Surgical intervention and its role in Takayasu arteritis

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Abstract

Vascular surgery remains an important option in the management of Takayasu arteritis. Its use is predominantly confined the treatment of symptomatic organ ischaemia or life-threatening aneurysm formation. In most cases this follows the failure of medical therapy to prevent arterial injury. Open surgery and endovascular approaches are used. The choice between them, at least in part, is determined by the site and nature of the lesion. Although more invasive, open surgery offers enhanced duration of arterial patency. For endovascular intervention, primary angioplasty without stenting is preferred, with stenting reserved for primary or secondary angioplasty failures. Although there is increasing interest in the role of stent grafts and tailor-made endovascular stents, long-term outcomes remain to be reported. Interventional outcomes are improved and complications reduced by therapeutic control of disease activity pre- and post-surgery. The wider use of combined immunosuppression and the introduction of biologic therapy for refractory Takayasu arteritis may reduce future requirements for surgical intervention.

Key words: Takayasu arteritis, endovascular, open surgery, angioplasty, restenosis, stenting, stent grafts

Introduction

The nature of Takayasu arteritis and its propensity for the development of arterial stenoses and aneurysmal dilatation, suggests that surgical intervention is a logical approach to treatment. However, the focus of the autoimmune response in the adventitia, leading to a granulomatous vasculitis invading the media and resulting in intimal thickening, raises important caveats. The actively inflamed arterial wall responds poorly to endovascular or open surgical intervention. A response to injury phenomenon including early restenosis or development of anastomotic aneurysms is reported. Therefore surgical approaches are only considered in emergency, following the failure of medical therapy, or to treat severe consequences of arterial damage. The outcome for carefully selected cases with specific surgical indications is usually good. Ideally surgery should be undertaken in a specialist centre and following adequate control of disease activity with medical therapy. In these circumstances patient outcomes are significantly improved with reduced morbidity and mortality (1, 2).

Early diagnosis and prompt initiation of therapy remains a major challenge in the management of Takayasu arteritis. The rarity of the disease and the non-specific nature of the presenting symptoms typically result in a delayed diagnosis so increasing the risk of severe arterial injury (3, 4). However, recent data suggest that wider availability of non-invasive imaging and the use of combined immunosuppressive strategies are improving outcomes (5-8). Furthermore, as more patients with refractory disease receive biologic therapies, including those targeting TNF-α and IL-6-driven pathways, there is hope that outcomes will be further improved (9, 10). This may in turn reduce the need for surgical intervention.

Immunopathogenesis

Immunohistochemical analysis of arterial tissue from patients with Takayasu arteritis is rarely performed because specimens are only available from those undergoing surgery. Prominent lymphoid follicles are often found in a markedly thickened adventitial layer. Hyperplastic vasa vasora provide access for infiltrating leukocytes to the arterial wall. α/β and γ/δ T cells are present. CD8 T cells are the most

abundant and are accompanied by CD4 cells and occasional B cells. Local release of chemotactic cytokines encourages infiltration by monocytes and macrophages. Occasional multinucleate giant cells are present and they often align closely with sites of fragmentation in the internal elastic lamina.

The granulomatous arteritis predisposes to arterial remodelling. Myofibroblast proliferation leads to intimal medial thickening and progressive narrowing of the arterial lumen. The active inflammatory phase is eventually replaced by progressive fibrosis and further arterial remodelling. The resultant stenotic lesions are fixed and may completely occlude the artery. Stenosis affecting the coronary, renal, superior mesenteric and coeliac arteries are typically ostial in nature. Those seen in the subclavian/axillary arteries are often long and irregular. On occasion the arterial injury predisposes to aneurysm formation, most commonly affecting the aorta. In the ascending aorta this is often accompanied by aortic valve regurgitation.

When might surgery be considered?

Five patterns of Takayasu arteritis have been described. These range from disease affecting the ascending aorta or one or more of the supra-aortic vessels alone, up to pan-aortic disease (Type V) (11). On occasion, surgery may be indicated for the treatment of any of these variants. However, except in emergency, surgical intervention should be considered as a last resort and following failure of medical therapy to prevent or control arterial injury. Patient selection is critical. A retrospective study of 106 Japanese patients separated them on the basis of severity criteria (12) and assessed outcomes. In those with the most severe disease with ≥2 major complications including aortic regurgitation, severe hypertension or aneurysm development, the 15-year survival rate was increased from 43% (in those treated historically with medical therapy) to 67.5% following the addition of surgical intervention (2). However, those graded as stage II derived no survival benefit, while survival was shortened in those with stage I who underwent surgery (2). These findings and recent data (13) suggest that careful consideration should be given to alternative options when considering surgery. When intervention is planned, discussion should also include a rescue strategy if the first surgical approach fails. This is particularly true for open surgery.

