High-Dose **Intravenous**Epoprostenol and Adjunct Therapies for Refractory Raynaud's Phenomenon Associated with Anti-Jo-1 Antibodies: A Case Report

Abstract

This case report highlights the use of intravenous high-dose Epoprostenol for managing severe digital ischemia in a patient diagnosed with antisynthetase syndrome (ASyS) exhibiting anti-Jo1 antibodies positivity, emphasizing its vasodilatory benefits and challenges with tolerability at higher doses. A multi-modal treatment strategy, including calcium channel blockers, phosphodiesterase inhibitors, hyperbaric oxygen therapy, and prostacyclin analogs, was critical for optimizing outcomes in refractory Raynaud's phenomenon.This case underscores the importance of individualized treatment regimens and the need for ongoing monitoring and adjustments to balance therapeutic efficacy with patient safety. The report contributes to the limited literature on the management of severe digital ischemia in ASyS and emphasizes the potential role of adjunct therapies in improving patient outcomes.

Keywords:*antisynthetase syndrome, digital ischemia, adjunct therapies, hypotension*

Introduction:

Digital ischemia and necrosis are severe manifestations of vascular **impairment** often seen in autoimmune conditions. Antisynthetase syndrome (ASyS) is a rare autoimmune disorder characterized by the presence of anti-synthetase antibodies, such as anti-Jo-1**(anti-histidyl-tRNA synthetase)**, **classically associated with a constellation of clinical manifestations including**myositis, interstitial lung disease (ILD), arthritis, Raynaud's phenomenon, and "mechanic's hands." [1]While the full spectrum of ASyS includes these features, patients can present with isolated symptoms, complicating diagnosis and management.

Current recommendations for the management of chronic inflammatory process in patients affected by myositis emphasizes the use of systemic corticosteroids as initial therapy, while immunosuppressant therapy should be employed as adjuncts.[23]**However, therapeutic strategies addressing vascular involvement in ASyS are still lacking, particularly in refractory forms of Raynaud's phenomenon. In such instances, intravenous prostacyclin analogs, including epoprostenol, should be considered**. [3] Known for its potent vasodilatory **properties** - epoprostenol improves blood flow and **alleviates** ischemic symptoms in various conditions. [3] Despite its potential benefits, **intravenou**s high-dose epoprostenol therapy is associated

with significant side effects, including hypotension and systemic reactions, which can limit its utility in certain patients.

This case report details the clinical course of a71-year-old male with severe digital ischemia and necrosis, **anti-Jo-1** antibodies, and a working diagnosis of ASyS without the typical features of myositis or ILD. **The patient's treatment trajectory, with a specific focus on the utilization of intravenous high-dose epoprostenol and subsequent therapeutic modifications, is discussed in detail, highlighting the challenges and considerations in managing this complex presentation.**

Case Presentation:

A 71-year-old male, living independently was referred to the intensive care unit (ICU) for systemic vasodilators due to digital ischemia. His medical history includes pre-diabetes, dyslipidemia, hypertension, and colonic polyps.

Three months prior to admission, the patient presented to the emergency department with left foot pain, swelling, and erythema, initially treated for cellulitis or gout with Cephalexin and nonsteroidal anti-inflammatory drugs (NSAIDs). **However**, four weeks later, he returned, presenting with bilateral inflammatory polyarthritis and new purple discoloration of his fingertips. **Concurrently, he reported unintentional weight loss of approximately 40 pounds and worsening fatigue, although he denied experiencing fevers or night sweats.**

The patient was subsequently admitted to the medical ward and commenced on prednisone therapy, initially at a dose of 30 mg daily, which was subsequently increased to 70 mg daily for a 48-hour period before being tapered to 50 mg daily. He was then discharged with a referral to the internal medicine clinic for outpatient follow-up.**Despite this initial treatment, the patient experienced progressive acrocyanosis and necrosis of his left fifth digit,leading to the initiation of methotrexate therapy by the rheumatology service. Due to further clinical deterioration, he was subsequently referred for systemic vasodilation therapy and thus admitted to the ICU.**

Investigations:

