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Optimal perioperative blood pressure management

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Keywords

Perioperative BP; BP targets; BP variability; Dynamic targets; BP complexity

Introduction

With an ever-increasing surgical burden and an aging population, the number of high risk patients, with multiple comorbidities undergoing complicated surgical procedures is on the rise. End organ related major adverse events (MAE) is a matter of concern in this population, as they lead to morbidity, prolonged hospital stay, increased health care costs and up to an 8 fold increase in mortality in the perioperative period [1]. Since most of these adverse events are related to impaired perfusion, optimizing intra-operative hemodynamics is one of the many objectives of 'safe anesthesia'. There are reasons why emphasis is placed on blood pressure (BP), rather than any other hemodynamic parameter, when it comes to perioperative optimization. BP is a surrogate measure of perfusion to ischemia-prone end organs like brain, heart and the kidney. Patients may have a paced rhythm, and BP may be the only parameter that allows for variability analysis in such patients [2].

Association of preoperative hypertension with major adverse events has been long recognized. Preoperative BP control and pharmacological management of a hypertensive surgical patient have been extensively studied and there are guidelines for preoperative BP optimization [3-5]. This review article will focus on intraoperative BP management. It will also discuss the recent paradigm shift, from viewing BP as an optimizable target, to a physiological output that provides an insight into the functioning of a complex system.

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Significance of intraoperative hemodynamic instability

The total global surgical volume for the year of 2012 was estimated to be 312.9 million operations [6]. Hemodynamic instability is a common intraoperative phenomenon. The risk of intraoperative hypotension ranges from 5-99% depending on the threshold employed to define hypotension [7]. Major morbidity occurs in 3-16% of all surgical patients, with permanent disability or death occurring in 0.4-8% [8, 9]. As the population ages and survives with comorbid conditions, more patients with increasing age, congestive heart failure, diabetes, pulmonary disease, and acute myocardial infarction present for high risk surgeries, with the associated increase in the frequency of perioperative major adverse events (MAE). MAEs have far reaching consequences, including a 1.4-8 fold increased risk of mortality and vastly greater hospital costs [1, 10].

Vital organ perfusion

The scientific basis of association between hemodynamic instability and MAE is impaired vital organ perfusion, causing ischemia and subsequently reperfusion injury. Constant perfusion to vital organs is maintained across a wide range blood pressures called the autoregulation range, which varies with the organ system.

For instance, autoregulation range of the brain ranges from 60-160 mmHg of cerebral perfusion pressure, which is determined by mean arterial pressure and intracranial pressure. This range is reset to higher values in hypertensive patients. Though the mean arterial pressure (MAP) at the lower limit of cerebral autoregulation has been historically described as 50 mmHg [11], in a recent study using transcranial Doppler and Near-infrared Spectroscopy (NIRS) cerebral oximetry, a wide range of MAP was found corresponding to the lower limit of autoregulation (LLA) during cardio-pulmonary bypass. In the 225 participants, the MAP at LLA was 66 mmHg, with a wide 95% prediction interval of 43 to 90 mmHg [12]. The authors observed no relationship between preoperative MAP and LLA, after adjusting for variables. Cerebral autoregulation was also found to be impaired during hypothermic cardio-pulmonary bypass and subsequent rewarming [13].

Myocardial perfusion depends largely on the diastolic blood pressure, while renal perfusion depends on MAP and cardiac output within its autoregulation limits [14]. When the cardiac and cerebral perfusion are maintained constant at normal MAPs, renal perfusion can still be impaired if cardiac output is low [15].

There are considerable differences in autoregulation limits from person to person according to the associated comorbid conditions. Anesthesia is also known to impair autoregulation [16]. Thus it becomes clear that intraoperative BP management towards an absolute BP target or within fixed limits of population mean or even within percentage changes from patient baseline may not be able to ensure absolute safety. This is demonstrated by the inconsistent results of various studies in this regard.

Defining hemodynamic instability

While intraoperative hemodynamic instability has been retrospectively associated with worse perioperative outcomes [17-20], exact thresholds of BP are still undefined. There are many reasons to this. While profound fluctuation in blood pressures even for a shorter duration may lead to major adverse events, minimal fluctuations for prolonged duration are known to be associated with adverse outcomes as well. Hence the magnitude as well as duration of fluctuations account for the adverse events.