Across a number of series, the predominant indications for surgery are as follows: refractory hypertension related to renal artery stenosis, aortic disease including coarctation and ascending aortic dilatation ± aortic valve regurgitation, ischaemic

heart disease, supra-aortic disease with cerebral ischaemia, mesenteric ischaemia, severe limb-threatening claudication and aneurysm repair (13-18) (Table 1). Comparison of patient cohorts illustrates differences in the proportion of patients referred for surgical intervention from 17-52% (13-18). These figures reflect in part local expertise, referral patterns and case mix. A large recently reported Chinese series of 411 patients followed over 24 years shows comparable data, with 42% undergoing open or endovascular surgery with surgical bypass procedures undertaken most frequently (19).

Pros and cons of endovascular and open surgery

The decision when to use an endovascular or open approach may be influenced by a number of factors (Table 1). In certain circumstances, such as a dilated aortic root with a failing aortic valve, an open procedure is typically used. However, in many vascular beds both approaches may be considered. Some centres opt for open surgery more often because they consider the recurrence rate of endovascular approaches to be too high (20), while in other centres the overall risk of the endovascular procedures is considered lower (21). The pan-mural nature of the arteritis needs to be considered. Mature stenotic lesions are often long and fibrotic. They can be challenging to cross with a guidewire and require higher inflation pressures than a typical atherosclerotic lesion. A recent meta-analysis has confirmed that restenosis rates are higher following endovascular procedures. However, apart from the incidence of cerebrovascular accident, which was higher following open surgery, morbidity and mortality were otherwise equivalent (22).

Angioplasty with or without stenting has been used to treat lesions affecting the aorta, carotid, subclavian, vertebral arteries and coronary arteries, the renal arteries, coeliac trunk, superior mesenteric and iliac arteries (16, 21, 23-25). Opinion regarding the use of stents as a primary procedure, or confining their application to the treatment of complications or recurrent lesions remains divided. In our centre angioplasty alone is used preferentially. The majority of studies now report higher restenosis and recurrence rates following the use of stents (23-27), but this finding is not universal (21). Furthermore, additional work is needed to explore the role of stent grafts. Stent grafts comprise a metal stent lined by an impervious fabric tube. The stent grafts are expanded to fit the shape of the artery and are most commonly used in the aorta. Experience in the use of stent grafts in TA is small. A retrospective review identified 8 patients undergoing endovascular intervention and although initial outcomes were excellent and directly comparable, stent grafts remained patent

longer than bare metal stents and were less likely to require secondary intervention (28). Reports concerning the use of drug-eluting stents are rare. No sustained benefit was seen in a patient in whom both bare stents and drug-eluting stents were employed (29). Endovascular protocols likely vary from centre to centre. For patients undergoing renal artery procedures for severe uncontrolled hypertension Sharma and Gupta have recommended aspirin and clopidogrel daily for 3 days prior to the angioplasty procedure. Heparin is prescribed intravenously during the procedure and stopped before closure. Dual anti-platelet therapy is continued for 3 months if a stent is placed and then aspirin is continued lifelong thereafter. For planned angioplasty, or stenting of visceral arteries in less acute circumstances, clopidogrel is suggested for 3 days prior to the procedure and for 3 months thereafter (24). Another important factor to consider is the young age of the patients involved and hence arterial stenting is typically reserved for procedural complications, bearing in mind that the patients may be candidates for open surgery in the future (23, 30).

Specialist expertise improves outcomes and our practice is to adopt a multi-disciplinary approach to intervention planning. As appropriate this process variously involves cardiothoracic and vascular surgeons, cardiologists, interventional radiologists, renal physicians and rheumatologists. Input from the patient is essential and the pros and cons must be discussed clearly with them. The difference in long-term patency rates must also be considered, bearing in mind that higher restenosis rates are typically reported following angioplasty ± stenting than with open surgery (14, 16, 17, 31).

