Visceral Artery Interventions in Takayasu's Arteritis

Sanjiv Sharma, M.D.,¹ and Ashish Gupta, M.D.¹

ABSTRACT

Takayasu's arteritis is an idiopathic chronic inflammatory disease affecting the aorta, its major branches and the pulmonary arteries. It leads to stenosis, occlusion, dilatation, and aneurysm formation in the involved vessels. Visceral arterial involvement occurs in 11 to 68% cases. Steno-obstructive lesions are most commonly seen and are usually symptomatic. Dilative and aneurismal lesions are uncommon and, when present, are usually clinically silent. Renal arteries are most commonly involved (24 to 68%), resulting in renovascular hypertension, whereas mesenteric arterial involvement is seen in 11 to 28% cases and is usually clinically silent. The assessment of disease activity is of utmost importance in its management as revascularization is best performed in the inactive phase. The disease activity can be assessed by clinical, biochemical, or radiological markers. The primary objectives of treatment include the control of disease activity by drug therapy, pharmacologic control of blood pressure (BP), supportive management and revascularization (surgical or endovascular) of the symptomatic ischemic territory. Surgical treatment is challenging due to the diffuse nature of the disease and involvement of adjacent aortic walls. It has a high incidence of anastomotic aneurysm formation (12 to 14%) and graft failure (20 to 40%) over time. Endovascular therapy (usually in the form of balloon angioplasty) has specific technical and procedural issues, but is safe and effective in the control of hypertension with success rates ranging between 80 to 96%. The overall complication rates are low. The cumulative 5-year patency rate for the management of renal artery stenosis is 67%. The use of stents is usually restricted as a bailout to treat obstructive dissection after angioplasty, due to a variety of reasons as their use may adversely affect the long-term outcome of treatment. Angioplasty is less effective in relieving obstruction in the mesenteric arteries and the outcomes are also infrequently reported.

KEYWORDS: Takayasu's arteritis, arteritis, renal artery, mesenteric artery, stenosis, angioplasty

Objectives: Upon completion of this article, the reader will be able to explain the proposed etiopathogenesis, morphologic types of involvement, various markers of disease activity and their role in management, and state the advantages and disadvantages of revascularization strategies in Takayasu's arteritis.

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¹Department of Cardiac Radiology, All India Institute of Medical Sciences, New Delhi, India.

Address for correspondence and reprint requests: Sanjiv Sharma, M.D., Professor and Head, Department of Cardiac Radiology, All India Institute of Medical Sciences, New Delhi 10029, India (e-mail: meetisv@yahoo.com).

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Takayasu's arteritis was first described by Mikito Takayasu in 1908¹ and is eponymously called nonspecific aortoarteritis (NSAA), aortic arch syndrome, and pulseless disease, among others. It is a rare idiopathic, chronic disease with cell-mediated inflammation involving the aorta, its major branches, and the pulmonary arteries.² It leads to inflammation and fibrosis in the involved vessel walls resulting in stenosis, occlusion, dilatation, or aneurysm formation of the vessel lumen.³ Even though reported worldwide, it is more frequently seen in Asia, the Mediterranean basin, South Africa, and Latin America.⁴ Racial variation also occurs as the disease is uncommon in Caucasians. Moreover, in Israel, NSAA is seen in Sephardic Jews but not in Ashkenazi Jews.⁵ Heterogeneous angiographic manifestations have been reported from different geographical areas with predilection for stenotic versus dilative and thoracic versus abdominal aortic involvement in different geographic locations.⁶⁻¹⁰ Dilative and aneurismal lesions predominate in Philippines, Thailand, Israel, Japan, and Western India, whereas stenotic lesions are more commonly seen in North India and Japan.^{11,12} Sites of involvement by steno-occlusive lesions also show geographic predilections. It has been reported that the aortic arch and its branches were mainly involved in Japanese patients whereas the abdominal aorta and its branches were mainly involved in Indian patients.^{13,14}

There is an overall female preponderance although the female to male ratio seems to decline from eastern Asia toward the West.^{15,16} The disease commonly occurs in the second and third decade of life. In an earlier study, we have observed that as many as 32% patients from India were under 16 years in age.^{8,17} Irrespective of the type of involvement, almost all patients have ischemic disorders in the territory of involved vessels.¹⁸ The disease is characterized by a slowly progressive cardiovascular (48%), neuroophthalmic (36%), and skin morbidity (13%). Systemic hypertension and heart disease have been reported as significant mortality predictors.¹⁹ In most patients, vascular involvement occurs in a contiguous fashion. However, skipped involvement and coexistence of active and inactive lesions can also occur.²⁰ These have major implications on long-term outcomes of revascularization procedures.

