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Optimizing outcomes in heart transplantation: multidisciplinary Heart Teams and mechanical circulatory support for primary graft dysfunction

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Heart Team

Heart transplantation (HTx) is a definitive treatment for selected patients with advanced heart failure. However, primary graft dysfunction (PGD), a severe early complication, is a major cause of post-HTx morbidity and mortality. This paper explores the pathophysiology, diagnostic approaches, and management strategies for PGD, with a particular focus on temporary mechanical circulatory support (MCS) devices such as venoarterial extracorporeal membrane oxygenation and Impella. It also highlights the essential role of the multidisciplinary Heart Team in optimizing outcomes through patient-tailored MCS selection and timely intervention.

Introduction

Heart transplant (HTx) is a life-saving intervention for patients with advanced heart failure (HF) who have exhausted medical and device-based therapies. Despite significant advancements in surgical techniques and perioperative care, complications such as primary graft dysfunction (PGD) continue to present substantial challenges. Characterized by early allograft failure within hours to days post-HTx, PGD is a leading cause of morbidity and mortality in this population. Its multifactorial pathophysiology, encompassing donor and recipient risk factors, ischaemia–reperfusion injury (IRI), and immune-mediated processes, underscores the complexity of its management. The emergence of temporary mechanical circulatory support (MCS) devices, including veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and the Impella device, has revolutionized the management of PGD,

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providing critical haemodynamic support. However, the choice of MCS device and timing of intervention require a deep understanding of individual patient needs, often guided by a multidisciplinary Heart Team. This manuscript explores the pathophysiology, diagnosis, and management of PGD, with a focus on the evolving role of MCS in clinical practice. It also highlights the importance of early intervention, tailored therapeutic approaches, and the Heart Team's integral role in improving survival and quality of life for patients pre- or post-HTx.

The role of the Heart Team in managing post-transplant deterioration and pre-shock states

The Heart Team, comprising cardiologists, cardiac surgeons, interventionalists, nurses, psychologists, dieticians, and other specialists, plays a critical role in evaluating a patient's eligibility for HTx and in managing pre- and post-HTx care. Typically convening weekly, the Heart Team conducts detailed reviews of each patient's hospital course and clinical status, with focus on identifying and addressing emerging complications. When a patient's condition deteriorates, the team thoroughly evaluates the underlying cause, its implications, and potential interventions, including temporary MCS. Before making critical decisions, such as MCS implantation, the multidisciplinary board engages in comprehensive deliberations to address challenges ranging from optimal cannulation strategies to immunosuppressive regimen adjustments and escalation or de-escalation of support.[1] The team also anticipates and plans for potential outcomes, including unsuccessful MCS weaning attempts.[2,3] This interdisciplinary approach ensures a holistic assessment of each patient, enabling well-informed decision-making and individualized treatment plans tailored to the complexities of this high-risk population.

Pathophysiology following heart transplantation

Impaired myocardial function after HTx can result from PGD or secondary organ failure due to underlying causes such as acute rejection or pulmonary hypertension in the recipient. Primary graft dysfunction is the leading cause of early mortality post-HTx and typically manifests within 24 h of HTx surgery. According to the International Society for Heart and Lung Transplantation (ISHLT) registry, up to 14% of recipients die within 30 days of HTx due to severe PGD.[4] International Society for Heart and Lung Transplantation defines PGD as allograft dysfunction occurring within the first 24 h after transplantation, in the absence of an identifiable cause like acute rejection.[5] Moreover, PGD is further classified into left ventricular (PGD-LV), right ventricular (PGD-RV), or biventricular dysfunction, based on the affected cardiac regions.

