

A critical reappraisal of the treatment modalities of normal appearing thoracic aorta mural thrombi

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Abstract: Mural thrombus in non-atherosclerotic or aneurysmatic thoracic aorta is a relatively uncommon entity. Currently there is no consensus on the appropriate therapeutic algorithm of its management. We aim to present the current knowledge on the treatment of thoracic aorta mural thrombi (TAMT) in minimally atherosclerotic vessels and we hope that the juxtaposed discussions will shed light on the uncharted waters regarding this rare syndrome. The MEDLINE/PubMed database was searched for publications with the medical subject “aortic mural thrombus” and keywords “thoracic”, “embolism”, “normal vessel”, “minimally atherosclerotic vessel” or “treatment”. We restricted our search to English language, till January 2017. The electronic literature search yielded 23 reports that were deemed appropriate for further analysis. Anticoagulation is the standard of care for the treatment of the thrombus whereas surgical and interventional treatment seems to be related with increased mortality and lower recurrence rates. TAMT treatment is controversial. Anticoagulants are the mainstay of treatment but surgery seems to gain ground in several settings as an only therapy or a combined treatment modality. More data are needed on the role of novel oral anticoagulants and endografts.

Keywords: Thoracic aorta; mural thrombus; minimally atherosclerotic; normal-appearing; endovascular, anticoagulants

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Introduction

Thoracic aorta mural thrombus (TAMT) in the absence of atherosclerotic or aneurysmatic disease is characterized as “cryptogenic” and represents a relatively uncommon entity. Although the cause of aortic thrombus is idiopathic in many clinical situations, pro-thrombotic conditions such as primary polycythemia vera (1), antiphospholipid antibody syndrome (2), hypercoagulable states (2-5), malignant diseases (infiltration of aortic wall, paraneoplastic

syndrome due to malignancy in visceral organs) (6,7), primary endothelial disorders or even iatrogenic causes (intra-aortic balloon pumping) (4,6,7) have also been reported. In addition, heparin-Induced thrombocytopenia (HIT) (7), hyperhomocysteinemia (6,8) and familial dysfibrinogenemia (6) have been suggested as well.

The first case of TAMT was published in 1967 (9). Since then, few case reports or cases series of patients with “cryptogenic” thrombus are available in the literature (10-13). Advanced

imaging modalities, such transthoracic echocardiography (TTE), trans-esophageal echocardiography (TEE), and the computed tomography (CT)/magnetic resonance imaging (MRI) have increased the diagnostic accuracy of this entity and can partially explain the increased number of cases diagnosed the recent years (10,14,15).

Currently there is no consensus on the appropriate therapeutic algorithm of managing this entity. Factors such as the presenting symptoms, the age and performance status of the patient but also thrombus-related characteristics such as the location and the morphology seem to be crucial for the design of any therapeutic plan.

We aim to present the current knowledge on the treatment of TAMT in minimally atherosclerotic vessels and we hope that the juxtaposed discussions will shed light on the uncharted waters; it is to be hoped that some global insights will emerge.

Methods

The MEDLINE/PubMed database was searched for publications with the medical subject “aortic mural thrombus” and keywords “thoracic”, “embolism”, “normal vessel”, “minimally atherosclerotic vessel” or “treatment”. The search was conducted both on basis of the MeSH tree and as a text search. We restricted our search to English language, till January 2017. We sought to review all updates on the subject after the introduction of endovascular surgery in the treatment armamentarium.

Definitions

In our review, we searched all the cases of “cryptogenic” aortic mural thrombus. As “cryptogenic” was defined the thrombus attached to the aortic wall in the absence of any atherosclerotic or aneurysmatic aortic disease and a cardiac source of embolus. The thrombus could be either sessile (eccentric or concentric thrombus with no free floating component) or pedunculated (with a free-floating intraluminal segment of variable length). We restricted our search only in type II thrombus (localized in descending thoracic aorta (DTA), distal to left subclavian artery up to celiac artery), a classification that has been recently proposed by Verma *et al.* (16). Moreover, symptomatic was defined the patient who has experienced embolization either to the viscera circulation or most commonly the upper/lower extremities.

Results

The electronic literature search yielded 23 reports that were presented in *Table S1*.