These thresholds cannot be generalized, because each individual is different, with varying comorbid factors, different baseline levels and differing limits of tolerance to hemodynamic insults. Even in each individual, the autoregulation limits differ for various organ systems. The preoperative BP obtained may not accurately reflect the baseline of the patient due to multiple factors like white coat hypertension, surgical anxiety etc. With aging population, there is an increasing risk of isolated systolic hypertension. Isolated systolic hypertension (ISH) has been associated with adverse cardiac, cerebrovascular events and increased mortality [21]. BP management based on baseline pressures may not be possible in patients with ISH, considering the fact that they may have relatively lower MAP at a higher SBP compared to those with essential hypertension.

Another factor to consider is that adverse events are related more to the cause of the hypotension (e.g., hypovolemia, myocardial dysfunction, sepsis, anesthetic overdose) than to the BP per se [22]. For these reasons developing an agreed upon consensus for intraoperative BP management has proven unsuccessful.

A review of literature shows that there are over 140 different definitions of hypotension used in various studies leading to conflicting association with major adverse events [7]. Bijker et al, in an observational study used various different definitions for intraoperative hypotension (IOH) and found no association between IOH and 1-year mortality after non-cardiac surgery [17]. The most frequently used definitions of IOH identified by the study include SBP less than 80 mmHg and SBP fall greater than 20% below the baseline. Thus, from the perspective of MAE prediction, preoperative baseline comorbid factors of the patient still prove to be more useful than intraoperative hemodynamic fluctuation [22, 23].

Intraoperative Blood Pressures Targets

Is there a defined target range of intraoperative BP that ensures safety and can it be individualized? At the current moment, the answer is 'no'. Though arterial BP monitoring at least every five minutes has been listed as a standard monitoring practice by American society of anesthesia [24], literature search shows no guidelines on BP values to be maintained during surgery [19]. Most of the work done in this area, came up with numbers that suit a population-wide application, but clearly one size does not fit all. Thus, the BP optimization goals should be tailored to each individual patient. This should take into account the baseline hemodynamics of the patient, comorbidities and the nature of surgery. Obtaining an accurate picture of the patient's baseline hemodynamics is a challenging task. This is due to the highly variable nature of hemodynamic parameters. May be, this variable

nature of the physiological signals holds the key to the holy grail of intraoperative hemodynamic goals.

Current literature

Historically, Goldman et al, in 1978 reported an increased incidence of postoperative cardiac death was associated with a 33% or greater fall in SBP for more than 10 minutes intraoperatively [25]. Charlson et al, in 1990 concluded that prolonged changes in MAP of more than 20 mmHg or 20% from the patient's preoperative levels were associated with postoperative complications [26]. Both the above-mentioned studies were prospective in nature.

In a prospective observational study of over 1000 patients undergoing non-cardiac surgery, the authors observed that the patient's comorbidities showed the strongest association with one-year mortality. Intraoperative systolic hypotension below 80 mmHg was also found to be associated with mortality depending on the duration of hypotension [22]. The same author, in a later retrospective cohort study used three different methods to assess intraoperative hemodynamic instability and its association with postoperative outcome namely, 30-day mortality [19]. They were: 1) population thresholds and area beyond the threshold of 2 standard deviations from the population mean, 2) absolute thresholds and 3) percentage change from baseline. Using the first method, they found intraoperative systolic blood pressure (SBP) < 67 mmHg for more than 8.2 minutes, mean arterial pressure (MAP) < 49 mmHg for more than 3.9 minutes and diastolic blood pressure (DBP) < 33 mmHg for more than 4.4 minutes were associated with 30-day mortality. Using the second method, SBP < 70 mmHg or MAP < 49 mmHg or DBP < 30 mmHg for more than 5 minutes were associated with the outcome. Using the third method, MAP decrease to more than 50% from patient baseline for over 5 minutes showed outcome association. There was no correlation between intraoperative hypertension and mortality.

Reich et al, in their retrospective investigation, concluded that hypotension during cardiopulmonary bypass was independently associated with mortality, stroke and myocardial infarction (MI) after cardiac surgery [20]. In another study, the authors observed intraoperative hypertension (SBP > 160 mmHg) to be associated with adverse events after non-cardiac surgeries lasting more than 220 minutes. The outcomes studied were hospital stay more than 10 days with morbidity and in-hospital mortality [27].

In an observational cohort study, Bijker et al used a total of 48 different definitions of intraoperative hypotension with varying BP thresholds and durations, to analyze association with 1-year mortality after general and vascular surgeries. They found no causal relationship between IOH and 1-year mortality [17].

