

## Fast Fourier Transforms as Prophecy

### Predicting Hypotension during Spinal Anesthesia

HYPOTENSION during spinal anesthesia for cesarean delivery has been of concern since the 1960s.<sup>1</sup> Along with multiple strategies aimed at treating or preventing hypotension, some investigators have attempted to identify patients more likely to have hypotension in the hopes of targeting treatment. In this issue of ANESTHESIOLOGY, Hanss *et al.*<sup>2</sup> report that measurement of heart rate variability (HRV), an assessment of sympathetic and parasympathetic balance, can identify those women at risk for spinal-induced hypotension.

Heart rate variability investigations started in obstetrics, with the observation that changes in fetal HRV precede changes in actual heart rate in cases of intrauterine asphyxia.<sup>3</sup> Power spectral analysis of HRV uses fast Fourier transforms to display power (variance) by frequency and reflects autonomic control of the cardiovascular system.<sup>4</sup> Standards for performance and analysis of HRV have been published.<sup>5</sup> Using spectral analysis of 2- to 10-min electrocardiographic recordings, two main power “components” of variability can be identified: low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.4 Hz). The major contributor to HF variability is vagal efferent activity. LF variability is a result of parasympathetic and sympathetic outflow. The ratio of LF to HF power is an indication of the balance of sympathetic to parasympathetic influences. A larger LF/HF ratio is interpreted as reflecting higher sympathetic *versus* parasympathetic activity. HRV has clinical relevance: Decreased variability is associated with heart failure, mortality after myocardial infarction, and is an early sign of diabetic neuropathy.<sup>5</sup> HRV is altered by pregnancy,<sup>6</sup> preeclampsia,<sup>7,8</sup> and regional anesthesia or analgesia.<sup>9</sup>

The current report from Hanss *et al.*<sup>2</sup> consists of two separate, closely related studies: The investigators first retrospectively determined a threshold LF/HF ratio related to the risk of development of hypotension and then prospectively confirmed its validity. HRV was assessed in 41 women at three separate times before elective cesarean delivery: the day before surgery, and the day of surgery before and after intravenous hydration. Based on

the systolic blood pressure response to spinal anesthesia, responses were classified as mild (no systolic blood pressure < 100 mmHg), moderate (lowest systolic blood pressure 80–100 mmHg), or severe (systolic blood pressure < 80 mmHg or requiring more than 1 ml of the vasopressor mixture) hypotension. LF/HF ratios on the day before surgery were not significantly different between groups. However, on the day of surgery, before hydration, the patients “destined” for development of moderate or severe hypotension had significantly higher LF/HF ratios (median 2.8 for moderate, 2.7 for severe) than those who went on to have mild hypotension (median 1.2). After hydration, moderate-hypotension patients decreased LF/HF ratios to mild levels, whereas severe patients were unchanged. Based on these results, the authors prospectively studied 19 patients to examine the hypothesis that a LF/HF ratio of 2.5 or greater on the day of surgery would predict hypotension. This hypothesis was confirmed; patients with high LF/HF ratio had significantly more hypotension than the patients with low LF/HF ratios.

Is it physiologically plausible that HRV parameters can predict hypotension during cesarean delivery? Are the criteria defined by Hanss *et al.*<sup>2</sup> optimal? Can this type of technology be adapted to the routine clinical environment? Will it be? Should it be?

Heart rate variability as a predictor of hypotension seems physiologically plausible. A recent report by Chamchad *et al.*,<sup>10</sup> using a retrospective protocol similar to the first part of the current report by Hanss *et al.*,<sup>2</sup> used a nonlinear mathematical method of analysis but also suggested that HRV predicts hypotension during spinal anesthesia. The underlying assumption that pre-existing higher sympathetic activity indicates a higher risk of hypotension during anesthesia is consistent with classic teaching in anesthesiology. Other measurements that may reflect sympathetic activity, including systemic vascular resistance index,<sup>7</sup> a “supine stress test,”<sup>11</sup> and baseline heart rate,<sup>12</sup> have been reported to correlate with the risk of hypotension. However, recent studies suggest that hypotension during spinal anesthesia is significantly less likely in preeclamptic patients than in healthy pregnant women,<sup>13</sup> despite higher sympathetic tone and LF/HF ratios in preeclampsia.<sup>14</sup>

Have Hanss *et al.*<sup>2</sup> determined and defined the correct criteria and threshold for prediction of hypotension? This seems unlikely to have resulted from this one study. Further work replicating, refining, and/or refuting these qualitative and quantitative findings will no doubt be necessary. It should also be noted that the HRV criteria

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from the day before surgery did not correlate with hypotension risk. Only the LF/HF prehydration and perhaps the response to hydration seemed to be determinative, suggesting that it was the acute preoperative condition rather than the chronic stable physiologic state that influenced the occurrence of hypotension.

