Liposomal Bupivacaine's Effect on the Diaphragm: Comment

To the Editor:

We read with great interest the article by Berg *et al.*[1] about the evaluation of diaphragmatic excursion after interscalene nerve block with liposomal bupivacaine *versus* plain bupivacaine.

In their study, the authors investigated as a primary outcome the effect of liposomal bupivacaine combined with plain bupivacaine *versus* plain bupivacaine alone on diaphragmatic excursion during sigh (deep) and sniff (shallow) breathing in patients undergoing total shoulder arthroscopy in the immediate postoperative period and after 24 h.[1]

The study did not detect a difference between the two groups in absolute values of diaphragm excursion during a sigh breath at 24 h ($P = 0.112$), despite a greater than 1 cm difference observed. In addition, a significant difference between groups was noted in the percentage change with respect to preblock levels: −24% in the liposomal bupivacaine with bupivacaine group compared with +9% in the bupivacaine group.

The authors concluded that the addition of liposomal bupivacaine to bupivacaine, in an interscalene block, results in statistically significant reductions in diaphragm excursion and pulmonary function testing 24 h after block placement compared with bupivacaine alone. The accompanying editorial underlined the need for caution in the use of liposomal bupivacaine for interscalene nerve block in patients with any pulmonary compromise.[2]

We have two comments on this study. First, we observed that the two groups were already rather different in their baseline values, as reported in their table 2. This was particularly true for the diaphragmatic excursion (higher in the liposomal bupivacaine with bupivacaine group), the percent change of which at 24 h was the primary outcome of the study.[1] The authors did not discuss this issue, but, indeed, this baseline difference might have influenced the finding of a larger percent change in diaphragmatic excursion at 24 h compared with baseline.[1]

Second, the authors used the percentage change in diaphragmatic excursion as a measure of the level of diaphragmatic paralysis, as defined by Renes *et al.*,[3] who proposed that a 0 to 25% reduction from baseline could be considered as no paralysis, 25 to 75% reduced could be considered as partial paralysis, and a greater than 75% reduction could be considered as complete paralysis. However, as recently reported in this journal, 24 h after interscalene nerve block, the level of diaphragmatic paralysis measured with diaphragmatic excursion may be compensated by parasternal muscle activity.[4] Therefore, we believe that changes in diaphragmatic excursion alone cannot be considered as an adequate measure of diaphragmatic function.

For this reason, we propose that diaphragmatic thickening fraction can be a more appropriate tool for investigating the action of medications on the diaphragm. The thickening fraction is calculated as the maximal diaphragm thickness (assessed using linear probe) during inspiration (Tdi, pi) minus the diaphragm thickness at end-expiration (Tdi, ee) divided by the Tdi, ee and multiplied by 100.[5] Compared with diaphragmatic excursion, thickening fraction is a more sensitive and qualitatively accurate parameter and provides a more comprehensive measure of diaphragm contraction.

Excursion of the left hemidiaphragm is more difficult to assess than the right one and this is due to interference from gastric contents and the less favorable spleen's window. Berg *et al.*[1] performed 13 left blocks, but they did not comment on difficulties experienced in the evaluation of the excursion of the left hemidiaphragm. In any case, use of the thickening fraction to measure and evaluate diaphragm activity would overcome this problem and should be used in the research field.

Of course, we understand that standard perioperative ultrasound practice does not normally include calculating the thickening fraction, being a more difficult measure to obtain and is mostly used to assess weaning from mechanical ventilation in the intensive care unit.[5] As a matter of fact, there is a bit of a schism between point-of-care ultrasound use in the operating room and intensive care settings. However, the skills required to measure thickening fraction are relatively easy to acquire under expert supervision.[6]

In conclusion, considering the aforementioned limitations, we suggest caution in assessing the risk of adverse events in terms of diaphragmatic and pulmonary function, including dyspnea and oxygen need, with the use diaphragmatic excursion only.

Competing Interests

Dr. Cammarota declares a financial relationship with Getinge MSD (Växjö, Sweden). The other authors declare no competing interests.

