Lou *et al. Vessel Plus* 2022;6:38
DOI: 10.20517/2574-1209.2021.108

Vessel Plus

Review

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Malperfusion syndromes in acute type A aortic dissection

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How to cite this article: Lou X, Chen EP. Malperfusion syndromes in acute type A aortic dissection. *Vessel Plus* 2022;6:38. https://dx.doi.org/10.20517/2574-1209.2021.108

Received: 24 Jul 2021 **First Decision:** 6 Sep 2021 **Revised:** 19 Jan 2022 **Accepted:** 14 Feb 2022 **Published:** 9 Jun 2022

Academic Editors: Davide Pacini, Yajing Wang **Copy Editor:** Xi-Jun Chen **Production Editor:** Xi-Jun Chen

Abstract

Acute aortic dissection complicated by malperfusion syndrome is a devastating condition that significantly impacts morbidity and mortality. Malperfusion syndrome can affect any vascular bed with varying degrees of end-organ involvement. While conventional management of acute type A aortic dissection (ATAAD) with or without malperfusion syndrome is emergent central aortic repair, growing evidence suggests that this approach results in unsatisfactory outcomes for those presenting specifically with mesenteric malperfusion. With the established short and long-term benefits of thoracic endovascular aortic repair in the management of acute complicated type B aortic dissection, there is an emerging paradigm shift towards initial reperfusion of distal organs with a variety of endovascular and transcatheter techniques followed by central aortic repair in an otherwise stable patient whose risk of aortic rupture is low. A multidisciplinary team and a patient-specific approach remain paramount in the successful management of this high-risk, high-complexity subset of ATAAD patients.

Keywords: Aortic dissection, mesenteric malperfusion, malperfusion syndrome, thoracic endovascular aortic repair

INTRODUCTION

In patients presenting with acute aortic dissection, malperfusion syndrome is an often-devastating condition that significantly impacts morbidity and mortality. Malperfusion can impact any vascular bed with varying degrees of end-organ involvement, necessitating a multi-disciplinary, patient-specific approach

to optimize treatment. The conventional management of acute type A aortic dissection (ATAAD) with or without malperfusion is emergent central aortic repair, which involves a hemiarch replacement with the addition of a total arch replacement for patients with pre-existing arch aneurysms, primary intimal tears identified in the distal arch or descending thoracic aorta, and/or evidence of visceral or peripheral extremity malperfusion. However, evidence has been gradually accumulating to suggest a potential benefit for initial reperfusion of distal organs using endovascular techniques followed by central aortic repair. This approach has been fueled by the success of thoracic endovascular aortic repair (TEVAR), which is now regarded as the gold standard in the treatment of complicated acute type B aortic dissection (TBAD) with malperfusion.

This focused review highlights the pathogenesis and challenges in management, provides an overview of malperfusion syndromes by organ systems, and addresses the ongoing areas of controversy and new frontiers in the treatment of acute aortic dissection with malperfusion. ATAAD complicated by mesenteric malperfusion (MMP) has historically portended the worst outcomes, and its management has undergone the most flux in recent years. Therefore, we will focus the latter part of our discussion on the evolving role of end-organ revascularization first followed by central aortic repair.

CLINICAL DEFINITIONS

When discussing end-organ malperfusion, it is first necessary to establish the clinical definition of malperfusion *vs.* malperfusion syndrome. Malperfusion itself is defined as inadequate end-organ perfusion, secondary to dissection-related obstruction of the aorta and its branch vessels. This can result from multiple mechanisms of obstruction, categorized as dynamic, static, or both[1].

The relationship between the mobile septum and the true lumen is complex. In dynamic obstruction, the repetitive motion of the intimal flap within the aortic lumen covers and protrudes into branch vessel ostia to an end-organ resulting in ischemia. This mechanism is the most common cause of malperfusion (80%) and results in variable symptoms given the dynamic nature of the occlusion[2]. Static obstruction occurs when the dissection flap continuously occludes the branch vessel ostia or the branch vessel dissects and extends distally. The mechanism of obstruction, static *vs.* dynamic, dictates the treatment strategy, with dynamic generally resolving with medical management of hemodynamics and central aortic repair. In contrast, static malperfusion generally requires some form of additional intervention to treat in addition to central aortic repair.

