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Recent Advances in Understanding the Pathophysiology and Risk Stratification of Post-Intubation Hypotension

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Abstract

Research indicates that post-intubation hypotension (PIH) is the most frequent complication of intubation, potentially leading to acute myocardial infarction, renal failure, extended hospitalizations, and poor outcomes. Key physiological parameters such as age, body mass index, and baseline blood pressure are closely linked to PIH incidence. Induction drugs significantly influence the mechanisms of PIH, with varying drugs and administration methods impacting hemodynamic stability. Furthermore, the complexity of the intubation procedure exacerbates PIH by stimulating the vagus nerve and affecting cardiac output. Although current research aims to identify risk factors and physiological mechanisms of PIH, the absence of uniform diagnostic criteria impedes the comparability of results. Future studies should focus on establishing clear diagnostic standards, optimizing induction drug choices and procedural techniques, and integrating early warning indicators with personalized intervention strategies to decrease PIH incidence and enhance patient outcomes.

Keywords

Tracheal Intubation, Hypotension, Mechanisms, Risk Factors, Research Advances

Introduction

Endotracheal intubation (ETI) is a critical life-saving intervention to ensure airway patency during surgery, emergencies, intensive care, and perioperative periods. Despite its crucial role in resuscitation and life support, ETI is associated with various complications, especially post-intubation hypotension (PIH). As a common complication of intubation, PIH is strongly linked to acute myocardial infarction, renal failure, prolonged hospital stays, and adverse patient outcomes. Its occurrence may be influenced by a range of factors, including patient physiological parameters, pre-existing conditions, the complexity of the intubation process, and pre-intubation medications.

Research suggests that PIH mechanisms involve suppression of the sympathetic nervous system, activation of the vagus nerve, hemodynamic alterations due to positive pressure ventilation, and direct effects of induction drugs. However, inconsistencies in diagnostic criteria, research methodologies, and result comparability hinder the development of effective clinical prevention and management strategies. Thus, elucidating the mechanisms of PIH, identifying its primary risk factors, and exploring effective prevention measures have become central to research efforts aimed

at enhancing patient outcomes and minimizing postoperative complications.

This review systematically summarizes and analyzes current research on post-intubation hypotension following tracheal intubation. It focuses on elucidating associated mechanisms and risk factors to offer effective guidance and intervention strategies for clinicians, laying the groundwork for future studies.

Diagnostic Criteria for Post-Intubation Hypotension

PIH is defined as a significant decrease in blood pressure following endotracheal intubation, potentially leading to tissue hypoxia, organ dysfunction, neurological impairment, and in severe cases, life-threatening shock. The reported incidence rates of PIH vary considerably, ranging from 19% to 52% [1-4]. This variability stems not only from individual patient factors and intubation techniques but also from significant inconsistencies in diagnostic criteria. Currently, substantial differences exist in the definitions and criteria used to diagnose PIH across studies. For example, Heffner AC and colleagues [1] suggest a more conservative criterion that excludes patients with pre-existing hypotension, yielding a lower incidence of PIH. This approach is appropriate for assessing newly developed hypotension post-intubation. In contrast, Green and others [2] use a broader standard, identifying PIH as any reduction in blood pressure exceeding 20% from baseline or the requirement to maintain or increase vasopressor doses, which more accurately reflects clinical realities and results in a higher reported incidence.

Furthermore, a study in the emergency department that compared the effects of different induction agents (ketamine versus etomidate) on the incidence of hypotension post-intubation found that although ketamine is more frequently used in patients with a high shock index (SI), there was no significant association between the choice of induction agent and the occurrence of post-intubation hypotension [3]. This study also demonstrated that patients with an elevated SI, irrespective of the induction agent used, are at an increased risk of cardiovascular failure post-intubation. These findings underscore the importance of considering pre-intubation physiological parameters to assess and manage the risk of PIH more effectively.

Conversely, research by Smischney et al. [4] examined whether there was an initiation or increase in vasopressor infusion within 30 minutes' post-intubation, highlighting the importance of early hemodynamic management following the procedure. The variety in these standards not only reflects the distinct focus of each study but also underscores the complexity of defining PIH in clinical practice. As shown in **Table-1**, variations in diagnostic criteria among different studies complicate the interpretation of data and comparison of research outcomes. In this context, future studies should strive to establish more uniform and clinically relevant diagnostic criteria, facilitating more effective comparison of data across studies and enhancing the integration of findings to improve the standardization and precision of PIH management in clinical settings.

