Long-term experience in patients undergoing endovascular revascularization procedures for symptomatic Takayasu arteritis (RCD code: I-3A.1)

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Abstract
Takayasu arteritis (TA) is often manifested by a prolonged limb claudication, renovascular hypertension or a sudden ischemic stroke (IS) or myocardial infarction (MI) occurring in young adults. The study aimed to assess the long-term outcome in patients with TA referred to endovascular revascularization procedure (PTA).

Methods. The study group comprised 20 patients with TA (19 women, 1 men), at the mean age of 45.3±6.6 (range 30–52) years at the time of the first diagnosis of an arterial stenosis. In 70% of patients significant stenosis or occlusion affected more than one major arterial territory. Significant coronary stenosis was observed in 8(40%) patients. All patients were assessed for the prevalence of cardiovascular risk factors, inflammatory activity (hs-CRP, white blood count: – WBC) and the incidences of restenosis (RS), cardiovascular death (CVD), MI, IS/TIA or symptomatic lesion progression at follow-up (SLP).

Results. A total of 28 PTAs were performed as a result of the initial evaluation, including 11 subclavian or innominate, 6 carotid, 8 renal, 1 vertebral, 1 coronary and 1 PTA of the abdominal aorta. During the follow-up period of 98 ±28 months (range 12–165 months), CV events occurred in 3(15%) patients, including 1(5%) CVD, 1(5%) IS, and 1(5%) IM. SLP was observed in 11(55%) patients in 17 previously non obstructed arterial locations. 14 of these lesions required PTA. Significant RS in at least one revascularized artery concerned 11(55%) patients and was observed in case of 13 previously performed PTAs; 11 of those lesions required re-PTA. Recurrent RS was noted in 4 patients. Conclusions. In patients with TA, RS and SLP rates are high, thus the follow-up of these patients is crucial. PTA is a valuable alternative to surgery for patients with TA. JRCD 2013; 1 (5): 8–13

Key words: Takayasu arteritis, endovascular revascularization, cardiovascular events, restenosis, lesion progression, long-term outcome

Introduction
Takayasu arteritis (TA) is a rare form of vasculitis involving the walls of the aorta and its main branches, leading to occlusive disease or aneurysm formation in the affected arteries. The annual incidence of TA is estimated at 1–3 cases per million population in Europe [1]. The pathology most commonly affects women under the age of 40 years. Typical clinical presentation includes general symptoms like weight loss, night sweats, weakness, easy fatigue, fever and anemia [1,2].

Beside constitutional symptoms, patients with TA typically present the signs of organ ischemia caused by narrowing of the aorta, and its main branches like: limb claudication, renovascular hypertension, renal insufficiency, dizziness, visual disturbances, chest pain and in some instances even myocardial infarction or ischemic stroke [3,4,5,6].

TA is usually treated with corticosteroids and/or immunosuppressants, however, the relapse rate is high. As steno-occlusive disease of the arteries progresses, these patients are frequently referred to vascular or endovascular specialists due to ischemia-related symptoms [1,2,7]. Young age of patients and inflammatory etiology of this chronic disease may suggest a different course and long-term results of revascularization procedures in this group.

The present study aimed to assess the long-term outcome in patients with a diagnosed TA who underwent percutaneous transluminal angioplasty (PTA) for a significant arterial stenosis or occlusion.
Methods

This retrospective study comprised 20 consecutive patients (19 women) with TA in the mean age of 45.3 ± 6.6 years (range 30–52 years) at the time of the first diagnosis of an arterial stenosis, referred to our department for endovascular revascularization between 2001 and October 2013.

In each case the diagnosis of TA was made using ACR criteria [8]. Consultant rheumatologists and clinical immunologists were included in the diagnostic process. The above mentioned experts conducted the anti-inflammatory pharmacotherapy and referred patients for percutaneous procedure when indicated.

All patients were assessed for the inflammatory process activity by evaluation of the high-sensitivity C-reactive protein (hs-CRP) level and white blood count (WBC). Current treatment status and the prevalence of cardiovascular risk factors were also assessed. Clinical characteristics of the studied group as well as lesion location are presented in Table 1.

In each patient the arterial occlusion extent was initially assessed on the basis of presenting symptoms, physical examination including pulse evaluation, blood pressure readings on both arms and auscultation for arterial bruit presence.

The location and grade of arterial stenoses was then assessed in detail by duplex ultrasonography (Toshiba Aplio SSD 5500), computed tomography angiography (Siemens Somatom Definition Dual Source), and confirmed when indicated by invasive angiography (Coroscop Siemens), were the lesions were visualized in at least 2 views and a quantitative assessment of the stenosis grade was performed with the use of Quantcor QCA V2.0.