Visceral arterial involvement is common and is reported to occur in 11 to 68% patients, usually in the form of stenooclusive lesions (Fig. 1).^{8,21,22} The renal arteries are most commonly involved, usually presenting as renovascular hypertension (RVH). The incidence ranges between 24 and 68%. The involvement is frequently ostial and proximal, and is also often bilateral, usually with coexistent stenosis of the perirenal aorta. Dilative and aneurismal lesions in the renal arteries are rare. NSAA is a common cause of RVH in India.

Figure 1 A 10-year-old boy with Takayasu's arteritis. Flush abdominal aortogram in anteroposterior (A) and lateral (B) projections shows diffuse significant disease of suprarenal and juxtarenal abdominal aorta with poststenotic dilatation of infrarenal abdominal aorta. There is also ostial and proximal tight stenosis in the celiac, superior mesenteric, right and left renal arteries. Also, note the enlarged artery of Drummond supplying collateral circulation from inferior mesenteric artery to superior mesenteric artery territory.

Chugh et al²³ studied the causes of RVH in India and reported that NSAA was responsible for 61%, fibromuscular dysplasia for 28% and atherosclerosis for 8% of the patients. Celiac and superior mesenteric arteries (SMA) are also commonly involved in this disease (11 to 28%), mostly by stenocclusive lesions.^{8,21,22} The inferior mesenteric artery is usually spared and provides an important collateral network (the marginal artery of Drummond) in patients with SMA obstruction (Fig. 1). The obstructive lesions in the mesenteric circulation are usually clinically silent and rarely, if ever, present with intestinal angina or mesenteric vascular ischemia due to abundant collateral supply. This is despite the fact that the perirenal segment of the aorta is frequently diseased in these patients. The involvement of the visceral arteries is usually ostial and proximal with involvement of the aorta around their origins showing coexistent lesions. Dilative lesions are uncommonly seen in the abdominal aorta, but are distinctly rare in the visceral branches. Similarly, aneurismal involvement of the visceral branches is rare.

ETIOLOGY

The exact etiopathology remains unknown. The pathologic basis for this disease is a vasa vasorum in the adventitia of large and medium-sized arteries.²⁴ Proposed triggering mechanisms for this inflammation are multifactorial and debatable. Genetic factors and infective agents, as well as autoimmune mechanisms are thought to play a role.²⁴ Among infections, tuberculosis may have a role due to its high incidence in clinical studies in patients with NSAA,^{25,26} high incidence of tuberculosis in patients with NSAA in autopsy series,²⁷ an association of tuberculin test positivity in many patients, and heightened immune response to mycobacterium tuberculosis antigens among these patients. It has been postulated that this disease is caused by an immune response after the human host is exposed to mycobacterium tuberculosis bacterial heat shock protein (HSP).²⁸ This HSP is a major immunogenic component of mycobacterium tuberculosis and the expression of this protein is shown to be strongly induced in the aortic tissue by enhancing cytotoxicity of infiltrating lymphocytes. Aggarwal et al²⁸ have reported high levels of antibodies to tubercular antigens, especially HSP, thus suggesting a role of mycobacterium tuberculosis in the pathogenesis of NSAA. Sagar et al²⁹ have found significant blast transformation in response to purified human aortic antigen suggesting an autoimmune mechanism. Purified protein derivative also evoked variable response suggesting that though autoimmunity may be responsible, the antigen might not necessarily be mycobacterium tuberculosis. More recently, viral infection is being investigated as a trigger of vasculitis. The influence of genetic factors is supported by reports of familial occurrence of this disease, different clinical manifesta-

