This brings us to the second comment; the present study does not provide any information regarding the original plethysmographic signal processing used by the equipment manufacturer, Nellcor. As pointed out by Dr. Feldman, when clinical monitors are used as research tools, subtle differences in proprietary software may have a profound impact on the results. This is of major importance since both figure 4 and figure 5 strongly suggest that a less processed plethysmographic waveform was used for the analysis than previous studies. Figure 4 is especially eloquent because it shows very large oscillations in frequencies < 0.1 Hz. In the typical commercial pulse oximeter, frequency in that range would be suppressed as part of their autocentering algorithm. The presence of signal in that range alone may explain the significant discrepancy observed between ΔPP and ΔPOP in the present study. In fact, the automated system, as described, would not be able to distinguish between variations in the plethysmographic waveform amplitude that are related to respiration (at a frequency around 0.2 Hz; i.e., respiratory rate of 12 breaths/min) or those of any other cause of variations (such as those observed for frequencies < 0.1 Hz that may be related to changes in vasomotor tone). To avoid such confusing factors, a high-pass filtering (with a threshold above 0.1 Hz) would suppress the low frequency signals found in the study and would likely improve relationship and agreement between ΔPP and ΔPOP (fig. 1).

Our third comment is that it is clear that the cyclic variations in the plethysmographic waveform amplitude do not depend only on respiratory variations in the left ventricular stroke volume. As demonstrated by the present study, changes in vasomotor tone strongly influence the waveform. Thus, we believe that several factors would enhance the clinical use of ΔPOP. First, more standardized conditions, as those observed in the operating room during general anesthesia (as demonstrated by Landsverk et al. themselves in a previous study), will reduce the oscillatory components of the perfusion signal related to sympathetic myogenic activity as well as the component modulated by the endothelium. Monitoring the depth of anesthesia during experiments may also be useful to standardize ΔPOP calculations. Standardization of positive end-expiratory pressure, tidal volume, and temperature may also have an impact on the results. Second, alternative sites of measurement (such as ear or forehead) may improve the accuracy of ΔPOP, because these sites do not present the same sensitivity to changes in vasomotor tone as compared to the finger. In addition, these sites of measurement also impact ΔPOP itself up to 10-fold. Further studies should compare these different sites of measurement.

Our fourth comment is that we believe that while testing the relationship and agreement between ΔPP and ΔPOP is interesting, the key feature for further investigation is the ability of these measurements to predict fluid responsiveness and guide fluid therapy.

Finally, we feel that the study by Landsverk et al. provides important insights into the understanding of the oscillations observed in the plethysmographic waveform. These oscillations do not only depend on respiration, even if respiration plays a key role as demonstrated by spectral analysis performed in the present study and in previous ones.

We believe that in more standardized conditions, such as those observed in experimental settings or in the operating room, ΔPOP monitoring would be more robust than in intensive care unit patients. However, in more challenging situations such as in the intensive care unit, the use of improved digital signal processing (such as high-pass filtering and joint time frequency analysis) to isolate respiratory effects from other cyclic changes may have significant impact on plethysmographic waveform analysis. This kind of systematic approach will help to distinguish between artifacts and real phenomenon hidden in the morphological analysis of the plethysmographic waveform.

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References

In Reply.—First of all we would like to thank Cannesson et al. for the positive critique and discussion of our recent study in ANESTHESIOLOGY. Our motivation for performing the study was the increasing number of publications reporting that respiratory variations in the photoplethysmogram could predict fluid responsiveness in mechanically ventilated patients, based on correlation and agreement between respiratory variations in the photoplethysmographic waveform amplitude (ΔPOP) and in the invasive arterial pulse pressure (ΔPP). Because of our previous work on the complexity of human skin microcirculation these data surprised us, especially in intensive care unit (ICU) patients based on only a few measurements from each patient. Thus, we questioned the relationship between respiratory variations in ΔPOP and ΔPP in ICU patients, and found a large variability of ΔPOP and poor correlation between ΔPOP and ΔPP. We believe that the comments by Cannesson et al. are highly relevant, and below we respond to the different issues.

First, our findings are in contradiction with several studies focusing on the relationship, agreement, and ability of ΔPP and ΔPOP to predict
fluid responsiveness in mechanically ventilated patients in the operating room and in the ICU. Three studies were performed on deeply sedated ICU patients. The study by Wyffels et al. was performed on postoperative cardiac surgery patients, whereas Natalini et al. examined hypotensive ICU patients. Our study and three of the others were performed on heterogeneous ICU patients. Patient characteristics could explain some of the contradiction between the studies. However, we believe that the most important difference is how values of ΔPP and ΔPOP were selected. To be able to calculate inter- and intraindividual variability, we performed calculations continuously and time-synchronized over a period of approximately 15 min. By this continuous analysis system, we avoided potential bias in selection of data. Thus, we believe that our study illustrates the importance of performing analysis of repeatability when comparing methods.

Second, all pulse oximeters process the raw data in different ways. We agree that subtle differences in software may have a profound impact on the results. We used the analogue signal from an Oximax 451N5 (Nellcor, Boulder, CO) in our study, but do not have access to its signal algorithms. This could have given valuable information. However, details regarding signal algorithms are not given in other ICU studies. Cannesson et al. suggested that our signal is less processed than in previous studies, and that including a high-pass filter would improve the agreement. By performing a high-pass filtering, one could remove the slower oscillations from the original signal. We agree that this could be an interesting approach. However, the important question is whether filtration improves the part of the signal related to fluid responsiveness. We filtered, with a Butterworth high-pass filter (Labview, National Instruments Corp., Austin, TX), signals from one patient in our study (Patient 3), who demonstrated large, slow oscillations (fig. 1). The average values and the variability of ΔPOP and ΔPP were only modestly reduced. Even though only performed in one patient, this example illustrates that filtration of the photoplethysmogram is not a straightforward solution of the problem. In our paper we also showed that other, and probably more important, mechanisms than slow oscillations contribute to the great variability found in our study. Further investigations are needed in this field.

Third, we agree that more standardized conditions, as in the operating room during general anesthesia, monitoring depth of anesthesia, standardization of all aspects related to ventilation, temperature, and sites of measurements should be emphasized in future studies. We also agree that the key feature for future studies is the ability to predict fluid responsiveness and guide fluid therapy. However, before introducing a new method, it is imperative to demonstrate repeatability and agreement between the method and the present gold standard.

Finally, we believe that our findings in ICU patients relate to a combination of factors both in the patient (medication, diagnosis) and to the equipment, and how these factors affect the physiology and the measurement of the photoplethysmographic signal. We still believe that the photoplethysmogram has the potential to give valuable information about the volume status of patients. As the photoplethysmogram is more complex than the invasive blood pressure curve, we believe that an algorithm used in the photoplethysmogram should reflect this complexity. Regardless of algorithms, future studies comparing methods should include measurement of repeatability.

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