arterial blood gases in 60 patients after 2 months of placebo (P) and after 2 months of theophylline (T). The solid line represents the line of identity. Bars represent 1 SE.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21609/)

![FIGURE 4. Mean values in dyspnea score for 60 patients studied after 2 months of placebo (P) and 2 months of theophylline (T). Dyspnea score is expressed as a percentage, 100% representing maximal dyspnea, and 0% no dyspnea. Bars represent 1 SE.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21609/)
PaO₂ increasing by 5 mm Hg (p<0.0001) and PaCO₂ decreasing by 6 mm Hg (p<0.0001) on the average (Fig 3). Dyspnea was reduced significantly (Fig 4), and PpV/Pplmin amounted to 0.43±0.17±0.11 (p<0.0001) after 2 months of placebo and 2 months of theophylline, respectively, suggesting that respiratory muscle reserve was enhanced markedly in these patients.

No significant change in lung function data was observed after 2 months of theophylline administration. At the end of the 2-month placebo period, no significant changes in any of the above parameters were noted. These data clearly demonstrate that, in severe COPD patients, theophylline improves dyspnea and arterial blood gases, with these improvements probably related to an enhancement of respiratory muscle performance. Long-term administration of theophylline therefore appears to be clinically useful in these patients.

**DRUGS ACTING ON RESPIRATORY MUSCLE ENERGY SUPPLY**

Dopamine, a vasoactive drug widely used in patients with hypoperfusion syndrome, increases myocardial contractility, visceral, and particularly renal and splanchnic blood flow, thus possibly also increasing diaphragmatic blood flow. We determined the effects of dopamine on diaphragmatic function in patients with chronic obstructive pulmonary disease during acute respiratory failure secondary to pulmonary infection.

The changes in transdiaphragmatic pressure during electrical bilateral supramaximal stimulation of the phrenic nerve were evaluated in 5 patients with chronic obstructive pulmonary disease during acute respiratory failure. In 3 patients, changes in diaphragmatic blood flow were also measured. All patients were intubated and artificially ventilated. Stimulated transdiaphragmatic pressure, cardiac output, evaluated with a Swan-Ganz catheter, and diaphragmatic blood flow, evaluated by timed volume collections of left phrenic venous effluent (a catheter was introduced into the right femoral vein and advanced into the left inferior phrenic vein), were measured before dopamine infusion, every 10 minutes after the onset of dopamine infusion (10 µg/kg body weight/min during 30 minutes), and 15 minutes after the end of dopamine infusion. Arterial blood gases and pH were measured before and at the end of dopamine infusion.

Arterial blood gases and pH were maintained within normal range by mechanical ventilation throughout the study. With dopamine infusion, heart rate increased by 17% (p<0.001) and cardiac output by 40% (p<0.001) on the average. The increase in cardiac output was accompanied by a marked increase in diaphragmatic blood flow (30% on the average) in the three patients in whom it was measured (p<0.001) (Fig 5). Diaphragmatic strength also increased significantly during dopamine administration. Transdiaphragmatic pressure for an identical phrenic stimulation increased by 30% (p<0.001) on the average (Fig 5). The changes in cardiac output, diaphragmatic blood flow, and transdiaphragmatic pressure persisted throughout the infusion period; all values returned to control levels 15 minutes after the end of dopamine administration.

The results show that diaphragmatic function can be markedly improved by administering dopamine to these patients. The data also suggest that the beneficial effect of dopamine on the diaphragm is the result of increased diaphragmatic blood flow.

**CONCLUSION**

Certainly, many compounds may interfere with the contractile processes of the respiratory muscle, particularly the diaphragm. These compounds act by different mechanisms, either at the level of the excitation-contraction coupling process or by modulating respiratory muscle blood flow. A review of all the agents capable of improving respiratory muscle function is not possible because only a very few compounds have been tested so far. However, because the respiratory muscles seem to play an important role in the pathogenesis of dyspnea and respiratory failure, further research in the pharmacotherapy of the respiratory muscle is certainly needed.
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Effects of Theophylline (T) on Diaphragmatic Contractility in Dogs*

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In order to distinguish T-induced alterations in diaphragmatic "contractility" from potential changes in respiratory muscle interaction or diaphragmatic blood flow, we re-examined the effects of T on contractile properties and high-frequency fatigue of canine diaphragm, in 2 different studies. In the first study, aminophylline was administered to 5 animals in a dose of 40 mg/kg intravenously, and 10 bundles were removed from these animals at serum levels of 24±10 mg/L. Contractile properties and high-frequency fatigue of these small diaphragm bundles (thickness less than 2 mm) were studied in vitro in comparison to 10 matched control bundles. In the second study, contractile properties and high-frequency fatigue of 6 T-treated bundles at concentrations of 100, 200, 300, and 400 mg/L were compared to 6 matched control bundles in vitro. In vitro attainable serum levels did not modify contractile properties and, moreover, appeared to promote fatigue in a 4-minute fatigue run with 100-Hz stimulations applied every 2 seconds. High supratherapeutic concentrations in vitro enhanced force production at low stimulation frequencies, particularly at 10 Hz, and caused a significant increase in twitch-tetanus ratio (at 400 mg/L: 0.29±0.03 control vs 0.36±0.05, p<0.01; +27±14%). Both exhibited clear dose-response behavior. Control and T-treated bundles fatigued similarly whether investigated with interpolated 100-Hz stimulations during the force-frequency curve or with repetitive 100-Hz stimulations applied every 2 seconds in a 4-minute fatigue run.

We conclude that: (1) T increases force production at low stimulation frequencies and twitch-tetanus ratio of canine diaphragm only at high supratherapeutic concentrations; (2) potential effects observed at in vitro attainable serum levels are thus unlikely to reflect effects on "contractility"; (3) T does not protect against the development of muscle fatigue.

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