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Status of thrombolytic therapy in patients with posterior wall MI: from an Indian prospective

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Abstract

Posterior wall MI (PMI) is known for it's electrocardiographically silent (mimicking NSTACS) and clinically malignant manifestations like LVF, cardiogenic shock, death, etc. Emergent reperfusion therapy can change outcomes in favour of patients. The most common modality of emergent reperfusion therapy in India is thrombolytic therapy. Because thrombolytic therapy is beneficial in PMI patients but not beneficial, and may even be harmful, in NSTACS patients, it should only be used after electrocardiographic confirmation of PMI. However, confirmation of PMI and decision-making about the administration of thrombolysis are tough challenges due to limitations both at the guideline and implementation levels. Therefore, a systemic review was conducted, collecting and compiling all the relevant literature to discuss those limitations, arising issues, and possible countermeasures. During analysis, we obtained useful information, as described below. The guideline mentions different possible criteria to suspect PMI from secondary ST depression in conventional right anterior precordial leads and recommends a threshold (close to normal value) criteria to confirm PMI from ST elevation in nonconventional posterior leads. The absence of uniformity among guidelines, reliability of posterior leads, credibility of R wave in V1 and V2, ECG interpretability among physicians, and accessibility of PMI in guideline (for pre-hospital thrombolysis) are the major limitations, which can create tough challenges during the administration of thrombolysis. Patients with acute PMI may miss the opportunity offered by thrombolytic therapy, developing devastating complications. whereas patients with NSTACS or late-developed PMI may get the opportunity for thrombolysis, which is not beneficial but rather harmful. Conclusion: Thrombolytic therapy can't be administered based on either non-uniform, possible ST depression criteria in the right anterior precordial lead or on non-reliable ST elevation criteria in the posterior leads. A uniform, specific criterion to confirm PMI based on electrocardiographic findings in conventional right anterior precordial leads is in deep need. The development of ECG interpretation skills among physicians, health

workers, and paramedics to detect PMI can help avoid missed diagnoses during the "golden hour." Inclusion of posterior wall MI in the guidelines for pre-hospital thrombolysis could improve the outcome of patients with PMI.

Key words: thrombolytic therapy, posterior wall MI, NSTACS, limitations, right anterior precordial lead, posterior leads.

Introduction

Posterior wall MI (PMI) is a silent and dreadful MI that accounts for one-third of all STEMI cases (1).PMI is known for its electrocardiographically silent and clinically malignant manifestations. At one end, patients with PMI electrocardiographically present with ST depression in the right anterior precordial leads secondary to ST elevation in the posterior leads, mimicking NSTACS (2). On the other hand, due to the higher prevalence of high-grade MR (3-5) caused by papillary muscle dysfunction (6-7), patients clinically manifest devastating complications such as left ventricular failure, cardiogenic shock, cardiac arrest, and so on. Early emergent reperfusion therapy has the potential to improve clinical outcomes for patients. Thrombolytic therapy is the most common modality of emergent reperfusion therapy, adapted in developing countries like India (8). Because thrombolytic therapy is beneficial in patients with PMI within the 12-hour window but not beneficial, and may even be harmful, in patients with NSTACS (9-10), it should only be used after electrocardiographic confirmation of PMI.A clear-cut and confirmatory electrocardiographic criteria to differentiate such patterns is critical when deciding whether to administer thrombolysis in PMI. Also, there should be a clear-cut recommendation for the administration of thrombolysis in patients with PMI. Guidelines mentioned different criteria for confirmation of PMI and recommendations for the administration of thrombolysis in patients with PMI. However, there are many limitations, both at the guideline and implementation levels, which can create tough challenges when making decisions about the administration of thrombolysis in patients with PMI. Therefore, a systemic review was conducted with the following objectives:

Objective;

1. To discuss the importance of thrombolytic therapy in patients with PMI in an Indian setting
2. To discuss guideline criteria for confirmation of PMI and recommendations for thrombolysis in PMI.
3. To discuss limitations of guideline criteria for confirmation of PMI and recommendations for thrombolysis in PMI
4. To enumerate the issues that arise during decision-making about thrombolysis in PMI due to the above limitations
5. To derive possible countermeasures to solve the above issues so that decision-making for thrombolysis in PMI can become easier for primary contact physicians,

Methods: A systematic search was performed using electronic databases through the Cochrane Library, Medline, EMBASE, Web of Science, and Scopus databases. The retrieval of information was accomplished by using Boolean operators to search terms and keywords such as "posterior wall MI," "thrombolysis," "guideline," and "strategy" without regard for language. All the relevant literature and guidelines on topics of interest are included. Diverse information and data were collected, compiled, and qualitatively analysed to achieve the study objectives.

