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REVIEW

Left Ventricular Pseudoaneurysm Formation in the Context of Acute Myocardial Infarction: A Perspective Review of the Mechanistic and Clinical Implications

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ABSTRACT

Background: Coronary slow flow (CSF) is a frequently observed angiographic and clinical condition linked to various complications, including stable and unstableangina pectoris, acute coronary syndromes, hypertension, and potentially fatal arrhythmias. Semaphorin 4D (Sema4D), a recently identified type 1 transmembrane glycoprotein, has been implicated in processes such as inflammation, oxidative stress, atherosclerosis, and angiogenesis. Elevated Sema4D levels have been documented in individuals with atrial fibrillation, acute coronary syndrome, and heart failure.

Aim: This study aimed to assess the association between Sema4D levels and both the presence and severity of CSF.

Study Design: Cross-sectional observational study.

Methods: The study comprised 79 patients diagnosed with CSF and 81 healthy control subjects. Serum levels of Sema4D were measured, and coronary flow was assessed using the thrombolysis in myocardial infarction frame count (TFC) method.

Results: Sema4D concentrations were significantly higher in the CSF group compared to the control group ($p<0.001$). Notably, Serum4D levels showed a positive correlation with high-sensitivity C-reactive protein ($r=073$, $p<0.001$), mean TFC ($r=088$, $p<0.001$), and the neutrophil-to-lymphocyte ratio ($r=0.37$, $p<0.001$).

Conclusion: Sema4D may serve as a biomarker associated with CSF and could aid in identifying patients with CSF-related unstable angina.

Keywords: Acute myocardial infarction, intramyocardial hemorrhage, left ventricular pseudoaneurysm, myocardial rupture, percutaneous closure

INTRODUCTION

Left ventricular pseudoaneurysm (LV-PSA) formation in the context of acute myocardial infarction (AMI) has been regarded as a rare but potentially fatal entity, particularly in cases of a missed diagnosis.[1,2] Structurally, this form of LV-PSA has been attributed to a subtle myocardial rupture, usually in the posterobasal (or inferior) segment, which leads to the evolution of a blood-containing pericardial sac with a narrow neck.[2] In this perspective paper, we attempted to underscore certain aspects of LV-PSA in the context of AMI, as detailed below:

First, LV-PSAs can exhibit atypical presentation patterns, challenging conventional diagnostic expectations. As such, cardiologists must remain open-minded, avoiding preconceived notions or stereotypical assumptions about this potentially fatal condition. Awareness of unusual clinical manifestations is essential in real-world practice.[1] LV-PSAs may occur in atypical locations, including the apex, may appear exceptionally large, and critically, may lead to unexpected complications, such as stroke.[1]

Second, LV-PSA, mechanistically, may be regarded as a form of free wall rupture in patients with AMI. Therefore, the potential mechanisms and temporal characteristics of myocardial rupture should be considered in the categorization of various scenarios in these patients. Free wall rupture in the post-AMI setting is a highly fatal complication, possibly presenting with one of the following clinical scenarios, largely depending on the severity of the rupture (Figure 1):

1. Cardiac arrest (due to the complete drainage of intraventricular blood into the thoracic cavity),[2]

2. Pericardial effusion (without or with tamponade)

3. LV-PSA.[2]

Temporally, free wall rupture mostly commonly occurs in the subacute phase of AMI, typically resulting from progressive erosion of the infarcted segment (called histopathological type-2 myocardial rupture). In rare cases, it may present acutely within the first 24 h of AMI, particularly in patients with intramyocardial hemorrhage (IMH) (called histopathological type-1 myocardial rupture). Even more

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rarely, free wall rupture can complicate a pre-existing true aneurysm in the post-recovery phase, corresponding to histopathological type-3 myocardial rupture.[2-4] Among these, type-1 rupture is more frequently associated with cardiac tamponade and sudden cardiac arrest, whereas LV-PSAs typically develop as a sequel of type-2 myocardial rupture.[2-4] An overview of the histopathological types of myocardial free wall rupture in the context of AMI is presented in Table 1.

Third, LV-PSAs, in addition to the classical symptoms, including dyspnea and angina, may present with atypical symptoms, such as persistent cough, hiccup (due to diaphragmatic irritation), dysphagia, and dizziness (possibly due to enhanced Bezold-Jarish reflex).[2] These symptoms may be more likely in the setting of huge aneurysms and should therefore alert the clinician to fully explore the potential of LV-PSA in the post-AMI setting.

