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Sources of funding

All sources of support for the research should be listed under this heading.

Original Data

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Very Large ASD Device Closure, Feasibility and Safety

Goutam Datta

Abstract

Background: There is limited data regarding feasibility and safety of very large ASD devices deployment. Percutaneous closure of very large atrial septal defect (ASD) is a valid alternative to surgical approach. But complications like erosion, cardiac perforation, atrioventricular block, pericardial effusion, infective endocarditis, or cardiac arrhythmias may occur following ASD device closure.

Methods: Forty four patients with very large ostium secundum ASD were studied in a tertiary medical centre. Adult patients with defect size of 38 mm or more and device size of 40 mm or more were selected for device closure. Patients having suitable anatomy, significant left to right shunt(>1.5:1) ,right ventricular volume overload and without significant pulmonary arterial hypertension were chosen for device closure.

Results: There were thirty six female patients and eight male patients in our study. Majority of our patients (twenty four) were in forty to fifty years age group. Device could be deployed successfully in forty two (95.5%). Twelve patients had device size of 46 mm (27%). Eight patients had 44 mm devices (18%). Forty two millimeter devices were used in sixteen patients (36%). Eight patients had device size of 40 mm (18%).Device embolization occurred in two patients. There were two cases of pericardial effusion and pericardiocentesis was needed in one patients. Transient complete heart block was seen in one patient. Four patients had suffered from transient and self terminating atrial arrhythmias. There was no mortality or erosion in our study.

Conclusion: Percutaneous closure of very large ASD is feasible and associated with low complication rate.

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Keywords: ASD device closure, very large devices, complications.

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Introdution

Atrial septal defects (ASD) is a common congenital heart disease and it accounts for approximately 10% of all congenital heart defects in children. The prevalence of ASD is 1 /1000 live births.[1] Ostium secundum type ASDs constitute for 75% of all ASDs and it is amenable to device closure. The first successful surgical closure of an ASD was performed by F. John Lewis in 1952. Transcatheter closure of ostium secundum ASD is a safe and effective procedure. The first ASD device closure was performed by King and Mills in 1974.[2] The devices most commonly used are Amplatzer Septal Occluder (ASO; nickel and titanium alloy wire mesh, polyester fabric filling, US Food and Drug Administration approved in 2001) and the Helex occluder (nitinol wire covered with an ultrathin polytetrafluoroethylene membrane, US Food and Drug Administration approved in 2006). There is a paucity of data on transcatheter closure of very large ASDs (defect size 38 mm or more),[3] especially using the 40-mm devices.Surgical closure is the preferred approach for very large ASDs.This very large defect comprises approximately 20% of patients with ASDs.[4] But device closure is not free of complications. Device embolization is the most common adverse event (0.2%-1%). Major early adverse events occurred in 1.2 % of the cases. Some of the documented risks of ASD device closure include device embolization (1%), temporary or permanent tachyarrhythmia and heart block (0.3%), erosions (0.28%), thromboembolic complications, fractures, valve injury, pericardial effusion, infections and mortality (0.05%).[5] Our aim is to study feasibility and safety of very large ASD device closure.

Methods

Forty four patients with very large ostium secundum ASD were studied from January, 2018 to December, 2020. Study was done in a tertiary care University hospital. Study protocol was ethically approved and informed consents were taken from patients. Patients with very large ostium secundum ASDs were defined as defect size of 38 mm or more by Transesophageal echocardiography. Device size of 40 mm or more was selected as very large devices. Our objective was to study feasibility and safety of device closure in these large defects. All cases were selected based on both transthoracic and trans esophageal echocardiographic evaluation. All procedures were done under conscious sedation and transesophageal echocardiography guidance (TEE). Balloon sizing was not done in any of the cases. Invasive arterial blood pressure monitoring were done in all cases.

Selection criteria:

(1) Age more than eighteen years
(2) Very large Ostium secundum ASD.
(3) Evidence of right ventricular volume overload
(4) Significant left to right shunt (>1.5:1)
(5) No significant pulmonary arterial hypertension (pulmonary artery systolic pressure less than half of systemic arterial pressure)
(6) Anatomical suitability of device closure.
(7) Minimum follow up period was six months.

Statistical Analysis

It was an prospective, observational epidemiological study. Results are expressed in absolute numbers and percentage only.

Results

Thirty six patients were female and eight patients were male. Female male ratio in our study was 4.5:1 (chart 1). Female patient overwhelmingly predominates in our study in contrast to male predominance in ASD population.

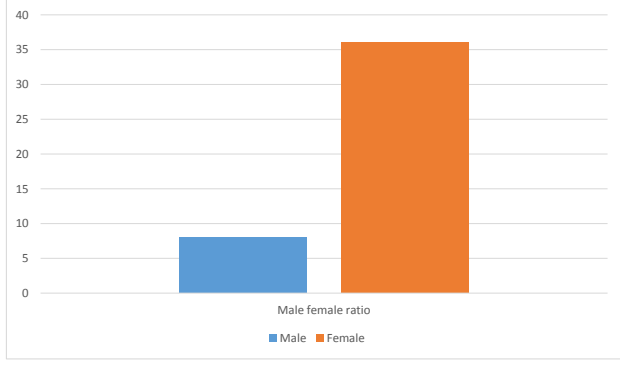

Figure 1. Male to Female ratio

Majority of our patients (twenty eight) were in between forty one to fifty years age group (64%). Four patients were in thirty one to forty years age group (9%). There were twelve patients in eighteen to thirty years age group (27%). (Chart 2)

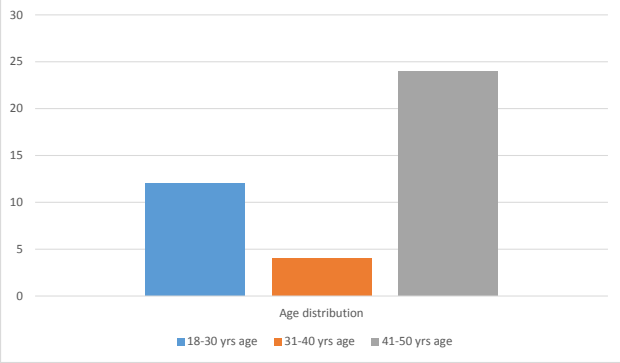

Figure 2. Age distribution

Anatomically there was deficient aortic rim in thirty two patient (73%). Posterior rim was inadequate in eight patients (18%). Five millimeter was taken as adequate rim. Superior and inferior vena caval rims were adequate in all cases. Devices were deployed successfully in forty cases(95.5%). Life Tech ASD devices were used in all patients. Twelve patients had device size of 46 mm (27%). Eight patients had 44 mm devices (18%). Forty two millimeter devices were used in sixteen patients (36%). Eight patients had device size of 40 mm (18%). (Chart 3)

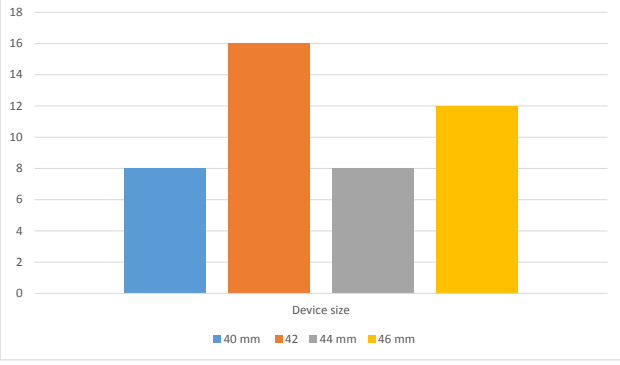

Figure 3. Device Size

There was no mortality in our study group. Even in our follow up of six months to two year no patient died. We have no attrition in our follow up. But complications did happen in our procedure. There were two incidence of device embolization (4.5%). Both cases device size were 42 mm and 44 mm respectively. In one case device got embolized immediately after deployment. In another patient there was device embolization after five minutes of successful deployment. Both cases devices were retrieved surgically and patients underwent surgical closure of the defects. We have experienced one cases of transient complete heart block in peri procedure period (2.2%). Device size was 44 mm and complete heart block persisted for four minutes. There was spontaneous recovery but temporary pacemaker support was kept for twenty four hours. Coronary angiography was done immediately and there was no impingement on right coronary or left circumflex artery. Pericardial effusion were observed in two patients (4.5%). (Table 1)

Table 1. Procedure-related complications.