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References

1. Berg AA, Flaherty JM, Habeck JM, Harrison AK, Braman JP, Kaizer AM, Hutchins JL: Evaluation of diaphragmatic function after interscalene block with liposomal bupivacaine: A randomized controlled trial. Anesthesiology 2022; 136:531–41

2. Xu L, Tsui BCH, Horn JL: Prolonged phrenic nerve blockade with liposomal bupivacaine. Anesthesiology 2022; 136:525–7
3. Renes SH, Rettig HC, Gielen MJ, Wilder-Smith OH, van Geffen GJ: Ultrasound-guided low-dose interscalene brachial plexus block reduces the incidence of hemidiaphragmatic paresis. Reg Anesth Pain Med 2009; 34:498–502
4. Dres M, Dubé BP, Goligher E, Vorona S, Demiri S, Morawiec E, Mayaux J, Brochard L, Similowski T, Demoule A: Usefulness of parasternal intercostal muscle ultrasound during weaning from mechanical ventilation. Anesthesiology 2020; 132:1114–25
5. Vetrugno L, Guadagnin GM, Barbariol F, Langiano N, Zangrillo A, Bove T: Ultrasound imaging for diaphragm dysfunction: a narrative literature review. J Cardiothorac Vasc Anesth 2019; 33:2525–36
6. Garofalo E, Bruni A, Pelaia C, Landoni G, Zangrillo A, Antonelli M, Conti G, Biasucci DG, Mercurio G, Cortegiani A, Giarratano A, Vetrugno L, Bove T, Forfori F, Corradi F, Vaschetto R, Cammarota G, Astuto M, Murabito P, Bellini V, Zambon M, Longhini F, Navalesi P, Bignami E: Comparisons of two diaphragm ultrasound-teaching programs: a multicenter randomized controlled educational study. Ultrasound J 2019; 11:21

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Liposomal Bupivacaine's Effect on the Diaphragm: Reply

In Reply:

We thank Vetrugno *et al.*[1] for their relevant comments on our article.[2] As Vetrugno *et al.* pointed out, the liposomal bupivacaine group started at a higher baseline diaphragmatic excursion than the bupivacaine-alone group. This was an unavoidable consequence of our randomization scheme. The difference between the groups, however, was not significant, and we do not believe it contributed to our primary outcome.

The goal of our study was not just to detect statistical differences, but to gain insights into the clinical significance of the observed changes. To do this, we used the clinical definitions by Renes *et al.*[3] of diaphragmatic paralysis. We felt that it was important to use the same technique used in that study, rather than trying to cross compare different techniques.

Although we do agree that the addition of diaphragmatic thickening would have added to the article, we stand by our conclusions. We are not aware of a comparative study of diaphragmatic thickening and excursion with clinical findings, and our results correlated well with the traditional measure of pulmonary function we measured *via* spirometry, lending credence to its validity. We still appreciate their word of caution regarding its use as a sole measure of pulmonary function, because recent research shows that diaphragmatic excursion can be influenced by accessory muscle use.[4]

Indeed, we believe that the reduction we detected in diaphragm excursion in the liposomal bupivacaine group combined with the reductions found in forced expiratory volume and forced vital capacity provides valuable insight into the clinical impact of liposomal bupivacaine interscalene blocks on respiratory function. Hence, we are confident that the addition of liposomal bupivacaine to an interscalene block did not create a clinical difference in this population.

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Competing Interests

Dr. Hutchins was a speaker, consultant, and has received research funds from Pacira Pharmaceuticals (Parsippany-Troy Hills, New Jersey); he is a consultant and owns stock with Insitu Biologics (Oakdale, Minnesota); a consultant and speaker for Acel RX (Hayward, California); a consultant for Worrell (Minneapolis, Minnesota) and Johnson and Johnson (New Brunswick, New Jersey); a consultant for Atricure Inc (Minnetonka, Minnesota); and a speaker for Avanos (Alpharetta, Georgia). Dr. Berg was a consultant for Avanos and is a consultant for Pacira Pharmaceuticals. No companies were involved with any aspect of this manuscript. The other authors declare no competing interests.