The patient's investigations revealed the following significant findings: elevated

immunoglobulin A (IgA) of 4.3 g/L, positive anti-Jo-1 antibodies, and an **erythrocyte sedimentation rate** (ESR) greater than 120 mm/hr, with **C-reactive protein** (CRP) levels of 99 mg/L upon presentation. Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, proteinase 3 (PR3) antibodies, myeloperoxidase (MPO) antibodies, anti-Ro/SSA antibodies, anti-EJ antibodies (anti-glycyl-tRNA synthetase), anti-Ku antibodies, anti-OJ antibodies (anti-isoleucyl-tRNA synthetase), anti-Mi-2 alpha antibodies, anti-Mi-2 beta antibodies, anti-NXP-2 antibodies (anti-nuclear matrix protein 2), anti-PL-7 antibodies (anti-threonyl-tRNA synthetase), anti-PL-12 antibodies (anti-alanyl-tRNA synthetase), anti-signal recognition particle (SRP) antibodies, anti-melanoma differentiation-associated gene 5 (MDA5) antibodies, and anti-double-stranded DNA (anti-dsDNA) antibodies were all negative. Cold agglutinins were positive with a titre of 1 and a thermal amplitude of 22°C. Cryoglobulins and the direct antiglobulin test (DAT) were negative.

Further investigations, **including urine protein electrophoresis (UPEP), serum protein electrophoresis (SPEP),** free light chains, hepatitis B and C serologies, and neoplastic workup, **yielded negative results**. Computed tomography angiography (CTA) of the chest and abdomen revealed no evidence of medium vessel vasculitis, and bilateral hand radiographs demonstrated no erosive changes.

Treatment:

Upon admission to the ICU, **a comprehensive management plan was formulated to address the patient's severe digital ischemia and evolving antisynthetase syndrome**. The initial treatment regimen consisted of systemic corticosteroids, with prednisone administered at a dose of 50 mg daily. This dosage had been previously adjusted, including a temporary increase to 70 mg daily for 48 hours, before returning to 50 mg daily to achieve anti-inflammatory and immunosuppressive effects. Concurrent with prednisone, methotrexate was initiated at 20 mg weekly, supplemented with folic acid 5 mg. Regular monitoring of renal function and hepatic enzymes was implemented to assess treatment tolerance and facilitate early detection of adverse effects.

To address the worsening digital ischemia, the treatment strategy was augmented to include both topical and systemic therapies. Topical nitrate patches were applied to the affected digits (digits 2, 3, and 4 of the left hand, and digits 3, 4,

and 5 of the right hand) to promote localized vasodilation. Systemically, epoprostenol, a prostacyclin analog, was commenced at a dose of 2.5 ng/kg/min for refractory Raynaud's phenomenon. The dosage was carefully titrated based on the patient's clinical response and tolerance. Initially, the patient received 2 ng/kg/min for the first 24 hours. **Due to insufficient clinical improvement, the dose was escalated to 5 ng/kg/min on the second day and further increased to 7.5 ng/kg/min on the eighth day.** Following consultation with the rheumatology service, the epoprostenol dose was increased to 10 ng/kg/min on the ninth day; however, the patient experienced significant adverse effects, including flushing and a presyncopal episode. Consequently, the dose was subsequently reduced to 7.5 ng/kg/min and then further decreased to 2.5 ng/kg/min over the subsequent 24 hours. Given the patient's adverse reactions at higher doses and the lack of substantial clinical benefit, he was transferred to a tertiary care center on the twelfth day of ICU admission for hyperbaric oxygen therapy, with the objective of enhancing oxygen delivery to the ischemic tissues and promoting tissue healing.

The patient tolerated the hyperbaric oxygen therapy **without incident** and continued to receive lower doses of the epoprostenol infusion. However, an increase in pain and digital discoloration was observed following discontinuation of the epoprostenol infusion, prompting the clinical team to consider long-term prostacyclin analog therapy. Sildenafil, a phosphodiesterase type 5 inhibitor, was administered at the **maximum recommended dose** of 50 mg three times daily. The calcium channel blocker nifedipine XL was initiated at 90 mg daily, with the option to titrate up to 120 mg daily based on blood pressure tolerance. Fluoxetine was prescribed at 20 mg daily to promote vasodilation through enhanced nitric oxide bioavailability and improved endothelial function via serotonin receptors. Aspirin, at a dose of 160 mg daily, was included due to the vaso-occlusive nature of the patient's Raynaud's phenomenon. Additionally, atorvastatin at 40 mg daily was added for its pleiotropic effects on endothelial function.