Later stages of end-organ malperfusion result in malperfusion syndrome, characterized by necrosis and/or end-organ dysfunction. As a syndrome, it entails a set of clinical, laboratory and radiographic findings as described below:

- Clinical features (e.g., abdominal pain, hematochezia, pulselessness, loss of motor function, oliguria);
- Laboratory findings (e.g., lactic acidosis, elevated liver and pancreatic enzymes, elevated creatinine);
- Radiographic findings of dynamic or static obstruction resulting in absent or decreased flow to the organ.

PATHOGENESIS AND CHALLENGES

Malperfusion syndrome itself results in an inflammatory cascade resulting from end-organ ischemia, increased myeloperoxidase production, and complement consumption. Free radical generation through neutrophil activation in ischemic tissue mediates endothelial injury and compromises membrane integrity. The downstream upregulation of TNF-alpha and IL-1 results in a positive feedback loop, which is mediated by leukocyte extravasation and cytokine release, leading to further end-organ injury. Thus, the inflammatory cascade brought on by end-organ ischemia significantly impairs clinical outcomes even after successful operative repair of the dissection[1].

In MMP, several factors further contribute to the poor outcomes in ATAAD. First, the insidious onset makes it difficult to pinpoint the diagnosis leading to delays in treatment. Forty percent of patients presenting with MMP do not present with abdominal pain, and 20% of patients with abdominal pain do not have mesenteric malperfusion[3,4]. Moreover, there are no definitive laboratory studies that accurately identify visceral ischemia, which is often associated with other organ system malperfusion. Radiographic findings can allude to MMP but cannot always distinguish between dynamic and static obstruction.

The pathogenesis of MMP creates an added layer of complexity. Intestinal ischemia disrupts the gut mucosal barrier, which incites endotoxin release to the portal system and mediates reperfusion injury. Perhaps the greatest contributor to the high mortality rate in MMP syndrome is the autoregulatory response of the splanchnic vessels to ischemia, which occurs when there is a > 75% decrease in blood flow to the celiac and superior mesenteric artery vascular beds[5]. This leads to a compensatory arteriolar vasodilatory response that converts to vasoconstriction when the ischemic period is prolonged. This vasoconstriction is often irreversible even after restoring blood flow. Both of these mechanisms can be further compounded by aortic surgery and likely account for the high incidence of necrotic bowel and persistent acidosis that may be observed after central aortic repair.

MALPERFUSION SYNDROME BY ORGAN SYSTEM: AN OVERVIEW

Malperfusion complicates 20%-30% of all ATAAD cases with relative incidences as listed below[6]:

- Coronary and acute myocardial infarction (MI): 1.7%-10%;
- Spinal cord: 0.3%-4.8%;
- Cerebral and associated stroke: 5.2%-13.1%;
- Visceral/extremity:
  - Mesenteric: 3.6%-14%
  - Renal: 2.3%-12%
  - Lower extremity: 2.3%-23%

Coronary malperfusion

Coronary malperfusion with acute MI is a rare but potentially fatal complication of ATAAD. The available data and management of this condition remain scant, given difficulties with its diagnosis and the high-associated mortality rate.

While acute aortic dissection often extends to the coronary ostia (particularly favoring involvement of the right coronary artery), it does not always lead to myocardial ischemia. Other considerations such as the size and location of the primary entry tear and false lumen flow pattern may impact the onset and severity of coronary malperfusion. A thorough evaluation is not always possible under static conditions, and coronary malperfusion may occasionally be diagnosed clinically when flow is resumed after aortic de-clamping.