Fourth, as mentioned earlier, certain LV-PSA patterns[1] may surprisingly emerge in the acute phase of AMI (possibly due to a type-1 rupture), potentially highlighting their interesting temporal features along with the potential role of IMH in their evolution.[2] Several risk factors have been associated with the occurrence of IMH, including delayed myocardial reperfusion [with percutaneous coronary intervention (PCI) or thrombolysis], elevated glucose levels at the time of admission, smoking, and anterior AMI.[5] In this context, every effort should be made to prevent and/or manage the risk factors for IMH evolution (if any).[5] Particularly, early reperfusion with PCI and a strict control of blood glucose level should be given critical importance in the prevention of IMH.[5] Importantly, late-stage thrombolytic therapy should be avoided, as it significantly increases the risk of IMH.[2] Early LV-PSAs resulting from IMH may manifest with a secondary rise in troponin levels, either due to the rupture itself[2] or, more rarely, due to a coronary or cerebral embolism[6-8] originating from LV-PSA thrombus, or a combination of these mechanisms.

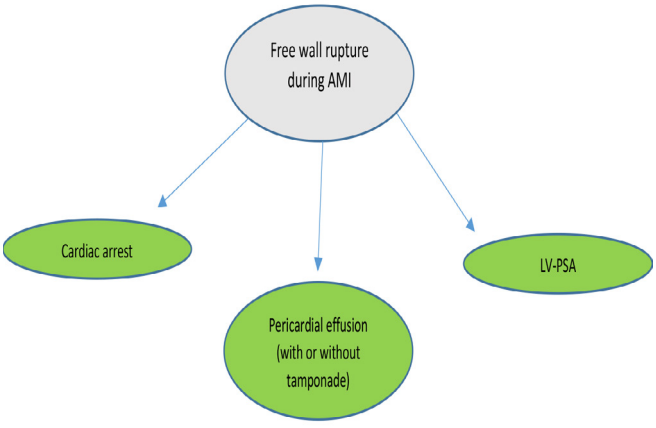

Figure 1. Clinical scenarios in the setting of AMI-related free wall rupture
AMI: Acute myocardial infarction, LV-PSA: Left ventricular pseudoaneurysm

Table 1. Histopathological types of free wall rupture in the setting of AMI[2-4]

Type-1	Free wall rupture (due to an intramural hematoma) arising within the first 24 hours of AMI
Type-2	Free wall rupture (due to the erosion of the infarct tissue) arising during the subacute stage of AMI
Type-3	Free wall rupture (secondary to the erosion of a left ventricular true aneurysm) arising in the late stage of AMI

AMI: Acute myocardial infarction

Fifth, advanced diagnostic tests, including cardiac magnetic resonance imaging (MRI) and computed tomography (CT), have proved useful in several cardiovascular disorders, particularly in challenging cases.[9,10] Similarly, cardiac MRI and CT might uncover further aspects of LV-PSA and the accompanying signs, such as IMH and absolute differentiation from true aneurysms or rare variants, including pseudo-pseudo aneurysms, thereby conferring higher diagnostic sensitivity and specificity relative to echocardiogram.[2,11-14] Therefore, we strongly advocate that any AMI patient with echocardiographic findings highly suggestive of an LV-PSA should undergo further evaluation with cardiac MRI or CT for definitive characterization.

Sixth, surgical excision has been considered as a routine management strategy of LV-PSAs owing to the extremely high risk of secondary late rupture (and sudden death) with medical therapy alone.[2,14] On the other hand, although surgical excision has been the primary management strategy in such cases, successful percutaneous closure has been previously reported in select patients using a variety of devices such as Amplatzer occluder, vascular plugs, and coil embolization.[14-17] In this context, percutaneous closure has been mostly recommended in patients at a high surgical risk.[14] However, patient eligibility (such as anatomical factors) for percutaneous closure has been the fundamental factor in this context.[14] Although percutaneous closure has been considered relatively safe compared to surgery, certain complications may arise. A systematic review of published cases (involving the analysis of outcomes for 71 patients) reported a complication rate of 9.9% following percutaneous closure (the reported complications included coil loss, residual leak, neurological deficits, and mechanical compression, all of which could be managed successfully).[14] On follow-up, a mortality rate of 8.5% was determined, largely attributable to diverse clinical conditions.[14] Interestingly, conservative management was previously reported in the context of high-risk features for radical management strategies.[14,18] The general recommendations and pitfalls regarding the management of LV-PSAs[14-17] are summarized in Table 2. Notably, LV-PSAs, in addition to being encountered in the post-AMI setting, may arise as a complication of cardiac surgery, chest trauma, or infections.[14] However, the management strategies of LV-PSAs are generally similar in such conditions.[14]

Finally, every effort should be made to prevent aneurysm rupture until definitive management can be implemented. It is well established that areas of micro- or macro-bleeding increase tissue fragility, thereby highlighting the risk of rupture, particularly in vulnerable conditions such as aortic dissection. This vulnerability may similarly apply to the setting of LV-PSAs. In the post-AMI setting, patients are often on heparin therapy for various clinical indications. However, the use of protamine for rapid heparin reversal following the diagnosis of an LV-PSA remains controversial. While protamine is routinely employed during interventional procedures, such as in cases of coronary perforation

