Respiratory Muscle Failure: Fatigue or Weakness?*

The Role of Theophylline

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Dr. Richard L. Hughes: The purpose of today's conference is to determine how theophylline enhances respiratory muscle function. Four possible mechanisms will be discussed: fatigue; muscle membrane phenomena; potential effects within the muscle cell; and finally, the clinical and animal responses to theophylline. Dr. Edwards will begin the discussion.

Fatigue or Weakness?

Dr. Richard H. T. Edwards: I will deal first with respiratory muscle fatigue before coming to talk about weakness, from which fatigue must be distinguished. Table 1 is a summary of the different types of fatigue, based on what can be demonstrated both in isolated muscle preparations and in man. This sequence should be the basis for thinking about drug strategies aimed at reversing fatigue in respiratory muscles. There are many different steps in the chain of command that may produce loss of force in a muscular contraction. These can be graphically represented by what can be called the catastrophe theory of muscle fatigue (Fig 1), which is one method of describing the delicate balance among loss of force, energy depletion, and reduction in excitation or activation of the muscle. This figure is not to suggest that fatigue is a catastrophe, although, of course, it may be in the case of respiratory muscles, but because this theory is a model for describing a discontinuous function. If it were possible to maintain excitation and excitation-contraction coupling optimally (Fig 1, arrow A), one could deplete energy sources to a low level; however, energy sources are never depleted absolutely by activity, because this would result in "rigor mortis." The other extreme (Fig 1, arrow B), complete loss of excitation and activation, is most nearly represented by myasthenia gravis or complete curarization. In real life, respiratory muscles function

<table>
<thead>
<tr>
<th>Physiologic Mechanism</th>
<th>Clinical Condition</th>
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<tbody>
<tr>
<td>Central fatigue</td>
<td></td>
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<tr>
<td>Failure of neural drive; reducing number or firing; frequency of functioning</td>
<td>Neurasthenia; Hysterical paralysis; Impaired motivation</td>
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<td>motor units</td>
<td></td>
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<tr>
<td>Peripheral fatigue</td>
<td></td>
</tr>
<tr>
<td>High-frequency fatigue:</td>
<td></td>
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<tr>
<td>a) Impaired neuromuscular transmission</td>
<td>Myasthenia gravis; Cooling of muscle; Partial curarization</td>
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<td>b) Failure of muscle action potentials</td>
<td>Myotonia congenita; Glycolytic disorders</td>
</tr>
<tr>
<td>Low-frequency fatigue:</td>
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<tr>
<td>Impaired excitation-contraction coupling</td>
<td>Mitochondrial disorders; Dantrolene sodium (therapy for spasticity); Myotonia congenita; Hypokalemic periodic paralysis; Duchenne muscular dystrophy</td>
</tr>
</tbody>
</table>

*Participants in addition to speakers: Drs. Mark Dunn; Byron Hamilton; Richard Kern; Eleanor Miller; and Vinod Sahgal.

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somewhere between these two extremes. There is clear evidence for excitation failure of muscles, particularly with ischemia.4 We now believe this failure in excitation serves as a self-protective mechanism which prevents energy stores (adenosine triphosphate) from being depleted to the state of rigor, where actual damage to cross bridges could occur. Fatigue, therefore, is not simply due to a lack of energy but also to mechanisms that interact at the muscle membrane level; for example, the degree of excitation of a muscle membrane has a direct effect on the energy used within the muscle fiber. This is most clearly shown in the laboratory in the case of high-frequency fatigue, where reducing the frequency of stimulation results in an increase in the force generated by the muscle. Conversely, competition between hydrogen ions (lactic acid) and calcium binding in muscle can result in reduced energy exchange and force generation for the same degree of excitation.5