The assessment involved the following arterial territories: aorta, aortic arch branches and abdominal aorta branches. A given arterial location was considered affected if at least 70% of lumen reduction of a corresponding vessel was documented. On the whole, only 6 patients (30%) had significant stenosis in one arterial territory, whereas 14 (70%) presented significant stenosis in at least 2 arterial territories (Table 2).

Symptomatic, significant stenoses were referred to PTA after careful clinical evaluation, consultation with a vascular surgeon and a neurologist when indicated. The indications were in concordance with the international cardiovascular societies guidelines on peripheral artery disease, despite the fact that those documents focus mainly on atherosclerosis and with the policy of other centers experienced with revascularization in TA [6, 9, 10, 11].

On the whole, 28 PTA’s were performed as a result of the initial evaluation. Six (30%) patients were subject to more than one procedure as a result of the initial evaluation. An overview of performed procedures is presented in Table 2.

8 patients underwent PTA of the subclavian or innominate artery (SA/IA) due to severe upper limb claudication and symptoms of the posterior fossa ischemia; 3 of them underwent bilateral SA/IA PTA.

2 patients during the PTA of SA/IA underwent simultaneous procedures: 1 vertebral artery PTA and 1 left main coronary artery PTA.

6 patients after stroke or TIA with critical carotid stenosis were qualified by an independent neurologist for carotid artery stenting.

7 patients with drug-resistant renovascular hypertension underwent renal artery PTA, including 1 patient who underwent two procedures – a successful PTA of the right renal artery and an unsuc-
cessful recanalization attempt of the occluded contralateral artery. It was the only unsuccessful PTA of the 28 performed procedures (3.6%). Among the patients who were subject to renal PTA, 4 had a critical arterial stenosis to a solitary functioning kidney.

In addition, 1 patient was referred to PTA of the stenosed abdominal aorta due to intense lower limb claudication.

All endovascular procedures were performed on dual antiplatelet therapy (Aspirin 75mg/d and clopidogrel 75 mg/d or ticlopidine 2 × 250 mg/d) administered for at least 3 days prior to PTA. During the procedure, standard doses of unfractionated heparin were administrated. Aspirin was then recommended indefinitely and clopidogrel or ticlopidine for 3 months following the PTA.

The majority of angioplasties were performed via transfemoral access through a guiding catheter or a long guiding sheath of 6–8 F in diameter. One case of a renal artery PTA was performed via transbrachial route and one case of recanalization of an occluded SA was accomplished via simultaneous transfemoral (8F guiding catheter) and transbrachial (6 F guiding catheter) approach.

The technique of the procedure was as follows: after obtaining a vascular access by means of the Seldinger technique, a guide wire introduced through a guiding catheter or a guiding sheath was passed across the lesion. Then, whenever technically feasible, direct stenting was performed. In cases where the lesion could not be crossed with a stent, a predilation was done prior to stenting.

Carotid, SA/IA or renal artery PTAs were performed according to the protocols described in detail previously [12,13,14]. Self-expandable stents were placed in carotid arteries and in the middle or peripheral portions of subclavian arteries. Among the studied patients balloon expandable stents were deployed in the proximal segments of the subclavian and innominate arteries, as well as in the renal arteries. Angioplasties of the common or internal carotid arteries were performed with the use of the neuroprotection systems. The PTA of the left main coronary artery in one patient was performed with a drug eluting stent placement. The PTA of the vertebral artery in another patient was performed with a coronary bare metal stent implantation. And finally, one patient underwent a balloon angioplasty of the abdominal aorta. Optimal result of the procedure was defined as a residual stenosis of <30% of the lumen diameter with gradient across the lesion <10 mm Hg.

**Follow-up**

Clinical and ultrasound assessment was performed 6 and 12 months after the procedure and then at yearly intervals. The mean follow-up time was 98 ±28 months (range 12–165 months).

The incidences of cardiovascular (CV) events: CV death, myocardial infarction (MI), ischemic stroke (IS) and incidences of revascularization for a symptomatic disease progression were recorded. CV death was defined as a fatal IS, fatal MI, and any cases of a sudden or unexpected death unless proven as non-cardiovascular on autopsy. IS had to be documented by a neurologist to ensure a reliable diagnosis.

The disease progression was defined as development of a new stenosis of ≥70% with occurrence of symptoms requiring revascularization, in the location with prior stenosis of <50%.

Restenosis was defined as recurrence of at least 50% lumen reduction within the stent and adjacent 5 mm segments on either side of the stent.

**Statistical analysis**

Continuous variables were presented as mean ± one standard deviation (SD), categorical variables were expressed as frequencies and percentages. Means of the analyzed parameters across groups were tested with the Analysis of Variance (ANOVA) test. Frequencies were compared by the Chi-squared test for independence.

