Perioperative and Anesthetic Considerations for Post-Acute Sequelae of COVID (PASC)/ Long COVID

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Article

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Abstract: Post-Acute Sequelae of COVID (PASC), commonly known as Long COVID, presents with a broad spectrum of medical conditions and symptoms persisting beyond three months post-SARS-CoV-2 infection, affecting over 18 million Americans and 65 million people worldwide. Despite its prevalence, to date, there are no specific clinical guidelines for the perioperative management of PASC patients. PASC is a complex, multisystemic condition leading to neurological, respiratory and endocrine sequelae, potentially resulting from persistent viral presence, immune dysregulation, and/or end-organ damage. This manuscript discusses the implications of these sequelae on anesthesia practice, emphasizing the need for vigilance in pre-operative assessments to identify PASC and associated conditions through detailed patient history, understanding of off-label medication use, and familiarity with medical terminologies like POTS, MCAS and brain fog. Key perioperative considerations include cautious use of anesthetics, especially in patients with neurological and cardiovascular complications. Pulmonary management strategies for PASC patients, such as lung-protective ventilation and non-invasive post-operative support could mitigate any perioperative respiratory complications. Finally, we underscore the importance of a multidisciplinary approach to manage PASC patients effectively during surgery, advocating for personalized anesthetic plans and calling for more evidence driven guidelines for this emerging patient group as research progresses.

Keywords: PASC; long COVID; anesthesiology; perioperative

Introduction

Post-Acute Sequelae of COVID (PASC), commonly known as Long COVID, presents with a broad spectrum of new onset symptoms and medical conditions persisting beyond three months post-SARS-CoV-2 infection, affecting over 18 million Americans and 65 million people worldwide[1,2]. Despite its widespread occurrence, there is a notable lack of specific clinical guidelines for managing PASC in the perioperative settings. Commonly reported medical conditions include excessive fatigue, post-exertional malaise (PEM), memory loss, cognitive impairment, dysautonomia, postural orthostatic tachycardia syndrome (POTS), and persistent shortness of breath, even years after the initial infection[3]. Although these conditions overlap with those of other chronic inflammatory diseases like myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia, and chronic vector-borne diseases, research is emerging distinguishing PASC by a unique immune signature [4,5]. Several mechanisms are proposed for the pathophysiology of PASC, including replication-competent SARS-CoV-2 virus, persistent S1 spike proteins in CD16+ monocytes causing immune dysregulation and endothelialitis, the production of

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autoantibodies following infection, mast cell activation syndrome (MCAS), and the reactivation of herpes family viruses like CMV and EBV [6,7,8,9]. Additionally, long-term damage to organs from the initial infection, such as pulmonary fibrosis, cardiac and vascular issues, and brain and nervous system changes, must be considered. Interestingly, there is also a parallel condition, post-COVID-19 vaccine syndrome (PCVS), which shares similar symptoms and clinical features with PASC, suggesting it should be part of the PASC discussion[10].

Currently, there are no specific guidelines for the perioperative management of PASC patients, nor is there published evidence suggesting that anesthetic agents exacerbate PASC symptoms. However, given the condition's prevalence and impact, anesthesiologists need to stay informed about ongoing research to manage these cases with heightened awareness. This vigilance begins in the preoperative phase, where understanding PASC-related medical terminology allows for the identification of the condition through thorough history-taking and knowledge of the medications being researched. Moreover, potential complications and challenges during and after surgery require anesthesiologists to be adept at recognizing, managing, ordering appropriate tests for, and consulting with specialists to ensure safe anesthesia delivery for these complex patients.

Perioperative Considerations

Patient Communication

The complexity of researching and treating chronic inflammatory diseases like PASC has long posed challenges for the medical and scientific communities, leading many patients to feel overlooked or "gaslit"[11]. This sense of dismissal often results in patients being reluctant to discuss their symptoms fully, including their use of off-label medications or alternative treatments, out of fear of judgement or further invalidation. Therefore, anesthesiologists must foster trust, asking explicitly about each medication’s purpose rather than assuming standard indications, to capture a full clinical picture.

PASC Terminology

Anesthesiologists need to be well-versed in the terminology and acronyms frequently used by those with PASC and similar conditions. Key terms include POTS, MCAS, PEM, dysautonomias, and "brain fog." Although these aren't terms unique to PASC, they serve as important flags for anesthesiologists to delve deeper into the patient's history—exploring when conditions started, what treatments have been tried, and which medications are currently in use. This approach ensures a more nuanced understanding of the patient's condition, fostering a more empathetic and effective perioperative management strategy.

