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 \( \Delta PP \) and \( \Delta POP \) 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 \( \Delta PP \) and \( \Delta POP \) (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 \( \Delta POP \). First, more standardized conditions, as those observed in the operating room during general anesthesia (as demonstrated by Lænsverk 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 \( \Delta POP \) 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 \( \Delta POP \), 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 \( \Delta POP \) 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 \( \Delta PP \) and \( \Delta POP \) 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 Lænsverk 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, \( \Delta POP \) 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.

**References**


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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 \( \Delta POP \) and the invasive arterial pulse pressure \( \Delta PP \). 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 \( \Delta POP \) and \( \Delta PP \) in ICU patients, and found a large variability of \( \Delta POP \) and poor correlation between \( \Delta POP \) and \( \Delta PP \). 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 \( \Delta PP \) and \( \Delta POP \) to predict...
We agree that subtle differences in software may have a profound effect on the measurement of the photoplethysmogram. We still believe that the key feature for future studies is the ability to predict fluid responsiveness in the operating room. Regardless of algorithms, future studies comparing methods should include measurement of repeatability.

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