Heart rate variability technology seems to be reasonably well suited to the anesthesiology environment (although as with most new technology, it would probably reach the labor and delivery suite last of all the possible anesthetizing locations). In principle, what is needed is a good-quality electrocardiographic signal and the appropriate software. Transferring what is still predominantly a research tool to the clinic always involves problems and compromises, but HRV seems to be as validated and interpretable as processed electroencephalographic and "cerebral function/anesthesia depth monitors" were when they made the transition to the operating room. One can imagine HRV equipment configured with a single number readout, with all the advantages and disadvantages that sort of output implies. Will a manufacturer start to offer this option on operating room patient monitors? If so, will anyone opt to buy it? The answer to the both questions is probably no, at least not without additional studies suggesting a predictive or therapeutically directive role for HRV. Can HRV do a better job than blood pressure, heart rate, and central pressure measurements in determining whether trauma patients need fluid or vasopressors or when intensive care unit patients are becoming septic? Can it do a better job than the electrocardiogram alone at detecting when coronary perfusion pressure is insufficient?

Finally, there is the question of whether this kind of monitoring is necessary, even if available. In reality, what should one do with the information that a patient is likely to become hypotensive after spinal anesthesia? Without HRV or some other predictor, clinicians assume that 50% or more of cesarean delivery patients will develop hypotension; how much would or should clinical practice change if we could identify which 50 or 70% were more likely to? Several editorials over the past decade have suggested that the search for the right drug, the correct amount of fluid, or some other formula to avoid hypotension may not be worth the effort, given how relatively easy and effective it is to treat hypotension when it does occur.<sup>15,16</sup>

It is a natural human tendency to want to predict the future, whether of the stock market, the outcome of a sporting event, events in our own lives, or the response

of our patients to drugs and other interventions, so this sort of work is undeniably attractive. The quest to predict the future in the clinical environment is of value, both for the potential to improve clinical care and because measurements that can predict physiologic responses usually reflect something inherent in the mechanism underlying that particular physiology, thereby improving both medical care and understanding. The quest for accurate and available predictive tools in this and other clinical arenas will no doubt continue, and HRV may well belong in the toolbox of the would-be prophets.

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## You (Still) Can't Disprove the Existence of Dragons

**CME** This editorial accompanies the article selected for this month's *Anesthesiology* CME Program. After reading the article and editorial, go to <http://www.asahq.org/journal-cme> to take the test and apply for Category 1 credit. Complete instructions may be found in the CME section at the back of this issue.

IN 2003, I commented on the decision by the US Food and Drug Administration (FDA) to issue a so-called black box warning on the use of droperidol for antiemetic prophylaxis.<sup>1</sup> Other authors have also expressed concern regarding what is widely viewed as an inappropriate action by the FDA.<sup>2,3</sup> The risk of developing ventricular dysrhythmias as a result of the administration of droperidol is again being addressed by two articles in this issue of *ANESTHESIOLOGY*. White *et al.*<sup>4</sup> demonstrated a prolongation of QTc when droperidol (either 0.625 or 1.25 mg) is administered intravenously at the beginning of surgery for prophylaxis of postoperative nausea and vomiting (PONV). However, the observed prolongation was not statistically different from that seen in those patients receiving saline placebo. Charbit *et al.*<sup>5</sup> compared QTc prolongation in patients receiving either 0.75 mg droperidol or 4 mg ondansetron for the treatment of PONV in patients experiencing symptoms while in the postanesthesia care unit after surgery. The observed mean maximal prolongation in QTc ( $17 \pm 9$  ms for droperidol and  $20 \pm 13$  ms for ondansetron) was consistent with the QTc prolongation reported by White *et al.*<sup>4</sup> ( $12 \pm 35$ ,  $15 \pm 40$ , and  $22 \pm 41$  ms for placebo, 0.625 mg droperidol, and 1.25 mg droperidol, respectively).