To provide ongoing vasodilatory benefits while minimizing the side effects associated with epoprostenol, monthly infusions of iloprost were planned for outpatient management. Throughout the patient's hospitalization, regular monitoring of blood pressure, renal function, and hepatic enzymes was performed to facilitate medication dosage adjustments as clinically indicated. Consultations with the rheumatology and vascular surgery services were conducted to ensure comprehensive multidisciplinary care.

Discussion:

Managing digital ischemia and necrosis in antisynthetase syndrome is complex, as demonstrated by this patient's case. In refractory Raynaud's phenomenon, prostacyclin analogues play a crucial role by promoting vasodilation, providing anti-platelet effects, and protecting endothelial cells. These agents are particularly useful in cases with underlying vascular damage, as they can help compensate for the loss of endogenous prostacyclins caused by the disease. Epoprostenol, a potent vasodilator, has shown effectiveness in improving peripheral blood flow and alleviating severe digital ischemia symptoms. However, the patient's inability to tolerate higher doses of epoprostenol highlights a significant challenge: while the medication can be beneficial, its side effects and potential adverse reactions at higher doses require careful monitoring and personalized dosing adjustments.

Epoprostenol's effectiveness in enhancing digital blood flow is well-established, but its use can present significant challenges. Early protocols from the 1980s, which involved administering 10 ng/kg/min for 72 hours, were applied to patients without ischemic ulcers. In Dowd *et al*.'s study, patients tolerated doses of 5-7 ng/kg/min, with only two patients tolerating 10 ng/kg/min. Similarly, Rustin *et al*. reported an average tolerated dose of 7 ng/kg/min over 72 hours, starting from 2.5 ng/kg/min and gradually increasing by 1 ng/kg/min up to 10 ng/kg/min. **It is pertinent to acknowledge that many of the investigations examining dose-related adverse effects of epoprostenol were conducted during the 1980s and 1990s, coinciding with the initial phases of research focused on establishing the optimal therapeutic dose. While subsequent research has explored the use of epoprostenol in related conditions, a comprehensive contemporary assessment of dosing strategies and associated adverse effects in the specific context of digital ischemia and Raynaud's phenomenon remains limited.For instance, the 2017 study by Law *et al*., one of the larger investigations examining intravenous epoprostenol infusion for scleroderma spectrum digital vasculopathy, employed a protocol that typically titrated the dose to 8 ng/kg/min, maintaining this dose unless clinical circumstances necessitated further titration. Notably, in this study, only six of 47 patients experienced flushing, and only four experienced**

hypotension; however, the precise epoprostenol dose at which these adverse events occurred was not explicitly reported. Consequently, a relative paucity of contemporary literature persists regarding optimal dosing strategies and the characterization of associated adverse effects in current clinical practice, particularly concerning the management of digital ischemia and Raynaud's phenomenon.

I**n this case, it became evident that higher doses of epoprostenol, required to manage the worsening ischemia, resulted in significant adverse effects, including increased pain and pre-syncopal symptoms.**Other studies have shown that protocols using higher doses (≥7.5 ng/kg/min) administered as intermittent infusions weekly for 4 to 5 hours over three weeks in patients with digital ulcers appear to improve tolerability. [1][11]**This observation underscores**the importance of a tailored approach to dosage and underscores the need for continuous assessment to balance therapeutic benefits with patient safety.