The severity of PGD is determined using echocardiographic and haemodynamic parameters. Mild-to-moderate PGD is characterized by a LV ejection fraction (LVEF) $\leq$40%, pulmonary capillary wedge pressure (PCWP) >20 mmHg, cardiac index (CI) >2.0 L/min/m^2, and a variable need for inotropic support. Severe PGD necessitates either left-sided or biventricular temporary MCS. Right-sided PGD is defined by right atrial pressure >15 mmHg, PCWP < 15 mmHg, a transpulmonary gradient <15 mmHg, or the need for right-sided MCS.[5]

The underlying pathophysiology of PGD is multifactorial, involving both donor- and recipient-related factors. Donor-specific risks include the effects of brain death, which can lead to calcium overload in myocardial cells, necrosis, and contractility impairment.[6,7,8] It may also lead to the activation of pro-inflammatory pathways, like complement activation, which further exacerbate myocardial failure.[9] Additional donor factors, such as prolonged ischaemic times, inadequate preservation temperatures, older donor hearts, or those with pre-existing conditions such as LV hypertrophy or coronary artery disease, increase the susceptibility of the graft to damage.[10,11] Recipient-derived risk factors for PGD include congenital heart disease, a history of multiple cardiac surgeries, retransplantation, and the use of pre-operative mechanical support.[12] Perioperative risks, such as high transfusion requirements, prolonged cold ischaemic durations, and donor–recipient sex mismatch, also amplify the risk of PGD.[13,14]

Ischaemia–reperfusion injury following HTx is another factor that contributes to allograft impairment. During cold ischaemia, cellular hypoxia creates an anaerobic milieu, resulting in intracellular acidosis and calcium overload.[15] Upon reperfusion, the generation of reactive oxygen species and the release of damage-associated molecular patterns trigger endothelial dysfunction, complement activation, and cytokine release. High intracellular Ca^{2+} levels lead to the opening of mitochondrial permeability transition pores and cytochrome C release, initiating apoptosis.[16] Collectively, these processes drive allograft dysfunction, inflammation, coagulation pathway activation, and cardiomyocyte death.[17]

Ischaemia–reperfusion injury-induced endothelial dysfunction also predisposes allografts to rejection, which can occur by either cellular or humoral (antibody-mediated) mechanisms. In cellular rejection, donor antigen-presenting cells (APCs) activate recipient CD8+ T cells, resulting in cytotoxic T-cell-mediated allograft destruction. Histological patterns typically include perivascular lymphocyte infiltration and myocyte damage.[18,19] Humoral rejection results upon activation of B cells by recipient-derived APCs, which leads to the production of donor-specific antibodies that bind allograft antigens and trigger complement activation and cell death.[20,21]

Pre-operative identification and management of human leucocyte antigen (HLA) antibodies in HTx recipients are crucial to reduce the risk of antibody-mediated rejection. Strategies for antibody elimination include perioperative plasma exchange, immunoglobulin treatment, and B-cell depletion.[22] Recently, a protocol that incorporates intraoperative tocilizumab, an IL-6 receptor antagonist, has demonstrated comparable survival outcomes for recipients with pre-operative HLA antibodies to those without, marking a significant advancement in rejection prevention.[23]

Disease-orientated diagnostics and immediate monitoring

Provided there are no absolute contraindications, HTx is the definitive treatment for patients with advanced HF refractory to medical or device-based therapies.[24] One-year survival post-HTx ranges between 80 and 90%, influenced by factors such as geographical region, accepted donor age, and the age and condition of recipients. The first months after transplantation represent the most critical phase, particularly for patients transplanted from the urgent list in INTERMACS Class I–III with signs of multiorgan dysfunction.[23] The most common complications during this period are PGD-RV dysfunction with pulmonary hypertension, bleeding, multiple organ failure, infections, arrhythmias, and acute rejection over time.[24]

To address these challenges, the ISHLT guidelines emphasize comprehensive monitoring after HTx, including continuous and post-operative 12-lead electrocardiogram, invasive haemodynamic evaluation, arterial and mixed venous saturation measurements, echocardiography, and endomyocardial biopsy (EMB).[25] During and immediately following HTx, meticulous haemodynamic monitoring is required. Pulmonary artery catheter (PAC) is particularly valuable, as it provides over 20 haemodynamic parameters, both measured and derived, that aid in assessing LV and RV function, as well as pulmonary and systemic vascular resistance (SVR).[26] PAC and ultrasonographic measurements help guide decisions on the need for MCS. During and after HTx, RV dysfunction may necessitate support with central ECMO, a right ventricular assist device with ProtekDuo cannula, or Impella RP.[27] Frequent haemodynamic monitoring in the days following HTx is key for determining whether to escalate, prolong, or de-escalate MCS.

