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Coronavirus Disease 2019 (COVID-19) has quickly progressed to a global health emergency. The COVID-19 pandemic has affected health and economy worldwide on an unprecedented scale. Patients have diverse clinical outcomes, but those with preexisting cardiovascular disease, hypertension, and related conditions incur disproportionately worse outcome. The COVID-19 pandemic forced the scientific community to think about possible, alternative solutions to counteract the multiorgan damage by the virus. COVID-19 infection has been associated with myocardial injury, which has been implicated with more severe disease courses and even death. Remarkable efforts are being done to elaborate underlying mechanisms of myocardial injury. Due to the acuteness of this pandemic, the scientific world currently lacks randomized controlled trials in order to fully elucidate the pathophysiological mechanisms and therapeutic measures. However, there are a handful of clinical trials on the way to assess possible therapeutic targets for the treatment and prevention of this disease.

This issue of the journal focuses the impact of COVID-19 pandemic on the hospital admission and treatment strategies of acute coronary syndromes (ACS). Rahman M et al studied the impact of COVID-19 pandemic and strict lockdown on ACS admission and change in treatment policy in a tertiary referral cardiac hospital with 24 hour primary percutaneous coronary intervention (PPCI) facility in Dhaka City during last 1 year period, 6 months pre COVID era and 6 months during COVID time.

They reported overall 37.9% decline in ACS admission during COVID time. Admission of ST elevation myocardial infarction (STEMI) declined remarkably. In their analysis diagnostic and interventional procedures also showed a remarkable downward trend during COVID time as well (percentage reduction 68.9%). PPCI rate dropped dramatically in COVID time compared to pre COVID era (percentage reduction 91.7%). During COVID period number of STEMI patients treated with thrombolytics increased and number of patients undergoing PPCI decreased. Their analysis is in conformity with the other international data published in recent past in different peer reviewed journals.

Doctors are on the frontline of efforts to treat patients during this COVID-19 pandemic. Sadly many Physicians, Cardiologists and Healthcare workers in Bangladesh lost their lives to COVID-19 while in the line of duty. The death of a fellow doctor is always tragic, but to lose so many at the hands of the virus is devastating. We offer our profound sorrow and heartfelt condolences to the families, friends and colleagues of these committed clinicians who cared for patients in the most challenging of times, battling against this highly infectious and deadly virus. We owe them our gratitude, our respect, and a pledge that we will remember them.

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Management of ST elevation Myocardial Infarction (STEMI) in COVID era.

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ST-segment elevation myocardial infarction (STEMI) is a cardiovascular emergency requiring rapid reperfusion treatment. During the coronavirus disease-2019 (COVID-19) pandemic, medical professionals need to strike a balance between providing timely treatment for STEMI patients and implementing infection control procedures to prevent nosocomial spread of COVID-19 among health care workers and other vulnerable cardiovascular patients. Understanding possible physiopathological links between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and acute coronary syndromes (ACS) is of the greatest importance for the cardiologists. Moreover, the Covid-19 outbreak has put a lot of pressure on overloaded healthcare systems. All possible efforts have been made in order to give the maximum number of patients the chance to be admitted and treated in hospitals. In many countries all non-urgent procedures have been cancelled and routine clinical practice has been completely modified. In the context of an overwhelmed healthcare system, screening and elective treatments of coronary artery disease (CAD) have been underestimated, meaning dealing with ACS has become more complicated and apparently less frequent.[1]

The treatment of ACS is controversial in COVID-19 patients. In patients diagnosed with STEMI and COVID-19, the American College of Cardiology (ACC) states that while fibrinolysis may be considered in those with "low risk STEMI", defined by inferior STEMI with no right ventricular involvement or lateral AMI without hemodynamic compromise, percutaneous coronary intervention (PCI) is more commonly performed at most institutions and remains the treatment of choice. [2]If PCI is pursued, staff should don appropriate personal protective equipment (PPE), and a full decontamination of the catheterization laboratory should be performed following the procedure. For all suspected COVID-19 in the setting of non-ST elevation myocardial infarction (NSTEMI), diagnostic testing prior to catheterization is recommended; the ACC note that, in properly selected patients with confirmed COVID-19, conservative therapy may be sufficient. Patients who are hemodynamically unstable in the setting of NSTEMI should be managed similarly to those with STEMI. [2] But still now during the COVID-19 pandemic, primary percutaneous coronary intervention (PPCI) remains the standard of care for STEMI patients at PCI-capable hospitals when it can be provided in a timely manner, with an expert team outfitted with PPE in a dedicated cardiac catheterization laboratory (CCL).[3]

The growing COVID-19 pandemic caused by SARS-CoV-2 poses a severe challenge to the care of STEMI patients. On the one hand, performing PPCI—the preferred reperfusion strategy recommended by most STEMI guidelines —for a patient with unconfirmed COVID-19 status is a high-risk procedure that may expose health care workers and other hospitalized cardiovascular patients, who are particularly vulnerable if infected by SARS-CoV-2. [4-7] On the other hand, the screening and infectious control procedures required to reduce the nosocomial spread of COVID-19 may substantially delay primary PCI and negatively impact patient prognosis. [8,9] The scarcity of personal protective equipment and rapid testing for COVID-19 further exacerbates the problem, as most medical facilities could not afford to engage full personal protective equipment (PPE) for all STEMI patients with confirmed COVID-19 status.[7]

In China nation wide study reveals there were reductions in STEMI patients' access to care, delays in treatment timelines, changes in reperfusion strategies, and an increase of in-hospital mortality and heart failure during the COVID-19 pandemic. Based on the data of 28,189 STEMI patients admitted to 1,372 Chest Pain Centers in China between December 27, 2019 and February 20, 2020, the study analyzed how the COVID-19 outbreak and China Chest Pain Center's modified STEMI protocol influenced the number of admitted STEMI cases, reperfusion strategy, key treatment time points, and in-hospital mortality and heart failure for STEMI patients. The COVID-19 outbreak reduced the number of STEMI cases reported to China Chest Pain Centers. Consistent with China Chest Pain Center's modified STEMI protocol, the percentage of patients undergoing PPCI declined while the percentage of patients undergoing thrombolysis increased. With an average delay of

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approximately 20 min for reperfusion therapy, the rate of in-hospital mortality and in-hospital heart failure increased during the outbreak, but the rate of in-hospital hemorrhage remained stable. [10]The COVID-19 outbreak led to a substantial drop in the number of admitted STEMI cases as well as delays in patients' access to care. The proportion of patients undergoing PPCI decreased and that of thrombolysis increased, but the proportion of patients receiving effective reperfusion therapy remained stable. [10]

During this time, the management of patients with STEMI and COVID-19 has become a global issue, especially since preexisting cardiovascular disease is a risk factor for the presence and the severity of COVID-19. The number of people with STEMI has decreased during the pandemic and delays in the time looking for medical care have been reported. In addition, the diagnosis of ACS may have been difficult due to possible underlying myocarditis or other clinical entities. Regarding management of people with STEMI, although the superiority of PPCI over thrombolysis is well established, the notable exposure risks due to absence of negative pressure in catheterization rooms and the increased difficulty in fine manipulation on guidewires under proper protection equipment may contribute to the relatively secondary role of PPCI during the COVID-19 pandemic; thus, fibrinolytic therapy or robotic-assisted PCI in early presenting STEMI patients may have an alternative role during this period if prevention measures cannot be taken. Healthcare stuff should take the proper measures to avoid the spread of and their exposure to the virus.[11]

As there is an asymptomatic period in which infected patients are shedding the virus, those presenting as emergency STEMI could drive viral transmission to first responders and those performing PPCI. COVID-19 diagnostic tools are not sufficiently rapid yet to permit screening prior to emergency PPCI for STEMI, and while screening with CT-thorax is useful in more elective settings, it is unfeasible in a STEMI setting. As PPCI can involve cardiac arrest, a recognized 'aerosol generating procedure', it is agreed that full PPE is recommended for all those performing PPCI. Services should consider shielding members of staff at highest risk from COVID-19: those with lung conditions or those over the age of 65 years have been redeployed to non-patient-facing activities appropriately.[12,13]

A dedicated catheter laboratory is recommended by the British cardiovascular intervention Society.[12] A designated area for donning and doffing of PPE is essential; staff should observe each other to provide support in this process. All team members should have sufficient PPE with FF2 or FFP3 mask, gown, goggles and/or visor. As PPE remains scarce, some may choose to limit PPE usage to operators only. However, in the event of a cardiac arrest, team members will need to leave the cardiac catheter lab to don PPE before exposure to cardiopulmonary resuscitation (CPR) maneuvers.[12,14]

There is a recognition of two major challenges in providing recommendations for STEMI care in the COVID-19 era: 1. Cardiovascular manifestations of COVID-19 are complex with patients presenting with STEMI, myocarditis simulating STEMI presentation, stress cardiomyopathy, non-ischemic cardiomyopathy, coronary spasm, or nonspecific myocardial injury. 2. The prevalence of COVID-19 disease in the population of any country remains unknown with risk of asymptomatic spread. 3 During treatment of STEMI few things must be taken into consideration:(a) varied clinical presentations; (b) appropriate PPE for health care workers; (c) the roles of the emergency department, emergency medical system, and the cardiac catheterization laboratory; and (d) regional STEMI systems of care. 4. COVID-19 is highly contagious, with proximity-dependent spread and viability in aerosols for hours, or on surfaces for days. Infection of healthcare workers is a major concern; in Italy and Spain, 8% to 12% of those infected are healthcare workers. The use of PPE minimizes risk but does not remove it.[6,15,16]

The coronavirus disease 2019 (COVID-19) pandemic has dramatically altered the delivery of reperfusion therapy for patients with STEMI. At this crucial time, it seems prudent to re-evaluate STEMI reperfusion pathways. Preferably rapid diagnostic test (RDT) for COVID 19 should be done in all patients with STEMI. If RDT is negative case may proceed to CCL but if positive, procedures can be done in dedicated CCL. If RDT is not available in the hospital pharmacoinvasive therapy is the standard modality of treatment for all patients with STEMI.

A recent consensus statement from the Society for Cardiovascular Angiography and Interventions (SCAI), the American College of Cardiology (ACC), and the American College of Emergency Physicians (ACEP) on STEMI therapy during the COVID-19 pandemic supports the fibrinolytic therapy and pharmacoinvasive strategy , especially at hospitals without PCI-capability. [3] Some North American hospitals with PCI-capability, including the New York-Presbyterian/Columbia University Irving Medical Center, have adopted a selective fibrinolytic therapy and pharmacoinvasive strategy on a case-by case basis through a tiered approach, whereas others use it for low-risk patients.[16,17] In Canada, a pharmacoinvasive strategy has been endorsed as an alternative strategy for treating STEMI patients in circumstances where restriction in regular services exist during the COVID-19 pandemic.[18]

The key points of the Consensus Statement from the SCAI, ACC and ACEP about management of STEMI during the COVID-19 pandemic include: [2,3,5,19] (1) Two point-of-care assays have recently received Food and Drug Administration approval for rapidly making the diagnosis of COVID-19. As these tests become widely available, they should be routinely implemented in all STEMI patients to better characterize patient diagnosis and risk, optimize the treatment plan for a given patient (for AMI ± COVID-19), and guide appropriate placement within the hospital, including a dedicated cardiac catheterization laboratory (CCL) and post-procedure unit. (2) At this time, all patients requiring emergent activation of the CCL should be treated as COVID-19 possible. Given the potential risk of aerosol generation during all emergency AMI procedures, this

writing group recommends personal protection equipment (PPE) with aerosolization protection (including gowns, gloves, full face mask, and an N95 respiratory mask) for the entire CCL staff during PCI for all AMI patients during this COVID-19 pandemic. (3) PPCI is the standard of care for patients presenting to PCI centers (within 90 minutes of first medical contact). This should remain the standard of care for STEMI patients during the COVID-19 pandemic with some important caveats only in designated CCL. (4) Each PPCI center will need to monitor the ability to provide timely PPCI based on staff and PPE availability, need for additional testing, as well as a designated CCL, which will require terminal cleaning after each procedure. In the absence of these resources, a fibrinolysis first approach should be considered. There may be longer door-to-balloon times during the COVID-19 pandemic. (5) Due to the logistical issues and time delays secondary to diagnostic uncertainty of STEMI with COVID-19, direct transport of the patient to the CCL is not felt to be prudent at this time. [2,3,5,19]

Indian consensus document highlights the clinical challenges and systematic approach for the care of STEMI based on expert wisdom, and the best currently available published information and recommends : 20

* Fibrinolytic therapy provides a more rapid and logistically easier approach to reperfusion therapy may be considered (or even preferred) in STEMI reperfusion while reducing staff exposure to infection.

* Fibrinolytic is most reasonable for hospitals without PCI-capability provided contraindications for fibrinolytic therapy and STEMI mimics have been excluded

* At PCI-capable hospitals with adequate staffing and resources, primary PCI is still preferred.

* If PCI is must, dedicated Cath Lab for COVID patients is advisable.

* Postponement of non-urgent procedures to reduce demand on staff and other resources [hospital beds, PPE kits] in "stable" ischaemic heart disease patients

* Training of staff in proper PPE donning and doffing is mandatory

* Fragmentation of staff into teams, interdepartmental [Cardiology, Emergency Casualty, Anaesthesia and Radiology] coordination and cooperation's is highly desirable

* Universal precautions can mitigate risk of infection exposure and will promotes efficiency of staff and reduces stress in practice

In view of this epidemiological scenario, it is necessary to improve the management of patients with STEMI to prevent the spread of SARS-CoV-2. We will have to consider each ACS patient to be possibly COVID-19 infected. This is of outmost importance for the safety of other hospitalized patients, the hospital environment, and healthcare workers. In the absence of previous SARS-Co-V2 testing, all STEMI patients should be managed as if they are COVID-19 positive. Even while lacking substantial evidence, certain conclusions can be drawn. Namely, it appears extrapulmonary manifestations are more likely with this SARS outbreak, and clinicians should maintain a high index of suspicion for COVID-19 infection even in patients without respiratory symptoms, as delayed testing will result in increased community and healthcare worker spread.

During the COVID-19 pandemic, PPCI remains the standard of care for STEMI patients at PCI-capable hospitals when it can be provided in a timely manner, with an expert team outfitted with PPE in a dedicated cardiac catheterization laboratory but pharmacoinvasive therapy is a valid alternative to PPCI in this COVID era.

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Cardiovascular Complications of COVID-19 Infection

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The coronavirus disease of 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While systemic inflammation and pulmonary complications can result in significant morbidity and mortality, cardiovascular complications may also occur. The virus binds and enters cells through angiotensin-converting enzyme 2 (ACE2) receptors. COVID-19 can result in systemic inflammation, multiorgan dysfunction, and critical illness. The cardiovascular system is also affected, with complications including myocardial injury, myocarditis, acute myocardial infarction, heart failure, dysrhythmias, and venous thromboembolic events. Current therapies for COVID-19 may interact with cardiovascular medications.

Respiratory illness is the major cause of morbidity and mortality in these patients with the disease spectrum ranging from asymptomatic subclinical infection, to severe pneumonia progressing to acute respiratory distress syndrome. ACE2 receptors play a pivotal role in the pathogenesis of the virus. Disruption of this receptor leads to cardiomyopathy, cardiac dysfunction, and heart failure. Patients with cardiovascular disease are more likely to be infected with SARS-CoV-2 and they are more likely to develop severe symptoms. [1]Hypertension, arrhythmia, cardiomyopathy and coronary heart disease are amongst major cardiovascular disease comorbidities seen in severe cases of COVID-19. There is growing literature exploring cardiac involvement in SARS-CoV-2. Myocardial injury is one of the important pathogenic features of COVID-19. As a surrogate for myocardial injury, multiple studies have shown increased cardiac biomarkers mainly cardiac troponins I and T in the infected patients especially those with severe disease. Myocarditis is depicted as another cause of morbidity amongst COVID-19 patients. The exact mechanisms of how SARS-CoV-2 can cause myocardial injury are not clearly understood. The proposed mechanisms of myocardial injury are direct damage to the cardiomyocytes, systemic inflammation, myocardial interstitial fibrosis, interferon mediated immune response, exaggerated cytokine response by Type 1 and 2 helper T cells, in addition to coronary plaque destabilization, and hypoxia.[1-3]

Increasing data have shown a significant burden of cardiac injury in COVID-19. Up to 20% of patients in a cohort in China demonstrated cardiac injury, often associated with more severe disease. They were more likely to be older, to have acute respiratory distress syndrome (ARDS), and to experience higher mortality rates. [4]Cardiovascular disease (CVD) is a common comorbidity among patients with symptomatic COVID-19 infection. The co-existence of hypertension ranges from 35% to 57%, coronary artery disease 10% to 17% and congestive heart failure (CHF) 6% to 7%. [5-8]Cardiovascular comorbidity prevalence is likely even higher amongst those that are critically ill; one case series found a 42.9% prevalence of preexisting CHF in those requiring intensive care unit (ICU) care.9 The explanation of this association is unclear and whether COVID-19 has a specific predisposition for patients with CVD has not been studied. Notably, patients with CVD appear to be at increased risk of severe manifestations of COVID-19 disease, and 30% to 35% of COVID-related deaths have underlying CVD. [10,11]Chinese reports demonstrate an increased case fatality rate (10.5%) in those with CVD compared with a case fatality rate of 0.9% in those with no comorbidities.[12]

COVID-19 impact on the cardiovascular system will be divided into primary or secondary cardiac involvement; there is of course much overlap between the two. Primary cardiac manifestations of COVID-19 disease include arrhythmias, acute coronary syndrome (ACS), and myocarditis. Secondary cardiac involvement is usually because of a systemic inflammatory syndrome and can manifest as acute myocardial injury/biomarker elevation and heart failure. Secondary cardiac involvement is often accompanied by other evidence of end-organ damage.

Myocarditis

One of the first reports of myocardial injury associated with SARS-CoV-2 was a study of 41 patients diagnosed with COVID-19 in Wuhan, China, wherein 5 patients (12%) had a high-sensitivity troponin I above the threshold value.[13] Subsequent studies have found that myocardial injury with

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an elevated troponin level may occur in 7–17% of patients hospitalized with COVID-19 and 22–31% of those admitted to the intensive care unit (ICU).[13-15] Myocarditis has also been identified with high viral loads and mononuclear infiltrates identified on autopsy of some patients with COVID-19 .[16-17] In fact, one study suggested that up to 7% of COVID-19 related deaths were due to myocarditis.[18]The COVID-19 myocarditis generates striking ECG changes with marked and even regional ST elevation ('STEMI-mimic').

Acute heart failure and cardiomyopathy

Acute heart failure can be the primary presenting manifestation of COVID-19 infection. One study found that acute heart failure may be present in 23% of patients in their initial presentation for COVID-19, with cardiomyopathy occurring in 33% of patients. [14]Another study found that heart failure was present in 24% of patients and was associated with an increased risk of mortality. [19]Among those with heart failure, nearly half did not have a known history of hypertension or CVD. [19] It is currently unknown if heart failure is due to new cardiomyopathy versus an exacerbation of previously undiagnosed heart failure. It is important to be conscious of this potential cardiac dysfunction when administering intravenous fluids and avoid overaggressive fluid replacement. Importantly, right heart failure may also occur, particularly among those with ARDS and acute lung injury .[20,21]

Atrial Fibrillation

Based on available literature, among COVID-19 patients, AF was detected in 19% to 21% of all cases. [22-24] One study reported a prevalence of 36% in patients with cardiovascular diseases, with AF being observed in 42% of patients who did not survive. [24] In a small report, up to 75% of hospitalized COVID-19 geriatric patients had a past history of AF .[21] In patients with severe pneumonia, ARDS and sepsis, the incidence of AF during hospitalization is usually high. For instance, 23–33% of critically ill patients with sepsis or ARDS have AF recurrences and 10% develop new-onset AF. However, reliable data regarding first-diagnosed AF in patients with COVID-19 are limited. Based on case reports and small clinical studies new-onset AF varies between 3.6% and 6.7% in patients with COVID-19. [18,21,25] If dysrhythmias are associated with an elevation in serum troponin in COVID-19 patient , the clinician should consider myocardial injury, acute myocarditis, and ACS in the differential diagnosis. [21]

Acute Coronary Syndrome

Hypoxemia, increased respiratory workload, tachycardia, and hypertension may develop while the patient is maintained in spontaneous or noninvasive-assisted ventilation. Intubation may improve hypoxemia but general anesthesia causes hypotension, arrhythmias, and the need of inotropic support, triggering a vicious circle with worsening myocardial ischemia in the presence of severe coexistent coronary artery disease (CAD). This is the most likely explanation in non-ST-segment elevation (NSTEMI), the most frequent ACS observed in SARS-COV-2 patients. ST-segment elevation myocardial infarction (STEMI) patients are less common than NSTEMI patients. Anxiety, interruption of preexisting medication, and the general pro-inflammatory effect of the acute infection may explain the development of plaque rupture in patients with existing diffuse coronary disease. [26] Several mechanisms that could explain the onset of ACS related to myocardial ischemia in SARS-CoV-2 infection have been proposed. Some of them may resemble the ones identified for other respiratory infectious agents, such a pro-inflammatory state and a cytokine storm (which could cause plaque instability), or a prothrombotic state and hypoxaemia-related damage due to acute respiratory failure. The rise in troponin tracks with other inflammatory biomarkers, such as D-dimer, interleukin-6, and lactate dehydrogenase, raises the possibility that this may reflect cytokine storm more than isolated myocardial injury.[27,28]

Pulmonary and Venous Thromboembolism

Patients with COVID-19 are also at an increased risk of venous thromboembolism (VTEs). Systemic inflammation, abnormal coagulation status, multiorgan dysfunction, and critical illness are all potential contributing factors to the increased risk of VTE .[13,29,30] Studies suggest significant coagulation pathway abnormalities in patients with COVID-19, including elevated D-dimer. [29] One study of 25 patients with COVID-19 pneumonia found that an elevated D-dimer was present in all patients with a median of 6.06 micrograms/ml, with 10 patients having a pulmonary embolism (PE) diagnosed on computed tomography pulmonary angiography (CTPA). [31] Patients with confirmed PE on CTPA demonstrated a median D-dimer level of 11.07 micrograms/ml. D-dimer levels greater than 1 μg/mL were associated with an increased risk of death during hospitalization (odds ratio 18.4) in COVID-19-infected patients. [14] One study suggests anticoagulation, mainly with low molecular weight heparin, may be associated with reduced mortality in severe COVID-19 infections or those with D-dimer greater than six times the upper limit of normal. [32]

COVID-19 is associated with a number of cardiovascular complications, including myocardial injury and myocarditis, ACS, heart failure, cardiogenic shock, dysrhythmias, and VTE. Some of the medications utilized to treat COVID-19 also have potential cardiac complications. It is important for the clinicians to be aware of these complications when treating the COVID-19 patient.

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ACE Inhibitor and ARB Usage in COVID-19 era: Evaluating the Evidence

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With the spread of severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) pandemic, evidence is rapidly accumulating on the risk factors of severe COVID-19 and death. In the wake of some preliminary, unadjusted reports, individuals with pre-existing comorbidities such as hypertension, diabetes and cardiovascular diseases have been identified as those highly vulnerable. Notably, such chronic conditions frequently require prescription of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). Angiotensin-converting enzyme 2 (ACE2) is an enzyme attached to the cell membranes of cells located in the lungs, arteries, heart, kidney, and intestines.[1-3] ACE2 lowers blood pressure by catalyzing the hydrolysis of angiotensin II (a vasoconstrictor peptide) into angiotensin (1–7) (a vasodilator). ACE2 counters the activity of the related angiotensin-converting enzyme (ACE) by reducing the amount of angiotensin-II and increasing Ang (1-7), making it a promising drug target for treating cardiovascular diseases. ACE2 also serves as the entry point into cells for coronaviruses.[4-5] Concerns have been raised regarding the safety of ACEIs and ARBs in patients with coronavirus disease of 2019 (COVID-19), based on the hypothesis that such medications may raise expression of ACE2, the receptor for SARS-CoV-2. The basis of this concern involves whether ACEIs/ARBs increase expression of ACE2, the primary cellular receptor for the SARS-CoV-2, thereby possibly increasing severity of the infection.[6] Uncertainty regarding the role of ACEIs and ARBs in the COVID-19 disease course has generated several questions for clinicians. Does use of ACEIs or ARBs among adults before infection with SARS-CoV-2 increase the risk for COVID-19? Is the use of these medications before infection associated with more severe COVID-19 disease and worse outcomes? What are the benefits and harms of initiating these drugs as treatment for patients with COVID-19?

In this uncertain scenario, some observational studies with multivariable analyses found no association between use of renin–angiotensin–aldosterone system (RAAS) inhibitors and COVID-19 severity,[7-9] a few studies found a significant reduction in the risk of death or severe disease[10,11] and one study found a increased risk of mechanical ventilation and admission to the intensive care unit (ICU).[12] The magnitude of the association also varied across studies, which differed for patients' characteristics, setting (inpatient or outpatient), population targeted by serological testing protocols and extent of measured confounding.

Virus–host interactions affect viral entry and replication. SARS-CoV-2 is an enveloped positive single-stranded RNA (ssRNA) coronavirus. About two-thirds of viral RNA, mainly located in the first open reading frame, encode 16 non-structure proteins (NSPs). The remaining part of the virus genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, and also several accessory proteins. The S glycoprotein of SARS-CoV-2 binds to host cell receptors, ACE2 which is assumed to be a critical step for the entry of the virus. However, the possible molecules facilitated membrane invaginations for SARS-CoV-2 endocytosis are still unclear and other virus proteins may contribute to pathogenesis.[3,6,9] Two opposite hypotheses have been proposed for the effects of RAAS inhibition with ACEIs or ARBs on the lungs (harmful vs beneficial effects).[5] In the "harmful effect" hypothesis, RAAS inhibition upregulates ACE2 expression at the cell surface, thus promoting SARS-CoV-2 entry. In the "beneficial effect" hypothesis, RAAS inhibition reduces the production of Ang II, which would otherwise, upon SARS-CoV-2 binding, activate AT1R, driving inflammation and fibrosis in the lung.

Published data typically make assertions on a relationship between ACEI/ARB use and ACE2 expression levels but lack a detailed, comprehensive breakdown of available data in humans and animals. The strength of the experimental data is, thus, unclear regarding ACEI/ARB use and ACE2 protein expression. Early reports from Wuhan, China, showed that hypertension and diabetes were common among patients with COVID-19 and were associated with worse outcomes.[5] Although these early studies did not specify whether patients were using ACEIs or ARBs before becoming infected, these medications are widely used to treat hypertension and diabetes.[4-5] But still now the role of ACEIs

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and ARBs in COVID-19 disease susceptibility, severity, and treatment is unclear.

13 retrospective cohort studies and 1 case–control study have examined whether a history of ACEI or ARB use was associated with severity of illness in patients with COVID-19. Overall, these studies included a total of 23 565 patients with COVID-19, had consistent results, and provided high-certainty evidence that a history of ACEI or ARB use is not associated with increased severity of COVID-19 illness. 8 studies were conducted in China, 2 in Italy, 1 in the United Kingdom , 2 in the United States , and 1 in several countries.[13-17]

Three studies, which included a total of 8766 patients with COVID-19 and presented analyses adjusted for important confounding factors, had consistent results and provide moderate-certainty evidence that ACEIs or ARBs are not associated with a higher likelihood of positive SARS-CoV-2 test results among symptomatic patients . Two U.S. studies examined patients tested for SARS-CoV-2. A Veterans Health Administration study found that prior ACEI or ARB use was not associated with an increased likelihood of a positive SARS-CoV-2 test result (adjusted odds ratio [aOR], 0.98 [95% CI, 0.78 to 1.23]) . A study from the New York University Langone Health System found that the proportion of patients with positive SARS-CoV-2 test results was similar between patients treated and those not treated with ACEIs or ARB.[8,15,18] Two retrospective cohort studies found that ACEI and ARB use was not associated with a higher likelihood of receiving a positive SARS-CoV-2 test result, and 1 case–control study found no association with COVID-19 illness in a large community (moderate-certainty evidence). Fourteen observational studies, showed consistent evidence that neither medication was associated with more severe COVID-19 illness (high-certainty evidence).[17]

A recently published meta-analysis found no association between COVID-19 illness and use of ACEIs or ARB drugs.[19] A total of five studies, enrolling 7489 hypertensive patients, were included in a meta-analysis comparing the risk of severe/ lethal COVID-19 between ACE inhibitors users versus non- users. Overall, the risk of severe or lethal disease was comparable among treated and untreated patients (summary OR: 0.90; 95% CI 0.65 to 1.26). Two studies showed significant results, with opposite direction. The first included 682 hypertensive subjects and showed an increased risk of severe illness among the 112 patients treated with ACE inhibitors. The second enrolled 105 hypertensive subjects and reported a lower risk among the 38 treated patients. Excluding one or both of these studies did not change the results, which remained non- significant (all $p>0.05$).[7,8,11,12,15] Five studies, enrolling 7462 hypertensive subjects, were included in the meta- analysis comparing the risk of severe illness between ARBs users and non- users. All of them showed non- significant differences between treated and untreated patients, with a summary OR of 0.92; 95% CI 0.75 to 1.12. When the above antihypertensive treatments were considered together (five studies, enrolling 11 334 hypertensive patients), the risk of developing severe COVID-19 was again comparable between treated and untreated patients (summary OR: 1.00; 95% CI 0.84 to 1.18).[19,20]The risk of death among RAAS inhibitors users versus non- users was compared in four studies, including a total of 2412 hypertensive subjects.8,[10,12,15,21] Overall, no differences in risk emerged between the two groups, with a summary OR of 0.88 (95% CI 0.68 to 1.14). A single study from China, enrolling 1128 hospitalized hypertensive patients, showed a significant risk reduction among treated subjects; when its results were excluded from the analyses, the overall estimates did not change (pooled OR 0.95; 95% CI 0.76 to 1.18).[10] One meta- analysis based on 10 adjusted observational studies (enrolling almost 10 000 hypertensive subjects), from different countries, and provides the first summary estimate on the association between ACE inhibitors or ARBs use and COVID-19 severity or mortality. All analyses showed a comparable risk of severe or fatal illness among treated and untreated subjects, either considering ACE inhibitors or ARBs separately, or combined.[19]

As per Fang et al , it was hypothesized that the use of ACE2 receptor increasing drugs is at higher risk for severe COVID-19 infection.[3] ACEI initially inhibits ACE leading to decreased angiotensin I levels, causing a possible negative feedback loop that ultimately up-regulates more ACE2 receptor to be able to interact with the decreased angiotensin I substrate available. This ACE2 receptor up-regulation results in increased binding sites for SARS-CoV-2, leading to preferential COVID-19 infection. This is particularly observed in patients with diabetes and/or hypertension since they are usually taking ACEIs/ARB. It was, therefore, suggested that patients with cardiac diseases, hypertension, or diabetes, who are treated with ACE2-increasing drugs, are at higher risk for severe COVID-19 infection and, therefore, should be monitored for ACE2-modulating medications, such as ACEIs/ARBs.[3]

On the contrary, some studies indicated that ACEIs/ARBs use may be beneficial in COVID-19 infection prevention. Because of a proposed mechanism that ACEI inhibition of ACE may stimulate a negative feedback (given the lack of angiotensin II, up-regulating ACE2 receptors and decreasing overall inflammation). In severe lung injury animal models, preclinical studies have shown that ACE2 is significantly downregulated and it has been shown that the inhibition of the angiotensin type 1 receptor by ARB like losartan reduces severe acute lung injury in mice administered with the spike glycoprotein of SARS-CoV. The above complementary approach reflects that ACE2 is protective in lung injury during infection of coronavirus. [22,23] Treatment of patients with hypertension who are infected with SARS-CoV-2, ACEIs or ARBs may improve clinical outcomes, according to study results published in Emerging Microbes and Infections.[16] Given that ACE inhibitors and ARBs are prescribed to tens of millions patients worldwide, clear recommendations are strongly needed to elucidate whether these drugs should be suspended during the pandemic, or patients and physicians should be definitely reassured.[19,24]

Based on the data summarized above, current evidence, especially from human studies , does not support the idea that treatment with ACEIs or ARBS produces pathophysiologically relevant increases in ACE2 protein abundance. The hypothesis that the use of these drugs increases SARS-CoV-2 virus infectivity and/or severity of COVID-19 is, therefore, not supported by the available evidence. It would thus seem prudent for patients to continue receiving these medications, as recently recommended by multiple health associations and other publications.

Sacubitril/valsartan combination (Entresto) is an angiotensin II receptor blocker indicated to treat heart failure, found to reduce the risk of cardiovascular death and hospitalization related to heart failure. Recently, Zhang et al demonstrated that sacubitril/valsartan (Entresto) reduced the concentration of pro-inflammatory cytokines and neutrophil count, while increasing lymphocyte count more than valsartan alone or placebo.[25] This finding might be related to the increase in plasma levels of atrial/brain/C-type natriuretic peptide, Ang I/II, substance P, bradykikin, and endothelin secondary to neprilisin inibition by sacubitril. Studies have recently shown that early sacubitril/valsartan administration reduces high sensitivity C-reactive protein levels and increases lymphocyte count in patients with acute heart failure.[26-27]

In COVID-19 patients, with and without symptoms attributable to pneumonia, there is evidence of a significant increase in NT-proBNP, regardless of left ventricular dysfunction. NT-proBNP levels are also the results of acute renal injury and pro-inflammatory molecules such as interleukin-1 and C-reactive protein, which are independent of cardiac function. Shi et al. showed that patients with cardiac injury had a higher rate of mortality during the interval both from symptom onset to admission and from admission to clinical endpoint. Increased death rates were associated with higher levels of NT-proBNP.[28] Gao et al. reported that higher NT-proBNP was an independent risk factor for in-hospital death in patients with severe COVID-19 after adjusting for sex, age, hypertension, coronary heart disease, chronic obstructive pulmonary disease, myoglobin, creatin kinase-MB, high sensitivity troponin-I, white blood cell count, lymphocyte count, C-reactive protein, and procalcitonin.[29]

Recently studies have shown that early sacubitril/valsartan (Entresto) administration reduces high sensitivity C-reactive protein levels and increases lymphocyte count in patients with acute heart failure. These pieces of evidence support the biological plausibility of early administration of sacubitril/valsartan in COVID-19 patients, in order to maximize the anti-inflammatory effects of sacubitril.[28-30]

The role of ACEIs and ARBs in the setting of the coronavirus disease 2019 (COVID-19) pandemic is hotly debated. High-certainty evidence suggests that ACEI or ARB use is not associated with more severe COVID-19 disease, and moderate-certainty evidence suggests no association between use of these medications and positive SARS-CoV-2 test results among symptomatic patients. Most of the published data found no association between ACEI or ARB use and COVID-19 test positivity. These clinical data support current professional society guidelines to continue ACEIs or ARBs in the setting of the COVID-19 pandemic. Almost all analyses showed a comparable risk of severe or fatal illness among treated and untreated subjects, either considering ACE inhibitors or ARBs separately, or combined. These findings strongly support the recommendation of several scientific societies to continue ARBs or ACE inhibitors medication for all patients, unless otherwise advised by their physicians.

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Prior Thrombus Aspiration Reduces Myocardial Necrosis During Primary Percutaneous Coronary Intervention in Patients with ST-Elevation Myocardial Infarction.

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Abstract

Objective The effect on myocardial necrosis from intracoronary thrombus aspiration before primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) is uncertain. We aimed to evaluate whether prior thrombus aspiration reduces myocardial necrosis.

Background Several randomized trials evaluating thrombus aspiration during primary PCI used surrogate end points. Four trials have produced conflicting results. Three studies showed improved myocardial perfusion. There is no compelling recommendation for thrombus aspiration during primary PCI for STEMI but certain indication may exist. Routine use of thrombus aspiration is not recommended (Class III, Level A, ESC Guideline 2017) but in case of large residual thrombus burden after opening the vessel with a guide wire or a balloon, thrombus aspiration may be considered (ESC Guideline 2017). The ACC/AHA/SCAI guidelines have been updated so that routine thrombectomy during primary PCI for STEMI has been given a class III indication and selective or bailout thrombectomy has been given a class IIb indication. Many investigators concluded that patients with large thrombus should be treated with thrombus aspiration especially when large filling defects grade >3 are seen and strong contraindications exist against the use of high dose anticoagulant or antiplatelet.

Methods We conducted a prospective clinical trial, with enrollment of patients from Labaid Cardiac Hospital, Dhaka, Bangladesh during September 2015 to August 2017. A total of 120 patients with STEMI undergoing PPCI were randomly assigned into two groups during Primary PCI. One group belonged to those who underwent manual thrombus aspiration during PPCI and another group without manual thrombus aspiration during primary PCI in patients with STEMI. Biomarker of myocardial necrosis Troponin I and CK MB were estimated in both groups at different times in pre and post procedure. A comparison was made between two groups regarding cardiac enzyme changes reflecting myocardial necrosis using paired t test and ANOVA test.

Results No patients were lost to follow-up. Among 120 patients, 23(19.2%) underwent thrombus aspiration during PPCI and 97(80.8%) undergone PPCI without thrombus aspiration. Myocardial necrosis was evidenced by release of cardiac enzymes, Troponin I and CK-MB. By statistical analysis it was found that Troponin I did not reveal any significant difference between two groups; CKMB level were higher in thrombus non aspirated patients in comparison with thrombus aspirated group. P-value for Troponin I did not reach statistical significance but CK-MB level were statistically significant.

Conclusion Primary PCI with or without prior thrombus aspiration did reveal conflicting results as evidenced by statistically insignificant rise of troponin I and statistically significant rise of CKMB level in different times of pre and post procedure to reduce myocardial necrosis.

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Introduction

ST-segment elevation myocardial infarction (STEMI) usually results from acute thrombotic occlusion of a coronary artery and is a leading cause of death[1]. The goal of reperfusion therapy with fibrinolytic drugs or primary percutaneous coronary intervention (PCI) is to restore blood flow to ischaemic, but still viable, myocardium, and reduce infarct size (IS). Accordingly, reducing time to treatment and maximizing myocardial salvage—in keeping with the mantra that 'time is muscle'—represents a major

challenge in the management of STEMI[2]. Initials trials on primary PCI had shown myocardial salvation. However, those promising results did not translate in a clinical benefit in subsequent randomized trials[3,4,5]. Routine use of thrombus aspiration is not recommended[6] (Class III, Level A, ESC Guideline 2017) but in case of large residual thrombus burden after opening the vessel with a guide wire or a balloon, thrombus aspiration may be considered[6]. The 2015 ACC/AHA/SCAI Guidelines have been updated so that routine thrombectomy during PPCI for STEMI has been given a class III indication and selective or bailout thrombectomy has been given a class IIb (LOE C-LD) indication due to lack of data[7]. However, in patients with angiographic evidence of large thrombus burden, the use of the Angiojet mechanical thrombectomy device demonstrated an acute improvement in ST resolution (STR) and a lower MACE rate at 1 year in the Angiojet group compared with the direct stenting group[8]. Many investigators concluded that patients with large thrombus should be treated with thrombus aspiration especially when large filling defects grade > 3 are seen and strong contraindications exist against the use of high dose anticoagulant or antiplatelet.

Angiographically detected Coronary thrombus burden can be classified according to TIMI thrombus grade (TG)[9]. TIMI TG 0 –No thrombus, TIMI TG 1-suggestive of thrombus are detected reduced contrast density, haziness, irregular lesion contour, TIMI TG 2- definite thrombus with greatest dimensions < ½ the vessel diameter, TIMI TG 3-thrombus with greatest linear dimension > 1/2 but < 2 times the vessel diameter, TIMI TG 4-thrombus largest dimension > 2 vessel diameter and TIMI TG 5-total occlusion, the size of thrombus cannot be assessed[10].

The objective of the study was to evaluate the prior manual thrombus aspiration during primary PCI reduces myocardial necrosis compared with conventional PCI in patients with ST–elevation myocardial infarction (STEMI) as evidenced by Troponin I and CKMB.

Methods

We conducted a prospective clinical trial, with enrollment of patients from Labaid Cardiac Hospital, Dhaka, Bangladesh during the period of 2 years from September 2015 to August 2017. A total of 120 patients with STEMI und ergoing PPCI were randomly assigned into two groups during Primary PCI. One group belonged to those who underwent manual thrombus aspiration during PPCI and another group without manual thrombus aspiration during PPCI in patients with STEMI. Biomarker of myocardial necrosis Troponin I and CK MB were estimated in both groups at different times in pre and post procedure. A comparison was made between two groups regarding cardiac enzyme changes reflecting myocardial necrosis using paired t test and ANOVA test. Statistical analysis was done using SPSS 16.0 version.

Results

Among 120 patients, females were 17.5 %, age (M±SD, 53.5±10.2) ranges from 30 to 80 years (Table-1). Risk factors (Table-2) were Hypertension 65 (54,2%), Diabetes Mellitus 57 (47.5%) and Dyslipidemia 35 (29.2%). The most frequent coronary arteries affected (Table-3) are LAD 64 (53.3%) and RCA 45 (37.5%) Among them 23(19.2%) underwent thrombus aspiration during primary PCI and 97(80.8%) undergone primary PCI without thrombus aspiration (Table-4). Cardiac biomarkers Troponin I and CKMB levels were measured at pre-procedure, just after procedure (0 hour), at 4 hours, 8 hours, 16 hours and 24 hours after procedure (Table-5). Statistical analysis did not reach significance to reveal higher myocardial necrosis as evidenced by release of cardiac enzyme Troponin I level in thrombus non-aspirated patients in comparison with thrombus aspirated group (Fig-1). But for CKMB level P-value reached statistical significance (Fig-2).

Table- 1. *Demographic characteristics of the study patients (n=120)*

Parameters	Number	Percentage
Males	99	82.5
Females	21	17.5
Age in years	53.5±10.2	
Range of age (Low-max)	30	80

Quantitative data expressed as mean±SD, Qualitative data expressed as % of patients

Table- 2. *Risk factors of the study patients (n=120)*

Risk Factors	Number	Percentage
Hypertension	65	54.2
Diabetes mellitus	57	47.5
Dyslipidemia	35	29.2

Table- 3. *Type of vessels of the study patients (n=120)*

Vessels	Number	Percentage
OM	1	0.8
LAD	64	53.3
LCX	8	6.7
RCA	45	37.5
LAD+LCX	1	0.8
LAD+RCA	1	0.8

LAD and RCA were found most common vessels among the study patients.