Historical perspective: In 1964, for the first time in the history of myocardial infarction, Perloff, a pioneer of cardiology, provided a new recognition of PMI as an AMI and conveyed that an R wave in the right anterior precordial leads, a confirmatory electrocardiographic sign, develops secondary to a Q wave registered in the posterior leads (2). However, when the Q-wave paradigm was replaced by the STEMI paradigm, PMI was once again left in the dark due to the lack of the traditional STEMI sign on standard conventional leads. For a long time, most PMI cases were misclassified as NSTEMI due to the characteristic ST depression in the anterior precordial leads and retracted from emergent reperfusion therapy (11). However, over the next few decades, different guidelines recommended treating PMI with emergent reperfusion therapy such as primary PCI and thrombolytic therapy (12–14).

 The importance of thrombolytic therapy in PMI

Because it occurs in a small inferobasal segment of the heart, posterior wall MI is frequently underestimated.(15) Papillary muscle associated with the infero-basal segment, i.e., postero-lateral papillary muscle, is supplied by a single blood vessel, either LCX or RCA, without having any collaterals (16) and is therefore prone to ischemia-related complications like papillary muscle dysfunction or rupture (6-7). Therefore, 2/3 of patients with posterior wall MI develop acute MR (17–18) and present with life-threatening complications like left ventricular failure, cardiogenic shock, etc., leading to a higher mortality rate (21%) comparable to that of anterior wall MI (1). Emergent reperfusion therapy like primary PCI (PPCI) or thrombolytic therapy can prevent those complications. PPCI has superseded thrombolysis as a first-line emergent reperfusion therapy in patients with STEMI (STEMI equivalent) (19), though the evolution of the STEMI paradigm started with thrombolysis. Primary PCI has been shown to be superior to thrombolytic therapy in reducing short-term mortality, nonfatal re-infarction, stroke, etc. (19-20). It is also shown to be superior to thrombolysis in maintaining higher rates of infarct artery patency and TIMI flow along with lower rates of recurrent ischemia, emergency repeat revascularization procedures, and intracranial haemorrhage (19–20). As a result, in developed countries, PPCI is the most commonly used emergent reperfusion therapy. However, surprisingly, only around 1/10th of cases of STEMI receive primary PCI in developing countries like India (8). Poor health infrastructure and emergency transport system, lower availability and accessibility of primary PCI capable centres per population, lower insurance coverage and less awareness about MI among the public, and higher preference of patients for non-invasive procedures are also major causes of delay in primary PCI in India (21-22).whereas the mortality risk at one year increases by 7.5% for every half-hour delay in treatment.(23) Mortality benefit is lost when PCI-related delay exceeds 60 minutes, as per the Global Registry of Acute Coronary Events

(23). Therefore, onsite or pre-hospital thrombolysis seems to be a better option to bridge the gap for the implementation of time-bound emergent reperfusion therapy in developing countries like India. Thrombolytic therapy is equivalent to PPCI in terms of the primary endpoint (i.e., composite of death, shock, congestive heart failure, or re-infarction up to 30 days) if administered during the early golden hours (24–26). Thrombolytic therapy is also cost-effective, easily available, accessible, and administrable. As a result, it is the most commonly used (in roughly two-thirds of cases) adapted emergent reperfusion therapy in India (8).Thrombolysis is also extremely beneficial during the "golden hours" in reducing the prevalence of acute ischemic MR that arises due to papillary muscle dysfunction in patients with PMI (17).

Existing guidelines and recommendations for the diagnosis and treatment of patients with PMI

1. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

- The guideline mentions that "ST depression in two or more leads of V1-4 may indicate trans-mural posterior injury" (12).
- The guideline recommends primary PCI in patients with STEMI and ischemic symptoms of less than 12 hours' duration. It recommends thrombolytic therapy (in the absence of contraindications) as an alternative choice to PPCI when it is anticipated that primary PCI cannot be performed within 120 minutes of FMC (12). It also suggests thrombolytic therapy (in the absence of contraindications) as an acceptable emergent reperfusion therapy in patients with STEMI and cardiogenic shock who are unsuitable candidates for either PCI or CABG (12). It also mentions that thrombolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead Avr (12).
- The guideline encourages the administration of thrombolytic therapy within a benchmark time goal, i.e., within 30 minutes of hospital arrival when indicated or chosen as the primary reperfusion strategy (12).

