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Perioperative Statin Therapy May Be Implicated in a Wide Array of Drug-Drug Interactions

To the Editor:—We read with interest and appreciation the excellent article by Le Manach *et al.* in the June 2008 issue of ANESTHESIOLOGY entitled “Statin Therapy within the Perioperative Period: Clinical Concepts and Commentary.”¹ However, there is an important area, namely drug-drug interactions involving statins, which merits more attention than the brief treatment in that review. We would like to make readers aware that a wide array of interactions can occur in the perioperative period and have been responsible for considerable morbidities.

The authors are certainly correct that the risk of statin-induced rhabdomyolysis is associated with coadministration of such drugs as “cyclosporin, antifungal agents, calcium-channel blockers, and amiodarone.” However, there is a much broader array of medications that is likely to inhibit the metabolism or otherwise raise blood levels of statins to increase the risk of rhabdomyolysis. Atorvastatin, lovastatin, and simvastatin are primarily metabolized by the enzyme cytochrome P450 3A4 (CYP3A4). Coadministration of any of the many inhibitors on CYP3A4 (including cyclosporin, *etc.*) will raise blood levels of these specific statins. In addition, fluvastatin is metabolized by CYP2C9, and inhibitors of that enzyme’s function will raise fluvastatin levels as well. Pravastatin’s metabolism is primarily through phase II, or conjugative, metabolism, which is more difficult to inhibit to a clinically significant degree, so it is much less susceptible to these metabolic drug interactions. Rosuvastatin undergoes^{2*} very little hepatic metabolism and it is generally excreted unchanged. How-

ever, through nonmetabolic mechanisms (probably inhibition of various transmembrane transporters), coadministration of either cyclosporin or gemfibrozil will significantly raise both pravastatin and rosuvastatin blood levels.

There is an entire other dimension to drug-drug interactions involving statins that was not mentioned at all in the article: Coadministration of statins with enzymatic inducers. These drugs will, over the course of days to weeks, increase the quantity of enzymes available for metabolism of these statins. The addition of enzymatic inducers such as phenytoin, carbamazepine, and rifampin are likely to significantly decrease the concentrations of various statins. This is a particularly important interaction, especially in view of the ramifications for cardiac morbidity, as discussed in the authors’ section on the risks of statin discontinuation in the perioperative period.

In summary, this subject is clearly quite detailed and complex. A thorough treatment of this topic was published by Bellosa *et al.*²

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* Additionally, a comprehensive table listing rigorously verified substrates, inhibitors, and inducers of the various P450 enzymes can be found at <http://medicine.iupui.edu/flockhart/table.htm>. Last date accessed December 17, 2008.

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In Reply:—We appreciate the valuable commentary provided by Marcucci *et al.* in response to our recent article on perioperative statin therapy.¹

The data supporting the efficacy and relative safety of statin therapy in the nonsurgical population continues to increase.² Statin-induced myopathy most often accompanies chronic statin therapy in patients receiving multiple concurrent medications. The perioperative period, characteristically associated with acute administration of a multitude of medications and with hemodynamic perturbation, increases the potential for drug-drug interactions with statin therapy and for altered clearance of statins. Thus, Marcucci *et al.* rightly point out that concurrent medication administration in the perioperative period might alter statin plasma levels *via* the hepatic cytochrome P450 system or other adverse drug-drug interactions, with an implication of either a reduced therapeutic effect³ or increased risk of adverse effects.^{4,5}

However, despite the theoretical concern of Marcucci and colleagues, reported adverse effects associated with perioperative statin therapy are extremely rare.⁶ We consider that the clinical relevance of these drug-drug interactions to be largely theoretical as, to the best of our knowledge, no large studies have reported considerably morbidity associated with continued statin therapy in the perioperative period, and is contrary to the unreferenced implication by Marcucci *et al.*

Marcucci *et al.*, however, reiterate a valuable point that should be considered in the daily practice of caring for the perioperative and critically ill patient—that of being aware of potential drug-drug interactions. Marcucci *et al.* provide a valuable reference against which to check the potential for drug interactions. This may also have increasing relevance in patients being exposed acutely to high-dose statin therapy—especially as we see increasing literature support a protective effect of statin therapy introduced acutely in the preoperative period.

Finally, in the absence of a large cohort reporting significant statin-associated morbidity, we feel confident that the current risk-benefit ratio strongly favors the continued administration of perioperative statins in patients who otherwise have no other contraindications to statin therapy because of their proven protective effects on adverse postoperative outcomes.