tions in different geographical regions and consistent association seen with specific HLA antigens and geographical variation.³⁰⁻³² In Japan, 16 families with familial Takayasu's arteritis have been reported.³³ In India, Mehra et al³⁴ studied 104 patients and suggested an association of this disease with human immune response genes, namely HLA-B5 as well as its serological subtypes, B 51 and B52. In HLA-B52 positive patients, aortic regurgitation, ischemic heart disease and pulmonary infarction are more common. Renal artery stenosis is reported more frequently in HLA-B39 positive patients. The HLA association is thought by some to strengthen the argument in favor of an autoimmune pathogenesis. Judge³⁵ noted high levels of gamma globulins, raised erythrocyte sedimentation rate (ESR), leucocytosis, arthralgia, and antiaorta antibodies in patients with NSAA. The role of autoimmune hypothesis is strengthened by its association with other autoimmune disorders and the presence of auto antibodies (anti-endothelial cell antibodies).^{36,37} The predominant involvement of females has prompted investigators to study the role of sex hormones. Urinary estrogens were elevated in 80% of the patients (16 of 20 patients) as compared with healthy controls in one study.³⁸ Overall, the most widely held opinion regarding its etiopathology is that this disease probably occurs due to an autoimmune reaction to the vessel wall in response to an unknown antigen (probably infectious) in genetically predisposed individuals in certain specific, but as yet unknown environmental settings and perhaps in a specific hormonal milieu.

DIAGNOSTIC CRITERIA

The diagnosis requires correlation of clinical, radiologic, and biochemical findings. The criteria for diagnosis include the presence of (1) symptoms caused by ischemia of the central nervous system (CNS), upper extremities, or kidneys; (2) fever, absent or decreased pulses, bruits, and fundoscopic findings; and (3) increased erythrocyte sedimentation rate and presence of C-reactive protein.³⁹ Angiographic findings considered diagnostic of NSAA include a spectrum of changes ranging from minimal intimal irregularity to typical rat-tail narrowing, complete obstruction, or aneurysm formation in the involved vessels. Involvement of the aorta and/or at least two medium-sized branches is considered essential for diagnosis. Conditions such as Burger's disease, Kawasaki's disease, syphilis, Behçet's disease, tuberculosis, giant cell arteritis, collagen vascular disease, developmental anomalies (such as coarctation of the aorta, Marfan's syndrome), atherosclerosis, thromboembolism, and congenital vascular malformation should be excluded.⁴⁰

The disease is characterized by an early phase marked by nonspecific constitutional symptoms and signs such as arthralgia, fever, fatigue, headaches, rashes,

and weight loss. In the late occlusive phase, ischemic symptoms in the involved vascular territories predominate. The presence of active vascular inflammation may include aggravation of clinical features, aggravation or appearance of new angiographic lesions, or presence of abnormal serological tests showing increased levels of acute phase reactants, such as the ESR, C-reactive protein, or antistreptolysin O (ASLO) titers. These may be present alone or in combination. The presence of an active disease has important therapeutic implications. The outcome of various revascularization techniques is adversely affected by the presence of active disease. Hence, it is important to identify clinical remission before advocating endovascular or surgical revascularization to treat the complications of vascular inflammation. The National Institute of Health (NIH) has described "active" disease if there is fresh onset or progression of at least two of the following features⁴¹:

1. Signs and symptoms of vasculitis or ischemia (including claudication, feeble or absent pulses, differential blood pressure in extremities, bruits, or carotidynia)
2. Raised ESR
3. Angiographic abnormalities
4. Systemic symptoms such as fever, polyarthralgia, or polymyalgia

Overall, the clinical and biochemical markers remain poor predictors of clinical activity. Surgical biopsy specimens from patients with clinically inactive disease have shown histologically active disease in as many as 44% of the patients.⁴² No known serological test is able to supplant vascular histopathology in determining disease activity.³ In one study, 61% of patients with remitting disease showed new lesions on angiography, thus emphasizing the need for more reliable accurate markers for disease activity.³⁴