In a retrospective observational study including data from over 33,000 patients undergoing non-cardiac surgeries, MAP less than 55 mmHg even for short durations was found to be related to the risk of postoperative acute kidney injury (AKI) and myocardial infarction (MI). Outcome measures with better sensitivity were used in this study, including creatinine elevation, graded by AKI network (AKIN) definition for AKI and cardiac enzyme elevation

(Troponin T and Creatine Kinase-MB) for MI. The risk increased with increasing duration of hypotension [28].

Another study that analyzed outcomes after non-cardiac surgery in over 57,000 patients, concluded that both absolute threshold of MAP below 65 mmHg and relative BP threshold based on patient baseline were comparable in predicting postoperative AKI and MI [29].

A composite score including intraoperative blood loss, lowest heart rate and lowest mean arterial pressure called the 'surgical Apgar score' has been found to be associated with major complications or death within 30 days post general or vascular surgery [30, 31].

Existing gaps in knowledge

From the above discussion, the impact of a lack of generalized definition becomes obvious. The outcomes analyzed in most of the above studies include 30 day or 1 year mortality, in-hospital mortality, or duration of hospital stay. These are relatively non-sensitive to detect the impact of the exposure and may also be non-specific in that, they may be attributed to other factors in addition to intraoperative hypotension. Two of the studies used sensitive tools namely, AKI diagnosed by AKIN criteria and MI diagnosed by biomarker levels. Though sub-clinical end organ injuries may escape detection in most cases when 30-day or 1 year mortality is used as the outcome, they can still be associated with long term mortality [32-34].

Another common underlying factor in the above studies is that most of them are retrospective and observational in nature and any correlation found would merely be an association but a true causal relation is difficult to establish. Randomized controlled trials are necessary to establish a cause - effect relationship. Ethical considerations may limit performing a randomized trial in this domain. A randomized multicenter trial published in 2017 examined the effect of individualized vs. standard management of intraoperative BP on organ dysfunction after major surgery [35]. 298 high-risk patients were randomized. In the individualized group the aim was to maintain SBP within 10% of the patient's resting value. In the standardized group, BP management was initiated when SBP fell below 80 mmHg or more than 40 % below the reference value. It was found that individualized management of BP was better at reducing postoperative organ dysfunction compared to standard management.

All these studies viewed BP as a static parameter, chasing a pre-determined BP value, rather than paying attention to the variable nature of the BP waveform. Studying variability could possibly enable us to better understand an individual's physiology and tailor perioperative management accordingly.

Blood pressure variability

Heart rate variability and its significance has long been recognized and applied clinically. The past decade has seen an increase in BP variability analysis. A number of parameters to describe variability were studied. Aronson et al analyzed invasive blood pressure, sampled at 30-second intervals in 7,504 patients undergoing CABG. They calculated the area under the

curve for SBP beyond the threshold of 95-135 mmHg, which included both the magnitude and duration of excursion beyond the thresholds. They found a positive association between the duration of excursion beyond the thresholds and increased 30-day mortality [36].

Levin and colleagues used lability, defined as the modulus of percentage change in MAP in consecutive five-minute intervals, in BP data obtained from 52,919 subjects, sampled every 15 seconds to 5 minutes (invasive as well as non-invasive BP). The number of episodes of lability beyond 10% and 20% was counted. They found an inverse association between lability and 30-day mortality. They concluded that the BP lability denoted the intactness of the autonomic responsiveness to the stress of surgery and hence is protective [37].

Mascha et al analyzed blood pressures of 140,312 patients undergoing non-cardiac surgeries lasting more than 60 minutes. Both invasive and non-invasive pressures recorded at intervals of 1 to 5 minutes were included for analysis. The authors calculated the time-weighted averages of the mean arterial pressures (TWA-MAP) and also the average real variability of the mean arterial pressure (ARV-MAP) as a measure of variability. They found a strong association of lower TWA-MAP with 30-day mortality. But they were only able to demonstrate a mild association between lower ARV-MAP and mortality [38].

Hirsch et al found that BP fluctuation as measured by variance was better predictive of delirium after non-cardiac surgery compared to absolute or relative hypotension thresholds [39]. The above-described analytical techniques do not describe the temporal dynamics of the BP waveform.