Table-1: Diagnostic Criteria Variations Across Studies

Category	Pre-Intubation Status	Post-Intubation Criteria	Reference
Type 1	SBP ≥90 mmHg AND MAP ≥65 mmHg	SBP <90 mmHg OR MAP <65 mmHg OR	[1]
	No vasopressor support	Initiation of vasopressor support	
Type 2	SBP ≥90 mmHg AND MAP ≥65 mmHg	SBP <90 mmHg OR MAP <65 mmHg	[2]
	On vasopressor support	Continuation of same vasopressor support	
Type 3	SBP <90 mmHg OR MAP <65 mmHg	>20% decrease from baseline blood pressure	[3]
	No vasopressor support	No vasopressor support	
Type 4	SBP <80 mmHg OR MAP <65 mmHg	Requirement for vasopressor support within 30 minutes post-ETI	[4]
	No vasopressor support		
Type 5	Requiring vasopressor support within 30 minutes post-ETI	Requirement for increased vasopressor dosage within 30 minutes post-ETI	[2,4]

Mechanisms Related to Hypotension Following Tracheal Intubation

Research indicates that the mechanisms underlying PIH are multifaceted, involving the patient's pre-existing conditions, physiological characteristics, the complexity of the intubation procedure, and the direct effects of medications. Patients suffering from trauma, hypoxemia, shock, hypertension, or internal environmental imbalances are particularly prone to PIH, potentially due to the fragility of their hemodynamic regulation mechanisms. To thoroughly explore the pathophysiological foundations of PIH, this section will examine three critical dimensions: disease-related factors in patients, operation-related factors, and the pharmacodynamics of the drugs involved.

Disease-Related Factors in Patients:

Before intubation, a patient's underlying conditions and physiological state significantly influence the stability of postoperative hemodynamics. Elderly patients are particularly susceptible to PIH due to diminished cardiovascular reserve and reduced sympathetic nervous system responses, which result in impaired vascular regulation. Additionally, patients with low blood volume or low body weight, resulting in relatively reduced circulating blood volume, are more likely to experience blood pressure drops during positive pressure ventilation. In such cases, positive pressure ventilation and mechanical stimuli may trigger a vagal nerve reflex, reducing vascular tone and suppressing sympathetic nervous system activity, which in turn decreases catecholamine release and cardiac output [5-7]. This cascade of events increases the risk of hemodynamic instability and hypotension postoperatively. Overall, there is a complex interaction between a patient's physiological status, underlying pathological conditions, and the development of PIH.

Factors Related to the Intubation Procedure:

The complexity of the intubation procedure significantly impacts hemodynamics and should not be overlooked. Multiple attempts at laryngoscopy and repeated intubations stimulate the vagus nerve, further exacerbating hypoxemia and suppressing the sympathetic nervous system, which leads to a rapid decline in heart rate and a sudden drop in blood pressure [8]. Repeated procedures may also cause laryngeal edema or laryngospasm, worsening ischemia in the myocardium and brain, and in severe cases, potentially resulting in cardiac arrest (CA). In this context, the complexity and duration of the intubation are critical triggers for PIH, highlighting the need for clinical procedures to be standardized in order to minimize the risk of repeated intubations.

Mechanisms of Drug Action:

The use of sedative and analgesic drugs during intubation is a key mechanism contributing to the development of PIH. The choice of drug and method of administration directly influence hemodynamic stability. For instance, while ketamine provides analgesia and sedation, it may diminish the catecholamine response in some patients, leading to reduced vascular tone and peripheral resistance, impaired myocardial contractility, and a decrease in both pre- and afterload, ultimately resulting in hypotension [9]. Additionally, other sedative drugs used during intubation can induce vasoparalysis, increase intrathoracic venous pressure, and decrease venous return, thereby exacerbating the drop in blood pressure [10]. Consequently, drug selection should be carefully tailored to the specific condition of the patient to minimize the risk of PIH.

In summary, the development of PIH is closely linked to the patient's underlying conditions, the technical complexity of the intubation process, and the sedative drugs administered. A comprehensive understanding of these factors and their interactions is crucial for minimizing the incidence of PIH and enhancing patient outcomes.