IMAGING

Recently, noninvasive imaging techniques, including duplex sonography, computed tomography (CT), and magnetic resonance imaging (MRI), have been used for the detection of active disease. High resolution B-mode ultrasound can detect intimal-medial thickness (IMT) with or without obstructive stenosis (Fig. 2). An increased IMT may suggest the presence of an active disease.⁴³ We have observed that this is a more reliable marker of clinical activity than the above biochemical parameters. MRI and CT have also been used to demonstrate mural involvement. Whereas unenhanced CT scans may show a high density wall of variable thickness in the aorta or its branches along with calcification, helical CT angiography may show enhancement of the thickened aortic wall in patients with an active inflammation (Fig. 3). The thickened wall can show enhancement with low attenuation ring on delayed phase scanning.^{44,45} These mural changes correlate with disease activity and have been shown to decrease on follow-up after clinical remission.⁴⁶ Late phase shows luminal changes, which can be contiguous in ~80% cases and skipped in 20%. Active and inactive disease can be coexistent in around 11% cases. Isolated branch vessel involvement can be seen in 5% cases.²⁰ MRI can show subtle wall thickening in early cases. T2-weighted images may show bright signal due to edema in and around the inflamed vessel (Fig. 4). During the acute phase, enhancement of the aortic wall and periadventitious soft tissues can also be observed (Fig. 5).⁴⁷ It has been suggested that contrast-enhanced MRI may be more sensitive than serological markers of clinical activity in this disease. Overall, these MR criteria are not highly sensitive, but are highly specific of disease activity.⁴⁷ It has also been reported that sensitivity of T2-weighted imaging in the detection of active disease seemed to be inferior to that of contrast-enhanced T1-weighted imaging. There is emerging

Figure 2 Longitudinal B mode sonogram of left mid-carotid artery shows markedly increased intima-media thickness (between calipers) and narrowed lumen.

Figure 3 (A) Computed tomography (CT) angiogram in arterial phase at the level of carina shows increased mural thickness of ascending as well as descending thoracic aorta. (B) CT angiogram in delayed phase shows diffuse mural enhancement of aorta suggesting active disease.

evidence that aortic wall thickness by itself may reflect activity of the disease.⁴⁸ In this study, most patients with inactive disease had a wall thickness of <4 mm and most of those with an acute or chronic active disease had a wall thickness of 5 to 7 mm.

Intravascular ultrasound techniques have shown thickening of the vessel wall and altered echogenicity of the media, adventitia, and periarterial tissues in patients with active disease.⁴⁹ The [fluorine-18]fluorodeoxyglucose positron emission tomography ([F-18]FDG PET) images coregistered with enhanced CT images have also been shown to demonstrate the distribution and inflammatory activity in the aorta, its branches (Fig. 6), and the pulmonary artery in patients with active disease. The intensity of accumulation has been shown to decrease in

response to therapy.⁵⁰ Further, increased incidence of myocarditis has been reported in patients with active disease suggesting that presence of myocarditis may be an indicator of active disease.⁵¹ Overall, serologic markers along with the above imaging techniques or endomyocardial biopsy may be useful in assessing the disease activity more reliably and assessing its response to therapy, thereby, helping in timing of the revascularization procedures.

TREATMENT

The goals of therapy in NSAA include the control of clinical activity by pharmacologic treatment with steroids and/or immunosuppressive therapy, restoration of

Figure 4 T2-weighted axial magnetic resonance image at the level of the diaphragm shows increased mural thickness and signal intensity of the aortic wall suggesting active disease.

Figure 5 T1-weighted precontrast (A) and postcontrast (B) axial magnetic resonance images in the same patient and at same level as in Fig. 4 show circumferential mural thickening of the descending thoracic aorta (A) with marked postcontrast enhancement (B).

blood flow to the stenosed vessel by surgical or endovascular techniques, pharmacologic control of blood pressure (BP) and supportive management. Some form of revascularization is necessary to relieve ischemia secondary to a hemodynamically significant stenosis in the visceral artery. Surgical treatment can be offered in the form of a bypass graft, excision of segment and replacement graft, patch angioplasty, and end-arterectomy among others. This repair is recommended in the “burnt-out” phase of the disease when further progression is unlikely.⁵² The complexity of pathologic changes in the wall of the aorta and its branches, widespread nature of this involvement and long length of the stenosis often extending into the renal hilum or within the mesentery make surgical revascularization technically difficult. Further, these young patients tend to outgrow the bypass grafts over time. There is also a