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References

1. Vetrugno L, Valent F, Cammarota G, Maggiore SM: Liposomal bupivacaine's effect on the diaphragm: Comment. Anesthesiology 2022; 137:651–2
2. Berg AA, Flaherty JM, Habeck JM, Harrison AK, Braman JP, Kaizer AM, Hutchins JL: Evaluation of diaphragmatic function after interscalene block with liposomal bupivacaine: A randomized controlled trial. Anesthesiology 2022; 136:531–41

3. Renes SH, Rettig HC, Gielen MJ, Wilder-Smith OH, van Geffen GJ: Ultrasound-guided low-dose interscalene brachial plexus block reduces the incidence of hemidiaphragmatic paresis. Reg Anesth Pain Med 2009; 34:498–502
4. Dres M, Dubé BP, Goligher E, Vorona S, Demiri S, Morawiec E, Mayaux J, Brochard L, Similowski T, Demoule A: Usefulness of parasternal intercostal muscle ultrasound during weaning from mechanical ventilation. Anesthesiology 2020; 132:1114–25

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Dural Puncture Epidural in Obese Parturients: Comment

To the Editor:

We are writing to raise some concerns about the study conducted by Tan *et al.*[1] Their article "Quality of Labor Analgesia with Dural Puncture Epidural *versus* Standard Epidural Technique in Obese Parturients: A Double-blind Randomized Controlled Study" demonstrated that dural puncture epidural did not provide additional benefits in improving labor analgesia in obese parturients.

In their study, labor analgesia was maintained with programed intermittent epidural boluses of 6 ml of 0.1% ropivacaine with 2 μg/mL fentanyl every 45 min. With such small bolus volumes, the analgesic improvement resulting from drug translocation through the dural conduit with the dural puncture epidural technique may be obscured. Moreover, the delivery rate of programed bolus dose administration was not reported in this study. Generally, high-rate epidural boluses increase injectate pressure and might facilitate drug translocation. We speculated that the inadequate bolus volume and/or the low delivery rate failed to generate sufficient pressure gradient and made the drug hard to "press" from the epidural space into the subarachnoid space.

We noticed another study conducted in the same institution using the same programed intermittent epidural bolus protocol (6 ml every 45 min) that failed to find improved outcomes compared to conventional epidural continuous infusion (8 mL/h),[2] although the attempts of patient-controlled epidural analgesia were significantly higher with programed intermittent boluses compared to that with continuous infusion. The increasing analgesia demands for pain control of patient-controlled epidural analgesia might be a surrogate for inadequate pain relief. Since there are many variables in the programed intermittent epidural bolus settings, Wong *et al.*[3] believe that the programed intermittent bolus volume and interval time might influence the quality of analgesia during the maintenance of epidural labor analgesia. In our randomized controlled study, we used relatively larger programed intermittent volumes and longer intervals (8 ml every 60 min) compared to the current study and found improved analgesia quality and drug-sparing effect with dural puncture epidural compared to standard epidural technique.[4]

For the mechanism, Tan *et al.*[1] explained that the small drug mass might fail to generate the required pressure to drive ropivacaine molecules across dural hole. However, in our study,[4] with the same concentration of ropivacaine, the results were not consistent, possibly indicating that the major reason for the failure of primary outcome of the current study might be the inadequate volume of the programed intermittent bolus rather than the drug mass.

Competing Interests

The authors declare no competing interests.

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References

1. Tan HS, Reed SE, Mehdiratta JE, Diomede OI, Landreth R, Gatta LA, Weikel D, Habib AS: Quality of labor analgesia with dural puncture epidural *versus* standard epidural technique in obese parturients: A double-blind randomized controlled study. Anesthesiology 2022; 136:678–87
2. Ojo OA, Mehdiratta JE, Gamez BH, Hunting J, Habib AS: Comparison of programmed intermittent epidural boluses with continuous epidural infusion for the maintenance of labor analgesia: A randomized, controlled, double-blind study. Anesth Analg 2020; 130:426–35
3. Wong CA, McCarthy RJ, Hewlett B: The effect of manipulation of the programmed intermittent bolus time interval and injection volume on total drug use for labor epidural analgesia: A randomized controlled trial. Anesth Analg 2011; 112:904–11
4. Song Y, Du W, Zhou S, Zhou Y, Yu Y, Xu Z, Liu Z: Effect of dural puncture epidural technique combined