Name of complication	Number	Percentage
Embolization	2	4.5%
Pericardial effusion	2	4.5%
Complete heart block	1	2.2%
Atrial arrythmias	4	9%

It was 10 -12 mm in one patents and did not require any pericardiocentesis. Effusion subsided of its own in follow up. But there were moderate to massive effusion in one patients with haemodynamic compromise. Pericardiocentesis was done immediately and patient recovered uneventfully. There was no recurrent pericardial collection. There were four cases of atrial arrhythmias during device closure (18%). Atrial fibrillation occurred in two patients and atrial flutter in two patients. Atrial flutter and fibrillation did not last long. All arrhythmias subsided without any pharmacological or electrical cardioversion. There was no haemodynamic instability. There is no incidence of erosion or air embolism in our study

Discussion

Transcatheter closure has now become the standard treatment strategy for ostium secundum ASD . Device closure is indicated for ostium secundum ASD patients if rims are suitable and there is significant left to right shunt (>1.5:1) without any evidence of significant pulmonary arterial hypertension (pulmonary artery systolic pressure

less than half of systemic arterial pressure). There are six rims which are evaluated by echocardiography. These are superior, inferior, aortic, posterior, superior vena cava and inferior vena caval rims. Ideally all rims should be present and at least five millimeter in length. But in cases of very large ostium secundum ASD retro aortic rim is not adequate in many times.[6]

Data regarding very large ASD device closure is limited. There is no consensus or guideline about definition of very large ASD device. Here we have taken 40 mm or more device size as very large ASD device. Till now maximum size available is 46 mm. Problem with very large devices are a) challenging deployment b) increased risk of embolization c) complications particularly aortic erosion in follow up. Majority of very large ASD had deficient aortic rim. In our study incidence is around 73 %. There is belief that deficient aortic rim may help to position very large devices. But on the flipside it increases incidence of aortic erosion and device embolization. Success rate of device deployment was in twenty cases (95.5%). Device embolized in two cases-one immediately and one after five minutes after deployment. There were no incidence of air embolism, thrombus formation or infection in our study.

Device embolization is a known phenomenon. Incidence varies between 1 to 3%.[7] Failure of rim assessment and large device size are two important factors for device embolization. Percutaneous retrieval is possible in many cases but surgical help should be sought in failed cases. In our study it happened in two patients. Both the cases we failed to retrieve them percutaneously. Devices size were 42 mm and 44 mm respectively. They went for surgical retrieval and closure successfully. In one case inferior vena caval rim was not adequate and other case Eustachian valve was mistaken as inferior vena caval rim. These were surgical finding in two patients. There were twenty one device embolizations out of 3,824 implants (0.55%) in USA in 2003. Fifteen were retrieved using a transcatheter approach (71.4%) and six were retrieved surgically (28.5%).[8] In another study device was retrieved surgically in 77.2% of cases and by transcatheter approach in

16.7% of cases. There were 2 deaths related to embolization.[9] It is difficult to retrieve very large ASD devices and repeated attempt to retrieve may invite more complications. In one of our case we have perforated right atrial wall and left atrial roof leading to massive pericardial effusion, cardiac tamponade, haemodynamic instability leading to urgent cardiac surgery. It is preferable to opt directly for cardiac surgery rather than prolonged percutaneous retrieval. There was another case of pericardial effusion in our study. Mechanisms of pericardial effusion is unclear. Probably it was terumo wire induced pulmonary vein perforation which sealed off of its own. Inadvertently LA appendage also may get perforated by terumo wire. Terumo wire was used to cross the defect and to guide delivery sheath to pulmonary veins. Device erosion was another possibility. Cardiac CT was done to find out the site of perforation but nothing could be found in post operative period.

There was one incidence of complete heart block in our study but rhythm reverted back to sinus after four minutes. Right coronary artery was checked and it was found to be normal as also left circumflex artery. Mechanism of complete heart block in ASD device closure is unknown. It could be due to stretching of interatrial septum which may interfere with atrio ventricular (AV) nodal conduction time. Large device may impinge on right coronary artery or rarely left circumflex artery which are supplying AV nodal artery. The risk of bundle branch block in patients with large ASD, particularly patients with deficient rims, may be increased, A retrospective study of six hundred and ten device closure patients showed clinically significant AV block occurring in 0.3% of patients.[10]

Incidence of erosion is around 0.043-0.3%.[11] Deficient retro aortic rim and oversized devices are two important predisposing factors for erosion. Erosion usually occurs within one to three months of device deployment. Erosion will lead to fistula formation and it may communicate with different cardiac chambers. It is a lethal complication of device closure and necessitates surgical intervention. Rarely late erosion may occur. In our study we did not experience any case of erosion in one year follow up though many of our patients had very large devices with deficient retro aortic rims. Twenty eight cases of erosion with hemodynamic compromise were reported between 1998 and March 2004 in USA. Erosion rate in USA was 0.1% (9 of 9,000 known U.S. implants). Aortic or superior rim was deficient in twenty five patients. Amongst twenty eight patients: Five involved perforation at the roof of the left atrium and the aorta; six had perforation at the roof of the right atrium and the aorta; in one case, both atria were

involved; in three cases, there was aortic perforations.[12] Atrial arrhythmia was observed in perioperative period in four patients. Two cases of atrial flutter and two cases of atrial fibrillation were seen in our study. All of them were self terminating and did not produce any haemodynamic instability. These are may be due to guidewire, sheath or device induced irritation of atrial wall. In the MAUDE analysis, arrhythmias were seen in five percent of patients. There is a concern that device closure of ASD may preclude future electrophysiology procedures that require transseptal access.[13]

The FDA analysis of the MAUDE medical-device reports (MDR) showed 0.8% incidence of infection or endocarditis.[14] There is no case of nitinol allergy, infection or haemoglobinuria in our device closure patients. All the cases we tried to deploy device from left pulmonary vein approach. We succeeded in all cases barring one where we had to come from right superior pulmonary vein. In the setting of a very large ASD maintaining the posterior orientation of LA disc is difficult. Often the LA disc tilts tangentially across the defect and prolapse back in to the RA. There are notably two manoeuvres which facilitate successful device deployment a) BAT (Balloon assisted technique) b) Greek manoeuvre.In BAT technique one can place inflated Tyshac balloon either in the contralateral pulmonary vein or ipsilateral pulmonary vein which will prevent prolapse of left atrial disc in right atrium. Even few have kept in at left atrium itself to prevent left atrial disc prolapse.(14) The Greek maneuver is applied when there is left atrial disc protrusion into the right atrium from aortic end. To circumvent this, left disk is recaptured and the whole delivery system is pushed inward and leftward into the left atrium. After that left atrial disk and the 2/3 of right atrial disk are simultaneously released into left atrium and positioned properly. Left atrial disc becomes parallel to the septum preventing the protrusion of the device into the right atrium.[15] We didn't use any of the manoeuvre for device deployment. Our inference is key to success are proper sizing of the defect and rims by TEE. Vena caval rims are of utmost important for device deployment. The success of very large ASD closure mainly lies on the proper imaging techniques. We have used 2D TEE but 3D TEE is preferable. Complex anatomical features like extreme malalignment with sinusoidal septum, aneurysm, and fenestrated defects require careful delineation before intervention. Balloon sizing was used in these cases by many operators but we have never used it.

Conclusion

Transcatheter closure of very large ASDs is safe and effective procedure. Complications after device closure is rare. There was no mortality in our study. Proper assessment of rims and defect size are key to success.