2. AHA/ACC 2017 Clinical Performance and Quality Measures for Adults With ST-Elevation and Non–ST-Elevation Myocardial Infarction

- The guideline introduces the term "STEMI equivalent" for a rare, atypical group of ECG presentations and includes isolated PMI in the same (13).
- The guideline recommends primary PCI in patients with STEMI (or STEMI equivalent) and ischemic symptoms of less than 12 hours' duration. The guideline suggests thrombolytic therapy [within Door To Needle (DTN) time 30 min] as an acceptable alternative therapeutic strategy to primary PCI in patients with STEMI (STEMI equivalent) if primary PCI cannot be performed in a timely manner (within FMC-to-device time 90 min, including the inability to transfer the patient timely from

a non–PCI-capable to a PCI-capable hospital to achieve FMC-to-device time 120 min) (13).

3. **2017 European Society of Cardiology ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation**

- According to the guidelines, isolated ST-segment depression (≥0.5 mm) in leads V1-V3 is the most common finding in posterior wall (inferobasal) MI (14).It advises mandatory recording of posterior leads (V6, V7, and V8) for confirmation of the diagnosis of PMI in patients with ACS with above ECG finding. The guideline defines posterior wall MI as "isolated ST-segment depression ≥0.5 mm) in leads V1-V3 with ST elevation 0.5 mm) in leads V7V9" (14).
- It also recommends classifying an ECG entity as "isolated ST-segment depression in leads V1-V3" as STEMI and classifying it as part of a separate class of atypical ECG presentations requiring prompt PCI. Though the ESC guideline specifically does not mention thrombolysis in PMI, it generally recommends thrombolytic therapy (in the absence of contraindications) in patients with STEMI within 12 h of symptom onset if primary PCI cannot be performed within 120 min of STEMI diagnosis (14).
- ESC further recommends initiating thrombolytic therapy as soon as possible (most preferably in the pre-hospital setting) after a STEMI diagnosis (14).

4. **Fourth Universal Definition of Myocardial Infarction (2018) (ESC/ACC/AHA/WHF expert consensus)**

- The guideline defines acute myocardial ischemia as "new horizontal or down sloping ST-depression ≥0.5 mm or greater in two contiguous leads and/or T inversion >1 mm in two contiguous leads with a prominent R wave or R/S ratio >1" (27).
- The guideline mentions that "isolated ST-segment depression ≥0.5 mm in leads V1–V3 may indicate left circumflex occlusion and be suggestive of inferobasal myocardial ischemia (previously termed posterior infarction), especially when the terminal T wave is positive (ST-elevation equivalent); however, this is nonspecific (27)."
- It strongly recommends recording posterior leads in patients with ST-segment depression in leads V1–V3 to confirm PMI (27).
- The guideline does not suggest any specific recommendations for emergent reperfusion therapy in PMI.

5. The National Cardiovascular Data Registry (NCDR) defines isolated PMI as ST elevations in leads V7-V9 or ST depressions maximal in V1-V3, without ST elevation in other leads, which is considered a STEMI equivalent and qualifies for emergent reperfusion (PPCI or thrombolytic therapy) (28).

6. The 2009 Standardization of ECG Interpretation Guidelines defines isolated PMI as 0.05 mV of abnormal J-point elevation in leads V7-V9 or "abnormal J-point

depression of -0.05 mV in V1-V3 or -0.1 mV in all other leads" without qualification of what indicates abnormal J-point depression (29).

Limitations at the guideline and implementation level creating difficulties during thrombolytic therapy in patients with PMI

1. Absence of uniformity while defining guideline criteria; uniformity not maintained among guidelines while defining patterns of ST depression [like V1-V4 (12-13) vs. V1-V3 (14, 27-29)], isolated (12-14, 27), maximal depression in diffuse pattern (28), etc., and including components [like R wave (27) vs. no R wave (12-14, 28-29)] in guideline criteria. Therefore, none of the guideline criteria completely fits all cases of acute PMI. As a result, specific ECG patterns can be misdiagnosed as NSTEMI while strictly following a single guideline criteria. Patients may miss the opportunity for thrombolytic therapy. Secondly, disparity among guidelines, while defining criteria for PMI, increases complexity during the diagnosis of posterior wall MI. As thrombolysis can't be administered without clarity about the diagnosis, decision-making for thrombolysis may be delayed during the golden hours of PMI.

