Table 1 Comparison of a hemodynamic parameters between the responders, non-responders, and discordant groups. Values are expressed as mean (standard deviation) or mean ($CI_{95\%}$). CO, cardiac output; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; ΔrespSV, respiratory stroke volume variation. Data were compared using ANOVA with the *post hoc* Bonferonni test. [a]$P<0.05$ non-responder *vs* responder. [b]$P<0.05$ non-responder *vs* discordant. [c]$P<0.05$ responder *vs* discordant. *$P<0.05$ between baseline and volume expansion

	Non-responders ($n=58$)	Responders to SV and CO ($n=64$)	Discordant ($n=16$)
HR (beats min^{-1})			
Baseline	67 (18)	67 (17)	78 (18)[b,c]
Volume expansion	66 (17)	69 (17)	68 (12)*
MAP (mm Hg)			
Baseline	75 (13)	76 (12)	74 (15)
Volume expansion	77 (15)	81 (14)*	77 (13)
SV (ml)			
Baseline	84 (20)	69 (16)[a]	72 (19)[b]
Volume expansion	87 (22)*	91 (20)*	88 (22)*
CO (ml min^{-1})			
Baseline	5.5 (1.9)	4.5 (1.2)[a]	5.5 (1.5)[c]
Volume expansion	5.6 (1.9)	6.3 (2)*	6 (1.7)*
ΔrespSV (%)			
Baseline	11 (5)	21 (9)[a]	26 (10)[c]
Volume expansion	10 (4)	11 (6)*	15 (11)*[b,c]
Variation of HR with volume expansion (%)	−1 (−4; 2)	3 (0; 6)	−11 (−17; −6)[b,c]
Variation of SV with volume expansion (%)	3 (1; 6)	34 (28; 40)[a]	20 (17; 24)[b,c]
Variation of CO with volume expansion (%)	2 (−2; 5)	38 (32; 44)[a]	6 (0; 12)[c]

be interpreted in terms of the variations of its two determinants (HR and SV). In some cases, the absence of increase in CO in response to fluid infusion may not indicate the absence of effect. Monitoring SV may provide more reliable information concerning the effect of fluid infusion. It may be preferable to use a definition of fluid responsiveness based on SV variation in studies testing the ability of an indicator to predict fluid responsiveness.

Declaration of interest

None declared.

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Efficacy of dexmedetomidine compared with midazolam for sedation in adult intensive care patients

Editor—In a recently published article,[1] Dr Adams and colleagues review, among others, two of our studies addressing dexmedetomidine for sedation in critically ill patients.[2 3] While we agree with their overall conclusion that 'so far the evidence of advantages of dexmedetomidine in the ICU setting remains limited', we would like to address some of their criticism of our studies.

Dr Adams and colleagues mention that we did not find statistically significant differences in sedation between midazolam and dexmedetomidine treatment groups. We believe that they have missed important aspects of our study design:[3] our main interest was to assess the effect of the sedative drugs on length of mechanical ventilation, with the prerequisite that dexmedetomidine is not inferior to midazolam (and propofol) in maintaining the target sedation. We therefore used two hierarchial co-primary endpoints—first, assessing non-inferiority, and then comparing the effect on duration of mechanical ventilation. Only if the non-inferiority was confirmed, could the effect on mechanical ventilation be assessed. Non-inferiority designs have not been used before in assessing any current sedative drugs: our design requesting proof of non-inferiority in maintaining sedation before testing the hypothesis of shorter mechanical ventilation should be considered more rigorous compared with the conventional designs showing 'no difference'. We also tested the secondary outcome variables with the prerequisite that dexmedetomidine sedation was non-inferior (or at least as good) as sedation with the standard drug—something that has not been shown for any prior sedative.

Further, the authors state that 'The main problem with assessing the effectiveness of sedation is that most measurements are made from subjective scales and that only one

study[4] included BIS as an objective measurement'. We find this statement misleading. BIS has never been adequately validated for monitoring sedation in the ICU. We and others have demonstrated the major problems associated with BIS-guided sedation at light to moderate sedation levels.[5 6] In contrast, standard sedation assessment with RASS has been validated.[7] While the proposal of Adams and colleagues that all assessments should have been performed by the same blinded investigator is scientifically correct, this is a highly unrealistic suggestion for a multi-centre study including 1000 patients and 2-hourly sedation assessments.

We believe that there are other inaccuracies of important features in their critique of our studies. The claim that we did not report blinding of RASS assessors is incorrect: we described the double-blinded, double-dummy design, where sedatives and dummys were prepared, connected, and removed by independent personnel, so that those making the RASS assessments were indeed blinded to the treatment (Methods section, paragraph 'randomization and masking'). Adams and colleagues also comment that patients who received or did not receive rescue sedation were not independently analysed. In both PRODEX and MIDEX trials,[3] almost 50% of the patients needed rescue sedation at some time point (Table 2 of the original manuscript). In the study by Ruokonen and colleagues,[2] the percentage was close to 80% in each group (Electronic supplement, paragraph 'rescue medication'). The result of analysing the primary outcome separately in only those patients who could be sedated by the study drug alone would be of little clinical significance. We do not agree that omitting such an analysis 'leads to difficulties in accurately interpreting the conclusions'.

Finally, Adams and colleagues claim that there are numerical inconsistencies with respect to total number of excluded patients, and of patients with treatment withdrawal. We are surprised by this claim, especially since we have explained this to the authors in response to their direct correspondence with us: the total numbers are smaller than the sum of all reasons since several reasons could simultaneously apply, as clearly mentioned in the legend to Figure 1 of the original manuscript.[3] The 'inconsistency' in the number of patients with serious adverse events in the article by Ruokonen and colleagues[2] relates to mix-up of 'numbers of SAE' and 'patients with SAE': the correct numbers of SAE and patients with SAE are found in the electronic supplement of the manuscript by Ruokonen and colleagues.

Declaration of interest

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Reply from the author

Editor—Thank you for the opportunity to respond to the letter of Jakob and colleagues which was written regarding a recent review published in the *British Journal of Anaesthesia*.[1] I should say at the outset that we accept that Jakob and colleagues have performed the best designed trials in this area and apologize if the article gave the impression that this was not the case.

On the subject of non-inferiority trials, I am afraid we are going to have to agree to disagree. I acknowledge that there is a problem facing clinical research in that trials are increasingly being required to show benefits on clinically meaningful endpoints rather than surrogate endpoints (e.g. biochemical). This has resulted in investigators using an 'equivalence' or