The role of the characteristics of the thrombus

The etiology of TAMT is not clear. Factors such as young age, smoking, family history of atherosclerotic disease, malignancy, hypercoagulable state, primary endothelial disorders or even iatrogenic causes may be crucial for the appropriate treatment modality (5,13,21,30,37-39). Moreover, the morphological (sessile *vs.* pedunculated) and dynamic (mobile/floating *vs.* fixed) properties of the thrombus, the size of the thrombus, the length of the aortic involvement and the site of thrombus could play a role on the embolic phenomena and they deserve special attention to defend this clinical situation. The most common site of thrombus consistently reported in almost all cases is the zone between the distal aortic arch and DTA (74%) without evident cause followed by the abdominal (14%) and the ascending aorta (12%) (16). Embryologic defects at the aortic isthmus and shear, bending attributed to aortic trauma during blunt chest injuries have also been reported (5,30,40).

So the appropriate management ranges from anticoagulation to surgery (open/endovascular) keeping in mind the aforementioned factors and the patient’s general health status.

Anticoagulation as standard of care

Anticoagulation has been proposed as the primary modality of treatment by several authors with complete resolution of aortic thrombus, thus favoring a non-surgical approach (3,6,13,14,28). However, more than 25% of the patients experienced secondary aortic surgery to treat recurrence of peripheral arterial embolization or persistence or recurrence of aortic mural thrombus. Recurrent embolization significantly increases the risk of major amputation and the life-threatening visceral ischemia (16,21). The proposed anticoagulant treatment is still unclear. Some authors published their experience using unfractionated heparin followed by lifelong anticoagulants (coumadin derivatives) in case of hypercoagulable states or malignant diseases. On the other hand, aspirin was maintained only in cases without hypercoagulable/malignant states and normal findings on follow-up CT aortography (16). The duration of oral

anticoagulation is not clear either. This discrepancy in the literature varies from short duration until the symptoms resolve to lifelong (18,41-43). In a review of 23 cases, anticoagulants achieved complete thrombus resolution occurred in 74% of the cases (11,13,20,22,26,35).

The role in thrombolysis in the treatment of TAMT

Minimally invasive options such as catheter aspiration/systemic or catheter-directed thrombolysis and thrombectomy using an aortic balloon catheter have been described with varying success rates (10,44). Although, the main complication of this approach was the high risk of distal embolization during the procedure itself and the no reliability of complete removal or exclusion of thrombus (10,44). Reber *et al.* (10), discussed the underestimated potential of embolic events after thrombolysis due to the liberation of thrombi into the bloodstream and thus causing massive embolization. Similarly, a recent study (17) reported a case of massive distal embolization and death after streptokinase treatment in a patient with TAMT.

Surgery as the last resort of treatment in TAMT

Surgical treatment is reserved for patients who fail to respond in anticoagulants. This method has the advantage that the aortic wall could be evaluated during the procedure, which may be of diagnostic utility in this relatively unknown entity. Surgical options include thrombectomy with or without resection of the minimally atherosclerotic plaque, with repair of the aorta using either Dacron or polytetrafluoroethylene (PTFE) graft (17). Another study (19) suggested that the surgery should be considered for non-responders after 2 weeks of anticoagulation with heparin on therapeutic doses. Additional to the failed anticoagulant treatment, mobile thrombi, large thrombi and recurrent embolisms have been proposed as indications for surgical approach (45). However, the surgical options are not complication-free with a reported mortality of 2.6% (19) and perioperative complications ranging from 28.9% to 71% (45,46). This was the main reason why some investigators do not consider operative management of aortic thrombus as first-line management (25,31).

Endovascular treatment as a new tool in the therapeutic armamentarium

Endovascular stenting has been recently suggested as

a therapeutic option for TAMT (23,24,27,29,30,32-34,36,47). Several publications reported their results with decrease of the size of residual thrombus and recurrent embolization in comparison to anticoagulation alone (27,29,34,36). Another benefit of the endovascular approach is the fact that it facilitates peripheral embolectomy through the same surgical access. In addition, fewer perioperative complications in comparison to open surgical thrombectomy have been reported (40). The selection of the appropriate stent for exclusion of TAMT has also been described in the literature with the bare metal stents (BMS) and stent grafts (SG) to be the most common. BMS are characterized from low radial force and a closed-cell design to be effective for TAMT lesions. Closed-cell stents have a theoretical advantage of preserving flow to the arteries supplying the anterior spinal cord and lowering the risk of spinal cord ischemia (16).