Table- 4. *Use of Aspiration Catheter among the study patients (n=120)*

Aspiration Catheter	Number	Percentage
Yes	23	19.2
No	97	80.8

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Table- 5. *Mean difference of Troponin I and CK-MB level in use of aspiration catheter at different times pre and post procedure (n=120)*

Markers	Aspiration catheter used (n=23)	Aspiration catheter not used (n=97)	P value
	Mean difference between base & 0 hrs	Mean difference between base & 0 hrs	
Troponin I (mean±SD)	22.8±21.9	13.2±71.8	0.53ns
CK-MB (mean±SD)	193.2±307.1	64.9±360.3	0.12ns
	Base & 4 hrs	Base & 4 hrs	
Troponin I (mean±SD)	2.9±24.2	-8.8±39.1	0.16ns
CK-MB (mean±SD)	87.8±210.5	-52.8±271.8	0.02s
	Base & 8 hrs	Base & 8hrs	
Troponin I (mean±SD)	36.3±19.9	18.6±48.8	0.09ns
CK-MB (mean±SD)	318.7±447.5	142.3±358.5	0.04s
	Base & 16 hrs	Base & 16 hrs	
Troponin I (mean±SD)	36.1±21.7	19.3±50.8	0.12ns
CK-MB (mean±SD)	280.7±290.3	40.2±294.6	0.001s
	Base & 24 hrs	Base & 24 hrs	
Troponin I (mean±SD)	34.9±23.2	18.9±50.9	0.14ns
CK-MB (mean±SD)	287.4±372.2	22.1±279.8	<0.001s

s = Significant (p<0.05); ns= Not significant (p>0.05). p value reached from unpaired t test.

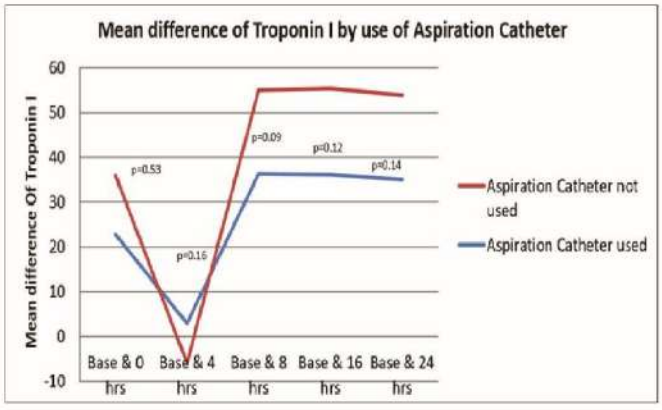

Figure-1.

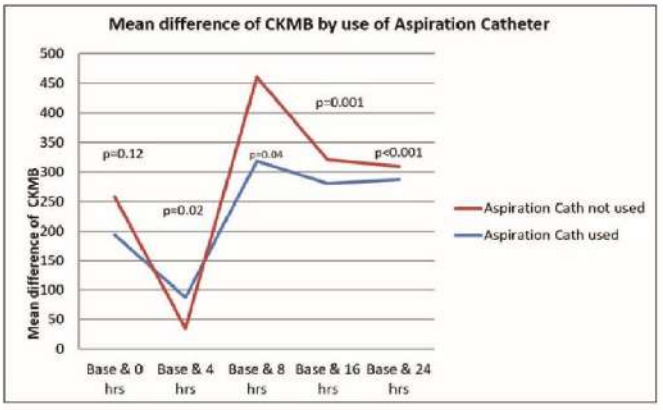

Figure-2.

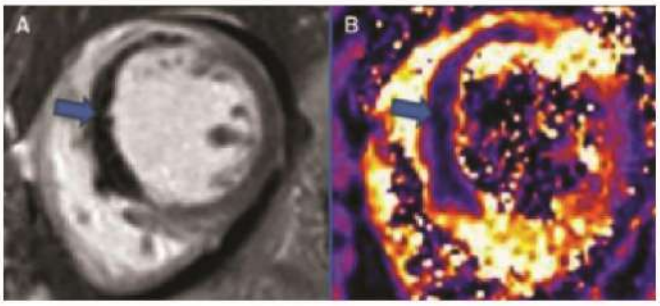

Figure-3. *Visualization of microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH) by cardiac magnetic resonance (CMR). Visualization of MVO (A) and IMH (B; arrows) on short-axis late gadolinium enhanced (A) and T2* mapping (B). CMR images were performed 4 d after acute ST segment– elevation myocardial infarction due to occlusion of the left anterior descending artery. (Adapted from Ref 10)*

Discussion

Initial studies demonstrated that the use of manual thrombus aspiration during primary PCI reduced microvascular obstruction (MVO) occurrence[11,12]. Microvascular obstructions is an independent predictor for adverse left ventricular remodeling and major adverse cardiovascular events (MACE) after myocardial infarction[11]. However, a limitation of Primary PCI is distal embolization of thrombus during either balloon pre-dilatation or stent deployment, which can lead to impairment of microvascular perfusion from microvascular obstruction (Fig-3). Removal of thrombus during primary PCI prior to stent deployment has been thought to be a logical way to reduce distal embolization and improve prognosis. The single center TAPAS 2008 trial (n=1071) showed that routine manual thrombectomy during primary PCI improved the surrogate outcome of blush grade (primary outcome) but was also associated with marked reduction in mortality at 1 year [13,14]. The larger TASTE trial (n=7244) showed no reduction in mortality with routine thrombectomy during PCI for STEMI either at 30 days or 1 year [3,4]. The TOTAL trial is the largest trial of manual thrombectomy (n=10,732) and randomized patients to a strategy of routine manual thrombectomy vs. PCI alone with only bailout thrombectomy[15]. TOTAL demonstrated that thrombectomy improved ST segment resolution and angiographic distal embolization. However, thrombectomy had similar rates of primary outcome of CV death, recurrent MI, cardiogenic shock and class IV heart failure at 180 days; but a significant increase in stroke at 30 days compared to PCI alone[5]. These findings were similar at 1 year[16]. In this study, it did not reveal that prior thrombus aspiration reduced myocardial necrosis in comparison to PCI alone.

Study limitations

This is a single center study and number of enrolled patients were small. The prior thrombus aspirated group is very small compared to the non-aspirated group. So the results shown here may not be representative.

Conclusion

Routine thrombus aspiration during primary PCI revealed conflicting results in relation to myocardial necrosis in comparison with primary PCI alone in patients with STEMI. It was supported by statistical insignificant level of Troponin I and significant CK-MB level in thrombus aspiration versus non-aspirated groups. Further study is required to evaluate this for a conclusive result.

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Electrocardiographic Analysis of 44 Cases of Hyperkalemia.

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Objective Hyperkalemia is a common electrolyte disorder observed in the emergency department and intensive care unit associated with significant morbidity and mortality. The aim of this study was to evaluate the electrocardiographic (ECG) changes according to serum potassium level.

Background The toxic effects of hyperkalemia on the cardiac conduction system are potentially lethal. The ECG is a mainstay in managing hyperkalemia. ECG manifestations in hyperkalemic patients typically include tall and symmetric T waves, widening of the QRS complex, progressive flattening and eventually disappearance of P waves, sine waves and life threatening dysrhythmias, ventricular escape rhythms and ultimately cardiac arrest. Timely intervention of hyperkalemia can prevent unfortunate fatality.

Methods Total 44 patients were detected to have hyperkalemia in a coronary care unit of a tertiary care cardiac hospital during last 2 years. Out of these 44 patients ECG evidence of hyperkalemia was present in 36 patients (81.8%) and ECG was non diagnostic of hyperkalemia in the remaing 8 patients (18.2%). Total 36 patients were detected to have ECG evidence of hyperkalemia. Each ECG was examined for the following: rhythm, heart rate, PR interval, AV block, length of QRS interval, ST-T alterations, length of QTc interval.

Results Tall peak T wave with sinus bradycardia was detected to be the most common ECG finding (n-36) and this single ECG abnormality was noted in 11 patients (30.5%), followed by broad QRS complex in 10 patients (27.7%). Combination of tall peak T waves with broad QRS complex was noted in 17 patients (47.2%). Sine wave configuration was detected in 3 patients (8.3%) and 2 patients (5.5%) presented in emergency department in the state of cardiac arrest with extreme bradycardia and intubated immediately. 1 (2.8%) patient had complete heart block (CHB) and another one had severe bradycardia with Junctional rhythm. In 11 paients (30.5%) hyperkalemia was drug induced with combination of angiotensin-converting enzyme (ACE) inhibitors/ angiotensin II receptor blockers (ARB) with potassium-sparing diuretics like spironolactone/eplerenone. 3 patients (8.3%) required temporary pacemaker insertion (TPI) as their bradyarrhythmias were resistant to intial conservative treatment. In this series, among the patients with ECG changes of hyperkalemia (n-36), 1 patient (2.8) died who had severe left ventrcicular systolic dysfunction.

Conclusion Our findings support the use of the ECG to risk stratify patients with hyperkalemia to prevent short-term adverse events. Severe hyperkalemia is a potential life-threatening cardiac emergency especially in the patients with renal impairment who are on combination of ACEI/ ARB with potassium-sparing diuretics.

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Introduction

Hyperkalemia is defined as a serum potassium concentration of >5.5 mmol/L in adults.It is a common metabolic disorder that can lead to clinical manifestations such as hemodynamic instability, neurologic sequelae, and fatal arrhythmias. Most individuals with hyperkalemia are initially asymptomatic or present with nonspecific signs and symptoms (e.g., weakness, fatigue, or gastrointestinal [GI] hypermotility). The incidence of hyperkalemia has been reported from 2.6% to 3.2% in the United States. A study in Canada showed the incidence to occur in 2.6% of emergency department visits and 3.5% of hospital admissions.[1,2] Diagnosis of hyperkalemia is usually based on laboratory studies, although the ECG may contain changes suggestive of hyperkalemia. Typical ECG findings in hyperkalemia

progress from tall, 'peaked' T waves and a shortened QT interval to lengthening PR interval and loss of P waves, and then to widening of the QRS complex culminating in a 'sine wave' morphology and death if not treated.[3-5] Treatment of life-threatening hyperkalemia focuses on blocking the effects on myocyte transmembrane potential and cardiac conduction, as well as decreasing extracellular potassium levels.

Methods

This was a prospective study performed at the emergency department and coronary care unit (CCU) of a tertiary care cardiac hospital during last 2 years. Patients were required to have had an ECG performed within 15 minutes of presentation in hospital and blood gas analysis within half an hour of admission in the CCU.Data including the medical history, comorbidities and medication record were abstracted from the past medical records and from the history obtained from the relatives. The following data were gathered from each record: demographics (age, gender), previous renal status, previous serum potassium levels, old ECG, medication taken by the patients prior to obtaining the ECG along with comorbidities of the patients on the date of admission. Most of the patients in this series presented with non specific symptoms like muscle weakness, numbness and tingling, nausea and vomiting, palpitation and shortness of breath. 2 patients presented in emergency department in almost collapsed state and intubated immediately.

Total 44 patients were detected to have hyperkalemia. 36 patients who had laboratory evidence of high potassium level along with some hyperkalemic ECG changes were included in this study group. Hyperkalemia was graded as mild with potassium level (5.5-6.0 mmol/L), moderate hyperkalemia (6.0-7.0 mmol/L) and severe hyperkalemia when serum potassium level detected to be >7.0 mmol/L. [6]

Each ECG was examined for the following: rhythm, heart rate, PR interval, AV block, length of QRS interval, ST-T alterations, length of QTc interval. Cardiac arrest was documented in cases of pulseless electrical activity, pulseless ventricular tachycardia, ventricular fibrillation or asystole. PR interval was considered 'prolonged' if PR duration> 200 ms, QRS interval was considered 'wide' if the QRS duration was > 120 ms. QTc interval was deemed short if QTc < 350 ms and prolonged, if QTc > 450 ms. Tall, narrow, symmetrically peaked T-waves are characteristically seen in hyperkalemia. Narrow and tall peaked T wave is an early sign of hyperkalemia. It is unusual for T waves to be taller than 5 mm in limb leads and taller than 10 mm in chest leads in normal subjects . Hyperkalemia should be suspected if these limits are exceeded in more than one lead.ECG alterations were also considered suggestive of hyperkalemia if the following were recorded: AV junctional escape rhythm, Ventricular escape rhythm, bradycardia, Ist-2nd-3rd degree AV blocks etc. Although not generally considered as typical ECG manifestations of hyperkalemia, the following ECG changes were also recorded: atrial fibrillation, ST depression and short QTc.

Results

Total 44 patients were detected to have hyperkalemia in a CCU of a tertiary hospital during last 2 years. Out of these 44 patients ECG evidence of hyperkalemia was present in 36 patients (81.8%) and ECG was non diagnostic of hyperkalemia in the remaining 8 patients (18.2%).

Among the 36 patients with some ECG evidence of hyperkalemia, there were 23 male (63.8%) and 13 (36.2%) patients were female . Age of the patients varied from 26 years to 83 years (average 62+/-19) years. Out of these 36 patients 16 patients (44.4%) had previous history of chronic kidney disease (CKD) and in 11 paients (30.5%) hyperkalemia was drug induced with combination of ACEI/ARB with potassium-sparing diuretics like spironolactone/eplerenone (Table-1). 6 patients (16.6%) developed symptomatic hyperkalemia due to acute kidney injury (AKI) and in 1 patient (2.8%) hyperkalemia was induced by the use of nonsteroidal anti-inflammatory drugs (NSAIDs). 16 patients (44.4%) who had previous history of CKD, 7 (19.4%) patients were on regular hemodialysis.

Tall peak T wave with sinus bradycardia (n-36) was documented to be the most common ECG finding and this single ECG abnormality was noted in 11 patients (30.5%), followed by broad QRS complex in 10 patients (27.7%). Combination of tall peak T waves with broad QRS complex was noted in 17 patients (47.2%). Sine wave configuration was detected in 3 patients (8.3%) and 2 patients (5.5%) presented in emergency department in the state of cardiac arrest with extreme bradycardia and intubated immediately. 1 (2.8%) patient had CHB and another one had severe bradycardia with Junctional escape rhythm (Table-2). 5 patients (13.8%) in this cohort required emergency hemodialysis as their hyperkalemia was resistant to conservative management. 3 patients (8.3%) required TPI as their bradyarrhythmias failed to respond to standard therapy and due to haemodynamic compromise. In this series 1 patient (2.8%) died who had severe left ventrcicular systolic dysfunction, due to previous dilated cardiomyopathy (DCM).

Table- 1 *Predisposing Factors for Hyperkalemia (n-36)*

Predisposing Factors	No	Percentage
Chronic Kidney Disease (CKD)	16	44.4%
ACEI/ARB combination with potassium-sparing diuretics like spironolactone /eplerenone.	11	30.5%
Acute kidney injury (AKI)	6	16.6%
GI cause	2	5.6%
Nonsteroidal anti-inflammatory drugs (NSAIDs) induced	1	2.8%

Table- 2 *ECG manifestations of Hyperkalemia (n-36)*

ECG criteria	No	Percentage
Tall peak T waves with sinus bradycardia	11	30.5%
Only tall peak T waves	4	11.1
Broad QRS complex	10	27.7%
Combination of tall peak T waves with broad QRS complex	17	47.2%
Flattening of P waves	9	25%
First degree heart block	8	22.2%
Atrial Fibrillation	4	11.1%
Sine-wave appearance	3	8.3%
Complete heart block	1	2.8%
Escape rhythm with severe bradycardia	1	2.8%

Discussion

Hyperkalemia is a common electrolyte disorder observed in the emergency department. It is often associated with underlying predisposing conditions, such as moderate or severe kidney disease, heart failure, diabetes mellitus, or significant tissue trauma. Additionally, medications, such as inhibitors of the renin-angiotensin-aldosterone system, potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs, succinylcholine, and digitalis, are associated with hyperkalemia. [7,8] The toxic effects of hyperkalemia on the cardiac conduction system are potentially lethal. The ECG may be the mainstay in managing hyperkalemia. Membrane stabilization by calcium salts and potassium-shifting agents, such as insulin and salbutamol, are the cornerstone in the acute management of hyperkalemia. However, only dialysis, potassium-binding agents, and loop diuretics remove potassium from the body. Frequent reevaluation of potassium concentrations is recommended to assess treatment success and to monitor for recurrence of hyperkalemia. [9-11]

Out of these 44 patients, ECG evidence of hyperkalemia was present in 36 patients (81.8%) and ECG was non diagnostic of hyperkalemia in the remaing 8 patients (18.2%). Even 3 (6.8%) patients with severe hyperkalemia had unremarkable ECG changes. This observation is also in conformity with the other data published in recent past. Hyperkalemia is not always expressed with ECG changes , therefore ECG is not always a reliable indicator of the severity of hyperkalemia. Profound hyperkalemia can be seen in absence of classic ECG changes, but the presence of ECG changes mandates treatment. [12,13] . So some times ECG may be insensitive for diagnosing hyperkalemia. The Kidney Disease: Improving Global Outcomes (KDIGO) potassium controversies conference recommended cardiac monitoring and 12-lead ECG for potassium concentrations >6.0 mmol/l. [7,14] The fact that severe hyperkalemia may not necessarily be associated with ECG changes and that hyperkalemia can lead to 'atypical' ECG changes under certain circumstances must always be kept in mind. Therefore, one should put all hyperkalemic patients on continuous monitoring even if no typical ECG changes appear initially.[14-16]

As hyperkalemia worsens, the ECG first demonstrates peaked T waves resulting from global action potential duration shortening causing more synchronous repolarization across the ventricular wall. Subsequently, the P wave broadens and decreases in amplitude, eventually disappearing, and the QRS widens because of conduction velocity slowing. Severe hyperkalemia >7.0 mmol/L can lead to heart block, asystole, and VT/VF. In humans, the precise level of hyperkalemia producing (or not producing) these changes varies considerably.[17] In the present series of 44 patients ECG evidence of hyperkalemia was present in 36 patients (81.8%) and ECG was non diagnostic of hyperkalemia in the remaing 8 patients (18.2%). In some recently published data ECG evidence of hyperkalemia is much less. In one published series 46% of patients with elevated potassium levels had some kind of ECG alteration suggestive of hyperkalemia.[6]

Tall, peaked T waves can, however, be the early ECG signs of hyperkalemia.[18]. In our present study 30.5% of patients showed evidence of tall and peak T waves with sinus bradycardia. The classic ECG pattern of hyperkalemia, which occurs with more severe QRS broadening and fusion of the QRS complex with broadened ST-T segments, is the sine wave pattern.[19,20] In our study sine wave configuration was detected in 3 patients (8.3%) and 2 patients (5.5%) presented in emergency department in the state of cardiac arrest.In a retrospective study of 188 patients, the ECG abnormalities associated with adverse outcomes were QRS prolongation, symptomatic bradycardia, and junctional rhythms. An increased likelihood of short-term adverse event was found for hyperkalemic patients whose ECG demonstrated QRS prolongation, (relative risk [RR] 4.74, 95% CI [2.01–11.15]), bradycardia (HR<50) (RR 12.29, 95%CI [6.69–22.57]), and/or junctional rhythm (RR 7.46, 95%CI 5.28–11.13).[21] There was no statistically significant correlation between peaked T waves and short-term adverse events (RR 0.77, 95% CI [0.35–1.70]).[21] In the present series broad QRS complex was noted in 10 patients (27.7%) and escape rhythm with severe bradycardia was noted in 1 patient (2.8%).

Combination of tall peak T waves with broad QRS complex was noted in 17 patients (47.2%) in this study and all these patients had either moderate (5 patients) or severe hyperkalemia (12 patients) .Those patients presented with escape rhythm with severe bradycardia, CHB and sine wave pattern ECGs had severe hyperkalemia with serum K+ level > 9.0 mmol/L. TPI may be a life-saving procedure in patients with severe bradyarrhythmia and cardaic arrest. [22-24] 3 patients (8.3%) in this series required TPI as their bradyarrhythmias were resistant to intial conservative treatment and had uneventful recovery.

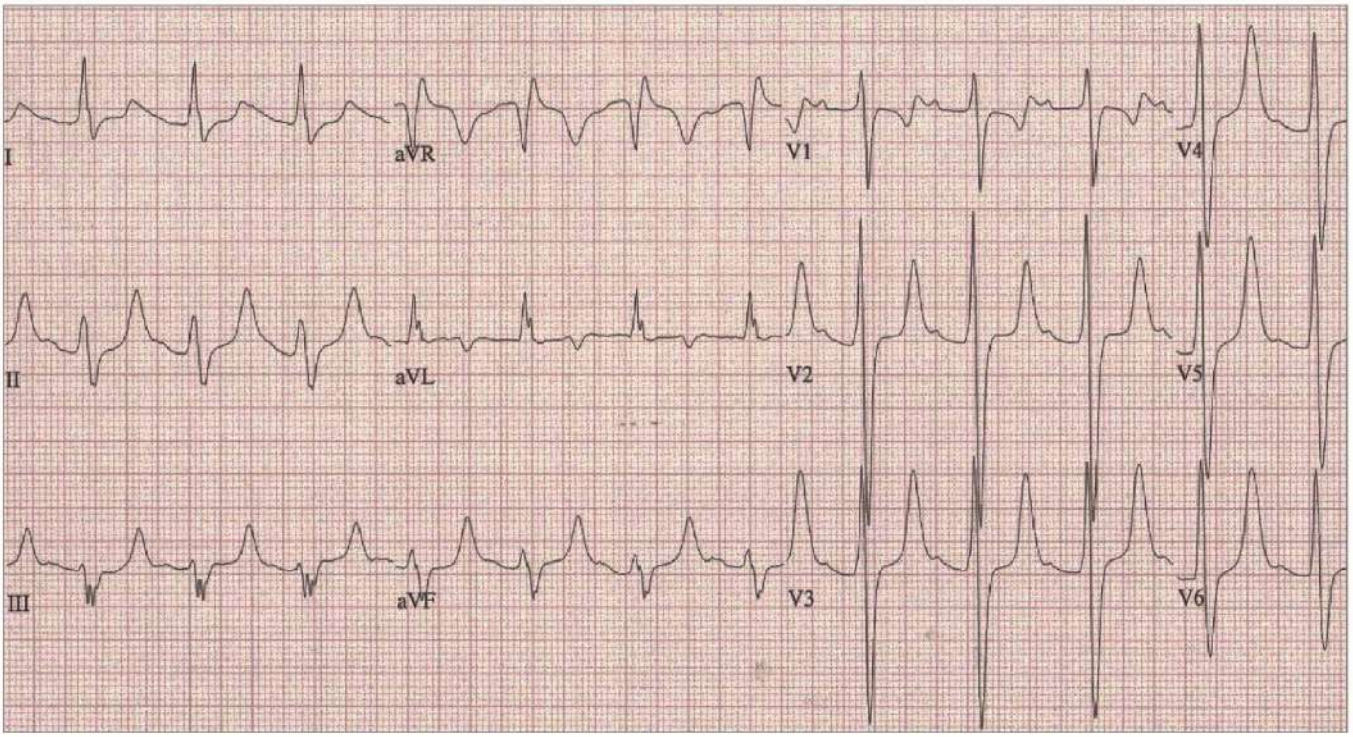

Figure-1. *ECG of a patient with mild hyperkalemia showing features of hyperkalemia with tall peaked T waves, flattened P waves, prolonged PR interval and widened QRS complex (Serum potassium level – 6.5 mmol/L).*

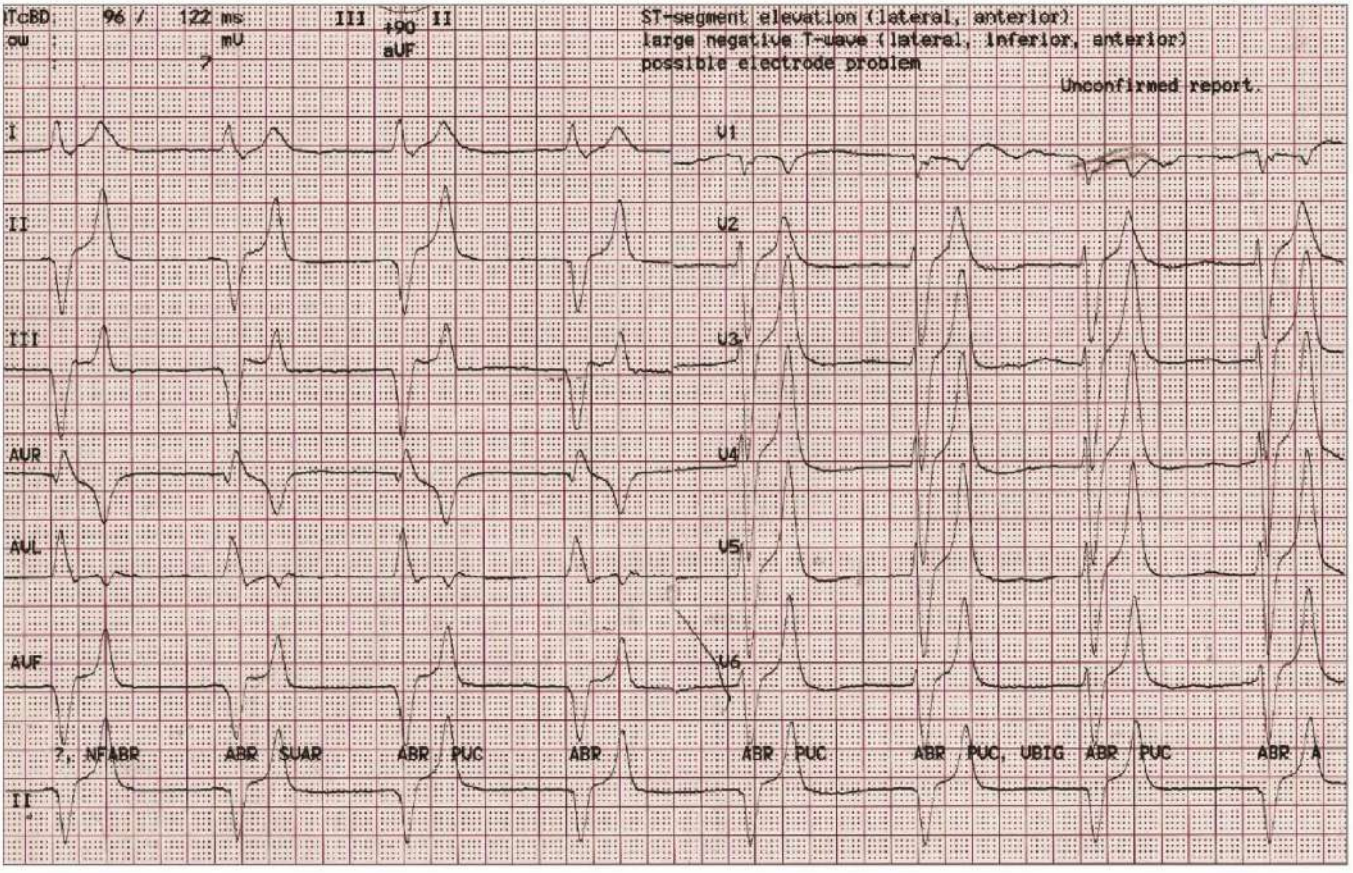

Figure-2. *ECG of a patient with moderate hyperkalemia showing broad and bizarre-looking QRS complexes, tall peaked T waves, absent of P waves and bradycardia. (Serum potassium level – 7.0 mmol/L).*

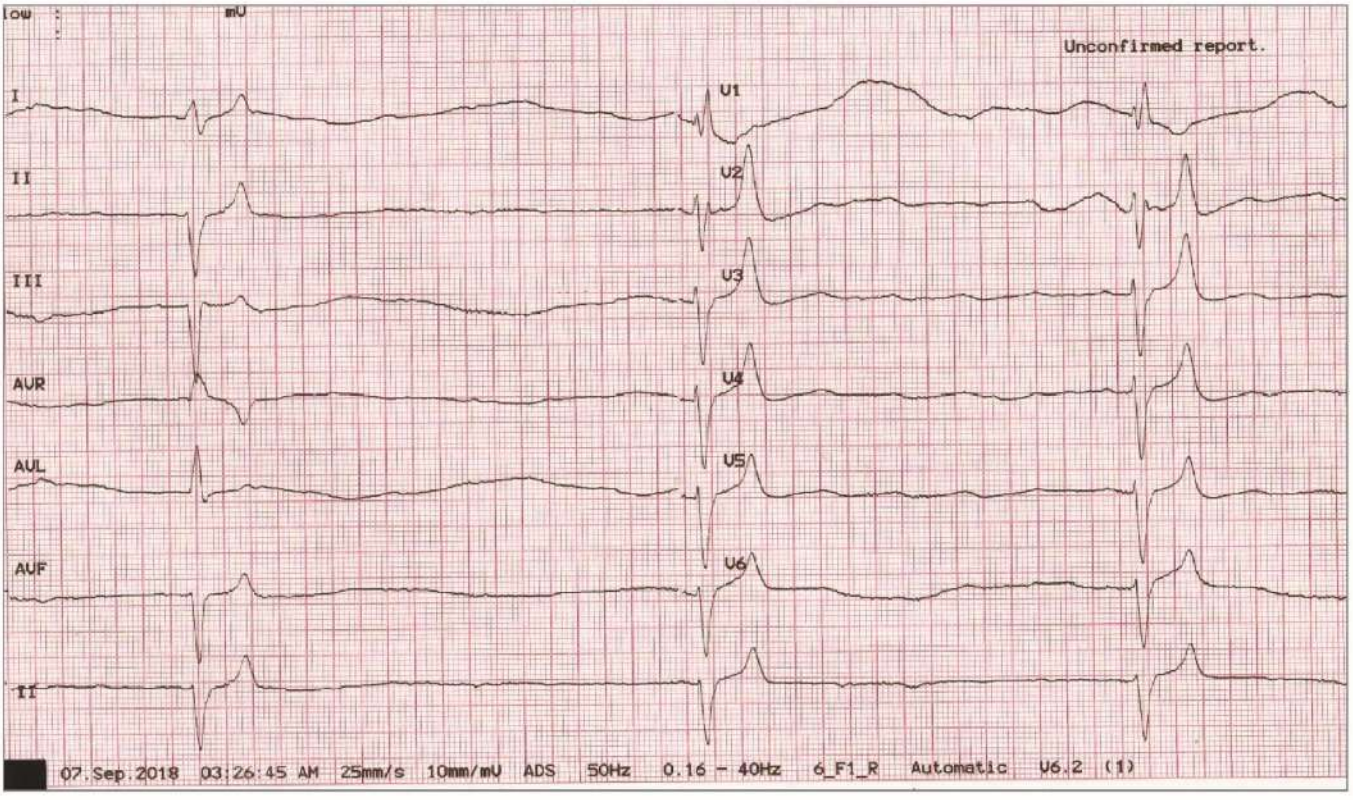

Figure-3. *ECG of a patient with severe hyperkalemia showing escape rhythm with severe bradycardia. This patient required TPI during first 24 hours of admission. (Serum potassium level – 9.0 mmol/L).*

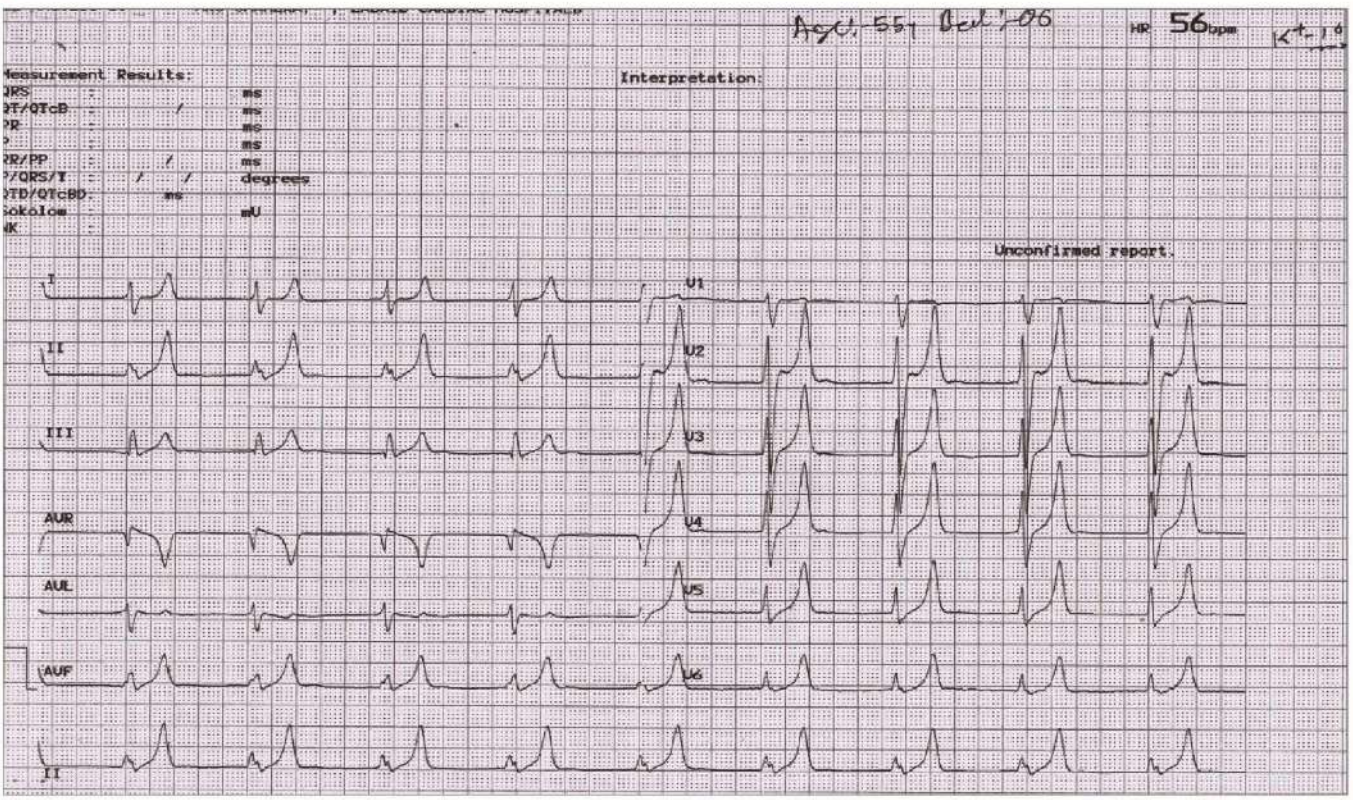

Figure-4. *ECG of a patient with severe hyperkalemia showing absent of P waves, broad and bizarre QRS complexes, very tall and peaked T waves and bradycardia. (Serum potassium level – 10.0 mmol/L).*

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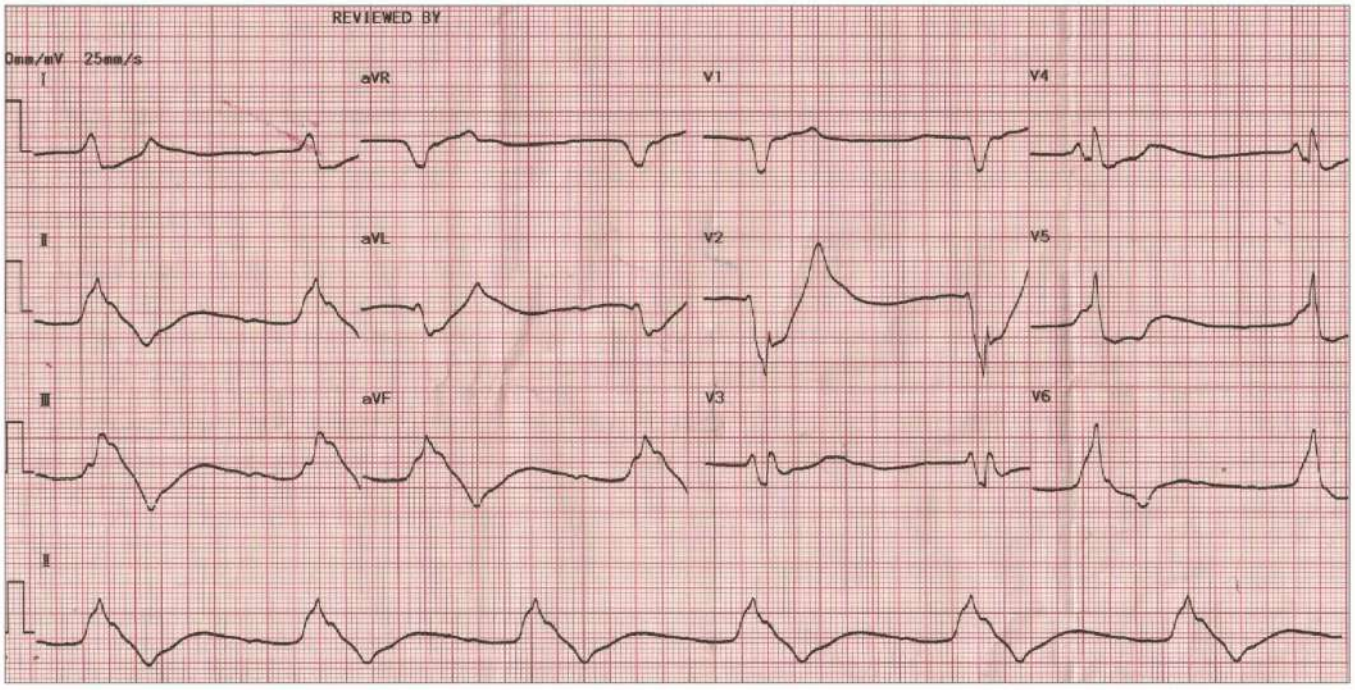

Figure-5. *ECG shows wide and bizarre QRS complex with sine wave configuration with marked bradyarrhythmia suggestive of severe hyperkalemia during admission in hospital (Serum potassium level – 9.4 mmol/L). This patient required TPI during initial hours of admission.*

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Conclusion

Our findings support the use of the ECG to risk stratify patients with hyperkalemia for short-term adverse events. Severe hyperkalemia is a potential life-threatening cardiac emergency especially in the patients with renal impairment or DCM who are on combination of ACEI/ARB and potassium-sparing diuretics. Emergency hemodialysis and TPI may be of life saving procedures in some patients. High degree of suspicion is required in assessing patients with suspected hyperkalemia as hyperkalemia is not always expressed with ECG changes , therefore ECG is not always a reliable indicator of the severity of hyperkalemia in all cases. Profound hyperkalemia can be seen in the absence of classic ECG changes and the diagnosis may be missed. So high degree of suspicion is required in high risk patients to avoid unfortunate fatality.

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Impact of COVID -19 Pandemic on the Hospital Admission and Treatment Strategies of Acute Coronary Syndromes A Single Centre Analysis.

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Objective The aim of this study was to define the impact of COVID-19 pandemic on the hospital admission and management of acute coronary syndrome (ACS) patients in a tertiary care cardiac hospital.

Background Bangladesh announced the first confirmed coronavirus case on 8th March 2020.[1] Rapidly progressing COVID-19 pandemic has impacted every aspect of cardiology practice, including clinical and logistical challenges in the treatment of ACS. Most of the countries affected by the COVID-19 pandemic have reported a substantial drop in the number of patients attending the emergency department with ACS and a reduced number of invasive cardiac procedures. In this study we aimed to understand the scale, nature, and to evaluate whether in-hospital management of patients has been affected as a result of the COVID-19 pandemic.

Methods We studied the impact of COVID-19 pandemic and strict lockdown on ACS admission and change in treatment policy in a tertiary referral cardiac hospital with 24 hour primary percutaneous coronary intervention (PPCI) facility in Dhaka city during last 1 year period, 6 months pre Covid era and 6 months during Covid time.

Results This retrospective analysis showed overall 37.9% decline in ACS admission during COVID time (620 cases versus 385 cases). Admission of ST elevation myocardial infarction (STEMI) declined remarkably. During pre COVID 6 months total 221 STEMI were admitted in our hospital but during same period of time in COVID era only 90 STEMI patients were admitted (percentage reduction 59.3%). In pre COVID time 22.6% patients with STEMI were treated with thrombolytics whereas in COVID era 68.8% patients admitted with STEMI were treated with thrombolytics. Interventional procedures also showed a remarkable downward trend during COVID time as well. In pre COVID time total 1885 procedures were done during 6 months whereas during COVID time 587 cases of diagnostic and interventional procedures were performed (percentage reduction 68.9%). During this time number of coronary angiogram (CAG) reduced from 1464 cases to 449 cases (percentage reduction 69.3%), percutaneous coronary intervention (PCI) cases declined from 337 procedures to 131 cases (percentage reduction 61.1%) and primary percutaneous coronary intervention (PPCI) showed remarkable downward trend, 84 versus 07 cases (percentage reduction 91.7%).

Conclusion It appears that the COVID-19 outbreak is associated with a significantly lower rate of hospital admissions for ACS. For STEMI patients rate of thrombolysis has increased and number of PPCI has dropped. Reduction of the number of all interventional procedures were also reflected in this study.

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Introduction

The coronavirus disease-2019 (COVID-19) outbreak has become a worldwide healthcare emergency.[2,3] The causative organism of the COVID-19 pandemic is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), transmitted through respiratory droplets and fomites. It binds to ACE2 receptors present on lung alveolar cells, in the heart, vascular endothelium, kidney and in gastrointestinal tract.[4-7] COVID-19 is now known to have potentially serious cardiovascular consequences. It could be related to direct cardiac injury, cytokine storm and inflammatory milieu and hypoxia due to respiratory failure. COVID-19 patient may present with myocarditis, cardiomyopathy, cardiogenic shock, myocardial injury, acute

coronary syndromes, pulmonary embolism, stroke, heart failure and arrhythmia.[8-11] ECG changes can be present and these can mimic STEMI. Thorough evaluation should be entertained before urgent cardiac catheterisation/CAG/PPCI or thrombolysis is considered.[12,13]

The COVID-19 pandemic has greatly impacted healthcare delivery across the world. Many hospitals and health systems cancelled non-urgent procedures and closed clinics, and governments messaged to the public to stay home and avoid going to hospitals for non-urgent care.[14] There was a substantial decrease in ACS hospitalization rates in the COVID-19 period suggesting that a significant number of patients with ACS initially avoided hospitalization during the COVID-19 pandemic, possibly related to apprehension of catching SARS-CoV-2 infection from the hospital.[15] It has been postulated that in the midst of this healthcare crisis, in USA and Europe hospital admissions for ACS have dramatically decreased, mostly due to the fact that patients do not activate emergency medical services (EMS) because of the "do not come to the hospital" policy and due the fact that hospitals are now perceived as dangerous places.[16] Despite being eclipsed by COVID-19 outbreak, ACS are still a major cause of morbidity and mortality worldwide and should not be overshadowed in this era, especially because of the possible physiopathological links with SARS-CoV-2 infection.

Methods

We conducted a retrospective study on the incidence rates of ACS-related admissions and treatment strategies during a 6-month period of the COVID-19 outbreak and the corresponding control period before COVID time.The primary outcome of this retrospective analysis was to evaluate the pattern of hospital admissions for ACS and to define the management policy of such patients after hospitalization during a specific time frame 6 months pre COVID and 6 months in COVID era. Pre COVID era encompasses the time from October 2019 to March 2020 and COVID era covers the time April 2020 to September 2020. All ACS admissions were classified as STEMI, non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA) according to the standard diagnostic protocol. Cardiac catheterization laboratory (Cath Lab) procedures (ie, CAG, PCI, PPCI) undertaken during this time were identified from the Cath Lab documents. In pre COVID time total 620 patients were admitted in the hospital with ACS (UA-239 ,NSTEMI-160 and STEMI 221 patients). Among these 620 patients there were 472 male (76.1%) and 148 (23.9%) patients were female. During the 6 months period of COVID time 385 patients were admitted with ACS (UA-152, NSTEMI-143 and STEMI 90 cases). Among the admitted patients 300 subjects were male (77.9%) and 85 patients (22.1%) were female. Treatment policy of each case was documented from the coronary care unit (CCU) register.