Pre-surgery assessment and peri-operative medical therapy

There is no fail-safe method for the assessment of disease activity for Takayasu arteritis. However, there is widespread and evidenced-based agreement that outcomes for open and endovascular surgery are improved in patients with clinically inactive disease at the time of intervention. Thus, those prescribed effective immunosuppressive therapy leading to clinically inactive disease prior to the procedure have improved long-term outcomes (16, 17, 20, 32, 33). Of note, rates of revision at 5 and 10 years post-procedure were zero in patients with quiescent disease not requiring steroids; 5% at 5 years and 19% at 10 years in those with quiescent disease on maintenance steroids; 43% at both 5 and 10 years in patients with evidence for active disease for which they were currently receiving steroids, and finally 67% at both 5 and 10 years in those with active disease not prescribed steroids (20). Recent data support these findings and highlight the association

between cardiovascular risk factors and a current smoking history and higher restenosis rates (13, 34, 35). In addition to effective pre-operative treatment, our practice is to continue this during surgery and in the peri-operative period. We also recommend 100-200 mg intravenous hydrocortisone pre- and post-procedure for all patients. In the face of active arteritis and the need for emergency surgery we have used intravenous biologic therapy with anti-IL-6 receptor or anti-TNFα monoclonal antibodies in the pre-operative period to reduce the inflammatory burden, an approach recently reported by others (36).

For planned surgical procedures, the question remains how to optimally assess pre-procedural disease activity. Indeed, this remains a challenge for all patients with large vessel vasculitis and represents an important area of research activity (37). We have adopted a pragmatic approach and delay surgery until the physician's global assessment and Indian Takayasu arteritis score (ITAS.A) (38) suggest clinically inactive disease. Ideally, haemoglobin, C-reactive protein and erythrocyte sedimentation rate should be within the normal range. If concern persists regarding disease activity confined to the arterial wall, an ^{18}F-fluorodeoxyglucose positron emission/CT tomography scan can be performed, while recognising the relative limitations of this technique for detecting low-grade persistent inflammatory disease (39, 40). If active arteritis is suspected, surgery should be delayed where possible while immunosuppression is increased for 3-6 months.

Surgical approaches in different vascular beds

The range of procedures adopted is summarised in Table 1. It is important to note that opinions vary between centres and surgical approaches are constantly evolving.

Supra-aortic disease and cerebral ischemia

Symptomatic cerebral ischemia occurs in patients with severe involvement of the supra-aortic arteries. Symptoms include visual dimming or loss on exertion, dizziness, amaurosis fugax, dysphasia, hemiparesis, transient loss of consciousness and stroke. In those with persistent severe symptoms despite optimal medical therapy, both open and endovascular surgical approaches have been employed. Outcomes are optimal in those with controlled disease activity at the time of surgery. Aorto-carotid bypass is the most commonly used technique (Figure 1A) (41-43). Although the risk of complications is higher during or following open surgery, long-term patency is good with restenosis rates in the region of 12.5% (41, 42). Endovascular approaches are often complicated by long occluded segments and this

approach is typically reserved for those with short focal lesions or for those patients considered to be too high risk for open surgery (44). Long-term patency rates are in the range of 50-75% at 3-5 years respectively (41, 45). The risk of cerebral hyperperfusion ± haemorrhage can be reduced by tight pre-operative blood pressure control and the use of unilateral as opposed to bilateral aorto-carotid bypass (41, 43).

Subclavian/axillary arteries

Upper limb claudication is the most frequent indication for surgical intervention in many Takayasu arteritis series (13, 17). Symptoms often interfere with day to day life leading to patient requests for a solution. However, our practice is to avoid open or endovascular intervention if possible. Symptoms are rarely severe and complications of failed surgery can be devastating. Intervention is confined to those with arterial ischaemia that is considered limb threatening, or for short proximal lesions amenable to angioplasty. This approach is also adopted for iliac stenoses. The typical stenosis in the subclavian/axillary artery is long and irregular (Figure 1B). This renders angioplasty more technically challenging than treatment of an atherosclerotic lesion (46). Likewise, open bypass surgery is often complicated by the small size of the distal uninvolved artery, leading to a difficult anastomosis and high risk of restenosis. Successful intervention in the upper limbs is reported in the literature (13, 46, 47), although restenosis rates are higher than that typically seen in the renal arteries for example. Whenever possible, we avoid intervention and advise an upper limb exercise programme to encourage development of a collateral circulation (Figure 1B).

