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Beyond the Culprit Lesion: Interacting Ischemic and Catecholamine-Mediated Stress in STEMI

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Abstract

ST-elevation myocardial infarction (STEMI) is classically understood as the consequence of plaque disruption, thrombotic coronary obstruction, and downstream ischemic myocardial injury. This framework remains fundamentally correct and continues to justify urgent reperfusion as the cornerstone of treatment. In some patients, however, the acute STEMI phenotype may also reflect a sympathetic stress response that occurs alongside ischemia. We hypothesize that ischemia, pain, and distress can trigger this response and that catecholamine effects may amplify myocardial stress globally or within the ischemic territory. The word "parallel" therefore describes co-occurring and interacting processes, not a proven independent injury pathway. The magnitude and clinical importance of any catecholamine-mediated contribution remain uncertain. Takotsubo syndrome offers biological plausibility for catecholamine-related myocardial dysfunction, but it is a multifactorial syndrome and does not establish the same mechanism in STEMI. A previously published retrospective series of 21 hemodynamically stable STEMI patients reported rapid symptom improvement after intravenous metoprolol before transfer. This clinically striking signal motivates our hypothesis that early beta-blockade may be underused in carefully selected, stable STEMI patients before reperfusion. The uncontrolled series cannot establish treatment efficacy, mechanism, or the prevalence of underuse: symptom relief may reflect reduced myocardial oxygen demand or concomitant care, and angiography performed later cannot establish coronary flow when symptoms resolved. Current guidance permits intravenous beta-blockade in selected, hemodynamically stable STEMI patients without acute heart failure or other contraindications, but COMMIT found no overall mortality benefit and showed fewer reinfarctions and episodes of ventricular fibrillation alongside more cardiogenic shock. Later trials differ. These findings leave uncertainty about patient selection, timing, outcomes, and mechanisms; they do not establish that trial regimens were inadequate. Future studies should test this

underuse hypothesis with contemporary utilization data and a carefully selected, guideline-bounded approach, not presume that individualized escalation improves outcomes.

Keywords

STEMI, Beta-Blocker, Metoprolol, Catecholamine Response, Takotsubo Syndrome, Myocardial Dysfunction, Reperfusion Injury

1. Introduction

STEMI is caused by acute coronary plaque disruption and thrombosis with downstream ischemia. Contemporary management therefore prioritizes urgent reperfusion, and nothing in this paper challenges that foundation [1] [2]. This hypothesis-generating paper asks whether territorial ischemia alone explains the full acute phenotype in some STEMI patients. Evidence discussed here predominantly concerns STEMI; the proposed mechanism and treatment implications should not be generalized to NSTEMI or unstable angina without direct evidence.

The practical relevance of this question includes the pre-reperfusion period for patients who first present to a hospital without PCI capability. A national analysis based on American Hospital Association survey data reported that 1739 of 4686 acute-care hospitals (37.1%) had PCI capability in 2008 [3]. In a U.S. registry cohort from 2018 through 2021, only 17% of transferred STEMI patients met the ≤120-minute first-hospital-arrival-to-device benchmark. For transferred patients, the registry defined first medical contact as arrival at the first hospital [4]. These measures describe different aspects of access and treatment time; neither establishes that beta-blockade improves outcomes during transfer.

The STEMI phenotype may include severe chest pain, sympathetic activation, electrical instability, and transiently broad left ventricular dysfunction. Some dysfunction improves after reperfusion, consistent with a mixture of irreversible injury and potentially reversible processes such as stunning, neurohumoral effects, microvascular dysfunction, and reperfusion injury [2] [5]. These observations motivate a testable hypothesis but do not establish that ischemia is insufficient to explain an individual patient's presentation.

We propose that, in a subset of STEMI patients, direct ischemic injury co-occurs with a sympathetic stress response that may amplify myocardial stress. "Parallel" here means temporally overlapping and potentially interacting; it does not imply an independent pathway demonstrated by this paper. Ischemia and pain may themselves trigger sympathetic activation, and the size and causal importance of any additional catecholamine-mediated injury remain unproven.