The presence of symptoms and its role to therapeutic plan

Owing to rarity of the TAMT, no definitive consensus on treatment for symptomatic and asymptomatic patients exists. In symptomatic emboli anticoagulation is indicated, not necessarily accompanied by surgery (16). When appropriate, endovascular approach seems to be feasible and safe. In cases of non-favorable thrombus location and size, open approach should be considered after taking into consideration the increased related early mortality and morbidity rates. In asymptomatic or patients with small thrombi, surgical or endovascular treatment should be avoided. Anticoagulation therapy, without surgical procedures has shown good outcomes (20,44).

The factor of age and the treatment choices

TAMT is likely an underestimated problem and should be suspected in those patients with peripheral arterial emboli and no identifiable cause (10,48,49). This is particularly true in younger patients with an established hypercoagulable state and a history of smoking. In these patients TAMT can be considered as a variant of atherosclerosis and characterized by pure and local clot formation (12). The diagnostic work-up of these patients should include a combination of imaging studies such as TEE, CT angiography (CTA) to thoroughly evaluate the heart and entire thoracic aorta. On the other hand, in elderly patients TAMT is suspected due to the presence of extensive atherosclerosis that can generate thrombus formation,

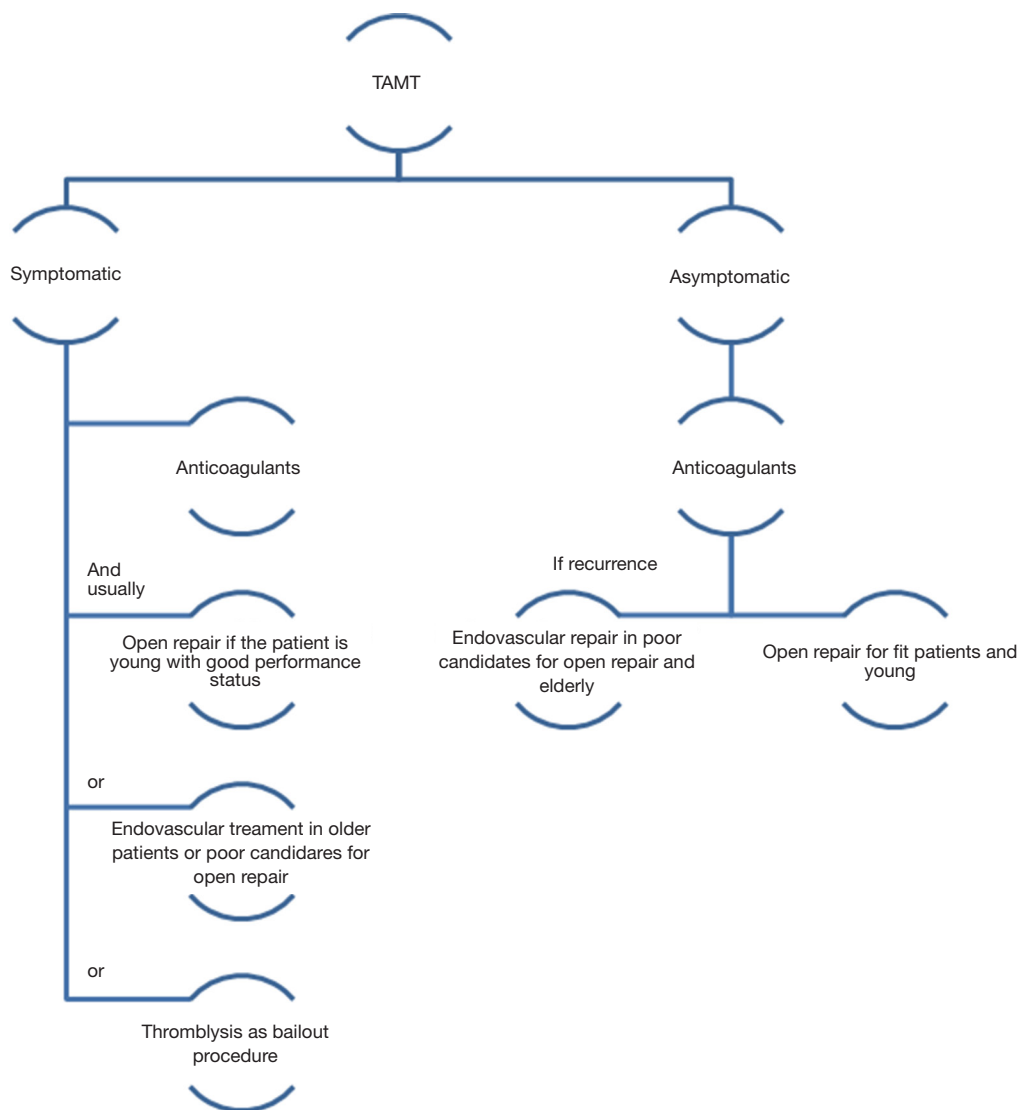


Figure 1 Proposed algorithm for the treatment of TAMT. TAMT, thoracic aorta mural thrombus.

which can liberate distal emboli. *Figure 1* illustrates the proposed algorithm for the treatment of TAMT.