According to the Neri definition of coronary malperfusion in acute aortic dissection[7], there are three types of dissections based on operative findings: type A, ostial dissection with disruption of the inner layer but limited to the coronary ostium; type B, dissection extending into the coronary artery; and type C, coronary disruption (i.e., intimal detachment). While some groups advocate for CABG repair in all patients[8], others including the Penn group have suggested a more tailored strategy based on the type of lesion involved. In their analysis of 76 patients presenting with coronary artery malperfusion, Kreibich *et al.*[9] reported successful ostial repair in 88% of type A patients, 63% of type B patients and 0% of type C patients. They therefore recommended CABG primarily for patients with type C lesions or in those with underlying coronary artery disease for which optimal delivery of cardioplegia could not be achieved[9].

Spinal cord malperfusion

Spinal cord malperfusion is due to extension of the dissection with compromised flow to intercostal or lumbar arteries, including the artery of Adamkiewicz. In ATAAD, this is most often due to a dynamic mechanism for which central aortic repair to restore true lumen flow with or without lumbar drain insertion is generally sufficient to resolve[6]. In patients with descending or thoracoabdominal aortic dissection involvement, the main treatment is TEVAR with endovascular fenestration and/or stenting if there is false lumen thrombosis and occlusion of intercostal arteries.

Cerebral malperfusion

Cerebral malperfusion complicating ATAAD is a clinical challenge that has not been extensively investigated in the literature. The available studies demonstrate that cerebral malperfusion and stroke are predictive of increased in-hospital mortality[10]. In an IRAD study of 2402 patients undergoing surgical repair of ATAAD, 15.1% presented with cerebral malperfusion and neurologic deficits[11]. Compared to patients with normal cerebral perfusion, patients with cerebral malperfusion had an increased incidence of postoperative cerebrovascular accident (17.5% *vs.* 7.2%; $P < 0.001$), acute kidney injury (28.3% *vs.* 18.1%; $P < 0.001$), and in-hospital mortality (25.7% *vs.* 12.0%; $P < 0.001$).

There have been some reports of using an endovascular approach with carotid artery stenting and/or external shunting (femoral artery to common carotid artery) with improvements in neurological status prior to delayed open central aortic repair. However, the general consensus is that immediate central aortic repair should be performed to restore cerebral perfusion. Central cannulation is preferred, and in some cases, it may be preferable to directly cannulate the carotid artery either with a cut-down technique or a graft sewn end-to-end to eliminate the false lumen flow and ensure true lumen cerebral perfusion.

The ongoing areas of debate in the management of ATAAD complicated by cerebral malperfusion are the appropriateness of central aortic repair and the timing of this repair. In another IRAD analysis by Di Eusanio *et al.*[12] of 1873 patients presenting with ATAAD, including 87 (4.7%) with stroke and 54 (2.9%) with coma, patients who were selected to undergo surgical management demonstrated enhanced survival and often times reversal of neurological deficits. All patients presenting with coma and 76.2% of those with stroke died with isolated medical management. For those patients undergoing surgical repair, mortality was 27.0% for patients presenting with stroke and 44.0% for those with coma ($P < 0.001$). Surgery was found to be protective against mortality in ATAAD patients presenting with cerebral malperfusion (OR = 0.058, $P < 0.001$). Moreover, postoperative stroke and coma resolved in 84.3% and 78.8% of cases, respectively. Thus, the authors concluded that "*in patients selected to undergo surgery demonstrated improved late survival and frequent reversal of neurologic deficits….intervention should always be considered*".

Although somewhat contentious, the IRAD data suggest that there is evidence to support a role for surgical intervention in comatose ATAAD patients. In these patients, the timing of intervention becomes particularly critical with the earlier the intervention being associated with improved outcomes. Tsukube *et al.*[13] analyzed their results of 181 patients with ATAAD, 27 of whom presented with coma (GCS < 11), who were managed with central aortic repair at index hospitalization. Of this group, 21 patients were immediately operated upon within 5 h of presentation and the remainder were treated medically, three of whom eventually underwent repair. Hospital mortality was 14% in the immediate group and 67% in the delayed group, and full recovery of consciousness was seen in 86% of the immediate group and 17% in the delayed group. While the available data are scant, they do indicate that the presence of brain malperfusion or cerebral dysfunction is not a contraindication to surgical intervention, and an individualized approach must be considered for optimal patient outcomes.