I would like to emphasize that muscle weakness and muscle fatigue are different. Weakness is a failure to generate force in an otherwise fresh muscle. Fatigue is a problem which arises as a result of previous activity. The strength of a muscle depends on the strength and number of individual fibers. There are good data that demonstrate the relationship between respiratory muscle mass and that of other muscles under the conditions of malnutrition.6 It may well be that some patients with malnutrition, cancer, or chronic obstructive pulmonary disease (COPD) die because their respiratory muscles are weak; that is, they have lost strength because of loss in fiber size. Indeed, it has been shown that in poorly nourished patients without pulmonary disease, there is a considerable reduction in respiratory muscle strength, as estimated from maximum mouth pressures;7 but, paradoxically, weak muscles are not necessarily ones that are most fatigable. It is a well-recognized phenomenon that dystrophic muscles are less fatigable than normal.8 This may also be true to a limited extent in malnourished patients;9 however, as a therapeutic strategy in a patient with compromised respiratory function, the first step is to decide whether the muscles are suffering from fatigue or from weakness, both of which can produce hypoventilation. If the muscles are suffering from fatigue, then it is reasonable to find a drug which will reverse fatigue; however, if the muscles are weak, the best strategy may be some means to increase muscle mass in order to increase muscle strength.

Dr. Charis Roussos: Why cannot a weak muscle in the fresh state be improved by a drug?

Dr. Edwards: If a muscle is fully activated, then it is fully activated. Unless you have a fresh muscle that is not generating maximum force per cross-sectional area, you cannot increase the tension in that muscle.

Dr. John A. Faulkner: Charis is raising an interesting question. If a muscle is weak and develops less than 25 to 30 newtons/sq cm, the appropriate drug might increase force development back up to the expected level. In this circumstance, weakness would mean that the muscle is not fully activated.

**MEMBRANE PHENOMENA**

Dr. Shirley Bryant: I would agree with Dr. Edwards that, thus far, no one has come up with a drug that permits a muscle to exceed its normal maximum tetanic contraction in the fresh state. There are four potential regions where drugs might influence excitation-contraction coupling or alter the membrane such that greater tension might be developed (Fig 2 and 3). Perhaps the easiest is to lengthen the surface membrane action potential to allow more tubular events to occur; for example, in an environment low in chloride, mammalian muscle fibers have a longer action potential and improved excitation-contraction coupling. The second region is in the tubule membrane potential as it invades the T system and propagates throughout the motor unit. There is a weak link between these two regions—between the surface membrane and T-tubule membrane—in terms of how much depolarization occurs in the T system as a result of the surface membrane's potential. One could develop a drug that might
Figure 2. Highly diagrammatic cross-section of muscle fiber (not to scale). Motor nerves divide repeatedly before tunnelling single side branch under collagenous coating of muscle cell. Axon ends in neuromuscular junction on outer surface of sarcolemma. Motor impulse depolarizes the neuromuscular junction and initiates action potential that spreads rapidly over sarcolemmal surface and spills into interior of cell via T tubes.

work at this location. In the third region, between the T tubules and the sarcoplasmic reticulum (the so-called triad), there is a great mystery at the moment in terms of the mechanism of excitation. The hypothesis with the most popularity is the one involving voltage-dependent charge movement with a specific threshold, resulting in a sigmoid-shaped relationship between the T-tubule potential and the amount of voltage-dependent charge which is moved into the sarcoplasmic reticulum. This movement of charge can be detected and measured and is associated with the degree of calcium released from the sarcoplasmic reticulum. There are definitely drugs which operate in this region of the muscle and which appear to potentiate reduced contractions. There is a great deal of interest as to whether caffeine and theophylline have any influence in this region of charge movement and the excitation-contraction coupling cascade. The fourth region, of course, is the most important. It is in the sarcoplasmic membranes which run parallel with the myofibrils themselves (Fig 3). This region affects the strength of muscle contractions by the release and uptake of calcium at the level of the myofibril. This release and uptake from the sarcoplasmic reticulum determine what level of calcium will react with troponin to initiate the contractile event.

How do the xanthine drugs affect these processes? This is a ping-pong problem, because these drugs could affect release of calcium more than uptake, affect uptake only, control the leakage of that small amount of calcium which affects the release of calcium, or do all these things together. Recent work has suggested that the re-uptake of calcium was being inhibited by caffeine, and this may be the major effect of xanthine drugs; however, other authors propose that these drugs affect the specific calcium current that permits calcium buildup near the papillae, or whatever one wishes to call the anatomic structures between the sarcoplasmic reticulum and the T system. It is in this critical area that leakage of calcium (the so-called "trigger calcium") produces a large release of the muscle calcium which is involved in the excitation-contraction coupling process. Thus, the exact role of caffeine and theophylline in muscle contraction remains controversial. It is certainly much more complex than simple phosphodies- terase inhibition.