Impact of Post-Intubation Hypotension on Patient Outcomes

The impact of PIH on patient outcomes has been a critical focus of clinical research. Studies suggest that PIH may affect both short-term and long-term outcomes to varying degrees. Research by Émond et al. [11] indicates that, while there was no significant difference in 48-hour in-hospital mortality and length of stay between patients with and without PIH, this finding may suggest that PIH does not substantially affect short-term outcomes in certain cases. Similarly, Colleran et al. [12] found no significant correlation

between PIH in emergency department (ED) patients and mortality or discharge rates, highlighting that the impact of PIH may differ across clinical settings and patient populations. However, discrepancies in research findings warrant further attention. A study by Green et al. [13] reported a significant increase in in-hospital mortality and length of stay among patients with PIH, suggesting an association with poorer outcomes, particularly in those requiring complex in-hospital management. This association is even more pronounced in patients with severe trauma, where the incidence of PIH reaches 36%, and the in-hospital mortality rate is twice that of patients without PIH, with more than a threefold increase in emergency department mortality rates [14]. These findings underscore the potential severity of PIH in high-risk patients. To further quantify its impact, a meta-analysis by Ferrada et al. [15] found that the mortality rate among patients with PIH was 33.2%, significantly higher than the 19.6% observed in those without PIH. Additionally, the INTUBE study [16] confirmed that patients with hemodynamic instability during the peri-intubation period had a significantly higher risk of ICU mortality, with an adjusted odds ratio of 2.47. Collectively, these studies highlight a potential link between PIH and higher mortality rates, though variations in findings may be attributed to factors such as study population, thresholds for hypotension, pre-intubation management of hypotension, and the use of vasopressor agents.

In summary, despite the variability in research outcomes, the majority of evidence supports a significant association between PIH and adverse outcomes, particularly in high-risk patients. These findings suggest that clinicians should prioritize the prevention and management of PIH during preoperative assessments. In the future, standardized research protocols and consistent evaluation methods will help clarify the true impact of PIH on patient outcomes and facilitate the development of more targeted treatment strategies for different patient subgroups.

Risk Factors for Post-Intubation Hypotension

Physiological Parameters of Patients (Age, Body Mass Index, Blood Pressure Levels, Lactate Levels, Albumin Levels, Comorbid Chronic Diseases):

Age is a significant independent risk factor for PIH. Studies have shown that patients aged 70 and older are more susceptible to PIH, which is associated with reduced cardiovascular reserve and the presence of chronic comorbid conditions. These factors collectively impair hemodynamic stability in elderly patients, thereby increasing the risk of postoperative hypotension [17]. Clinical observations also indicate that the sympathetic nervous response is attenuated in elderly patients, further exacerbating the decline in blood pressure regulation.

Body Mass Index (BMI) is another influential factor in the development of PIH. Research indicates that muscle-strengthening physical activities (MSPA) significantly affect blood pressure, particularly in men with prehypertension, with an increase in MSPA associated with a rise in systolic pressure. This finding suggests that, in certain populations, the relationship between BMI and blood pressure must also account for the potential impacts of physical activity and muscle activity. While a higher BMI may reduce the risk of hypoxia during intubation, the incidence of PIH remains elevated [19]. Conversely, patients with a low BMI (under 18.5) are more likely to experience PIH due to insufficient blood volume, reduced cardiac output, and decreased peripheral vascular resistance [20]. These patients often exhibit more pronounced hemodynamic instability postoperatively, which is related to the suppression of the renin-angiotensin-aldosterone system and reduced sympathetic nervous system activity [21].

Preoperative blood pressure levels directly influence the occurrence of PIH. Research indicates that patients with lower preoperative systolic (SBP) and diastolic blood pressures (DBP) are more likely to experience PIH postoperatively. This may be due to impaired organ function in these patients, which can lead to hypoxemia and hypercapnia, subsequently affecting hemodynamic stability [20,22]. Thus, strict monitoring and management of blood pressure before surgery are crucial for reducing the risk of PIH.

Lactate levels are also an important indicator of tissue hypoxia and volume status. Elevated lactate levels often suggest insufficient fluid volume, indicating a potential risk of shock [23]. When patients are administered

sedative and analgesic drugs, underlying volume deficiencies may become evident, leading to the sudden onset of PIH. Studies show that patients with lactate levels higher than 2.0 mmol/L have a significantly increased incidence of PIH. Therefore, lactate levels can serve as a useful reference parameter in preoperative assessments [24].