Visceral/mesenteric malperfusion

While rare, visceral/mesenteric malperfusion is the most challenging and devastating variant of all the malperfusion syndromes. It is associated with a 3- to 4-fold increase in mortality in both type A and B aortic dissections, resulting in a mortality rate of 70%-100%[14]. In an initial IRAD analysis of 464 patients with ATAAD, the most common cause of death after aortic rupture was MMP[15].

The traditional strategy for management has been central aortic repair followed by a period of expectant management with return to the operating room for exploratory laparotomy and possible bowel resection if clinically indicated. Unfortunately, while central aortic repair restores true lumen flow and resolves dynamic malperfusion, branch vessel ischemia can persist in 25% of patients due to the presence of distal re-entry tears, persistent false lumen flow, and static branch vessel involvement[16]. This strategy is associated with an operative mortality of 40%-75% and has recently undergone increasing scrutiny in the literature[14].

In a subsequent IRAD analysis of 1809 consecutive patients with ATAAD presenting to 18 referral centers worldwide from 1995 to 2010, the incidence of MMP was 3.8% (n = 68)[12]. Notably, these patients were critically ill and more likely to be older, present with coma, cerebrovascular accident, spinal cord ischemia, acute renal failure, limb ischemia, and any kind of pulse deficit. Hospital mortality was 63.2% in those with mesenteric malperfusion syndrome *vs.* 23.8% without (P < 0.001). Of the 502 patients undergoing immediate surgery, 12 had MMP. The in-hospital mortality was 15% without malperfusion syndrome and 70% for patients with MMP. Moreover, MMP was identified as an independent predictor of in-hospital mortality on multivariate analysis (OR = 2.5, 95%CI: 1.2-5.6). In patients with MMP, mortality was 95.2% after medical management (n = 21), 72.7% after endovascular therapy alone, 41.7% after an open surgical or hybrid approach (P < 0.001).

Other recent analyses have also suggested that central repair alone is insufficient to salvage these critically ill patients. In an analysis of a Japanese database by Kawahito *et al.*[17] of 1026 ATAAD patients undergoing emergency central aortic repair, mortality was higher for those with an increased number of organ systems affected: from 4.8% with 0 systems to 30.0% with 3 systems. In patients with malperfusion syndrome, obesity (BMI > 30), preoperative shock (SBP < 80 mmHg), and MMP were independent predictors for hospital death[17].

Given these poor outcomes with emergent central aortic repair for ATAAD with MMP, there has been an emerging interest in the role of endovascular therapy.

INFLUENCE FROM ACUTE TBAD TREATMENT - THE EVOLVING ROLE OF ENDOVASCULAR APPROACHES IN ATAAD MANAGEMENT

TEVAR in acute TBAD with malperfusion syndrome

In complicated acute TBAD patients with malperfusion syndrome of visceral/mesenteric vessels as well as the lower extremities, TEVAR is now considered the gold standard. TEVAR relieves true lumen compression as the endograft expands against a compliant dissection septum in the descending thoracic or abdominal aorta, mitigating malperfusion related to the dynamic flap and re-establishing flow to the visceral vascular beds as well as downstream lower extremities. Additionally, there is growing evidence that TEVAR in the acute phase of TBAD improves aortic remodeling as well as long-term aortic-specific survival.