The potential factors that might be associated with CV-event, RS or SLP risk were identified with the univariate analysis.

The Kaplan–Meier CV event-free, SLP and restenosis free survival curves were constructed.

Statistical analyses were performed with the Statistica 6.0 software; p-value <0.05 was considered statistically significant.

**Results**

A total of 28 PTAs were performed as a result of the initial evaluation (Table 2).

Technical success was achieved in all procedures, except one unsuccessful unilateral renal artery recanalization.

The 30-day periprocedural complication rate was 2/28 procedures (7.1%). No deaths MI or IS were observed. Among the complications was a case of a minor hemorrhage to a previously infarcted brain area with self limiting symptoms and good clinical outcome, that occurred after recanalization of an occluded SA in a patient with concurrent bilateral carotid artery occlusion. The second complication was an occlusion of the right branch of an implanted in the past aortofemoral Y graft, during a simultaneous PTA of the subclavian and the left main coronary artery, performed through the left femoral approach. Due to a preserved collateral circulation to the affected limb and no signs of ischemia the patient was managed conservatively with continuous unfractionated heparin infusion as recommended by a consultant vascular surgeon.

During the follow-up CV events concerned 3 patients (15%). Among those, one patient died as result of a pulmonary embolism, one had a non-fatal IS and one non-fatal MI. Furthermore, two patients died from a non-cardiovascular cause. The Kaplan–Meier CV event-free survival at 1-, 3- and 5- years was respectively 95%, 87%, and 87% (Figure 2A).

SLP concerned 11 (55%) patients and it was observed in 17 previously non obstructed arterial territories i.e. 7 carotid, 3 iliac, 2 subclavian or innominate, 2 mesenteric arteries, 2 coronary, and in 1 renal artery. Of these, 14 lesions required revascularization. The Kaplan–Meier SLP-free survival at 1-, 3- and 5- years was respectively 81%, 37% and 28% (Figure 2B).

Significant RS affected 11 (55%) patients and was observed in case of 13 out of 42 (30%) all-performed PTAs (including 28 PTAs following the initial evaluation and another 14 PTAs carried out as a result of the disease progression). Eleven lesions required repeated PTA. At this step, 2 lesions were managed by stent implantation.
Long-term experience of endovascular revascularization in Takayasu arteritis

and 9 with balloon angioplasty including 4 with the use of a drug eluting balloon (DEB). Of these eleven, the further follow-up 4 cases were again complicated with RS. This time 2 stent implantations and 1 balloon angioplasty were performed; the forth patient after an unsuccessful attempt of percutaneous recanalization of an occluded subclavian artery was referred for carotid-subclavian bypass surgery. In one patient RS recurred for the third and then for the fourth time. Every time successfully managed with PTA. Presently, the patient is free of symptoms. The Kaplan–Meier primary restenosis-free survival was 88%, 66% and 49% at 1-, 3- and 5- years (Figure 2C). Secondary stent patency rate was 90% at 5 years.

Patients with cardiovascular event, RS or SLP consistently differed significantly from those with an uneventful observation only in the initial white blood count (11.4 ±1.9 vs. 8.6±2.8; p = 0.022, 10.4 ±2.6 vs. 8 ±2.7; p=0.031, 10.6 ±2.3 vs. 7.7 ±2.7; p = 0.039; respectively).

Discussion

The present study focuses on the endovascular revascularization outcome and long-term prognosis in patients with TA.

Significant predominance of female patients in our study is in concordance with other reports [15,16,17]. However, most of cohorts described in literature are younger [15,16,17,18]. There are few registries of patients with TA with a relatively later presentation [6,18]. A similar age characteristics was observed in another two European studies. In an Italian cohort of patients with TA, the mean age at onset was 40 years, while in a French cohort the mean age at the time of the arterial procedure was 45 years [6, 19].

The main cause of morbidity and mortality in the course of TA are progressive intimal thickening, advancing obstruction of the arteries or aneurismatic formation, which are the complications of the inflammatory arterial wall injury. Thus, great effort is put to restrain the inflammation as a the first line of therapy. Glucocorticosteroids are the mainstay in immunosuppressive treatment [20], however the disease relapses or steroid dependence is frequent in TA [16]. In such cases, pharmacological treatment requires use of the adjunctive or alternative drugs like azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil or monoclonal antibodies use: antagonists of TNF-alfa (infliximab), soluble IL-6 receptor (tocilizumab) or CD20 (rituximab). The preferred combination of drugs largely depends on the individual centre experience.