Dynamic nature of BP

Another important quality of BP is the temporal variability. BP waveform is complex and non-stationary: the statistical parameters used to describe variability keep varying with time [40]. The human body is a complex dynamic system of multiple interacting feedback loops marked by interdependence, pleiotropy and redundancy [41]. BP could be viewed as a complex signal, a physiological output that provides a peek into the complex nature of the human system. The importance of this complex variability has been well studied in heart rate [42]. Beat-to-beat variability of fetal heart rate has long been emphasized to signify health. The blood glucose levels have been demonstrated to show this complex variability [43]. This moment-to-moment, unpredictable complex variation is a signature quality of health. Illnesses cause a systemic functional alteration in the patient, and the properties of the complex system break down to varying degrees depending upon the duration and severity of the illness. This loss of integrative function generates abnormal patterns or rhythms in physiological waveforms such as heart rate and blood pressure. The characterization of these rhythms provides much more distinct and useful information than the absolute values [44].

Complexity in health and disease

The complexity of many physiologic signals is known to reduce with disease. Heart rate entropy predicts postoperative atrial fibrillation following cardiac surgery [45], and it decreases in healthy adults infused with endotoxin [46]. Reduced orderliness and irregularity

of growth hormone patterns was observed with entropy measurements in patients with acromegaly [47]. Similar observations were seen in other endocrine disorders [48]. EEG entropy reduces with sedation and anesthesia and has been proposed as a means to measure the depth of anesthesia [49]. Physiological signal complexity is also known to decrease with older age [50]. Figure 1 demonstrates the heart rate tracing with differing complexities, indicating the state of health.

Decoding complexity

Variability is often confused with complexity. Complexity describes the variable nature of a system. A system can show complex or non-complex variability. A non-complex system is linear, stationary and predictable. It shows proportionality, which means, the signal output is proportional to the input provided. This is not the case with a complex system. Non-linearity [2], non-stationarity [40], time irreversibility [51], multi-scale entropy [52] and multi-fractality [53] are some of the qualities of a complex signal.

- Non-linearity describes the unpredictable nature of the system. It implies non-proportionality and is due to 'constructive' or 'destructive' interferences between various subcomponents of the system.
- Non-stationarity describes the constantly varying statistical properties of a complex system.
- Entropy describes the degree of disorderliness of a complex system.

The importance of temporal structure of a complex waveform, such as the BP, could be demonstrated by a simple example described by Subramaniam et al [2]. The following two sequences: $A = \{1232123212321\}$ and $B = \{1111222222333\}$, have the same variability, as measured by range and standard deviation, but completely different structures. While sequence A defines a triangular wave, sequence B is a step function. With evolving technology to obtain accurate, beat-to-beat BP values with high temporal resolution, and development of sophisticated computational techniques, analysis of this complex property of BP is becoming easier. Caveats in BP monitoring and the significance of monitoring resolution in variability analyses has been demonstrated by a study comparing variables obtained from beat by beat BP data Vs. BP data obtained every 15 seconds [54]. More material on understanding complexity can be availed on tutorial named 'Variability vs. Complexity' on PhysioNet [55].

BP Complexity and anesthesia:

Surgery and anesthesia impose a stress on the system. BP complexity reflects the adaptive responsiveness of the system and could be imagined as a physiological reserve of adaptability to stress. An analogy could be drawn with the cardio-pulmonary reserve of an athlete against an amateur. A seasoned athlete could perform a physical challenge with relative ease. The same level of physical challenge causes rapid exhaustion of the reserve in an amateur and inability to perform. Thus, the baseline BP complexity in a surgical patient could be imagined to denote the patient's baseline physiological reserve. This is dynamic, like an exercise stress test that is used to define the stress level at which the patient sustains

myocardial ischemia. Predictably, the complexity gradually decreases or in other words, the reserve gets used up with the imposed stress of anesthesia and surgery and this change in complexity should be a real-time, dynamic predictor of post-operative major adverse events. Figure 2 shows a simplified representation of BP complexity, contributing factors and outcome correlates.

There are a few studies on perioperative BP complexity. In a pilot study by Subramaniam et al, multi-scale entropy (MSE) was used as the BP complexity index [2]. The authors reported a significantly lower complexity in those with major adverse events compared to those without. This difference was seen despite similar BP variability in the groups measured in terms of standard deviation.