Aortic and pulmonary artery intervention

The aorta and aortic valve are amongst the most common sites of surgical intervention in many series of Takayasu arteritis (13, 15-17). Ascending aortitis may be complicated by aortic root dilatation and aortic valve regurgitation. The results of surgical replacement of the aortic valve are good and often accompanied by replacement of the ascending aorta with a graft (Figure 2). Whenever possible, patients should be referred to specialist centres for surgery and subsequent monitoring. Late aneurysmal dilatation of the ascending aorta can occur following aortic valve replacement and all patients need lifelong monitoring (14, 16, 48, 49).

Although relatively rare, aortic aneurysms can be identified at sites throughout the aorta in Takayasu arteritis and on occasion, multiple aneurysms are found (50). A variety of approaches have been adopted for the treatment of aortic aneurysms. All

aneurysms require careful monitoring and those less than 2 cm without evidence of progressive enlargement do not need intervention (30). Open surgery using prosthetic grafts remains the most commonly used technique for surgical treatment of thoracic and thoraco-abdominal lesions (51). Endovascular approaches are increasingly employed and these include the successful use of stent grafts (52) and tailor-made stents to occlude aneurysms (16).

Management of aortic coarctation in Takayasu arteritis is particularly challenging. The associated refractory hypertension predisposes to stroke and cardiac failure and on occasion lower-limb claudication is severe despite the development of a collateral circulation. Open surgery is most commonly indicated for those with limiting claudication, and aorto-bi-iliac grafts typically resolve the symptoms for the majority of patients (14, 20) (Figure 2C). In contrast, improved blood pressure control is only seen in 40-50% of these patients following surgery (53). Endovascular approaches to aortic stenosis are of interest, particularly in these young patients. Some lesions may be amenable in carefully selected patients and outcomes are often good. However, further data is required, particularly concerning long-term outcomes. Balloon angioplasty has been applied and on occasion repeated procedures employed (21, 24, 47). Preliminary data is also available for the use of stents and stent grafts. These are again encouraging but the authors stress the need for follow-up and outcome data (28, 54, 55)

Optimal approaches for the management of pulmonary artery involvement in Takayasu arteritis remains to be determined and our approach has focused upon medical management. Successful surgical intervention has been reported and a variety of techniques have been employed. These include bypass grafts, angioplasty and stenting (56-58). A recent study has explored the potential role of percutaneous transluminal pulmonary angioplasty (PTPA) (59). Results were mixed and further data is required before this can be recommended. Moreover, pre-existing pulmonary hypertension constitutes a significant risk factor for surgery, with a 13-fold increased risk recently reported (60).

Coronary artery intervention

Vasculitic lesions affecting the coronary arteries are commonly encountered in TA and can be further complicated by premature atherosclerosis ± calcification. Primary vasculitic lesions are most often short and ostial, involving the left main stem, left anterior descending and right coronary arteries (61-63). The optimal surgical

management of those with symptomatic disease despite medical therapy remains to be determined. However, coronary artery bypass grafting (CABG) is currently considered the first choice (Figure 3A). Whenever possible, disease remission should be achieved prior to intervention as this may complicate the proximal anastomosis and increase the risk of complications. Angioplasty ± stent insertion and coronary endarterectomy are available as alternatives (64-66).

Two recent studies comparing percutaneous intervention (PCI) and CABG have reported. In the first, a significantly higher rate of restenosis was observed following PCI (63%), despite the use of drug-eluting stents (rapamycin n=7, zotarolimus n=3 and paclitaxel n=2), when compared to CABG (25%) at follow-up of ~100 months (66). The second report notes that the incidence of major cardiovascular events was significantly higher following PCI than CABG (median follow-up 48 months), especially in those undergoing intervention during an active phase of arteritis. However, in those with disease in long-standing remission PCI offers a suitable alternative to CABG (65).