Despite the development of novel biomarkers and imaging techniques, EMB remains the gold standard for diagnosing acute cellular and antibody-mediated rejection. This procedure allows for histopathological and immunohistochemical evaluation of allograft tissue, typically obtained from the RV side of intraventricular septum. Endomyocardial biopsy is often performed routinely in asymptomatic patients during the first year post-HTx or triggered by clinical deterioration. The standard surveillance schedule includes EMBs weekly in the first month, every second week in the second month, and then once monthly until the end of the first year, though the exact practices vary by centre. However, EMB's diagnostic yield for detecting significant rejection is low, prompting a shift towards reduced EMB frequency and greater reliance on non-invasive methods.[28] Biomarkers such as cardiac troponins and B-type natriuretic peptide can be helpful but have limited utility, especially during the early post-HTx period due to baseline elevation and potential false negatives.[29] Multimodality imaging, including echocardiography, cardiac magnetic resonance, computed tomography, and nuclear imaging techniques, is increasingly used, particularly for diagnosing graft vasculopathy in the longer-term post-HTx period.

Immunosuppressive therapy, while essential for preventing rejection, significantly increases the risk of infectious complications. Perioperative antibacterial prophylaxis should target Staphylococci, gram-negative pathogens, and *Candida* spp. Cytomegalovirus (CMV) prophylaxis is recommended for CMV-negative recipients receiving a CMV-positive donor heart. In other cases, pre-emptive antiviral therapy guided by regular CMV diagnostics, such as polymerase chain reaction or pp65 anti-genemia assays, may be an alternative. While Epstein–Barr virus (EBV) prophylaxis is not as well established, pre-emptive monitoring of EBV viral load is advisable to mitigate the risk of post-transplant lymphoproliferative disorders.[25]

Mechanical circulatory support for primary graft dysfunction after heart transplantation

Primary graft dysfunction is a critical complication following HTx, manifesting as severe ventricular impairment within 24 h post-surgery. It is often hard to distinguish from secondary causes and carries an incidence ranging from 2.3 to 28.2%, significantly contributing to early mortality.[30] Data from the ISHLT indicate PGD-related mortality rates of 10% at 1 month and 14% at 3 months post-transplant.[4,5] The underlying mechanisms of PGD include IRI, inflammatory mediator release, and myocardial stress from both donor- and recipient-related factors.[31] Clinically, PGD is characterized by reduced cardiac output (CO) and hypotension, often necessitating immediate MCS.[31]

Venoarterial extracorporeal membrane oxygenation is a common MCS modality for severe PGD, but it is associated with considerable complications, including an increased risk of bleeding and renal dysfunction. Alternatively, the Impella, which is a percutaneous microaxial flow LV assist device, offers direct LV unloading, reduces myocardial workload, and provides full-flow arterial support. Impella has several advantages compared with VA-ECMO.[30] As such, it uses a single arterial cannulation site, avoids extracorporeal flow,[4] enables genuine LV unloading,[5] and allows for extended support durations. VA-ECMO requires both arterial and venous cannulas, often inserted peripherally through the femoral vessels, introducing retrograde flow to the aorta that increases LV afterload. This retrograde flow creates a 'mixing zone' where oxygenated blood from VA-ECMO blends with non-oxygenated blood from the failing LV, potentially impairing coronary oxygen delivery and complicating treatment in severe PGD.

Impella use in PGD is limited in the literature but holds promise in cases of isolated LV dysfunction with adequate RV function. By reducing pulmonary vascular resistance (PVR), Impella may also improve RV haemodynamics in cases of mild-to-moderate RV dysfunction.[32] However, Impella alone is unsuitable for biventricular PGD, as it relies on sufficient pulmonary circulation.[32] In such cases, combining VA-ECMO with Impella, referred to as ECMELLA, can provide comprehensive support, though patients experience a high rate of bleeding complications and multiple reoperations.[33]

Moreover, HTx recipients pre-operatively supported with the Impella 5.5 and post-transplantation for an average of 3.8 days resulted in no incidences of RV failure (RVF), complications, or mortality. As such, these results highlight the potential for Impella to serve as a

bridge-to-transplant and post-operative support device in carefully selected cases.[34] More specifically, although mortality rates are similar in PGD cases supported with VA-ECMO and ventricular assist devices (VADs), patients treated with VA-ECMO had lower renal failure incidence and reduced inotropic support needs in comparison.[35] Similarly, the survival rate was 48% in VA-ECMO-supported patients compared with 25% in patients receiving VADs and developed PGD within 48 h post-transplant.[36]