In comparison to optimal medical therapy and open surgery with an associated in-hospital mortality of 30%-35%[15], TEVAR has dramatically decreased early mortality in acute complicated TBAD patients with low in-hospital mortality rates of 0%-8%[18-20]. One of the initial reports of TEVAR for complicated TBAD by

the Penn group reported a 30-day postoperative mortality rate of 2.8% at 30 days and relatively low incidences of other adverse events: 2.8% incidence of permanent renal failure, 2.8% stroke, 5.7% paraparesis, and 2.8% paralysis. One-year survival was 93.4%[18]. In another series out of Duke, there were no deaths in the first 30 days after TEVAR, and similar rates of renal failure, stroke and spinal cord ischemia were reported[19]. In our previously published analysis of complicated TBAD patients receiving TEVAR at index hospitalization, the in-hospital mortality was 5.0% with a 1.3% incidence of renal failure, 7.5% stroke, 2.5% paraparesis, and 0 cases of paraplegia[21].

New frontiers in ATAAD management

The success with TEVAR as highlighted in the previous section on the management of complicated TBAD has led to endovascular techniques to manage MMP in ATAAD. This approach views end-organ failure as the most immediate threat to life in relatively stable (i.e., absence of shock//rupture/tamponade) patients in order to improve survival. TEVAR reverses true lumen compression in the descending and abdominal aorta due to a dynamic flap and re-establishes flow to the visceral vascular beds as well as affected lower extremities.

The Michigan group has published their extensive experience with percutaneous interventions to re-establish end-organ perfusion and delaying operative repair until after the resolution of malperfusion syndrome. In their initial series, of 196 patients with ATAAD presenting between 1997 and 2007, 70 patients underwent endovascular fenestration or branch vessel stenting first. Among the 47 patients who survived to delayed central aortic repair after a median of 4 days, mortality (8.5%) was comparable to that of patients presenting without malperfusion syndrome[22]. The same group has recently analyzed their 20-year data with this strategy[23]. From 1996 to 2017, in 597 patients presenting with ATAAD, 135 patients with malperfusion syndrome (visceral or extremity) but without evidence of aortic rupture/tamponade were managed with endovascular reperfusion upfront (via fenestration/stenting) followed by delayed open aortc repair. In-hospital mortality improved over the two decades of analysis (from 21.0% to 10.7%, $P < 0.001$). The authors reported that 69.5% of patients ultimately underwent delayed open repair and 26.5% died from end-organ failure prior to delayed open repair. Interestingly, even after the resolution of branch artery obstruction with fenestration and/or stenting, the likelihood of dying from end-organ failure was 7×'s higher than that of dying from aortic rupture. The authors thus concluded that it is reasonable to presume that "*not every untreated type A dissection will rupture, but every untreated malperfusion syndrome will result in death*"[23].

For stable patients with MMP, the risk of aortic rupture is low, and data from Emory also supports that a TEVAR-first approach with delayed proximal aortic replacement may be the strategy of choice to improve outcomes. In an institutional analysis of 618 patients presenting with ATAAD from 2003 to 2017 at an Emory Healthcare facility, 34 patients (5.5%) presented with MMP with mean serum lactate of 4.3 ± 2.1 mmol/L[24].

Over the course of the study period, the management strategies for these patients evolved[24]. From 2004 to 2009, the favored treatment was immediate ascending aortic replacement followed by exploratory laparotomy, bowel resection, and femoral-femoral bypass as needed (n = 13). From 2009 onwards, some patients received axillary-bifemoral (Ax-Bifem) bypass prior to sternotomy with perfusion of both the right axillary artery and Ax-Bifem graft during cardiopulmonary bypass (n = 3). Finally, after 2012, endovascular techniques began to be integrated into the treatment algorithm using either an antegrade TEVAR (n = 5) or a TEVAR-first (n = 13) approach. The antegrade TEVAR approach involved obtaining wire access in the descending aorta and deployment of the endograft under direct vision at the time of open ascending/arch replacement. The distal end of the ascending/arch Dacron graft was then sewn to the aorta incorporating

the proximal edge of the endograft in the suture line. The TEVAR-first approach consisted of emergent TEVAR followed by delayed central aortic repair.