Results

Overall, from April to September 2020, there had been approximately 235 fewer admissions for ACS than would be expected compared to preceding 6 months. During the period of declining admissions, there were reductions in the numbers of admissions for all types of ACS, including STEMI, UA and NSTEMI, but relative and absolute reductions were larger for STEMI, with 221 admissions during pre COVID era versus 90 admission during COVID era (percent reduction, 59.3%) (Table-1). In parallel, reductions were recorded in the number of Cath Lab procedures both emergency and elective for patients with coronary artery disease (CAD). This retrospective analysis showed overall 37.9% decline in ACS admission during COVID time (620 cases versus 385 cases). Admission of STEMI declined remarkably. During pre COVID 6 months total 221 STEMI patients were admitted in our hospital but during same duration of time in COVID era, only 90 STEMI patients were admitted (percentage reduction 59.3%). In pre COVID time 22.6% patients with STEMI were treated with thrombolytics whereas in COVID era 68.8% patients admitted with STEMI were treated with thrombolytics. In pre COVID time out of 221 patients admitted with STEMI 84 patients (38.0%) underwent PPCI but during COVID era out of 90 patients with STEMI only 7 patients (7.7%) underwent PPCI.Number of late presenter for STEMI also increased during COVID time and this group of patients were not suitable for immediate reperfusion therapy, thrombolytics/PPCI. Diagnostic and interventional procedures also showed a remarkable downward trend during COVID time as well. In pre COVID time total 1885 procedures were done during 6 months whereas during COVID time 587 cases of diagnostic and interventional procedures were performed (percentage reduction 68.9%). During this time number of CAG reduced from 1464 cases to 449 cases (percentage reduction 69.3%), PCI cases declined from 337 procedures to 131 cases (percentage reduction 61.1%) and PPCI showed remarkable downward trend in the two groups 84 versus 07 cases (percentage reduction 91.7%) (Table-2). During COVID period number of STEMI patients treated with thrombolytics increased and number of patients undergoing PPCI decreased.

Discussion

This report shows a significant decrease in ACS-related hospitalization rates and reduction of number of Cath Lab procedures during COVID time compared to pre COVID period. Our observation is in conformity with the other data published in recent past. Multiple studies have found that the incidence of hospitalization for ACS have decreased by as much as 40 to 50 percent during the COVID pandemic.[17-19]A study from Northern California compared weekly incidence rates of hospitalization for acute MI (STEMI and NSTEMI) before and after March 4th, 2020. These data were also compared with data from the same time period in 2019. The weekly rates of hospitalization decreased by about 48 percent during the COVID-19 period.[19] A study from Italy compared admissions for acute MI to CCU from March 12th to 19th in 2020 with those during the equivalent week in 2019 . There was a 49.4 percent reduction , and the reduction was significant for both STEMI and NSTEMI. The STEMI case fatality rate was higher, comparing 2020 with 2019.[20] A large database study from England compared

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hospital admissions for ACS between mid-February and end of March, 2020 and also compared them with the weekly average in 2019. There was a substantial reduction in the weekly numbers of patients with ACS admitted to hospitals in England by the end of March, 2020 (1813 per week; 40 percent reduction) compared with the 2019 weekly average.[21]

Parallel to reductions in hospital admission for ACS , reductions were recorded in the number of Cath Lab procedures, both emergency and elective for patients with CAD in our present study.In pre COVID time we did total 1885 procedures during 6 months whereas during COVID time we performed 587 cases of diagnostic and interventional procedures (percentage reduction 68.9%). During this time number of CAG reduced from 1464 cases to 449 cases (percentage reduction 69.3%), PCI cases declined from 337 procedures to 131 cases (percentage reduction 61.1%). This observation is also in agreement with the other published series. In the US and Spain, approximately 38% and 40% reductions in cardiac catheterization laboratory STEMI activations were experienced respectively.[17,22] In one recently published study a total of 34 127 patients with STEMI were included. There was a decline in the number of procedures by 43% in April 2020 compared with the average monthly procedures between 2017 and 2019 . But in-hospital mortality remained static. The in-hospital mortality rate was 4.8% before the lockdown and 3.5% after the lockdown (p=0.12). Following adjustment for baseline characteristics, no differences were observed for in-hospital death.[23] In England, they observed a decline in PPCI procedures for STEMI and increases in overall symptom-to-hospital and door-to-balloon time for patients with STEMI. Restructuring health services during COVID-19 has not adversely influenced in-hospital outcomes.[23]

COVID-19 pandemic is associated with a reduction in STEMI admissions and PPCI procedures.[17,19,20,24] In our study the decline in PPCI procedures is very remarkable.We observed 91.7% reduction rate of PPCI procedures during COVID time compared to pre COVID era. Multiple factors are contributory for this sudden decline in PPCI, though the superiority of PPCI over thrombolysis in STEMI cases is well established. Lack of COVID dedicated Cath Lab, shortage of organized use of resources, scarcity of guideline directed personal protective equipment (PPE) and initial medical care avoidance by the patient and his relatives, all contribute this decline in STEMI admission and reduction PPCI procedures. Another question of importance is whether the fibrinolytic therapy in early presenting (within 3 h) STEMI patients may play a leading role during the pandemic. Though superiority of PPCI over thrombolysis is well documented, however, the notable exposure risks due to absence of negative pressure in catheterization rooms and the considerable increased difficulty in fine manipulation on guidewires under the proper protection equipment may all contribute to relatively secondary role of PPCI during the COVID-19 pandemic . [25,26] Even during the COVID-19 pandemic, PPCI remains the standard of care for STEMI patients at PCI capable hospitals with an expert team equipped with proper PPE in a dedicated COVID Cath lab.

In our experience, we have considered each ACS patient to be possibly COVID-19 infected. This is of outmost importance for the safety of other hospitalized patients, the hospital environment, and healthcare workers. Therefore, a cardiologist has to be prepared to manage an emergency situation within a co-existing COVID-19 pandemic, ensuring the appropriate treatment for these patients and, on the other hand, preventing infection of healthcare workers, through the optimization of PPE.

Table - 1 *Pattern of ACS admission during pre COVID (6 months) versus COVID era (6 months).*

Type of ACS	Pre COVID	COVID era	Percentage Reduction
Total ACS cases	620	385	37.9%
UA	239	152	36.4%
NSTEMI	160	143	10.6%
STEMI	221	90	59.3%

Table - 2 *Cardiac Procedures during pre COVID (6 months) versus COVID era (6 months).*

Procedure	Pre COVID	COVID era	Percentage Reduction
Total Cardiac Procedures	1885	587	68.9%
CAG	1464	449	69.3%
PCI	337	131	61.1%
PPCI	84	07	91.7%

Conclusion:

Compared with the pre COVID time there was a substantial reduction in the numbers of patients with ACS who were admitted to our hospital. Number of inteventional procedures also decreased profoundly, particularly PPCI for STEMI. ACS admission rates have declined during the COVID-19 pandemic, perhaps partly because, the patients are unwilling to access the emergency medical system or due to risk of hospital exposure to COVID-19. It is not a true reduction in incidence of ACS.Medical care avoidance by the patient, scarcity of dedicated COVID cath lab, shortage of guideline directed PPE for the healthcare workers and fear of hospital spread, are contributory in profound reduction of ACS admission and invasive procedures during COVID era.

During treatment of ACS in COVID era few things should be taken in consideration (1) Timely reperfusion of STEMI patients with or without COVID-19. (2) Emphasis on protection and safety of all health care personnel. (3) Organized use of resources (including staff, PPE) (4) Minimise adverse outcomes.

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Peripartum Cardiomyopathy: Follow up Study of 27 Patients.

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Objective Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy that causes systolic heart failure (HF) in previously healthy young women. PPCM establishes late in pregnancy or in the first postpartum months. Many patients recover well within the first year, but long-term outcome studies on morbidity and mortality are rare. Here, we present average 3-year follow-up data of 27 patients with documented PPCM.

Background Cardiovascular disease is an important cause of mortality and morbidity during pregnancy. PPCM is a rare form of unexplained cardiac failure of unknown origin, unique to the pregnant woman with highly variable outcome associated with high morbidity and mortality.

Methods 27 cases of documented PPCM were followed up for 2 to 5 years (average 3.2 years). Age of the patients varied from 21 to 45 years (average age 34.2±9.1 years). Diagnosis of PPCM followed the criteria adopted by the World Health Organization Committee, defined in 1980 and modified in 1996.1 We performed clinical, electrocardiographic and echocardiographic examinations to establish the diagnosis. Diagnosis was established after delivery in 22 cases (81.5%) and in the remaining 5 cases (18.5%) diagnosis was established during last month of pregnancy.

Results Out of these 27 patients 17 patients (62.9%) showed improvement in left ventricular ejection fraction (LVEF) , 6 women (22.2%) had persistent left ventricular systolic dysfunction without any deterioration from baseline and in 4 cases (14.8%) LVEF decreased during followup. Maximum LVEF improvement was noted during first year of diagnosis and after the first year systolic function improvement was rather slow.19 patients (70.4%) of this series had history of pre-eclampsia. Advanced maternal age was documented to be an independent predictor of PPCM. and the average maternal age in the series of patients was 34.2±9.1 years. Multiparity was noted in 17 patients (62.9%), diabetes mellitus in 8 patients (29.6%) and multiple pregnancies in 5 patients (18.5%). 3 patients (11.1%) died due to progressive heart failure during followup.

Conclusion LVEF improves in a significant number of patients with PPCM and this improvement is more marked during first year of initial diagnosis. Pre-eclampsia, advanced maternal age, diabetes mellitus, multiparity and multiple pregnancies are commonly associated with PPCM. LVEF at the time of diagnosis is an independent predictor of the prognosis.

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Introduction

Peripartum cardiomyopathy is idiopathic heart failure occurring in the absence of any determinable heart disease during the last month of pregnancy or the first 5 months postpartum.[2,3] The incidence varies worldwide but is high in developing nations; the cause of the disease might be a combination of environmental and genetic factors. Diagnostic echocardiographic criteria include left ventricular ejection fraction <0.45 or M-mode fractional shortening <30% (or both) and end-diastolic dimension >2.7 cm/m^2.[4-6]In the United States, incidence varies from 1 in 1,000 to 1 in 4,000. Risk factors for PPCM include African ancestry, pre-eclampsia and hypertension, multifetal pregnancies, and older maternal age. Etiology of PPCM is poorly understood. Existing studies suggest that PPCM is a

vascular disease, triggered by peripartum hormonal changes with prolactin breakdown products having vasculotoxic effects. Genetic studies have identified pathogenic variants in the titin gene in afflicted patients supporting a two hit hypothesis.[7] Symptoms of heart failure mimic those of normal pregnancy, often resulting in a delay in diagnosis and preventable complications. Echocardiography showing decreased myocardial function is essential for the diagnosis. Medical management is similar to heart failure with reduced ejection fraction of other etiologies, but drug adjustments during pregnancy are necessary to ensure fetal safety. Variable outcomes include complete recovery, persistent heart failure, arrhythmias, thromboembolic events, and death. Subsequent pregnancy confers substantial risk of relapse and even death if there is incomplete myocardial recovery. Additional research about the etiology, optimal therapy including the use of bromocriptine, long-term outcomes, and duration of treatment after recovery are needed.[8-10]

Methods

27 patients were documented to have PPCM in a Government Medical College Hospital and in a tertiary care Cardiac Hospital during last 2-5 years (average 3.2 years). Age of the patients varied from 21 to 45 years (average age 34.2±9.1 years). Diagnosis was established after delivery in 22 cases (81.5%) and in the remaining 5 cases (18.5%) diagnosis was established during last month of pregnancy. Diagnosis of PPCM followed the criteria adopted by the World Health Organization Committee, defined in 1980 and modified in 1996 and as endosed by the Study Group on PPCM from the Heart Failure Association of the European Society of Cardiology (ESC), i.e. an LVEF ≤45% assessed by echocardiography and the absence of pre-existing cardiac disease. [1,2]The diagnosis of PPCM was based on exclusion. The diagnosis for PPCM was suggested when patients presented with heart failure symptoms in late pregnancy or within the first five months postpartum. Heart failure symptoms were verified by transthoracic echocardiographic examination, which showed a LVEF of less than 45%. Finally, other causes for heart failure and cardiomyopathy, such as pre-existing hypertension, coronary artery disease, heart valve disease, congenital heart disease, and tachycardia-induced heart disease, were also excluded.

Each diagnosis was confirmed and, in doubt, further medical reports were requested from the patient. LVEF varied from 20%- 45% (mean 32+/- 9%) at diagnosis. All patients were treated with beta-blockers, digoxin, angiotensin-converting enzyme inhibitors (ACEI) /angiotensin receptor blockers (ARB), and/or mineralocorticoid receptor antagonists) and other diuretics. 6 patients (22.2%) also received Entresto (sacubitril and valsartan combination). In 5 cases (18.5%) diagnosis was established during last month of pregnancy and among them 2 patients (7.4%) underwent emergency caesarean section operation due to intractable heart failure and both of them had uneventful recovery. 10 patients (37%) had LVEF 20-30%,12 patients (44.4%) had LVEF between 30-40% and the remaining 5 patients (18.5%) had LVEF around 45% at diagnosis. Functional status of the patients were assessed by using New York Heart Association (NYHA) Functional Classification NYHA class I-IV. [3] 19 patients (70.3%) presented with the symptoms of progressive exertional dyspnea, 5 patients (18.5%) developed left ventricular failure (LVF) following childbirth and 3 patients (11.1%) presented with features of congestive heart failure. All the patients who developed LVF responded well to intravenous diuretics and ionotropic support. All the patients were followed up in the out patient department at six months interval. Their health status was assessed clinically and also by the Echo-Doppler study at each visit. All patients were advised against repeat conception and to maintain contraceptive policy strictly.

Results

Diagnosis was established after delivery in 22 cases (81.5%) and in the remaining 5 cases (18.5%) diagnosis was established during last month of pregnancy. Out of these 27 patients 17 patients (62.9%) showed improvement in LVEF , 6 women (22.2%) had persistent left ventricular systolic dysfunction without any deterioration from baseline and in 4 cases (14.8%) LVEF decreased during first year of followup. Maximum LVEF improvement was noted during first year of diagnosis and after the first year left ventricular systolic function improvement was rather slow. At 1 year, mean LVEF had improved to 40± 8% (n = 27) and further increased to 45 ± 9% at 3-year follow-up with 15 patients (55.5%) having achieved full cardiac recovery (LVEF >50%). Three patients conceived against medical advice. Therapeutic abortion was done in one and in the remaining two, caesarean section was done with maximizing anti failure treatment. 19 patients (70.4%) of this series had history of pre-eclampsia. Advanced maternal age (average maternal age 34.2±9.1 years), multiparity in 17 patients (62.9%), diabetes mellitus in 8 patients (29.6%) and multiple pregnancies in 5 patients (18.5%) were noted in this cohort of patients.Premature ventricular complex (PVC) was the commonest arrhythmia noted, followed by atrial fibrillation (AF). 8 patients (29.6%) developed frequent PVCs and 3 patients (11.1%) developed permanent AF. 3 patients (11.1%) died due to progressive heart failure during followup. All the three patients who died during followup had LVEF in between 20-30% at the time of intial diagnosis.

Discussion

PPCM is a severe form of idiopathic cardiomyopathy, affecting previously healthy young women during late pregnancy or postpartum, which can be life threatening. PPCM presents with HF secondary to LV systolic dysfunction towards the end of pregnancy and in the months following delivery, with the majority diagnosed post-partum. Careful history taking is necessary to identify and exclude other causes of HF. [11,12] The LV may be non-dilated, but the EF is usually <45%. [13,14] Symptoms and signs are often typical for HF with numerous phenotypes reported. Patients frequently present with acute HF, but also with ventricular arrhythmias and/or cardiac arrest. [15,16] In the present study out of these 27 patients 17 patients (62.9%) showed improvement in LVEF , 6 women (22.2%) had persistent left ventricular systolic dysfunction without any deterioration from baseline and in 4 cases (14.8%) LVEF decreased during first

year of followup. This observation is in conformity with other studies published in recent past. In one study at 1-year follow-up (n = 50), full cardiac recovery was present in 60%, partial recovery in 28%, and no recovery in 12%. [17] At 5-year follow-up (n = 60), the rate of patients with full cardiac recovery had further increased to 72% whereas the rate of patients with partial (23%) or no recovery (5%) had slightly decreased. Mean LVEF had further improved to 54± 7% (n=58), though without reaching statistical significance. [17] Currently, strong risk factors for PPCM include advanced age, black race, preeclampsia, hypertension, multiple gestations, anemia, and prolonged tocolysis. Nonetheless, most of preeclampsia women do not manifest as PPCM, and a large proportion of patients with PPCM is young primiparous women. [18,19] In the present series 19 patients (70.4%) had history of pre-eclampsia. So, pre-eclampsia appears to be an independent risk for PPCM. But it must be remembered that most of preeclampsia women do not manifest as PPCM. Average maternal age in this group patients was 34.2±9.1 years and advanced age appears to be an independent predictor of PPCM in this study. In the present series multiparity was noted in 17 patients (62.9%), diabetes mellitus in 8 patients (29.6%) and multiple pregnancies in 5 patients (18.5%). The incidence of multiparity appears higher (62.9%) in this study population but in some recently published data young primiparous women were more prone to develop PPCM than multiparous women.[18] In another series of patients PPCM has been reported in 24-37% of young primigravidae.[20] and in our series 37.1% patients were primiparous women.Racial, sociodemographic and perhaps environmental factors may be contributory for this disagreement of incidence of PPCM in multiparous and primiparous women.

ECG abnormalities are often noted on presentation, most commonly sinus tachycardia, nonspecific ST-T segment changes, LV hypertrophy, premature ventricular contractions, AF and bundle branch block.[21] Various arrhythmias are not uncommon in this population. In PPCM, sudden cardiac death (SCD) contributes to 25–39% of all-cause mortality. Indeed, in a retrospective analysis of 9,841 hospital admissions for PPCM in the USA, arrhythmias were reported to have occurred in 18.7% of cases.[22] In that study, ventricular tachycardia (VT)—seen in 4.2% of patients—was the most common arrhythmia, followed by atrial fibrillation (1.3%) and ventricular fibrillation (VF) (1%).22 However, literature on the exact underlying mechanisms of SCD in the course of PPCM is scarce, particularly that pertaining to the burden of malignant ventricular arrhythmias. Nevertheless, studies show that reduced LVEF in the early stages of PPCM is accompanied by a high risk of life-threatening ventricular arrhythmias, which may lead to SCD. [22,23] In the present series 8 patients (29.6%) developed frequent PVCs and 3 patients (11.1%) developed permanent AF. SCD or VT was not reflected in this group of patients. 3 patients (11.1%) of this cohort died due to progressive heart failure during followup and arrhythmic death was not documented. All the three patients who died during follow up had LVEF in between 20-30% at the time of intial diagnosis.

Early delivery or termination of pregnancy should be considered in case of hemodynamic instability. Stable patients are delivered vaginally unless there are obstetric reasons for a cesarean section. Postpartum risk of decompensation should be anticipated.[7] In this series of patients 3 patients conceived against medical advice. Therapeutic abortion was done in one and in the remaining two, caesarean section was done with maximizing anti failure treatment. If LV dysfunction persists, medications should be continued indefinitely. In those with LV recovery, available observational data support continued therapy indefinitely. If HF medications are stopped, they should be weaned in a stepwise manner with frequent clinical and echocardiographic assessments.[7] When the EF has not recovered to >50–55%, subsequent pregnancy should be discouraged. Even with normalized EF, counselling is required due to potential recurrence. With expert interdisciplinary management and immediate bromocriptine treatment post-delivery, successful subsequent pregnancies, especially in patients with recovered EF, have been reported.[24] Initial LVEF <30%, marked LV dilatation (LV end-diastolic diameter ≥6.0 cm), and RV involvement are associated with adverse outcomes. All the 3 patients (11.1%) who died during followup, had LVEF <30% at the time of initial diagnosis.

Conclusion

Peripartum cardiomyopathy is characterized by its rapid clinical course and a probability for spontaneous recovery. Patients with PPCM are relatively older, had a higher prevalence of preeclampsia and gestational diabetes mellitus, and are more likely to be multiparous and have multiple pregnancies. LVEF is the determinant factor in pregnancy following the diagnosis of PPCM . Based on present understanding, discouragement of a new pregnancy must be reserved for patients with PPCM who have ventricular dysfunction.Appropriate counselling should be provided for patients considering additional pregnancies. If LV dysfunction persists, women must be counselled about worse maternal and fetal outcomes. Women who recover to EF >50% still have an increased risk for HF, which may persist after pregnancy.

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Conductive Tissues of the Heart

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Introduction

During the last few decades cardiac electrophysiologic studies have evolved from a research and technical tool to an important clinical and interventional procedure frequently performed for the diagnosis and treatment of cardiac arrythmias. For a better understanding of the cardiac arrythmias brief description of the conductive tissue of heart is needed.

Anatomy of the cardiac conduction system

The nodes and networks of the so-called specializad myocardial cells constitute the cardiac conduction system (Figure-1). The components of this system are the sinoatrial and atrioventricular nodes, the atrioventricular bundle with its left and right bundle branches and the subendocardial plexus of ventricular conduction cells (Purkinje cells).

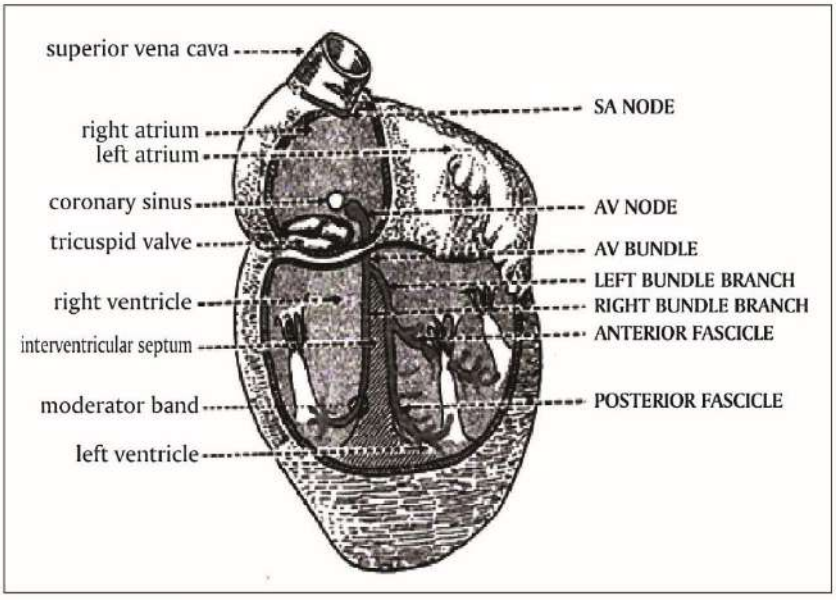

Figure-1. *Conduction system of the heart (upper case labels at right) and major anatomical features (lower case lables at left). AV-atrioventricular, SA sinoatrial. (Modified from Benninghoff 1944)*

(From the book: Physiology of the heart. Fifth edition. Arnold M. Katz. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia 2011)

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Sinoatrial node

The Sinoatrial node (SAN) is the primary pace maker of the heart. In general, although it typically cannot be seen grossly, the location of the sinoatrial node is on the roof of the right atrium at the approximate junction of the superior vena cava, the right atrial appendage, and the sulcus terminalis (Figure-2). In the adult human, the node is approximately 1 mm below the epicardium, 10–20 mm long, and up to 5-mm thick[1,2]. In hearts over 65 years of age, a layer of connective or fatty tissue between the sub endocardium and the body of the SAN may sometimes render it visible to the naked eye[3]. It extends to the right from the crest of right atrial appendage typically courses posteroinferiorly into the upper part of the terminal groove; penetrating through the thickness of the terminal crest to terminate in a tail that is buried deep in the myocardium. In most of the hearts, the SAN is a crescent-shaped structure; in about 1 in 10 hearts it extends in horseshoe fashion across the crest of appendage[4]. SAN wraps around a large central artery, that originates from either the right coronary artery in 55% of individuals or from the circumflex artery in the remainder[5]. Nodal cells are arranged circumferentially around the sinoatrial nodal artery, packed within a dense matrix of connective tissue as interlacing strands of myocytes.

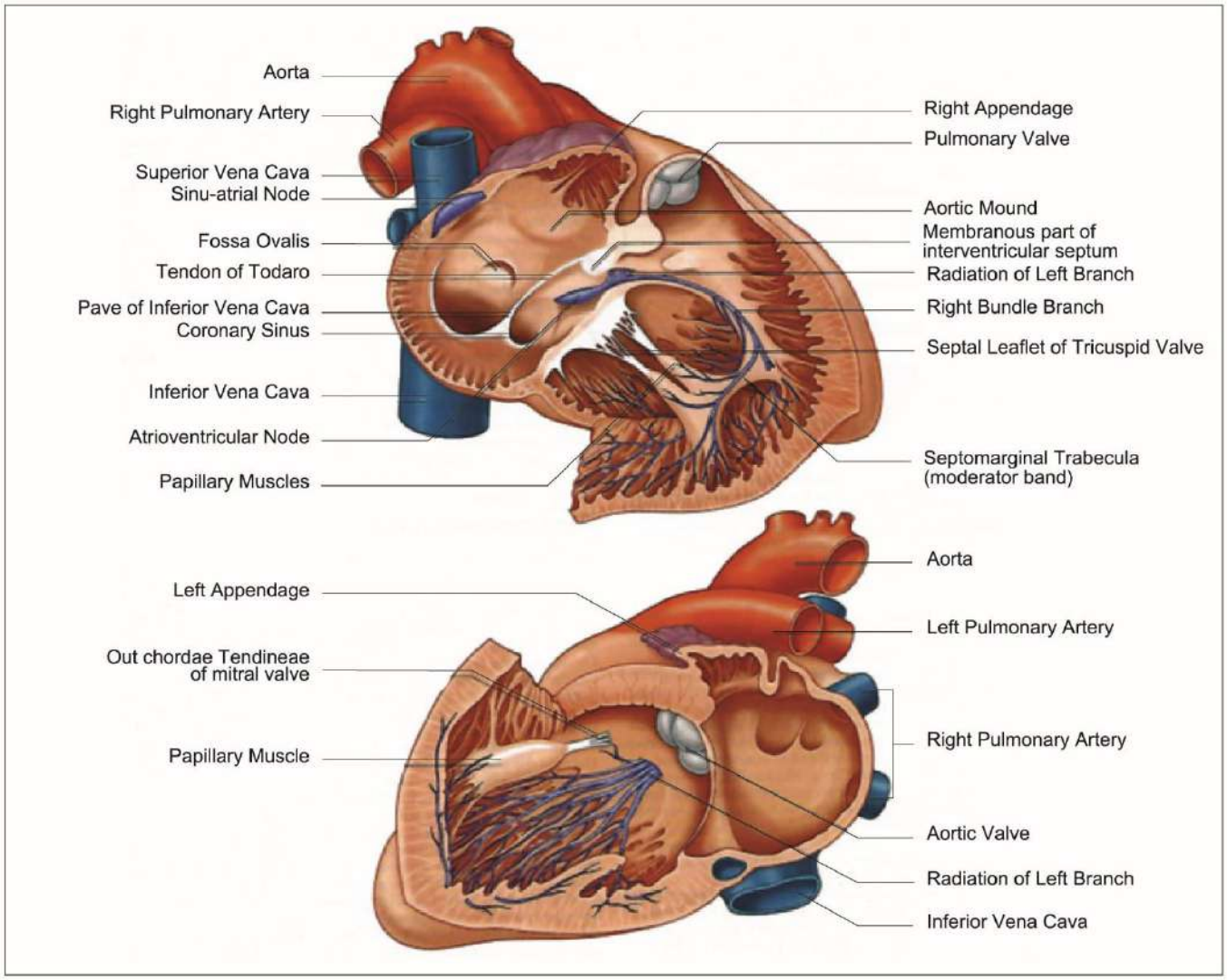
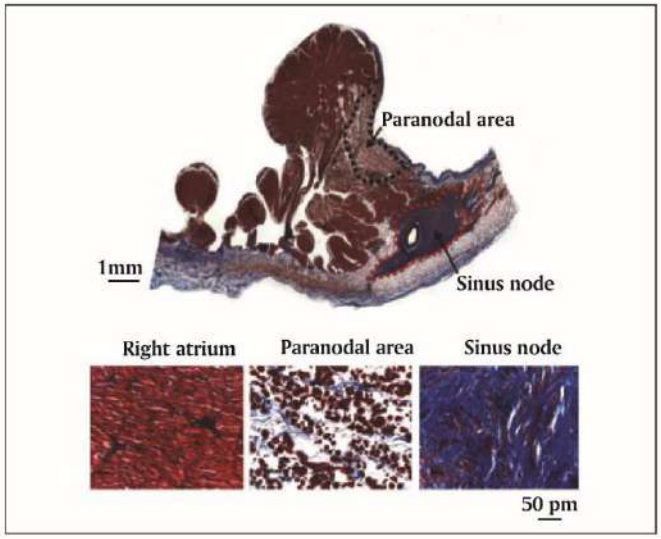


Figure-2. *The conductive tissue of the heart. A, right ventricular aspect. B, left ventricular aspect. The elements of conductive system are shown in purple. SA node is a crescent-shaped structure; in about 1 in 10 hearts it extends in horseshoe fashion across the crest of appendage.*

(From the book: Gray's Anatomy, Forty-first edition, Elsevier, 2016)



An extensive area within the terminal crest, intermingling with the sinoatrial nodal cells and the contractile atrial cardiomyocytes, histologically discrete, being recognized as specialized cells, possessing properties of both nodal and atrial tissues has been identified[1,6-10]. This paranodal area is separated by shorts zones of atrial myocardium from the SA node itself (Figure-3).

Figure-3. *The upper panel shows the location of the sinus node in a normal human heart, along with the extensive paranodal area of cells within the terminal crest. The lower panels show the histological features of the working myocytes making up the terminal crest, the myocytes in the paranodal area, and the specialized myocytes making up the sinus node. As can be seen, the cells within the paranodal area are intermediate in morphology between the nodal and working myocytes.*

(From Anderson RH, Yanni J, Boyett MR, et al. The anatomy of the cardiac conduction system. Clin Anat 2009; 22:99–113.)

Review Article

Intra and inter atrial conduction

There is no anatomic data supporting the presence of specific internodal tracts that facilitate internodal conduction between sinoatrial and atrioventricular node[11]. Although there are three so-called preferential pathways of atrial conduction exist[12]. The anterior tract leaves from anterior portion of SAN, bifurcating into two, one arm (Bachmann's bundle) goes to left atrium (LA) and the other arm enters the anterior portion of the Atrioventricular node (AVN). The middle tract (Wenckebach's bundle) leaves from dorsal and posterior margin of SAN and on its way gives off a few sparse fibers to the LA and thence into the superior margin of the AVN. The posterior tract (Thorel's bundle) leaves the posterior margin of SAN and reaches the lower and posterior portion of AVN (Figure-4). These pathways of atrial conduction appear to be related to the spatial and geometric arrangement of atrial fibers rather than to specialized tracts.

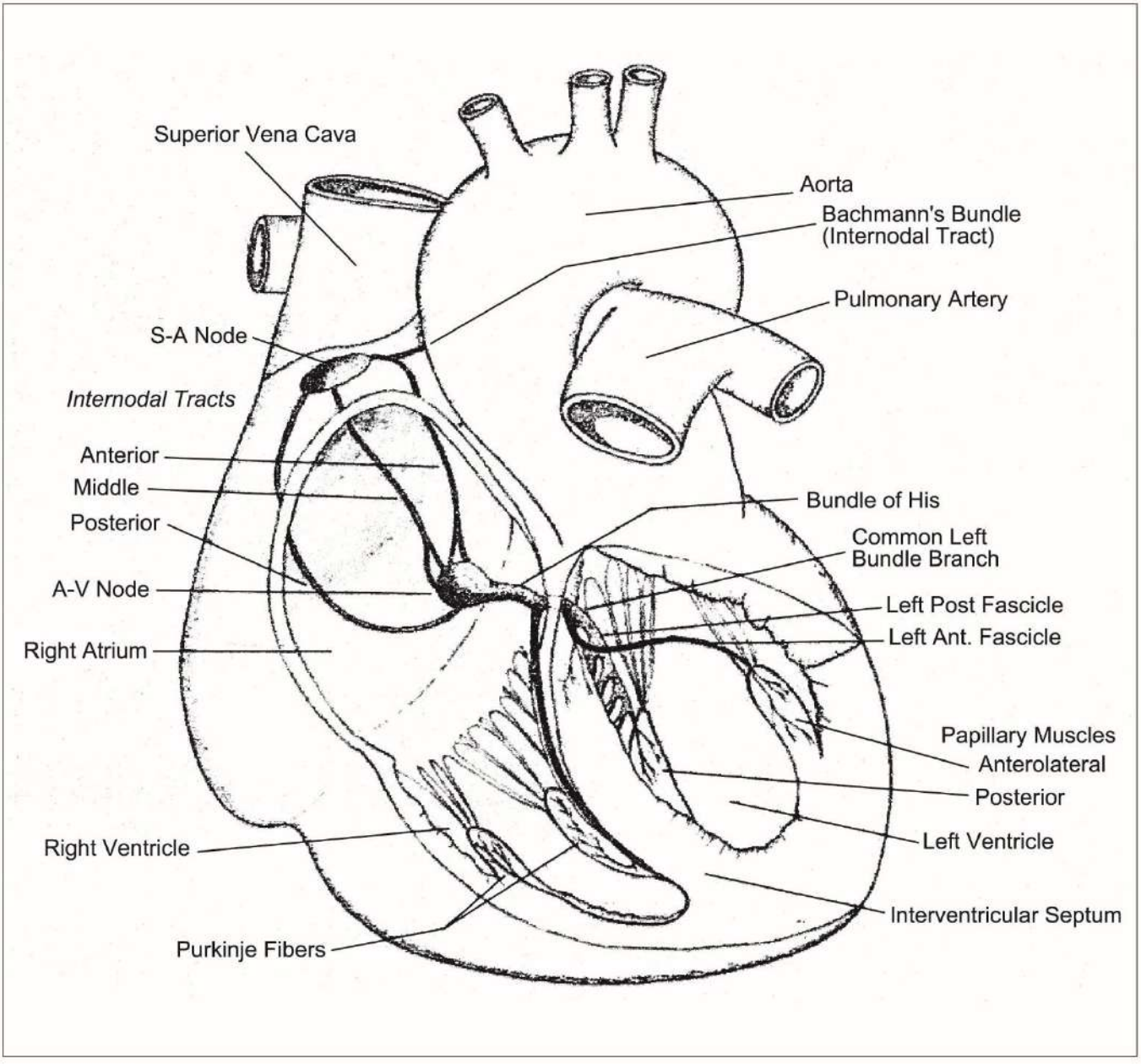


Figure-4. *Schematic representation of the of distribution of the specialized conductive tissue in both atria and ventricles showing the impulse generating and conducting system of the heart. The electrical impulse originates in the SA node traverses the atria to the AV node where it delays, cross the fibrous skeleton through the central fibrous body as His bundle. This bifurcates in RBB and LBB. The RBB continues towards the apex enters the moderator band ramifies as Purkinje fibers. The LBB takes off a little down as fine filament of fibers sub endocardially and grouped as left anterior fascicle and left posterior fascicle to enter the anterolateral papillary muscle and posteromedial papillary muscle then ramifies as Purkinje fibers.*

(From the book: Lipman-Massie Clinical Electrocardiogrphy, Eighth edition. Jayppee Brothers)

Other electrical pathways may join the atria and ventricles. These are the Kent's bundle, the James' bundle and the paraspecific septal fibers of Mahaim[13]. The *bundle of Kent*, these are strands of atrial myocardium that cross the central fibrous body at many locations linking the atria to ventricles causing a peculiar manifestation on ECG called pre-excitation. Other conduction pathways, called *bypass fibers of James*, link the atria to the upper portion of the AV bundle, so bypass the normal conduction delay in AV node. *Mahaim* fibers, which provide another abnormal pathway, connecting upper part of the AV bundle to the ventricles (Figure-5).

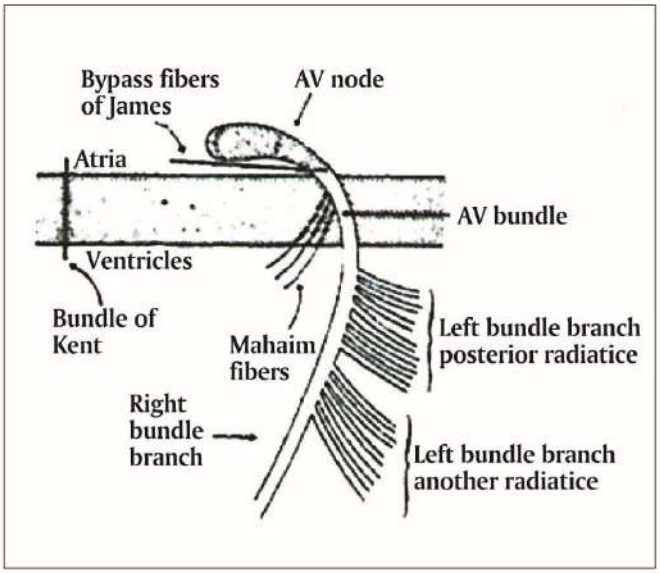


Figure-5. *Abnormal conduction pathways that can link the atria and ventricles. These include accessary pathways bundle of Kent, whose location vary; bypass fibers of James, which connect the atrial myocardium to the upper portion of the AV bundle; and Mahaim fibers, which connect the AV bundle to abnormal sites in the ventricles.*

(From Katz AM. Physiology of the Heart, Fifth edition. Philadelphia: Lippincott Williams and Wilkins, a Wolters Kluwer business 2011)

An electrical impulse originating in the SAN must traverse the both atria and reach the AVN. In addition to excitation along these so-called preferential conduction pathways, general excitation spreads from cell to cell throughout the entire atrial myocardium via the specialized connections between cells, the *gap junctions*, that exist between all myocardial cell types.

The atrioventricular node and Axis

In the normal heart, the atrial components of the atrioventricular axis are contained in a triangular area named after its discoverer the Triangle of Koch[14]. The atrial border of the triangle is formed by the continuation of the commissure between the eustachian and thebesian valves into the atrial myocardium, a fibrous structure known *as the tendon of Todaro*. The ventricular border of the triangle is the hinge of the septal leaflet of the tricuspid valve at the AV junction. The apex of the triangle is seen to be formed by the membranous part of the ventricular septum and the coronary sinus is found at the base. An isthmus is present within the triangle (septal isthmus), between the mouth of the coronary sinus and the hinge of the septal leaflet of the tricuspid valve (Figure-6).

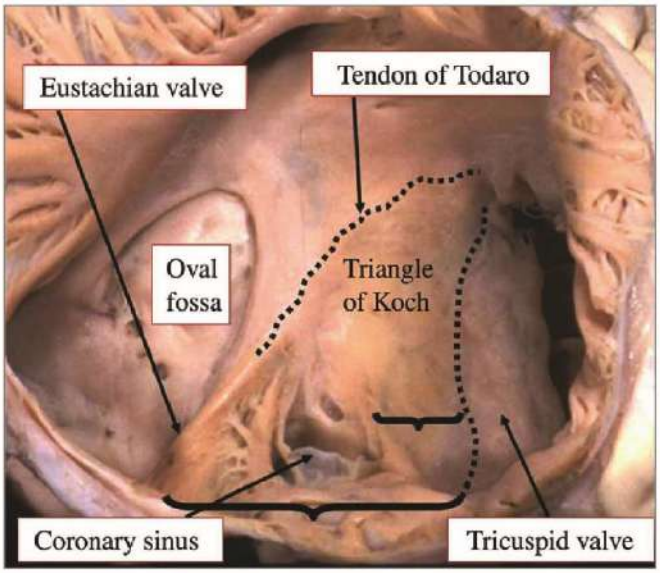


Figure-6. *The atrial border of the triangle is formed by the continuation of the commissure between the eustachian and thebesian valves into the atrial myocardium, a fibrous structure known as the tendon of Todaro. The ventricular border of the triangle is the hinge of the septal leaflet of the tricuspid valve at the AV junction. The apex of the triangle is seen to be formed by the membranous part of the ventricular septum and the coronary sinus is found at the base.*

(Down loaded from internet: pinterest.com)

The atrioventricular node is an oblique, half oval atrial structure, located within the atrial component of the muscular atrioventricular septum. The atrial aspect of the node is convex and overlain by atrial myocardium. Its left margin is concave and abuts on to the superior aspect of the of the central fibrous body. The basal end projects into the atrial muscle and the antero- inferior end enters the central fibrous body to become the penetrating atrioventricular bundle. The node itself consists of two zones, compact and transitional zones. Atrial myocytes from the right and left atrial walls, atrial septum feed directly into the compact zone. The transitional zone consists elongated transitional cells envelops the compact portion of the node. When traced inferiorly, the compact part of the node bifurcates into rightward and leftward inferior extensions when traced toward to orifices of the tricuspid and mitral valves[15]. From the anterior portion of the triangle of Koch near the compact AVN the transitional cells in continuity with the atrial myocytes streaming down cephalad to the oval fossa that forms the so-called *fast*

pathway (Figure-7). into the node. It is either the inferior transitional cells, along with the atrial myocytes of the septal isthmus or else the inferior extension of the compact nodal myocytes run in the direction of the coronary sinus along the tricuspid annulus, which forms the *slow pathway* [16,17]. The node itself lies directly adjacent to the central fibrous body of the heart, a fibrous insulating structure. About the conduction axis, when traced cephalad within the triangle of Koch, the compact node is seen to bury itself within this mass of insulating fibrous tissue. Once having entered the central fibrous body, the conduction axis is insulated from the atrial myocardium. It was this anatomical transition seen as the axis passes from the atrial tissues into the central fibrous body that Tawara [18] identified as the most reliable landmark for distinction of the node from the penetrating bundle, also known as the *bundle of His*. Once the axis has become the penetrating

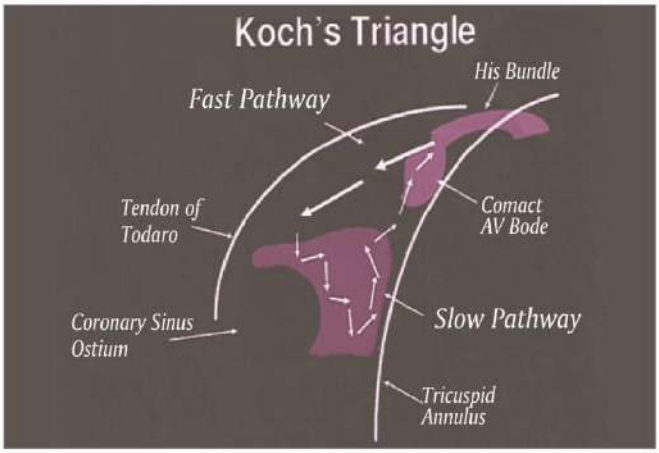


Figure-7. *The Fast and slow pathways. In the anterior portion of the triangle of Koch near the compact portion of the AV node is the fast pathway; extensions of the nodal cardiomyocytes run in the direction of the coronary sinus along the tricuspid anulus is the slow pathway.*

(Down loaded from internet: researchgate.net)

bundle, encased within the fibrous tissue of the so-called central fibrous body, the distal components of the axis continue to be insulated from the ventricular musculature until they reach their terminations at the peripheral extent of the network of Purkinje fibers.