Limitations

It is an observation study. Study population size is small. Both Type 1 and type 2 error may occur in interpretation as it is a small single centre study.

Financial disclosure

None.

Conflict of interest

None.

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Original Article

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Correlation Of Left Ventricular Ejection Fraction and Spatial Qrs-T Angle In Old Myocardial Infarct Patient

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Abstract

Background: Half of patients with coronary artery disease (CAD) died from sudden cardiac death (SCD) with Left Ventricular Ejection Fraction (LVEF) as a predictor. Spatial QRS-T angle (the angle between the QRS and T vectors) is a strong independent predictor of cardiovascular death. The aim of this study was to correlate spatial QRS-T (sQRST) with LVEF in patients with old myocardial infarction (OMI).

Methods: This is a cross-sectional study in patients with OMI that have not undergone revascularization and have achieved medical therapy. OMI was defined based on universal definition of myocardial infarction electrocardiography (ECG) criteria. 12-lead ECG and echocardiography were done simultaneously. sQRST angle was measured by Kors visual transform applications. Statistical analysis was performed using Pearson correlation and multivariate analysis with linear regression.

Results: 46 patients meet the inclusion criteria. Baseline characteristics: mean age 58 ± 8 years, 89% male, mean sQRST was 108.72 ± 43° with mean LVEF 39.39 ± 10%. The sQRST angle and LVEF was strong negative correlation ($r=-0.66$, $p<0.01$) after adjusted with left ventricular mass index (LVMI) correlation between sQRST angle and LVEF decreasing ($r=-0.57$, $p<0.01$). The SQRST angle and LVEF of patients with OMI is negative correlation.

Conclusion: The sQRST angle and LVEF of patients with OMI had negative correlation. sQRST angle may be an easier index for assessing cardiac dysfunction in patients with OMI.

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Keywords: Left ventricular ejection fraction, Old myocardial infarction, Spatial QRS-T angle

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Introdution

The sQRST angle measures the difference in the angle of the QRS wave vector and the T wave vector in 3 dimensions. Wide QRS-T angle is associated with increased cardiovascular events, high mortality and SCD mainly due to increased ventricular arrhythmias.[1] Existing studies showed that the sQRST angle can predict cardiovascular events, SCD, or overall mortality better than other conventional ECG markers such as ST segment depression, T wave inversion, left ventricular hypertrophy, increased QT interval, and T wave dispersion.[1-3] Wide sQRST angle (>100°) is a strong predictor (7-fold increased risk) of developing ventricular arrhythmias. The gold standard tool for measuring the sQRST angle was to use vectorcardiography proposed by Frank using orthogonal leads X, Y, and Z.[4] This lead system was impractical so it is rarely used in daily clinical applications. Researchers have attempted to calculate sQRST angle by reconstructing Frank's vectorcardiogram with the commonly used 12-leads ECG. Based on existing studies regarding the comparison between various methods of measuring the spatial angle of QRS-T waves using a 12-leads ECG, the Kors matrix calculation is considered the best because it shown the closest result to Frank's vectorcardiogram measurement.[5-6]

Myocardial necrosis will lead to a prolonged action potential of the heart, and heterogeneity of repolarization. Changes in the cellular level in the area of necrosis cause disruption of the electrical flow of the heart to the surrounding area. This change ¬in action potential morphology will cause changes in the entire QRS-T complex which are recorded as spatial changes in the QRS-T wave.[7] Necrotic area will cause an inertia region towards cardiac electrical activity, causing distortion of normal cardiac excitation and inhomogeneity of myocardial repolarization. This will cause the sQRST angle to widen.[1]

Research conducted by Li et al.[8] using the frontal QRS-T angle had an inverse correlation with ejection fraction. The lower the ejection fraction, the wider the frontal QRS-T angle with an angle of >90° has the optimal sensitivity and specificity (76% sensitivity and 74% specificity) for diagnosis of ventricular dysfunction. Research conducted by Brown et al. stated that sQRST angle was more accurate than the frontal QRS-T angle in the case of cardiac diseases.[9] This study is different from previous studies because it tries to correlate the spatial QRS t angle as a more accurate marker of sudden cardiac death in old myocardial infarction patients who have not been revascularized but have received drug therapy.

Methods

This is a cross-sectional study conducted at Hasan Sadikin Hospital, Bandung from October to December 2015. We recruited subjects with OMI who were on regular follow up at cardiology outpatient clinic and inpatient ward receiving medical therapy without undergoing revascularization procedure. We excluded patients with acute coronary syndrome, stable angina pectoris, diabetes mellitus, end-stage renal disease, acute stroke, arrhythmia, and left or right complete bundle branch block. The study protocol was reviewed and approved by Research Ethics Committee, Faculty of Medicine, Padjadjaran University, Bandung.

Patients were given informed consent, had clinical history taken, physical exam and additional examination. Patients who meet the inclusion criteria as OMI will be included in the study and treated according to the applicable procedure. Supporting examinations performed on the patient is an ECG, echocardiography, and blood sample (fasting blood sugar and blood sugar 2 hours post prandial). The Simpson method was used to measure left ventricular ejection fraction (LVEF) by echocardiography machine (GE Vivid 7). Identical electrocardiographs (Philips Page Writer TC50) were used and standard 12-lead ECGs were recorded for all subjects using strictly standardized procedures. Calculation of the QRS-T spatial angle with an ECG, usually done with a system called the spatial peak angle of the QRS-T wave which only requires the peak voltage value of the QRS wave and the T wave. This peak voltage value can be seen easily on an ordinary 12 lead ECG. These numbers are then entered into the desired QRS-T spatial angle transformation formula. We used Kors regression matrix because closely related to Frank leads as gold standard.[5]

Statistical analysis was carried out in accordance with the proposed objectives and hypotheses, starting with a descriptive description, data normality test, then a correlation test analysis was carried out between the

LVEF and the spatial angle of the QRS-T wave using Pearson correlation analysis if the data was linear or using Spearman correlation if the data is non-linear. Confounding variables that have not been eliminated at the research design stage will be analyzed through multivariate analysis. Statistical calculations were performed using the International Business Machine (IBM) Software Package for Statistical Analysis (SPSS) version 17.

Results

A total of 53 patients met the inclusion criteria, and 7 patients were excluded with the following reasons: four patients with a diagnosis of stable angina pectoris; two patients with uninterpretable data and one patient with left-branch bundle block. The general characteristics of the study subject can be seen in table 1 below.

In this study, the average age was 58 (8) years. Men (89%) is more than women (11%). Smoking is the most common risk factor (74%) followed by hypertension (50%), dyslipidemia (32%) and family history (6%). Majority of patients received antiplatelet agents (91%); the rest received warfarin (6%). As many as 85% of OMI patients received betablockers, Angiotensin Converting Enzyme (ACE) inhibitors (63%), Statins (72%), Angiotensin Receptor Blockers (22%), Diuretics (54%), Aldosterone Antagonists (17%). Anterior OMI was more common than inferior OMI (67% vs 39%). Half of OMI patients (50%) had no known onset of first-time heart attack, while the other half (50%) had a documented history of previous infarction with a mean onset 5 months after infarction.

Examination of the sQRST angle and LVEF in the study subjects listed in Table 2. The median sQRST angle was 108.72° and the mean LVEF was 39.39%.

Based on table 2, the analysis to determine the relationship between the spatial angle of the QRS-T wave and the LVEF was carried out using the Pearson correlation test because the data were normally distributed. The results obtained are as shown in table 3 and Figure 1 which are mapped in a scatter plot.

From Figure 1. it can be concluded that there is a strong negative correlation between the sQRST angle and the LVEF with r = 0.66 and p <0.05. This means that the higher the sQRST angle, the lower the LVEF.

sQRST Angle also correlated significantly with left ventricular mass index (LVMI) (p = 0.001, r 0.449) with moderate level of correlation. The larger the LVMI, the greater the spatial angle.