Albumin levels are crucial for maintaining vascular osmotic pressure and blood volume. Although current evidence on the impact of albumin levels on PIH is limited, hypoalbuminemia is still considered a potential risk factor. In patients with hypoalbuminemia, plasma colloid osmotic pressure decreases, and effective blood volume is reduced, particularly in the presence of multi-organ failure or sepsis. This condition increases capillary permeability, further reducing blood volume and significantly elevating the incidence of PIH [25]. A study related to COVID-19 infections found that patients with low albumin levels had a higher risk of PIH, suggesting that albumin levels may serve not only as a risk factor but also as a predictive marker for PIH [26].

The impact of chronic diseases cannot be overlooked. Research indicates that patients with comorbidities such as chronic obstructive pulmonary disease (COPD) or chronic kidney disease are more likely to experience PIH postoperatively [3]. These chronic conditions exacerbate postoperative blood pressure instability by affecting the patient's hemodynamic status and organ function. While some studies have not identified respiratory diseases as independent risk factors, this may be related to sample size and study design limitations [21,27].

Induction Agents in Tracheal Intubation:

During rapid sequence induction for tracheal intubation, the type, dosage, and method of administration of induction agents are crucial factors influencing postoperative blood pressure changes. The choice of induction agents should be tailored to individual patient characteristics to minimize the risk of PIH. The primary induction agents used in current clinical practice include sedative-analgesics and neuromuscular blocking agents.

Sedative Hypnotics:

Etomidate, known for its rapid onset, short half-life, and minimal impact on hemodynamics, is considered a preferred drug for high-risk patients. It performs well in stabilizing cerebral perfusion pressure, reducing intracranial pressure, and decreasing cerebral oxygen metabolism [28].

However, its adrenal suppressive effect may induce adrenal insufficiency in patients with sepsis, thereby increasing the risk of postoperative hemodynamic instability [29,30]. Although some studies suggest that the use of etomidate does not necessarily increase mortality rates [31], reducing the dosage of etomidate has been proposed as a potential strategy to lower the risk of PIH [32].

Midazolam is widely used due to its rapid onset and short duration of action, with effects including sedation, hypnosis, and muscle relaxation. However, its inhibition of sympathetic nerve activity may lead to decreases in heart rate and blood pressure, increasing the risk of post-intubation hypotension (PIH) [33]. Recent studies suggest that midazolam itself is not an independent risk factor, but its effects may be related to combined use with dexmedetomidine [20]. Dexmedetomidine can alleviate the blood pressure reduction caused by midazolam by decreasing blood pressure variability [34]. The specific impact of midazolam on PIH still requires further research and validation.

Propofol is a commonly used induction agent known for rapidly providing optimal intubation conditions. However, it is also a high-risk medication for inducing hypotension due to its vasodilatory effects and reduction in peripheral resistance [35]. Studies indicate that propofol administration may lead to frequent episodes of hypotension and apnea during induction [36]. Therefore, the dosage of propofol should be carefully adjusted according to the patient's physiological status to minimize the risk of PIH.

Ketamine is considered relatively stable in terms of hemodynamics and is notable for its stability in the cardiovascular system. It can maintain blood pressure by stimulating the sympathetic nervous system [37,38],

but its potential psychiatric side effects and risk of respiratory depression should not be overlooked [39]. Research indicates that combining midazolam with ketamine can reduce ketamine's side effects and provide better sedation [40]. Thus, ketamine is a preferred choice in patients where maintaining blood pressure is crucial, but its use should be managed with risk mitigation strategies involving other medications.

In conclusion, different sedative-hypnotic drugs play various roles during the induction process. Clinicians should select the appropriate induction agents and adjust their dosages based on the patient's condition and hemodynamic status to reduce the incidence of PIH and improve postoperative outcomes. Future research should further explore the effects of different drug combinations to optimize anesthesia induction strategies.