The arterial supply of the AVN is from a characteristic vessel that originates from the dominant coronary artery at the crux of the heart the so-called atrioventricular (AV) nodal artery.

Bundle of His and Purkinje fibers

The bundle of His is the direct continuation of the compact AVN electrically insulated as it traverses through the central fibrous body crosses the fibrous skeleton of the heart[19]. The His bundle is located adjacent to the annulus of the tricuspid valve, distal to the AV node. The functional origin may be ill defined, it is typically considered to anatomically begin at the point where the atrioventricular nodal tissue enters the central fibrous body. The *bundle of His* is described as having three regions – the penetrating bundle, nonbranching bundle, and branching bundle. The penetrating bundle is the region that enters the central fibrous body. At this point, the His fascicles are insulated but are surrounded by atrial tissue (superiorly and anteriorly), the ventricular septum (inferiorly), and the central fibrous body (posteriorly). Thus, the exact point where the atrioventricular nodal tissues end, and the bundle begins is difficult to define, because it occurs over a transitional region. The nonbranching bundle passes through the central fibrous body and is surrounded by the central fibrous body. In this cardiac region, the His bundle still has atrial tissue superior and anterior to it, the ventricular septum inferior to it, and now the aortic and mitral valves posterior to it. It should be noted that His myocytes are innervated, but to a lesser extent than those in the AV node[20]. The common branching bundle is described to begin as the His exits the central fibrous body. At this point, it is inferior to the membranous septum and superior to the ventricular septum. After leaving the central fibrous body, it then bifurcates into the right and left bundle branches. Thus, having passed through the central fibrous body as the *bundle of His*, the axis emerges into the left ventricular outflow tract, being positioned on the crest of the muscular ventricular septum. The axis then branches on the crest of the muscular ventricular septum into the right and left bundle branches, with the part of the axis located on the septal crest being described as the branching part of the AV bundle. The right bundle branch first courses, as if it were a continuation of the bundle of His, as a thin cord of insulated cells within the myocardium and then subendocardially towards the ventricular apex, entering the septomarginal trabeculation (Moderator band) to reach the anterior papillary muscle. In its septal course it gives a few branches to the septum. At the origin of the anterior papillary muscle, it divides profusely into fine subendocardial fascicles that first embracing the papillary muscle then ramifying the remaining right ventricular walls. The axis itself, however, does not finish at the point of bifurcation; it continued beyond the take-off of the right bundle branches the so-called dead-end tract[21]. The left bundle branch arises as numerous fine, intermingling fascicles from the left margin of the branching bundle. These fascicles form a flattened sheet down the left ventricular septal surface, towards the apex and subendocardially trifurcating into anterior, septal and posterior divisions [18]. The subendocardial fine ramifications first surround the papillary muscles then rest of the left ventricular walls. Because the Purkinje network is subendocardial, muscular excitation proceeds from endocardium to epicardium (Figure-8). Unlike the sinoatrial and atrioventricular nodes, the *bundle of His* has no large blood vessels that supply it specifically.

Review Article

Repair and replacement of cardiac myocytes

Damaged cardiac muscle cells have extremely limited abilities to repair themselves or to replace dead cells via mitosis. Recent evidence indicates that at least some stem cells remain within the heart that continue to divide and at least potentially replace these dead cells. However, newly formed or repaired cells are rarely as functional as the original cells, and cardiac function is reduced. In the event of a heart attack or MI, dead cells are often replaced by patches of scar tissue. Autopsies performed on individuals who had successfully received heart transplants show some proliferation of original cells. If researchers can unlock the mechanism that generates new cells and restore full mitotic capabilities to heart muscle, the prognosis for heart attack survivors will be greatly enhanced. To date, myocardial cells produced within the patient *(in situ)* by cardiac stem cells seem to be nonfunctional, although those grown in Petri dishes *(in vitro)* do beat. Perhaps soon this mystery will be solved, and new advances in treatment will be commonplace.

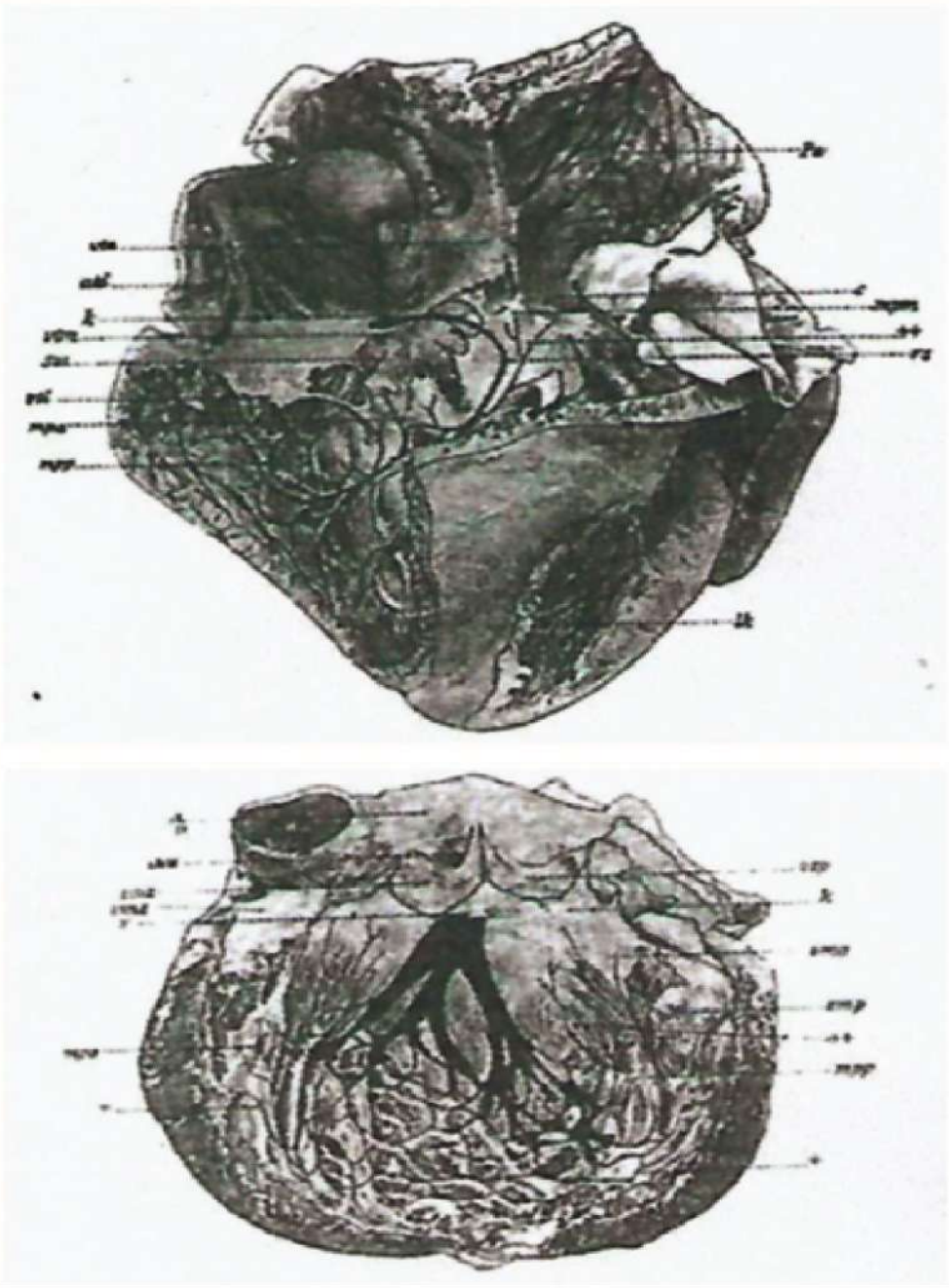


Figure-8. *Illustrations scanned from Tawara's monograph (18) show in exquisite detail the right bundle branch (upper panel) and the fan like trifascicular left bundle branch (lower panel) in the human heart.*

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Physiology of Cardiac Conduction

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Introduction

All myocytes within the heart have the capacity to conduct the cardiac electrical impulse. A population of myocytes is specialized as evident histologically to generate the cardiac impulse. Then to conduct it from the atrial to the ventricular musculatures across the insulating fibrous skeleton of the heart. This population of myocyte has become known as the conduction system[1]. Synchronized contractions of the atria and ventricles are regulated by the transmission of electrical impulses that pass through an intricate network of these modified cardiac myocytes, and they are interposed within the contractile myocardium. This intrinsic conduction system is composed of several specialized sub-populations of cells that spontaneously generate electrical impulse (pacemaker cells) or preferentially conduct this impulse throughout the four chambers of heart. Following an initiating impulse generation (or depolarization) within the myocardium, this electrical excitation spreads throughout the heart in a rapid and highly coordinated fashion. This system of cells functionally controls the timing of the transfer of activity between the atrial and ventricular musculatures also, allowing for optimized hemodynamic performance.

Overview of the cardiac conduction

The sinoatrial node serves as the natural pacemaker (Figure-1). The nodal cells manifest spontaneous depolarizations and are thus responsible for generating the normal cardiac rhythm; such a heart rate can also be described as intrinsic or automatic. Importantly, the frequency of this earliest cardiac depolarization is well modulated by both sympathetic and parasympathetic efferent innervation. In addition, the nodal rate can also be modulated by local changes within perfusion and/or the chemical environment (i.e., neurohormonal, nutritional, oxygenation, etc.). It is to note that the last part of the heart to lose activity when the whole organ dies, is the pacemaker region *ultimum moriens* [2-3].

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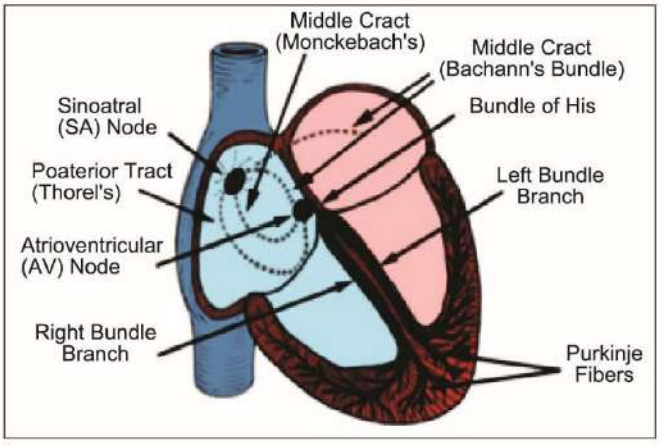


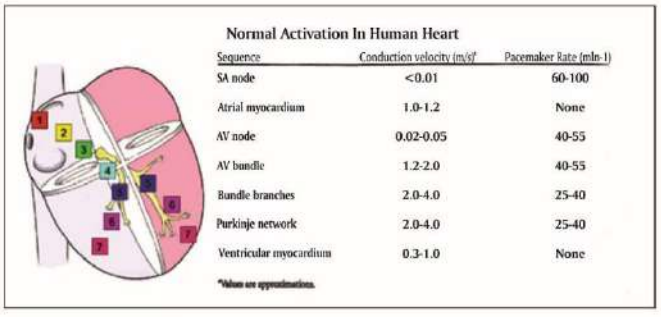
Figure-1. *The conduction system of the heart. Normal excitation originates in the sinoatrial (SA) node and then propagates through both atria (internodal tracts shown as dashed lines). The atrial depolarization spreads to the atrioventricular (AV) node, passes through the bundle of His, and then to the Purkinje fibers that make up the left and right bundle branches; subsequently, all ventricular muscle becomes activated.*

(From the book. Iaizzo PA, Laske TG, Chap-4, Anatomy and Physiology of the cardiac conduction system. In: Sigg DC, Iaizzo PA, Xiao YF, He B. editors. Cardiac Electrophysiology Methods and Models. Springer & Dordrecht Heidelbberg, London 2010)

Although the atrial rhythms normally emanate from the sinoatrial node, variations in the initiation site of atrial depolarization have been documented outside of the histological nodal tissues, particularly when high atrial rates are elicited, and may include paranodal tissue [4-8].

After initial sinoatrial nodal excitation, depolarization spreads throughout the atria. The exact mechanisms involved in the spread of impulses (excitation) from the sinoatrial node across the atria are somewhat controversial [1,9]. However, it is generally accepted that (a) the spread of depolarizations from nodal cells can go directly to adjacent myocardial cells; and (b) preferentially ordered myofibril pathways allow this excitation to rapidly transverse the right atrium to

to both the left atrium and the atrioventricular node (Figure-1). In addition to excitation along these preferential conduction pathways, general excitation spreads from cell to cell throughout the entire atrial myocardium via the specialized connections between cells, the gap junctions, that exist between all myocardial cell types. In a healthy heart, it takes approximately 30 msec for excitation to spread between the sinoatrial and atrioventricular nodes, and the widespread atrial activation occurs over a period of approximately 70–90 msec (Figure-2 and 3). The speed at which an action potential propagates through a given region of cardiac tissue can be described as the relative conduction velocity (Figure-2). The propagation velocity varies considerably within regions of the heart and is directly dependent on the relative diameter of given myocyte populations. For example, action potential conduction is greatly slowed as it passes through the AV node but is rapid in the bundle branches connected via the His bundle. This nodal slowing is due to the (a) small diameter of these cells; (b) tortuosity of the cellular pathway and (c) slower rates of rise of elicited action potentials. Nevertheless, this delay is essential to allow adequate time for ventricular filling.



Normal Activation In Human Heart

Sequence	Conduction velocity (m/s)*	Pacemaker Rate (mln-1)
SA node	<0.01	60-100
Atrial myocardium	1.0-1.2	None
AV node	0.02-0.05	40-55
AV bundle	1.2-2.0	40-55
Bundle branches	2.0-4.0	25-40
Purkinje network	2.0-4.0	25-40
Ventricular myocardium	0.3-1.0	None

*Values are approximations.

Figure-2. *The conduction system (left) and normal conduction velocity in the different parts of the heart and the corresponding pacemaker rate (right). The structures are listed in the order of activation during a normal cardiac contraction, beginning with the SA node. Note that the intrinsic pacemaker rate is slower in structures further along the activation pathway.*

(Figure, from the book: Iaizzo PA, Laske TG, Chap-4, Anatomy and Physiology of the cardiac conduction system. In: Sigg DC, Iaizzo PA, Xiao YF, He B. editors. Cardiac Electrophysiology Methods and Models. Springer & Dordrecht Heidelbberg, London 2010)

(Table, From the book: Physiology of the heart. Fifth edition. Arnold M. Katz. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, 2011).

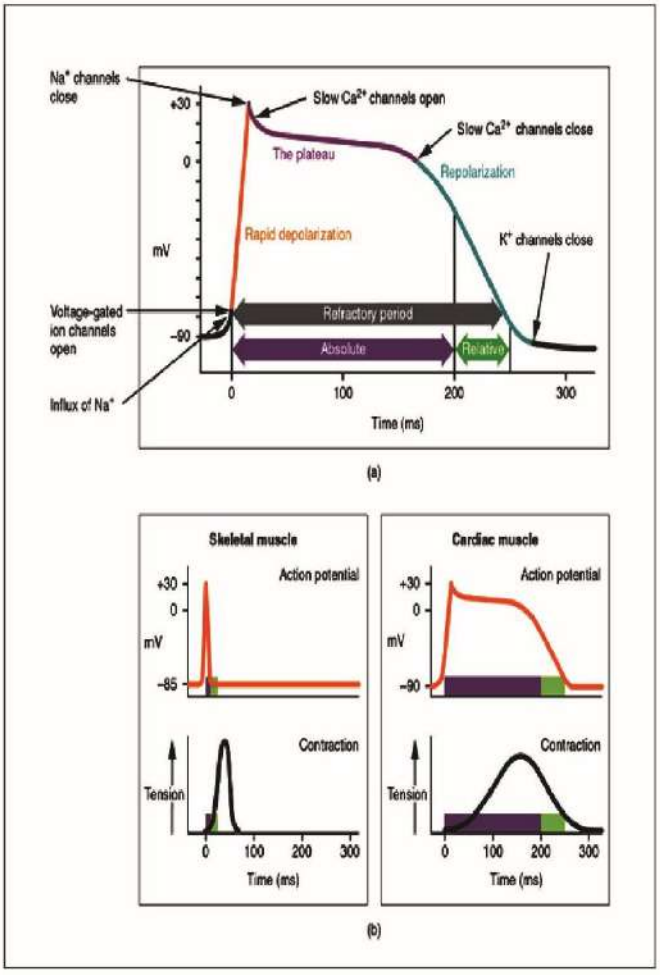


Figure-3. *Action Potential in Cardiac Contractile Cells. (a) Note the long plateau phase due to the influx of calcium ions. The extended refractory period allows the cell to fully contract before another electrical event can occur. (b) The action potential for heart muscle is compared to that of skeletal muscle. The refractory period and timing of ventricular contraction are indicated also*

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Most likely because of this direct cell to cell and preferential pathways high grade or complete heart block from atrial disease in human is virtually unknown. On the other hand, prolonged atrioventricular conduction (1st degree AV block) from atrial conduction delay is not uncommon in human.

From there, the impulse propagates rapidly through the atrial muscle and is slowed in the AVN. Towards the end of atrial depolarization, the excitation reaches the AV node via the atrial routes, with the final excitation of the AV node. These routes are known as the slow or fast pathways that are considered functionally and anatomically distinct. The *slow pathway typically* crosses the septal isthmus; it has a longer conduction time, but a shorter effective refractory period. The *fast pathway* is commonly a superior route has a faster conduction rate but, in turn, a longer effective refractory period. Normal conduction during sinus rhythm occurs along the fast pathway, but higher heart rates and/or

premature beats are often conducted through the slow pathway, because the fast pathway may be refractory at these states.

Though the primary function of the *atrioventricular node* may seem simple, that is to relay conduction between the atria and ventricles, its structure is very complex[1]. To describe these complexities, mathematical arrays and finite element analysis models have been made to know the underlying structure-function relationship of the node [10]. The delay in propagation of the impulse allows the ventricles to be diastolic during atrial systole and provides protection from ventricular arrhythmias which may be triggered by the atria [11,12].

In certain atrioventricular reentrant tachycardias, direct accessory connections from the atrioventricular node and the penetrating portion of the bundle of His to the ventricular myocardium have been described[13]. Conduction velocity in an accessory pathway is more rapid than the AV node, which allows these pathways to provide a "short circuit" that bypasses the normal delay caused by slow conduction in the AV node. Yet, the function and prevalence of these connections, termed *Mahaim* fibers, is poorly understood. A rare *bundle of Kent*, an accessory pathway when present between the atria and ventricles is responsible for a condition called Pre-excitation. Rapid conduction of atrial impulses through these accessory pathways is associated with the clinical manifestation of atrioventricular reentrant tachycardias, also known as *Wolff-Parkinson-White (WPW) syndrome*. Therapeutically, this accessory pathway is electrically identified and then commonly ablated as a curative procedure. Dual conducting pathways (slow and fast) in the AV node are an even more common cause of supraventricular tachycardias.

Following atrioventricular nodal excitation, the slow pathway conducts impulses to the His bundle, indicated by a longer interval between atrial and His activation. Currently, there is interest in the ability to place pacing leads to preferentially activate the bundle of His; in such approaches, various modalities are used to map the characteristic electrical His potentials to position the pacing leads [14].

In general, the *bundle of His*, typically considered to anatomically begin at the point where the atrioventricular nodal tissue enters the central fibrous body. After leaving the central fibrous body the His branches in right and left bundle branches those ends up in the ramification of Purkinje fibers in the ventricles [15]. Embryologically the AV node and His bundle derived separately. Sinus horn myocardium gives rise to the SA node, atrioventricular canal myocardium to the atrioventricular node and atrioventricular junction. The ventricular septum crest part of the primary ring will form the atrioventricular bundle [16].

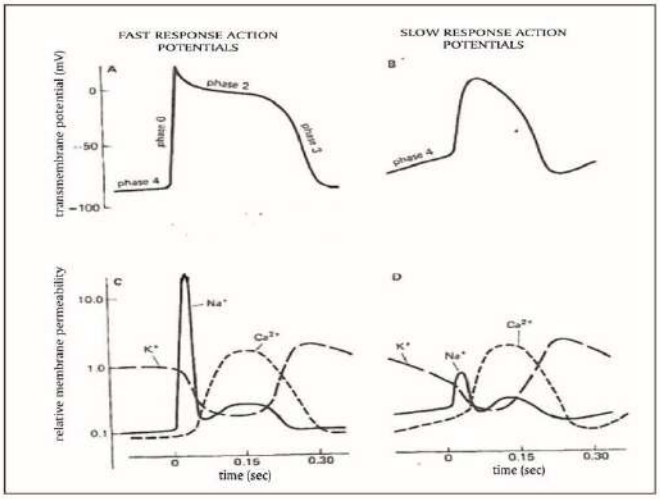
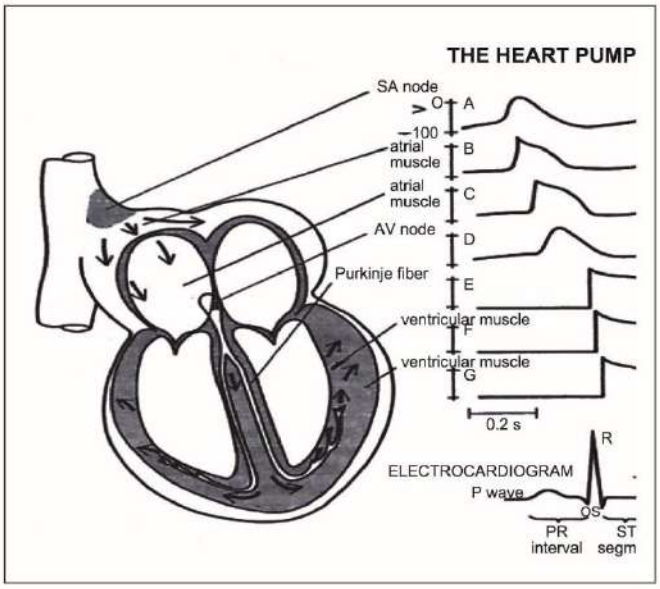


Figure-4. *The time course of membrane potential and ion permeability changes that occur during 'fast response' cell (left) and 'slow response' cell (right) action potentials. Fast response is in ventricular myocyte through Purkinje fibers and slow response is in nodal myocytes. (Modified from Mohrman DE, heller LJ. Cardiovascular Physiology, fifth edition, New York: Langer Medical Books/Mcgraw-Hill, 2003)*

(From the book: Mohrman DE, heller LJ. Cardiovascular Physiology, fifth edition, New York: Langer Medical Books/Mcgraw-Hill, 2003)

Action potentials in the Purkinje fibers are of the fast response type (Figure-4). i.e., rapid depolarization rates that, in part, are due to their large diameters. This allows the Purkinje system to transfer depolarization to most myocytes in the ventricular myocardium nearly in unison. It is important to note that the ventricular cells that are last to depolarize have shorter duration action potentials (shorter Ca2+ current), and thus are typically the ones to repolarize first (Figure-5). The ventricular myocardium repolarizes within the period represented by the T-wave in the ECG, thus a change in the duration of this wave indicates a change in the duration of functional repolarization of the ventricular cells.



Review Article

Figure-5. *Electrical activity of the heart: single cell voltage recordings (traces A to G) and lead II electrocardiogram. In the left, shown are the predominant conduction pathways in the heart and the relative time, in msec. To the right are typical action potential waveforms that would be recorded from myocytes in these specific locations. The SA and AV nodal cells have similar shaped actions potentials. The atrial contractile cells elicit action potentials that have shapes somewhat between the slow response (nodal) and fast response (ventricular) cells. The ventricular cells elicit fast response type action potentials; however, their durations vary in length.*

(From the book: Mohrman DE, Heller LJ. Langer medical books/McGraw-Hill, New York 2003) Cardiovascular Physiology. fifth edition.

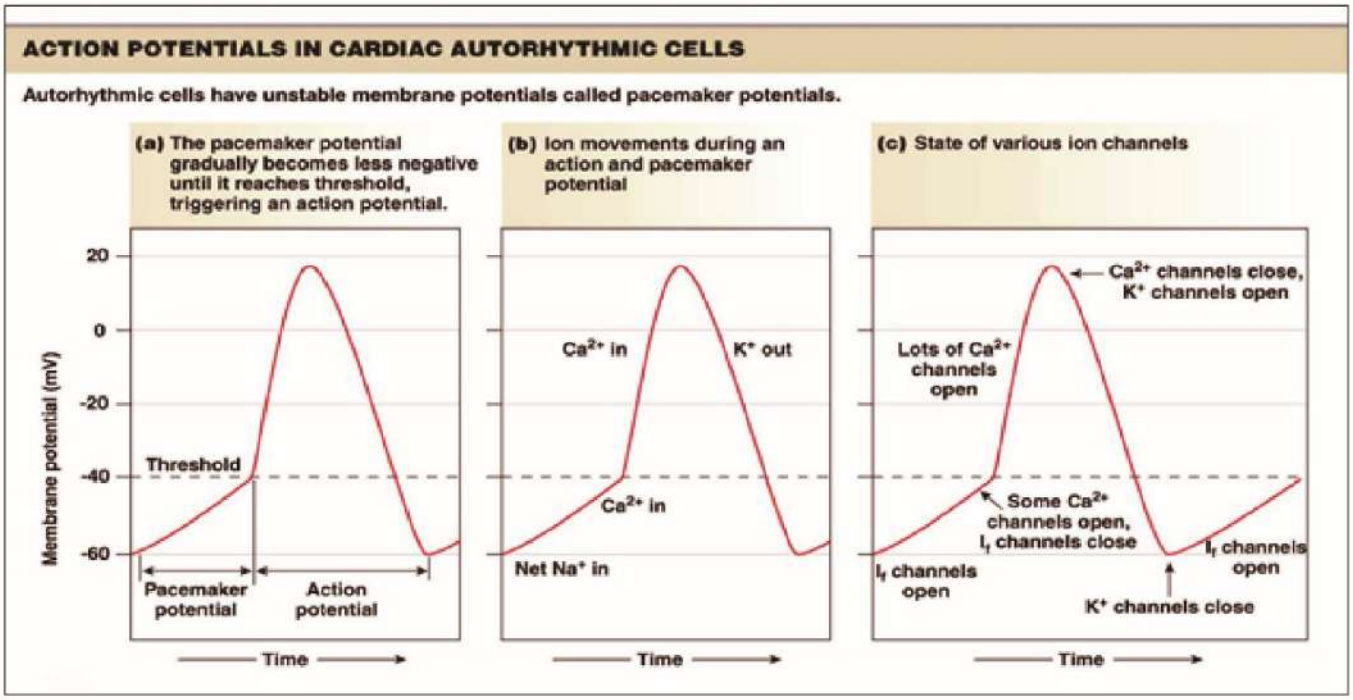


Figure-6. *The action potential at the SA node (a). The pacemaker potential (diastolic depolarization or prepotential) is marker of autorythmicity. (b) Slow inward diffusion of Na+ starts diastolic depolarization. (c) Opening of If causes inward current of Na+ corresponds to the diastolic depolarization. Note the lack of a resting membrane potential.*

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Review Article

All electrical conduction in the heart is via the cardiac myocytes; nerves serve only to regulate impulse generation and conduction. Normal activation sequence reflects the heart's embryology and anatomy. The electrical impulse that originates in the SAN first activates the atria, after which it is conducted through the AVN, AV bundle, bundle branches and Purkinje system before it can activate the ventricles. The last regions of the ventricles to be activated are the posterobasal left ventricle (LV) and the right ventricular (RV) out flow tract, both of which are derived in part from the truncus arteriosus. Conduction velocity is most rapid in the AV bundle, bundle branches and Purkinje network; less rapid in atrial and ventricular myocardium and much slower in the SA and AV nodes (Figure-2).

Cardiac Electrical Activity

Cardiac contraction is triggered by a rapid voltage change across the cell membrane called action potential. Cardiac action potential has three distinct characteristics; they are self-generating, they conduct directly from cell to cell and they have long durations. Action potentials are considerably different between cardiac conductive cells (SAN, AVN, bundle of His and Purkinje fibers) and cardiac contractive cells (atrial and ventricular contractile myocyte). While Na+ and K+ play essential roles, Ca2+ is also critical for both types of cells. It is to be noted, however, that electrophysiology of the cardiac pacemaker cells has put into evidence the relevance of ionic channels in cardiac automaticity and particularly, the specific role of the 'pacemaker' current I_f in the genesis and autonomic regulation of cardiac automaticity[17]. Thus, I_f current is the electrophysiological marker of cardiac automatic cells. I_f is a mixed cationic current carried by Na+ and K+ ions[18]. However, the main current through f-channels is due to Na+ ions which have higher permeability than K+ [19]. I_f channel is strongly expressed in SAN [20,21]. Particularly, the density of I_f is higher in the periphery of the SAN [22]. The typical ion concentrations for a mammalian cardiomyocyte are summarized in Table-1. All cardiac myocytes have an electrical potential across their membrane called membrane potential (Figure-3). The cardiac action potential underlies signaling within the heart, and various myocyte populations elicit signature waveforms. The recording or active sensing of these action potentials is important in both for research and clinical purposes.

Action potential in Cardiac Contractile Cells

A cardiac contractile myocyte has a stable resting membrane potential of approximately -80mV in atrial and -90mV in ventricular muscles. An action potential is initiated when this resting potential become shifted towards a more positive value of approximately -70 to -60mV (Phase-4) by spontaneous inward movement of Na+ ion. At this threshold potential voltage gated fast Na+ channels actively open **(Phase-0)** with rapid influx of Na+ inside cell as the Na+ concentration is higher in the extracellular fluid (fast response action potential). This rapid influx of Na+ ions raises the membrane potential to approximately +30 mV **(Phase-1)** at this point the Na+ channels close. The rapid depolarization period typically lasts 3–5 msec. Depolarization is followed by the plateau phase, in which membrane potential declines relatively slowly **(Phase-2)**. At this time fast Na+ channels automatically inactivated and activated the opening of voltage gated slow Ca2+ channels. Which allows the intracellular concentration of Ca2+ to increase rapidly. At the same time K+ channels start closing This relatively long plateau phase lasts approximately 175 msec. During this plateau phase the membrane potential stays close to 0 mV (i.e., depolarized relative to at rest), as a small outflow of K+ just balances the inflow of Ca2+. Once the membrane potential reaches approximately 0, the active repolarization begins. After this long delay, voltage gated K+ channels open and the Ca2+ channels close, allowing K+ to diffuse out of the cell due to its concentration gradient. The repolarization lasts approximately 75 ms (Phase-3). At this point, membrane potential drops until it reaches resting levels once more to the negative resting membrane potential to approximately -90 mV and the cycle repeats. The entire event lasts between 250 and 300 msec (Figure-3).

The absolute refractory period for cardiac contractile muscle lasts approximately 200 msec, and the relative refractory period lasts approximately 50 msec, for a total of 250 msec. This extended period is critical, since the heart muscle must contract to pump blood effectively and the contraction must follow the electrical events. In artificial electrical stimulation, this shift of the resting potential and subsequent depolarization is produced by the excitation delivered through the pacing system.

Action potential in Cardiac Conductive Cells

Cardiac conductive cells do not have a stable resting potential. The slow diastolic depolarization phase in cardiac pacemaker cells (SAN) is the electrical basis of cardiac automaticity (slow response action potential). Possibly I_f channel constitutes the first voltage-dependent gating to initiate pacemaker activity. Particularly I_f is activated upon membrane hyperpolarization following repolarization phase of the action potential to initiate the diastolic depolarization. In the SAN pacemaker cells, I_f current reverses nearly -20mV[19]. Indeed, I_f current allows a slow influx of Na+ ions that causes the membrane potential to rise slowly from an initial value of −60 mV up to about –40 mV. The resulting movement of Na+ ions creates diastolic depolarization (or prepotential depolarization). At this point, calcium ion channels open and Ca2+ enters the cell, further depolarizing it at a more rapid rate until it reaches a value of approximately +5 mV. At this point, the calcium ion channels close and K+ channels open, allowing outflux of K+ and resulting in repolarization. When the membrane potential reaches approximately −60 mV, the K+ channels close and Na+ channels open, and the prepotential phase begins again. This phenomenon explains the autorhythmic properties of cardiac muscle (Figure-6). Action potentials from such cells are also characterized by a slower initial depolarization phase, a lower amplitude overshoot, a shorter and less stable plateau phase, and repolarization to an unstable, slowly depolarizing resting potential.

Intercalated disc: Gap junctions, connexins

In the heart, cardiac myocytes are connected end to end by structures known as *Intercalated disks*. Adjacent to the intercalated discs are the *gap junctions* that allow action potentials to directly spread from one myocyte to the next. Non-selective channels found in the gap junctions, of the intercalated discs contain pores that account for the low electrical resistance between adjacent cells that is essential for longitudinal conduction. These channels contain a protein called *Connexon*. Each connexon contains six *Connexin subunits*. Several connexin isoforms are found within the various populations of myocytes. More specifically, within the human myocardium there are four connexin isoforms identified to date: Cx43, Cx40, Cx45, and Cx30.2/31.9. Importantly, Cx43 and Cx40 are primarily associated with the fast conduction pathways, whereas Cx45 and Cx30.2/31.9 are generally expressed in the slow conduction pathways [23].

Cell-to-cell conduction of cardiac action potentials

In the heart action potentials are conducted over the surface of the individual cells. Active depolarization in any one area of the membrane produces local currents in the intracellular and extracellular fluids which passively depolarize immediately adjacent areas of the membrane to their voltage threshold for active depolarization. Action potentials are propagated by electrical circuits from cell to cell, where impulse propagation depends on the current flow between the interiors of adjacent cells across an intercalated disc through *gap junctions*. These longitudinal currents reflect the very low electrical resistance made possible by *gap junction* channels which differ from the voltage-gated ion channels that control current flow through the plasma membrane. So, the longitudinal conduction is much faster than the transverse conduction in the heart (Figure-7).

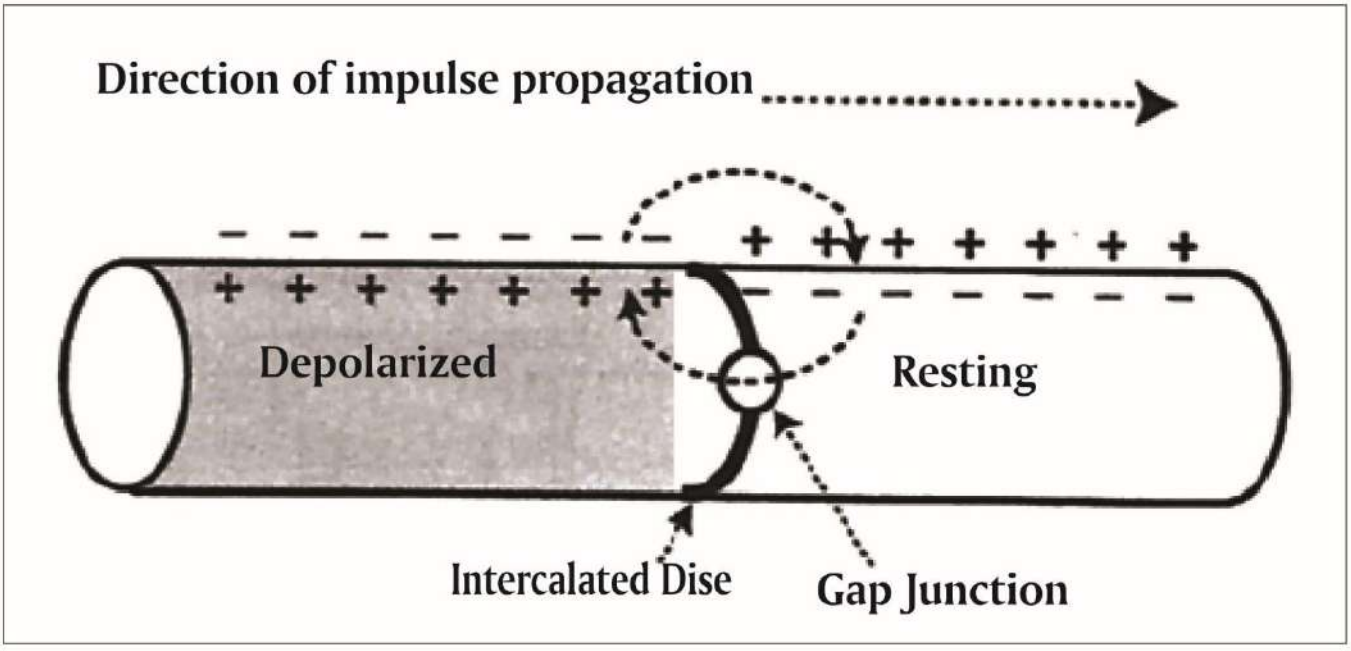

Figure-7. *Schematic diagram of two cardiac myocytes are connected by intercalated disc. During depolarization, the transmembrane potential in the depolarized cell is reversed compared to that in the resting cell. Longitudinal current is because of electron movements that flows from left to right in the extracellular space and from right to left in the intracellular space. Current flow between the cells depends on the low internal electrical resistance of gap junctions of intercalated disc.*

(From the book: Physiology of the heart 2011. Fifth edition. Arnold M. Katz. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia).)

As noted above, not all cells elicit the same types of action potentials, even though excitation is propagated from cell to cell via their gap junctions. Nevertheless, via *gap junctions* the slow response action potentials elicited in the sinoatrial nodal cells will trigger fast response action potentials in adjacent myocytes and then those within the remainder of the atria (Fig. 2.6).

Heart rate control

Under normal physiologic conditions, without nervous or endocrine control, the pacemaker cells in the sinoatrial node initiate an electrical impulse at a rate of approximately 60-100 beats per minute. Although each component of the conduction system can generate its own impulse, the rate progressively slows from the SA node to the Purkinje fibers hence not altering the intrinsic atrial rate (Figure-2). While a few exceptionally trained aerobic athletes demonstrate resting heart rates in the range of 30–40 beats per minute; for most individuals, rates lower than 60 beats per minute would indicate a condition called *sinus bradycardia*. In addition to the normal sources of cardiac rhythms, myocardial tissue can also exhibit abnormal self-excitability; such a site is called an *ectopic focus* and the rhythm is called *escape rhythm*. It should also be noted that any cardiac myocyte(s) can take over pacemaker function if driven to do so, such as in electrical pacing via an electrophysiologic catheter and from an implanted electrode of a cardiac implantable electrical devices.

Importance of His bundle in electrophysiology

His potentials are commonly be mapped by deploying an electrode in one of three ways; (a) endocardially in the right atrium at a point on the tricuspid annulus near the membranous septum; (b) epicardially at the base of the aorta near the right atrial appendage; or (c) radially within the noncoronary cusp of the aortic valve [24–28].

Today, His potentials are commonly mapped to provide a landmark for ablation of the atrioventricular node as well as to assess A-to-V conduction timing. In addition to direct electrical mapping, much can be learned about the general anatomical and functional properties of the cell lying within the bundle via attempts to directly stimulate it. For example, direct stimulation of the His produces normal ventricular activation due to the initiation of depolarization into the intrinsic conduction pathway [24,25,29]. Thus, if one frequently experiences failed attempts to selectively stimulate the His bundle, it may be assumed to be due to pathological changes [27].

Beyond these positioned catheters, numerous other sophisticated mapping systems have been developed and are described in other chapters within this book. Current clinical interest in the atrioventricular node and His bundle has focused research on their potential stimulation to ultimately improve hemodynamics in patients requiring pacing [24–27,29,30], and their use in treating atrioventricular nodal reentrant tachycardias [31-34].

Review Article

Ion Activities Inside and Outside Mammalian Myocytes

Ion	Intracellular Concentration	Intracellular Activity	Extracellular Concentration	Extracellur Activity
Sodium	5-34"	8	140	110
Potassium	104-180"	100	5.4	4
Chloride	4.2"	45	1.7	88
Calcium		0.0002"	2	1

Valus act in mM. Activities are 'averages' weighted arbi by the author for use in various
Taxed on data from Waller, 1986
Based on data from Hillic, 2001
Based on data from blints, 1985

Table-1. *Ion concentrations for mammalian myocytes*

(Adapted from Katz AM. Physiology of the Heart, fifth edition.
Philadelphia: Lippincott Williams & Wilkins, a Wolters Kluwer business 2011)

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Echocardiographic Update in Pulmonary Thromboembolism

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ABSTRACT

Pulmonary thromboembolism (PTE) is a common condition encountered in clinical practice and remains a major contributor to global disease burden. It is one of the leading causes of morbidity and mortality, especially when associated with hemodynamic instability. One of the commonest associations is thrombi forming in deep veins of the legs (DVT) from where it can travel through the venous system to pulmonary circulation leading to pulmonary embolism (PE). Within this combination, PTE accounts for almost one third of cases. The basic pathophysiological feature, which account for clinical and echocardiographic presentation, is an acutely increased pulmonary vascular resistance (PVR), leading to increased right ventricular (RV) overload, mainly contributed by an anatomical obstruction to the pulmonary vasculature, coupled with pulmonary artery vasoconstriction induced by release of certain neurohormonal substances and RV hypoxia. The clinical classification of massive, sub-massive and non-massive is based mainly on hemodynamic status and presence or absence of RV dysfunction and are determining factors in prognosis and management of APE.

PTE remains a diagnostic enigma. This could be due to several reasons like not having a high index of suspicion, variable clinical presentation, can be silent and associated with other diseases, absence of triad of rapid onset dyspnoea, tachycardia, pleuritic or substernal chest pain, hemoptysis etc and no provoking factors in almost 25-30% cases. The diagnosis of acute PTE is usually made by contrast enhanced computed tomography or ventilation-perfusion (V/Q) nuclear scan. However each modality has its own limitations. Echocardiography (TTE) has proved to be an important initial tool for the diagnosis, prognosis and guide to management of PE, especially in high risk patients. It also allows exclusion of other life-threatening conditions causing chest pain or hemodynamic instability. Despite its low to moderate sensitivity, TTE is still an integral part of diagnostic workup. A carefully performed echo, in conjunction with clinical history, gives a useful clue to the diagnosis, in the form of unexplained RV and RA enlargement/RV dysfunction/ pulmonary hypertension. TTE has indirect and direct evidences in diagnosis of PTE. The indirect evidences mainly pertain to quantitative and qualitative criteria of RV functions, pulmonary hypertension, changes in inferior vena cava collapsibility etc. Direct evidences mainly include visualization of floating thrombus in venous system, and cardiac chambers, Echo also contributes to prognosis of PTE, follow-up and management which have been discussed. These mainly pertain to role of echocardiogram.