Discussion

TAMT in normal or minimally atherosclerotic aorta is a rare entity with potential dismal outcomes due to the generation of multiple or massive distal emboli (1-6). Nevertheless, even with the expanding availability of advanced diagnostic modalities (CT, TEE, MRI etc.), that have increased the sensitivity in detecting TAMT the last few years, the condition is today still very sporadically

observed.

Because of its low incidence and thus, the lack of well-designed studies, there are not clear and valid guidelines on the treatment of TAMT. To date, anticoagulation should be considered as the standard of care in TAMT (19,28). There are reports of thrombus resolution with anticoagulation therapy (28,50,51) but its value is not validated with long-term results. The main drawback of the anticoagulants is the relative high recurrences varying from 26.4% to 50% (19,28,52,53) and a tendency for distal (limb) emboli (53). On the other hand, the role of antiplatelets as a therapeutic or recurrence-prevention modality is not well-established

(19,28). Of interest would be the evaluation of novel oral anticoagulants in this setting, but no data are available to date.

Surgical intervention (open/endovascular), as primary or adjuvant treatment, is mainly indicated in cases where conservative treatment has failed or is contraindicated. Reports of open surgical treatment of symptomatic mobile thrombus with thrombectomy only (10,52,54) or graft replacement (19), is performed through a thoracotomy (10,19,52,54) or trans-abdominally (10), with simple aortic clamping or left atrial to femoral artery bypass (55). These interventions are associated with high mortality rate (2.6–5.7%) but lower than conservative treatment alone (6.2%) (45,53). So, there is discussion about whether it is necessary to treat a symptomatic mobile thrombus by such an invasive surgical approach in generally poor-conditioned patients.

The feasibility and efficiency of endografts as treatment modality on TAMT have been recently highlighted in the literature (23,24,27,29,30,32–34,36,47). This treatment modality mandates a vascular team with a high level expertise in endovascular surgery and the availability of necessary logistic programs for the appropriate planning, sizing and accurate deployment of the stent. There are a few considerations when deciding to treat TAMT with endografts. First of all, meticulous and careful handling of wires should take place to avoid chopping the thrombus and cause distal embolization. In this frame, angiography can be used to map the affected aortic segment and design the appropriate proximal and distal landing zones of the endograft. Finally, it is crucial to evaluate the mesenteric and lower extremity vessels after the procedure (55). Unfortunately, endovascular treatment does facilitate the histological analysis of the thrombus to offer insights about its origin, including malignancy. Moreover, there were no reports found about the cost-effectiveness of this therapeutic option and a comparative study would be compulsory.

Conclusions

Treatment of TAMT is still a matter of controversy. Each available treatment modality is correlated with crucial advantages but major drawbacks. Of course, they are not mutually exclusive. Instead, it is likely that a triple therapeutic approach may be needed to best treat TAMT. Anticoagulation is the mainstay of treatment related with effective thrombus resolution but also high recurrence rates. Open surgical approach is a definite treatment linked with increase early mortality and morbidity rates. Endovascular

treatment could be an alternative to open approach with the drawback of high expenses and strict follow-up.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Summary of the findings of studies included in the present review

