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Conservative management of COVID-19 associated hypoxaemia

From the authors:

We would like to thank A. Supady and co-workers [1] for their interest in our paper [2], and the important discussion they initiated. We are very pleased to take this opportunity to respond to the questions and comments raised and to make some additional remarks. We may also refer to our response to the correspondence to the editor by Windisch *et al.* [3], which already answers some of the objections [4].

In our publication, we exclusively analyse patients from the first wave of the coronavirus disease 2019 (COVID-19) pandemic in Germany and describe a predefined treatment concept that follows known principles of physiology or pathophysiology [5]. The focus here is that even significant hypoxaemia alone does not allow conclusions to be drawn about hypoxia, and hypoxaemia alone is not a good reason for intubation. At the time we defined our treatment concept, a strategy of early intubation was recommended by many experts, resulting in mortality rates of up to 90% [6]. This concept was primarily based on the incorrect assessment that COVID-19 pneumonia is always equivalent to acute respiratory distress syndrome (ARDS), that early intubation should be used to pre-empt the rapid deterioration of patients, and that hypoxaemia is a good indication for invasive ventilation. The essential orientation parameters in all guidelines are oxygen saturation, oxygenation index (arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2})) and respiratory rate. The high mortality rates in compliance with the guideline recommendations led to certain adjustments in the target values for these parameters in newer versions of the guidelines and, by necessity, to relativisation of the recommendation grades due to a lack of evidence.

For ARDS, too, there is no evidence that intubation improves prognosis, it is merely accepted clinical practice [7]. In our opinion, the discussion about ARDS in COVID-19 only makes sense if one could derive a reliable treatment concept from it, for which, however, there is no evidence, especially in COVID-19. For this reason, the results of noninvasive ventilation (NIV) from previous studies on NIV in ARDS [8] cannot be transferred without further ado. If the indication is hypoxaemia, there is a warning against NIV failure and delayed intubation when using NIV. In the study by Karagiannidis *et al.* [9], an increased mortality under invasive ventilation is currently associated with a longer time under NIV. However, causality has not been proven here, but only assumed. It could also be a selection of patients with *a priori* worse outcome, which is much more likely and, incidentally, is not a valid argument for intubation. A recent meta-analysis concludes that timing of intubation may have no effect on mortality and morbidity and that these results might justify a wait-and-see-approach, which may lead to fewer intubations [10]. Furthermore, there is also a warning about a disease under NIV labelled as patient self-induced lung injury, the existence of which is not certain [11]. A. Supady and co-workers probably have this phenomenon in mind when they point out that lung damage also occurs under NIV. The decision to intubate should always depend on the underlying pathophysiology. Only ventilatory failure, *i.e.,* hypercapnia, is a confirmed and pathophysiological comprehensible indication for ventilation. In our patient population we have never seen hypercapnia or even respiratory acidosis under NIV.

In the first German guideline, as well as in updates of the guideline, we saw an overemphasis on hypoxaemia and the oxygenation index under spontaneous breathing, as well as a lack of consideration of the parameters oxygen content and oxygen delivery. However, the latter are decisive for the development of hypoxia [12]. The increase in lactate then indicates the switch from aerobic to anaerobic metabolism. We were able to show in our patient cohort that the critical limits of oxygen content of 11 mL per 100 mL

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was not reached by any patient, despite oxygen saturation measured by pulse oximetry (S_{pO_2}) values of often clearly <90%. We agree with A. Supady and co-workers that a direct measurement of oxygen delivery would be desirable. However, correct measurement is not possible without invasive measures and we did not see sufficient indication in our patient population. We relied on the calculation of oxygen content for estimation and monitored cardiac function, especially by regular determination of troponin and brain natriuretic peptide during the course, and of course by (noninvasive) blood pressure measurements and echocardiography when needed. We did not see a drop in blood pressure in any patient on oxygen or NIV therapy, but we did see it regularly after intubation.

Our paper is criticised for insufficient description of disease severity in our patients. In particular, clinical scores such as Sequential Organ Failure Assessment (SOFA) or Simplified Acute Physiology Score (SAPS) II are postulated. We have deliberately refrained from using these clinical scores, as they are not validated for COVID-19 and are mainly used as prognostic parameters in ventilated patients in intensive care, but are certainly no help in finding the most effective therapy. Moreover, these scores are also worsened by intubation itself with a drop in the oxygenation index and the almost always necessary catecholamine administration due to the drop in blood pressure. Therefore, the score systems are not helpful for the primary understanding of the pathophysiology; this also applies to P_{aO_2}/F_{IO_2}, which is an essential component of SOFA and of SAPS II. Thus, the oxygenation index becomes the focal point of all discussions. The oxygenation index is methodologically already difficult to determine under spontaneous breathing and is not validated here. In a right-to-left shunt, which is typically the main cause of gas exchange disturbance in pneumonia, one can easily increase oxygen administration to over 10 L without a significant increase in P_{aO_2} or S_{pO_2}. So, practically, P_{aO_2}/F_{IO_2} can be brought below 100 quickly without changing anything in the pathophysiology or disease severity [13].

The use of clinical scores may be helpful in everyday life for estimating prognosis and they are also established in some countries for calculating cost expenditure and thus for the reimbursement system. However, they only lead to a very limited comparability of groups, which is an inherent problem of the system.

We are well aware that any generalisation of study results is wrong. Medical interventions should always be individual. The pathophysiological principles, however, always apply and should always be in the foreground. We are also fully aware that any comparability of patient groups and of intensive care unit studies in general has limitations. Given the large and obvious differences in mortality between invasive ventilation and NIV or non-ventilation in COVID-19, a randomised study may be a problem for ethical reasons.

In order to avoid an inappropriate comparison of our group with others, we compared our mortality of ~8% with the mortality of all patients in German hospitals across all degrees of severity and all age groups from the first wave [14]. This group of "all comers" may certainly be regarded as less ill.

We are convinced that the current mortality of ~50% under invasive ventilation, which means ventilation failure, is also a clear call to look for better treatment concepts and, in the absence of other evidence, to avoid intubation as long as possible and to orientate ourselves primarily on the clinical gestalt of the patients. Last, but not least, we should be aware of all facets of post-intensive care syndrome in the group of survivors after intubation. Not all problems are resolved after a patient is weaned from the ventilator and discharged from the hospital [15].

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