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INTRODUCTION & NATURAL HISTORY

Venous thromboembolism is a common condition encountered in clinical practice. It is a combination of deep vein thrombosis (DVT), a common association, and acute pulmonary embolism (APE). Within this combination, PTE accounts for almost one third of cases. PTE is a major contributor of global disease burden. Annual incidence is about 75- 269 cases per 100,000 patients. Risk doubles with each decade after 40 years age. Risk is usually highest in first two post-operative weeks. Mortality for PE is about 2% in normotensive patients without evidence of right ventricular dysfunction (RVD), but rises up to 30% in patients with shock and up to 65% in patients with cardiac arrest at presentation. If left untreated, approximately one-third of patients who survive an initial pulmonary embolism die of a subsequent embolic episode.[1-4] The International Cooperative Pulmonary Embolism Registry (ICOPER) demonstrated 90-day mortality rates of 58.3% in patients with massive PE versus 15.1% in sub-massive PE.. Furthermore, a small fraction (upto 4%) of surviving patients will later on develop chronic thromboembolic pulmonary hypertension (CTEPH), Untreated CTEPH carries a poor prognosis, especially if associated with right ventricular dysfunction. Its development is multifactorial like incompletely resolved thrombi, shear stress, remodelling of the pulmonary vascular bed and microvascular inflammation.

PATHOPHYSIOLOGY

The pathophysiological response to acute PE is of utmost importance to understand its hemodynamic consequences, which in turn will affect patient prognosis. It depends on four factors (a) the size of the pulmonary embolus determines the initial hemodynamic compromise. Patient prognosis depends on the extent to which pulmonary artery blood flow is obstructed (b) pre-existing cardiopulmonary disease (c) chemical vasoconstriction due to release of vasoactive humoral factors from clots (d) reflex vasoconstriction due to pulmonary artery dilatation. The main manifestations of major PE are acute right ventricular (RV) failure and hypoxia. The basic pathophysiology is an acutely increased pulmonary vascular resistance (PVR) which is mainly contributed by (a) anatomical obstruction to the pulmonary vasculature (b) pulmonary artery vasoconstriction induced by release of neurohormonal substances (serotonin from platelets , thrombin from plasma and histamine from tissues (c) right ventricular hypoxemia.

The sequence of APE is shown in Flow charts 1 & a simplified version in 2. In brief this acute increase in PVR, which right ventricle (RV) is not able to handle, leads to increased RV overload which in turn manifests as RV dilatation, hypokinesis and failure. The dilatation of RV leads to increased RV wall tension leading to increased RV oxygen consumption, further aggravated by tachycardia, resulting in RV ischemia. This in turn leads to decreased RV contractility and output. The coexisting reduced cardiac output and hypoxemia aggravates RV ischemia resulting in RV dysfunction. This dilatation of RV affects the left ventricle function due to displacement of interventricular septum into LV cavity thereby worsening the distensibility of left ventricle (LV) and decreases diastolic filling leading to reduced LV preload further reducing cardiac output. This in turn leads to systemic arterial hypotension, cardiogenic shock, cardiac arrest and ultimately death.[3-5]. Most of the echocardiographic findings are based on this pathophysiology and hence remains an important imaging modality in clinical categorisation and management of a case of APE.

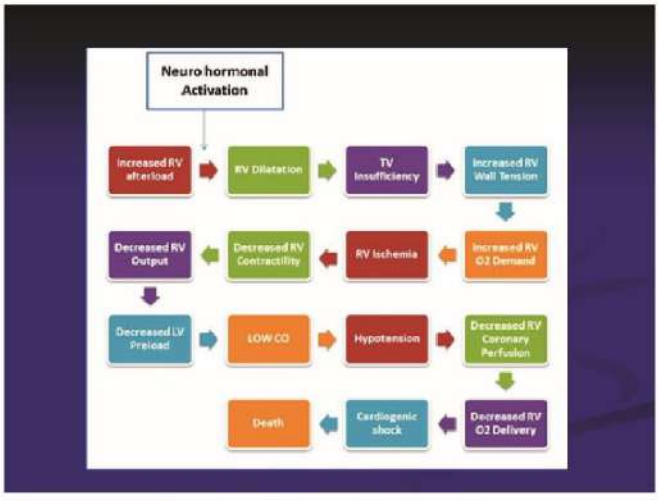
PREDISPOSING FACTORS

Some of the important risk factors for pulmonary embolism, as shown in Table 1, are divided into strong, moderate or weak factors based on odds ratio for causing PE. Few of the weak factors deserve emphasis like; air travel which is increasing worldwide and involves prolonged sitting especially in long haul flights, bed rest >3 days, pregnancy, presence of varicose veins etc. These risk factors must to be taken into account during history taking.[5-7] Some of the inherited major thrombotic disorders like Protein C & S deficiency, Antithrombin 111 deficiency, Prothrombin gene mutation 20210 (3.7%), Factor V Leiden – activated protein C resistance, dysfibrinogenemia are getting less importance now.

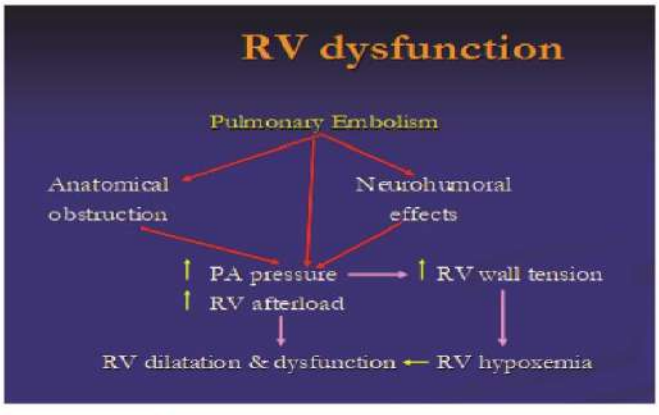
Strong factors (OR > 10)	Moderate factors (OR 2-9)	Weak factors (OR < 2)
Bone fracture (hip, leg)	Arthroscopic knee surgery	Bed rest >3 days
Hip or knee replacement	Central venous lines	Immobility due to sitting (e.g., prolonged car or plane travel)
Major general surgery	Heart or respiratory failure	Increasing age
Major trauma	Hormone replacement and oral contraceptive therapy	Laparoscopic surgery (e.g., cholecystectomy)
Spinal cord injury	Malignancy, chemotherapy	Obesity
	Immobility after stroke	Pregnancy (antepartum)
	Pregnancy (peripartum) - Lactation	Chronic venous insufficiency, varicose veins
	Previous VTE	
	Thrombophilia	

OR – odds ratio for different predisposing factors

Table-1. *Showing various risk factors for pulmonary embolism*



Flow Chart-1. *Pathophysiology of effect of acute pulmonary embolism. Abbreviations: RV, right ventricle, LV-left ventricle, TV-tricuspid valve*



Flow Chart-2. *A simplified version showing pathophysiology of right ventricular dysfunction: RV, right ventricle, PA, pulmonary artery*

SEVERITY OF APE BASED ON CLINICAL PRESENTATION

The assessment of severity, based on hemodynamic status and RV involvement, plays a significant role in prognosis and deciding management. These can be subdivided into the following categories.

Massive pulmonary embolism: This is characterized by systolic BP < 90 mmHg for > 15 mins or requiring inotropic support to maintain BP > 90 mmHg together with features of RV involvement and dysfunction or cardiac arrest. It has an in-hospital mortality of about 25-50%.

Sub- massive pulmonary embolism: The patient is hemodynamically stable (BP > 90 mmHg.) with evidence of RV dysfunction, tachycardia, tachypnoea, elevated biomarkers etc, The in-hospital mortality varies between 3-15%

Non- massive pulmonary embolism: There is neither systemic hypotension nor RV dysfunction and usually constitute about 95% of cases., with a mortality of < 3% [6-8]

DIAGNOSIS

Diagnosis of PTE poses a fair amount of diagnostic problem as it masquerades many other illnesses, and it can be silent and occur concomitantly with other diseases. Moreover clinical presentation may range from incidentally detected PE to shock, arterial hypotension (<90 mmHg) to sudden death. ECG can be non-contributory in about 25% cases. Some useful approaches in diagnosis are as follows:

- Having high index of suspicion
- Clinical pretest probability as assessed by modified Wells criteria
- Awareness of predisposing factors which can be present even 4-8 weeks prior to an episode of APE and not in recent past
- Careful evaluation of presenting signs & symptoms
- Other diagnostic techniques

OTHER DIAGNOSTIC TESTS

These include (a) plasma D-dimer assay (b) CT pulmonary angiography which has good diagnostic sensitivity, specificity and negative predictive value (c) V/Q Scan which could be inconclusive in elderly patients (d) Venous Doppler of lower limbs which is mandatory in all cases of APE (e) Echocardiography (f) weak supportive biomarkers like BNP. NT-pro-BNP, troponins etc

It may be worthwhile to mention the significance of plasma D-dimer assay which is usually the first test performed in emergency units. D-dimer is a fibrin degradation product (FDP), a small protein fragment present in the blood after a blood clot is degraded. D-dimers are not normally present in human blood plasma, except when the coagulation system has been activated, as in the presence of thrombosis or disseminated intravascular coagulation. D-dimer assays are characterized by having good sensitivity and negative predictive value, but poor specificity because elevated D-dimer may be present in various other conditions s like liver disease, high rheumatoid factor, inflammation, malignancy, trauma, pregnancy, recent surgery as well as advanced age. The causes of false negative D-dimer results are small emboli, pre-treatment with anticoagulant therapy and symptoms lasting for more than 10 days. Depending on the clinical probability of APE, it has high sensitivity (96% -100%) & negative predictive value (100%), but low specificity (37.5%) and also low positive predictive value[9]. As such It alone cannot confirm or exclude APE. Despite this an absence of elevation usually favors exclusion of APE. Though contrast enhanced computed tomography or ventilation-perfusion (V/Q) nuclear scan are extremely useful tests, especially the former one, but echocardiography plays a multifaceted role in PTE

ROLE OF ECHOCARDIOGRAPHY

Echo is an important investigative modality due to following reasons:

- It is a simple and widely available
- Bedside modality in critically ill patients which can also assess any other cause of hemodynamic instability, like shock, and identify a subset of patients who can be benefited by an aggressive therapy in the form of thrombolytics.
- Allows evaluation of RV size and function as involvement of RV, as per pathophysiology of APE, is an important component in APE in about 40-70% of cases
- Provides immediate result
- Guides in risk stratification
- Serial follow-up

How diagnostic is transthoracic echo (TTE) [10-12] : Based on several studies the sensitivity of TTE has varied between 41% -51% and specificity between 87% -91%. Because of the negative predictive value of 40-50%, a negative result does not exclude pulmonary embolism[10-12]. However there is significant role for exclusion of other confounding diagnosis and other roles as mentioned below. The diminished overall sensitivity of TTE for the diagnosis of PE limits the utility of echocardiography as a screening tool for all patients with this suspected disorder. Still it continues to be an important modality due to reasons mentioned above. However in those with massive PE, echocardiographic evidence of PE may be seen in up to 80% of patients. The specificity is about 80% -90%. Despite the various limitations a combination of echo + ECG + D – dimer has a high diagnostic specificity. Echocardiography has indirect and direct evidences in diagnosis of APE. The indirect evidences have relatively more value in presence of a nidus for APE or high pre-test probability of PE.

Indirect evidences: These evidences can be effectively utilized to give a clue to diagnosis. Some indirect evidences are as follows:

- Unexplained RV and right atrial enlargement (Fig 1). This is because of acutely increased RV afterload
- RV dysfunction, if present in some cases, as assessed by various parameters like RV fractional area shortening (<35%), tricuspid annular plane systolic excursion (<17 mm), tricuspid annular systolic velocity (<10.0 cm/sec), RV myocardial performance index (> 0.43 or > 0.55 by TDI) and abnormal RV longitudinal strain (<-20%)
- Pulmonary hypertension with systolic flattening of interventricular septum due to decreased IVS gradient (Fig 2)
- Dilated IVC with decreased inspiratory collapse due to increased RA pressure consequent to increased RV pressure

McConnels Sign: It is defined as a regional contractile dysfunction of RV characterized by hypokinesia or akinesia of mid and basal free wall of RV with preserved or hypercontractility of the apical segments. It is believed to be present in acute massive pulmonary embolism with a large thrombus in main PA or in lobar pulmonary artery.[13] Its pathophysiology has been studied by various workers based on 2-D Speckle tracking[14-16] It has been postulated that an often hyperdynamic left ventricle that shares the ventricular apex with the right ventricle pulls the hypo-contractile RV free wall toward the left in systole in a way that tethers the RV apex and hence it appears to be contracting vigorously. McConnells sign can be found in any cause of an acute increase in pulmonary vascular resistance with acute PE being the most common aetiology.

60/60 sign: This sign comprises of (2) tricuspid pressure gradient of < 60 mmHg but more than 30 mmHg. (b) pulmonary artery acceleration time of <60 msec. In the presence of RV failure, it is consistent with acute elevation of RV overload which is commonly due to acute PF. This sign is not very sensitive but quite specific (94%)

Direct Evidences: These are more diagnostic as they involve direct visualization of thrombus in the venous system including various cardiac chambers. There are basically three sub-classifications of right heart thrombi: Type A thrombi are morphologically serpiginous, highly mobile and associated with deep vein thrombosis and pulmonary embolism. It is hypothesized that these clots embolize from large veins and are captured in-transit within the right heart. Predisposing factors include prominent eustachian valves, tricuspid regurgitation, low cardiac output and pulmonary hypertension. Type B thrombi are believed to form in situ in association with underlying cardiac abnormalities. Type C thrombi are rare, share a similar appearance to a myxoma and are highly mobile. As such a careful evaluation should start from deep veins of leg and gradually followed in a step wise sequence from IVC (Fig-3), then proceed sequentially to right atrium (Fig-4), right ventricular outflow tract(Fig-5) right ventricle (Fig 6), pulmonary arteries usually at the level of bifurcation (Fig-7) or in one of the branches (Fig-8). This is usually possible with transthoracic echo (TTE). In the right atrium, important differential diagnosis include prominent Eustachian valve, Chiari network, tumors, large vegetations etc.

An important aspect of RV functions in PE is 2-D strain. Myocardial deformation or strain is defined as deformation of an object compared with its initial shape and is expressed as percentage. The most important measure is the global longitudinal strain (GLS). It is a measure of % of shortening of RV free wall, from base to apex, compared to diastole. This contractility is due to longitudinally aligned deep muscle fibers. GLS of the RV free wall is an objective and accurate marker of global RV systolic function in various conditions like PE leading to pulmonary hypertension (Ju-Hee Lee) etc. It has a good prognostic power in acute PE. It significantly correlated with in hospital mortality in one study (Kathleen et al). The normal reference average value is about -25%. Fig-11 shows significant RV dysfunction with GLS of -7.7%

Transesophageal echo: This is useful in (a) inaccessible portions of main PA (b) significant portion of right PA until it branches to the right lobar pulmonary arteries. (c) proximal portion of left PA as interposition of the left main bronchus interferes with the ultrasound beam in the middle portion. It is of the left pulmonary artery. Therefore, thromboembolism is more difficult to detect in the left pulmonary artery. (d) in about 60-70% cases of central emboli (Fig-9). From a practical point of view, PE should be suspected in three unexplained situations namely, RV enlargement, RV dysfunction and pulmonary arterial hypertension.

Role in prognosis: The presence of RV dilatation and systolic dysfunction has a significant impact on the outcome. Toosi et al[17] reported their data associated with risk stratification of 159 patients with acute PTE. In their study, moderate to severe RV hypokinesis and RV/LV end diastolic area ratio >1.0 were significantly associated with higher in-hospital mortality and demonstrated the best predictive values for short-term outcomes. In another prospective study of 209 consecutive patients diagnosed with an acute PTE without hemodynamic compromise, 65 patients (31%) had echo assessed RV dysfunction[18]. In these patients, the mortality rate was much higher than those patients without RV dysfunction (5% with RV dysfunction vs. 1.2% without RV dysfunction). In the ICOPER registry (International Cooperative Pulmonary Embolism Registry)[19] which included 2454 consecutive patients with acute PTE, 40% of the patients had RV dysfunction, and 4% had free-floating cardiac thrombi. The overall 90-day mortality was 15.3%. Multiple-regression modelling revealed that RV dysfunction was a strong and significant predictor of death.

Dahhan et al[20] studied 69 cases of confirmed acute PE of which 14 died over a 30 days period. RV functions were studied in detail by several well-established methods including longitudinal strain of RV free wall, longitudinal strain of RV septum and global longitudinal RV strain (RVLS). They observed that Tei Index, global and free wall RVLS were significantly different between survivors and

non-survivors ($p \leq 0.05$). A significant proportion of non-survivors had global and free wall LS of more than −12.5, a value which has been demonstrated to be associated with worse outcomes in pulmonary hypertension. TAPSE, RVFAC, subjective RV dilation and subjective RV dysfunction were not statistically different between survivors and non-survivors ($p > 0.05$). Similarly Vitarelli et al[21] showed that changes in 3D RVEF and MFW RVLS were the most sensitive predictors of adverse events. By multivariate analysis, RV systolic pressure (P=.007), MFW RVLS (P=.002), and 3D RVEF (P=.001) were independently associated with adverse outcomes.

Contrary to the above, an interesting study was performed by Khemasuwan et al[22] on 235 confirmed cases of acute pulmonary embolism. The primary outcomes of interest were ICU (death that occurred during the ICU stay), hospital (death that occurred at any point during the hospitalization, including the ICU stay). Besides the analysis of RV strain and strain rate by two-dimensional speckle-tracking, some other measured RV parameters included RV outflow tract diameter and time-velocity integral, RV EDD (basal, midcavity, and longitudinal), RV end-diastolic wall thickness, RV systolic pressure (RVSP), RV-to-LV EDD ratio (RV/LV EDD), right atrial (RA) midcavity diameter, and end-systolic area. Tricuspid annular plane systolic excursion (TAPSE). IVC collapsibility was assessed. 13% patients died during ICU stay and 18% died during period of hospitalization with median stay of 2.8 to 11.1 days respectively. The four simple parameters that measure different aspects of the right ventricle (ratio of RV to left ventricular end-diastolic diameter >1.0, RV systolic pressure, tricuspid annular plane systolic excursion, and inferior vena cava collapsibility) were independently associated with mortality in patients presenting with acute PE who were admitted to the ICU. There was a lack of prognostic value of McConnell's sign to predict mortality, length of stay, or clinical deterioration. RV strain analysis by speckle-tracking imaging was not correlated with hospital or long-term mortality. As such more studies are needed on the prognostic information about deformation imaging.

Combining echocardiographic data and laboratory tests can give additional prognostic implications. Binder et al.[23] reported their results about the combination of echocardiographic data with either NT-pro B-type natriuretic peptide (BNP) or cardiac troponin T (cTnT) in the prediction of complicated in-hospital course or death. With a positive echocardiographic results and either NT-proBNP >1000 pg/mL or cTnT >0.04 ng/mL, the risk of severe complication or death was approximately 38%. In another study[24] evaluating the association of RV enlargement, elevated cardiac troponin I (cTnI) and 30 day mortality in patients with acute PTE, the mortality rate for patients with cTnI >0.1 ng/mL was 32%, with RV enlargement 28% and for patients with both findings it was 38%.

In summary some of the adverse echo prognostic signs are (a) RV dilatation & hypokinesis – RV diameter / LV diameter >0.9, (b) interventricular septal flattening and paradoxical leftward septal motion (c) presence of tricuspid regurgitation and pulmonary hypertension (d) RV free wall hypokinesis with apical sparing (McConnell's sign) (e) ? increased shock index i.e. heart rate / systolic blood pressure, normal value being <0.7. However it is less robust as compared to pulmonary embolism severity index (f) Simplified pulmonary embolism severity index, the adverse features being age >80 years, history of chronic cardio-pulmonary disease, presence of cancer, heart rate >110 / min, BP < 100 mmHg, arterial oxygen saturation <90%.

Serial follow up: Being a non-invasive and bedside technology, echo can be utilized in follow up of confirmed cases of acute pulmonary embolism. The success or failure of an individual patient's therapy can be monitored by serial assessment of right ventricular function. Following a reduction in size of embolus, the degree of RV strain will be reduced. After anticoagulation therapy, there will be a reduction in PA pressure, the RV and RA gradually reduce in size and the function of RV improves. Fig-10 shows almost a complete regression of thrombus in RV following therapy who initially had a large RV thrombus (Fig-6). As such echo can be a guide to the response to therapy.

In view of the above, despite variable reported sensitivity and specificity of echocardiography in PE, it still remains the first diagnostic tool in these cases. A carefully performed echo, in conjunction with clinical history, gives a useful clue in the diagnosis, a mentioned above, in the form of unexplained RV, RA enlargement/RV dysfunction/ pulmonary hypertension. A sequential and careful examination from IVC to RA to RV to PA should always be made to see for a thrombus.

Role in management: This will be briefly confined to role of echo and not detailed management of APE which needs a multidisciplinary approach. There are multiple strategies of treatment of acute pulmonary embolism namely:

- Anticoagulation
- Thrombolysis
- Percutaneous catheter directed reperfusion techniques or clot retrieval from main PA including novel ultrasound-assisted catheter directed thrombolysis (UA-CDT)
- Surgical embolectomy as a last resort

Of these the first two are more important and of practical significance. Echo plays a role in risk stratification on the basis of which the treatment strategy is based. Though it is mainly clinical, but echo parameters classifying in various categories of severity, as mentioned earlier, are crucial. Majority of the patients are beneficiary of anticoagulation, including all newer oral anticoagulants. The duration of therapy is individualized and in provoked PE is usually 3 months which, however, can be extended in view of safety profile of NOAC. In special subgroup of patient's a life long anticoagulation is recommended (unprovoked PTE proven

Protein C and S deficiency, presence of lupin anticoagulant, ongoing thrombosis in proximal veins, and active cancer)A combination of hemodynamic stability like persistent hypotension, tachypnoea, echo parameters of degree of RV enlargement, RV dysfunction, pulmonary hypertension demarcate high risk patients. Based on these parameters of echo severity, thrombolytics, as per meta-analysis of various trials, have been found to reduce mortality in massive APE with unstable hemodynamics. The early resolution of pulmonary obstruction leads to a prompt reduction in pulmonary artery pressure and resistance, with a concomitant improvement in RV function. Accelerated regimens administered over 2 hours are preferable to prolonged infusions of first-generation thrombolytic agents, like Reteplase / Tenecteplase. over 12–24 hours of first generation. In sub-massive APE, rescue fibrinolysis, is employed if clinical signs of hemodynamic decompensation occur during treatment. Catheter directed reperfusion techniques with or without fibrinolytics is utilized based on institutional experience and can be an alternative to surgical embolectomy. It aims to relieve obstruction quickly and restore pulmonary blood flow, thus improving cardiac output and converting a hemodynamically unstable situation to stable. This therapy might include clot fragmentation, aspiration, and low dose fibrinolytic injection. It may be employed in patients with obstructing thrombus in main or lower lobe PE + RV changes. Low dose thrombolytics can be administered in so called pharmaco-mechanical thrombolysis. This technique can also be utilized in those with contraindication to thrombolytics. Multiple trials show survival in 86% cases of massive PE and 97% in sub-massive PE. The IVC filter is less used but main indications are (a) acute PE with absolute contraindication to anticoagulants (b) acute PE with major bleeding events (c) objectively confirmed recurrent PE despite adequate anticoagulation

A highly individualized approach encompassing patient selection, type of therapy, operator and hospital level of experience should be followed to maximize the benefits of an interventional strategy as well as minimize the risk of harm. Irrespective of approach one important take home message is to avoid aggressive fluid resuscitation as it may lead to RV overstretch, leading to RV ischemia with worsening of RV failure

In conclusion, bedside echo is very helpful for evaluation of acutely ill patients in whom diagnosis of APE is doubtful. By determining signs of RV strain and PAH it can be of help in these patients. It helps in excluding other causes of hemodynamic instability. It is able to assess which patient is at highest risk for adverse outcome and hence guides in pattern of management, As compression ultrasonography is a part of non invasive testing, hence is an integral part of study. The finding of a proximal DVT in patients of suspected PTE is sufficient to warrant anticoagulant treatment without further immediate testing. Detailed management is discussed by Konstantinides et al,

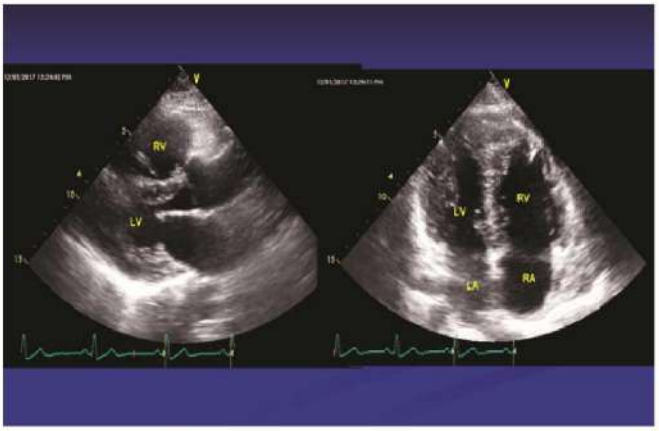


Figure-1. *Shows unexplained enlargement of right ventricle (RV) and right atrium (RA) and patient also had raised PA pressure, hence was provisionally diagnosed as acute pulmonary embolism which was subsequently confirmed by CT pulmonary angio. LV: left ventricle, LA: left atrium*

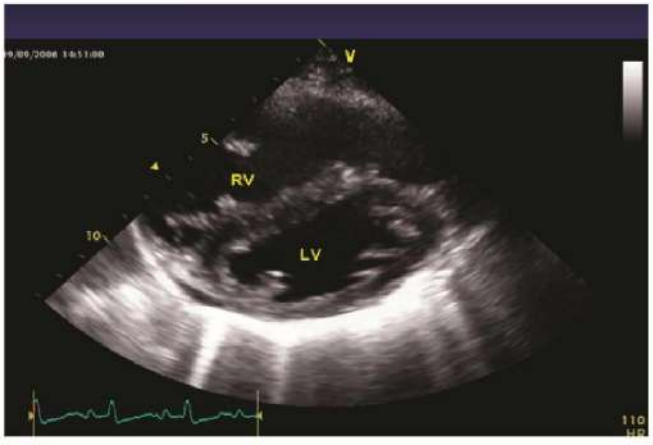


Figure-2. *There is flattening of interventricular septum due to increased PA/RV pressure. RV: Right ventricle. LV: Left ventricle*

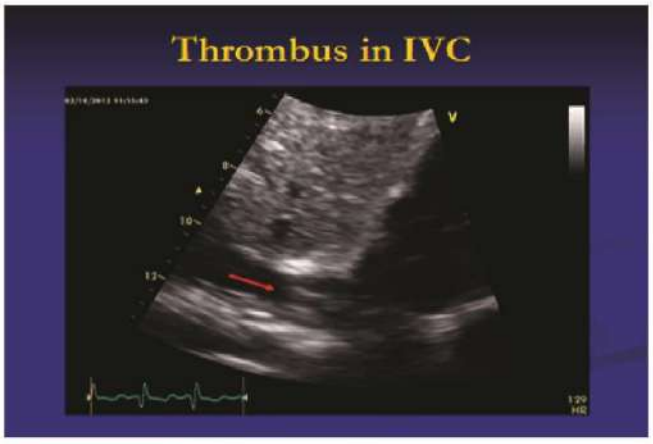


Figure-3. *A thrombus (arrowed) seen in inferior vena cava (IVC)*

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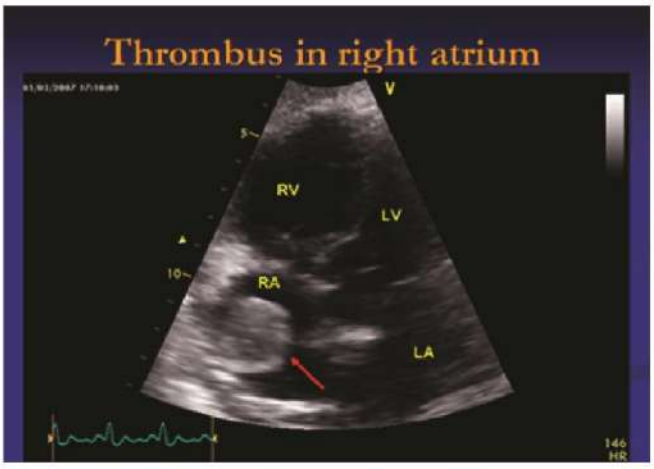

Figure-4. *A large thrombus (arrowed) present in right atrium (RA) which led to acute pulmonary embolism leading to shock. Abbreviations as per earlier figures*

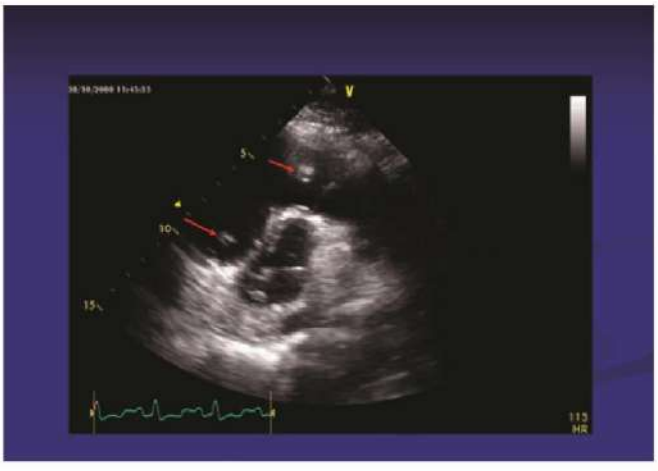

Figure-5. *Clots migrating to right ventricular outflow tract (upper arrow). Systolic flattening of interventricular septum also seen*

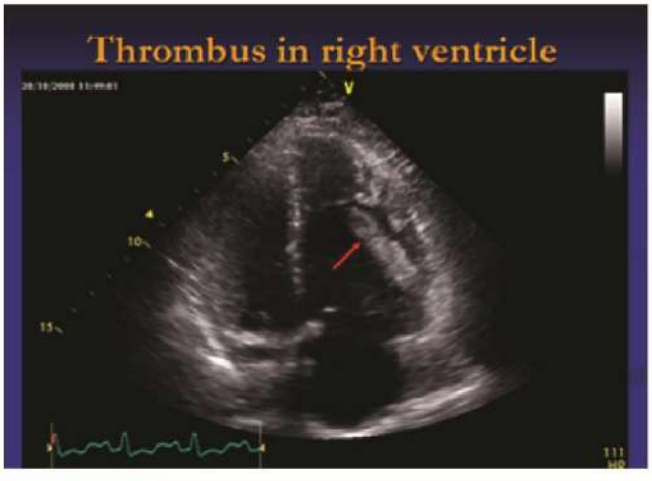

Figure-6. *A large thrombus present in right ventricle (arrowed) with enlargement of right ventricle and atrium*

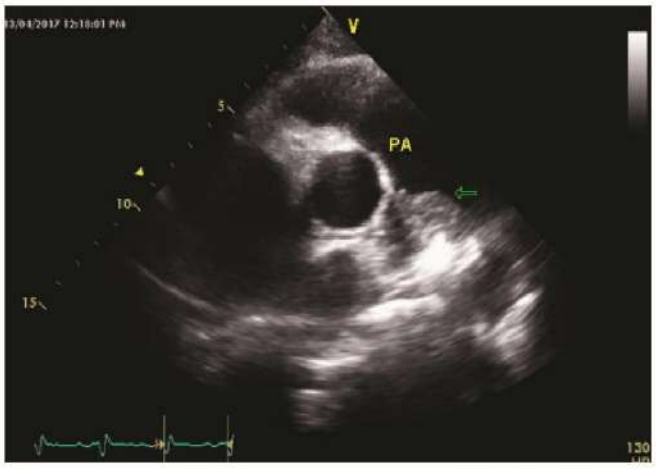

Figure-7. *A case of acute pulmonary embolism with saddle thrombus at bifurcation of pulmonary artery (arrowed) PA: Pulmonary artery*

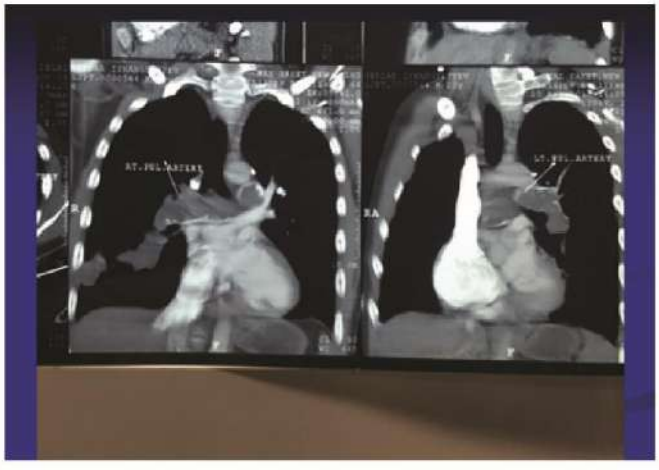

Figure-8. *Contrast enhanced CT angio of patient in Fig 7. The thrombus is more marked In right branch of pulmonary artery*

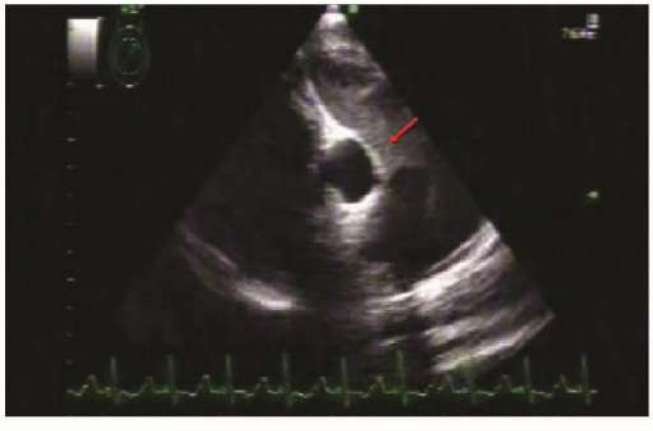

Figure-9. *Transesophageal echo (TEE) in a patient of PE , in which spontaneous contrast echo and thrombus in right pulmonary artery (arrowed) could be seen only by TEE (Image: Courtesy R. Alagesan)*

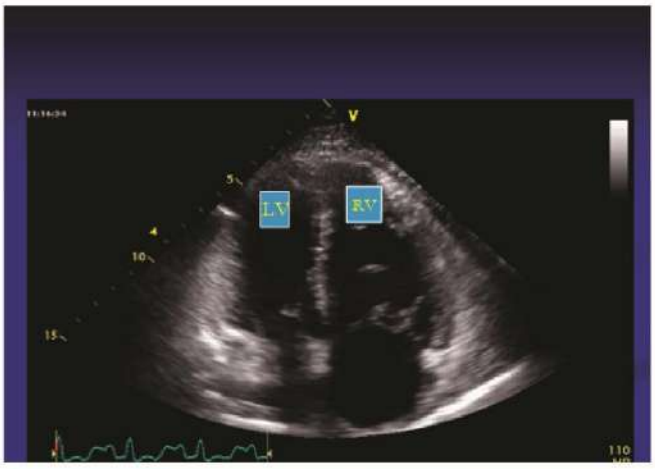

Figure-10. *A follow up of case of APE (fig 6) showing almost complete resolution of RV thrombus following anticoagulation*

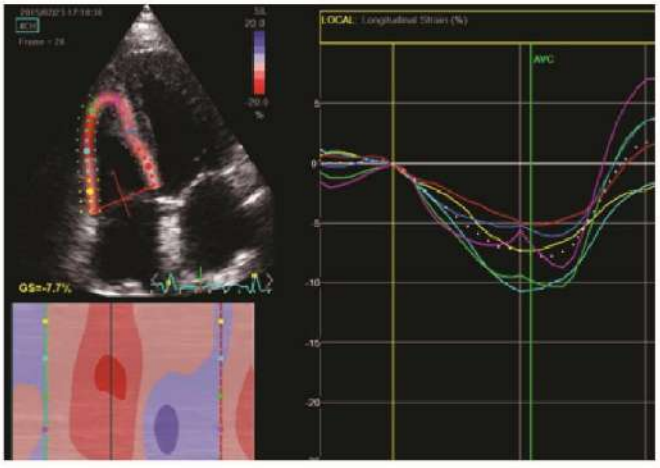

Figure-11. *GLS of RV free wall with value of -7.7%*

Review Article

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Prognosis and Risk Outcome in Acute Myocardial Infarction : Role of Echocardiography

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Abstract

Echocardiogram is recommended in acute (0–48 h) and sub acute (Day 3–7) phase of Acute Myocardial Infarction to provide baseline assessment of cardiac functions and exclude mechanical complications; and within first 3 months of infarction to document ventricular remodelling.

Various conventional echocardiography parameters such as left ventricular volumes,ejection fraction,wall motion score index and left atrial volume are established in providing invaluable prognostic information. Advanced techniques like tissue Doppler and speckle-tracking strain imaging have further added prognostic information with parameters such as global left ventricular strain, global atrial strain and mechanical dyssynchrony in risk prognostication. Myocardial contrast echocardiography with low dose stress echocardiography provides information on myocardial viability by showing perfusion in akinetic (stunned) segments. 3D echocardiography has further optimised information on left ventricular volumes, function and adverse ventricular remodelling.

Introduction

Echocardiography plays a central role in management of patients suffering from acute myocardial infarction.Imaging with echocardiography provides the treating physician a plethora of diagnostic and prognostic information in acute setting.Main focus of imaging is kept on assessment of ventricular dysfunction,mechanical complication and alteration in haemodynamics.

Pathophysiological changes after acute myocardial infarction:

Shortly after myocardial infarction acute increase in LV filling pressures stretch and elongate infarct region leading to acute LV dilatation, infarct expansion and thinning. This increases wall stress which initiates the chronic left ventricular remodelling. The aim of this process is to maintain adequate cardiac output and minimize wall stress. Infarct remodelling is defined as an increase in end-diastolic left ventricular volume by 20% at 6 months after MI compared to baseline and may be seen in app. 30% of patients.

It is divided into two phases:
Acute phase: early ventricular dilatation
Late phase: progressive compensatory hypertrophy of non infarcted myocardium [1, 2]

Assessment of ventricular systolic functions and volumes:

The first step in evaluation after acute myocardial infarction is assessment of ventricular systolic functions and volumes. Ventricular function assessment on echocardiography can be done by M mode using MAPSE; by 2D using Simpson method based volumetric assessment to calculate LV ejection fraction and more recently using global myocardial 2D/3D strain. MAPSE as an M mode parameter is easy and reproducible in providing a fair idea of reduced global LV functions as it checks atrio-ventricular plane displacement during systole. In 271 patients of AMI, reduced mitral annular plane systolic excursion was independently associated with all-cause mortality, HF hospitalization, reinfarction, and unstable angina. The incidence of death was 31.3% in patients with MAPSE <8 mm and 10.1% in those with MAPSE >8 mm. 3 Calculating LVEF provides both short-term and long-term prognostic value in AMI patients. Its estimation should be done from 3rd day onwards and rechecked at 14th day so as to overcome the effects of myocardial stunning. However it depends on clinical situation and is on a case to case basis. Patients who show improvement have 1.2% long term mortality risk while those who don't show improvement carry long term mortality risk of 5.6%(PREDICT study).LVEF mortality curve after AMI exhibits a typical hyperbolic increasing with an upturn in mortality occurring at values <40%.

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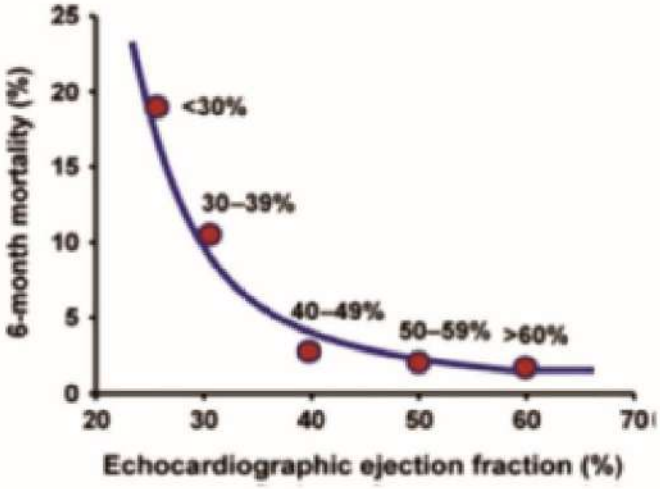

Figure-1. *Shows inverse relation between LVEF and 6-month all-cause mortality after AMI*

LVEF< 40% was an independent predictor of the combined endpoint of death, congestive HF, and recurrent AMI at 30 days after AMI (OR 3.82) while patients with LVEF < 30% and between 30% to <40% had an increased risk for SCD (hazard ratio [HR] = 5.99 and 3.37 respectively) and all-cause mortality (HR = 3.85 and HR= 2.06 respectively) in 417 patients with AMI.[4]

If a patient has suffered large MI (EF <35%) viability assessment takes priority before revascularisation while patients with EF > 40 % restoring patency of culprit vessel gains priority. Decisions based on EF should be individualised as it suffers from large inter-observer and test–retest variability. It has been advocated that LV end-systolic volume (LVESV) or LV end-diastolic volume (LVEDV) may be more meaningful predictors of prognosis than LVEF. In a group of 605 patients with acute MI, White et al demonstrated that LVESV was the primary predictor of survival after MI. LVESV was superior to LVEF in patients with depressed LVEF (<50%) or small LVESV (<100 ml). They reported that post-MI patients having EF < 40% and end-systolic volume > 130 cm3 had a 5-year survival rate of 65% and 52%, respectively. [5]

Evaluation of Regional LV Functions:

In acute MI, segmental function evaluation proves superior to global assessment in providing information regarding infarct size and subsequent ventricular remodelling. Segmental functions are measured using wall motion score index (WMSI),contrast defect index (CDI)or regional strain.

Wall motion score index (WMSI):

is an average of the wall motion score in all left ventricular wall segments, where the score is 1 for normokinesia, 2 for hypokinesia, 3 for akinesia, and 4 for dyskinesia; a completely normal left ventricle would therefore have a wall motion score index of 1.

As wall motion abnormalities increase in severity LV wall motion score index increase. There is a good correlation between the wall motion score index and functional LV impairment. An index of 1.1–1.6 represents small infarct while index > 2.0 predicts occurrence of complications. WMSI, unlike EF which is a marker of global LV functions, represents regional LV functions therefore it reflects mild wall motion abnormalities because it is not affected by compensatory hyperkinesia of remote segments

In 144 patients with first AMI treated with thrombolytic therapy, a pre discharge resting WMSI > 1.50 was superior to LVEF < 40% to identify patients who had post-AMI cardiac death, unstable angina, nonfatal re infarction, and HF.[4]

Contrast defect index (CDI):

calculated as the sum of the contrast scores (1 = homogeneous opacification; 2= heterogeneous opacification; 3= minimal/absent contrast opacification) of all LV interpretable segments divided by the number of LV segments analyzed. At multivariate analysis, elevated CDI as a marker of lower residual myocardial viability, was a predictor of the composite endpoint of cardiac death and nonfatal AMI. Dwivedi et al gave optimal cut off of CDI at 1.86 for the composite endpoint of cardiac death and nonfatal AMI (sensitivity, 62%; specificity, 84%) and for cardiac death (sensitivity, 87%; specificity, 84%).[7]

Doppler Echocardiography Assessment in acute MI:

In post infarction phase myocardial ischemia, cell necrosis, microvascular dysfunction, and regional wall motion abnormalities influence the rate of active relaxation and LV stiffness. These changes in myocardial relaxation are reflected by changes in normal mitral valve flow Doppler assessed using pulse wave Doppler. In acute phase (< 48 hours of AMI) restrictive filling patterns portend worse prognosis and persistence of these patterns in pre discharge echocardiography evaluation suggest adverse ventricular remodelling.