Specific clinical scenarios

Case 1: minimally invasive biventricular mechanical circulatory support with Impella pumps as a bridge-to-heart transplantation

In a case of a 67-year-old woman presenting with chest pain and diagnosed with total atrioventricular (AV) block, the initial evaluation showed a moderately reduced LVEF of 45% on transthoracic echocardiogram (TTE) with no evidence of obstructive coronary disease on angiogram.[37] After a dual-chamber pacemaker installation, she was discharged from the hospital. Three weeks later, she returned with recurrent HF symptoms. Repeat TTE revealed a significant decline in LVEF to 15%, with segmental wall motion abnormalities, and her ventricular tachycardia required amiodarone and lidocaine injections. Suspected diagnoses included sarcoidosis and giant cell myocarditis. Cardiac magnetic resonance imaging 26 days after pacemaker placement showed substantial septal myocardial weakening, modest mid and basal inferior myocardium thinning, and delayed myocardial enhancement. Empirical treatment with 1000 mg of methylprednisolone for a period of 3 days was initiated, but persistent cardiogenic shock (CS) and recurrent ventricular tachycardia necessitated an intra-arterial balloon pump (IABP) before transferring her to a specialized centre to evaluate advanced HF therapies. Endomyocardial biopsy was initially considered to determine the diagnosis but was postponed due to the patient's clinical instability. Another repeat TTE showed a low LVEF of 24%, RV systolic tissue Doppler velocity (*S'*) of 11.1 cm/s, and tricuspid annular plane systolic excursion (TAPSE) of 2.0 cm. Due to persistent low CI (1.5 L/min/m^2) and worsening RV function, MCS was escalated with an Impella 5.0 device. Initially planned for axillary insertion, the device was instead implanted via the femoral artery due to inadequate vascular access.

Post-operatively, the patient experienced elevated lactate levels and decreased mean arterial pressures, TTE showed a dilated RV with septal shift towards the LV, and invasive haemodynamics showed a reduced PAP index of 0.9. Together, these findings indicated acute RVF. To minimize donor heart availability waiting time due to the patient's small body size, a percutaneous Impella RP device was subsequently implanted via the right femoral vein. The Impella devices restored the CI to 2.4 L/min/m^2, although severe vasoplegia required treatment with intravenous methylene blue. After 5 days of biventricular MCS support, the patient was extubated but was unable to be mobilized due to the femoral biventricular Impella. Twenty days later, she successfully underwent orthotopic heart transplantation (OHT) with surgical decannulation of both Impella devices. The Impella devices did not cause any complications, and the patient did not require any blood transfusions prior to transplantation. Following inpatient rehabilitation, she was discharged 3 weeks post-transplantation with good functional recovery.

In summary, this case demonstrates that in patients with Impella 5.0 support who experience acute RVF, it may be a reasonable to escalate with Impella RP. Moreover, this case highlights the utility of biventricular Impella support as a bridge-to-transplant and suggests escalation to surgically implanted devices may be necessary if complications arise, or support proves inadequate.

Case 2: Impella RP flex rescues failing RV after heart transplantation

A 40-year-old male with familial dilated cardiomyopathy and a factor V Leiden mutation presenting with Society for Cardiovascular Angiography & Interventions (SCAI) stage B CS had the following haemodynamic parameters: RAP of 9 mmHg, pulmonary arterial pressure (PAP) of 53/21 mmHg, PCWP of 24 mmHg, CO of 2.5 L/min, CI of 1.5 L/min/m^2, SVR of 1.926 dynes s cm^{-5}, and PVR of 4 Wood units (WU).[38] Initial treatment for the patient included IABP support and milrinone at 0.25 µg/kg/min. After stabilization, repeat haemodynamics showed central venous pressure (CVP) was 9 mmHg, PAP was 47/19 mmHg, PCWP was 18 mmHg, CO was 4.64 L/min, CI was 2.76 L/min/m^2, SVR was 977 dynes s cm^{-5}, and PVR was 2 WU. The patient had an overall improved status, was listed as 2, and underwent OHT.

