Hypotension Prediction Index: from proof-of-concept to proof-of-feasibility

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Intraoperative hypotension (IOH) is increasingly recognized as a major contributing factor associated with the development of postoperative complications in terms of renal [1–6], myocardial [6–8] and possibly, cerebral injury [9–11], despite substantial variability in literature regarding its exact definition [12, 13]. As IOH is not only associated with perioperative morbidity but with perioperative mortality [5, 14–17] as well—which is the 3rd greatest global contributor to deaths after ischemic heart disease and stroke [18]—efforts should be made to reduce both the incidence and duration of IOH. Hence, recently a consensus statement by the Perioperative Quality Initiative-3 workgroup [19] advises that for adults undergoing non-cardiac surgery, there is substantial evidence supporting that mean arterial pressure (MAP) should be kept above 60–70 mmHg in order to reduce postoperative myocardial and renal injury, and death. Given that even brief periods of IOH may be harmful—e.g. after induction of anesthesia and before surgical incision [1]—it may be beneficial to change our current practice from a *reactive* approach (by monitoring the patient's *actual* hemodynamic status) [20, 21] to a *proactive* approach, by predicting vital signs [22], especially since (cumulatively) the longer a patients “spends” in IOH, the more likely it is that this will adversely affect outcome [14]. The current advances in medical technology include the use of machine-learning based algorithms [23, 24] to analyze large datasets in order to provide clinically useful information. Such predictive analytics may help in substantiating such a proactive approach.

1 In a nutshell: machine-learning algorithm in (bio)medical research

Arthur L. Samuels was in 1959 the first one to describe the concept of machine-learning. It was described as “the programming of a computer to behave in a way which, if done by human beings or animals, would be described as involving the process of learning”. The first machines were programmed to play checkers and in just a few hours the machines learned to play checkers better than the persons who programmed the computers [25]. Machine-learning algorithms differ substantially from traditional, rule-based algorithms. In such traditional algorithms, a pre-defined situation is handled by pre-defined criteria as set by the programmer. While this may be accurate, e.g. the administration of anesthetics using target-controlled infusion algorithms [23], its performance depends on the exact definitions and criteria, as set by the programmer. In machine learning, multiple input variables (features) are associated with output variable(s). Different forms of machine-learning exist, yet conceptually in medical practice, it allows the analysis of large (patient-derived) datasets for given output variables, so that a predictive model can be constructed in which the structure and weight of all identified features are considered by the algorithm. In the past decade, the development and use of machine-learning algorithms has grown exponentially in many sectors, including medical care. Recently, guidelines were developed for developing machine-learning algorithms and for reporting in (bio)medical journals [26].

1.1 Development and validation of the Hypotension Prediction Index (HPI)

A good example of a machine-learning derived algorithm that may be used perioperatively to improve patient outcome, is the commercially available HPI algorithm (Edwards Lifesciences, Irvine, USA) [27]. The HPI variable gives—in a unitless range between 0 and 100—the likelihood of

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impending hypotension—i.e. $\text{MAP} < 65 \text{ mmHg}$ —in the next 5–15 min, while the patient is still hemodynamically stable. The HPI algorithm continuously analyzes the arterial pressure waveform and has been trained on a large dataset from over 1300 patients (both perioperatively and from ICU patients) that contained many hypotensive episodes ($n = 25,461$) [27].

The HPI algorithm works on top of the FloTrac algorithm. The latter allows the identification of different pulse waves, and splits data into frames of 20 s for subsequent analyses. HPI splits the individual pulse waves in distinct (physiological) phases, and a total of 3022 individual characteristics of the waveform(s) are analyzed, as well as their interrelation. Based on the “training” of the HPI algorithm, the likelihood of impending hypotension is given. Further details on the development of HPI are given elsewhere [21, 27, 28].

After internal validation, the derived model was prospectively externally validated in a cohort of 204 surgical (perioperative) patients, containing 1923 episodes of hypotension. Here, hypotension could be predicted 15 min in advance with a specificity of 83% and a sensitivity of 84% with an area under the curve (AUC) of 0.91, and up to 5 min in advance with a sensitivity 87%, specificity of 88% and AUC of 0.95 [27].

Until recently, two studies [28, 29] have evaluated the performance of HPI in predicting hypotension. In one of these studies in 255 patients undergoing major surgery [28] HPI and other commonly used hemodynamic variables were analyzed in order to predict hypotension. HPI was superior in predicting hypotension compared to mean arterial pressure itself, the change in mean arterial pressure over 3 min, and any other hemodynamic variable such as stroke volume variation, cardiac output, heart rate, shock index and pulse pressure. HPI could predict hypotension 5 min in advance with a sensitivity and specificity of 86% with an AUC of 0.93.

In another study [29] in 23 patients undergoing (cardio) vascular surgery, the discrimination and calibration levels of the HPI 5–7 min before occurrence of a hypotensive event were evaluated. The HPI had a poor level of calibration at the cut-off value of 85, as sensitivity was only 62% and specificity was 77%, with an associated negative predictive value (NPV) of 98% and a positive predictive value (PPV) of only 13%. When the cut-off value was increased to a HPI value of 98, PPV increased to 64% and NPV decreased to 95%.