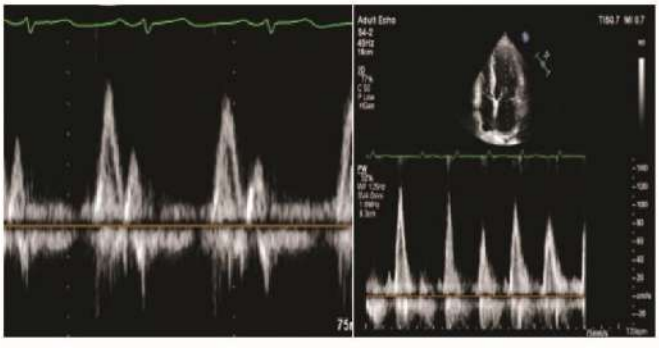

Figure-2. *Shows restrictive filling pattern on mitral valve pulse Doppler taken within 48 hours of thrombolysis, look at sharp deceleration times of E wave*

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The prognostic importance of a restrictive filling pattern after AMI was initially reported by Oh et al in 1992 in a cohort of 62 patients, it was associated with a high occurrence of in-hospital congestive heart failure. In patients with LVEF < 35%, mitral deceleration time less than 120 msec, denotes PCWP > 20 mmHg and the reversibility of these parameters at predischarge is associated with a more favourable late outcome, whereas its persistence is a powerful independent predictor of late mortality and adverse LV remodelling.[10]

Tissue Doppler imaging (TDI) uses Doppler principles to quantify the lower-velocity myocardial tissue signals along the axis of Doppler ultrasound beam. Prasad et al. performed serial Doppler echocardiographic assessment of LV diastolic dysfunction during and after STEMI and found that the predominant mitral inflow pattern was impaired relaxation pattern (E/A ratio <0.5), which was accompanied by a modest reduction in e', resulting in E/e' ratio in the range of 8 to 15 in the majority of patients. Serial tissue Doppler assessment within 12 months demonstrated persistence of diastolic dysfunction, suggestive of incomplete recovery despite successful revascularization.In patients having LVEF >40%, PCWP >20 mm of Hg can be reliably predicted by E/E' value using Nageuh formula.[11,12]

Recently regional diastolic strain rate has been proposed as a further marker of elevated LV filling pressure. In a study of 1,048 post-AMI patients with mildly impaired LV systolic functions the ratio of transmitral E velocity to global diastolic strain rate (E/e'sr at cutoff value >1.25) was superior to E/e' ratio and in predicting all cause mortality, HF hospitalization, stroke, and new onset AF.[13]

Evaluation of left atrium size /functions:

In AMI development of late left atrium remodelling is a sub acute maladaptive response to the acute event. Left atrium size/volume may increase as a response to acute/chronic persistent elevation of LV end diastolic filling pressures after AMI. The importance of left atrium volume for clinical outcome after MI was confirmed by Beinart et al in 395 consecutive patients with acute MI. They demonstrated that left atrium volume index, determined within the first 48 h of admission, was an independent predictor of 5-year mortality with incremental prognostic information over clinical and echocardiography data. Patients with LA volume index >32 ml/m2 had a significantly higher mortality than patients with LA volume index <32 ml/m2 (34.5% vs 14.2%, respectively).[14]

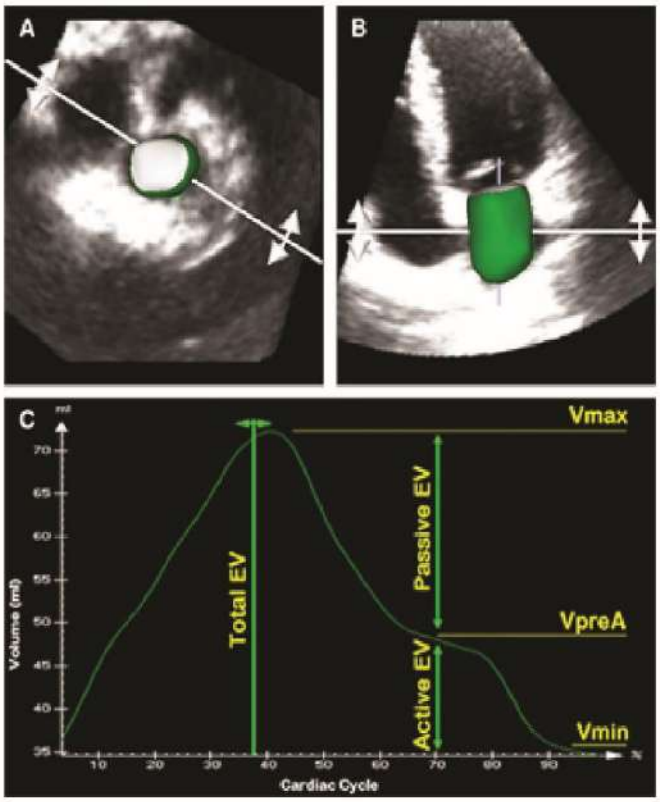


Figure-3. *LA distensibility ([difference of maximal and minimal left atrium volume]/minimal volume X100) was also an independent predictor of in-hospital mortality (HR = 2.37 for left atrium distensibility <60%; 95% CI, 1.108– 5.079; P = .026) in 521 post-AMI patients.*

Prognostic Impact of Right Ventricular Dysfunction in Acute MI:

Right ventricular involvement is associated with worse prognosis in AMI patients. RV dysfunction can be observed in about 30% of patients with LAD-related MI. RV involvement in the setting of LAD occlusion could be due to reduction in perfusion of anterior RV wall from the LAD branches or occlusion of the LAD collaterals supplying the right ventricle, while a large anterior MI could compromise RV function by affecting the interventricular septum.

Engstrom et al. observed that patients with acute MI complicated by cardiogenic shock had worse prognosis when RV dysfunction defined as TAPSE <14 mm on Admission was present. TAPSE < 14 mm predicted increased 2-year mortality in contrast to patients with TAPSE>20 mm.

Dokainish et al. reported that among patients with acute inferior MI, tissue Doppler derived S' of the free wall of RV < 8 cm/sec had sensitivity of 85% and specificity of 77% to predict cardiac mortality and rehospitalizations at 1 year. Antoni et al. gave cut off for RV strain of <22.1% was associated with an adjusted hazard ratio of 2.18 for the occurrence of the composite end point at mean period of 24 months in 621 patients post MI.[17]

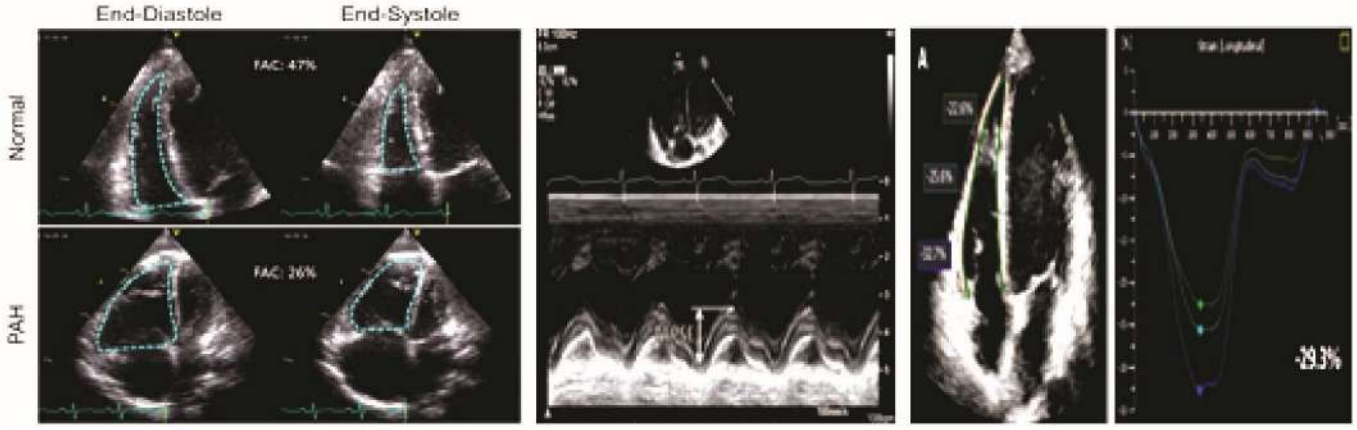


Figure-4. *(Left to right) showing RV fractional area change,TAPSE and RV free wall strain*

Post MI alterations in pulmonary pressures:

An increase in pulmonary artery systolic pressure (PASP) may be a hemodynamic consequence of AMI by pathologic mechanisms such as ischemic MR and LV systolic and diastolic dysfunction. PASP can be determined noninvasively by adding the value of estimated right atrial pressure (size and respiratory reactivity of inferior cava) to the right ventricular systolic presuures derived from maximal velocity of tricuspid regurgitation jet. Møller et al. enrolled 536 AMI patients, within 2 days after AMI. At multivariate analysis, PASP degree was correlated with age, LV diastolic function, MR, and WMSI. Each 10-mmHg increase in PASP, each grade increase of LV diastolic dysfunction, and evidence of moderate/severe RV dilatation were independent predictors of all-cause mortality.[18]

Myocardial Contrast Echocardiography in AMI

MCE has become an important clinical tool to delineate the spectrum of perfusion derangements that characterize AMI. In reperfused AMI, absence of microbubbles in the infarct bed is a strong indicator of necrosis. Its important to look for absence of contrast even at prolonged pulsing intervals during triggered imaging or up to 15 seconds using real-time techniques before making the diagnosis of necrosis.[19]

Hyperemic flow early after reperfusion, within hours and up to 24 hours, may lead to underestimation of infarct size (perfusion defect); a vasodilator stress MCE can unmask decreased flow reserve within the infarct bed and more accurately depict the extent of infarct size.[20]

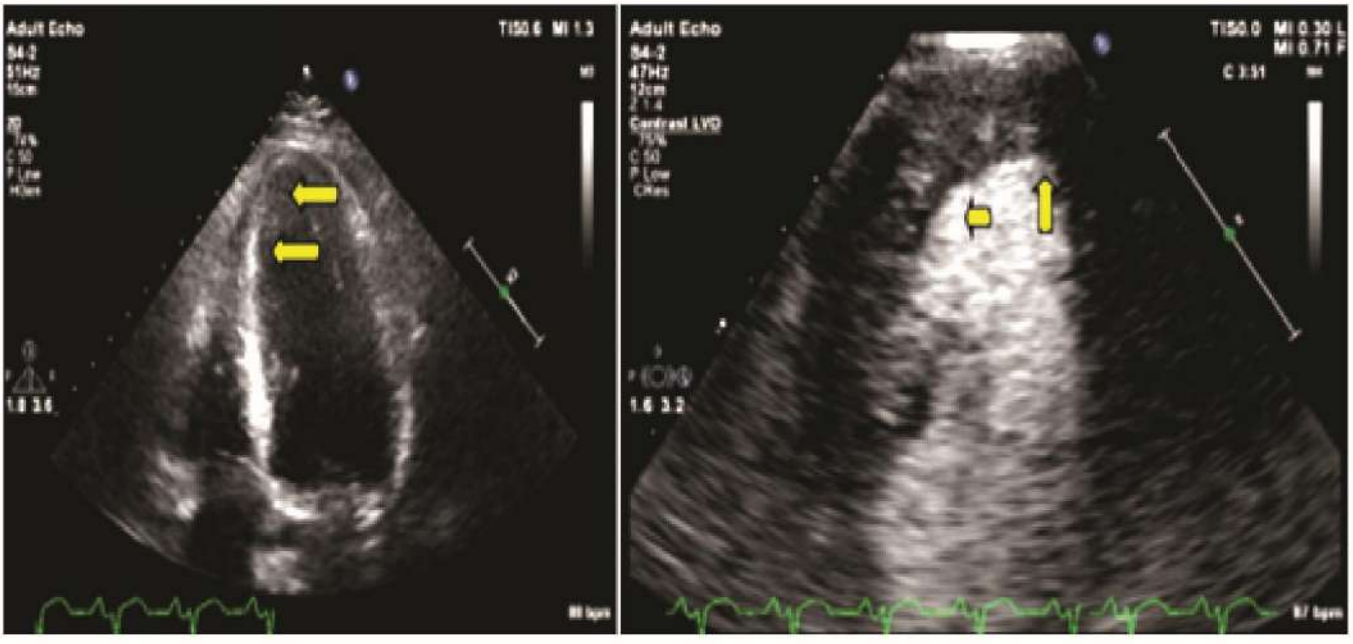


Figure-5. *Yellow arrows showing difference in delineation between the contrast uptake in fibrotic scarred myocardium on grey scale imaging (left) and using MCE (right) uptake of contrast in apical segments suggesting viable myocardium.*

In the clinical setting, an MCE study after reperfusion may be typically performed after 24 hours.A transmural myocardial perfusion defect with TIMI 3 flow in the (IRCA) indicates predominant irreversible myocardial necrosis and the spatial extent of this defect reflects ultimate infarct size. In a similar setting of TIMI 3 flow in the IRCA, a patchy or a slow (late filling) transmural opacification may both indicate varying degrees of myocardial viability.[21]

A nontransmural perfusion defect with a rim of epicardial flow at 24 hours poses a challenge since some of the no-reflow may be due to capillary microembolization that is potentially reversible. A dipyridamole MCE at this time may show an increase in the size of the no-reflow region which is indicative of a decreased flow reserve in the infarct bed with little likelihood of improvement in the follow-up period. It is the size of this dipyridamole perfusion defect and not the resting perfusion defect that is predictive of the final infarct size, because latter underestimates ultimate infarct size consequent to persistent hyperaemia as shown in flow chart

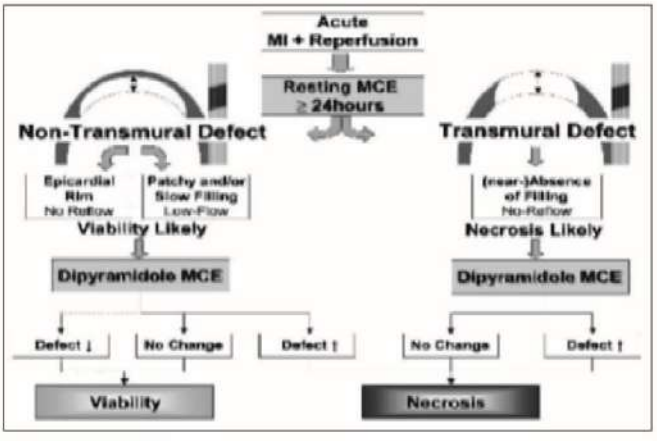


Figure-6.

Low dose stress echocardiography using dobutamine / vasodilators:

Dysfunctional myocardium with reduced contractility, with limited or absent scarring, that improves after restoration of coronary blood flow is termed as viable myocardium. After acute MI stress echocardiography can be used to detect residual ischaemia, which is associated with poor outcome if treated conservatively; viability (contractile reserve) can also be assessed, and is associated with spontaneous recovery of function and good outcome.It also helps in identifying viable myocardium, both in 'remote' myocardial territories and in the peri infarct area. Candidates for pre discharge evaluation are those who didn't undergo revascularisation or those who underwent partial revascularisation provided that they had stable ECG and no episode of HF or angina at least 72 hours before testing. Worsening of wall motion during high-dose dobutamine infusion is related to the presence of ischaemia, whereas improvement of wall motion during low-dose dobutamine infusion (contractile reserve) indicates the presence of viable (stunned) myocardium.To detect residual ischemia from stunned segments mainly two responses are seen one is that of sustained improvement (100% specific) signifying absence of residual stenosis and other is biphasic response (80% sensitive and specific) for residual stenosis requiring revascularisation.

Viability-Guided Angioplasty after Acute Myocardial Infarction trial demonstrated that in patients with AMI, not treated by primary or rescue PCI, the detection of myocardial viability at low-dose dobutamine identified a subgroup to be referred to viability-guided PCI of infarct-related coronary artery.[24]

Picano et al studied the value of dipyridamole stress echocardiography in predicting reinfarction in 1080 patients assessed early (10±5 days) after uncomplicated acute MI with follow up of 1 year. Stress echocardiography was positive for ischemia in 475 patients (44%). During follow-up, reinfarction occurred in 30 patients with positive and 20 with negative results (6.3% vs 3.3%, p, 0.01).[25]

Echocardiography evidence of possible non viability are marked LV enlargement,extensive scar,Grade III/IV diastolic dysfunction.

Global myocardial strain in systolic function assessment:

Global myocardial strain refers to relative change in length of myocardium during systole. Myocardial strain measurement provides better assessment of both segmental and global functions with very less test–retest variability in AMI patients as shown in a recent study which compared LV global strain by speckle tracking and LVEF as predictors of infarct size in STEMI patients treated with thrombolytic agents, using contrast-enhanced cardiac magnetic resonance as the reference method and confirmed that LV global strain at cut off of -13% measured in the acute phase of AMI predicts infarct size better than LVEF with 90% sensitivity and 86% specificity of GLS and 80% sensitivity and 55% specificity for Ejection Fraction.

Strain imaging is particularly helpful in risk stratification of small infarcts (LVEF >40%) as it is able to detect subtle changes in relatively preserved or mildly impaired systolic functions. Ersbøll et al. found that impaired systolic GLS(<-14%) but not reduced LVEF (<40%) is a powerful independent predictor of a composite endpoint of all-cause of mortality and HF hospitalization and cardiac death and is associated with a three-fold increase in risk for the combined endpoint of all-cause mortality and HF hospitalization (HR = 3.21).[6]

Regional strain:

Speckle tracking allows calculation of regional strain in affected and non affected segments in AMI patients.In a study of 576 AMI patients treated by primary PCI, systolic GLS and WMSI were independently associated with the composite endpoint of all-cause mortality, reinfarction, hospitalization, HF, or stroke within 1 year, whereas LVEF and ESV did not enter the model.47 patients with systolic GLS ≤10% experienced more adverse events than patients with systolic GLS ≤15% (HR = 4.6). Peak longitudinal systolic strain at cutoff <-5.3% identified segments with delayed enhancement upto>75% on ceCMR (sensitivity 83.1%, specificity 84.6%).[8]

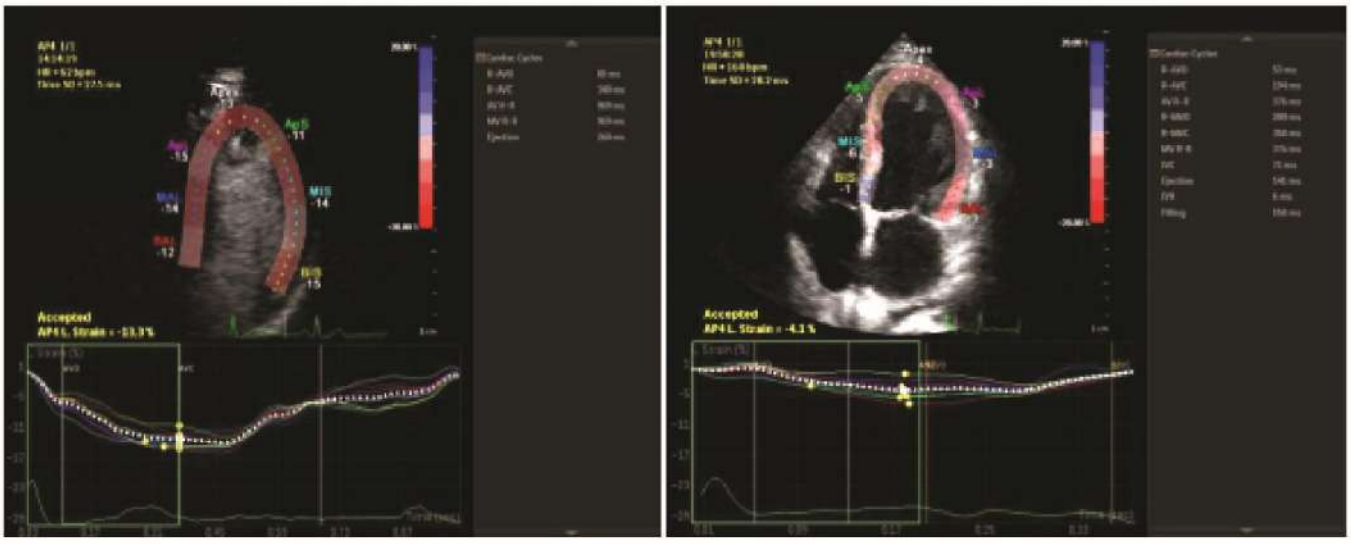


Figure-7. *Shows Global Left ventricular strain in small (-13.5%) left image and large infarct (-4.5%) right image*

A relatively new robust parameter in post MI risk stratification is Left ventricular mechanical dispersion using myocardial strain which reflects regional heterogeneity in myocardial contraction throughout the cardiac cycle .

A recent meta analysis including 12 studies and 3,198 patients has shown that each 10 msec increment of LVMD was signifificantly and independently associated with ventricular arrhythmic events (HR = 1.19; 95% CI, 1.09-1.29; P < .01).36 Another study showed LVMD>50 msec was a better predictor for mortality in post MI patients than conventional parameters.[9]

Assessment of LA Strain:

Although increased left atrial volume is known to reflect chronically elevated LV filling pressure; assessment of LA reservoir function using LA strain reflects indirectly the properties of the atrial myocardium. Reduced LA strain reflects reduced compliance of the left atrium which is more prone to remodelling.

Meris et al. described that LA remodelling was associated with worse outcomes during follow-up after high-risk AMI . They defined an optimal cut off value of a 9 mL/m2 increase in LA max for the composite end point of all-cause mortality or hospitalization for heart failure. Patients with smaller LA volumes at baseline more often developed remodelling during follow-up compared with those with larger LA volumes at baseline.LA strain assessed early after AMI was an independent predictor of the occurrence of LA remodelling at 1-year follow up; and in patients without LA remodelling, no changes in left atrial functions were observed.[16]

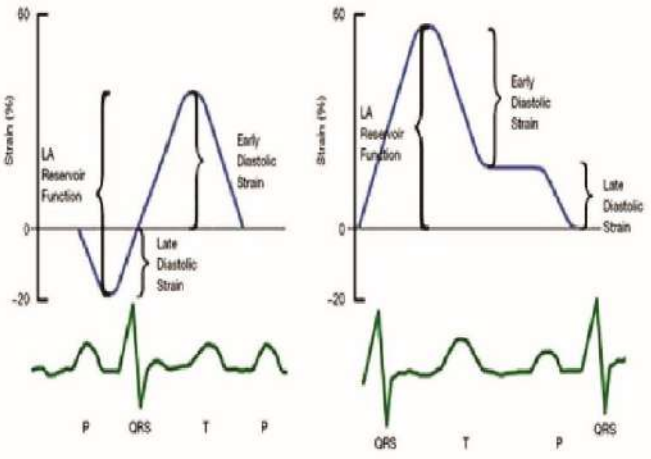


Figure-8. *Clearly shows how left atrial reservoir functions are depicted in strain measurements. Reservoir functions are maximally affected in Post MI phase on follow up.*

3D echocardiography for LV remodelling

3D echocardiography may prove more useful in assessment of Adverse remodelling on AMI follow up due to its inherent advantages and proven superiority over 2D datasets. Mannaerts et al in their small study evaluated 33 patients with acute MI with 3D echocardiography at baseline (6±4 days after MI) and at 6 and 12 months' follow-up. LV remodelling was defined as an increase in LVEDV by 20% or more at 6 or 12 months' follow-up have suggested 3D sphericity index as better marker of remodelling than 2D LV volumetric assessment. The sphericity index is derived from 3D echocardiography LVEDV divided by the volume of a sphere whose diameter is the LV end-diastolic long axis.[26]

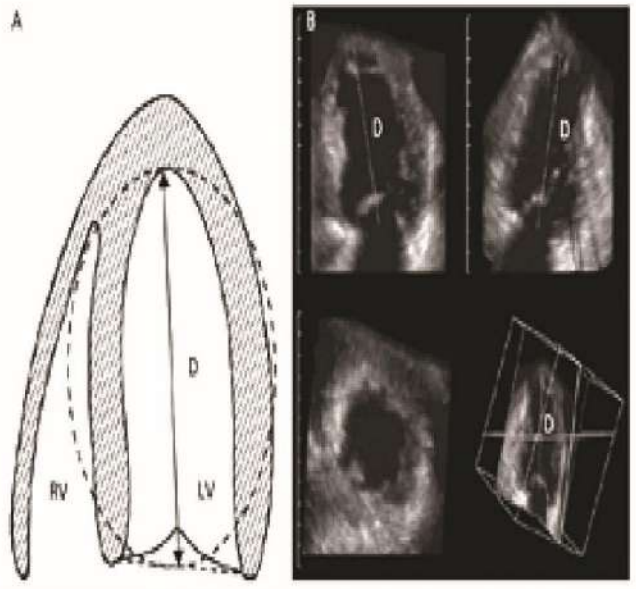


Figure-9. *3D sphericity index(A). The LV cavity is shown with D as the LV end-diastolic major long axis. Overview of the dynamic 3D dataset with two near perpendicular long axes (B, top), a short-axis (B, lower left), and a cubical display with corresponding cut planes (B, lower right).*

In a recent study of 100 patients with successfully reperfused first AMI, 3D Speckle Tracking Echocardiography discriminated transmural from non transmural extent of scar and predicted microvascular obstruction, using cardiac magnetic resonance as the gold standard. The best 3D strain component for detecting nonviable segments with microvascular obstruction was global area strain that includes longitudinal and circumferential strain. [27]

Recommended approach

1. Perform a limited emergency study as quickly as possible in every patient as long as reperfusion therapy is not delayed. Assess regional and global left and right ventricular functions, exclude other causes of chest pain e.g. Type A aortic dissection.

2. Exclude mechanical complications free wall/ventricular septum/ papillary muscle rupture

3. Identify signs of increased left ventricular filling pressures restrictive mitral inflow pattern, E/E' ratio, LA size, PA systolic pressures.

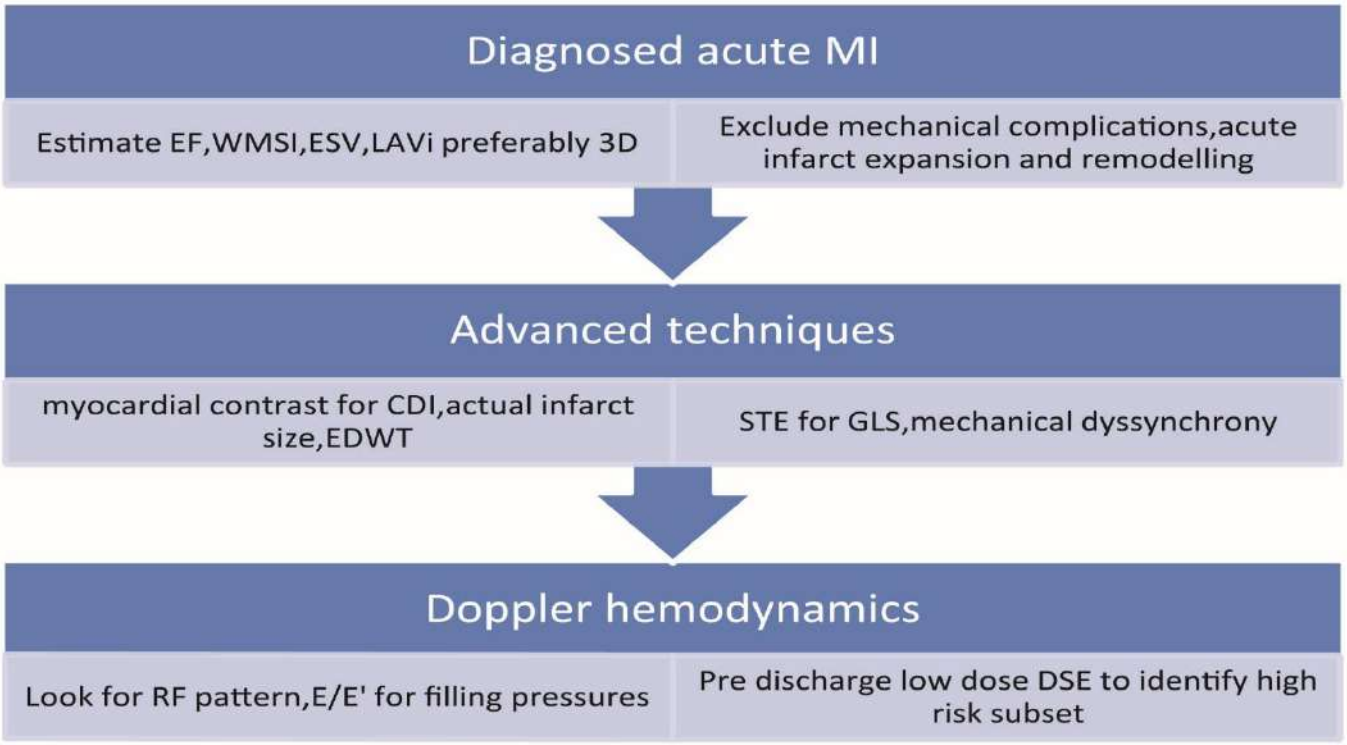
4. If large akinetic or dyskinetic left ventricular regions are present exclude thrombi

5. See for acute ischemic remodelling especially in apical segments

6. Use Myocardial contrast echocardiogram in accurate categorisation of stunned v/s scar segments and estimate CDI.

7. Global Left ventricular strain should be estimated in patients with small infarcts or baseline EF ≥40% and in patients with EF ≤35% for mechanical dispersion .

Flow chart



8. A low dose dobutamine stress test preferably using MCE should be performed after the acute phase of MI once the patient is stable usually after 4 days for identification of inducible ischemia and identification of viable myocardium.

Abbreviations used :

AMI: acute myocardial infarction
MCE: Myocardial contrast echocardiography
iRCA: infarct related coronary artery
STE-Speckle tracking echocardiography
EF-Ejection fraction
LS-Longitudinal strain
GLS-Global longitudinal strain
GCS-Global circumferential strain
MAPSE-Mitral annular plane systolic excursion
TAPSE-Tricuspid annular plane systolic excursion
LAVI-Left atrial volume index
PASP-Pulmonary artery systolic pressure

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Jailed Balloon Technique in Bifurcation Lesion-A Case Report.

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Abstract

Percutaneous coronary interventions (PCI) of true bifurcation is challenging. Provisional stenting is regarded as the optimal strategy. But side branch (SB) occlusion after main vessel (MV) stenting occurs in 7.4% to 8.4% of bifurcation lesions, with increased risk of peri-procedural cardiac mortality and myocardial infarction. Here we present a case report, using jailed balloon technique for coronary bifurcation lesions. This involves placing the MV stent in position and a jailed balloon in the SB, without inflating the SB balloon, subsequently inflating the MV stent at high pressure, removing the balloons and performing proximal optimization technique (POT) using a non-compliant balloon. This technique prevents carinal and plaque shift to the SB, keep the SB open, and is safe and feasible for true coronary bifurcation lesions.

Introduction

Coronary bifurcation lesions are one of the most challenging lesions in interventional cardiology in terms of procedural success rate as well as long-term cardiac events. Risk stratification based on coronary anatomy from the recent DEFINITION study showed the benefit of a simpler stenting approach for simple bifurcation lesions[1]. Provisional stenting using a jailed SB wire is the most extensively accepted simple technique and is effective for the vast majority of bifurcation lesions[2]. As a jailed wire is unable to prevent SB closure after stenting the MV for all lesions, the jailed balloon technique has proved effective to restoring SB flow[3]. Similar to the jailed wire approach, the jailed balloon technique requires a small balloon to be positioned in the SB before stenting the MV. Keeping the jailed balloon in position without inflation, MV stent deployed in nominal pressure. Jailed balloon removed, if any difficulty in balloon retrieval inflation and deflation in low pressure. The uninflated balloon, which remains jailed under the stent struts, serves to reduce both carina and plaque shifts due to its SB ostium spatial occupation [3,4]. If SB flow is preserved after MV stenting, the jailed balloon is removed uninflated. If the SB becomes occluded after MV stenting, the jailed balloon may either be used as a marker and a favorable angle modifier to facilitate rewiring or can be dilated to try to restore SB flow. SB rewiring and kissing balloon inflation must be performed to correct stent deformation or mal-apposition[3,4,5]. Here we report one case of successful PCI and stenting of a bifurcation lesion to LAD/D with jailed balloon technique.

Case Report

A 65 yrs. old lady presented with worsening angina of Canadian Cardiac Society (CCS) class -III with raised troponin. Her ECG shows–ST-T depression in anterior leads and bedside echocardiogram reveals anterior wall hypokinesia with estimated ejection fraction about 50%. She had history of hypertension, diabetes mellitus and hypercholesterolemia. Coronary angiography showed normal left main coronary artery(LMCA), left descending coronary artery(LAD) had long 80-90% stenosis at mid segment with involving 80% stenosis at ostio-proximal segment of diagonal artery (Medina1,1,1,) (Fig1). Bifurcation angle about 60-70° and diagonal artery(D) about 2-2.5 mm in size and lesion length about 10 mm (Fig-1). Left circumflex artery normal, OM1- subtotal occlusion proximally(Fig1). Right dominant circulation and normal right coronary artery .Decision of PCI by jailed balloon techinique of LAD/D lesion and PCI of OM lesion taken in the same setting. As we are approaching to double vessel complex angioplasty temporary pacemaker was inserted for safety concern.LMCA ostium was hooked with 6F XB-3.5 guiding catheter and LAD lesion is crossed with a 0.0014-inch BMW wire and distal end of wire was parked at distal LAD, another 0.0014-inch Run-through NS wire crosses the diagonal lesion and distal end of wire parked at

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distal diagonal artery. LAD lesion was pre-dilated with 2X15 mm Ryujin balloon at 12 ATM but due to calcification lesion not inflated in the tightest segment then putting an another 0.0014-inch BMW wire in LAD and using 2.5x9 sprinter balloon at 14 ATM inflated and succeeded to dilate the segment (Fig-2). Diagonal artery pre-dilatation was not done. After complete lesion preparation 3X32 mm Resolute Integrity stent was taken and placed properly in the lesion keeping both edge of the stent in healthy segment, thereafter 1.5x15 mm Tazuna balloon was taken and kept in LAD to Diagonal lesion and proximal end of balloon was kept just proximal to the stent (Fig-3). Than stent was deployed in nominal pressure at 9 ATM keeping the jailed balloon uninflated (Fig-4). After stent deployment check angiography done and revealed patent SB and satisfactory stent placement, then jailed balloon was retrieved without any difficulty keeping stent balloon in MV. Diagonal artery was re-crossed by an another guide wire through stent strut and jailed wire was withdrawn. LAD stent was dilated up to 16 ATM keeping wire in SB. Check angiography showed diagonal artery ostium is compromised (Fig-5). Then diagonal artery balloon dilatation done by using 1.5x15 mm Tazuna balloon at 12 ATM. Finally kissing balloon inflation was performed by inflating balloon simultaneously in LAD by 3.5X12mm Quantum Maverick up to 12 ATM and in LAD to Diagonal by Tazuna 1.5x15 mm up to10 ATM (Fig-6). Check angiography revealed TIMI-3 flow without any residual stenosis (Fig-7). The patient had an uneventful recovery and was discharged accordingly.

Discussion

Bifurcations account for 15-20% of all PCI and remain one of the most challenging lesions in interventional cardiology in terms of procedural success rate as well as long-term cardiac events [1,2]. LAD/D bifurcation lesion alone near 65-70% [1,2]. The optimal treatment strategy for coronary bifurcation lesions remains to be defined. Provisional stenting using a jailed wire in the SB has been widely accepted as the gold standard in the majority of simple bifurcation lesions but is associated with the risk of SB closure after MV stent implantation[1,2],. SB closure puts patients at high risk, as a significant increase of myocardial biomarkers suggests the presence of myocardial necrosis. Furthermore, the rescue procedure to restore the flow in the SB is more complex and is sometimes impossible[1,2,3] . The reason of SB closure after stenting the MV is the shift induced by either carina or plaque, and stent struts are usually seen in the ostium of the SB[3,4]. As a result, a jailed balloon technique has been proposed to avoiding SB closure. This technique prevents carina and plaque shift[3,4]. First of all, the MV stent is deployed with nominal pressure keeping jailed balloon uninflated. Next, the jailed SB balloon was withdrawn without inflation so as to push the carina from the SB to the MV. After rewiring the SB, the MV stent was opened with high pressure to maintain the carina position, minimizing the risk of carina or plaque shift and thereby avoiding SB compromise. To achieve full apposition of the MV stent POT procedure done, keeping jailed SB wire in the SB, for preventing further risk of acute closure by the POT approach [4,5]. Finally final kissing balloon inflation procedure done to correct stent deformation or mal-apposition [4,5].

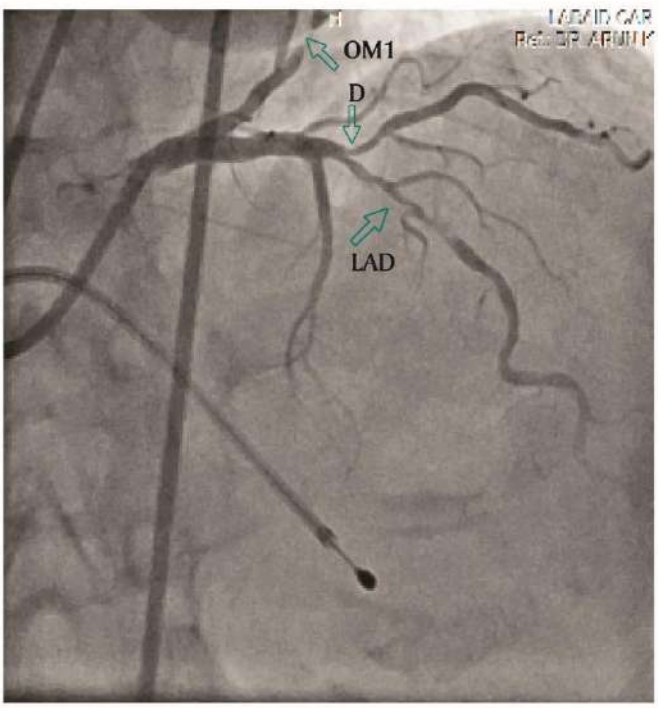

Figure-1. *LAD/D Bifurcation Lesion. LAD-80% to 90% mid segment stenosis, D-80% Ostio-proximal stenosis. OM1- Sub-total occlusion at proximal segment.*

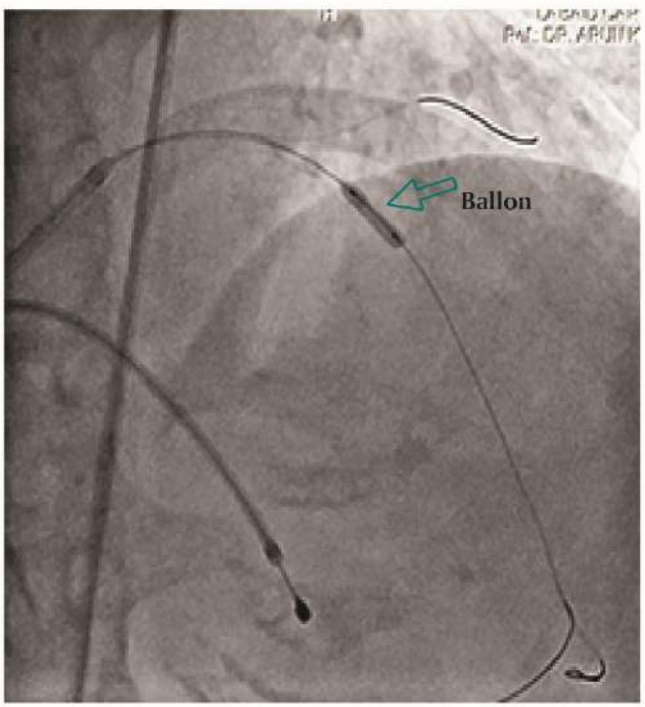

Figure-2. *Balloon dilatation of LAD*

Case Report

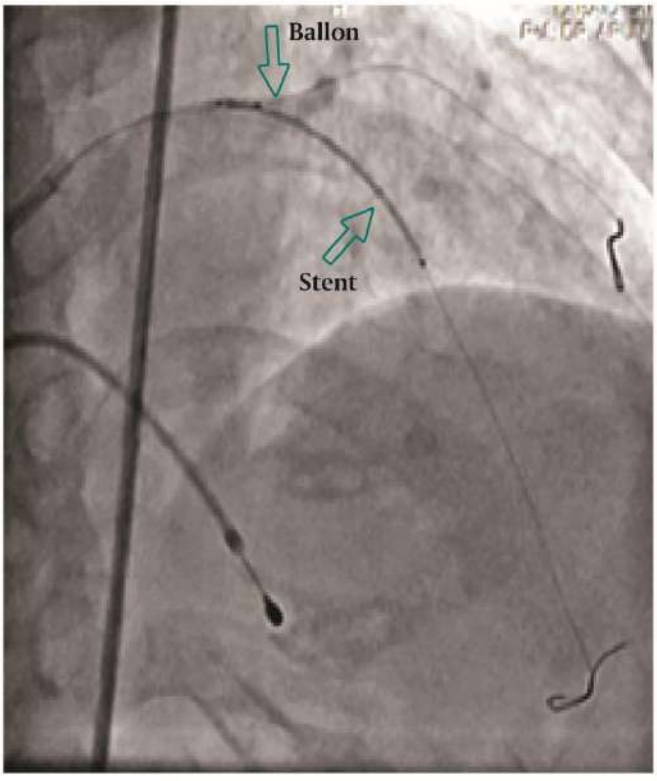

Figure-3. *Stent placement 3 X 32 mm Resolute integrity in LAD, Balloon placement 1.5 X 15 mm Tazuna LAD to D*

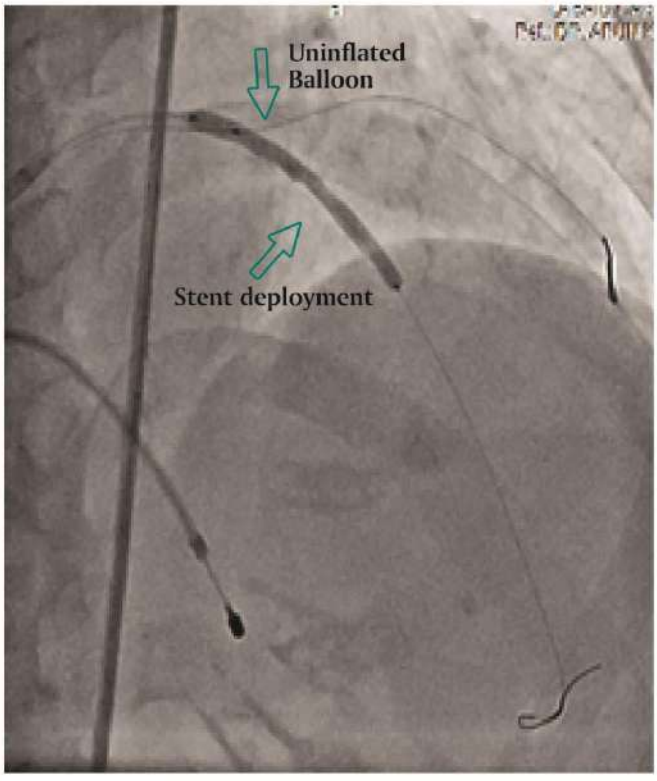

Figure-4. *Stent deployment in LAD with uninflated balloon in D*

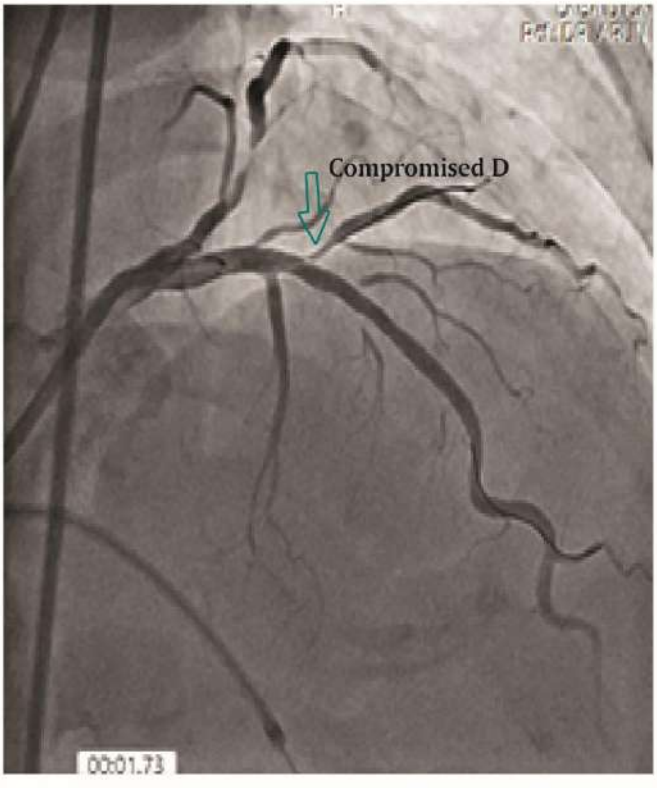

Figure-5. *Post stent deployment diagonal artery showing ostial compromised*

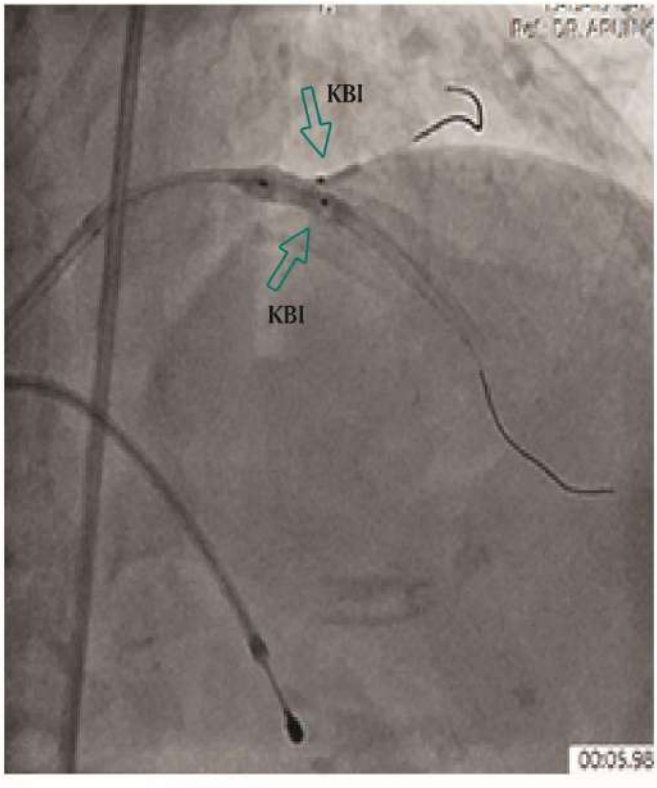

Figure-6. *Kissing balloon inflation*

Case Report

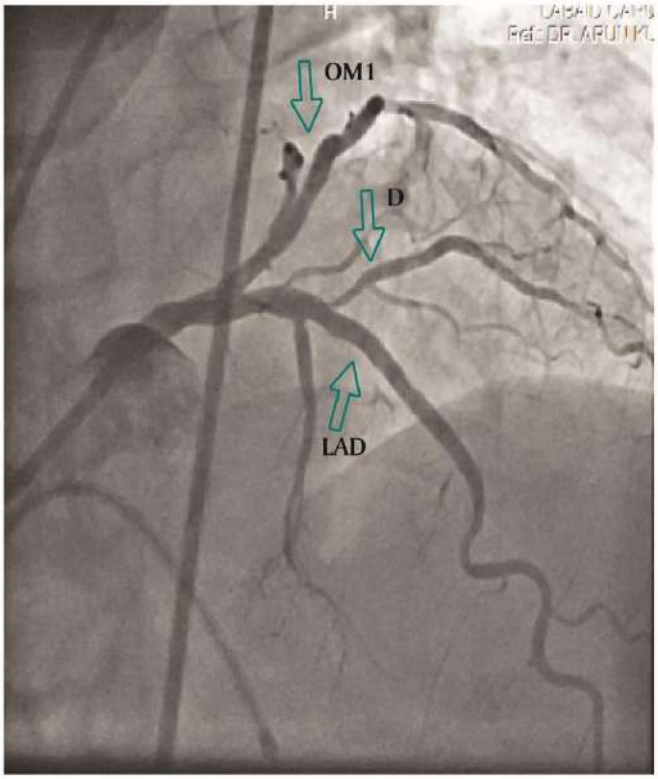

Figure-7. *Final angiography after PCI. No residual stenosis in LAD & diagonal.*

Conclusion:

The jailed balloon technique is a novel technique aimed at improving SB protection during provisional stenting of bifurcated lesions considered at high risk of SB compromise after MV stenting.