high prevalence of graft occlusion or aneurysm formation at the treatment site.⁴² Cumulative incidence of anastomotic aneurysms at 20 years ranges between 12 and 14%.^{53,54} Fields et al reported the outcome of surgery in 42 patients. Eleven (26%) patients required 15 graft revisions; five of whom had an active disease at the time of initial operation. All early revisions (< 1 year) were in patients with active disease. By Kaplan-Meier analysis, they found freedom from revision at 5 and 10 years was 100% in patients with quiescent disease not requiring steroids (group I, $n = 5$, 12%), 95% and 81% in patients whose disease was quiescent on steroids (group II, $n = 24$, 57%), 57% in patients with active disease on steroids (group III, $n = 7$, 17%), and 33% in patients with active disease and no long-term steroids. They observed that patients with active disease were more likely to require revision or develop progressive

Figure 6 [fluorine-18]fluorodeoxyglucose positron emission tomography computed tomography ([F-18]FDG PET CT) scans shows active Takayasu's arteritis involving abdominal aorta (arrow) and iliac arteries.

symptomatic disease at another site.⁵⁵ Taketani et al⁵⁶ reported overall cumulative survival and event-free survival rate at 20 years of 62.3% and 58.4%, respectively. They also reported serious long-term complications in the form of anastomotic aneurysms, congestive heart failure, cerebrovascular accident, graft deterioration, abdominal aortic aneurysms, and renal failure. Reddy et al⁵⁷ reported a redo surgery rate of 20% for stenosis or anastomotic aneurysms among those. Due to these reasons, nonsurgical revascularization techniques have been increasingly used in the treatment of this disease.

We accept patients with visceral arterial involvement for treatment by endovascular techniques if they have systemic hypertension uncontrolled by single-drug therapy and angiographic evidence of at least 70% stenosis in the renal artery with a pressure gradient of >20 mm Hg; or a clinically manifest mesenteric vascular ischemia in the presence of a focal, hemodynamically significant mesenteric artery stenosis; in the setting of clinically inactive disease with a normal ESR (<20 mm in first hour) and stable intimal-medial thickness (IMT) in the carotid artery. The only exceptions to the above approach include patients presenting with pulmonary edema or severe left ventricular dysfunction. In these cases, we perform endovascular revascularization even in the presence of an active disease as an emergency salvage. In patients with severe uncontrolled hypertension, blood pressure (BP) is maintained by intravenous infusion (IV) of nitroprusside during the 24-hour preceding angioplasty. Patients are treated with aspirin (150 mg) and clopidogrel (75 mg) for 3 days before the angioplasty. Clopidogrel (75 mg) is continued for 3 months if a stenting is performed. Aspirin (150 mg) is continued life-long. Heparin (100 IU/kg body weight) is given intravenously during the procedure. BP medications are withheld for 24 hours after the procedure, except for antihypertensive medication if BP is >160/100 mm Hg. Informed consent for the procedure is obtained. The femoral route is preferred. In difficult situations, such as an acute downward angulation of the involved artery or nonavailability of the femoral route due to concomitant obstructive disease, a brachial approach is used. At the beginning of the procedure, arterial access is secured by placing an arterial sheath in the femoral artery in each side of the groin. Subsequently, a high-flow pigtail catheter is positioned in the abdominal aorta just above the origin of the renal arteries for continuous pressure measurements and diagnostic digital subtraction angiography (DSA). The diseased renal artery is selectively catheterized and the transstenotic pressure gradient is measured. The angiographic catheter is then replaced by a commercially available appropriate-sized balloon catheter by using the standard exchange technique. The diameter of the involved vessel is measured and a same-sized balloon catheter is used for angioplasty. The balloon is inflated using an inflator 3 to 5 times,