Takotsubo syndrome provides a biologically relevant analogy, not proof of a shared STEMI mechanism. Catecholamine involvement is a leading pathophysiologic hypothesis within a multifactorial syndrome [6]. Separately, a small retrospective STEMI series reported symptom improvement after intravenous metopro-

lol, but it cannot establish that beta-blockade relieved symptoms by suppressing catecholamine-mediated injury or that the same mechanism operates in STEMI [7]. These observations support further study, not a change in practice.

2. The Strengths and Limits of the Artery-Centered Model

The artery-centered model remains indispensable because it accurately identifies the central lesion in STEMI. Current ACS guidelines continue to frame STEMI around plaque disruption, thrombus formation, and acute coronary occlusion, and continue to prioritize rapid reperfusion [1]. No conceptual reformulation of ACS can ignore this.

Territorial ischemia explains why reperfusion is essential. Other processes—including reperfusion injury, microvascular dysfunction, inflammation, and neurohumoral responses—may also influence final left ventricular performance after infarction [2] [5]. Their presence does not diminish the causal importance of coronary occlusion or establish the mechanism of symptoms in an individual patient.

In STEMI, therefore, it may be useful to distinguish between the lesion that initiates the event and the mechanisms that shape the full syndrome. The culprit lesion remains essential. But the final phenotype may depend on additional processes set in motion at the same time.

3. Clinical Observations Suggesting a Parallel Amplifying Mechanism

Ischemia, pain, emotional distress, and abrupt hemodynamic change may contribute to sympathetic activation during STEMI. The resulting tachycardia, hypertension, diaphoresis, and increased arrhythmic vulnerability can affect myocardial oxygen demand, coronary vasomotor tone, ventricular loading, and electrical stability. These effects are biologically plausible contributors, but their independent contribution to myocardial injury in STEMI has not been quantified.

The acute autonomic response is not exclusively beta-adrenergic. Alpha-adrenergic coronary vasoconstriction may impair perfusion, particularly in atherosclerotic vessels, and alpha-adrenergic blockade has been associated with improved perfusion and function after coronary stenting in a small study [8] [9]. Vagal influences are also complex and are not uniformly antagonistic: some reflexes may produce bradycardia and hypotension during ischemia or reperfusion, while vagal engagement can counter-regulate or interact with sympathetic activity depending on the pathway and infarct phase. Vagal activation has also been linked to cardioprotective effects [10]. These mechanisms add context to the proposed response; they do not establish a distinct catecholamine injury pathway in STEMI or prove that beta-blockade modifies it.

The previously published retrospective series included 21 hemodynamically stable STEMI patients treated at a rural hospital before transfer. It reported rapid symptom improvement after intravenous metoprolol. In one case, a 61-year-old man received a total of 115 mg intravenously over 35 minutes. This was a nonstandard

regimen. The guideline-supported standard intravenous regimen for selected stable patients is 5 mg every 2 minutes for up to three doses (15 mg total), with hemodynamic and electrocardiographic monitoring; the case series cannot establish the safety of a higher exposure or support its use. The report describes symptom improvement during treatment, but pain relief could reflect reduced myocardial oxygen demand, concomitant care, or other factors. Persistent ST elevation was documented before PCI, and later angiography showed an ostial right coronary occlusion; that later angiogram cannot establish coronary flow at the time the pain resolved [1] [7] [11].

This uncontrolled case cannot identify why symptoms improved or show that the artery had opened before PCI. Reperfusion remained necessary. The observation is hypothesis-generating and should not be used to justify treatment beyond guideline-supported dosing or safety limits.

4. Takotsubo Syndrome as Biologic Support

Takotsubo syndrome is distinct from STEMI. It is a multifactorial syndrome of transient left ventricular systolic dysfunction, often with chest pain, electrocardiographic changes, and troponin elevation without a culprit obstructive lesion sufficient to explain the syndrome. Catecholamine-mediated injury is a leading pathophysiologic hypothesis, among several proposed mechanisms that include direct toxicity, adrenoceptor effects, vasomotor changes, microvascular dysfunction, and myocardial stunning [6].

Takotsubo therefore supports biological plausibility that catecholamine-related processes can contribute to myocardial dysfunction. It does not demonstrate "catecholamine excess alone" as an established mechanism, nor does it establish that the same process independently causes injury in STEMI. In STEMI, ischemia may trigger sympathetic activation, which could in turn amplify stress in an already ischemic myocardium; this remains a hypothesis.