Author	Year	Type of study	No. of patients	Age (years)	Gender	Presence of symptoms	Comorbidities	Localization of thrombus	Diagnosis tools	Relevant concomitant disease	Anticoagulation treatment acute/chronic	Surgical therapy	Endovascular therapy	Follow-up (months)
Crutchfield <i>et al.</i> (17)	1998	CR	1	33	M	Yes	NR	Descending aorta	TEE	NR	-	+	-	NR
Hahn <i>et al.</i> (18)	1999	CS	1/6 with TAMT	67	F	Yes	Arthritis, HTN	From the posterior aortic arch to the descending aorta	CT, TEE	NR	+	-	-	2
Onwuanyi <i>et al.</i> (13)	2001	CR	1	48	F	Yes	HTN, DM, PAD	Aortic arch-descending aorta	TEE		+	-	-	1
Choukroun <i>et al.</i> (19)	2002	RS	2/9 with TAMT	mean age 49.2 (28–68) years	6 M/3 F	Yes	HTN, heavy smokers (n=6/9)	Descending aorta (n=5)	TEE/CT/MRI	NR	+	+	-	24
Bowdish <i>et al.</i> (3)	2002	RS	1/5 with TAMT	NR	NR	Yes	Asthma, DM, gout	Descending aorta	CT	Familial dysfibrinogenemia	+	+	-	2
Takagi <i>et al.</i> (20)	2003	CR	1	49	M	Yes	NR	Thoracoabdominal aorta	CT	NR	+	+	-	3
Hazirolan <i>et al.</i> (21)	2004	CR	1	52	F	Yes	HTN, DM, DVT	Descending aorta	CT/MRI	Protein S deficiency	+	+	-	NR
Mark <i>et al.</i> (22)	2005	CR	1	57	M	Yes	Smoker	Descending aorta	Thoracic aortogram, CT	Lung AdenoCa	+	-	-	9
Slabbekoorn <i>et al.</i> (6)	2006	CR	1	38	F	Yes	Smoker	Descending aorta	CT/MRI/TEE	Hyperhomocysteinemia	+	-	-	2
Piffaretti <i>et al.</i> (23)	2008	CR	1	56	M	Yes	Thymic hyperplasia, myasthenia gravis	Descending aorta	CT	Thrombophilia	-	-	+	6
Luebke <i>et al.</i> (24)	2008	CR	1	47	F	Yes	NR	Descending aorta	CT	NR	-	-	+	NR
Cañadas <i>et al.</i> (25)	2008	CS	2/3 with TAMT	47 & 52	F/M	Yes	HTN, hypercholesterolemia, smoker	Aortic isthmus	TEE	NR	+	+	-	NR
Roche-Nagle <i>et al.</i> (26)	2010	CR	1	42	M	Yes	HTN, DM, DVT	Descending aorta	TEE, CT	V Leiden mutation	+	-	-	NR
Martens <i>et al.</i> (27)	2010	CS	3	51/57/52	F/M/M	Yes	smoking/ex-alcoholic, HTN	Descending aorta	TEE, CT/CT/CT	Antithrombin III/chronic myeloproliferative syndrome/NR	+	+	+	1/NR/NR
Tsilimparis <i>et al.</i> (28)	2011	CS	8	mean age 55 (45–68) years	7/8 (F)	Yes	NR	Descending aorta	CT, MRA, TEE	Hypercoagulable disorders & malignant diseases	+	+	-	24
Giovanni <i>et al.</i> (29)	2011	CS	1/2 with TAMT	45	F	Yes	Negative medical history	Descending aorta	TEE/CTA/MRI	Uterine fibroma (F)	-	-	+	36
Morris <i>et al.</i> (30)	2011	CS	1/2 with TAMT	44	F	Yes	HTN, menorrhagia, estrogen therapy	Aortic arch & descending aorta	CT	NR	-	-	+	NR
Krishnamoorthy <i>et al.</i> (31)	2011	CR	1	63	F	Yes	HTN, rheumatoid arthritis	Descending aorta	CT/TEE	Thrombocytosis, rheumatoid arthritis	-	+	-	NR
Trindade <i>et al.</i> (32)	2012	CR	1	50	F	Yes	IBD	Descending aorta	TEE, CT	Inflammatory bowel disease	-	-	+	1
Boufi <i>et al.</i> (33)	2014	RS	10/13 with TAMT	mean age 53 (37–76) years	M (69.2%)	Yes	DM, HTN, smoking	Descending aorta (n=6)	CTA, TEE	Malignancy, steroid therapy, coagulation disorders	+	+	+	32
Lohrmann <i>et al.</i> (34)	2014	CR	1	58	F	Yes	None	Descending	CTA, TEE	NR	+	-	+	6
Maloberti <i>et al.</i> (35)	2016	CR	1	40	M	No	HTN, dyslipidaemia	Ductus arteriosus	CT, TEE	NR	+	-	-	1
Fukuhara <i>et al.</i> (36)	2015	CR	1	62	M	Yes	NR	Descending aorta	CT	Polycythemia vera	-	-	+	NR

DM, diabetes mellitus; HTN, hypertension; CR, case report; RS, retrospective study; NR, not reported; CT, computerized tomography; CTA, computerized tomography angiography; TEE, transesophageal echo; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; DVT, deep vein thrombosis; PAD, peripheral artery disease; M, male; F, female; AdenoCa, adenocarcinoma; TAMT, thoracic aorta mural thrombus.