Medication Management

Although no PASC-specific drugs are regulatory-approved, off-label therapies, meaning they are used for purposes not yet sanctioned by the US FDA, are widely explored. Drugs like ivabradine, low-dose naltrexone, antihistamines, and gabapentin are proposed for symptom management, while others such as nirmatrelvir/ritonavir (Paxlovid), monoclonal antibodies, direct-acting oral anticoagulants, and the combination of maraviroc with atorvastatin are thought to address specific underlying mechanisms of PASC (Table 1). Management of PASC medications on the day of surgery is currently not clear. Decisions on whether to discontinue, reduce, or maintain these treatments need to be made in consultation with the patient's primary care and the surgical team to tailor the approach to each patient's needs.

Neurological

PASC is associated with over 200 symptoms and medical conditions across multiple organ systems, but anesthesiologists should particularly note its impact on neurological, cardiovascular, respiratory, and endocrine functions[12]. Neurological consequences, include cognitive

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impairments, often described as "brain fog," concentration and memory issues, neuropathies and sleep disorders. Additionally, though less common, atlantoaxial subluxation and cranial instability have been linked to PASC. If patients experience neck stiffness or pain, consider using a video laryngoscope for intubation [13].

Dysautonomia, a significant aspect of PASC, is a broad term for disorders causing dysfunction in the autonomic nervous system, leading to issues like heart rate and blood pressure irregularities, gastrointestinal motility problems, and temperature regulation difficulties. Postural orthostatic tachycardia syndrome (POTS), a form of dysautonomia, is characterized by an increase in heart rate of at least 30 beats per minute upon standing, without a drop in blood pressure. One prevailing theory for POTS's pathophysiology involves an excessive adrenergic response, resulting in heightened sympathetic activity[14]. Given this, anesthesiologists must use epinephrine cautiously in PASC patients with dysautonomia during surgery to avoid exacerbating autonomic dysfunction and causing unpredictable hemodynamic effects. Alternatives like phenylephrine and vasopressin have demonstrated benefits in improving orthostatic tolerance and stabilizing hemodynamics in POTS patients and may be preferable during surgical procedures[15,16]. However, ephedrine should be avoided as it can both block the reuptake of norepinephrine and trigger its release from nerve endings, potentially aggravating POTS symptoms.

Patients with dysautonomia often take medications to control heart rate, such as ivabradine (I(f) channel blocker), calcium channel blockers, and beta-blockers. For blood pressure regulation, they might use midodrine (an alpha1 adrenergic receptor agonist) or fludrocortisone (a mineralocorticoid) [17]. For those on long-term fludrocortisone, consider stress-dose steroid replacement with IV hydrocortisone during surgery [18]. Acetylcholinesterase inhibitors like pyridostigmine (Mestinon) are being explored for symptom relief in dysautonomia. Since sugammadex is available, avoiding neostigmine as a reversal agent for muscle relaxants is advisable to prevent cholinergic crisis or severe bradycardia. Dysautonomia and POTS patients are prone to prolonged intraoperative hypotension, so their fluid status must be closely monitored. If heart or renal failure isn't an issue, consider and monitor adequate crystalloid fluid administration throughout the perioperative period to aid preload augmentation [19]. Temperature dysregulation being common, vigilant temperature monitoring and the use of warming systems like the Bair Hugger can help manage dysautonomic responses. While meperidine is a first-line treatment for postoperative shivering, second-line options like dexmedetomidine or clonidine should be used cautiously due to their vasodilatory effects, which might induce reflex tachycardia and worsen POTS. Coordination with dysautonomia specialists before surgery is crucial to manage potential autonomic and hemodynamic fluctuations.

Beyond autonomic symptoms, other debilitating neurological manifestations include headaches, tinnitus, peripheral neuropathy, motor deficits, and sensory sensitivities. Anesthesiologists, along with nursing and surgical staff, should be aware that these patients might require a calm, low-light environment throughout their perioperative journey to avoid triggering or worsening symptoms. This means minimizing noise, avoiding music, and delaying the use of loud equipment until the patient is fully anesthetized in the operating room.