Renal, coeliac and superior mesenteric arteries

The renal arteries remain one of the most common sites of intervention in Takayasu arteritis (25-27). While, the predominant indication is refractory hypertension, renal ischaemia ± deterioration in renal function is an important complication that can be overlooked, resulting in loss of a kidney. The classical renal artery lesion in TA is a short ostial stenosis (Figure 3B). Longer more irregular lesions are sometimes observed, particularly if there is disease involvement of the adjacent aorta. The surgical approach adopted is to some extent determined by local expertise and opinion. However, increasingly endovascular methods predominate.

Although, there is no doubt that open surgical revascularisation is effective, the majority of the young patients involved will opt for an endovascular approach. Open surgery utilises renal artery bypass grafting most commonly and on occasion renal artery reimplantation (67). Whilst much more invasive, there is an advantage with respect to long-term patency. Weaver et al reported that 79% of grafts remained patent at 5 years (67). The efficacy of aorto-renal bypass was more recently confirmed with comparable primary patency at 5 years. Although recurrence was detected in 15%, this was treated successfully with angioplasty (68). As renal artery intervention is rarely urgent, it is important to ensure whenever possible that disease activity is adequately suppressed. In those patients with inactive disease following

completion of any immunosuppressive therapy, no recurrence was detected at the 10 year follow-up (20).

Our experience favours the use of angioplasty as the initial approach for renovascular hypertension secondary to renal artery stenosis (Figure 3C). Stenting is used to manage complications associated with primary angioplasty or on occasions for recurrence. A Korean study suggested that primary angioplasty was associated with improved 5 year patency and a lower restenosis rate than angioplasty with stent insertion (8% v 66%) (23). Likewise, a large Indian study supports the use of primary angioplasty, keeping stent insertion as a second option for recurrence and complications. Patency at 5 years was reported as 67% (24). Recent studies have built upon these findings and reached similar conclusions. A meta-analysis of seven studies, involving 266 patients and 316 lesions, found that restenosis rates were significantly higher in renal arteries treated with a stent than those in which primary angioplasty was used. Notwithstanding, improvement in renovascular hypertension was equivalent and acute complications more likely during balloon angioplasty (25). In a Chinese cohort primary patency was higher following angioplasty (90.1%) versus stenting (75.6%) and the stenting group were more likely to restenose and need re-intervention (27). Finally, a report from Belgium also supports the primary use of angioplasty rather than stenting or surgery for Takayasu arteritis-associated renal artery stenosis (26).

Symptomatic involvement of the visceral superior mesenteric artery and coeliac trunk is much less common than in the renal circulation. However, angioplasty can be used with or without stenting in an attempt to improve the symptoms of mesenteric ischaemic (25). Sharma and Gupta report that symptomatic lesions are often long and irregular and respond poorly to intervention and that they rarely perform this procedure. Short proximal lesions are more amenable to intervention but the restenosis rate is higher than that seen in renal artery series (24).

Summary

Surgical intervention remains an important component of the management of patients with Takayasu arteritis. Although rates of intervention are falling, understanding the need for suppression of disease activity, increased endoscopic approaches and the remarkable advances in endovascular procedures are likely to offer reduced risk and improvements in efficacy. Major complications of surgical intervention in Takayasu arteritis are relatively rare and active disease at the time of

surgery represents a major risk factor (35). Restenosis, thrombosis, cerebrovascular accident, arterial dissection and bleeding constitute the major complications (13, 17, 20, 24). These risks can be mitigated by control of disease activity and hypertension, expert use of anti-coagulation and anti-platelet strategies, and a planned follow-up strategy including non-invasive imaging.

The introduction of biologic therapies has improved disease control in refractory Takayasu arteritis. Increasing access, early in the disease course to a variety of biologics targeting distinct pro-inflammatory pathways offers the exciting prospect of markedly improved disease control and reduced risk of relapse. Time will tell whether this reduces the degree and extent of arterial injury and hence the need for surgery.

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Conflicts

There are no conflicts of interest

Practice points

- Open surgery and endovascular approaches remain a key component of management in Takayasu arteritis
- Effective suppression of disease activity prior to and after surgery improves outcomes
- Restenosis rates are typically higher following endovascular procedures and stent insertion increases this risk
- Early use of available biologic therapies may ultimately reduce the requirement for surgery in the future

Research agenda

- The preliminary results of novel endovascular procedures and the use of stent grafts are encouraging, research is now required to determine indications for their use and demonstrate long-term efficacy.
- Improved access to biologic agents for Takayasu arteritis and studies to demonstrate their ability to reduce arterial injury are essential.