One final comment. In mammalian muscle fibers, it appears that chloride is also conducted down the T-tube system, which is where most of the calcium channels occur. Thus, there may be some intimate connection between chloride currents, calcium currents, charge movements, and the excitation-contraction coupling mechanism.

Dr. Hughes: In terms of transport and uptake of calcium, is there a difference between a weak muscle and a fatigued muscle?

Dr. Bryant: If you define fatigue by an inability to maintain tetanus, the answer is yes, because you could then use an agent which would improve excitation-contraction coupling, so that fewer action potentials would induce the same contraction. This might work, for example, in myasthenia; but, if fatigue were due to an overabundance of calcium, a further increase would be detrimental, and I doubt that any drug would have a beneficial effect.

Muscle Contractility

Dr. Faulkner: Whenever possible, the phenomenon of muscle weakness should be differentiated from that of muscular atrophy. Weakness is then defined as a rested muscle developing less than the expected force or power per cross-sectional area. Under these circumstances, weakness becomes an impairment in the activation of a motor unit or a muscle. The major problem

Figure 3. Highly diagrammatic magnification of single T tubule and three myofibrils (not to scale). Sarcolemma is not shown. Membrane action potential spreads through T system, through triad, into sarcoplasmic reticulum, and onto myofibril, where it initiates contraction of myofilaments.
in respiratory failure is that the respiratory muscles are inaccessible, and muscle weakness cannot be clearly separated from decreased force due to muscle atrophy. Furthermore, because these muscles are constantly in use, it is difficult to determine whether failure is due to atrophy, weakness, or fatigue.

The characteristics of weakness and fatigue may be observed in a single fiber, a single motor unit, or a muscle, or in the performance of a total organism. Regardless of the level of the assessment, weakness is evaluated most effectively relative to the maximum specific tetanic tension development of 25 to 30 newtons/sq cm, a maximum voluntary contraction. For voluntary contractions, the data must be normalized for gender, age, and body mass. Although fatigued fibers in limb muscles can be easily differentiated from nonfatigued fibers, the resistance of these fibers to becoming fatigued, or fatigueability, is more complex and dependent on (1) the nutritional status and environment of the fiber; (2) the type and number of fibers contracting; and (3) the type, frequency, intensity, and duration of the contractions. Fatigability, then, can only be evaluated on a relative basis, and it is a useful clinical concept only when comparisons are made under similar circumstances.

Traditionally, fatigue has been defined as the failure of muscle to maintain force or power during repetitive contractions. Fatigability can be defined either as the time required for the force to decrease to a given percentage of the initial value, or as the force development after a given period of time expressed as a percentage of the initial value. With volitional contractions of respiratory muscles, submaximum tasks may be sustained for hours with no apparent loss of force through the recruitment of additional motor units as the initial units fatigue. The degree of fatigue under these circumstances can be assessed by a frequency-force myogram taken before and after the task (Fig 4). Moxham and associates have used this procedure effectively to evaluate fatigue of the accessory muscles of respiration.

With regard to theophylline, little is known about the exact mechanism of the action of this drug, and there is some controversy as to its effects. It is important to distinguish between drugs that reverse the process of fatigue after it has occurred and those that delay or prevent the onset of fatigue. Currently, there is evidence that theophylline may reverse the process of fatigue, although not in every muscle. The role of theophylline in postponing or preventing the onset of fatigue is even less clear. There is also the issue of whether or not fatigue should be prevented or, with its occurrence, should be reversed. Many investigators now consider fatigue a protective device that prevents injury to skeletal muscle fibers. If fatigue does protect skeletal muscle fibers from injury, it would appear of questionable value to attempt to prevent or reverse the process with drugs. Although the mechanism of damage is unknown, it is probably tied in some way to the environment of the fiber.