Another recent study in 147 patients undergoing cardiac surgery, computed MSE to measure BP complexity from beat by beat BP data (systolic, diastolic, pulse and mean pressures) in the pre-operative period and analyzed correlation with traditional risk scores namely the Society of Thoracic Surgeons' (STS) Risk of Mortality and Morbidity Index and the European System for Cardiac Operative Risk Evaluation Score (EuroSCORE II) [56]. They found a statistically significant inverse correlation: lower complexity was associated with greater estimated risk of cardiac events. Similar correlation was not seen with standard deviation as the measure of variability.

Conclusion

Untreated hemodynamic fluctuations in the perioperative period, both excessive hypertension and hypotension can lead to multiple consequences like myocardial ischemia, infarction, stroke, renal dysfunction, prolonged hospital stay and even death. Attempts to maintain BP within a pre-determined range appears to be an overly simplistic solution to a complex problem. Perhaps it is high time we explored BP variability and complexity. More studies are needed, especially studies that are prospective in nature, to ascertain the predictive nature of BP complexity. Also, we do not know if interventions to preserve and optimize complexity could result in better perioperative outcomes. This requires randomized controlled trials. If this is true, prehabilitative methods to improve complexity, hence the physiological reserve in comorbid patients undergoing high risk surgeries could become a reality. Real-time monitoring and optimization of BP complexity to improve outcomes might as well be possible. Seely and Macklem in their recent review stated that: "Variability analysis represents a novel means to evaluate and treat individual patients, suggesting a shift from epidemiological investigation to continuous individualized variability analysis" [57]. Analysis of complex, multiscale properties requires nonlinear models, high-fidelity signal measurement, and real-time analyses. Thus "dynamic blood pressure targets" could hold the key for individualized management, which is the future of perioperative medicine.

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References

1. Glance LG, et al., Effect of complications on mortality after coronary artery bypass grafting surgery: evidence from New York State. *J Thorac Cardiovasc Surg*, 2007 134(1): p. 53–8. [PubMed: 17599486]
2. Subramaniam B, et al., Blood Pressure Variability: Can Nonlinear Dynamics Enhance Risk Assessment During Cardiovascular Surgery? A Feasibility Study. *J Cardiothorac Vasc Anesth*, 2014 28(2): p. 392–7. [PubMed: 24508020]
3. Lonjaret L, et al., Optimal perioperative management of arterial blood pressure, in *Integr Blood Press Control*. 2014 p. 49–59. [PubMed: 25278775]
4. Mancia G, et al., 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*, 2013 34(28): p. 2159–219. [PubMed: 23771844]
5. Aronow WS, Management of hypertension in patients undergoing surgery, in *Ann Transl Med*. 2017.
6. Weiser TG, et al., Size and distribution of the global volume of surgery in 2012. *Bull World Health Organ*, 2016 94(3): p. 201–209f. [PubMed: 26966331]
7. Bijker JB, et al., Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology*, 2007 107(2): p. 213–20. [PubMed: 17667564]
8. Gawande AA, et al., The incidence and nature of surgical adverse events in Colorado and Utah in 1992. *Surgery*, 1999 126(1): p. 66–75. [PubMed: 10418594]
9. Kable AK, Gibberd RW, and Spigelman AD, Adverse events in surgical patients in Australia. *Int J Qual Health Care*, 2002 14(4): p. 269–76. [PubMed: 12201185]
10. Song HK, et al., Improved quality and cost-effectiveness of coronary artery bypass grafting in the United States from 1988 to 2005. *J Thorac Cardiovasc Surg*, 2009 137(1): p. 65–9. [PubMed: 19154905]
11. Lassen NA, Cerebral Blood Flow and Oxygen Consumption in Man. 10.1152/physrev. 1959.39.2.183. 1959.
12. Joshi B, et al., Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg*, 2012 114(3): p. 503–10. [PubMed: 22104067]
13. Joshi B, et al., Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. *Anesth Analg*, 2010 110(2): p. 321–8. [PubMed: 20008083]
14. Brady K and Hogue CW, Intraoperative hypotension and patient outcome: does "one size fit all?". *Anesthesiology*, 2013 119(3): p. 495–7. [PubMed: 23835588]
15. Rhee CJ, et al., Renovascular reactivity measured by near-infrared spectroscopy. *J Appl Physiol* (1985), 2012 113(2): p. 307–14. [PubMed: 22628378]
16. Dagal A and Lam AM, Cerebral autoregulation and anesthesia. *Curr Opin Anaesthesiol*, 2009 22(5): p. 547–52. [PubMed: 19620861]
17. Bijker JB, et al., Intraoperative hypotension and 1-year mortality after noncardiac surgery. *Anesthesiology*, 2009 111(6): p. 1217–26. [PubMed: 19934864]
18. Bijker JB, et al., Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. *Anesthesiology*, 2012 116(3): p. 658–64. [PubMed: 22277949]
19. Monk TG, et al., Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. *Anesthesiology*, 2015 123(2): p. 307–19. [PubMed: 26083768]
20. Reich DL, et al., Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. *Anesth Analg*, 1999 89(4): p. 814–22. [PubMed: 10512249]