One must ultimately ask, what do these findings mean? However, an even more fundamental question is, why were these studies undertaken in the first place? QTc prolongation with the administration of droperidol has been known to occur since the drug was approved for use more than 30 yr ago. This phenomena is not unique. Indeed, potent inhalation anesthetics,<sup>6</sup> thiopental,<sup>7</sup>

propofol,<sup>8</sup> succinylcholine,<sup>9</sup> and drugs for reversing neuromuscular blockade<sup>10</sup> have all been shown to increase QTc. Of particular note is the fact that virtually all of the currently available antiemetics, including phenothiazines, antihistamines, and selective (5-hydroxytryptamine type 3) serotonin receptor antagonists, as reconfirmed by Charbit *et al.*,<sup>5</sup> increase QTc. Why would this journal consume valuable space to apparently restate the obvious?

By applying the black box warning to droperidol, the FDA has essentially removed one of the most effective and cost-efficient antiemetics from clinical use. This decision was based on 273 cases reported to the FDA between November 1, 1997, and January 2, 2002. Of those cases, 127 resulted in serious adverse outcomes. The details of these cases have been extensively reviewed elsewhere.<sup>2,11</sup> Nevertheless, several points are worth reiterating. Of the 127 cases, 94 were reported from outside the United States. Of all the cases reported, there were only 10 in which serious adverse cardiovascular events were reported when doses of 1.25 mg or less were administered. A careful analysis of those cases did not detect any evidence of a cause-and-effect relation between the arrhythmia observed and the administration of droperidol.<sup>2</sup>

Since its introduction into clinical practice in 1970, literally hundreds of millions of doses of droperidol have been administered for both the prevention and the treatment of PONV, but there has never been a single case report of dysrhythmia. Both of the studies presented here confirm that the peak QTc prolongation with the administration of droperidol occurs within minutes after administration. If QTc prolongation is indeed the underlying mechanism for dysrhythmias, it is inconceivable that case reports would not have appeared in the literature. It has been argued that a mechanistic basis for droperidol QTc prolongation is sufficient criteria for the action taken by the FDA.<sup>12</sup> Strict adherence to that mechanistic principle would have interesting and absurdly humorous effects. To reiterate, White *et al.*<sup>4</sup> demonstrated that a saline placebo has QTc prolongation indistinguishable from that of droperidol when administered before general anesthesia. Charbit *et al.*<sup>5</sup> showed that there was no difference in QTc prolongation between droperidol and ondansetron when administered postoperatively for PONV. If the FDA were to be consistent in its application of policy, both general anesthesia (or perhaps all anesthetic agents) and ondansetron (as well as all other selective [5-hydroxytryptamine type 3] serotonin receptor antagonists) should carry the same black box warning. The two studies here seem to indicate that if the decision regarding which antiemetic to

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use is based on QTc prolongation, the alternatives are no better than droperidol.

In 1992, the Prescription Drug User Fee Act allowed the FDA to augment its budget by charging fees to pharmaceutical firms.<sup>13</sup> Approximately \$825 million have been collected between 1993 and 2001.<sup>14</sup> It has also been reported that more than half of the members of the FDA expert advisory panels had direct financial interests in the products being evaluated.<sup>15</sup> In addition, the FDA has been subjected to intense lobbying by the pharmaceutical industry. These facts alone make it impossible not to suspect the possibility of conflict of interest, which is further confirmed by the recent events. For example, it took legal action by the New York Attorney General to bring to light the link between teenage suicide and the use of selective serotonin reuptake inhibitors.<sup>16</sup> More recently, concerns about the suppression of data regarding increase cardiovascular mortality associated with the use of certain cyclooxygenase-2 inhibitors have been widely publicized. Decisions about frequently prescribed, patent-protected medications have tremendous financial implications for their manufacturers. No such financial incentive exists for inexpensive generic formulations. In fact, it is tempting to speculate that when a generic medication is in direct competition with a more expensive proprietary medication, financial considerations may affect the decision-making process.