After performing the bivariate analysis, all variables met the criteria for multivariate analysis. All linear regression assumptions (i.e., linearity, residual normality, no outliers, independent, constant, and homoscedasticity) were met. After confounding variables (LVMI) was controlled, it was found that the correlation between the sQRST angle and the LVEF was still significant but with moderate correlation (p = 0.00 r = -5.76). This shows that after adjusting the LVMI the correlation with the spatial angle is moderate, showing contribution of LVMI to the correlation between spatial angles and LVEF.

Discussion

A metanalysis involving 22 studies, comprising 164,171 individuals of a diverse population, concluded that a wide QRS-T wave angle was associated with increased total mortality (RR: 1.40; 95% CI (confidence interval): 1.32-1.48) and cardiac mortality (RR). : 1.71; 95% CI: 1.54 -1.90).[10] On the other hand, LVEF is currently accepted as the main prognostic tool in predicting SCD.[11] Based on the existing literature, this study is the first to correlate the sQRST angle and LVEF.

The results of this study showed a strong negative correlation between the sQRST angle and the LVEF (r = -0.66 and p <0.05) but after adjusting for LVMI the correlation became moderate (r = -0.57 and p <0.05) so it can be concluded that the higher the sQRST angle, the lower the LVEF. Zapolski et al. found a strong correlation between the spatial angle of the QRS-T wave and left ventricular contractility calculated using mFS/ESS (mid wall fractional shortening/end systolic stress).[12] Studies in diabetics show a strong correlation between the sQRST angle and Tei index, an indicator of left ventricular contractility performance that combines systolic and diastolic functions.[13] Yan Hong Li et al. found a moderate negative correlation between the frontal QRS-T angle and the LVEF (r = -0.406, p <0.01) in patients with OMI.[8] The findings in this study corroborate the opinion of Brown et al. that spatial angle is better in detecting structural heart disease than frontal angle.

This study uses the peak calculation of the QRS-T

vector with the Kors matrix compared to the calculation of the average QRS-T vector because many studies recommend the calculation of the peak vectors. Cortez et al. revealed that the value of the sQRST angle in patients after myocardial infarction is close to examination value of Frank standardization with a strong correlation level (0.83).[5] The value of the spatial angle of the QRS-T wave after myocardial infarction in this study was higher than that of Cortez et al. The average value of Cortez's spatial angle was 76.4° ± 42, while in this study the mean value was 108.72° ± 43. Cortez's study had similar baseline sample characteristics with a mean age of 58.8 ± 11.3 years and 72% male gender. The difference was that the patient in Cortez's study was a recent myocardial infarction but the average onset of attacks that occurred was not mentioned. In this study 50% patients had an attack onset of 5 months, while the other 50% had no information regarding onset of previous attacks, yet this indicates a longer mean post-attack time in this study.5 Along with the continuous remodeling process, the sQRST angle will also get wider.[12]

This study also found a moderate correlation between the sQRST angle and the LVMI (p = 0.001, r 0.449). This finding is consistent with previous studies that the greater the LVMI, the wider the spatial angle will be. A total of 25 patients (54%) had severely abnormal LVMI (male ≥ 149 g/m2, female ≥ 122 g/m2).[12] After controlling confounding variables (LVMI), it was found that correlation between the sQRST angle and LVEF still significant but with moderate correlation (p = 0.00 r = -5.76). This result shows that after adjusting the LVMI, the correlation with spatial angle become moderate, pointing contribution of LVMI to the correlation between spatial angles and LVEF.

The correlation between the sQRST angle and the LVEF is not perfect, meaning that not all patients with LVEF ≤35% have high spatial angles. The value of the sQRST angle is divided into normal (0-105°), borderline (105-135°), and abnormal (135-180°).3 In this study, 14% of patients with LVEF ≤35% had borderline spatial angles, and 7% of patients had normal spatial angles. In these patient, electrical homogeneity occurs and is thought to have a limited arrhythmia substrate. Borleff et al. concluded that post-myocardial infarction patients with low LVEF attached to an ICD with a normal spatial angle did not develop fatal arrhythmias during 2 years of follow-up and the risk of subsequent arrhythmias was only 2% compared to those with a wide spatial angle who had 7 folds increased risk of ventricular arrhythmias.15 On the other hand, 21% of patients with LVEF ≥35% had abnormal spatial angles. Based on these findings, the spatial angle of the QRS-T wave can identify patients with a low risk of developing arrhythmias so that it can complement the LVEF in stratifying the risk of SCD. Its application in daily clinical practice needs further investigation.

This study has several limitations which include echocardiography and sQRST angle were only performed by one operator so that interobserver variability could not be assessed. This study also cannot rule out left ventricular hypertrophy with the LVMI criteria so that the relationship between the sQRST angle and the LVEF is influenced.

In conclusion, there is a moderate negative correlation between the spatial angle of the QRS-T wave and the LVEF in patients with OMI after multivariate analysis with LVMI. Increase in the sQRST angle can be used as an indicator of a decrease in LVEF in patients with OMI.

Publication Approval

All authors read and approved the final manuscript.

Conflict of Interest

None.

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Ethical Clearance

We proved ethical clearance from our ethical committee along with this submission.

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List of Abbreviations

ACE: Angiotensin Converting Enzyme
CI: Confidence Interval
CAD: Coronary Artery Disease
ECG: Electrocardiography
IBM: International Business Machine
LVEF: Left Ventricular Ejection Fraction
LVMI: Left Ventricular Mass Index
OMI: Old Myocardial Infarction
RR: Relative Risk
SPSS: Software Package for Statistical Analysis
sQRST: Spatial QRS-T
SCD: Sudden Cardiac Death

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Review Article

Emerging Role of Coronary CT in Non-ST Elevation Acute Coronary Syndrome (NSTE-ACS)

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Abstract
NSTEACS is subset of ACS that may present with a wide degree of stenosis from normal vessels to severe obstruction. Identification of which population of NSTEACS that has normal vessels has attracted a great attention. Several trials on non-invasive imaging such as coronary CT have been largely investigated. Current available trials have showed that coronary CT is accurately identify significant stenosis in patients with NSTEACS thus can be used to rule out the disease and reduce the need and duration of unneeded antithrombotic. However, several limitations of the studies has to be taken into account when translating into clinical practice. Nevertheless, current evidence are showing promising results on the role of coronary CT in management of NSTEACS.

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Keywords: Coronary CT, diagnosis, NSTEACS

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Introduction

Patients with NSTEACS may present with a wide range of stenosis from normal vessels to severe obstruction in coronary angiography. Current guideline still recommends to perform a diagnostic angiography in patients with NSTEACS based on its risk stratification. However, routine angiography may cause significant risk and needs a high resources.[1] During prolonged waiting for diagnostic angiogram, patients often has been administered with prolonged antithrombotic and anticoagulant, which provide no benefit in patients with non-significant stenosis but do increase bleeding risk. Not only did angiogram available only in few number of hospitals but also angiogram is prioritized for patients with ST-elevation myocardial infarction (STEMI) which resulted in more delay on decisive treatment for patients with NSTEACS. Several study on non-invasive imaging have been conducted to answer this problem. Widespread use of coronary CT in routine daily practice has caused several investigators to seek the role of coronary CT in the setting of acute coronary syndrome, especially in NSTEACS. In this review, current progress and recommendation regarding the role of coronary CT in NSTEACS is provided.[2]

Wide Range of Obstruction in NSTEACS

NSTEACS is subset of acute coronary syndrome that characterized by inconclusive ECG changes with no persistent ST segment elevation which can be divided into NSTEMI and unstable angina. Patients with NSTEACS is heterogeneous group whose the range obstruction may vary from normal vessel to heavy stenosis. Several studies in recent past years have demonstrated that patients with NSTEACS have consistently showed a proportion of no significant stenosis. The rate of non-significant stenosis is vary among studies, likely due to difference on diagnostic criteria. CRUSADE registry showed that 8,6% of 38.301 patients with NSTEMI from angiography. Several other trials also reported about 9-12% rate on non-significant stenosis in NSTEACS.