Patients who presented with hemodynamic instability, cardiac tamponade/hemopericardium, respiratory distress, intractable chest pain, stroke, coronary malperfusion, or severe aortic insufficiency were excluded from consideration of a TEVAR-first approach. In those who underwent TEVAR, additional branch vessel stenting was performed until abdominal aortography and femoral artery pressures matched radial artery pressures to confirm normal perfusion.

The limited number of patients in the series precludes any generalizable results. However, the trend was towards improved outcomes among patients who received end-organ re-perfusion prior to central aortic repair. In the ascending aortic/arch replacement followed by exploratory laparotomy group, 77% of patients developed postoperative bowel necrosis or intractable acidosis with an overall mortality of 69.2%. All patients in the Ax-Bifem bypass followed by ascending/arch replacement group survived; however, 66% needed postoperative renal replacement therapy. In the ascending/arch and concomitant antegrade/TEVAR group, the mortality was 80%. Of the 13 patients treated with a TEVAR-first approach, ten survived and ultimately underwent central aortic repair. Of these, four patients required additional branch vessel stenting for static malperfusion and three patients who underwent aortic repair died for an in-hospital mortality of 30% after central aortic repair.

Based on this accumulating experience, a new treatment algorithm for the management of ATAAD with mesenteric malperfusion syndrome has been proposed. Once ATAAD with MMP has been diagnosed, patients who are hemodynamically stable, free of chest pain, and without evidence of severe aortic insufficiency, cardiac tamponade/rupture should be considered for TEVAR with or without additional endovascular therapy. If within 24 h of observation, lactate levels have normalized, then the patient should undergo central aortic replacement. If lactic acidosis persists, however, these patients should undergo exploratory laparotomy, bowel resection and either withdrawal of care or additional delay of aortic replacement until their acidosis has resolved. Patients with ATAAD complicated by MMP who are hemodynamically unstable, present with evidence of aortic rupture, or intractable chest or abdominal pain should proceed with emergent Ax-Bifem bypass with antegrade and retrograde aortic perfusion, ascending/arch replacement with antegrade TEVAR deployment, followed by Ax-Bifem bypass completion.

Hybrid techniques with central aortic repair at the same time as endovascular management of distal malperfusion syndromes are also emerging[25,26], and there have been case reports of successful results of ATAAD with MMP management in hybrid operating rooms using interventional techniques to re-establish end-organ malperfusion first, followed by aortic root repair, total arch replacement with debranching, and retrograde stent graft implantation. The benefit of this approach is the ability to first relieve visceral and lower extremity malperfusion and subsequently prevent aortic rupture during the same operation.

CONCLUSIONS

In summary, malperfusion involving any vascular bed and organ system complicates acute aortic dissections and significantly impacts morbidity and mortality. Malperfusion syndrome itself results in an inflammatory cascade that mediates end-organ injury, which can persist even after aortic repair. Many types of malperfusion syndromes are effectively treated with central aortic repair. These include coronary malperfusion as well as cases of ATAAD complicated by stroke and coma. While the available data are limited, they do suggest that the presence of brain malperfusion or cerebral dysfunction is not a contraindication to surgical intervention. In these specific patient populations, early intervention is

indicated.

Other types of malperfusion syndromes may require alternative approaches. MMP is the most lethal variant of malperfusion syndromes with multiple studies demonstrating this condition to be an independent predictor of in-hospital mortality. Due to the poor outcomes after isolated central aortic repair and the excellent short- and long-term outcomes of TEVAR for the treatment of complicated TBAD, there has been an emerging role for the use of endovascular techniques in the management of ATAAD with MMP. Ultimately, for the successful management of ATAAD complicated by malperfusion, the involvement of a multidisciplinary team and a patient-specific approach are absolutely critical.

DECLARATIONS

Authors' contributions

Preparing and writing the manuscript, editing and revising the manuscript, approving the final version: Lou X, Chen EP

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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