Dr. Hughes: John, what do you mean by environment? Mechanical or biochemical?

Dr. Faulkner: Both; for example, the hydrogen ion is important in excitation-contraction coupling, and Edman and Mattiazzi have shown that fatigue is produced in a nonfatigued fiber merely by changing the hydrogen ion concentration.

Dr. Edwards: There is also the question of sodium. As you know, the tubular system in muscle permits rapid propagation of the action potential and more or less simultaneous contraction of the entire myofibrillar mass; however, Bezanilla et al showed some years ago that if a muscle is placed in a low-sodium state, the action potential fails to propagate completely through the fiber, and you get kinking of the myofibrillar fiber mass in its center. In other words, only the outer shell of myofibrils contracts, causing the central myofibrils to fold. We usually think of weakness and fatigue in terms of reduced force-per-unit of cross-sectional area of an entire muscle. This also applies to a single muscle fiber. In this instance, the loss of force would be weakness and not fatigue and would result from nonuniform
propagation of the action potential along the tubular system.

The other point I wish to make is the potential danger of reducing the extracellular space in patients. The extracellular space in muscle is quite small, and dehydration is one cause for muscle cramps. You can cramp with a low-sodium state or with a low-sodium space. You can change your sodium space markedly without changing sodium concentration merely through dehydration. Thus, one of the therapeutic strategies we should consider when trying to improve the muscular function is to preserve the uniform activation of the tubular system, which depends on both sodium and the extracellular space which surrounds the muscle fiber.

Dr. Roussos: Can a patient damage his respiratory muscles by breathing hard against airway resistance?

Dr. Faulkner: It is certainly possible. What is reassuring is that skeletal muscle fibers have a tremendous capacity to regenerate, even after severe injury.18

**Effects of Theophylline**

Dr. Roussos: What I would like to do today is briefly review some data regarding the effect of aminophylline on fresh and fatigued muscles, both in animals and humans. To address the problem of central vs direct action on muscle, we have stimulated the diaphragm directly and observed that aminophylline increases the transdiaphragmatic pressure in a dose-related manner.16 We have also given aminophylline to animals and found that we could enhance the recovery of the fatigued diaphragm with this drug.

**Figure 5.** Relation between electrical activity of diaphragm (Edi) and transdiaphragmatic pressure (Pdi), with (open circles) and without (closed circles) aminophylline. Increase in contractility with aminophylline was highly significant (p<0.001) (from Aubier et al).17

We then applied these observations to humans by comparing their transdiaphragmatic pressure at constant pulmonary volume. We had our subjects make inspiratory efforts of varying intensity against an occluded airway so that the pulmonary volume and the geometry of the diaphragm remained relatively unchanged. We then infused aminophylline to produce a blood level of 15 to 18 mg/L and produced a 10 to 15 percent increase in transdiaphragmatic pressure for a given electrical activity (Fig 5).18

We have also addressed the question that John Faulkner raised: does theophylline prevent fatigue? We asked our normal subjects to breathe against a high inspiratory resistance, either with or without aminophylline infusion (Fig 6).18 We controlled diaphragmatic geometry and fiber length at all times by placing a cast around the lower ribs. The dotted line (Fig 6)

**Figure 6.** Response of four subjects to percutaneous stimulation of right phrenic nerve before (solid line) and after (dotted line) resistive breathing for 20 minutes. A (top), Without aminophylline; B (bottom), with aminophylline infusion. Note that infusion of aminophylline before and during fatigue runs prevented loss in transdiaphragmatic pressure (Pdi) (from Aubier et al).1
represents 20 minutes of breathing against 80 percent of maximum transdiaphragmatic pressure. In every instance, the force-frequency curve was less shifted to the right than during the control infusion. This indicated to us that aminophylline permitted the same tasks to be performed with less fatigue.

Murciano and colleagues\(^*\) have applied the same idea to patients receiving long-acting theophylline orally. Both at 7 days and 21 days after starting theophylline, their transdiaphragmatic pressures were higher than during placebo control. This study looked only at transdiaphragmatic pressure and did not address the problem of the effects of theophylline on voluntary effort and central drive. In conclusion, in the isolated preparation in animals and in man, the introduction of aminophylline appears to improve diaphragmatic performance. It appears to do this both by increasing contractility and reversing fatigue and perhaps also by preventing fatigue.

