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Respiratory variability during NAVA ventilation in children: authors' reply

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A commentary on

Impact of ventilatory modes on the breathing variability in mechanically ventilated infants: a commentary
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We thank Dr. Mhanna for his interesting comment (1) on our recent article about respiratory variability during different pediatric ventilatory conditions (2). In this article, we described different patterns of respiratory drive variability depending on the ventilatory modes, using synchrosqueezing transform (SST) to gage changes in the variability of the electrical diaphragm activity (EAdi). In particular, neurally adjusted ventilatory assist (NAVA) was associated with a respiratory pattern most resembling that of the pattern observed in a separate group of "normally breathing" children, without ventilatory support or respiratory distress. Dr. Mhanna appropriately underlines the difficulty to draw definitive conclusions based on our study design, in particular, because of the *post hoc* nature of the analysis and the slight differences between the mechanically ventilated group and the control group. Indeed, the patients in the control group were smaller [median 3.9 kg (interquartile 3.5–5.0) vs. 5.7 kg (4.8–6.7), $p = 0.04$] and tended to be younger [1.5 months (1–3) vs. 4.5 (2.5–4.7), *n.s.*] (2). These limitations were acknowledged and discussed in our article, and we certainly agree to consider this work as a hypothesis-generating study rather than as a definitive study.

Future studies will be needed to further address the impact of NAVA on the respiratory variability and it is important to discuss some possible future directions and/or pitfalls. Future works should be conducted prospectively and should assess the impact of ventilatory modes among comparable groups. Regarding variability analysis strategy, although the mathematical and statistical properties of SST have been well studied (3–5) and seem pertinent to analyze the respiratory signals and in particular EAdi, there is room to improve the current approach. First of all, the underlying mathematical model, adaptive harmonic model (3, 5), is limited to oscillatory signals with slowly varying instantaneous frequency and amplitude modulation. As an illustrative example, the cardiac R to R interval (RRI) between consecutive beats is seemingly irregular in normal subjects, which is often called "heart rate variability." In other words, the frequency of heart beats is time-varying. However, in the extreme case like atrial fibrillation, the RRI behaves like noise – the heart rate changes fast from one beat to another. The time-varying frequency of a normal subject's heart beats can be understood as slowly varying, while the one of a subject with atrial fibrillation can be understood as fast varying. In general, when the instantaneous frequency varies fast, the features captured from the signal by SST might not be predicted by the current theorem. The respiratory signals are oscillatory in nature, but since non-stationary changes could also occur (e.g., sudden apneas, crying, hiccup, etc), extending the algorithm to capture the fast varying instantaneous frequency is an important topic in the methodology development. Second, the intrinsic meaning of the NRR index is a quantification of how well the signal can be captured by the adaptive harmonic model. As its potential usefulness has been shown in several applications (6, 7), we should not forget that it just reflects a single facet of a complicated system. Other combinations of features extracted from the signal via SST and other techniques should be established in order to capture other aspects of our physiological system. One possible feature combination has been shown in the ventilator weaning prediction problem (8): the amplitude modulation and instantaneous frequency are combined to predict the weaning success rate.

Combining information from different signals would also be important. In our recent study, the two signals – pressure and EAdi – were analyzed separately. Only at the level of the statistical analysis was the pressure signal considered a covariate with the EAdi as dependent variable. A combination of information from these two channels, as early as at the level of mathematical bivariate signal analysis, could provide a finer dynamical feature inside physiology. However, finding a suitable technique to integrate information from multiple time series with complicated dynamics, both deterministic and stochastic, in particular in the medical field, is still a challenging problem. One possible approach to this goal is the currently proposed non-linear independent component analysis or empirical intrinsic geometry analysis (EIG) (9, 10), which has been successfully applied to a sleep dynamical study (11). Another important direction is taking other physiological signals into account. For example, the electrocardiographic signal (ECG) is ubiquitous in ICU, and certain neurocardiac features of physiological dynamics could be inferred from the heart rate variability.

Besides its major positive impact on patient ventilator synchrony (12–14) and its interest for promoting the patient ventilatory drive during mechanical ventilation (15), our preliminary data suggest that NAVA may also favor a "physiological" respiratory variability pattern (2). The proposed directions for future validation studies may permit to deeper appreciate and enhance the clinical potential of these respiratory variability modifications, in particular regarding the lung recruitment (16, 17).

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