Another interesting findings from SWEDEHEART registry regarding the use of high sensitivity of troponin T in the diagnosis can also give some insight about the variable degree of obstruction in NSTEACS. In SWEDENHEART registry involving 48.594 patients, the analysis that divided the population based on its hs-cTnT levels (using Elecys troponin T, Roche) into four groups : hscTnT <6 ng/mL, 6-13 ng/mL, 14-49 mL, and > 50 ng/mL which correspondence into ESC recommended assay specific cut-off levels for very low, low, moderate, and high respectively. Although the analysis did not included dynamic changes of hs-cTnT, which may provide better information on ongoing process of myocardial infarction in coronary obstruction, the result of analysis give some insight on various etiologies of elevated cardiac enzyme. The percentage of non-significant coronary disease based on current ESC term for very low hs-cTn have a proportion normal angiography of 56.8%, low of 39%, "other" of 28.6%, and high of 12%. Current ESC guideline recommends to observe the "other" level of hs-cTnT which may contribute to prolonged course of antithrombotic or anticoagulant on this group which may be caused by other etiologies other than coronary artery disease.

There are several conditions that associated with elevated troponin levels are tachyarrhythmia, heart failure, hypertensive emergencies, critical illness (sepsis, burn), myocarditis, Takotsubo syndrome, valvular disease, aortic dissection, acute neurological event.[4] The fate of this particular group (non-obstructive NSTEACS) is also not quite good. Based on ACUITY trial evaluating the prognosis of non-obstructive NSTEMI and obstructive NSTEMI, the mortality rate of non-obstructive NSTEMI compared to obstructive STEMI is not significantly different at 1-month and 1-year. The most common cause of non-obstructive death NSTEMI in the study was non-cardiac cause with no significant difference of major bleeding from obstructive NSTEMI case indicating the side effect of prolonged unnecessary antithrombotic in this group.

Role of Coronary CT in NSTEACS

Coronary angiography for NSTEACS is a widely used tools in managing ACS patients. It reveals the presence of significant coronary stenosis that needs revascularization. However, in limited areas or centers with high load of cases, diagnostic work up of NSTEACS is often delayed and patients can posed to unnecessary treatment. Recent meta-analysis from 13 trials with 164.225 participants showed that there aspirin use in patients without cardiovascular disease does lower the risk for major cardiovascular events by

11% (HR 0.89, ARR 0.41%) but significantly increased risk of major bleeding by 43% (HR 1.43 ARR 0.47%). This implicate that in patients with normal coronary vessels, DAPT strategy did not recommended.[5]

Non-invasive imaging such coronary CT angiography has been a largely investigated tools on its role in coronary artery disease. Coronary CT has a high diagnostic accuracy for the detection of obstructive. There were at least 3 trials to date published regarding the role of coronary CT in NSTEACS: CARMENTA, VERDICT trial, and Kuhl et al. CARMENTA trial was a 3-arm, prospective, open label, single center, randomized controlled, comparative trial using CMR and coronary CT as a gatekeeper to coronary angiography in patients with NSTEACS. The study recruited 207 patients in which 69 patients assigned to routine clinical care, 68 were assigned to CMR first, and 70 were assigned to coronary CT first. Obstructive coronary disease defined by coronary CT as > 70% narrowing of coronary artery or Agatston score >1000 in the absence of extra-cardiac findings (such as aortic dissection or pulmonary embolism). Patients requiring immediate coronary angiography (very high risk feature), non-MI suggestive origin, and previously known CAD was excluded. Follow up coronary angiography performed in all routine clinical care group but only performed in selected cases in CMR and CT groups based on initial CMR or CT coronary result. If the scan was normal, equivocal, non-diagnostic, no formal recommendation was given to undergo ICA. The result of this study was there was significant reduction of coronary angiography in CT and CMR arm. Coronary angiography use reduced from 100% in routine clinical care to 66% in coronary CT group (p<0.001) and to 87% in CMR group (p<0.001). This protocol appeared to be safe that there was no significant increase of major cardiovascular events in coronary CT first protocol compared to routine clinical care in 350 days follow up (HR 0.64 (CI95% 0.18-2.27, p=0.49). CARMENTA trial has showed that non-invasive first imaging strategy is safely reduced the need for ICA for NSTEACS.[2]

The same positive result on coronary CT was also published by VERDICT trial. VERDICT trial is a prospective, randomized, and multicenter controlled trial. The study was conducted in 9 hospitals in Denmark with NSTEACS. The inclusion criteria of the study was age > 18 years, clinical suspicion of ACS, and has at least 1 of the high risk criteria (ECG changes indicating new ischemia, and elevated cardiac enzyme). The exclusion criteria was very high risk feature of NSTEACS, expected survival <1 year, and intolerance to platelet inhibitors or X-ray contrast. The study initially recruited 2.147 patients but only 1.822 patients eligible for coronary CT. however, only 1.023 patients were included in the study due to not specific reasons. The result showed that from 1.023 patients, 705 patients (69%) had positive CT result (stenosis >50%), 5 patients (5%) had non diagnostic result, and 265 (26%) had negative result. From this negative CT result, only 24 patients (9.05%) had positive result on coronary angiography and from 705 patients that has positive CT result, 666 (94.46%). This findings implicate that coronary CT has a sensitivity of 96.5% (CI95% 94.9-97.8%), specificity of 72.4% (CI95% 67.2-77.1%), PPV 87.9 (85.3-90.9%), and NPV of 90.9% (86.8-94.1%). They also found that the diagnostic yield of this study is not influenced by clinical risk profile. This highlight important finding that diagnostic performance is not affected by high GRACE score. This findings showed that coronary CT may have a role on NSTEACS cases.[1]

Findings from Kuhl et al6 also showed some positive results. The investigators evaluated the role of 64-detector CCTA presenting with NSTEMI prior to coronary angiography. NSTEMI diagnosis was made based on ESC guidelines and they recruited 400 patients consecutively. The study excluded patients with high risk feature, known renal disease, cardiac arrhythmias, and allergic to iodine contrast. All patients in the study underwent coronary CT and coronary angiography. The study have some positive results that coronary CT can detect significant coronary artery disease (>50%) with a sensitivity, specificity, PPV, and NPV of 99%, 81%, 96%, and 95%. The study also found that coronary CT correctly triage patients in 86% cases into PCI or CABG.

Translation to Clinical Practice

Current ESC recommendation regarding NSTEACS management is still rely on 0/1/3 hs-cTn rule in which patients with very low hs-cTnT or minimal increase of hs-cTnTcan be safely discharged and may be undergo several optional testing such as stress testing, coronary CT, or angiography meanwhile in high hs-cTNT should be admitted to CVCU and underwent angiography

Trial	No. patients	Design	Population	Primary end points	Secondary end points	Main findings	Study limitations
VERDICT trial (2020)[1]	1023	Prospective, observational, randomized, controlled, blinded	NSTEACS, non-very high risk NSTEACS	Ability of coronary CT to rule out significant stenosis (> 50%)	Diagnostic accuracy of coronary CT stratified by randomization groups	Coronary CT has a high diagnostic accuracy to rule out significant stenosis with NPV of 90,9% (95%CI 86.8-94.1%)	Large number of drop out (799 patients) without clear reason, significant stenosis cut-ff of 50%
CARMENTA trial (2019)[2]	207	3 arm (routine clinical care, CT, CMR), randomized, controlled, open label	NSTEMI, non-very high risk NSTEMI	Proportion of patients referred to coronary angiography during initial hospitalization	Occurrence of major adverse cardiovascular events within 1 month and 1 year	CT first strategy reduced the need of corangiography from 100% to 66% with no significant safety issues	No specific protocol of angiography referral from CT arm (based only independent cardiologist decision)
Kuhl et al[6] (2017)	400	Observational study, consecutive, non-controlled, blinded	NSTEMI, non-very high risk	Coronary CT to triage patients at high risk of CAD	-	Coronary CT detects significant stenosis >50% with sensitivity, specificity, PPV, and NPV of 99%, 81%, 96%, and 95% respectively	Consecutive patients, selection bias