**Discussion**

**Dr. Faulkner:** I would like to explore Richard’s catastrophe theory of muscle fatigue. In our observations of fatigue—in *vitro*, *in situ*, and with voluntary contractions—fatigue does not appear to be an event that occurs rapidly. Fatigue appears gradually, even in a single fiber. I agree that during high-frequency fatigue *in vitro*, fibers do drop out suddenly, but with low-frequency fatigue, portions of fibers, especially the inner portions, lose their ability to develop tension little by little. This does not appear to fit with the catastrophe theory.

**Dr. Edwards:** I do not think that the size of the dropout matters very much. The whole purpose of the catastrophe theory was to reconcile two views debated at a recent Ciba Foundation Symposium\(^*\) that fatigue has (a) nothing to do with chemistry and everything to do with electricity and (b) the reverse. It was an attempt to demonstrate that the truth probably lies somewhere in the middle. The whole point of the model is that muscle membrane fatigue inevitably results in a saving of energy expenditure.

**Dr. Faulkner:** Charis, your control subjects experienced a steady decrease in tension breathing at 80 percent transdiaphragmatic pressure, while those receiving aminophylline did not. This implies that theophylline is somehow increasing energy delivery and that we should not be looking for an effect on excitation-contraction coupling.

**Dr. Bryant:** I also have a question. To what extent did you find a correlation between contraction and the electromyogram (EMG)? In other words, is aminophylline affecting the EMG, rather than transdia-

**Dr. Rousos:** I want to point out that we have not determined where theophylline acts; but, for a given delivery of electrical activity, both during spontaneous breathing and electrical stimulation of the nerve, aminophylline produced a higher force in the muscle. During stimulation of the phrenic nerve, we measured the evoked action potential with a surface electrode and did not find any difference before and after theophylline.

**Dr. Edwards:** That is an important observation. What you measure from the surface of the diaphragm is the sum of many asynchronous events. If you change the excitability or the intrinsic firing frequency of the central motor neurons with theophylline, you could change their synchronization, which is an important factor in controlling the shape of the force-frequency curve. The reason we get such nice smooth muscle contractions while, for example, using our limbs, is because the low stimulation frequencies are asynchronous. If you change the degree of synchrony between motor units, you change the position of the force-frequency curve without fatigue.

**Dr. Hughes:** Charis, did your subjects feel weak or fatigued while breathing at those loads?

**Dr. Rousos:** I was one of those subjects, and I can assure you that, after breathing at 80 percent maximum transdiaphragmatic pressure for 20 minutes, I felt exhausted. After theophylline, I felt I could go on forever.

**Dr. Edwards:** That’s an unfair question. Physicians often use weakness and fatigue interchangeably, but to distinguish them, we must have some independent measure of how much respiratory muscle Charis has. Otherwise, you cannot decide whether he had inadequate (weak) musculature, or whether he used his muscles to a degree that they were failing to work properly. Force per unit of cross-sectional area is the best index of weakness. If you know the starting point of an illness and can determine that the force being generated is inadequate or gets worse with continuing activity, that is fatigue; but, if you don’t know the status of the patient at the start of his illness, you cannot tell the difference. Both, of course, may exist in respiratory failure, but you have to keep the patient alive, so you rest him. Rest will allow fatigue to recover but will also allow atrophy to proceed unless you attempt to prevent loss of muscular mass by nutritional support.

**Dr. Vinod Sahgal:** Does the percentage of type 1 and type 2 fibers influence muscular force?
**Dr. Faulkner:** Not to any significant degree. Type 1 fibers may develop slightly less force per unit area than type 2 fibers. For bundles of human muscle fibers, the force developed per square centimeter of cross-sectional area is not significantly different among the three types of fibers.