for up to 45 seconds each, until the balloon's "waist" has disappeared or decreased substantially. Alternatively, angioplasty is performed by positioning a preshaped guiding catheter at the ostium of the involved renal artery for the coaxial introduction of a guidewire and catheter. The lesion is then crossed and dilated by using an over-the-wire or monorail technique. In lesions where a branch vessel originates or is involved in the stenosis, a kissing balloon technique is employed using a coaxial approach. To avoid the risk of arterial rupture, we do not use oversized balloon catheters in patients with mild residual stenosis or transstenotic pressure gradients. Electrocardiography (ECG) and BP are monitored continuously throughout the procedure. Immediately after the procedure, transstenotic pressure is measured and a diagnostic angiogram is obtained to assess the adequacy of angioplasty (Fig. 7). If there is an obstructive dissection or a recurrent ostial stenosis, a stent placement is considered. For planned stenting, pretreatment with clopidogrel (75 mg once daily) is desirable, beginning 3 days before angioplasty. Alternatively, a single dose of 300 mg of clopidogrel is given, in patients in whom a bail-out stenting is performed. Subsequently, oral clopidogrel (75 mg daily) is continued for 3 months after the procedure. During the procedure, a preshaped renal guiding catheter is positioned at the ostium of the diseased renal artery over an exchange guidewire placed in a secure distal location. The selection of the diameter and length of the stent is based on the angiographic morphology of the involved artery. It is advisable to give sublingual nifedipine (5 to 10 mg) or an intraarterial bolus of trinitroglycerin (100 to 200 μ g) in the renal artery before stent placement. The stent is positioned across the lesion and released by inflating the balloon at the desired inflation pressure for up to 30 seconds. Various stent designs are available, but balloon-mounted stents are preferred. A check angiogram is obtained at the end of the procedure to assess the adequacy of stent release. Intravascular ultrasound is useful in defining the endpoint of intervention. Angioplasty or stent placement in the aorta, the celiac and superior mesenteric arteries is performed by a similar technique. Most patients experience an intense, transient backache during balloon inflation, often accompanied by a transient fall in the BP. This subsides soon after balloon deflation. If this finding persists, an obstructive dissection should be suspected and treated by stent placement, if present.

Angioplasty is considered technically successful if (1) the arterial lumen after angioplasty has <30% residual stenosis, (2) the arterial lumen is at least 50% larger than its pretreatment diameter, and (3) the pressure gradient is <20 mm Hg and has decreased at least 15 mm Hg from the pretreatment gradient. The clinical result of angioplasty in the treatment of hypertension is judged as follows: (1) cure (normal blood pressure after the procedure without antihypertensive drug therapy),

Figure 7 (A) Digital subtraction angiography shows a tight ostial left renal artery stenosis with a guidewire across the lesion. Note the guiding catheter positioned at the ostium for coaxial balloon angioplasty of the stenosis. (B) Postangioplasty check angiogram showing a good end result with no significant limiting dissection flap.

(2) improved (at least 15% reduction in diastolic pressure or a diastolic pressure <90 mm Hg with the patient taking less antihypertensive medication than before the procedure), and (3) failed (no change in BP after the procedure). All patients cured or improved are considered to have benefited from angioplasty. Follow-up examinations include BP and medication evaluation 1 day, 1 week, and 4 to 6 weeks after treatment, and then at 6-month intervals. Follow-up angiograms are performed in patients with recurrence of hypertension and in whom contralateral nephrectomy of a poorly or nonfunctioning kidney for residual hypertension is planned. Angioplasty is repeated if restenosis is detected.

OUTCOME

We have treated 276 patients with renovascular hypertension secondary to NSAA by interventional radiologic techniques over a 14-year period. These included 264 renal arteries in 193 patients, and 88 aortas in 83 patients. Among the renal arteries, technical success was achieved in 96% procedures. The stenosis decreased from 87 ± 6 (range, 70 to 100) % to 11 ± 11 (range, 0 to 40) %, and the pressure gradient fell from 95 ± 22 (range, 30 to 140) mm Hg to 9 ± 8 (range, 0 to 30) mm Hg ($p < 0.01$). Clinical benefit was seen in 91% patients and included cure in 32% and an improvement in 68% of them. The drug requirement for control of hypertension decreased from 3.9 ± 0.5 (range, 2 to 5) to 1.1 ± 0.9 (range, 0 to 3), the systolic BP improved from 181 ± 16 (range, 150 to 220) to 136 ± 25 (range, 110 to 210) mm Hg, and the diastolic BP fell from 115 ± 10 (range, 90 to 126) to 86 ± 16 (range, 60 to 116) mm Hg

($p < 0.01$). The complications included a groin hematoma in eight, transient renal artery spasm in seven, and renal vein injury requiring surgery in one patient. In addition, an obstructive dissection was seen in two patients, both of whom were successfully treated by stent placement. The follow-up period ranged from 3 to 104 (49 ± 22) months. Remodeling at the angioplasty site with further angiographic improvement was seen in most patients who underwent repeat angiography. Restenosis was seen in 17% lesions, all of whom were successfully retreated. The cumulative 5-year patency rate was 67%.