21. Fayad A and Yang H, Is Peri-Operative Isolated Systolic Hypertension (ISH) a Cardiac Risk Factor?, in *Curr Cardiol Rev*. 2008 p. 22–33. [PubMed: 19924274]
22. Monk TG, et al., Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg*, 2005 100(1): p. 4–10. [PubMed: 15616043]
23. Asopa A, et al., Preoperative pulse pressure and major perioperative adverse cardiovascular outcomes after lower extremity vascular bypass surgery. *Anesth Analg*, 2012 114(6): p. 1177–81. [PubMed: 21821518]
24. Standards for Basic Anesthetic Monitoring - American Society of Anesthesiologists (ASA).
25. Goldman L, et al., Cardiac risk factors and complications in non-cardiac surgery. *Medicine (Baltimore)*, 1978 57(4): p. 357–70. [PubMed: 661558]
26. Charlson ME, et al., Intraoperative blood pressure. What patterns identify patients at risk for postoperative complications? *Ann Surg*, 1990 212(5): p. 567–80. [PubMed: 2241312]
27. Reich DL, et al., Intraoperative tachycardia and hypertension are independently associated with adverse outcome in noncardiac surgery of long duration. *Anesth Analg*, 2002 95(2): p. 273–7, table of contents. [PubMed: 12145033]
28. Walsh M, et al., Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology*, 2013 119(3): p. 507–15. [PubMed: 23835589]
29. Salmasi V, et al., Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery A Retrospective Cohort Analysis. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, 2018 126(1): p. 47–65.
30. Gawande AA, et al., An Apgar score for surgery. *J Am Coll Surg*, 2007 204(2): p. 201–8. [PubMed: 17254923]
31. Regenbogen SE, et al., Does the Surgical Apgar Score measure intraoperative performance? *Ann Surg*, 2008 248(2): p. 320–8. [PubMed: 18650644]
32. Kork F, et al., Minor Postoperative Increases of Creatinine Are Associated with Higher Mortality and Longer Hospital Length of Stay in Surgical Patients. *Anesthesiology*, 2015 123(6): p. 1301–11. [PubMed: 26492475]
33. Redfern G, Rodseth RN, and Biccadd BM, Outcomes in vascular surgical patients with isolated postoperative troponin leak: a meta-analysis. *Anaesthesia*, 2011 66(7): p. 604–10. [PubMed: 21564046]
34. Willeit P, et al., High-Sensitivity Cardiac Troponin Concentration and Risk of First-Ever Cardiovascular Outcomes in 154,052 Participants. *J Am Coll Cardiol*, 2017 70(5): p. 558–568. [PubMed: 28750699]
35. Futier E, et al., Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *Jama*, 2017 318(14): p. 1346–1357. [PubMed: 28973220]
36. Aronson S, et al., Intraoperative systolic blood pressure variability predicts 30-day mortality in aortocoronary bypass surgery patients. *Anesthesiology*, 2010 113(2): p. 305–12. [PubMed: 20571360]
37. Levin MA, et al., Intraoperative arterial blood pressure lability is associated with improved 30 day survival. *Br J Anaesth*, 2015 115(5): p. 716–26. [PubMed: 26395645]
38. Mascha EJ, et al., Intraoperative Mean Arterial Pressure Variability and 30-day Mortality in Patients Having Noncardiac Surgery. *Anesthesiology*, 2015 123(1): p. 79–91. [PubMed: 25929547]
39. Hirsch J, et al., Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. *Br J Anaesth*, 2015 115(3): p. 418–26. [PubMed: 25616677]
40. Goldberger AL, Giles F. Filley Lecture. Complex Systems. 10.1513/pats.200603-028MS, 2012.
41. Seely AJ and Macklem PT, Complex systems and the technology of variability analysis. *Crit Care*, 2004 8(6): p. R367–84. [PubMed: 15566580]
42. Hanss R, et al., Heart rate variability predicts severe hypotension after spinal anesthesia. *Anesthesiology*, 2006 104(3): p. 537–45. [PubMed: 16508402]