**Dr. Edwards:** I would also agree with that. As you know, type 2 fiber atrophy is a common nonspecific finding in muscle, but it cannot be equated to muscle weakness. You must know the exact cross-sectional area of the muscle before defining weakness. John's group has also shown that the angle of a fiber is as important as the size in generating force, so muscle weakness is not merely a matter of fiber size and number.

I would like to return to the importance of a patient's history in terms of therapy. As you know, Gertz et al. detected profound reductions in muscle metabolites in patients with respiratory fatigue and chronic pulmonary disease. Since the endurance capacity of muscle is somehow determined by its glycogen level, it is apparent that managing these patients will be determined by how and why they have depleted their muscle metabolites. Bearing in mind that much of the interest in force generation in muscle has been dominated by thoughts of anaerobic metabolism, I would like to also draw your attention to the importance of the role of aerobic metabolism, since the extent to which a muscle can keep going clearly depends on its aerobic capacity well as its muscle glycogen. In this regard, there are some interesting data which suggest that mitochondrial oxidative metabolism may actually be damaged after a period of hypoxia. If this is really true, it may mean that giving oxygen after acute hypoxia could be ineffective, if the mitochondria are incapable of synthesizing high-energy phosphates. Improving diaphragmatic function in patients with COPD depends not only on muscle mass, glycogen level, and the presence of fatigue, but also on the state of the mitochondria. You might ask then: can the diaphragm in patients with COPD recover in the face of prolonged hypoxia? The answer is probably yes, since the oxidative metabolism in muscles that are chronically hypoxic, as in patients with intermittent claudication, is actually better than normal, with enzymatic activities that are close to those of a trained athlete. This almost certainly represents tissue adaptation to impaired oxygen delivery, a factor which is virtually impossible to define clinically but crucial in predicting what may happen if we intervene therapeutically.

**Dr. Hughes:** We frequently give aminophylline to patients recovering from acute respiratory failure and acute hypoxia. Would this influence the success of our weaning efforts?

**Dr. Roussos:** That is a crucial question about which we have very few data. It is our impression that patients do not wean as easily when aminophylline is discontinued, but this is anecdotal. Dr. Bryant, could you speculate on how verapamil blocks the action of theophylline?

**Dr. Bryant:** In vascular smooth muscle, there is some evidence that calcium blockers also block theophylline activity; however, the data in skeletal muscle are conflicting. Although verapamil decreases calcium currents, other blockers actually potentiate muscle twitches at very low concentrations of the drug. I cannot explain these actions in terms of calcium blocking activities.

**Dr. Edwards:** One factor we have not discussed is the effect of theophylline on blood flow. In the diaphragm, which has an extraordinarily large blood flow, a small change may make an enormous difference in its fatigability. Both aminophylline and verapamil are vasodilating drugs. Although blood flow is not important when it comes to static force generation, it is critical in preserving resistance to fatigue.

**Dr. Faulkner:** If the theophylline-treated diaphragm is more resistant to fatigue, two mechanisms are possible. If the efficiency of the contractile process does not change in fatigued compared to rested muscle, then more energy must be delivered to sustain a higher force development. An alternative mechanism might be for the theophylline to increase the efficiency of the contractile process. If theophylline increases the force development without increasing efficiency or energy delivery, muscle fibers are more likely to sustain an injury resulting from the imbalance between energy use and energy delivery.

**Dr. Roussos:** In our observations, I can only define "efficiency" in loose terms; after theophylline, we observed a greater force across the diaphragm. I would call this an improved "efficiency," even though by strict definition it may not be.

I would like to return to the patient with COPD who has all the problems we have mentioned: metabolite depletion, malnutrition, and perhaps disuse atrophy secondary to mechanical ventilation. If you take such a patient off the ventilator, and he maintains his carbon dioxide tension for three hours, but is then unable to continue generating adequate pleural pressure, how would you define this?

