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EDITORIAL

Theophylline and the respiratory muscles: where are we?

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Improving respiratory muscle function would be beneficial in a variety of situations relevant to clinical respiratory medicine including chronic obstructive pulmonary disease (COPD) [1–3], respiratory failure [4, 5], and weaning patients from artificial ventilation [6, 7]. In recent years, several drugs have been claimed to beneficially alter the function of the respiratory muscles, among which theophylline and other methylxanthines have received considerable attention [8–12]. Nevertheless, the precise mechanisms of their effects [10–12], their relevance to clinical medicine [13–18], and the dosage at which these effects would be obtained, all remain a matter of controversy [19, 20]. Several recent studies have re-examined the effect of theophylline on respiratory muscles *in vitro* and they throw new light on the mechanisms involved.

The evidence supporting the claim for improved respiratory muscle "contractility" was recently reviewed in this journal [19]. It consists of data obtained *in vitro* [19, 21, 22], in whole animals [23–26], in normal subjects [9, 27] and in patients [3, 28]. Although some of these observations have been disputed by other investigators [19], they essentially show that theophylline amplifies force production at low stimulation frequencies in both fresh and fatigued diaphragm. In three observations [3, 9, 29], it was implied that maximal tetanic force also increased with theophylline, but since the latter is likely to be determined by the intrinsic strength of contractile material during maximal actin-myosin cross-bridge interaction [30], this cannot be interpreted as an effect on the muscle itself. In contrast, other studies failed to demonstrate a theophylline-induced increase in force production at *in vivo* attainable serum levels on the diaphragm [20, 31, 32] or on other skeletal muscles [33–35]. The issue of the magnitude of the effect, its reproducibility and the question of whether or not it is achieved at *in vivo* attainable serum levels was more than adequately addressed in the aforementioned review [19]. The present paper will focus on what basic alterations in the contractile machinery of the muscle may be responsible for this "improved contractility".

In the aforementioned studies, the term "improved contractility" apparently meant increased twitch tension or increased unfused tetanic force in response to low frequency stimulation, demonstrated on both fresh and fatigued muscle. Recent work, however, showing that aminophylline promotes recruitment of expiratory muscles in supine anaesthetized dogs [36] points to potentially confounding variables. From the experimental point of view, recruitment of expiratory muscles emphasizes the need for *in vitro* experiments in which neural activation, muscle length and afterload are kept constant. Indeed, recruitment of expiratory muscles may reduce functional residual capacity (FRC) and lengthen the diaphragm and, hence, change diaphragmatic preload. In addition, tonic contraction of abdominal expiratory muscles may impose an afterload on the contracting diaphragm, whereas a similar contraction of rib cage expiratory muscles may impose an afterload on the inspiratory rib cage muscles.

It remains to be seen whether theophylline also promotes recruitment of expiratory muscles in patients. If so, it would probably correspond to a new and beneficial action of theophylline, never demonstrated before. Recruitment of expiratory muscles in patients with chronic obstructive lung disease may be beneficial for two reasons. Firstly, in the absence of expiratory flow limitation it divides the work of breathing over more muscles and, to the extent that it reduces the work performed by each individual muscle, it may reduce the sensation of dyspnoea in a way which is independent of an effect on respiratory muscle "contractility" itself. Secondly, if the optimal length of the diaphragm were to correspond to a lung volume below FRC in these patients [37], reduction of FRC may lengthen the diaphragm and, hence, optimize diaphragmatic function.

Nevertheless, irrespective of recruitment of expiratory muscles, in whole animal procedures, and in patient studies, it is not possible to distinguish between effects on the muscle itself and effects on muscle blood flow or substrate delivery. Moreover, in patients alterations in respiratory muscle strength may be susceptible to variations in patient co-operation in these performance tests. Recent *in vitro* experiments have contributed to development of another view on drug-induced alterations in respiratory muscle function and to distinction between effects on muscle "contractility" and other potential effects.