1.2 Implementation of HPI in protocolized perioperative hemodynamic care

In this issue of the journal, Schneek et al. [30] provide the first true clinical (feasibility) study that evaluates the value of HPI in minimizing the incidence and duration of IOH, in addition to the use of protocolized perioperative

hemodynamic care. In this study, 90 patients undergoing total hip arthroplasty under general anesthesia were included. An intervention group ($n = 25$) using goal-directed therapy guided by HPI was compared to a prospective control group ($n = 24$). In the intervention group, a HPI value > 80 triggered either colloid administration (if stroke volume variation (SVV) $> 12\%$), or the administration of inotropes [if Cardiac Index (CI) was under the individual threshold], or the administration of vasopressors (when CI was above the individual threshold). In the control group, it was aimed to keep $\text{MAP} > 65 \text{ mmHg}$, without using HPI. Both these prospective groups were additionally compared with a historical group ($n = 50$), in whom ‘routine’ anesthetic management was performed according to institutional practice (and in whom no study monitoring was applied). Interestingly, the incidence of hypotension was eliminated in the intervention group: with a median absolute time spent at a $\text{MAP} \leq 65 \text{ mmHg}$ of 0 s, albeit with a range of 0–140 s. In comparison: in the prospective control group, the median hypotension time was 640 [195–1315] seconds, which was similar to that in the historical control group (660 [180–1440] seconds). Although one may consider this study only as a first-step in the clinical implementation of machine-learning algorithms (i.e. HPI) in goal-directed therapy protocols, it is a very important first step, as it clearly shows that it may allow reducing the incidence and duration of IOH to almost zero in most patients treated using HPI monitoring. Furthermore, it is intriguing that in the prospective control group, in which it was aimed to keep MAP above 65 mmHg by the treating clinicians who were aware of the fact that they actively participated in a study that focused on the reduction of IOH, hypotension did still occur—with a duration that was equivalent to the historical control group in which ‘only’ institutional practice was performed. This observation emphasizes that a *reactive* treatment of IOH may indeed be inferior to a *proactive* treatment of impending IOH in reducing its incidence and duration.

Despite the promising results of this study in reducing IOH—that obviate(s) the need for future studies to assess the effect of HPI-based treatment on actual patient outcome—some remarks should be made.

Firstly, the current study has a very limited external validity since it is only a single-center study in patients undergoing one type of surgical procedure, both of which may be subject to substantial bias with respect to the primary outcome variable, in this case: IOH. It remains to be decided whether treatment based on HPI provides equivalent reductions in IOH in other patient populations in whom the risks of postoperative morbidity and mortality are actually increased based on their co-morbidity or the surgical procedure. Also, the study was aimed to show a reduction in the time of IOH only, and as such, does not provide any

evidence of a beneficial impact on patient outcome in terms of postoperative morbidity and mortality whatsoever.

Secondly, the results of the study do not provide sufficient information to elucidate what exactly decreased the incidence of IOH in the intervention group. Was it the (reduced) amount of fluids—or the timing of its administration? Was it the correct indication of vasopressors and/or inotropes, at the right moment? The results of the study would have been more clear if information were provided on goal-directed fluid therapy related variables, i.e. SVV and CI, as it is now not possible to discriminate whether it was mainly HPI “itself”, or the goal-directed fluid therapy in which HPI was embedded, that resulted in the reduction of IOH. In an ideal setting, another control group was defined in which HPI was monitored—but blinded—and goal-directed fluid therapy was performed. Most likely, it may have been a combination of the factors mentioned above, that reduced the incidence of IOH. In addition, the “secondary screen” variables that come along with the HPI algorithm and are meant to help deciding whether or not to treat any of the underlying mechanisms that may cause hypotension (i.e. dynamic preload variables for preload, dp/dt_{max} for contractility and dynamic arterial elastance for afterload; details are explained elsewhere [21]), were not used by the authors, which would otherwise have been very relevant as it would have allowed an initial assessment whether these variables truly help in optimizing hemodynamics.

Another important aspect, often neglected in hemodynamic studies, is the influence and depth of general anesthesia. Cumulatively, the authors found slight, but statistically significant differences in the dosage of fentanyl and sevoflurane between the prospective groups. It may well be that the “trick” in reducing IOH lies in optimizing preload by timely administrating the right amount of fluids, and in optimizing contractility and afterload by the timely and right dosage of inotropes and vasopressors, respectively, while adjusting the level of general anesthesia in order to maintain hemodynamic stability—even together with the information provided by the “secondary screen” variables. Such complex processes are however not easily recognized in studies as performed by Schneck et al. While they were unable to retrieve BIS and MAC levels—so that a comparable depth of anesthesia could not be proven—it may have been true that in the control group(s), there was a deeper level of general anesthesia, which may have resulted in longer periods of IOH.

Finally, it is unclear when exactly IOH occurred, and what the temporal distribution of IOH was; were most of the hypotensive events occurring after induction of general anesthesia (but before surgical incision) or did IOH mainly occur intraoperatively, after the surgeon had started the procedure? Such information may provide important information on the conduct and influence of the induction of general

anesthesia, since it was demonstrated previously that even post-induction hypotension contributes to the development of postoperative morbidity [1].

2 Conclusion

Despite these critical remarks, this elegant, very first proof-of-feasibility study on the use of HPI in the perioperative setting provides substantial evidence that a HPI-triggered goal-directed therapy approach may reduce the incidence and duration of IOH, which is a well-recognized factor that is associated with the development of postoperative morbidity and mortality. It may just be one of the very first studies in this new decade that helps improving perioperative patient safety further by using innovative technology such as the commercially available Hypotension Prediction Index.

Compliance with ethical standards

Conflict of interest TWLS received research grants and honoraria from Edwards Lifesciences (Irvine, CA, USA) and Masimo Inc. (Irvine, CA, USA) for consulting and lecturing and from Pulsion Medical Systems SE (Feldkirchen, Germany) for lecturing. TWLS is associate editor of the Journal of Clinical Monitoring and Computing but had no role in the handling of this paper. JJV and IDK have no conflicts of interest to declare.

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