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Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA) in a 13 Year-Old Boy- A Case Report.

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Abstract

Myocardial infarction in the absence of obstructive coronary artery disease (MINOCA) is found in ≈5% to 6% of all patients with acute infarction who are referred for coronary angiography. There are a variety of causes that can result in this clinical condition. Here we present a case of MINOCA in a 13 year-old boy without significant past medical history. He presented with severe chest pain and ECG showed evidence of recent high lateral myocardial infarction (MI) with dynamic electrocardiographic (ECG) changes. He was found to have elevations of cardiac troponin I (cTnI) and creatine kinase (CK)-MB. His coronary angiogram was normal and had an uneventful recovery.

Introduction

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a heterogeneous clinical entity, characterized by clinical evidence of myocardial infarction (MI) with nonobstructive coronary arteries on angiography (≤50% stenosis) and without an overt cause for the MI, such as cardiac trauma or injury.[1,2] There are a variety of causes that can cause MINOCA, and it is important that patients are diagnosed with the correct underlying pathological condition so that specific therapies to treat the underlying cause can be prescribed. The most common causes of MINOCA appear to be coronary plaque disruption, coronary dissection, coronary artery spasm, microvascular disease, coronary thromboembolism, and, finally, MINOCA of uncertain cause.[3-4]

Case Report

A 13 year-old boy presented in the emergency department of a tertiary care cardiac hospital on 11th September 2017 evening with complaints of severe chest pain and shortness of breath for one day duration. His past medical history was unremarkable. ECG taken in the emergency department showed pathological Q waves in leads L1 and aVL with T inversions (Fig-1, black arrows) suggestive of fully evolved high lateral MI. ECG also showed some degree ST elevation with concavity upwards with PR segment depression in leads LII,LIII, aVF, V5 and V6 (Fig-1, red arrows) suggesting concomitant pericarditis. He was admitted in the coronary care unit (CCU) and bed side echocardiogram did not reveal any segmental wall motion abnormality and there was no evidence of pericardial effusion. He was commenced on conservative treatment and his chest pain subsided. His initial cTnI and CK-MB levels were very high. On the second day of admission (12th September 2017) he again developed chest pain and ECG showed dynamic new changes in chest leads .ECG showed ST elevation with biphasic T waves in leads V2-V6 as new changes (Fig-2). In view of his recurrent chest pain with dynamic ECG changes he was scheduled for coronary angiogram (CAG). His CAG done on 13th September 2017 revealed normal epicardial coronary arteries. The diagnosis of MINOCA was confirmed and he was treated as such. His further hospital stay was uneventful and he was discharged on the 7th day of hospitalization.

Discussion

MI in the absence of obstructive coronary artery disease was first documented >75 years ago when autopsy reports detailed myocardial necrosis in the absence of significant coronary atherosclerosis. The pioneering angiographic studies by DeWood et al reported a prevalence of nonobstructive coronary artery disease (CAD) in ≈5% of patients with acute myocardial infarction (AMI). This figure was subsequently confirmed in several large AMI registries and in a large meta-analysis in which 6% of AMIs occurred in the absence of obstructive CAD.[5,6]

Because of the complex etiology and a limited amount of evidence, the treatment of MINOCA remains elusive. The etiology of MINOCA manifests from several causes including plaque disruption or erosion, epicardial coronary artery vasospasm, and coronary microvascular dysfunction. In addition, spontaneous coronary artery dissection, takotsubo, and myocarditis have been identified as contributing to the diagnosis of MINOCA. Patients with MINOCA are frequently young, non-white females with fewer traditional risk factors compared with those with an MI caused by obstructive coronary disease. Moreover,

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women who suffered an MI are 5 times more likely to be diagnosed with MINOCA with a trend for worse outcomes compared with men.[7] The case we presented here had normal coronary angiogram and cause of his MI remains unclear but myocarditis is a leading possibility. Myocarditis is a diagnosis that may be identified by cardiac magnetic resonance (CMR) imaging in patients with a provisional diagnosis of MINOCA. Patients with a provisional diagnosis of MINOCA are more likely to have CMR findings consistent with myocarditis if they have angiographically normal coronary arteries. [8]

The management of AMI with obstructive CAD is well established, with detailed evidence-based guidelines for both ST-segment–elevation myocardial infarction and non–ST-segment–elevation myocardial infarction. In contrast, the management of MINOCA has a limited evidence-based literature, with no prospective randomized, controlled trials undertaken to date.[6,9] Given these therapeutic shortcomings, it is important to define the management strategy for patients with MINOCA, which includes careful consideration of the following: (1) emergency supportive care; (2) a working diagnosis approach for patient evaluation; (3) cardioprotective therapies irrespective of the cause of the MINOCA; and (4) cause-targeted therapies.[6] Prognosis of MINOCA, interestingly, is very variable and related to the underlying cause, with some high-risk clinical subsets. [10]

In summary, this 13 year-old boy presented with chest pain with classical ECG findings of recent MI with elevations of troponin and CKMB. These findings are consistent with acute MI. But, the diagnostic challenge was to determine if the ECG changes and elevations in cardiac markers for ischemic heart damage did represent acute myocardial infarction in this very young patient, or whether the pattern indicated other cause for the ECG change and increase in the biomarkers. In this particular case the cause of MINOCA was probably myocarditis.

There is a paucity of evidence on treatment strategies for patients clinically diagnosed with MINOCA, but more importantly that MINOCA should be viewed as a "syndrome" with many different pathologic causes. This suggests that a standard protocol may not be useful for patients with MINOCA. Given the ongoing debate over the complexity of MINOCA, the main focus in the management of MINOCA should be to identify the underlying mechanism for targeted therapies that may optimize outcomes.

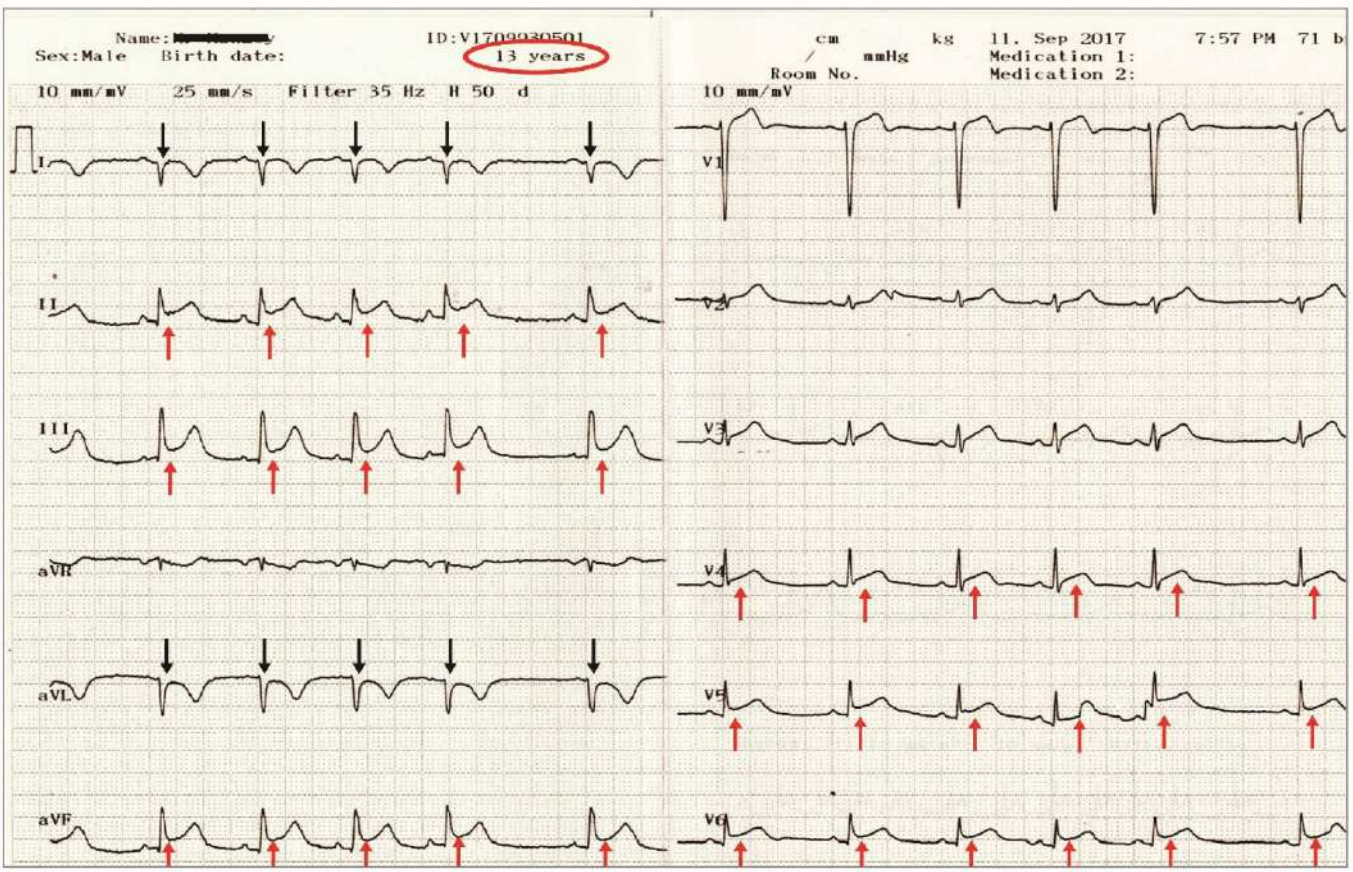

Figure-1 *ECG during admission shows pathological Q waves in leads L1 and aVL with T inversions (black arrows) suggestive of fully evolved high lateral MI. ECG also shows some degree ST elevation with concavity upwards with PR segment depression in leads LII,LIII, aVF, V5 and V6 (red arrows) suggesting concomitant pericarditis.*

Case Report

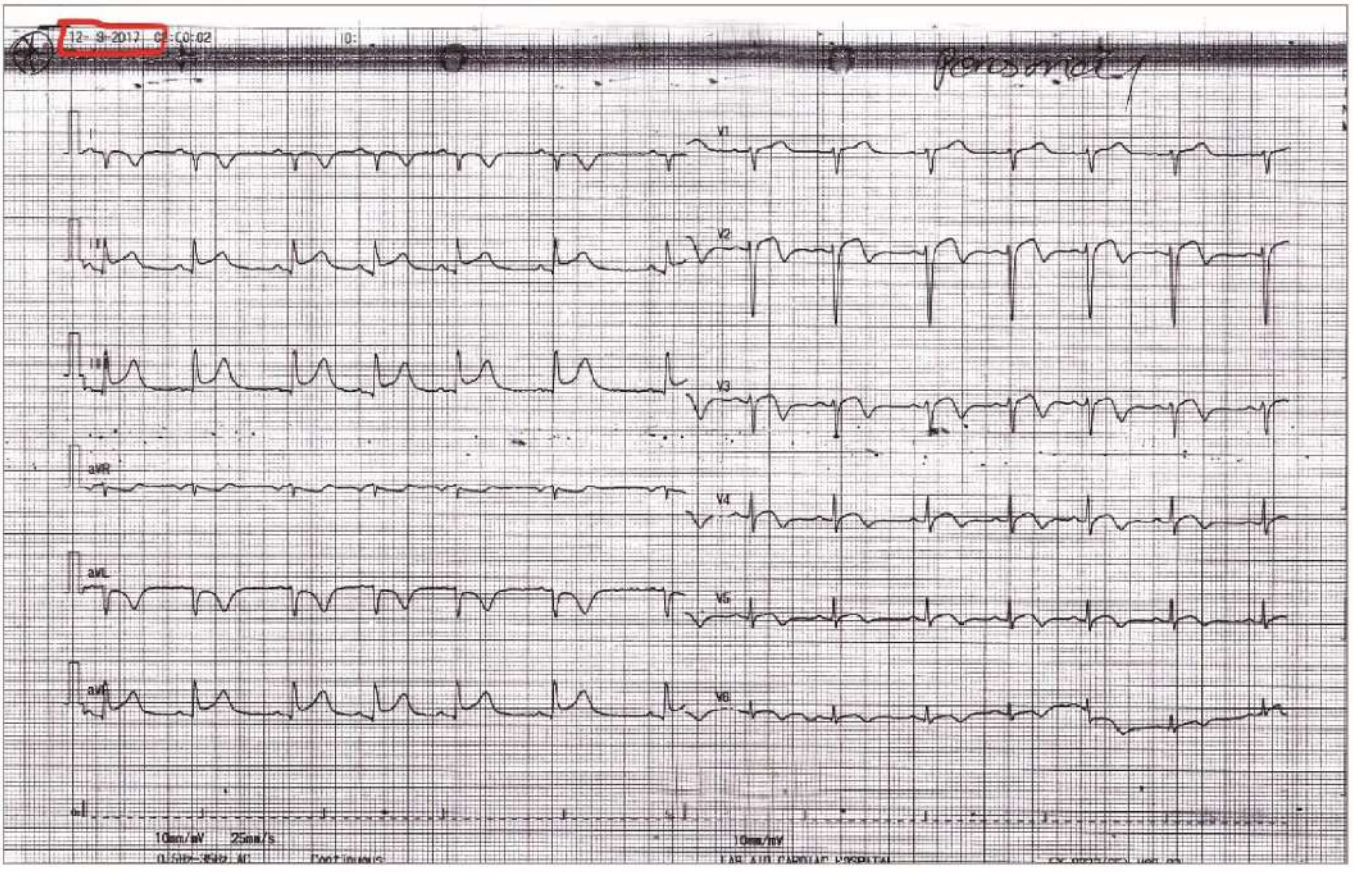

Figure-2 *ECG of the same patient on the second day of admission showing dynamic new changes in chest leads .ECG shows ST elevation with biphasic T waves in leads V2-V6 as new changes.*

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Total Correction and Multiple Postoperative Trans catheter Intervention in a Case of Tetralogy of Fallot.

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Abstract

A 17 years old girl reported at the age of 04 months to pediatric cardiology unit with severe cyanosis and was diagnosed as a case of tetralogy of Fallot (ToF) with small atrial septal defect(ASD) secundum type after work up. She had total correction at the age of 30 month as parents were not convinced for surgery advised at one year of age. ASD was left open during surgery . Patient developed both right pulmonary artery (RPA) and left pulmonary artery (LPA) origin stenosis observed at follow up and balloon angioplasty was offered twice at age of six years and eight years. During her regular follow up ASD secundum was found increasing in size gradually and there was occasional right to left shunt through it. At the age of ten years she underwent transcatheter ASD device closure. Patient was discharged from regular follow up in 2017 at the age of fourteen years.

Introduction:

Tetralogy of Fallot (TOF) was first described in 1888 by Étienne-Louis Arthur Fallot and is characterized by the presence of four anatomical anomalies: ventricular septal defect (VSD), pulmonary stenosis/outflow obstruction of the right ventricle (RV), RV hypertrophy and an aorta that overrides the VSD. The primary lesion is the cephaled and anterior deviation of the infundibular septum, which ultimately leads to the four classical alterations.[1,2] When TOF is associated with ASD, it is known as Pentalogy of Fallot. In 20 % cases it is associated with right sided aortic arch. Coronary abnormalities are also common in TOF. When coronary crosses RVOT, it is a great difficulty for surgeons. Sometimes surgeons kept left open Patent foramen ovale (PFO) or ASD for pop up.

TOF is one of the most common forms of cyanotic congenital heart disease.[3] Prolonged survival without surgical intervention is rare. Prolonged survival of patients with uncorrected TOF is often associated with a well-developed left ventricle.[4] This may happen cases with initial mild pulmonary stenosis that progresses or adaptations that ameliorate the right-to-left shunting, such as systemic to pulmonary collaterals, persistent patent ductus arteriosus or systemic hypertension. 1The main causes of death are cerebrovascular accident, intracranial haemorrhage, cyanotic spell, chronic congestive heart failure, secondary to the long-standing pressure overload and consequent pathological changes in the RV, and arrhythmias.[4] TOF patients carry a high risk for the development of infective endocarditis (IE), which is a serious and fatal complication in adults with congenital heart disease .[5,6,7] The incidence of IE in patients with TOF submitted to surgery, either corrective or palliative, is high (around 18%), whereas in patients with uncorrected TOF this incidence is small (around 4%).8,9The most common organisms are streptococci, followed closely by staphylococci.[6,7]Adult with repaired ToFmay develop complications in course of time. Pulmonary regurgitation, pulmonary stenosis , branch pulmonary artery stenosis, origin stenosis of RPA, LPA , aneurysmal dilatation of RV outflow tract are common.10A 17-years-old girl with a surgically corrected TOF had ASD device closure andtranscatheter RPA and LPA angioplasty in three separate occasions has been reported here.

Case report:

X, a 17-year-old Bangladeshi girl reported with a history of Surgically corrected TOF followed by balloon angioplasty of both RPA and LPA and transcatheter ASD Device closure in Paediatric cardiology OPD in September 2017. She had history of bluish discoloration of tongue, lips and nails, difficulty in feeding , not growing well and cyanotic spell at the age of four months (3rd September 2004), on examination patient was cyanosed, there was early clubbing , on auscultation single 2nd heart sound and an ejection systolic murmur found in upper left sternal border. Her Complete blood count revealed Hemoglobin concentration18 gm% and reticulocyte count 6%, chest X-Ray (CXR) revealed tilted apex, concavity of pulmonary area(Boot shaped heart)with oligemic lung field, Electrocardiogram (ECG) revealed sinus rhythm, right ventricular hypertrophy (RVH) and Right axis deviation (RAD). Echo revealed large malaligned VSD, right to left

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shunt, severe infundibular stenosis without valvular involvement, good sized confluent branch pulmonary arteries(PA), more than 5o % overriding of aorta, severe right ventricular hypertrophy (RVH), good right ventricular (RV) function, Small ASDII(3.7mm), left arch with normal coronaries.Final diagnosis was TOF with small ASDII. Initially patient was managed with propranolol, oxygen inhalation and other supportive measures. She was under regular follow up. At the age of thirty month (10th February 2007) she had undergone intracardiac repair (ICR) operation for TOF. Her post-operative period and subsequent follow up was uneventful. Three years later (02 March 2010), follow up echo revealed severe RPA and LPA origin stenosis she was asymptomatic. On 7th March 2010 patient had transcatheter RPA and LPA angioplasty with 8x2 mm Tyshak II (Numed , Canada Inc) balloon. After that she was again kept under regular follow up. Two years later (28 March -2012) echo revealed RPA and LPA origin restenosis and then next day again RPA and LPA angioplasty was repeated with 10x3 mm high pressure Andraballoon (Andramed, Germany). On routine follow up echo, it was noticed that her ASD size was increasing gradually and it was 08 mm from initial 3.7 mm with occasional right to left shunt . On 18 March 2014 it was closed with a 10 mm Cera TM ASD device (Lifetech scientific, Schenzen Co Ltd). In follow up till 2017, patient was asymptomatic with normal growth and development, so patient was discharged from regular routine follow up. Her last echocardiography performed in 2017 was completely normal with no residual problems. She was advised to report to adult congenital heart heart disease (ACHD) clinic in case of any problem.

Discussion:

TOF is a complex cyanotic congenital heart disease and is the most common cyanotic congenital heart disease occurring with the incidence of 577 per million live birth.11Frequency of the disease is increased with consanguinity of parents.[12] Adults with ToF developed late complications. It is believed to be abnormalities in the septation of truncusarteriosus into the aorta and pulmonary arteries during the first 3-4 weeks of gestation. We treated a 17 years old girl who had undergone ICR for TOF at the age of 2.5 years and developed pulmonary artery origin stenosis and restenosis at the age of 06 and 08 years respectively. Her small ASD secundum was left open during Surgery for pop up , which has been increased in size significantly over the time and has been closed percutaneously with an ASD Device at the age of 10 years. Device closure for secundum ASD is currently considered to be a preferred option and has shown good procedural outcome and fewer periprocedural complications compared with a surgical approach[13]. Tetralogy of Fallot when associated with ASD is known as Pentalogy of Fallot. Incidence is 3.7 % of all CHD.[14]Residual RVOT obstruction can persist after initialcorrective surgery due tohypertrophied muscle in thesubvalvular region, annular hypoplasia, and pulmonary valvestenosis, or branch pulmonary artery stenosi.[15] Mildobstruction is usually well tolerated, but significantobstruction may require reoperation or catheter-basedintervention. In this case , four years after corrective surgery in 2008, she developed significantpulmonary artery origin stenosis with peak pressure gradient(PPG) of 70 mm Hg and undergone balloon angioplasty with 8x2 mm Tyshak-2 balloon, with residual mild stenosisof 28 mm Hg. Six years after surgery in 2010, she again developed pulmonary artery origin stenosis with PPG of 80 mm of Hg and again undergone balloon angioplasty with 10x3 mm high pressure Andra balloon with insignificant gradient of 12 mm of Hg.For single balloon angioplasty, the recommended balloon diameter is about 120—140% of the stenosed partmeasured by a pulmonary artery angiography 16. Patient with ToF repair are now surviving into adulthood and many complications are also encountered among them. Cases of repair with transannular patch often develop pulmonary regurgitation. There is no medical management of pulmonary regurgitation, patient develop RV volume overload, dilated RV and RVOT and arrhythmia in course of time which ultimately led to right heart failure. Some cases develop aneurysmal dilatation of RVOT[16, 17, 18]

Some of these cases need surgical replacement of pulmonary valve or percutaneous pulmonary valve replacement (PPVI) . Many ToF cases required RV to PA conduit and conduit replacement is required in later part of life due stenosis or regurgitation .[19,20]

Figure-1 *Patient X at 4 months of age during diagnosis.*

Case Report

Figure-2 *Patient X at the age of 17 years, completely cured.*

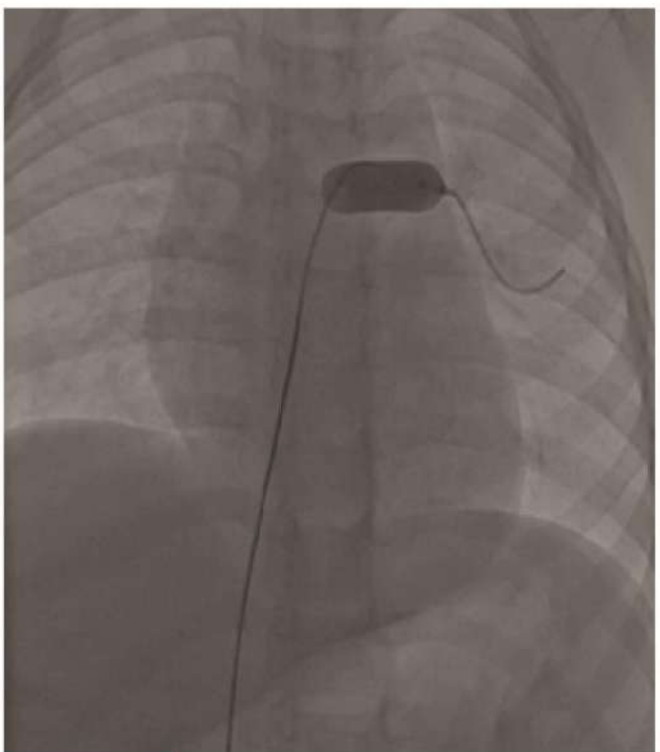

Figure-3 *Balloon angioplasty LPA.*

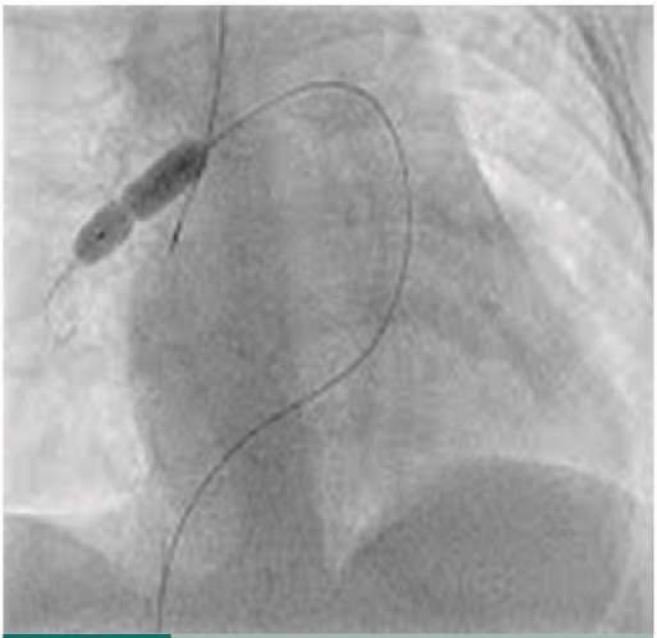

Figure-4 *Balloon angioplasty of RPA.*

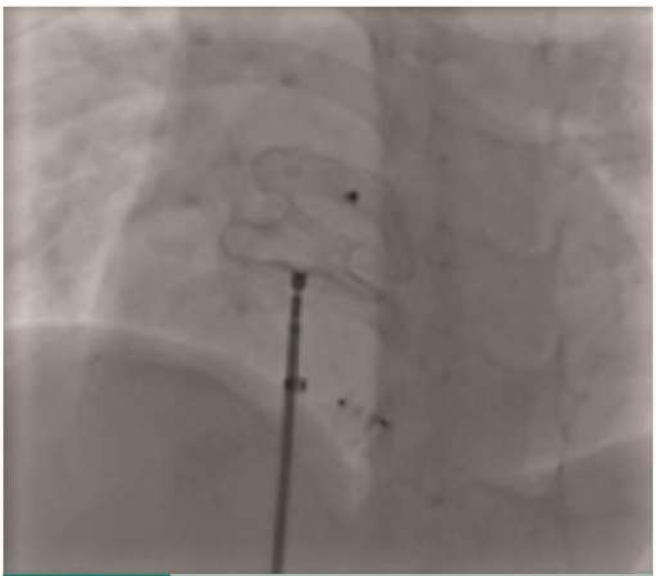

Figure-5 *Cera TM ASD occlude Device before release.*

Conclusion:

TOF is a complex cyanotic congenital heart disease. Symptoms depend upon severity of the anatomy. Patient may require palliative surgery, like Blalock Taussig shunt (BT), if the branch PAs are not suitable for total correction. Early diagnosis and timely intervention reduces the mortality and complications. Patient may require surgical or Transcatheter intervention for any post-surgical complications. Follow up of the patient before and after surgery is important in making decision for further management. In Bangladesh this is a unique case where surgical correction and trans catheter interventions over a period of seven years led to complete recovery of the patient.

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Takotsubo Cardiomyopathy- A Case Report

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Abstract

Takotsubo cardiomyopathy is a transient and reversible left ventricular dysfunction which mimics the symptoms of an acute myocardial infarction (AMI). However, coronary angiogram (CAG) indicates normal coronary vessels. A 22 year old young man presented to a tertiary care cardiac hospital with chest pain and dyspnea for more than 24 hours duration. ECG taken in the emergency department showed ST elevation in leads V4-V6 with biphasic T waves in V1-V3, suggestive of acute anterior myocardial infarction (MI). Bedside echocardiography done in coronary care unit (CCU) indicated apical akinesis with some ballooning and EF of 45%. He was found to have elevations of cardiac troponin I (cTnI) and creatine kinase (CK)-MB. He was treated conservatively and subsequently CAG was done which showed normal epicardial coronary arteries.

Introduction

Takotsubo cardiomyopathy, also called apical ballooning syndrome (ABS), broken heart syndrome, and stress-induced cardiomyopathy, is an increasingly reported syndrome generally characterized by transient systolic dysfunction of the apical and/or mid segments of the left ventricle that mimics myocardial infarction, but in the absence of obstructive coronary artery disease.[1-3] Takotsubo cardiomyopathy was first described in Japan and was subsequently reported in non-Asian populations, including the United States and Europe.[4-6] Takotsubo cardiomyopathy is a unique cardiomyopathy characterized by chest pain, ECG, and regional wall motion abnormalities closely mimicking acute myocardial infarction, in the absence of significant coronary artery disease. Classic ECG changes of Takotsubo cardiomyopathy include ST elevation or T wave inversion . About a third of patients with Takotsubo cardiomyopathy have ST segment elevation and another third have T wave inversions. ECG is normal or shows minor nonspecific changes in the remaining third. [6,7]

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Because clinical features of Takotsubo cardiomyopathy mimics those of acute anterior MI , the differential diagnosis is important in selecting the appropriate treatment strategy, especially in the acute phase . The absence of abnormal Q waves, absence of reciprocal changes, presence of ST-segment elevation in lead -aVR (i.e., ST-segment depression in lead aVR), and absence of ST-segment elevation in lead V1 can identify Takotsubo cardiomyopathy with sensitivities of 42%, 94%, 97%, and 94%, specificities of 74%, 49%, 75%, and 71%, and predictive accuracies of 71%, 53%, 77%, and 73%, respectively.[4] The combination of the presence of ST-segment depression in lead aVR and the absence of ST-segment elevation in lead V1 identified Takotsubo cardiomyopathy with 91% sensitivity, 96% specificity, and 95% predictive accuracy, which was superior to any other ECG findings . Compared with anterior MI, Takotsubo cardiomyopathy is associated with less ST-segment elevation and more frequent absence of abnormal Q waves, suggesting less myocardial damage. [4,7]

Case Report

The patient was a 22 year old man without any history of heart disease, presented to the hospital with severe chest pain and dyspnea for more than 24 hours duration. He had no history of hypertension, diabetes and hyperlipidemia. He did not mention any history of smoking, drug abuse or alcohol use. But on query he admitted that he was very worried for the last two weeks for a family matter and for his final university examination. In clinical examination he was haemodynamically stable. His blood pressure was normal and auscultation of lung bases were clear. An initial electrocardiogram in emergency room showed sinus rhythm with ST segment elevation in leads V4-V6 with biphasic T waves in leads V1-V3, suggestive of anterior myocardial infarction (Fig-1). The patient was immediately transferred to the CCU and cardiac monitoring was initiated. In bedside echocardiography, EF of 45% and apical akinesis with some ballooning of the apex were reported. Subsequently , a positive troponin result was obtained. He was treated in the line of acute coronary syndrome (ACS). After initial stabilization he was scheduled for CAG and it showed normal epicardial coronary arteries. He was discharged from the hospital in a reasonably stable state after 5 days of admission.

Discussion

Takotsubo cardiomyopathy is an acute onset of left ventricular apical ballooning without significant coronary artery stenosis which mimics acute MI symptoms and its ECG findings. Most patients manage to survive and a complete and rapid recovery occurs, although there is the possibility of relapse.[8] The modified Mayo Clinic criteria are used to make the diagnosis of Takotsubo cardiomyopathy and include the followings:1. Absence of coronary artery disease on angiography 2. Transient dyskinesis, hypokinesis or akinesis of the left ventricle midsegments with or without apical involvement. 3. ECG evidence of ST-segment elevation and/or T wave inversion. 4.Modest elevation of troponin levels. 5. Absence of myocarditis or pheochromocytoma. The exact number of people with the disorder remains unknown because not all patients undergo CAG following chest pain. The majority of patients are Asians or Caucasians and present with symptoms in the 6th decade of life. Close to 90% of cases have been reported in postmenopausal females.[9] The main presentation of the Takotsubo syndrome is transient and reversible left ventricular dysfunction occurring after severe emotional distress and/or physical stress without coronary artery stenosis. Mental stress in this particular case probably precipitated this form of cardiomyopathy. In this case exact stressors were identified.

Though the patient we presented here was a 22 year old young man but most patients are usually postmenopausal women. These patients also develop dyspnea, chest pain or pulmonary edema. There have been reports of progression to cardiogenic shock or ventricular fibrillation in some cases. Slight increase in cardiac markers is observed which is significant as compared to the extent of the akinetic area.[10-13]

Takotsubo cardiomyopathy must be distinguished from other entities that involve cardiac enzyme elevation with non-obstructive coronary arteries. Symptomatic

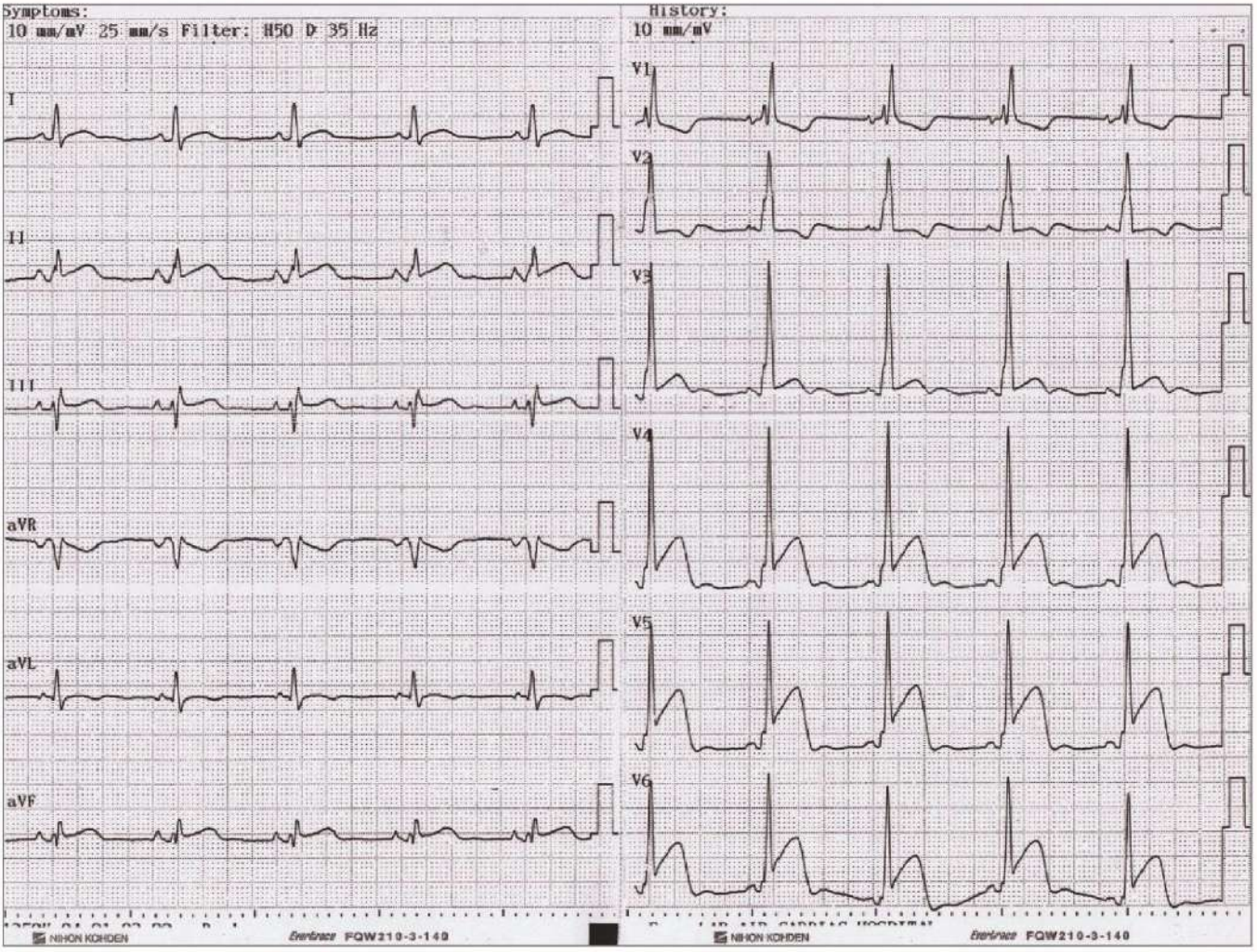

Figure-1. *ECG of the patient with Takotsubo Cardiomyopathy. ECG taken in the emergency department showed ST elevation in leads V4-V6 with biphasic T waves in V1-V3, suggestive of anterior myocardial infarction (MI). ECG shows RBBB pattern and no reciprocal ST depression in inferior leads. Note also some ST segment depression in lead aVR and no ST elevation in lead V1.ST segment depression in lead aVR combined with no ST elevation in lead V1 simply but accurately differentiates Takotsubo Cardiomyopathy from anterior MI.*

non-obstructive coronary artery disease (NOCAD) occurs with less than 50% coronary luminal stenosis.[14] Further functional and physiologic assessment of coronary endothelial function and the coronary microvascular system should be considered in these patients. Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease (MINOCA) occurs in as many as 5% of patients presenting with myocardial infarction who undergo CAG.[15]

During the acute and subacute phases of the disease, patients are prone to develop severe complications, including heart failure, cardiogenic shock, or life-threatening arrhythmias. Therefore, close monitoring during initial period is suggested in CCU, in a similar fashion as recommended for patients with ACS.[16]

Overall, Takotsubo cardiomyopathy patients had long-term outcomes comparable to age- and sex-matched ACS patients. Also, studies demonstrated that Takotsubo cardiomyopathy can either be benign or a life-threating condition depending on the inciting stress factor.[17-18] In short term prognosis of a series of total of 6,739 admissions for Takotsubo cardiomyopathy published in recent past showed the readmission rate for this disorder remained low (0.58%) at 180 day follow up period in a cohort of 3,332 index hospitalizations.[18] Prognosis of Takotsubo cardiomyopathy remains controversial due to scarcity of available data. Additionally, the effect of the triggering factors remain elusive.