A Hypothesis of Interacting Mechanisms in STEMI

We propose a hypothesis for STEMI in which direct ischemic injury and a concurrent sympathetic stress response may interact.

The first pathway is direct ischemic injury in the culprit-vessel territory. Severe coronary stenosis or acute occlusion reduces blood flow to the dependent myocardium, causing territorial ischemia and, if prolonged, infarction. This remains the essential initiating mechanism of STEMI.

The second proposed process is a sympathetic stress response that may affect myocardial oxygen demand, arrhythmogenicity, vascular tone, and ventricular loading. It may contribute to global dysfunction or amplify stress in jeopardized myocardium. The existence, magnitude, and causal importance of these effects in STEMI remain to be established.

The two processes are not presented as independent or equally important pathways. Coronary occlusion is the initiating lesion in classic STEMI. Ischemia, pain, and distress may provoke sympathetic activation, and the resulting catecholamine

effects could modify the clinical phenotype. The proposed amplification is possible, not established.

Final infarct size and long-term left ventricular function may be influenced by reperfusion injury, inflammation, microvascular dysfunction, and other downstream processes in addition to the initial coronary occlusion [2] [5]. This broader biology provides context for the hypothesis; it does not prove a separate catecholamine injury pathway.

5. Why Early Beta-Blockade Deserves Renewed Attention

If a sympathetic response contributes to the STEMI phenotype, beta-blockade is one potential way to modify some of its effects. Whether it changes myocardial injury through the mechanism proposed here is unknown.

The retrospective series reported symptom improvement after metoprolol but cannot determine whether this arose from reduced oxygen demand, other concurrent treatment, or a catecholamine-mediated mechanism [7]. COMMIT, which enrolled a broad acute myocardial infarction population, found no overall mortality benefit: early metoprolol reduced reinfarction and ventricular fibrillation but increased cardiogenic shock [12]. METOCARD-CNIC reported a smaller infarct size in selected anterior STEMI patients, while EARLY-BAMI did not show a clear reduction in infarct size in its broader STEMI cohort [13] [14]. Differences in patient selection, treatment timing, and reperfusion complicate comparisons. The trials leave uncertainty about clinical benefit and mechanism; they do not show that higher doses would improve outcomes.

This paper does not advocate indiscriminate beta-blockade or dose escalation. Patients with cardiogenic shock, hypotension, acute heart failure, significant bradycardia, or atrioventricular conduction disease remain poor candidates for early intravenous beta-blockade. Guideline-supported dosing and contraindications should define the boundaries for any study [1].

6. A Hypothesis of Potential Underuse in Selected STEMI Patients

COMMIT demonstrated why caution is necessary: early intravenous then oral metoprolol reduced reinfarction and ventricular fibrillation but increased cardiogenic shock, without reducing overall mortality [12]. This balance of outcomes argues for careful patient selection and monitoring, not for an assumption that the trial dose was too low.

Studies conducted in different populations and treatment settings have produced mixed findings. METOCARD-CNIC studied selected anterior STEMI patients before reperfusion, whereas EARLY-BAMI studied a broader STEMI cohort and did not show a clear infarct-size reduction [13] [14]. Differences in patient selection, timing, and reperfusion limit direct comparison and leave both the size of benefit and its mechanism uncertain.

A central hypothesis of this paper is that early beta-blockade may be underused

among carefully selected, hemodynamically stable STEMI patients, particularly before reperfusion or transfer. The 21-patient series provides a notable clinical signal that raises this possibility, but its uncontrolled design cannot show that treatment improves outcomes or that eligible patients receive it less often than appropriate. Contemporary registry data could measure treatment rates among eligible patients and examine reasons for nonuse; prospective studies could test benefit within established safety and dosing limits. This hypothesis does not support indiscriminate beta-blockade or dose escalation [1] [7].

7. The Limits of Fixed-Dose Trial Design in a Heterogeneous Syndrome

The mixed trial record should be interpreted as uncertainty about who may benefit, when treatment should be given, and which outcomes or mechanisms may be affected. Fixed-dose trials may not resolve every physiology question, but their findings do not demonstrate that their doses were inadequate or that individualized higher dosing is effective.