Cardiovascular

PASC cardiovascular disease (PASC-CVD) is an increasingly recognized consequence of COVID-19 that anesthesiologists must be prepared to address. Emerging evidence suggests that PASC-CVD arises from vasculopathy, particularly endothelialitis, which triggers activation of coagulation and complement pathways. This, in turn, heightens the risk of cardiovascular events, including myocarditis, pericarditis, microvascular dysfunction, nonischemic cardiomyopathy, cerebrovascular events, and arrhythmias [20,21,22]. Additionally, vascular inflammation has been linked to prevalent PASC conditions such as dysautonomia, chronic fatigue, and post-exertional

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malaise [23,24]. Suspecting endothelial dysfunction and a resulting prothrombotic state, some clinicians initiate treatment with direct oral anticoagulants (DOACs) like apixaban (Eliquis) or rivaroxaban (Xarelto), and/or dual anti-platelet therapy (DAPT) with agents such as clopidogrel (Plavix) and aspirin. There are no standardized guidelines for perioperative management of antithrombotics in PASC patients. Until more data are available, guidelines for perioperative

management of anticoagulants and antiplatelets in non-PASC patients should be followed. Particularly important in PASC is the continuation of aspirin therapy in those undergoing elective noncardiac surgery, as persistent platelet activation is the likely driver of hypercoagulability in these patients.

Interestingly, the incidence of atherosclerotic cardiovascular disease (ASCVD) rises during both acute COVID-19 and the post-acute phase. Post-COVID patients also exhibit unfavorable lipid profiles, including elevated low-density lipoprotein (LDL) cholesterol, triglycerides, and total cholesterol, alongside reduced high-density lipoprotein (HDL) cholesterol [25].

PASC patients undergoing anesthesia should be asked about new-onset or worsening hypertension, and should be given specific instructions for managing their antihypertensive medications perioperatively. PASC is associated with a persistent endothelial dysfunction and vasculopathy affecting pulmonary, cardiac and peripheral vasculature. Signs and symptoms of increased vascular reactivity such as Raynaud's and vasospastic chest pain should prompt the anesthesiologist to anticipate variations in vascular tone perioperatively such as pulse pressure variation, sudden blood pressure fluctuations and, if monitored, central venous pressure (CVP) and pulmonary artery pressure changes.

For patients with suspected PASC-CVD, the American College of Cardiology (ACC) Decision Pathway on Cardiovascular Sequelae of COVID-19 advises "triad testing" with cardiac troponin levels, electrocardiogram (ECG), and transthoracic echocardiogram (TTE). Ambulatory rhythm monitoring, chest imaging (X-ray or CT), and pulmonary function tests can also be considered, depending on the patient's presentation. The ACC further advises cardiology consultation for PASC patients with abnormal cardiac findings, worsening symptoms in the context of known cardiovascular disease, documented cardiac complications during acute SARS-CoV-2 infection, or persistent, unexplained cardiopulmonary symptoms[26]. Although there are no specific preoperative cardiovascular guidelines for PASC, anesthesiologists can adapt PASC-CVD recommendations and standard cardiac risk stratification guidelines as a reference. Despite accumulating literature supporting increased risk for cardiovascular events in the months and years following SARS-CoV-2 infection, none of the currently available perioperative risk scoring tools accounts for this risk. Therefore, for PASC patients without clear cardiac risk factors but who report persistent, unexplained cardiopulmonary symptoms, the threshold for referral to a cardiology specialist should be low.

Pulmonary

Respiratory complications from PASC, particularly dyspnea, are highly challenging for anesthesiologists in the perioperative setting. Dyspnea can stem from both pulmonary and extrapulmonary causes, with the latter often due to muscle weakness from deconditioning, post-exertional malaise (PEM), and malnutrition, all commonly seen in PASC. On the pulmonary side, PASC can lead to exacerbations of obstructive lung diseases, diffuse alveolar damage causing interstitial lung disease (ILD) and pulmonary fibrosis, and thromboembolic conditions from ongoing vascular inflammation [27]. The UK Interstitial Lung Disease Consortium (UKLID) reported that up to 11% of individuals still showed lung abnormalities like ground-glass opacities, reticulations, and traction bronchiectasis on high-resolution CT scans 140 days post-hospitalization for COVID-19 [28]. These findings, alongside physiological impairments, are indicative of post-COVID ILD [29]. While treatment for ILD largely involves supportive care like pulmonary rehab and oxygen therapy, drugs such as mTOR inhibitors and antifibrotics (pirfenidone, nintedanib) are under