Figure legends

Figure 1: Supra-aortic disease in Takayasu arteritis.

A. Supra-aortic disease resulting in symptomatic cerebral ischemia and stroke was treated successfully with an aorto-bi-carotid graft procedure. The arrows indicate the two grafts. **B**. A long stenosis of the left subclavian artery is shown (star). Blood flow is re-established by the well-formed collateral circulation (arrow).

Figure 2: Surgical treatment of aortic Takayasu arteritis.

A. A CT angiogram demonstrating aortitis complicated by ascending aortic aneurysmal dilatation and aortic valve regurgitation (arrows). **B**. Post-operative MR angiography showing successful aortic valve and root replacement (arrows). **C**. A patient suffering limiting lower limb claudication as a consequence of distal aortic stenosis was treated successfully with an aorto-bi-iliac graft (arrow).

Figure 3: Renal and coronary artery intervention in Takayasu arteritis.

A. Coronary CT angiography demonstrates proximal stenosis of the left main stem (arrow) with evidence of aortitis (stars). This was subsequently successfully treated by coronary artery bypass grafting. **B**. MR angiogram (MRA) demonstrating right renal artery occlusion (star) which led to loss of the right kidney. There is co-existent proximal left renal artery stenosis (arrow). **C**. Repeat MRA shows improved left renal artery calibre following angioplasty.

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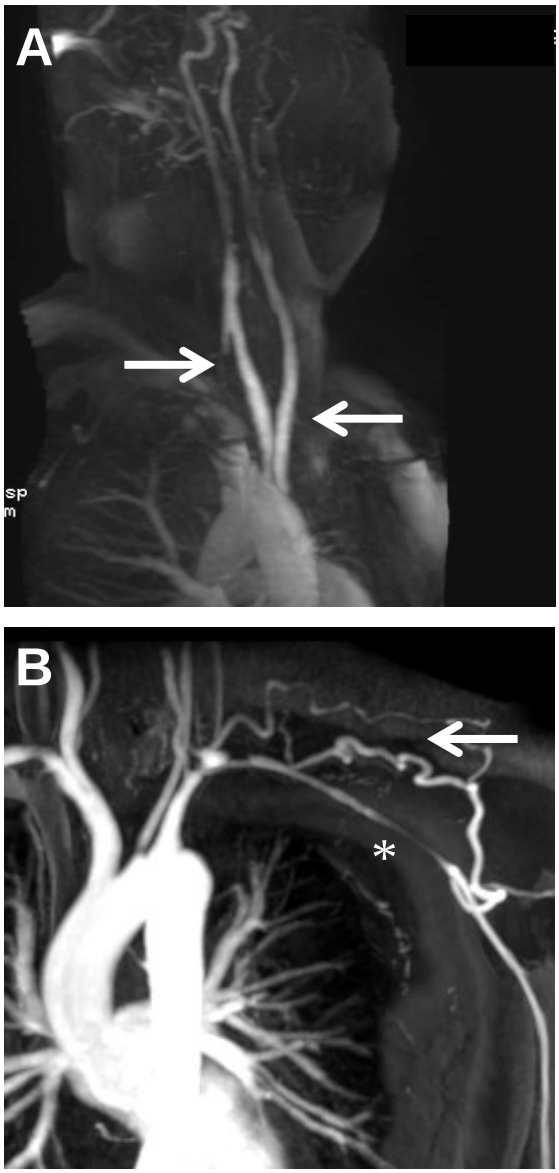