A perioperative transoesophageal echocardiogram and haemodynamic monitoring revealed no LV dysfunction, but moderate RVF necessitated the continuation of IABP support. The patient was supported with epinephrine (0.02 µg/kg/min), milrinone (0.5 µg/kg/min), and dobutamine (2.5 µg/kg/min). On post-operative day (POD) 1, TTE showed normal LV function but modestly decreased RV function after 24 h of epinephrine weaning. Moderate acute kidney injury and increased liver function were apparent, possibly from intraoperative hypotension. To reduce inhaled nitrous oxide (iNO) inhalation, IABP support was reduced to 1:2 and then withdrawn when CVP remained below 10 mmHg. However, worsening RVF became evident, with CVP rising to 22 mmHg, PAP of 37/21 mmHg, PCWP of 21 mmHg, CO of 3.14 L/min, CI of 1.84 L/min/m^2, SVR of 1535 dynes s cm^{-5}, PVR of 1.7 WU, and dobutamine was increased to 5 µg/kg/min and milrinone to 0.5 µg/kg/min. The patient required immediate pharmacological RV support, including increased dobutamine (7.5 µg/kg/min), milrinone (0.5 µg/kg/min), epinephrine (0.03 µg/kg/min), re-initiation of iNO, and enhanced diuresis. Transthoracic echocardiogram confirmed normal LV function, substantially decreased RV function with dilatation, tricuspid annular plane systolic excursion of 1.2 cm, and complete AV dissociation in the intrinsic rhythm.

Despite milrinone, dobutamine, epinephrine, iNO, and continuous renal replacement therapy (CRRT), RVF remained. Given persistent RVF and failure of medical therapy, the patient was transferred to the catheterization laboratory, where Impella RP Flex was

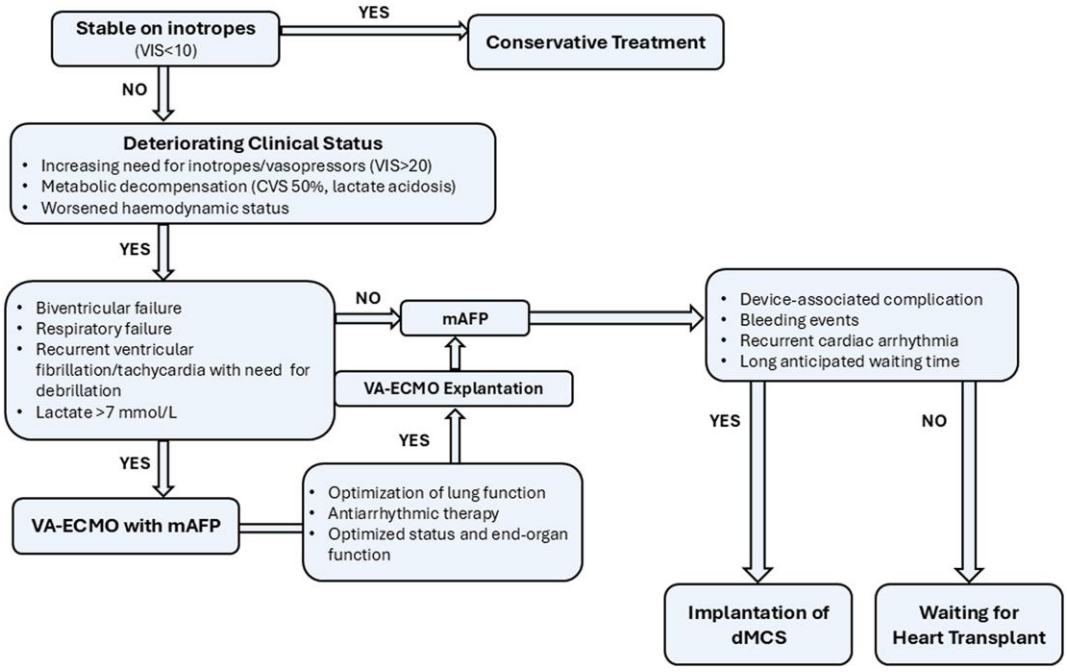

Figure 1 Algorithm for patients awaiting heart transplantation. mAFP, microaxial flow pump; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; dMCS, durable mechanical circulatory support; CVS, central venous saturation.

implanted into the right internal jugular vein on POD 12 for MCS escalation. The choice of Impella RP Flex over alternative percutaneous devices was informed by the patient's small stature, factor V Leiden with restricted venous access, ease of insertion, and the need for mobility and physical therapy. Institutional permission and staff training delayed device implementation. Systemic anticoagulation targeted and activated clotting time of 180–200 s due to the patient's hypercoagulable state.