Figure 1. Summary of Randomized Clinical Trials.

based on risk stratification. Patients with very high risk NSTEACS should undergo immediate invasive angiography (<2 h) and in high risk patient in less than 24-h. Patients with low-intermediate risk should be managed according to diagnosis and management of CCS in which non-invasive testing was preferred over invasive strategy.[6]

Coronary angiography strategy provide clarification on whether the angina chest pain originating from culprit lesion or non-coronary origin. However, coronary angiography also possess a procedural and bleeding risk. Multiple RCT and meta-analysis have showed that routine angiography does not reduce all-cause mortality risk in overall populations of NSTEACS thus only performed based on risk stratification. Current ESC recommendation regarding CT coronary was to use CT coronary as an alternative to invasive angiography to exclude ACS when there is low-intermediate likelihood of CAD and when troponin and/or ECG are normal or inconclusive. This recommendation is quite contrast to the findings of VERDICT, CARMENTA, and Kuhn's trial in which CT coronary can accurately identify patients with significant stenosis without increased in safety issues and can be used in NSTEACS case (except very high risk NSTEACS) as a gatekeeper to coronary angiography suggesting the need of better evidence to support the findings of current evidence.[7]

There are some points to needs to be considered interpreting the result of the findings. A large number of participants that excluded in the VERDICT trial have to be taken into account when interpreting the result. No clear reason on not performing CT scan on those patients may cause selection bias on the study. The stenosis cut-off 50% on Kuhn et al and VERDICT trial and 70% on CARMENTA also maybe provide little information about the effect of the stenosis on myocardial infarction that many investigators presume that 50% stenosis are not hemodynamically significant. Current clinical decision making on revascularization also not only depends on stenosis threshold but also depend on several other criteria such as FFR. Other point that has to be taken into account is the resources

used in VERDICT and CARMENTA trial. Coronary CT that was used in VERDICT trial was 320-detector CT and in CARMENTA with second generation dual source CT (128-slice) which can largely affect the result and implementation in clinical practice. Another limitation in the studies mentioned above is the lack of clarity and homogeneity of the diagnosis of NSTEMI or NSTEACS. In VERDICT trial, cardiac enzyme that used in the study is troponin and not a high sensitive troponin T. There are also lack of description on how dynamic changes of hs-cTnT affect the diagnosis of NSTEACS which was fundamental.[6,7]

Despite several limitations, the findings from the 3 studies showed that there may be a role of coronary CT on NSTEACS. Current study showed that coronary CT can be helpful in the diagnosis of significant coronary disease in NSTEACS and appear to be safe to be taken. However, due to its logistical and safety issues, there is a need for a larger study to evaluate the efficacy and safety of coronary CT in the setting of NSTEACS. Several studies are being conducted such as FFR-CT and CT-NSTEMI trial regarding its issues and may provide better understanding on the role of coronary CT on NSTEACS.

Conclusion

Although there is no clear guidance the usage of coronary CT on high risk NSTEACS, the findings of VERDICT and CARMENTA provide an insight of the future role of coronary CT on NSTEACS. Several trials is being conducted on the role of CT on NSTEACS for a better understanding of its role.

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Case Reports

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Heart Failure with Preserved Ejection Fraction (HFpEF): A Case Report

- Amanda Halimi[1], Nani Hersunarti[2]

Abstract

Background: The prevalence of Heart Failure with Preserved Ejection Fraction (HFpEF) currently reaches 50% of heart failure cases and continues to increase every year. HFpEF is an important clinical condition, but the diagnosis is far more challenging than HFrEF (Heart Failure with Reduced Ejection Fraction), and there has not been any proven effective treatment. In this case presentation, the latest HFpEF diagnosis and therapy will be discussed.

Case Illustration and Discussion: A man and a woman came to the emergency room with signs and symptoms of congestion suggestive of heart failure. Additional examination was performed to support the working diagnosis of HFpEF, namely ECG, NTproBNP and echocardiography. HFA-PEFF scores of the first and second patient was 3 and 4 respectively. During hospitalization, diuretics was given to overcome congestion according to guidelines, as well as ACE-inhibitor and beta-blocker. Both patients were also screened for cardiovascular and non-cardiovascular comorbidities, and were given appropriate therapy.

Conclusion: The diagnosis of HFpEF does not have a gold standard yet, meanwhile, the HFA-PEFF scoring can be used. Recommended HFpEF therapy includes diuretics for congestion and management of comorbidities. Several studies of HFpEF treatment are ongoing.

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Keywords: heart failure with preserved ejection fraction, HFpEF

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Background

The prevalence of Heart Failure with Preserved Ejection Fraction (HFpEF) currently reaches 50% of all cases of heart failure and continues to increase by 1% per year.1 ASIAN-HF study found that HFpEF occurred mostly in the elderly, those with atrial fibrillation, metabolic disease, and diabetes. Whereas in Indonesia, HFrEF (Heart Failure with Reduced Ejection Fraction) is more frequent with ischemic etiology. However, with aging population and increasing prevalence of HFpEF risk factors such as hypertension, obesity, and diabetes, HFpEF will be the most common phenotype of heart failure.[2,3]

Differentiation of heart failure patients based on ejection fraction is important because of the differences in etiology, demographic, comorbidity, and response to therapy. When compared to HFrEF patients, more HFpEF patients are older, female, and have a history of hypertension and atrial fibrillation, whereas a history of myocardial infarction is less common.[1,2]

HFpEF is a condition that is difficult to diagnose and treat. Also, most hospitalizations in HFpEF patients are caused by non-cardiovascular causes, with the same mortality as HFrEF. There is no proven scoring or treatment for HFpEF yet, however, in 2019, the Heart Failure Association of the European Society of Cardiology (HFA ESC) released the HFA-PEFF diagnosis algorithm.[2]

Case Illustrations 1

Mr. DT, a 55-year old man was admitted to the emergency room with chief complaint of breathlessness for two days before admission. There was dyspnoea on exertion, orthopnoea, and paroxysmal nocturnal dyspnoea. Patient felt frequent fatigue and activity intolerance for a month before admission. Other complaints were palpitations, bloating, and edema of both lower extremities. There were no chest pain, nausea, or vomiting reported.

He had a history of hypertension and smoking. He was newly admitted to NCC Harapan Kita. Possible trigger of the decompensated heart failure was suboptimal treatment. Patient's only medication was amlodipine 1x5 mg that he sometimes bought from the pharmacy by himself.

On physical examination patient was fully alert, moderately ill with blood pressure of 128/91 mmHg, heart rate was 132 bpm, respiratory rate of 24 times per minute, temperature was 37ºCelcius, and peripheral oxygen saturation was 94%. Body height was 155 cm, body weight 62.4 kg, with BMI 25.6. There was distended JVP. Heart examination revealed normal first and second heart sounds, no murmur, and no gallop. Lung examination revealed vesicular pulmonary sounds with crackles on both lung bases. Abdominal examination revealed hepatomegaly and minimal ascites. Extremities examination revealed bilateral pitting edema.

Laboratory examination revealed mild anemia with haemoglobin level of 11.1 g/dL and mild leukocytosis. There was reduced renal function with creatinine serum level of 2.16 mg/dL and eGFR was 32 mL/min/1.73m². There was hyperglycemia of 256 g/dL. Sodium was only slightly reduced with value of 134 mmol/L.

Electrocardiography showed sinus tachycardia with heart rate of 132 bpm, normal axis, normal P wave, PR interval 0.12 s, QRS duration 0.10 s, pathologic Q wave in leads II, III, aVF. Chest X-ray revealed cardiothoracic ratio 54%, dilated aortic segment, normal pulmonary segment, downward apex, and pulmonary vascular congestion.

Echocardiographic examination revealed left ventricular ejection fraction of 54% with concentric left ventricular hypertrophy and diastolic dysfunction grade 1. The global wall motion was normal and right

Table 1. Laboratory findings of Mr. DT at admission.