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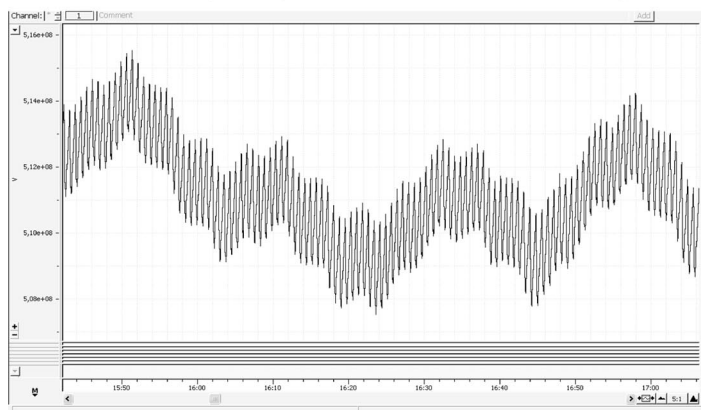
Oscillations in the Plethysmographic Waveform Amplitude: Phenomenon Hides Behind Artifacts

To the Editor:—We read with interest the study by Landsverk *et al.* investigating the relationship between the respiratory variations in the plethysmographic waveform amplitude (Δ POP) and in the systemic arterial pulse pressure (Δ PP) in intensive care unit patients.¹ We strongly feel that this is an important study because it adds new perspectives to the morphological analysis of the plethysmographic waveform, especially to the analysis of the respiratory variations in this waveform.

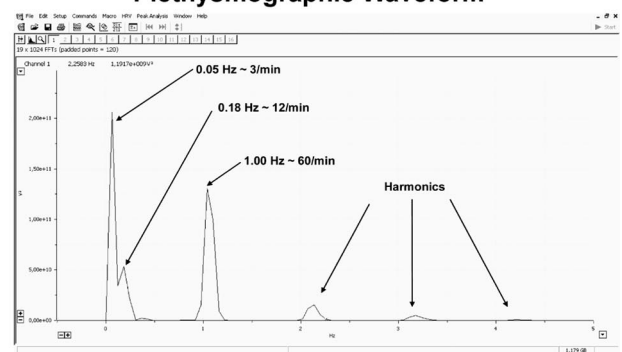
We would like to add a few comments that may help readers to better understand the implications of this study. First, it must be

emphasized that the results found by Landsverk *et al.* are in contradiction with several previously published studies focusing on the relationship, agreement, and ability of Δ PP and Δ POP to predict fluid responsiveness in mechanically ventilated patients in the operating room and in the intensive care unit.²⁻⁵ As stated by its authors, the present study uses an automated and continuous analysis system whereas previous ones used “hand filtered and analyzed” data. Thus, the study by Landsverk *et al.* is an example of how important the specifics of the algorithm used to determine Δ POP can be.

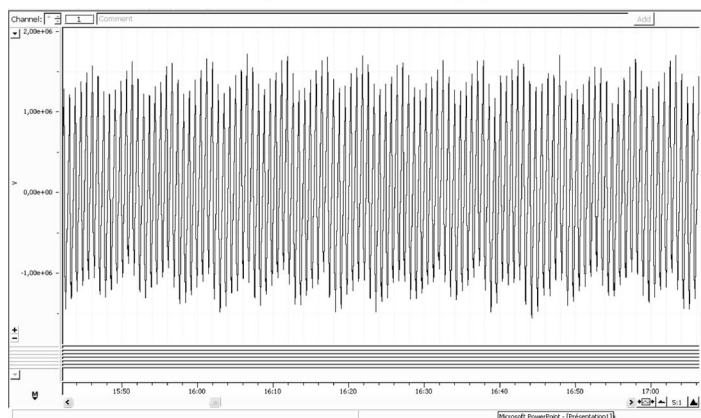
A Raw Plethysmographic Waveform Recording



Frequency spectrum of the Raw Plethysmographic Waveform



B The same Plethysmographic Waveform Recording after High-Pass Filtering (0.1 Hz)



Frequency spectrum of the same Plethysmographic Waveform Recording after High-Pass Filtering (0.1 Hz)

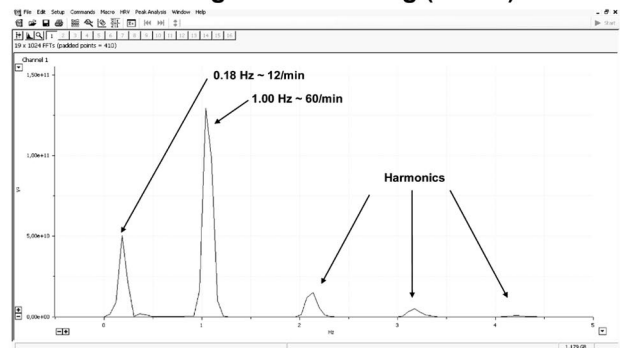


Fig. 1. Plethysmographic waveform recordings and frequency analysis of the plethysmographic waveforms in an intensive care unit patient.

This example illustrates the effects of a high-pass filtering with a threshold of 0.1 Hz on the plethysmographic waveform. The raw plethysmographic waveform (A) presents large oscillations, slower than the heartbeat (1 Hz) and respiration (0.18 Hz), as demonstrated by the frequency analysis. Applying a high-pass filtering with a threshold of 0.1 Hz reduces the low-frequency oscillations, making the estimation of the respiratory variations more robust and valid (B).