The outcomes of endovascular interventions in the mesenteric arteries are less rewarding. Due to the presence of diffuse lesions and increased wall thickness, the stenosis responds less well to balloon angioplasty. We rarely treat these lesions because even though they are commonly present, these are largely asymptomatic. When symptomatic, most lesions are long, often occlusive and not well suited for endovascular management. Among those with suitable angiographic morphology, the luminal stenosis and transstenotic pressure gradients are difficult to abolish as the stenosis often does not respond to multiple high pressure balloon dilatations. Even after initial successful angioplasty, restenosis rate is high.

It has been traditionally reported that NSAA involves all layers of the vessel wall.^{7,58} Its histopathology is characterized by inflammatory changes, with marked tissue destruction and connective tissue proliferation initiated at the junction of the media and adventitia or the outer layer of the media. There is an end-arteritis obliterans or onion skin-type fibrosis in the

vasa vasorum. Thickening of the intima results from an increase in the ground substance and proliferation of connective tissue.^{7,39,58,59} Underlying chronic inflammation, extensive periarterial fibrosis, thickening, and adhesions combine to produce tough, noncompliant, and rigid vessel walls. In view of these features, the stenotic lesions resist prolonged, repeated mechanical distension before responding to balloon dilatation. In addition, the risk of arterial tear or rupture would be high if the vessel were overdistended during angioplasty. Multiple, prolonged balloon inflations are usually necessary to obtain a substantial decrease in the stenosis. Most patients experience an intense, transient backache during balloon inflation, often accompanied by a transient fall in the BP. This subsides soon after balloon deflation. If this finding persists, an obstructive dissection should be suspected.

The results of renal angioplasty in this disease have been reported by many authors. Most of them concern a single case or a small group of patients. Dong et al⁶⁰ reported 30 patients. Of these, the lesion was associated with nonspecific arteritis in 22 patients. The procedure was successful in treating hypertension in 86% of them. Complications were encountered in seven patients (excessive bleeding in three, pseudoaneurysm needing surgery in one, occlusion of the renal artery in two, and dissection of the renal artery in one). Kumar et al⁶¹ reported the results in 9 patients, with clinical success in 55%. Procedure-related complications occurred in 33% of cases. Tyagi et al⁶² performed renal angioplasty in 35 patients. Of them, nonspecific arteritis was the cause in 31 cases. Clinical benefit was seen in 92% cases. Complications were not reported.

We have observed that the use of an angled hydrophilic guidewire reduces the risk of complications related to vessel spasm and perforation. The overall restenosis rate after a technically and clinically successful angioplasty in the presence of clinically inactive disease is low. We have also observed that the ostial stenosis, residual stenosis of >30% and residual pressure gradient of >10 mm Hg after angioplasty, coexisting juxtadiaphragmatic aortic stenosis, and reactivation of the underlying disease predispose to restenosis. In this clinical setting, even though an ostial stenosis is more likely to restenose, the restenosis is usually postostial and shows a good long-term result following successful repeat angioplasty. Overall, renal angioplasty is safe and effective in treating hypertension in this disease with encouraging follow-up results and a low complication rate. The underlying disease produces specific technical problems, but the technique can be suitably modified to successfully overcome them in most cases. We recommend the use of this treatment method in suitable cases.