Name	Result	Value
Hemoglobin	11.1	g/dL
Hematocrit	32.3	%
Leukocyte	11 610	cells/mm^3
Thrombocyte	182 000	cells/mm^3
Urea	49.2	mg/dL
BUN	23	mg/dL
Creatinine	2.16	mg/dL
estimated GFR	32	mL/min/1.73m^2
Blood glucose	256	g/dL
Sodium	134	mmol/L
Potassium	3.8	mmol/L
Chloride	97	mmol/L
Calcium total	2.19	mmol/L
Magnesium	2.5	mmol/L

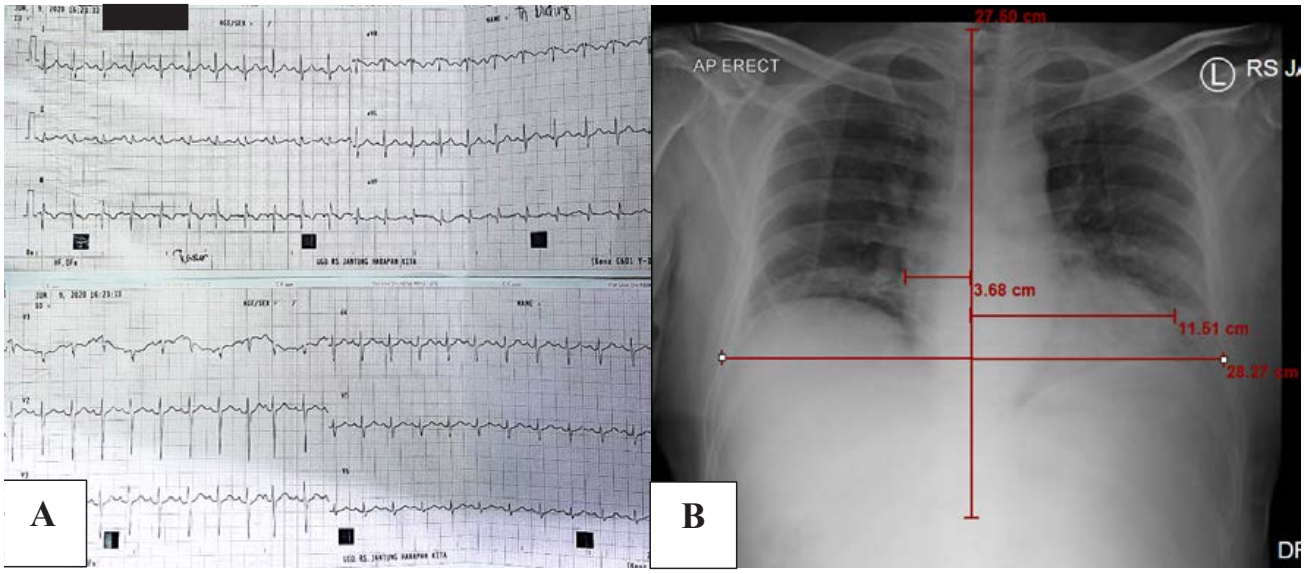


Figure 1. A. ECG of Mr. DT at admission; **B.** chest X-ray of Mr. DT at admission.

ventricular contraction was good with TAPSE of 21 mm. Septal e' was 5.3 cm/s, lateral e' 11.6 cm/s, average E/e' 9.1, LAVI (left atrial volume index) 18 mL/m², LVMI (left ventricular mass index) 127 g/m², and RWT (relative wall thickness) 0.47.

Based on history taking, physical examination, and supporting examination, patient was diagnosed with acute decompensated heart failure in HFpEF due to hypertensive heart disease with hyperglycemia, grade 1 hypertension, and renal insufficiency.

Patient was initially treated with furosemide 20 mg iv and continued with 2x40 mg IV, ramipril 1x2.5 mg, and insulin drip 2 units/hour. During treatment in the ward, diuretic was optimized to 3x60 mg IV. Blood glucose was well-controlled and insulin was switched to metformin 2x500 mg. NT-pro BNP was tested on the third day with result of 68.

During hospitalization, the clinical condition of the patient improved. Furosemide was down-titrated to oral 1x40 mg, ramipril increased to 1x10 mg, and bisoprolol was initiated at 1x1.25 mg. On the seventh day, patient was discharged with euvolemic and stable hemodynamic condition. Drugs given during discharge were furosemide 1x40 mg, ramipril 1x10 mg, bisoprolol 1x1.25 mg, simvastatin 1x20 mg, and metformin 2x500 mg. Patient was educated to limit fluid intake up to 1500 mL/day and to return for follow up in the polyclinic one week later.

Case Illustrations 2

Mrs. S, a 66-year old woman was admitted to the emergency room with chief complaint of breathlessness for one month before admission. There was dyspnoea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. Patient felt frequent fatigue and activity intolerance for three months before admission. There was also edema of both lower extremities. There were no chest pain, nausea, or vomiting reported.

She had a history of hypertension and menopause. Patient was newly admitted to NCC Harapan Kita with possible trigger of failure was suboptimal treatment. Patient routinely went to a nearby clinic and was given furosemide 1x40 mg, captopril 3x25 mg, and amlodipine 1x5 mg.

On physical examination patient was fully alert, moderately ill with blood pressure of 135/71 mmHg, heart rate 90 bpm, respiratory rate of 24 times per minute, temperature 37-degree Celsius, and oxygen saturation 98%. Body height was 143 cm, body weight 74.6 kg, with BMI 36.2. There was distended JVP. Heart examination revealed normal first and second heart sounds, no murmur, and no gallop. Lung examination revealed vesicular pulmonary sounds with crackles on both lung bases. Abdominal examination revealed hepatomegaly and extremities examination revealed bilateral pitting edema.

Laboratory examination revealed mild anemia with hemoglobin level of 11.9 g/dL and mild leukocytosis. There was hypokalemia with value of 2.9 mmol/L. Electrocardiography showed sinus rhythm with heart rate of 94 bpm, left axis deviation, normal P wave, PR interval 0.15 s, QRS duration 0.09 s, and normal ST-T segment. Chest X-ray revealed cardiothoracic ratio 74%, dilated aortic segment, normal pulmonary segment, downward apex, and congestion.

Echocardiographic examination revealed left ventricular ejection fraction of 57% with concentric left ventricular hypertrophy and diastolic dysfunction grade 1. Wall motion was global normokinetic and right ventricular contraction was good with TAPSE of 18 mm. Septal e' was 4.7 cm/s, lateral e' 5.8 cm/s, average E/e' 9.1, LAVI 26 mL/m², LVMI 126 g/m², and RWT 0.45.

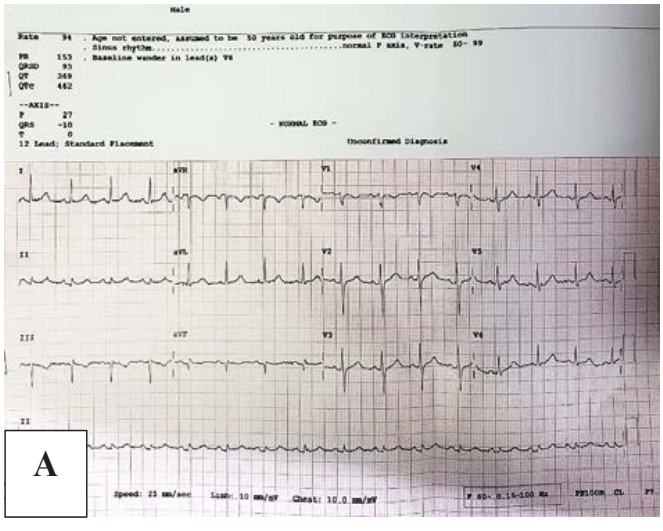
Based on the history taking, physical examination, and supporting examination, patient was diagnosed with acute decompensated heart failure in HFpEF due to hypertensive heart disease, hypertension with controlled blood pressure, hypokalemia, and obesity.

