and noise-to-signal ratio in healthy intubated subjects receiving mechanical ventilation. A DSA of 5% had the best reproducibility and lower noise-to-signal ratio [3]. As expected, in healthy subjects (fig. 1a in our paper [4]) V_{AE} corresponds narrowly to the difference between expired tidal volume and $V_{D,aw}$ measured either by the methods of FOWLER [5] or by the method of LANGLEY [6] (personal observations). In disease (fig. 1b in our paper [4]), alveolar heterogeneity is more prominent and V_{AE} (measured at 5% DSA) is progressively lower, and parametrizes, as R. Fletcher and G.B. Drummond pointed out, the progressive bending of the raising limb of the $V'_{CO_2}(v)$ curve. These phenomena are the consequence of the increased alveolar heterogeneity present during disease, no matter what its origin.

In fact, this model is used in the classical analysis of volumetric capnography (expiratory oxygen fraction; $F_{E,CO_2}(v)$) [7], as R. Fletcher and G.B. Drummond stated in their letter. Analysis based on the shape of Phase III, Phase II or the transition from Phase II to Phase III, the clinical use of end tidal CO_2, *etc.*, are implicitly based in the model of serial compartments, and the simplified hypothesis of serial alveolar gas exhalation. In other studies, the so-called "alveolar sampling" is frequently based on the same model.

A second point is related to our purpose of obtaining reliable and easily computerized parameters in order to increase the understanding and clinical use of capnography to monitor respiratory function. We believe that one of the reasons of the relatively low application of capnography is that usual parameters (Phase III slope, $V_{D,aw}$) need to be measured by hand. Indeed, $F_{E,CO_2}(v)$ curve is difficult to parametrize without a visual identification of reference points, even in healthy subjects. Moreover, the most sensitive part of the curve $F_{E,CO_2}(v)$, the Phase III, has a considerable amount of noise. Finally, some of the most usual parameters of the $F_{E,CO_2}(v)$ curve do not have a clear physiological basis, this is the case of the Phase III that assumes linearity for the rate of rise in the $F_{E,CO_2}(v)$ when usually the rate of raise is curvilinear. This implies that the identification of the beginning of the Phase III is subjective in the majority of patients, particularly in presence of significant heterogeneity (fig. 2c in our paper [4]). On the contrary, the $V'_{CO_2}(v)$ curve is easier to parametrize because it only has two phases and one transition point. Moreover, the level of noise is very low, particularly in the part where the amount of information is crucial.

In our opinion, the $F_{E,CO_2}(v)$ curve is acceptable for visual understanding of the pathophysiology of some lung diseases, but $V'_{CO_2}(v)$ allows automatic computerization of capnographic parameters, and seems more useful for continuous monitoring of alveolar heterogeneity.

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Difficult asthma

The European Respiratory Society report on difficult asthma indicates the need for more co-ordinated research in this area [1]. This is highlighted by recommendations of the use in brittle asthmatics of continuous subcutaneous infusion of terbutaline (CSIT) in this and other recent state-of-the-art reviews [2].

There has, in fact, only been one published randomized placebo-controlled trial of such therapy [3]. Four patients with brittle asthma were randomized to CSIT or placebo. Two patients showed significant improvements in peak expiratory flow during the study period, whereas the other two showed no improvement. The only other study published in full was an open study, in which 13 of 17 patients with brittle asthma showed subjective and objective benefit [4]. A more recent study of CSIT in difficult asthmatics has demonstrated reduced healthcare requirements [5].

Thus, while there appears to be some benefit, CSIT is a technical procedure and may therefore have a large placebo effect, particularly in a group of patients with high psychosocial morbidity [6]. Treatment does have significant side-effects such as painful cutaneous nodules, tremor and palpitations.

I feel, therefore, that continuous subcutaneous infusion of terbutaline cannot be recommended for use except as part of a randomized controlled trial with clearly defined enrolment criteria.

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