**Dr. Faulkner:** Muscle fatigue, probably brought on by muscle weakness.

**Dr. Edwards:** You are raising another important point—to what extent is weakness going to be a determinant of fatigue? Are they proportional? Weak-
ness must be a determinant of fatigue if you accept a standard work rate demanded by the mechanics of the chest. The time to fatigue will be a function of the percentage of maximum force being used, while the maximum force to a large extent will be determined by fiber composition, etc. That has to do with strength; however, if you set about training somebody with weakness, what is the relationship between weakness and endurance? If you change strength or maximal force generation only slightly, you will achieve a very large improvement in endurance (which merely reflects the curvilinear relationship between work and time). This is a very different situation from the Burke paradigm that weak muscles fatigue less readily than normal muscles. What Charis is asking is how to determine maximum force in such a clinical setting. In your patient, we would first have to test the maximum pressure at the mouth during obstruction, then intervene in some fashion, and then determine whether high-frequency or low-frequency fatigue is present.

**Dr. Roussos:** But how can you determine the maximum force in an acutely ill patient in an intensive care unit?

**Dr. Faulkner:** You define his change with time. Define the maximum force at time zero and again after 15 minutes, and determine the rate of change. If the pressure you measure is falling, it's fatigue. If it's being maintained, it's probably weakness that brought him into the intensive care unit. To really define the difference, you would have to estimate his customary maximum strength before his becoming acutely ill.

**Dr. Edwards:** That's right. The whole strategy behind weakness is to build up muscle, which is one of the major problems in the intensive care unit. It is very difficult to build muscle when patients are catabolic, their muscles inactive and their calories inadequate.

**Dr. Faulkner:** Another important aspect of weak muscles is their increased resistance to fatigue. This characteristic undoubtedly makes weak muscles more susceptible to injury than normal muscles.

**Dr. Hughes:** Can you assume that a patient in respiratory failure with normal body mass has fatiguing respiratory muscles, while the patient with a reduced body mass has weak muscles?

**Dr. Edwards:** I cannot answer that question precisely, but I would be much more worried about the patient with reduced body mass, especially since the mass of the diaphragm seems to parallel ideal body weight.

**Dr. Roussos:** I would say that the patient with reduced body weight has a higher probability of having both a weak muscle and a fatigued muscle. At the moment, I think that we can safely say that both of these patients should receive theophylline.

**Summary Comments**

**Dr. Edwards:** I believe we have achieved a considerable degree of agreement over what is meant by fatigue and weakness. Of the two, we are probably better able to define fatigue. Weakness may predispose to fatigue under certain circumstances, but it may also be associated with conditions where fatigue is less. The differences between fatigue and weakness require the development of new techniques to identify in the individual patient which mechanism is dominant. If there is clear evidence of fatigue, as expressed by failure of excitation-contraction coupling or incomplete activation of the muscle, then theophylline would probably be a useful intervention. On the other hand, if the muscle is not generating force because there is too little of it present, the therapeutic strategy must be an attempt to increase the mass of muscle. To help us separate fatigue from weakness, we need careful observations which are time-based in terms of force generation.

**Dr. Bryant:** From the perspective of drug-muscle interaction and theophylline in particular, there is a clear problem with dosage levels used for in vivo and in vitro experiments. The differences are somewhere in the order of several hundredfold. This emphasizes the fact that mechanisms by which theophylline affects muscle function are not really understood well. There may be a number of other drugs that improve muscle function, particularly the so-called twitch potentiators, which may prove more useful than theophylline in improving muscular tension. Antagonizing the effects of theophylline with a calcium-blocking agent is an interesting phenomenon and needs to be verified. We need to better coordinate the efforts of the clinical and experimental laboratories to help explain some of the differences we have discussed today.

**Dr. Faulkner:** For clinical purposes, weakness may imply either muscle atrophy or an impairment in activation. Although we are in fair agreement that low-frequency fatigue is caused by some process in excitation-contraction coupling, we are at a loss to explain the exact mechanism. This makes it difficult to interpret how theophylline affects the process of fatigue, but it appears to have some effect. We will need to know much more about the basic physiology of fatigue, as well as the pharmacologic effects of theophylline, before the drug can be used effectively.

**Dr. Roussos:** I think it is inescapable to say that theophylline, both at high doses and therapeutic doses, does increase the contractility of respiratory muscles, reverse fatigue, and perhaps prevent fatigue. Certainly, the mechanism is not known, and this is an area that needs much more work.
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