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investigation for PASC. Preoperative risk assessment should focus on predicting postoperative pulmonary issues like hypoxia, hypercarbia, ILD exacerbation, pneumonia, or pneumothorax within 30 days [30]. The ARISCAT score is recommended to gauge postoperative pulmonary risk, particularly for thoracic or abdominal surgeries [31,32]. Tools like pulmonary function tests, cardiopulmonary exercise testing, echocardiograms, ECGs, and chest imaging (X-ray/CT) help in crafting an anesthetic strategy. Depending on the surgery, monitored anesthesia care (MAC) or regional anesthesia might be preferred over general anesthesia to minimize airway manipulation complications. Given the association between obstructive sleep apnea and ILD, and its emergence in PASC, the STOP-BANG questionnaire may be useful in assessing sleep apnea risk [33].

For those with post-COVID ILD, employing strategies like pressure control ventilation (PCV), low tidal volumes (<8 ml/kg), minimal PEEP, and inspiratory pressure <30 mmHg are advised for lung protection. Careful management to prevent pulmonary hypertension triggers like hypoxia, hypercapnia, and pain is crucial. In recovery, non-invasive ventilation options like CPAP or BiPAP might aid in restoring pulmonary function.

New or worsened obstructive lung diseases, including asthma and bronchiectasis, along with increased airway reactivity, have been noted in post-COVID patients [34,35]. Thus, preoperative bronchodilator therapy with albuterol or albuterol/ipratropium could mitigate intraoperative or postoperative bronchospasm. Additionally, using laryngo-tracheal topical anesthesia (LTA) with lidocaine before intubation can reduce postoperative coughing [36].

Endocrine

Post COVID endocrine dysfunction such as hypocortisolemia, or low cortisol levels, thyroid dysfunction and new onset diabetes mellitus have been identified in some PASC patients [37,38,39]. Any identified endocrine imbalances should be corrected or managed prior to surgery to optimize patient outcomes. This might involve starting or adjusting hormone replacement therapy, managing blood sugar levels, or treating thyroid conditions. Coordination between endocrinologists, anesthesiologists, and surgeons is key to tailor the perioperative plan to the patient's specific needs, especially in those with PASC where symptoms might not fit traditional disease patterns. This approach underscores the importance of personalized medicine in the context of PASC, where traditional guidelines might not suffice due to the unique and sometimes unpredictable nature of PASC symptoms and complications.

Hypocortisolemia can manifest as fatigue, low blood pressure, or difficulty in handling stress. Preoperative screening for cortisol levels could be beneficial to avoid adrenal crisis during surgery, which can be precipitated by the stress of surgery itself. Avoiding etomidate should be considered, since this anesthetic agent can suppress adrenal cortisol synthesis, which might be particularly problematic in PASC patients with pre-existing low cortisol levels. Alternatives to etomidate should be considered to prevent exacerbating adrenal insufficiency.

There is evidence suggesting that thyroid function can be altered following a COVID-19 infection, leading to thyrotoxicosis or hypothyroidism. Symptoms like fatigue, weight changes, or changes in heart rate can be misleading or exacerbated under anesthesia or postoperative stress. Screening for TSH, free T4, and potentially T3 could help in managing or preempting thyroid-related complications. For patients with diabetes, both new onset or pre-existing, it is vital to monitor blood glucose levels closely before, during, and after surgery. This might involve adjusting insulin or other antidiabetic medications, ensuring appropriate hydration, and possibly using continuous glucose monitoring systems.

Conclusion

The management of anesthesia for patients with PASC demands a customized approach given the diverse and intricate symptom profile. A thorough preoperative evaluation should concentrate on assessing cardiovascular, respiratory, neurological, and endocrine/metabolic changes associated with PASC. Intraoperatively, the selection of anesthetics must consider individual patient conditions, alongside tailored strategies for fluid and pain management. Postoperative care involves intensive monitoring in the post-anesthesia care unit (PACU) for any signs of symptom exacerbation, implementation of multimodal pain management, and meticulous discharge planning in collaboration with the surgical team and the patient's PASC specialists.

As research into the etiology and clinical trial data for PASC continues to develop, there is an ongoing need to establish actionable clinical guidelines for anesthesiologists. Such guidelines would equip anesthesiologists to address the unique challenges of PASC with evidence-based strategies, thereby improving patient safety and surgical outcomes.

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Data and materials availability: All requests for materials and data should be addressed to the corresponding author.

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