Further evidence should define patient selection, treatment timing, reperfusion context, and safety monitoring. Any physiology-guided strategy should remain within guideline-supported dosing boundaries until evidence supports a change.

Differences among COMMIT, METOCARD-CNIC, and EARLY-BAMI—including patient selection, treatment timing, and reperfusion—may contribute to their differing results [12]-[14]. The current record does not determine whether beta-blockade benefits a particular phenotype through the mechanism proposed here.

8. Toward Individualized Early Beta-Blockade

The clinical implication is to test, not adopt, an individualized strategy in carefully selected, hemodynamically stable STEMI patients. Any protocol should follow guideline-supported dosing limits and account for blood pressure, heart rate, heart failure status, rhythm, atrioventricular conduction, right ventricular involvement, and hemodynamic trajectory. The reported 115 mg intravenous exposure is nonstandard and cannot be used to establish safety or justify exceeding those limits [1] [7].

A future study could evaluate whether symptoms, hemodynamic status, and other prespecified physiologic measures help identify patients who benefit from guideline-supported early beta-blockade. This small uncontrolled series cannot validate dose escalation, establish an optimal dose, or show that symptom improvement identifies a catecholamine-mediated mechanism [7].

Mechanistic plausibility is insufficient to change practice. Future studies must determine whether a selected STEMI population benefits, which outcomes are affected, and what safety limits are required. Any investigation should preserve guideline-supported dosing and contraindications unless stronger evidence supports a change [1] [12].

9. Future Research Directions

This hypothesis should be tested in contemporary STEMI care without delaying reperfusion or exceeding guideline-supported beta-blocker dosing.

Retrospective cohort studies in community hospitals and transfer networks could compare stable ACS or STEMI patients who did and did not receive early beta-blockade, with careful adjustment for baseline blood pressure, heart rate, Killip class, conduction status, culprit vessel, infarct location, reperfusion timing, transfer delay, and signs of right ventricular infarction. End points could include pain relief, ventricular arrhythmias, shock, peak troponin, left ventricular recovery, intensive care unit course, and early mortality.

Prospective pilot studies could examine guideline-bounded, physiology-informed beta-blockade in carefully selected, stable STEMI patients before reperfusion. Such studies should prespecify eligibility, dose limits, monitoring, rescue criteria, and clinical outcomes, and should not infer safety from the nonstandard 115 mg exposure in the retrospective series.

Mechanistic studies would also be valuable. Biomarkers of adrenergic activation, advanced imaging of left ventricular recovery, and indices of reperfusion injury or microvascular dysfunction could help determine whether early beta-blockade modifies the possible catecholamine-mediated contribution proposed here. The goal would not be to diminish the importance of reperfusion, but to clarify whether reperfusion and adrenergic modulation together provide more complete treatment of the acute syndrome than reperfusion alone.

10. Limitations

This manuscript is conceptual and hypothesis-generating. It does not claim that catecholamine-mediated stress is an independent, dominant, or established injury pathway in STEMI. Ischemia is the initiating lesion, and urgent reperfusion remains essential. The clinical observations are small and uncontrolled; they do not establish mechanism, treatment efficacy, or safety of the reported nonstandard 115 mg intravenous metoprolol regimen.

Takotsubo syndrome provides an analogy within a multifactorial disease, not proof of the same mechanism in STEMI. Existing trials show mixed effects and clinically important safety boundaries, including cardiogenic shock. Any future strategy must remain within guideline-supported dosing and contraindications unless new evidence supports a change [1] [6] [7] [12]-[14].

11. Conclusions

In some STEMI patients, direct ischemic injury may coexist with a sympathetic stress response that could amplify myocardial stress. This hypothesis preserves coronary occlusion as the initiating lesion and reperfusion as essential treatment. The available evidence does not establish a distinct catecholamine injury pathway or quantify its contribution.

The clinical implication is to study whether carefully selected, hemodynamically

stable STEMI patients benefit from early beta-blockade given within guideline-supported dosing limits. The mixed trial findings, observational symptom reports, and Takotsubo analogy do not establish efficacy, mechanism, or safety of dose escalation. A contemporary study should define patient selection, timing, outcomes, and safety before any practice recommendation is considered.

Author Contributions

Both authors contributed to the conception of the manuscript, drafting and revision of the text, and approval of the final version.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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