43. van Hooijdonk RT, Abu-Hanna A, and Schultz MJ, Glycemic variability is complex - is glucose complexity variable?, in Crit Care. 2012 p. 178. [PubMed: 23171831]
44. Glass L and Kaplan D, Time series analysis of complex dynamics in physiology and medicine. Med Prog Technol, 1993 19(3): p. 115–28. [PubMed: 8127277]
45. Hogue CW, et al., RR Interval Dynamics Before Atrial Fibrillation in Patients After Coronary Artery Bypass Graft Surgery. 1998.
46. Godin PJ, et al., Experimental human endotoxemia increases cardiac regularity: results from a prospective, randomized, crossover trial. Crit Care Med, 1996 24(7): p. 1117–24. [PubMed: 8674322]
47. Hartman ML, et al., Enhanced basal and disorderly growth hormone secretion distinguish acromegalic from normal pulsatile growth hormone release. J Clin Invest, 1994 94(3): p. 1277–88. [PubMed: 8083369]
48. Veldman RG, et al., Growth hormone and prolactin are secreted more irregularly in patients with Cushing's disease. Clin Endocrinol (Oxf), 2000 52(5): p. 625–32. [PubMed: 10792343]
49. Bruhn J, Ropcke H, and Hoeft A, Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. Anesthesiology, 2000 92(3): p. 715–26. [PubMed: 10719951]
50. Lipsitz LA and Goldberger AL, Loss of 'complexity' and aging. Potential applications of fractals and chaos theory to senescence. Jama, 1992 267(13): p. 1806–9. [PubMed: 1482430]
51. Costa MD, Peng CK, and Goldberger AL, Multiscale analysis of heart rate dynamics: entropy and time irreversibility measures. Cardiovasc Eng, 2008 8(2): p. 88–93. [PubMed: 18172763]
52. Costa M, Goldberger AL, and Peng CK, Multiscale entropy analysis of complex physiologic time series. Phys Rev Lett, 2002 89(6): p. 068102. [PubMed: 12190613]
53. Ivanov PC, et al., Multifractality in human heartbeat dynamics. Nature, 1999 399(6735): p. 461. [PubMed: 10365957]
54. Packiasabapathy S, Susheela AT, Mujica F and Subramaniam B. Significance of intra-operative blood pressure data resolution: A retrospective, observational study [version 1; referees: 1 approved]. F1000Research 2018, 7:275 (doi: 10.12688/f1000research.13810.1) [PubMed: 29946438]
55. Goldberger AL, et al., PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. Circulation, 2000 101(23): p. E215–20. [PubMed: 10851218]
56. Henriques TS, et al., Complexity of preoperative blood pressure dynamics: possible utility in cardiac surgical risk assessment. J Clin Monit Comput, 2018.
57. Seely AJ and Christou NV, Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear systems. Crit Care Med, 2000 28(7): p. 2193–200. [PubMed: 10921540]

Key points:

- Intra-operative blood pressure optimization is of paramount importance, especially in high risk patients with multiple comorbidities and the elderly.
- There is a lack of uniform definition or guidelines regarding blood pressure targets to ensure patient safety.
- Absolute intraoperative blood pressure and its variability have been correlated to post-operative outcomes. This outcome association of various BP parameters varies from study to study due to multiple reasons.
- Most studies viewed BP as a static parameter, leading to conflicting results and lack of generalizability.
- Learning the dynamic nature of BP may give more insight into the mechanism for adverse events and also provide optimal intraoperative targets

Synopsis

Hemodynamic stability is an important goal of safe anesthesia. Yet, after several years of research, the ideal intraoperative BP targets to ensure patient safety still remains elusive. Is there more to BP than just the values of systolic, diastolic and mean pressures? This article introduces the dynamic nature of the BP waveform and its possible clinical application, which might be the missing link.

Figure 1:

Heart rate time series A and B have similar mean and SD, but very different temporal structures. Series A is more complex than B and is of a healthy subject. Series B is from a subject during an episode of obstructive sleep apnea.

Adapted Goldberger, A.L., et al., *PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals*. Circulation, 2000. **101**(23): p. E215-2; with permission.

Figure 2:
BP complexity, contributing factors and outcome association