The addition of a calcium channel blocker, such as nifedipine, and a phosphodiesterase type 5 inhibitor, such as sildenafil, provided a multi-faceted approach to managing the patient's condition. Calcium channel blockers help reduce vascular resistance and improve blood flow, while sildenafil enhances vasodilation through its effects on nitric oxide pathways.[12] This combination, along with the addition of fluoxetine, acetylsalicylic acid, and atorvastatin aim to optimize vascular health and address underlying pathophysiological processes contributing to the patient's digital ischemia.[13]

Hyperbaric oxygen therapy was incorporated into the patient's treatment regimen to promote wound healing and enhance oxygen delivery to ischemic tissues, which is particularly beneficial in cases of severe ischemia. While the therapy was well tolerated, it did not achieve complete resolution of the ischemic issues, necessitating the continued use of oral medications and prostaglandin therapy on an outpatient basis. The selection of parenteral prostacyclin analogs for severe Raynaud's phenomenon is largely determined by their availability, given the paucity of comparative studies. Intravenous iloprost, administered intermittently over 6 to 8 hours for 3 to 5 days monthly, remains a valuable therapeutic option for outpatient management.

This case report has inherent limitations. Primarily, the retrospective design of this

case report may have influenced the thoroughness of identification, reporting, and documentation within the patient's medical chart. Furthermore, this report is based on a single patient's experience, which may limit its generalizability to the broader population of patients with antisynthetase syndrome and severe digital ischemia. The responses to treatments such as epoprostenol and hyperbaric oxygen therapy can exhibit significant inter-individual variability, further limiting the generalizability of these findings. Additionally, the absence of control or comparison groups precludes quantification of the effectiveness of specific treatments relative to alternative therapies or placebo. Future research incorporating larger cohorts and controlled study designs is warranted to better elucidate the efficacy and safety profiles of these treatments in diverse patient populations.

Overall, this case underscores the need for a nuanced and individualized treatment strategy, particularly when dealing with severe digital ischemia associated with Raynaud's syndrome. It also highlights the importance of ongoing evaluation and adjustment of therapies to achieve the best possible outcomes while minimizing adverse effects.

Conclusion:

This case report illustrates the complexities inherent in managing digital ischemia in refractory Raynaud's phenomenon, particularly in the context of intravenous high-dose epoprostenol therapy. While epoprostenol conferred some benefit in improving digital blood flow, the patient's intolerance to higher doses underscores the necessity for meticulous dose titration and the consideration of alternative or adjunctive therapies. The patient's multifaceted treatment approach, incorporating calcium channel blockers, sildenafil, and hyperbaric oxygen therapy, emphasizes the importance of a comprehensive and individualized management strategy.

This case underscores the importance of ongoing clinical evaluation and individualized treatment adjustments in managing severe digital ischemia, as treatment responses can vary significantly. It provides valuable insights into the complexities of this condition and highlights the need for continued research to optimize therapeutic strategies for similar presentations.

Consent:

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Disclaimer (Artificial intelligence)