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Acute Severe Mitral Regurgitation with Cardiogenic Shock Caused by Complete Anterior Papillary Muscle Rupture in Acute Myocardial Infarction. Successful Early Surgical Mitral Valve Replacement.

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Abstract

We report the successful treatment of a 46-year-old man after a difficult diagnosis of mitral valve regurgitation resulting from complete rupture of the anterior papillary muscle. The patient with cardiogenic shock had an emergency admission. An electrocardiogram showed evidence of acute lateral wall myocardial infarction. Bedside echocardiography revealed complete rupture of anterior papillary muscle resulting in acute severe mitral regurgitation. We performed coronary angiography, which showed complete obstruction of 2nd obtuse marginal coronary artery. We determined that the condition was caused by post myocardial infarction papillary muscle rupture. Emergency surgery showed the complete rupture of the anterior papillary muscle. The mitral valve was replaced with a Epic bioprosthetic valve along with concomitant coronary artery bypass grafting of the second obtuse marginal artery.The postoperative course was uneventful.

Introduction

Rupture of a papillary muscle is an uncommon but often fatal complication of acute myocardial infarction (MI) which is responsible for approximately 5% of death after MI[1.2] . The characteristics of the underlying coronary disease will define the clinical presentation and prognosis; the mortality could be as high as 80% during the first week of MI.The rupture of the posteromedial papillary muscle is most common, seen in about 75% of cases. The posteromedial muscle has a single blood supply from the posterior descending branch of a dominant right coronary artery,and is associated with inferior wall infarctions. The rupture of the anterolateral muscle is less common, occurring in 25% of cases, as it has dual blood supplies: from the first obtuse marginal, originating from the left circumflex; and from the first diagonal branch, originating from the left anterior descending. The rupture of the latter is seen with anterior or postero-lateral MI[3.4].

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Case Report

A 46-year-old man presented to the emergency room from another hospital as a diagnosed case of NSTEMI, DM, Hypertension, MR Gr-III and cardiogenic shock. He complained of chest tightness, diaphoresis, orthopnea, and paroxysmal nocturnal dyspnea over the last 4 days. Past medical history was nothing significant. On physical examination patient was in respiratory distress sitting up right, blood pressure was 80/60 mmHg, heart rate 143 bpm, regular, respiratory rate 32/min. Neck veins were not distended and he had no ankle edema. On examination of the cardiovascular system he had a regular S1 S2 with a S4 gallop. He had unilateral coarse crepitation over the right lung. Initial ECG showed ST depression in the II/III/aVF and V 3-5 at inferolateral leads (Fig-1). The chest radiography showed right sided asymmetric pulmonary edema (Fig-2).

The patient was admitted to the coronary care unit with the diagnosis of decompensated heart failure secondary to acute coronary syndrome ((CK-MB 77 u/L, Troponin-I 18.74 ng/ml, NT Pro BNP 9703 pg/ml and white Blood cell 28.9 X 10 ^ 9/L), and treated accordingly. A transthoracic bed side echocardiogram was performed, revealing a normal left ventricular ejection fraction (LVEF) and moderate to severe mitral regurgitation (MR) (Fig-3). A transesophageal echocardiogram was performed subsequently which showed that the mitral valve was normal in thickness with a flail anterior leaflet not coapting with the posterior leaflet. Color flow Doppler revealed severe MR. Effective Regurgitant Orifice (ERO) was 5 mm^2, regurgitant volume by PISA was 60 ml, regurgitation fraction was 60%, and the Vena Contracta width was 8 mm. There was a holosystolic flow reversal of the pulmonary vein. Echo density visualized in the left ventricle suggested complete ruptured anterior papillary muscle (Fig-4). Left ventricle was hyperdynamic, no wall motion abnormalities were seen and the LVEF was more than 60%. The diagnosis of severe MR with preserved left ventricular function was made. Subsequent coronary angiogram revealed 2nd obtuse marginal (OM2) artery totally occluded at proximal end (Fig-5). The other coronary arteries had minor irregularities but no significant stenosis, and the right coronary artery had 30 to 40% distal segment stenosis.

The patient underwent a mitral valve replacement with a St Jude Epic bioprosthetic valve and concomitant coronary artery bypass grafting of the second obtuse marginal

artery. He had an uneventful recovery, and was discharged with good physical condition. He was then seen in the follow up clinic 10 days after the surgical intervention, patient was asymptomatic and with no heart failure. The transthoracic echocardiogram performed in the clinic showed a normal LVEF, mild flattening of the IV septum – a common we functioning after a valve replacement – and a functional bioprosthetic mitral valve with no paravalvular leaks.

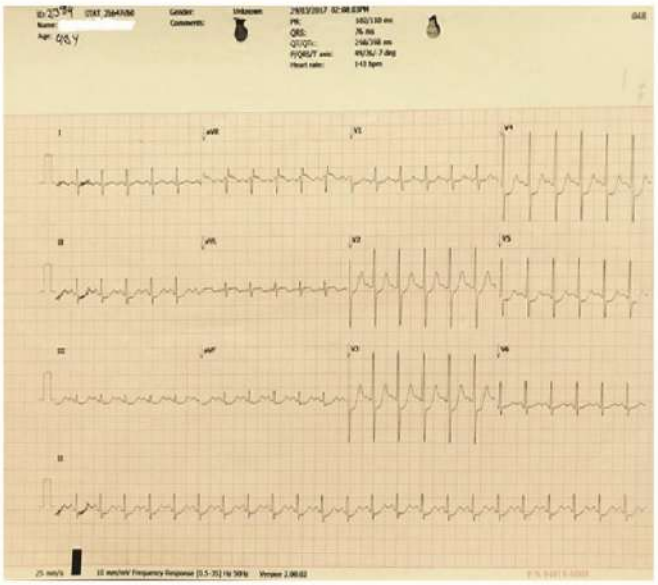

Figure-1 *ECG at Emergency Dept Showing sinus rhythm,HR 143/min,normal axis and ST segment depression in the II/III/aVF andV3-5 (Inferolateral Ischemia).*

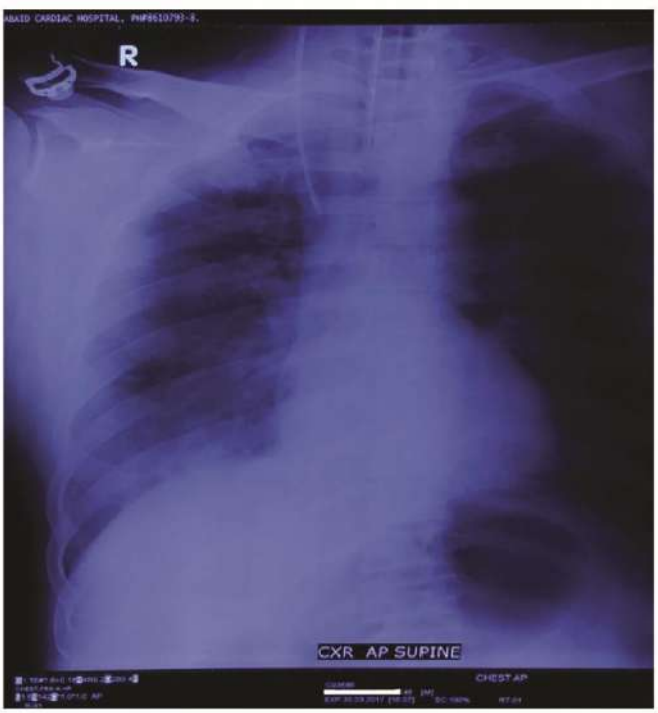

Figure-2 *In CCU portable preoperative CXR shows right sided asymmetric pulmonary edema.*

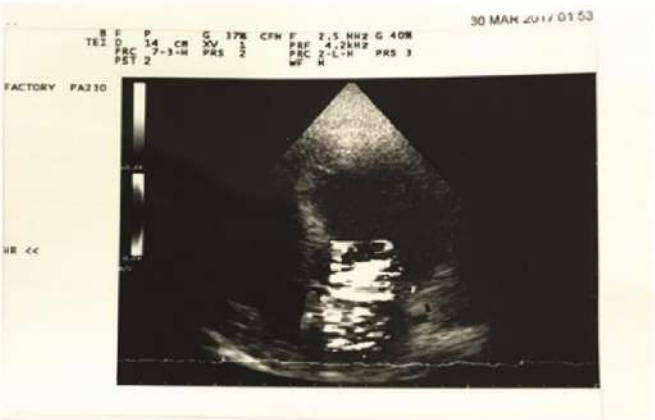

Figure-3 *Bedside Echo in CCU showing severe MR.*

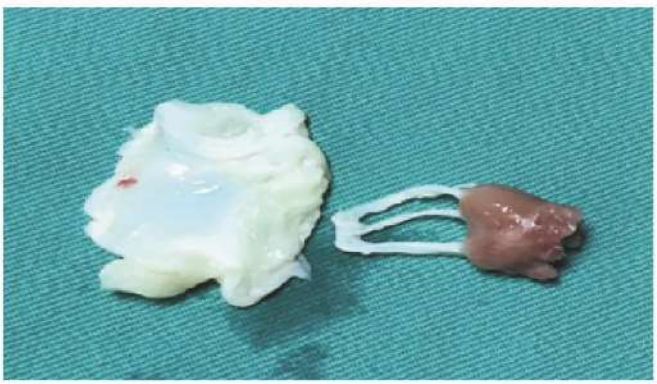

Figure-4 *Specimen: Anterior mitral valve leaflet with rupture of the anterior papillary muscle.*

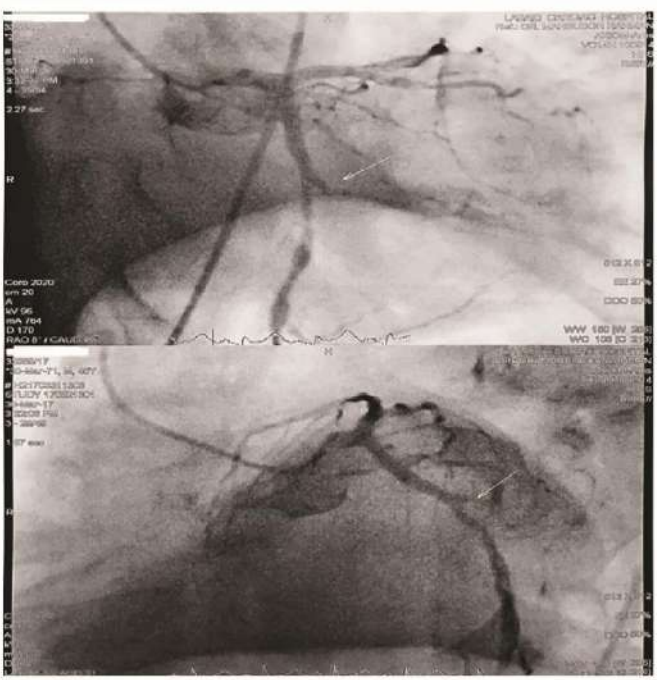

Figure-5 *Coronary angiogram Shows 2nd obtuse marginal (OM2) artery totally occluded at proximal end.*

Case Report

Discussion

Here we presented a case of a mechanical complication of MI and congestive heart failure. The patient developed cardiogenic shock due to severe MR secondary to total occlusion of the 2nd obtuse marginal artery. When the bed side transthoracic echocardiogram was performed the MR was found to be secondary to the rupture of the anterior papillary muscle.

The clinical presentation and severity of a papillary muscle rupture depends on the involved coronary artery and left ventricular performance. This is usually clinically apparent 2-8 days post-acute MI[1], compatible with the presentation of our patient. As stated previously, the anterior papillary muscle is less often involved in a rupture than the posterior papillary muscle, because of its dual blood supply[5].

Different types of lesions to the papillary muscle may occur as a complication of ischemia; prolapse, elongation or rupture in different degrees, partial rupture being the most common type of rupture[6]. The precise diagnosis of papillary muscle rupture can be difficult to establish by transthoracic echocardiography, as the ruptured head may not prolapse into the left atrium, making transesophageal echocardiography a more sensitive and useful tool for diagnosis[7-9].

Due to the high mortality rates with the medical management of papillary muscle rupture impose urgent surgical intervention, the timing of intervention being dictated by the patient's hemodynamic stability[10-13]. The survival rates seem to be related to the extent of papillary muscle rupture, with the best results occurring when a small portion of the tip is ruptured, related to small infarction and limited coronary disease[14].

Conclusion

This case confirms the importance of an immediate echocardiographic evaluation in establishing the diagnosis, whenever an acute mechanical complication from an acute MI is suspected. The definitive therapy is surgical valve repair or most often, replacement, which should be undertaken as soon as possible because clinical deterioration occurs suddenly.

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Cardiogenic Shock Following Acute ST Elevation Myocardial Infarction (STEMI)

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Abstract

Cardiogenic shock (CS) is a state of end –organ hypoperfusion due to cardiac failure, characterized by (a) Persistent hypotension, systolic blood pressure (BP) <80 to 90 mmHg. (b) Cardiac Index<2.2 L/min/m^2 (c) Wedge pressure>18 mmHg and diuresis usually <20 ml/hr. Shock is present if I.V. ionotropes and /or mechanical support are needed to maintain SB>90 mmHg. It complicates 6 to 10 % of all STEMI (Fig-1), remains a leading cause of hospital mortality>50% .We report here such a case of Cardiogenic shock following acute STEMI.

Case review

Mr " X " a 54 yrs old male,smoker presented to us on 2nd November 2019 with H/O 3 hours cardiac pain. Electrocardiogram showed STEMI (anterior),Fig-2, hemodynamically was stable.His coronary angiogram revealed severe triple vessel disease (TVD) Figure 3 with pLAD 100% occlusion, pLcx 100% occluded with thrombus and significantly diseased RCA. Patient relative refused high risk pPCI.We used thrombolytics Tenecteplase.Three hours after lytics ,ST segment became isoelectric. Fig-2.Echocardiography showed RWMA,MR with LVEF 30 to 35% .After 7 hours he developed pericarditis ,20 hours later his ECG again showed ST elevation Fig-2 with hypotension and cardiogenic shock.With isoprenalin,enoxaperin and other medication,shock improved a lot.Patient relative insisted for CABG as severe TVD .Next morning during talking with relatives he developed cardiac arrest .He did not recover after cardiopulmonary resuscitation.

Discussion

The first step in cardiogenic shock patient is to identify the mechanism and to correct any reversible cause like hypovolumia, drug hypotension or arrhythmias, alternatively, initiate the treatment of causes and complications[3]. Treatments include immediate reperfusion,with Primary PCI whenever possible[5,6]and complete revascularization[3].

Invasive monitoring with arterial line[7] and pulmonary artery catheter may be considered.Pharmacotherapy improve organ perfusion by increasing cardiac output and BP.Ionotrophs or vasopressors are usually required to maintain SBP>90 mmHg .Norepinephrin safer , effective than dopamine in CS and severe hypotension [8] . Diuretic is recommended when perfzusion is attained.

IABP does not improve STEMI patients and CS without mechanical complications (i,e severe MR or VSD)[9].

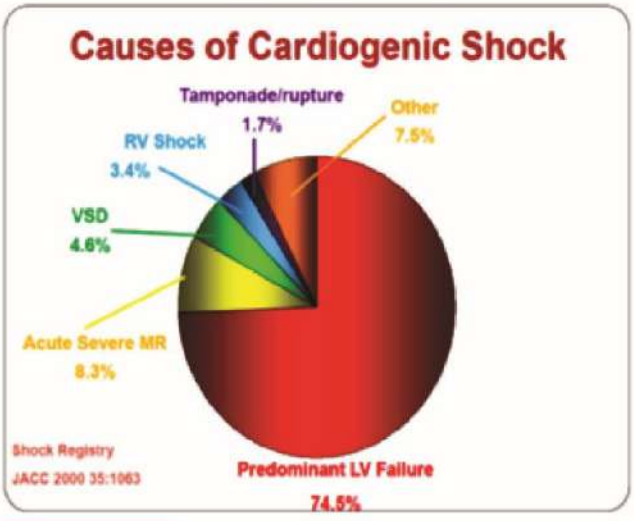

Figure-1. *Causes of Cardiogenic shock*

Mechanical LVADs have been used in patients not responding to therapy but benefits is limited10. Mechanical circulation may be considered as a rescue therapy in order to stabilize the patients and preserve organ oxygenation as a bridge for myocardial function,cardiac transplantation or even LV AD therapy[11,12].

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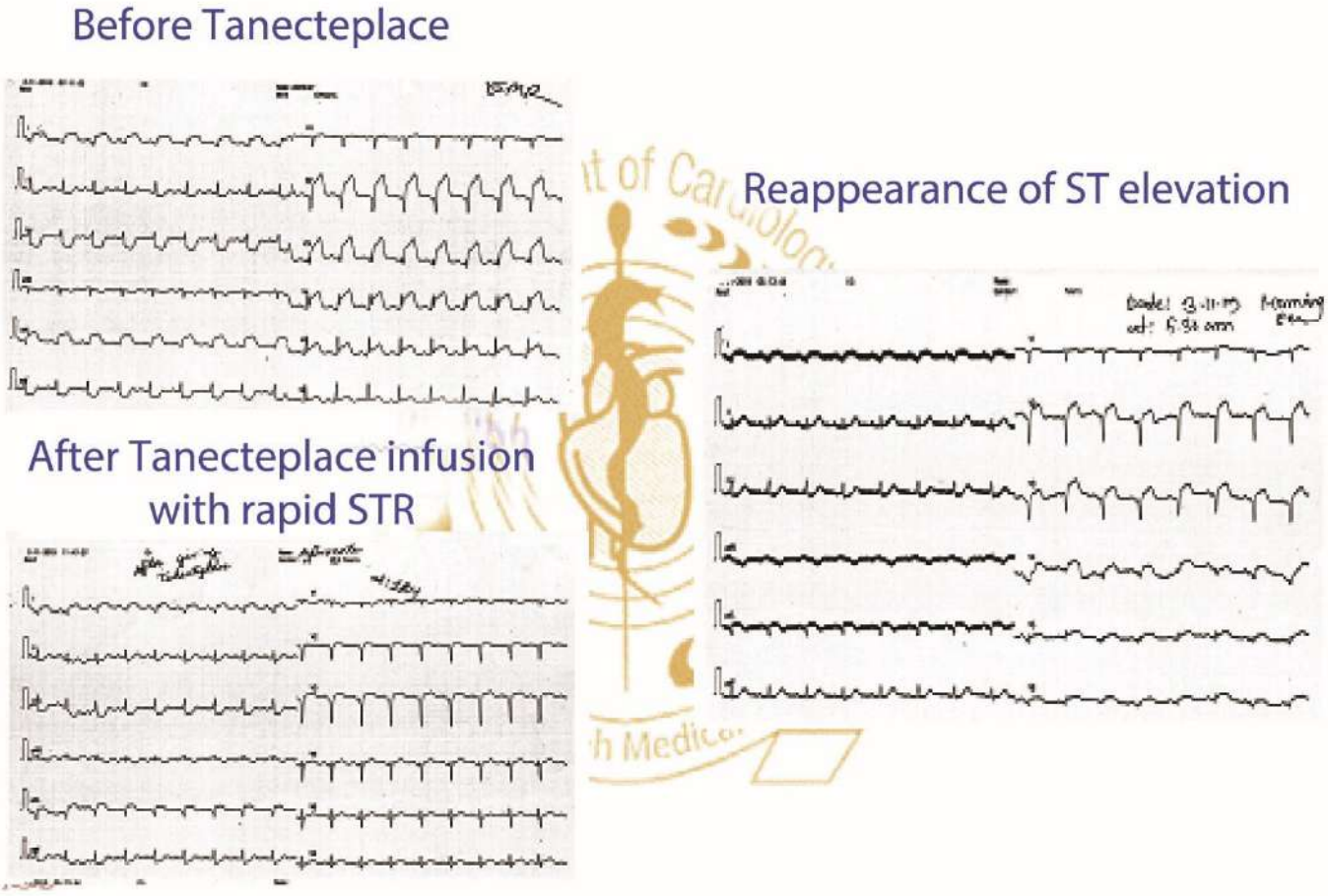

Figure-2.

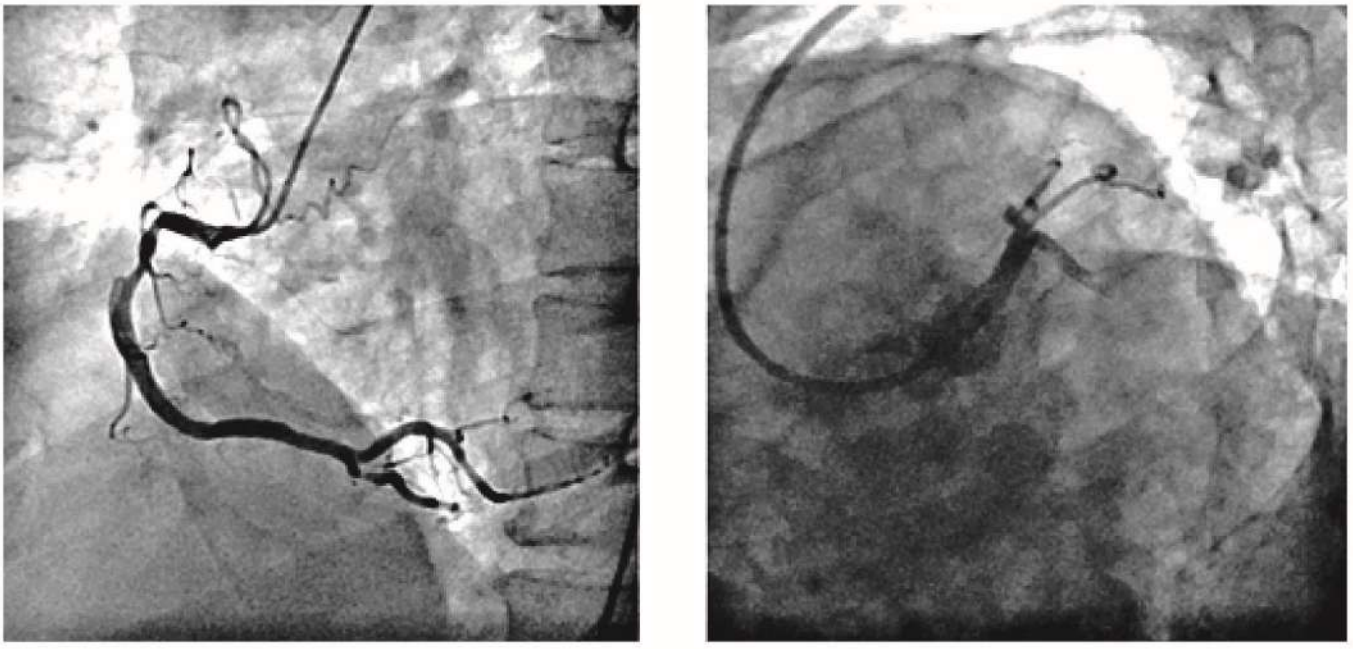

Figure-3.

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Hyperacute T waves in Pericarditis Mimicking Hyperacute Anterior Myocardial Infarction in a Patient with Recent Inferior Myocardial Infarction- A Rare Case Report

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Abstract

Hyperacute T waves are the earliest-described electrocardiographic (ECG) sign of acute ischemia, preceding ST-segment elevation. But regional pericarditis that occurs most frequently after transmural myocardial infarction may produce ECG evidence of hyperacute T waves rarely, which may mimic ST segment elevation myocardial infarction (STEMI) in a different arterial territory. Here the authors describe a rare case of hyperacute T waves in pericarditis mimicking hyperacute anterior myocardial infarction (MI) in a patient with recent inferior myocardial infarction.

Introduction

Acute pericarditis is an inflammation of the pericardium that can result in chest pain, pericardial friction rub, and serial ECG changes. The 4 ECG stages of pericarditis include: 1) diffuse ST elevation and/or PR depression, 2) normalization of ST- and PR-segments, 3) diffuse T-wave inversions with isoelectric ST-segments, and 4) normalization of the ECG.[1,2] Hyperacute T wave is a rare ECG findings in pericarditis, mostly associated with myopericarditis. The electrocardiographic differential diagnosis of the hyperacute T wave includes both transmural acute MI and hyperkalemia as well as early repolarization, left ventricular hypertrophy, and acute myopericarditis.[3,4] Clinical differentiation between myopericarditis and MI are especially important because adverse side effects can occur if reperfusion therapy is administered for a patient with acute pericarditis or if a diagnosis of acute MI is missed. [5]

Case Report

A 48-year-old male, with no known cardiovascular risk factor, presented to the emergency department of local hospital far away from Dhaka city with typical chest pain along with sweating with onset less than 12 h. ECG done in the emergency department showed ST segment elevation in LII,LIII and aVF suggestive of acute inferior wall MI . Due to non availability of cardiac catheterization laboratory (Cath Lab) and primary percutaneous coronary intervention (PPCI) facility in the presenting hospital, he was thrombolysed immediately. After thrombolysis his chest pain subsided and he remained haemodynamically stable. After thrombolysis, ECG showed remarkable ST segment elevation resolution along with the appearance of Q waves in inferior leads (Fig-1). But on the third day of admission, at evening he suddenly developed severe chest pain along with shortness of breath (SOB). Keeping in view the possibility of reocclusion of the culprit vessel ECG was done immediately and 12 ECG showed recurrence of ST elevation in the inferior leads along with new appearance of hyperacute T waves in the chest leads suggestive of hyperacute anterior infarction. At this stage the patient was transferred to a tertiary care cardiac hospital for possible PPCI. ECG taken in the emergency department of the tertiary care hospital revealed the same ECG findings with hyperacute T waves in the chest leads more marked in leads V2- V4 along with the evidence of recent inferior myocardial infarction (Fig-2) . Patient was immediately shifted to the coronary care unit (CCU) and Cath Lab was mobilized for urgent coronary angiography +/- PPCI. In CCU clinical examination findings revealed widespread friction rub all over the precordium and bedside echocardiogram showed markedly hypokinetic Inferior and posterior wall with normal contraction of the anterior wall. Echocardiogram also showed evidence of thin rim of pericardial effusion posteriorly and laterally (maximum 6 mm). Diagnosis of acute pericarditis was established and the decision of emergency coronary angiogram was deferred. He was commenced on treatment with high dose aspirin and colchicine in standard doses.[6] His symptoms subsided within 24 hours of admission but hyperacute T waves in anterior leads persisted as before (Fig-3). On the 3rd day of admission height of the hyperacute T waves normalized and ST elevation in the inferior leads resolved (Fig-4). He was discharged from the hospital on the 7th day of admission. After 4 weeks repeat echocardiogram showed complete resolution of the pericardial effusion. Then coronary angiogram was done which showed single vessel disease with significant lesion at proximal right coronary artery and PCI was done in the same setting. The procedure was uneventful and the patient was discharged from the hospital 2 days after PCI.

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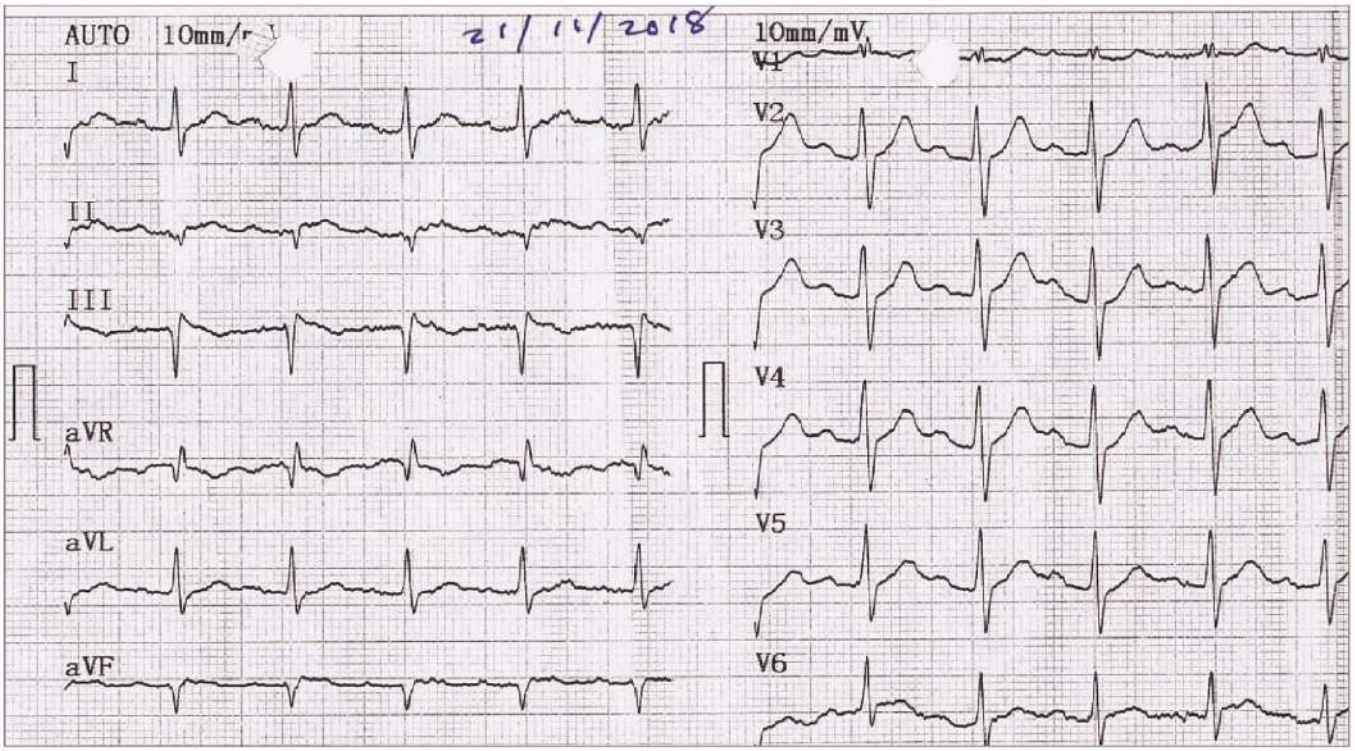

Figure-1. *24 hours after thrombolysis, ECG shows appearance of Q waves in inferior leads (LII,LIII and aVF) with mild degree ST elevation along with incomplete RBBB pattern.*

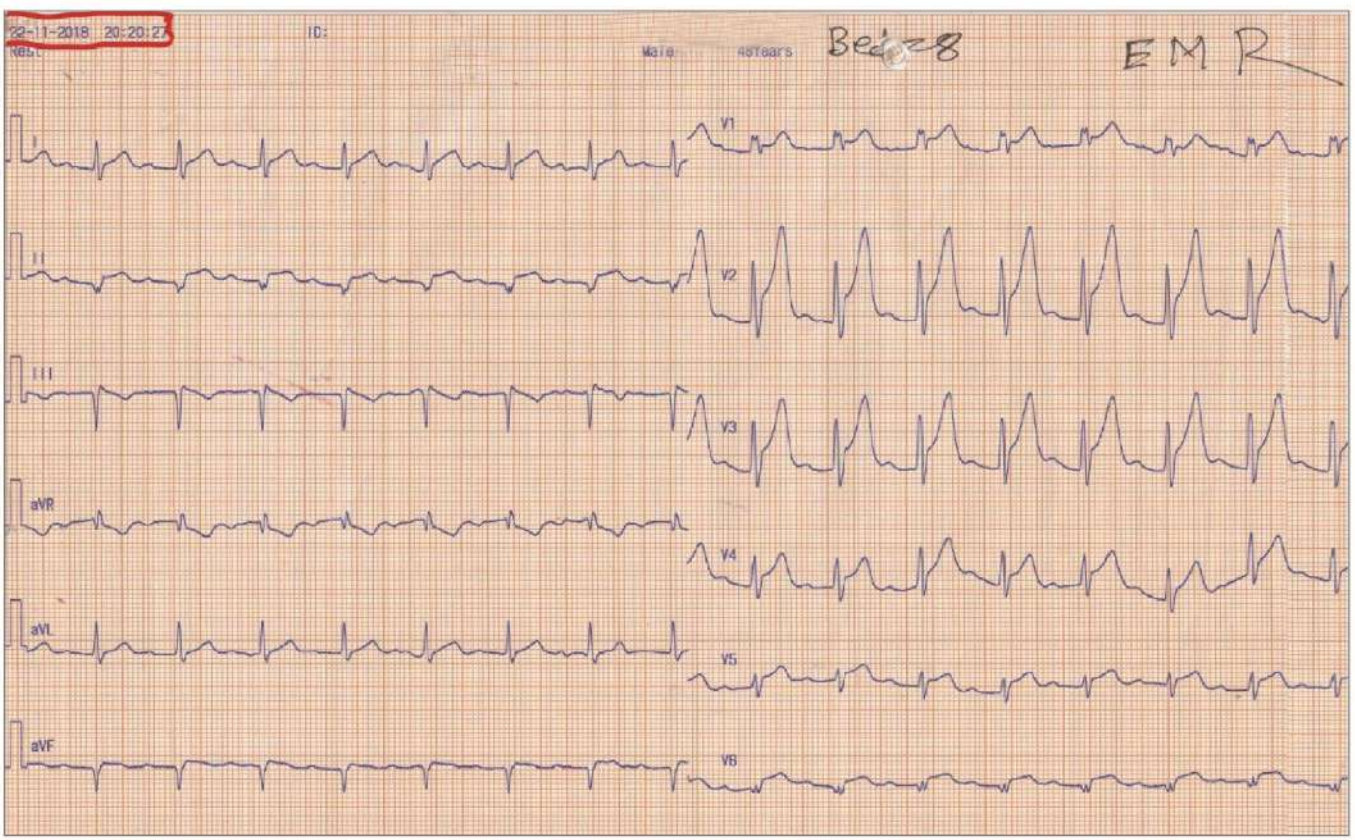

Figure-2. *ECG taken in the emergency department of the tertiary care cardiac hospital reveals hyperacute T waves in the chest leads more marked in leads V2-V4 along with the recurrence of ST elevation in inferior leads.*

Case Report

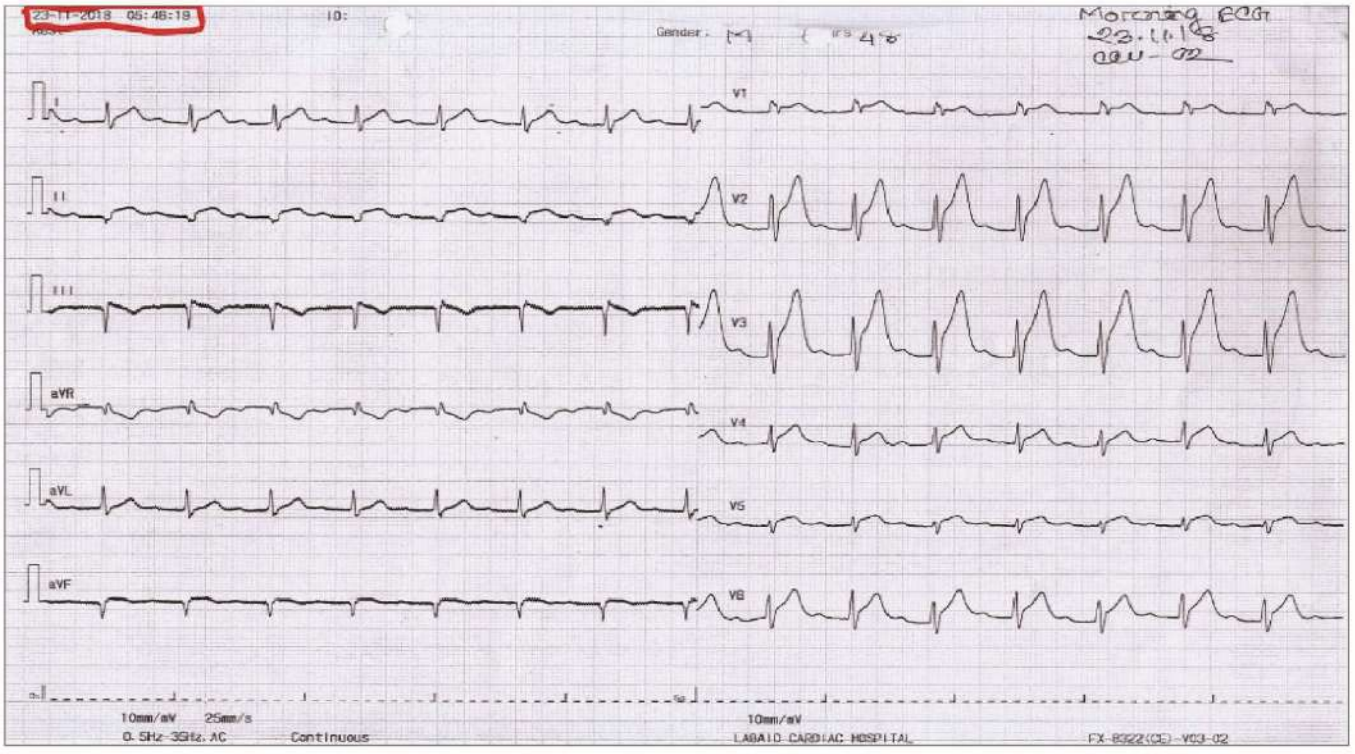

Figure-3. *Hyperacute T waves in anterior leads persisting on the 2nd day of diagnosis of pericarditis.*

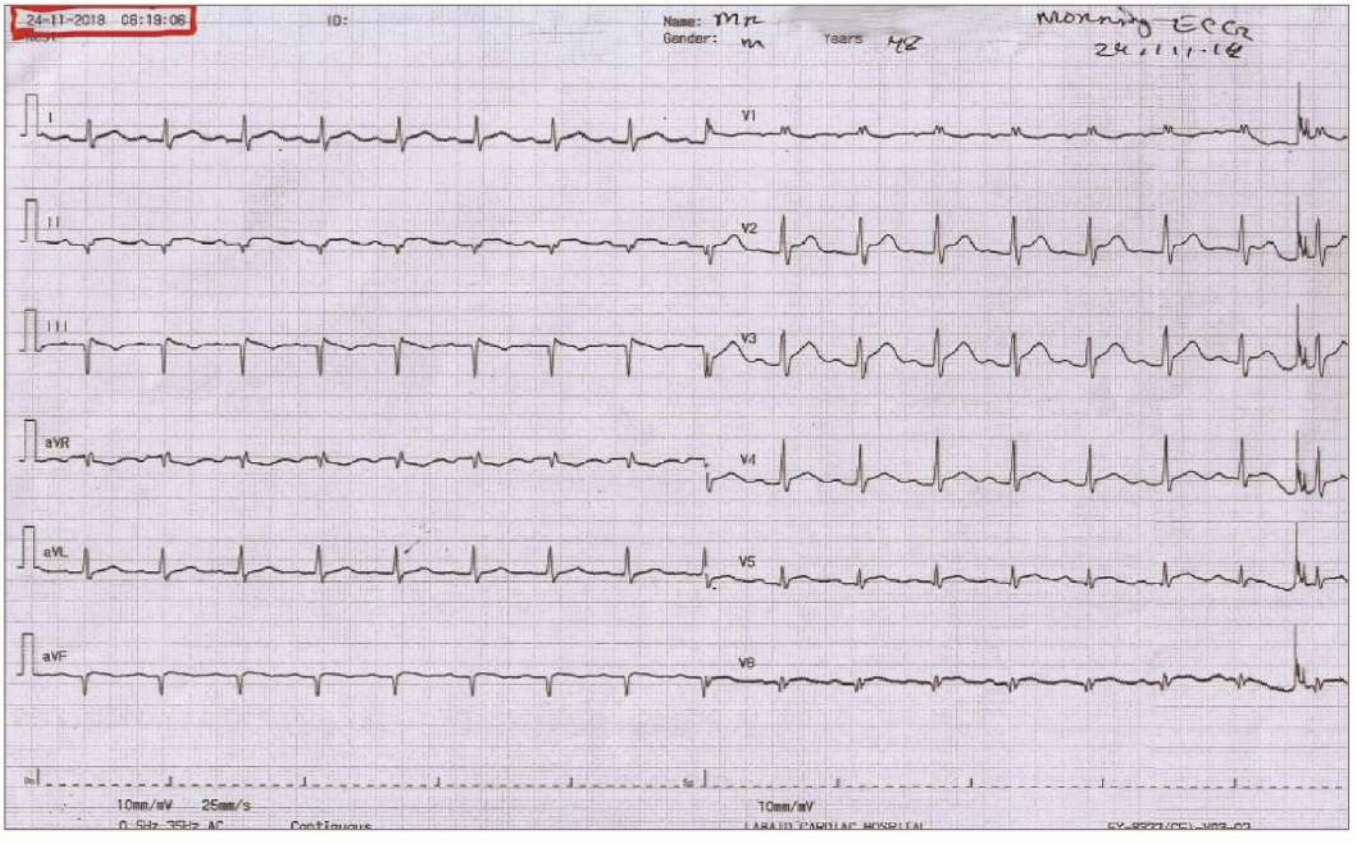

Figure-4. *On the 3rd day of admission height of the hyperacute T waves normalized and ST elevation in the inferior leads resolved.*

Discussion

T waves are generally considered hyperacute if they are greater than 10 mm in amplitude in precordial leads or greater than 5 mm in amplitude in limb leads. Hyperacute T waves are one of the earliest ECG abnormalities to occur in myocardial infarction. In STEMI tall T-waves with a characteristic broad-based morphology appear within 0 to 30 minutes after complete coronary artery occlusion and can be the earliest ECG signature of STEMI. Hyperacute T waves without ST segment elevation is usually a transient abnormality, present during the first 30 minutes after the onset of chest pain. Thereafter, the ST segment will begin to rise giving the more typically seen morphology of STEMI.[7] But in this case hyperacute T waves in the chest leads persisted for about 48 hours, which is not in agreement with the diagnosis of hyperacute anterior MI. Hyperkalemia is also an important cause of hyperacute T waves in ECG. T wave morphology of hyperkalemia may be confused with the hyperacute T wave of early transmural MI. In contrast to hyperacute T waves associated with myocardial ischemia or infarction, hyperkalemic T waves tend to be narrow and peaked with a prominent or sharp apex. Hyperkalemia is an acute life-threatening disorder presenting to the emergency department. Rapid determination of serum potassium level by bedside blood gas analyzers serve to be a useful guide. Tall peak T waves and ST segment elevation related to hyperkalemia will resolve with successful reduction of the serum potassium levels by appropriate therapy.[8,9] The case we presented here diagnosis of reinfarction in the inferior and posterior territory was also considered. But acute posterior MI usually give rise to horizontal ST depression, tall R waves and upright T waves in leads V1-V3. In patients presenting with ischaemic symptoms, horizontal ST depression in the anteroseptal leads (V1-3) should raise the suspicion of posterior MI. But in the ECG of this patient there was no ST depression in leads V1-V3 and acute posterior MI is never manifested by hyperacute T waves in chest leads.

In the current patient, pericarditis mimicked hyperacute anterior wall MI. Careful clinical examination and bed side echocardiogram are invaluable aid to rapid diagnosis. This case describes pseudo-myocardial infarction pattern probably due to myopericarditis. ECG findings of myopericarditis may mimic acute MI.[10-12] So, it is important for physicians to be aware of this condition as this will aid in initiating correct therapy and prevent the patient from unnecessary interventions and the associated risk of complications.

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