No one, save practicing clinicians, speaks for droperidol. In the doses routinely used for the prevention and treatment of PONV, its safety is unparalleled. The argument by the FDA that the minimum approved dose is 2.5 mg and the use of smaller doses is outside the jurisdiction of the FDA is clearly specious and does a tremendous disservice to the American public. The true incidence of dysrhythmias resulting from the administration of “low-dose” droperidol is likely to be vanishingly small. The number of patients necessary to establish the actual incidence is unknown. The cost of the study would be prohibitive and would not be a prudent use of research dollars. Consequently, we are left with studying

surrogate endpoints, such as the phenomena of QTc prolongation reported in this issue of *ANESTHESIOLOGY*,<sup>4,5</sup> as an indirect attempt at establishing the “safety” of droperidol. However, the current position adopted by the FDA leaves clinical scientists and practicing physicians with an impossible task—proving a negative. And, as Eger<sup>17</sup> pointed out more than 25 yr ago, you can’t disprove the existence of dragons.

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## Postoperative Opioid Sparing to Hasten Recovery

### What Are the Issues?

OPIOIDS continue to have a major role in pain management despite that they may contribute to increased in-hospital morbidity and costs.<sup>1,2</sup> In this context, postoperative patients may be at significant risk for opioid-related adverse effects (postoperative nausea and vomiting [PONV], sedation, sleep disturbances, urinary retention, and respiratory depression).<sup>3</sup> The recently defined new standard for pain management by Joint Commission for Accreditation of Health Care Organizations with increased efforts to reduce patients' pain scores may further increase the risk of adverse effects when sufficient analgesia is achieved by opioids.<sup>4</sup>

The concept of multimodal, balanced analgesia introduced more than a decade ago<sup>5</sup> suggested that both improved analgesia and reduction of (opioid-related) adverse effects could be achieved by combining different analgesics. Subsequently, it has been established that many analgesic techniques, such as nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX-2) inhibitors,<sup>6,7</sup> acetaminophen,<sup>8</sup> ketamine,<sup>9</sup> gabapentin and pregabalin,<sup>10</sup> and regional anesthetic techniques<sup>11</sup> provide 20–50% opioid sparing in the postoperative setting. However, it remains to be answered whether such opioid sparing would reduce “opioid-related” adverse effects, thereby hastening recovery and reducing morbidity. Results from the many previous investigations have not been consistent, probably because of underpowered studies, different dosage and drug regimens, different types of surgery, and inconsistent reporting and assessment of all opioid-related adverse effects. The topic is further complicated by the many concurrent factors that may contribute to “opioid-related” adverse effects such as pain *per se*, which may increase the risk of PONV,<sup>12</sup> and that high pain scores increase the opioid requirements.<sup>13</sup> In this context, the type of surgery may be associated with different pain patterns and consequently modify the effectiveness of analgesics<sup>14</sup> and thereby the “opioid-related” adverse effects. In addition, it is well established that opioid-like effects such as pulmonary dysfunction may be more

prominent with surgeries close to the diaphragm and the risk of urinary retention more prominent after pelvic, inguinal, and anorectal operations. Because PONV has been the most often addressed “opioid-related” adverse effect, predisposing factors to PONV *per se*, such as sex, location of the surgical injury, smoking habits, and previous postoperative PONV experiences, may also potentially influence the effects of opioid-sparing techniques,<sup>15</sup> although rarely assessed in previous studies.