Indeed, it was recently demonstrated that maximal fused tetanic force was not affected by theophylline in both rat [38] and dog diaphragm [39]. On the contrary, in dog diaphragm a tendency for maximal tetanic force to decrease was even present [39]. In accordance with previous studies, twitch-tetanus ratio and twitch tension

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were increased by theophylline. Twitch-tetanus ratio increased by about 50% in rat diaphragm at a concentration of 500 $mg \cdot l^{-1}$ [38], whereas in dog diaphragm it increased by about 24% at a concentration of 400 $mg \cdot l^{-1}$ [39], indicating that the observed effect was greater in rat diaphragm than in dog diaphragm. Moreover, the effects were much smaller and presumably non-existent at serum levels attainable *in vivo* [39, 40]. The drug was shown to diffuse rapidly and readily into the muscle bundles, since after a 30 min incubation period the drug concentrations in the bundle and in the tissue bath were virtually the same. This questions the significance of problems with drug diffusion that have been postulated before [21] on the basis of the greater responses in isolated rat diaphragm fibres than in rat hemidiaphragm preparations. In any event, since COPD patients probably activate their diaphragms at relatively low frequencies during respiratory efforts [5], this increased force output at low stimulation frequencies might be beneficial in clinical settings, provided it occurs at *in vivo* attainable serum levels.

In this context, it is noteworthy that force amplification at low stimulation frequencies was greater in rat diaphragm than in dog diaphragm, the former being similar to that previously observed in mice [8], guinea-pig [22] and hamster [41]. This indicates a species difference in the response of diaphragm fibres to theophylline. Although the precise mechanism of action of theophylline at the cellular level is still open to question, interference with transmembrane [12] or intracellular calcium transport mechanisms [10, 11] is likely to be important, although other effects such as hyperpolarization of the cell membrane [41, 42] or inhibition of adenosine receptors [43] may also be involved. As a consequence, since important species differences and important differences among muscles within one species are found in calcium reuptake mechanisms [44], a different sensitivity to drugs acting on these mechanisms appears highly probable.

In recent experiments, fatiguability of theophylline-treated bundles *in vitro* was also examined [38, 39]. Surprisingly, a tendency was present for theophylline-treated bundles to fatigue faster, although this was more evident with high frequency stimulation than with low frequency stimulation. Moreover, theophylline-treated bundles did not recover faster from fatigue than control bundles. When the drug was added to the muscle bath after induction of fatigue, low frequency, but not high frequency, stimulation yielded greater force production in accordance with previous studies [8]. Whether this observation should be interpreted as a fundamental alteration in the fatigue process and not merely as a "distortion of the force-frequency curve" as in fresh muscle remains open to question. In any event, no evidence for a protective effect against the development of muscle fatigue was found, suggesting that the increase in force production at low stimulation frequencies may be obtained at the expense of the increased muscle oxygen consumption or increased substrate utilization. Hence, studies of the effect of theophylline on muscle oxygen consumption, intracellular adenosine triphosphate (ATP) or phosphocreatin content need to be performed. Other recent work demonstrates that intracellular pH was decreased by theophylline (C.D. Shee, unpublished observations) and this in fact may contribute to increased fatiguability.

Although undoubtedly theophylline increases force production at low stimulation frequencies, provided a sufficient dose is administered, it does not affect maximum fused tetanic force, nor does it appear to protect against the development of muscle fatigue. *In vivo*, however, these effects may be overshadowed by potential effects of the drug on respiratory muscle blood flow or respiratory muscle interaction and, as a consequence, the immediate clinical relevance of our recent *in vitro* work may be limited. It is, however, of great relevance for future development of drugs acting on the respiratory muscles to distinguish between an effect on the contractility of the muscle itself and an effect on muscle blood flow or respiratory muscle interaction. Therefore, data on oxygen or substrate delivery and utilization of theophylline-treated muscle and observations on recruitment of expiratory muscles induced by theophylline, appear to be needed in assessing beneficial and adverse effects.

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