The Impella RP flex provided effective RV unloading, and the patient remained hemodynamically stable, and able to continue physical therapy. On POD 25, after 13 days of support, the device was removed. Epinephrine and dobutamine were gradually tapered, renal function improved, and CRRT, iNO, and milrinone were discontinued. Sinus rhythm was restored, and the patient was discharged on POD 50 with adequate kidney function.

This case illustrates successful application of Impella RP Flex in managing severe post-transplant RV dysfunction. The device provided effective haemodynamic support, allowing resolution of end-organ dysfunction and enabling the patient to achieve mobility and recovery. Impella RP Flex has emerged as a promising option for single or biventricular support post-HTx, particularly in patients with limited alternatives for support due to small size or hypercoagulable conditions.

Recommendations, guidelines, and flow charts

Current, OHT remains the treatment of choice for most patients with advanced HF. However, organ shortages, particularly in European countries, results in prolonged wait times. To qualify for HTx, patients must demonstrate advanced H severity, such as inotrope dependence, recurrent cardiac decompensation, or severe complications on durable VADs. Candidates must also lack contraindications such as severe systemic infections, disabling strokes, or CS.[39] Given these stringent criteria, even a single complication can render them ineligible for transplantation. Therefore, any clinical deterioration despite guideline-directed medical therapy should prompt immediate evaluation by a multidisciplinary Heart Team to assess therapeutic options. In such scenarios, MCS can be an effective strategy to stabilize and haemodynamic improve end-organ function, and interrupt the vicious cycle of shock.[40-42] This approach increases the likelihood of successful transplantation and enhances both short- and long-term survival outcomes.[43] As such, temporary MCS is an effective bridge-to-transplant option, in which 64.2% of patients successfully underwent HTx within 14 days and 80.1% within 30 days.[43]

Despite its benefits, temporary MCS is associated with risks, including thromboembolic complications and device malfunction.[44] Moreover, while extracorporeal life support is effective in stabilizing critically ill patients, complication rates increase over time and have inferior post-HTx survival rates,[45-47] whereas the application of Impella prior to HTx shows a steady increase.[43,48] In contrast, Impella has gained favour for pre-HTx support due to the preferable complication profile, particularly during extended support durations.[49] As such, the increasing use of Impella reflects their value as a critical addition to the therapeutic armamentarium in managing advanced HF patients awaiting HTx.[40,48,50] Based on the current available literature, an algorithm for device selection

has been proposed. In cases of isolated LV dysfunction leading to clinical deterioration with hypotension and hypoperfusion, implantation of Impella should be considered. However, in cases of biventricular or respiratory failure, recurrent ventricular arrhythmias, or severe CS (SCAI stages D and E), a combination of VA-ECMO and Impella (ECMELLA) should be considered for patient stabilization (*Figure 1*). Treatment of the underlying diseases and daily evaluation of VA-ECMO weaning potential is crucial to prevent device-associated complications and improve pre- and post-transplant survival.

Conclusions

Heart transplantation offers life-saving therapy for advanced HF, yet PGD remains a critical early complication with high morbidity and mortality. Temporary MCS devices, such as Impella and VA-ECMO, play essential roles in managing severe PGD. Impella, with its targeted LV unloading and reduced complications compared with VA-ECMO, is particularly promising for isolated LV dysfunction, while ECMELLA may benefit cases of biventricular failure. Early intervention with appropriately selected MCS can significantly improve outcomes, but careful patient selection is paramount. The multidisciplinary Heart Team is vital for guiding individualized treatment plans, integrating diagnostics, and optimizing MCS strategies. Further research is required to refine treatment algorithms, expand the evidence base for Impella, and enhance long-term outcomes for HTx recipients.

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Data availability

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