Figure 1

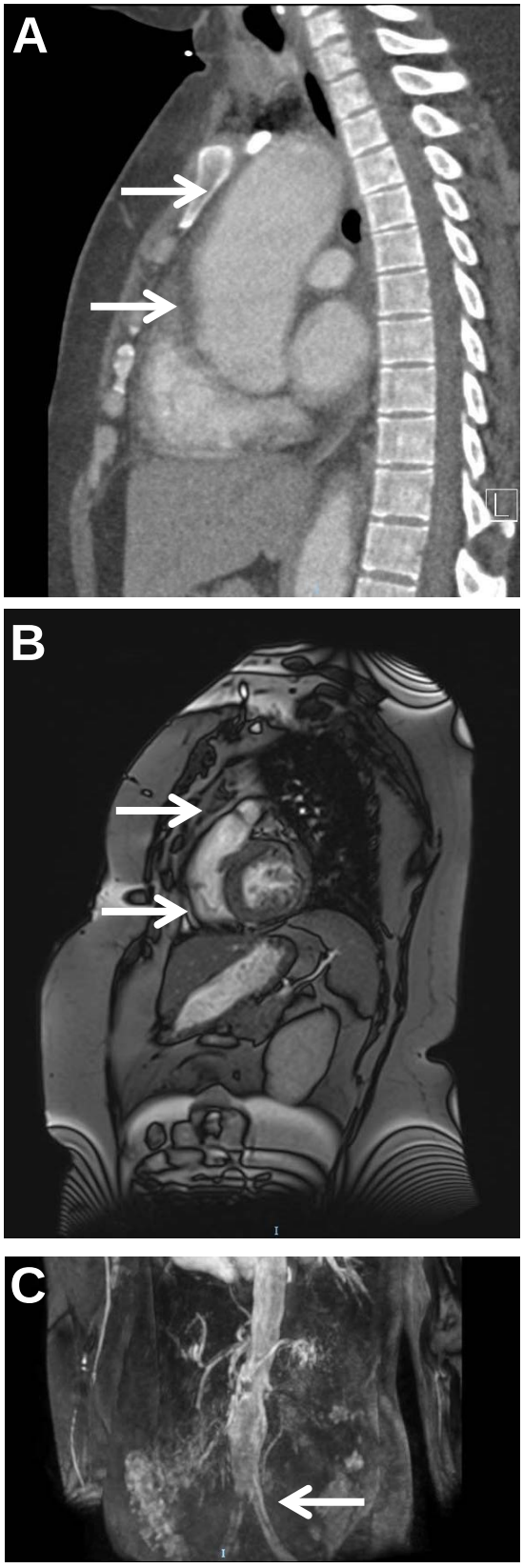

Figure 2

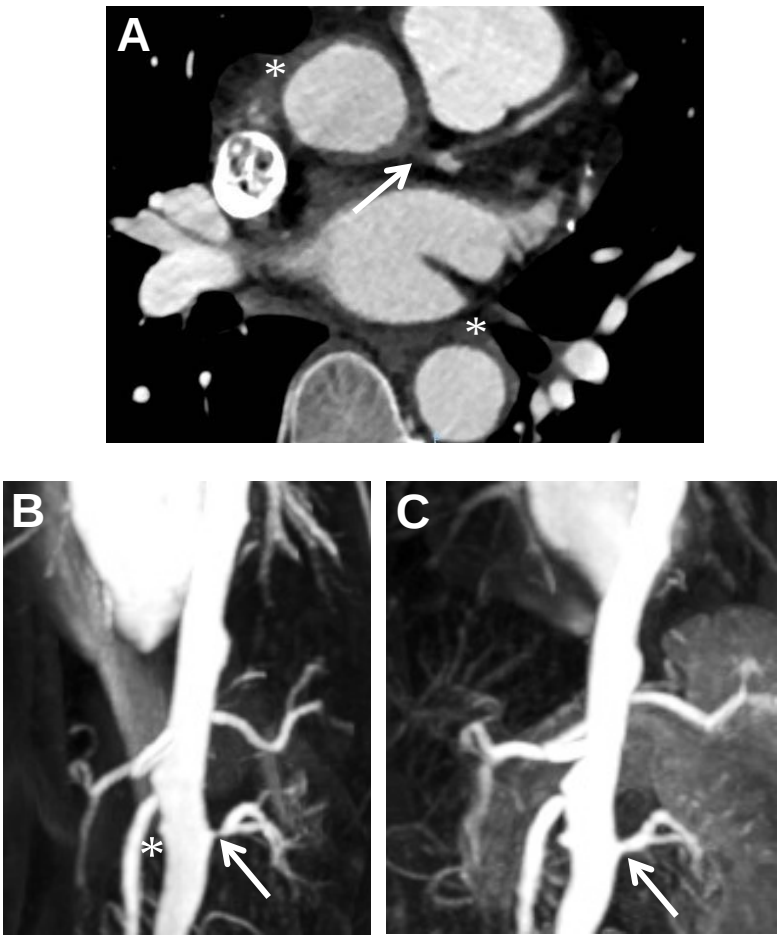

Figure 3