2. Suggestion of possible criteria for PMI: Guidelines provide likely or possible criteria for the diagnosis of posterior wall MI based on ST depression in right anterior precordial leads (12–14, 27). It implies that PMI can only be suspected rather than confirmed based on the characteristic ECG findings of PMI in the anterior precordial leads. A plan of action for PCI can be initiated in suspected cases of PMI based on these possible criteria and modified later after getting complete information about coronary anatomy during angiography. However, thrombolytic therapy can only be administered after confirmation of PMI from ECG findings. As a result, in order to administer thrombolytic therapy, clinicians must confirm PMI from posterior leads (12-14, 27).

3. Inclusion of the R wave (a late-developed sign) as a component in the criteria for acute PMI: Though guidelines updated criteria with evidence and facts, older recommendations of the Q wave paradigm left a deep imprint in recent guidelines. A recent guideline includes the R wave in V1 and V2 as a component in the criteria for acute PMI (27). Though Perloff was right in his view while conveying the message that the R wave in V1 and V2 is a confirmatory sign of PMI, it is a representative Q wave registered in the posterior leads (2). The ECG takes an average of 33 hours to develop (30), indicating a late-developed MI (31).Therefore, patients with late-developed MI may receive thrombolytic therapy due to the inclusion of such a component in the diagnostic criteria for acute PMI. Thrombolytic therapy can further deteriorate the hemodynamic conditions of patients due to its harmful natural complications.

4. Non-reliability of posterior leads: Many important guidelines recommend a threshold criteria for the ST elevation in posterior leads to confirm PMI. However, a non-assuring ST elevation in posterior leads does not always exclude PMI. The amplitude of ST elevation can be diminished due to damping of electrical signals arising from the posterior aspect of the

heart by the air in the lungs, the left atrium, and the pulmonary vein (32). As a result of the natural, inherent limitation of the posterior leads, a group of patients may be denied the opportunity to undergo thrombolysis. On the other hand, the guidelines fix the cut-off level for ST elevation in posterior leads at 0.5 mm, which is close to the normal value (33) Therefore, patients without PMI can have a chance to qualify as having PMI as per the criteria and get the opportunity for emergent reperfusion therapy like thrombolysis, which can be harmful for patients.

5. Lack of a clear-cut guideline for thrombolysis in PMI: In the modern era of PCI, thrombolytic therapy receives little attention, despite the fact that the STEMI paradigm is based on it. ESC Guidelines include PMI in a separate, rare group of atypical ECG conditions representing a STEMI equivalent pattern, recommending prompt PCI in a direct manner. whereas it suggests thrombolytic therapy for PMI in an indirect way while mentioning general recommendations for patients with STEMI (14). The AHA (2013) guideline suggests thrombolytic therapy in posterior wall MI in an indirect manner while mentioning the contraindications of thrombolytic therapy (12). The AHA (2017) guideline, on the other hand, includes posterior wall MI in a STEMI equivalent group and recommends thrombolytic therapy while making general recommendations (13).

Pre-hospital thrombolysis is a major emerging strategy to bridge the time gap between the onset of chest pain and primary PCI while salvaging the myocardium in a timely manner. It is found to be equivalent to PPCI in terms of the primary endpoint (a composite of death, shock, congestive heart failure, or re-infarction up to 30 days) when it is administered within the early hours of the window period (24 –26). However, the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) Guidelines, a guideline for ambulance paramedics, do not include PMI in the panel of indications for pre-hospital thrombolysis (34), despite the fact that other important guidelines 12–133) refer to posterior wall MI as STEMI equivalents or trans-mural ischemia.

6. Significant gap in guidelines implementation at the grassroots level: Despite the fact that guidelines recommend different criteria for detecting PMI based on ECG findings in the anterior and posterior precordial leads, a significant gap has been observed between the guidelines and their implementation at the grass-roots level. It has been reported that there is a lack of ECG interpretation skill among primary contacts or resident physicians to detect PMI from anterior precordial leads. A major proportion (approximately 80%) of resident doctors, health workers, and paramedics don't have an idea about the correct positioning of nonconventional posterior leads and the diagnosis of PMI based on ST elevation criteria in posterior leads (35). Emergency staff, even in cardiac centres, does not record posterior leads due to a lack of knowledge to do so (36). Only about 10% of cardiologists and emergency physicians use posterior leads on a regular basis (37). In hospitalised patients with ACS, approximately 40% of physician advice recording posterior leads (38). The recording of the posterior lead is nonconventional and therefore not practised routinely in different health care settings. Therefore, STEMI-equivalent patterns can be misinterpreted as NSTEMI patterns.