Neuromuscular Blocking Agents:

Neuromuscular blocking agents (NMBAs) are commonly used during tracheal intubation to relax muscles and ensure smooth intubation. These include depolarizing agents, such as succinylcholine, and non-depolarizing agents, such as pancuronium, atracurium, and vecuronium. However, the impact of NMBAs on hemodynamics may increase the risk of PIH. Research by Smischney et al. [17-31] suggests that the use of NMBAs may increase the incidence of PIH, which is associated with their effects on reducing peripheral vascular resistance and myocardial contractility. Studies indicate that depolarizing agents, such as succinylcholine, are more likely to cause PIH compared to non-depolarizing agents, due to their concurrent muscle relaxation, vascular dilation, increased pulse rate, and blood pressure reduction [41]. However, research by Green and Heffner suggests that the use of NMBAs can, to some extent, stabilize hemodynamics and reduce the incidence of postoperative hypotension [2].

Currently, there is controversy regarding the impact of NMBAs on PIH, and inconsistent results may stem from differences in patients' baseline states, drug dosages, and usage scenarios. Further research is needed to delineate the hemodynamic effects of different types of NMBAs in various patient groups more precisely, in order to assess their potential impact on PIH. Given the differential effects of various NMBAs, clinical considerations should include a comprehensive evaluation of the specific circumstances of the patient and the choice of drugs, with careful assessment of the potential impact of NMBAs on blood pressure stability.

Administration Method:

The order and control of dosages of anesthetic induction agents significantly influence hemodynamic stability. By using targeted controlled administration, it is possible to avoid peak onset times of various drugs, minimize adverse hemodynamic reactions, and enhance the safety of anesthetic induction. One study explored the impact of rapid changes in the concentration of different anesthetic agents on hemodynamics. The results indicated that a rapid increase in the concentration of sevoflurane (S) could induce epileptiform electroencephalogram (EEG) activity and tachycardia, whereas an increase in desflurane (D) concentration caused only tachycardia, with no epileptiform EEG changes observed. This suggests that during anesthetic induction, appropriate regulation of the choice and concentration of anesthetic agents, particularly when rapidly increasing drug concentrations, can effectively reduce negative impacts on the cardiovascular system and maintain hemodynamic stability [42]. Similarly, research by Stokes and Hutton pointed out that the dosage of propofol is significantly related to the incidence of PIH and has both respiratory and circulatory suppressive effects; thus, proper dose control is crucial to avoid hypotension [43,44].

Although existing studies have shown that different orders of administration and dosage adjustments can improve the incidence of PIH, current research primarily focuses on the combined use of remifentanil and propofol, with relatively small sample sizes. Future studies should increase sample sizes and further explore the impact of different administration methods of various induction agents on blood pressure, providing more evidence for the development of clinical anesthesia induction protocols.

Summary and Outlook

In summary, the mechanisms underlying PIH are

complex and multifactorial, involving a combination of physiological, pathological, and pharmacological factors. Research has identified several key mechanisms contributing to PIH, including sympathetic nervous inhibition, vagal nerve excitation, disturbances in internal environment homeostasis, vasodilation, insufficient blood volume, myocardial suppression, decreased cardiac output, and the hemodynamic effects of anesthetic induction agents. These mechanisms can vary significantly among patients, emphasizing the need for comprehensive preoperative and intraoperative assessments to identify and stratify those at high risk for PIH.

In clinical practice, effectively preventing and managing PIH requires a nuanced understanding of the patient's physiological characteristics, underlying comorbidities, preoperative blood pressure levels, and medication usage. Special attention should be given to elderly patients, those with low blood volume, and those with low body mass index (BMI). Tailored anesthesia plans and meticulous intraoperative monitoring are crucial to minimize hypotension-related complications. Several predictive and warning indicators, such as baseline blood pressure, shock index, hypotension prediction score, and ultrasonographic measurement of the venous index, have shown promise in identifying patients at higher risk for PIH. Integrating these indicators with the mechanisms and risk factors discussed in this review can provide valuable guidance for the prevention and early intervention of PIH.

Future research should aim to clarify diagnostic criteria and optimize intervention strategies for PIH. Large-scale, multicenter studies are needed to validate current findings and refine treatment protocols for different patient populations. Additionally, the integration of advanced monitoring technologies, such as artificial intelligence and machine learning, holds the potential to develop real-time warning systems that can swiftly identify and manage hemodynamic changes during surgery. This approach could reduce the incidence of PIH and enhance the precision of postoperative management. Understanding and addressing the mechanisms and risk factors of PIH are essential to improving patient outcomes and minimizing postoperative complications. With ongoing research and technological advancements, personalized strategies for the prevention and management of PIH are expected to progress significantly, offering more innovative solutions for clinical practice.

Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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