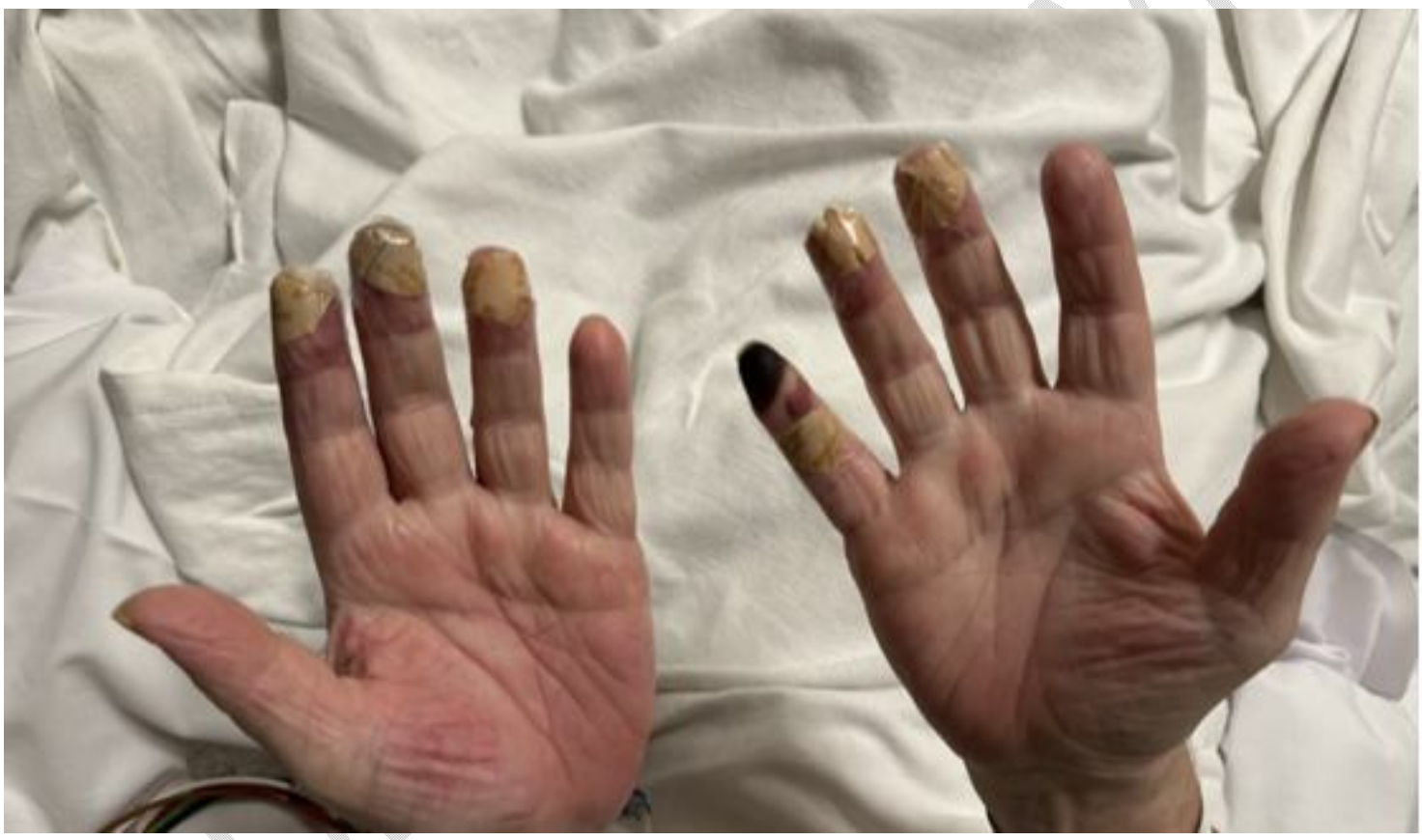
Option 2:

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. During the preparation of this manuscript, ChatGPT (version 3.5), a large language model, was utilized exclusively for proofreading and editing to improve grammar, spelling, and syntax. The authors affirm that this tool was not used to generate original content, develop ideas, create figures or images, or for any other generative AI function. All intellectual contributions and original research presented herein are solely attributable to the authors.

Table 1: Epoprostenol Dose and Clinical Effect

Admission	Epoprosterenol dose	Clinical effect/Patient Experience
Day 1	2 ng/kg/min	Initial dose, no significant adverse effects observed.
Day 2	5 ng/kg/min	Increased dose due to insufficient clinical improvement; slight symptom relief.
Day 5	5 ng/kg/min	Continued on same dose and continues to experience symptom relief.
Day 8	7.5 ng/kg/min	Further dose escalation, mild improvement noted.
Day 9	10 ng/kg/min	Increased dose; patient experienced significant side effects including flushing and presyncopal episode.
Day 10	7.5 ng/kg/min	Dose reduced due to adverse reactions; slight improvement in flushing
Day 11	5 ng/kg/min	Continued dose reduction, patient stabilization.
Day 12	2.5 ng/kg/min	Transferred to a tertiary care center for hyperbaric oxygen therapy due to lack of substantial improvement.

Figure 1. Day 3 of therapy: Epoprostenol @ 5 ng/kg/min. Topical nitroglycerin patches in situ.