Countermeasures to prevent issues arising during thrombolysis in posterior wall MI

Due to limitations at the level of the guideline and its implementation, there is a higher chance of treating patients with PMI as NSTACS and vice versa. According to one study, 99.6% of patients with a STEMI equivalent pattern suggestive of PMI were diagnosed with NSTEMI (11).In a PCI-capable centre, such misdiagnosis may not change the clinical outcomes of patients extensively, as emergent PCI (12–14) and early PCI (39) are the recommended management strategies for patients with PMI and NSTACS, respectively, as per guidelines. While it has a broad impact on a setup, where emergent or early PCI is not available within the time frame specified by guidelines. Thrombolytic therapy remains the one and only option for emergent reperfusion therapy for patients with PMI. Patients may miss such an opportunity due to misdiagnosis or the absence of clear-cut recommendations for pre-hospital or onsite thrombolysis, manifesting devastating complications like left ventricular failure, cardiogenic shock, and ultimately death. Therefore, following countermeasures (as described below) both at the guideline level and at its implementation level can prevent such complications in patients.

1. Guidelines should provide unanimous, conventional, confirmatory criteria for the diagnosis of PMI, so that complexity during diagnosis can be avoided. As posterior leads can be falsely negative or positive in certain circumstances, they are not always the most reliable source for confirmation of PMI. A decision about the administration of thrombolysis can't be taken completely based on the finding of posterior leads. On the other hand, ischemic ST depression of any amplitude in the right precordial leads is a specific and assuring sign of PMI (40). Over time, enough evidence has accumulated to confirm that ST depression in the right anterior precordial leads is not anything other than an early electrographic sign of PMI (41-48). Therefore, guidelines should provide a confirmatory criterion based on electrocardiographic findings in the anterior precordial leads. The R wave in v1 and v2 is one of the pathognomic signs of PMI (2), but it is hardly detected during the early golden hours of PMI. However, such signs left a deep imprint on clinicians' consciences as an acute sign of PMI. Few guidelines include it as a sign of acute PMI (27), whereas other guidelines do not include it (12–14). Clarity about such an electrocardiographic sign as a component of acute PMI should be ascertained.

2. Screening 2D echocardiography can fill the diagnostic gap and confirm the diagnosis of PMI by detecting regional wall motion abnormalities (RWMA) in the postero-basal area (1). Training of residents or primary contact physicians about echocardiographic detection of RWMA can alleviate the issue to some extent. The inclusion of 2D echocardiography in diagnostic criteria can raise the sensitivity for PMI detection to 100% (1), ensuring that patients do not miss out on thrombolytic therapy in the pre-hospital setting.

3. ECG interpretation skill was found to be two times more sensitive than ST elevation criteria in detecting acute coronary occlusion (49). Therefore, it is very essential on the part of the resident or first contact physician to develop an interpretation skill to

diagnose PMI from conventional leads. Inclusion of updated guideline criteria in formal textbooks for undergraduates and postgraduates can create a trend towards the diagnosis of PMI beyond STEMI and the Q wave paradigm. Training resident physicians, health workers, and paramedics in the diagnosis of PMI from the anterior precordial lead can help to avoid missed or delayed diagnoses at the ground level. At the same time, it will improve the status of pre-hospital thrombolysis in patients with PMI.

4. Guidelines should mention a clear-cut recommendation for the administration of thrombolysis for PMI instead of mentioning it in an indirect way, so that clarity among first-contact physicians for thrombolysis in PMI can be ascertained. Guidelines for pre-hospital thrombolysis, i.e., Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidelines (34) should include PMI for pre-hospital thrombolysis so that patients will not miss the opportunity and benefits of pre-hospital thrombolysis at the grass-roots level.

Conclusion

Administration of thrombolytic therapy requires a confirmatory electrocardiographic diagnosis. Recommended nonconventional posterior leads for confirmation of PMI are unreliable in some instances. Thrombolytic therapy cannot be given to patients with PMI, relying solely on posterior leads. The use of extremely uniform, specific criteria based on electrocardiographic findings in conventional right anterior precordial leads is critical for diagnosis confirmation. The development of ECG interpretation skills among resident physicians, health workers, and paramedics regarding the diagnosis of PMI from the anterior precordial lead can help avoid missed diagnoses during the "golden hour." Inclusion of echocardiographic criteria can help confirm missed cases. Inclusion of posterior wall MI in the guideline for pre-hospital thrombolysis could improve the outcome of patients with PMI.

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