As this disease usually affects young patients, primary stenting is not advisable for many reasons. First, the procedure is technically demanding in view of the

small access vessels making use of conventional hardware difficult to navigate to the diseased site, the frequent presence of vessel spasm during manipulations resulting in difficult stent selection and placement, the presence of coexistent perirenal aortic stenosis making stent positioning a challenging task, and the aorto-ostial location and long length of the stenosis often extending up to the renal artery bifurcation providing insufficient proximal and distal landing zones for stent placement. Second, the tough nature of the stenosis often precludes elimination of balloon waist and results in incomplete stent expansion even at high pressures, resulting in residual stenosis and creating a high risk of future significant in-stent restenosis. Third, the uninvolved segments of the arteries outgrow the stented segments over time, resulting in an iatrogenic stenosis difficult to manage nonsurgically. Fourth, the risk of restenosis remains high due to the likelihood of exacerbation of disease activity, development of myointimal hyperplasia over time, and the small diameter of devices used in view of the small arteries in these young patients. When it happens, restenosis in the stented artery often resists balloon angioplasty and is very difficult to manage. We have observed that even the cutting balloons do not offer much help in this treatment. Last, stenting in the renal arteries often precludes future surgical revascularization as the stent often extends and covers the extrahilar segment of the renal artery and provides little space for distal anastomosis of the graft. Even if the stent is removed at surgery, the resultant intimal changes make the region unhealthy and unsuitable for grafting. For these reasons, stenting should be reserved as a bail-out option for complications of angioplasty in this disease.

Until recently, it was felt that this disease was characterized by skip areas of involvement. The findings of recent studies, using cross-sectional imaging techniques, suggest that NSAA involves a continuous length of the vessel, producing mural and luminal changes in some areas, and only mural changes in the intervening segments.^{49,63} This observation has important therapeutic implications. The site of surgical reconstruction or balloon positioning in percutaneous transluminal angioplasty (PTA) is based on the demonstration of angiographically normal adjacent segments. The results of cross-sectional imaging suggest that there are extensive wall changes even in angiographically normal areas. The unpredictable outcome of PTA and surgical revascularization, in our opinion, is caused by the placement of a bypass graft or the balloon catheter within the diseased segments and not from normal to normal vessel segment. In this regard, intravascular ultrasound may be useful in guiding the interventional procedures.

Endovascular reconstruction is rarely performed for aneurismal disease in this clinical setting. There are no published reports of this treatment. In the past 22 years, we have performed only one endovascular

reconstruction for an infrarenal aortic aneurysm caused by NSAA. This is largely due to the fact that in most situations, the aneurysm typically involves the perirenal segment of the aorta with associated involvement of the visceral arteries, making endovascular reconstruction impossible. The presence of extensive mural involvement in the angiographically normal segment also contributes to the unsuitability for stent-graft placement as an adequate proximal landing zone free of disease is rarely available. The segment above the aortic bifurcation is also usually not large enough to accommodate the gate of the stent-graft. In view of these reasons, these patients are usually managed by reconstructive surgery. Aneurismal disease involving the visceral or renal arteries is rare and, when necessary, is treated by surgery for the same reasons.

CONCLUSIONS

Overall, interventional radiologic techniques, including angioplasty, stenting, and endovascular reconstruction are useful in the management of selected patients with visceral arterial involvement in NSAA. Judicious case selection and a proper understanding of the technical complexity of the procedures are essential for their optimal utilization in this clinical setting. Disease activity should be assessed before accepting patients for treatment by endovascular methods.

The natural history of this disease is better understood today, advances in imaging have made some impact in detecting clinical activity, the drug treatment of active disease is evolving, and longer-term outcomes of surgical and nonsurgical revascularization have validated an aggressive management of these patients. Despite these developments, NSAA remains an enigma as the etiopathogenesis is still not established, the course of the disease is unpredictable, reliable markers of activity remain elusive, and the optimal treatment strategy is, as yet, not validated. There is some evidence that in selected patients who are refractory to treatment with steroids and/or immunosuppressive therapy, antitumor necrosis factor therapy may be associated with remission, facilitating dose reduction or discontinuation of prednisolone and other immunosuppressive therapy.⁶⁴ Further research needs to evaluate this option. Importantly, research to identify a noninvasive marker of disease activity with high sensitivity and specificity will be the key to devising an optimal management strategy and monitor the response to therapy in the future. This will eventually change the way we treat these patients. There is a case for a randomized controlled trial to evaluate the best form of revascularization for treating stenooclusive lesions in this disease. Overall, the best therapeutic success can only be achieved by addressing both the inflammatory and the myointimal proliferative components of NSAA. New drugs that target refractory

disease and intimal hyperplasia, as well as drug-eluting balloons or biodegradable stents, need to be studied for possible utility as adjuncts to present treatments.

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