Table 2. General recommendations and pitfalls regarding the management of LV-PSAs[14-18]

Further evaluation of LV-PSA and co-existing complications (including aneurysmal thrombus formation) through advanced imaging modalities (CT, MRI, TEE, three-dimensional echocardiogram, etc.).
Consider surgery as the first-line management strategy in all cases (particularly in the setting of urgent or emergent clinical presentation).
Consider percutaneous intervention in surgically high-risk patients or previous sternotomy with suitable LV-PSA anatomical features [narrow neck (mostly <10-12 mm), absence of cavitary thrombus].
Consider using occluder devices and vascular plugs in moderate-to-large aneurysms and coil embolization in small to moderate aneurysms. Avoid using occluder devices at sites where impingement on other cardiac structures (including bioprosthetic valves, coronary arteries, etc.) seems likely.
Percutaneous intervention may be performed through antegrade (through major veins, transapical or direct puncture of the chest wall and aneurysm) or retrograde (through major arteries) routes, largely depending on the aneurysm location, technical feasibility, and operator experience.
Consider oversizing the VSD occluder device by 5-6 mm (relative to the aneurysmal neck diameter) due to potential enlargement in the neck diameter, hypermobility, etc. In general, a cut-off oversizing value of 3.3 mm or an oversizing ratio of 1.6 is highly recommended for occluder devices.
Following the deployment of occluder devices, the partial persistence of unidirectional flow from the LV cavity to the LV-PSA cavity may result in a progressive increase in the aneurysm diameter, potentially leading to late rupture. During the intervention, this should be tested and avoided, if possible, before the device is released.
Re-evaluate anatomical and clinical features in case of failed percutaneous closure. Consider reintervention or surgery accordingly.
Consider conservative management in select cases with extremely high surgical risk and unsuitable anatomical features, particularly in the presence of small to moderate (<30 mm) and asymptomatic aneurysms.

LV-PSA: Left ventricular pseudoaneurysm, CT: Computed tomography, MRI: Magnetic resonance imaging, TEE: Transesophageal echocardiogram, VSD: Ventricular septal defect, LV: Left ventricle

or access site hemostasis.[19] However, its use has been associated with serious thrombotic complications, including stent thrombosis, intrapericardial thrombus formation (which can hinder pericardial drainage), and peripheral ischemic events.[19] In cases of established LV-PSA, many clinicians choose to discontinue anticoagulation, primarily out of concern for secondary aneurysm rupture.[18] Nevertheless, long-term anticoagulation has been reported as a relatively safe option in conservatively managed, late-onset LV-PSAs.[18] Conversely, withholding anticoagulation may predispose to thrombus formation within the aneurysmal sac,[18] potentially leading to life-threatening embolic events. Based on the limited literature available and our expert opinion, we recommend that protamine use for rapid heparin reversal, along with the discontinuation of anticoagulation may be the preferred strategy just before the emergent or urgent surgical management of high-risk LV-PSAs (extremely huge ones or those leading to severe symptoms or hemodynamic compromise, etc.) to avoid postsurgical hemorrhagic complications. In the context of planned elective interventions (surgical or percutaneous) for lenient LV-PSAs, withholding protamine and the continuation of anticoagulation until the day of intervention may be the preferred strategy for the prevention of thromboembolic complications. However, in rare instances where LV-PSA is diagnosed within the first 24 h of an AMI admission (and hence, LV-PSA might be potentially attributable to a type-1 rupture due to an IMH), protamine administration and the discontinuation of anticoagulation (in an attempt to mitigate IMH propagation and secondary aneurysm rupture) may be the preferred strategy, irrespective of the existing LV-PSA features.

CONCLUSION

In summary, LV-PSAs following AMI may present with atypical features in terms of their location (involvement of segments other than the posterobasal segment), temporal evolution (emergence in the very early or late phase), and morphological characteristics (for instance, presentation with a relatively broad neck mimicking a true aneurysm).[1,2] Advanced imaging modalities may thus be necessary to avoid a missed or delayed diagnosis of LV-PSAs,[2,11-13] particularly in the setting of atypical presentation patterns. Therefore, a high index of suspicion is thus critical for the timely recognition and management of this potentially fatal complication.[2] Protamine use and continuation or discontinuation of anticoagulant therapy should be tailored in accordance with the clinical features and management type in this context.[19] Finally, although surgery has been the preferred strategy for the management of LV-PSAs, percutaneous closure may also be considered in select cases based on previous reports suggesting high procedural success.[14-18]

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