***All images were obtained with the patient's informed consent, ensuring their privacy and confidentiality were maintained in accordance with ethical standards.*

Figure 2. Day 5 of therapy: Epoprostenol @ 5 ng/kg/min

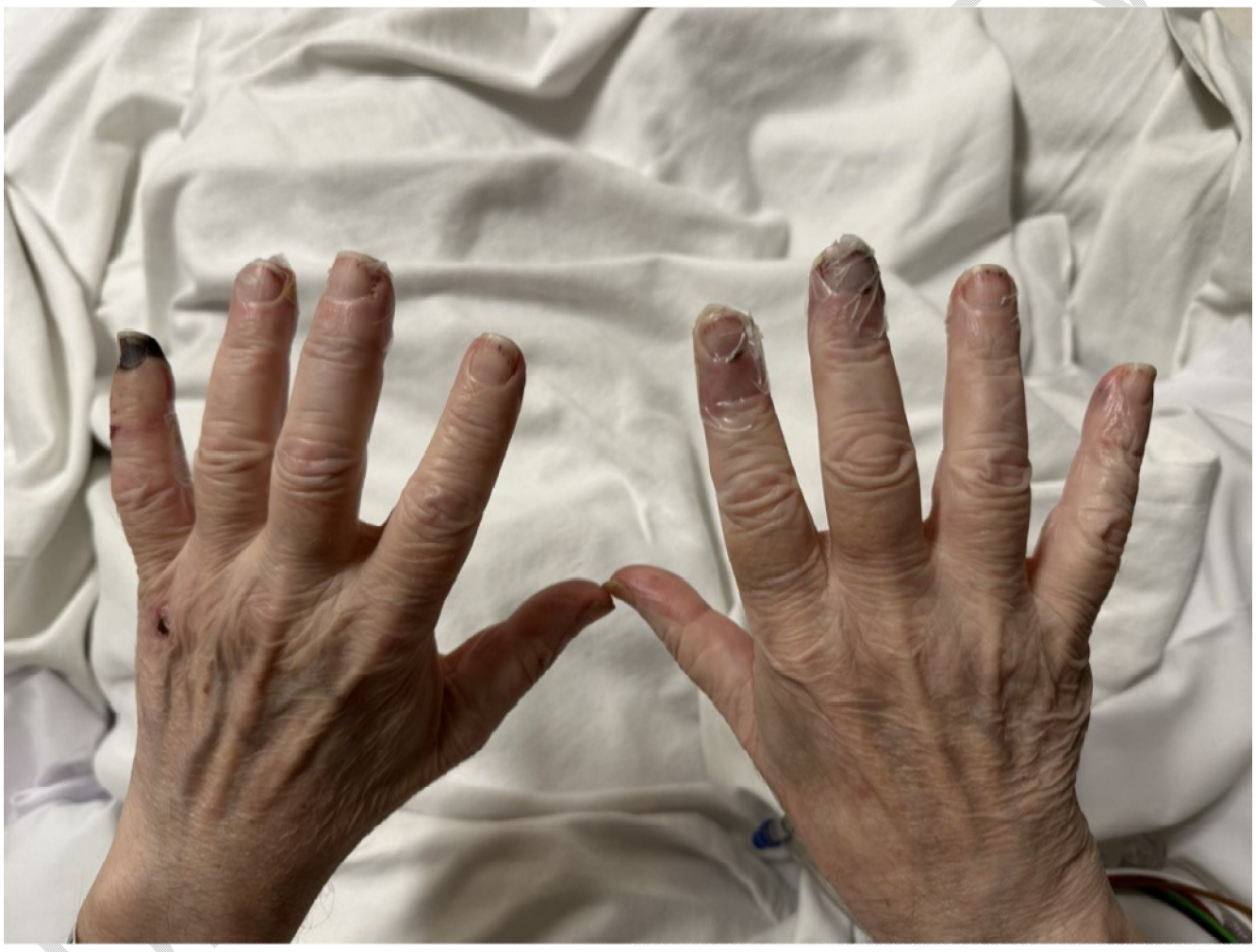


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Figure 3A:Day 11 of therapy. Epoprostenol at 5 ng/kg/min (Front Side)

***All images were obtained with the patient's informed consent, ensuring their privacy and confidentiality were maintained in accordance with ethical standards.*

Figure 3B:Day 11 of therapy. Epoprostenol at 5 ng/kg/min (Back Side)

***All images were obtained with the patient's informed consent, ensuring their privacy and confidentiality were maintained in accordance with ethical standards.*

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