These precautions being said, it is most welcome that Marret *et al.*<sup>16</sup> in this issue of ANESTHESIOLOGY have performed a meta-analysis of randomized controlled trials examining the effect of NSAID and COX-2 inhibitor treatment on PONV and other opioid-related adverse effects. The results show that the well-known opioid sparing (approximately 30%) by these drugs significantly reduced PONV and sedation by approximately 30%, whereas effects on urinary retention and respiratory problems were inconclusive. At first glance, this is important (but probably not unexpected) news for clinicians treating postoperative pain. The results of the analysis by Marret *et al.*<sup>16</sup> are further supported by recent studies with improved design to assess the clinical consequences of opioid sparing. Thus, a large, multicenter trial in a well-defined surgical operation (laparoscopic cholecystectomy) showed improved pain relief and the usual approximately 30% opioid-sparing by COX-2 inhibitor treatment.<sup>17</sup> In this study published in different versions,<sup>17-19</sup> the opioid-related adverse effects were assessed in detail on an opioid-related symptoms-distress scale and as clinically meaningful events. Postoperative recovery was improved with less opioid-related side effects compared with placebo treatment.<sup>17-19</sup> Interestingly, morphine sparing of 3 mg was related to reduction to one clinically meaningful event. Similarly, in their regression analysis, Marret *et al.*<sup>16</sup> were able to demonstrate a reduction in PONV of approximately 0.5% for each milligram of morphine spared by NSAID/COX-2 inhibitor treatment. Other recent studies with a more detailed assessment of opioid-related adverse effects have also shown less PONV and sleep disturbance together with approximately 30% opioid sparing with a COX-2 inhibitor after knee replacement<sup>20</sup> and faster and improved recovery after ambulatory inguinal herniorrhaphy.<sup>21</sup> Also, opioid sparing and improved pain relief by dexamethasone before laparoscopic cholecystectomy reduced PONV and fatigue and hastened resumption of normal activity.<sup>22</sup>

Although these data are of obvious benefit for our patients and to support opioid-sparing analgesic thera-

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pies, several questions remain to be addressed regarding the general applicability of the results. First, because PONV has been the main outcome parameter, more detailed studies are required to define whether the achieved effect is due to the reduced pain *per se* or strictly to the reduction in opioid use. Also, more procedure-specific data are needed because the type of surgical injury may influence PONV and respiratory and urinary bladder dysfunction *per se*. In addition, the pain-relieving effect by different analgesics is not equipotent in all procedures, as recently demonstrated in a reanalysis of acetaminophen data where the number-needed-to-treat values are significantly higher in major compared with minor surgery.<sup>14,23</sup> Furthermore, because postinjury pain may show large interindividual variability,<sup>24,25</sup> procedure-specific studies should assess the opioid-sparing outcome effects in different types of patients and operations. Finally, the benefits of opioid-sparing must be weighed against the adverse effects associated with the drugs to provide opioid sparing, examples being a bleeding risk with NSAIDs<sup>26</sup> and cardiovascular complications in certain high-risk patients with COX-2 inhibitors.<sup>27</sup>

In the analysis by Marret *et al.*,<sup>16</sup> the data were not analyzed in relation to pain scores, but the authors analyzed the opioid-sparing effects in relation to orthopedic *versus* abdominal surgery and found no differences. However, in these two surgical specialties, different types of orthopedic procedures were included, ranging from disc surgery to major joint replacement, as well as the abdominal procedures included major abdominal surgery, gynecologic surgery, and laparoscopic urologic procedures, which may have different risks for "opioid-related" adverse effects *per se*. Also, their analysis demonstrated inconsistencies in the reporting of "opioid-related" adverse effects in the available studies, which may pose a risk of publication bias thereby hindering definite interpretation.

Although the sophisticated analysis of existing data such as the study by Marret *et al.*<sup>16</sup> and the more detailed procedure-specific analyses in laparoscopic cholecystectomy,<sup>17-19,22</sup> knee replacement,<sup>20</sup> and inguinal herniorrhaphy<sup>21</sup> are of major clinical relevance at this time, the question is, where we go from here? First, future, well-designed studies are required, with detailed and complete assessment of *all* potential opioid-related side effects and being procedure specific to allow final conclusions. Also, such studies should report their results in milligrams of morphine spared because a percentage sparing may not be clinically relevant, as has been shown in a large negative multisurgery outcome study, where 30% opioid sparing was achieved by acetaminophen, but the amount of morphine spared was only 6 mg.<sup>28</sup> However, most importantly, because single-agent opioid sparing of 20-50% has been demonstrated by NSAIDs,<sup>6</sup> COX-2 inhibitor,<sup>7</sup> acetaminophen,<sup>8</sup> ketamine,<sup>9</sup>

gabapentin and pregabalin,<sup>10</sup> and regional anesthetic techniques,<sup>11</sup> achievement of more efficient analgesia and opioid sparing should be possible by multicomponent analgesic therapy. Unfortunately, limited data are available so far, but recent data suggest additional opioid sparing and reduction of opioid-related adverse effects after hysterectomy with combined treatment with a COX-2 inhibitor and gabapentin compared with either therapy alone.<sup>29</sup> The future is now for such clinically important studies.

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