Although, numerous anti-inflammatory drugs are at hand, the nature of TA is progressive and often drug-resistant, requiring multiple changes of pharmacological regimens [16]. What is more, the immunosuppressive treatment should be conducted with respect to the inflammatory activity, however CRP and erythrocyte sedimentation rate (ESR) assessment in TA can be misleading [21]. For example, in the Cleveland Clinic Foundation study, the levels of ESR and CRP were within the normal limits in 20% of patients with clinically active disease [15].

Due to the unsatisfying effectiveness of the contemporary pharmacological treatment of TA, as well as frequent delays in diagnosis, the disease usually progresses to a stage were arterial wall damage results in a significant arterial stenosis or occlusion which causes symptomatic ischemia of the supplied organs. In the present study,

Figure 1. Innominate artery and left subclavian artery angiography in 52 years old women, who underwent coronary artery bypass grafting 3 months earlier (please note, panel A – sternal clips after open heart surgery – white arrow) and bilateral aorto-iliac grafting at the age of 40 years of age. Panel A – ostial tight stenosis of the innominate artery (red arrow). Panel B – mid-subclavian artery stenosis (yellow arrow), involving ostia of the left vertebral and left internal mammary artery. Please note – wash out of the contrast agent related to the flow reversal in the left vertebral artery consistent with subclavian steal phenomenon.
At the time of presentation to our Department, 70% of patients with TA had already multiple arterial involvements.

At this stage, revascularization of the artery either by PTA or surgery plays the pivotal role [22]. Previously, surgery with bypass grafting was in advantage as compared to PTA in terms of long term patency. For instance, in the CCF study, after a 3-year follow-up period, preserved vessel patency was observed in 68% of cases after surgical intervention and in 25% after PTA [15]. Similar results were obtained by Saadoun et al., who observed 5-year arterial complication-free survival rates of 60% following the surgery versus 49% following PTA [6]. Of those, 85.7% of the observed complications were restenosis or thrombosis, the rest being bleeding and stroke.

Presently, results of endovascular treatment have much improved in patients with TA probably due to elective stent implantation and greater experience in procedure technique. In our study, we observed a Kaplan–Meier restenosis-free survival following PTA at 1, 3 and 5 years of 88%, 66% and 41%, respectively. This results were comparable with the results of surgery in the above mentioned reports [6,15]. In a Korean study by Kim et al., restenosis was seen in 10% of cases after the mean follow-up of 34 months [23]. Sharma and Gupta performed 264 renal PTAs in TA patients, and observed a 5-year patency rate of 67% [24].

Furthermore, the management of RS has became more feasible, due to the possibility of prompt detection of RS with non-invasive diagnostic modalities such as: Doppler ultrasonography, CT or MRI angiography and a possibility of a successful RS treatment with a repeated percutaneous intervention [25]. In many cases re-PTA involves the use of a cutting balloon, a drug eluting stent or a drug eluting balloon [12,26,27].

This technologically advanced diagnostic workup, also enables quick identification of progressive lesions, which cause new ischemic symptoms. They are quite a frequent finding and in our present study they concerned more than a half of patients and were observed in 17 previously non-obstructed arterial territories. Of these, 14 lesions required revascularization. The Kaplan–Meier SLP-free survival at 1-, 3- and 5- years was respectively 81%, 37% and 28%. Higher progression rate was also noted by other authors [15,17].

Patients with TA are at risk of an accelerated development of atherosclerosis [6,28,29]. Endothelial damage caused by active inflammation can be augmented by the overlapping dyslipidemia, diabetes, hypertension or disadvantageous lifestyle factors [30,31]. Traditional cardiovascular risk factors were commonly observed in our group of patient with TA. Therefore, lifestyle modifications, together with optimal medical therapy leading to appropriate atherosclerosis risk factors control as well as anti-inflammatory treatment seems to be a rational approach with respect to cardiovascular events reduction.

The statistical analysis of the collected data performed to identify factors related with the long-term outcome after PTA in TA patients, showed that the only risk factor related to future cardiovascular events, RS or SLP was the initial white blood count. Thus, multivariate analysis was impossible to perform. This finding is in agreement with the conclusion drawn by Saadoun et al. that active inflammation at the time of revascularization, defined as ESR >30mm/h and CRP >6mg/L, increases the likelihood of cardiovascular complications in the follow-up [6].

Thus, considering significant occurrence of drug resistance and relapses of ischemia related symptoms in TA, revascularization is vital in the long term management of many patients and is an important adjunct to pharmacotherapy.

**Conclusions**

Multifocal arterial involvement concerns majority of patients with TA. Follow-up of patients undergoing PTA appears to be of utmost importance as the rate of restenosis and development of
new stenoses is high. We conclude that PTA is a valuable alternative to surgery for patients with TA with a low periprocedural complication rate (7.1% in our study) However, restenosis rate is still relatively high.

References