Patient was initially treated with furosemide 40 mg iv and continued with 2x20 mg iv, ramipril 1x10 mg, and spironolactone 1x25 mg. During treatment in the ward, diuretic was optimized to 10 mg/hour and spironolactone increased to 1x50 mg. Oral glucose tolerance test result was 119 and 199, therefore patient was given metformin 2x500 mg. Potassium level improved to 3.7. Bisoprolol was also initiated at 1x1.25 mg.

During hospitalization, clinical condition of the patient improved. NT-proBNP was tested on the fifth day with result of 43. Furosemide was down-titrated to 2x40 mg, and bisoprolol was up-titrated to 1x2.5 mg. On the sixth day, patient was discharged with euvolemic and stable hemodynamic condition. Drugs given during discharge were furosemide 2x40 mg, ramipril 1x10 mg, bisoprolol 1x2.5 mg, spironolactone 1x50 mg, and metformin 2x500 mg. Patient was educated to limit fluid intake up to 1800 mL/day and to return for follow up in the polyclinic one week later

Table 2. Laboratory findings of Mrs. S at admission.

Name	Result	Value
Haemoglobin	11.9	g/dL
Haematocrit	35.7	%
Leukocyte	11 000	cells/mm³
Thrombocyte	325.000	cells/mm³
Urea	25.7	mg/dL
BUN	12	mg/dL
Creatinine	0.89	mg/dL
estimated GFR	68	mL/min/1.73m²
Blood glucose	148	g/dL
Sodium	138	mmol/L
Potassium	2.9	mmol/L
Chloride	97	mmol/L



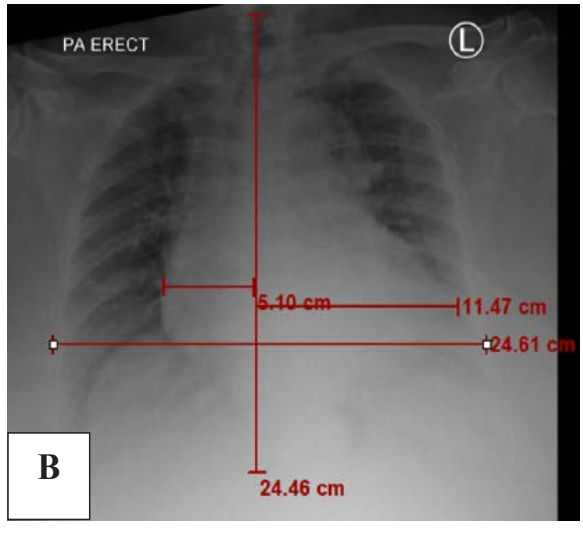


Figure 2. A. ECG of Mrs. S at admission; **B**. chest X-ray of Mrs. S at admission.

Discussion

Heart Failure with Preserved Ejection Fraction

Heart Failure with Preserved Ejection Fraction (HFpEF) was previously referred to as heart failure with normal systolic function or diastolic heart failure. Diastolic dysfunction itself is a myocardial relaxation disorder and impaired left ventricular compliance which causes an increase in left ventricular end-diastolic pressure (LVEDP). Diastolic heart failure is diastolic dysfunction accompanied with signs and symptoms of heart failure. HFpEF does not only consist of diastolic dysfunction, but also abnormalities of regional contractility and chronotropic incompetence, causing dyspnea and intolerance during activity. [1,4]

The definition of HFpEF from the ESC are symptoms and/or signs with left ventricular ejection fraction more than or equal to 50%, accompanied with elevated levels of natriuretic peptides and at least one additional criterion (relevant structural heart disease or diastolic dysfunction).[2]

Typical symptoms of heart failure include breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue, tiredness, increased time to recover after exercise, and ankle swelling. Meanwhile, specific signs of heart failure are elevated jugular venous pressure, hepatojugular reflux, gallop rhythm, and laterally displaced apical impulse. These signs and symptoms are often harder to identify and interpret in patients with obesity, advanced age, and chronic lung disease.[2]

Elevated levels of natriuretic peptides can support the diagnosis of heart failure. In non-acute setting, the upper limit of normal of B-type natriuretic peptide (BNP) is 35 pg/mL and for N-terminal pro-BNP (NT-proBNP) is 125 pg/mL. While in an acute setting, higher values are used (BNP >100 pg/mL, NT-proBNP >300 pg/mL).[2]

Diagnosis of HFpEF

In 2019, the Heart Failure Association of the European Society of Cardiology (HFA ESC) released the HFA-PEFF algorithm to diagnose HFpEF. The steps are Pretest assessment, Echocardiographic and natriuretic peptide score, Functional testing in case of uncertainty, and Final etiology.[5]

First, in breathless patients, assess the signs and symptoms. Patients with HFpEF usually experience reduced exercise tolerance and fatigue. ECG increases the likelihood of heart failure, but has low specificity. Atrial fibrillation (AF) is particularly predictive of HFpEF. In both patients, the pre-test results are suggestive of HFpEF, therefore the HFA-PEFF score can be calculated using echocardiography and NT-proBNP level.[2,5]

The HFA-PEFF score consists of three components: functional, morphological, and biomarker. Biomarker is further divided into sinus rhythm (SR) and atrial fibrillation (AF) because NP levels in patients with AF on average are 3 times higher than in patients with SR. Major criteria accounts for two points, while minor criteria accounts for one point.

In the first patient, major functional criteria and minor morphological criteria were fulfilled, adding up to 3 points. While the second patient fulfilled major functional and morphological criteria, resulting in 4 points. Both patients needed diastolic stress test or invasive hemodynamic measurements to confirm the diagnosis of HFpEF.[5] However, in these two patients additional testing was not performed. Furthermore, to identify the etiology, ergometry and cardiac magnetic resonance (CMR) can be performed. Possible etiologies include chronotropic incompetence, ischemia, or cardiomyopathy.

Natriuretic peptides may be affected by various factors. Beside atrial fibrillation, increasing age and renal failure can also increase NP. On the other hand, NP levels may be low in obese or euvolemic patients. In both patients, NT-proBNP was tested on the third and fifth days of treatment, when the patient's condition was probably euvolemic. In the first patient, renal insufficiency has improved on the third day, while the second patient is obese. In addition, NP values also tend to be lower in HFpEF because left ventricular hypertrophy (LVH) tends to normalize wall stress. These factors might cause normal NT-proBNP values in both patients.[2,5]

Treatment of HFpEF

Hospitalizations in HFpEF patients are mostly due to comorbidities, therefore it is very important to screen patients for cardiovascular and non-cardiovascular

comorbidities, then they should be treated accordingly. To relieve signs and symptoms of congestion, diuretics can be given, with the same principle as HFrEF. As for other therapies, none has been proven effective. There was not enough evidence relating to beta-blockers and mineralocorticoid receptor antagonists for treating HFpEF. Data was also inconsistent for ACE-inhibitors and ARBs.[2,6,7]

Typical demographics and co-morbidities associated with HFpEF are advanced age, arterial hypertension, AF, female gender, kidney dysfunction, metabolic syndrome, obesity, physical deconditioning, pulmonary disease, pulmonary hypertension, and sleep apnea. Hypertension and age are important risk factors for HFpEF. Increasing age causes arterial stiffness, resulting in systolic hypertension.[2] Whereas obesity was reported in 34% of patients in the I-PRESERVE study.[8] Data from the MESA (Multi-Ethnic Study of Atherosclerosis) study showed that EF usually increases with age and is higher in women than in men.[9] Central obesity is also associated with arterial stiffness and concentric LVH, especially in women. However, hospitalization and mortality were reported to be lower in women, with better prognosis in women without AF, renal insufficiency, angina pectoris, and severe NYHA class.[2,8,10]

In this case, the male patient had hypertension and kidney dysfunction, while the female patient had advanced age, hypertension, metabolic syndrome, and obesity. Heart failure was treated with ACE inhibitors, beta-blockers, and diuretics, according to the recommendation by the ESC. Both patients were also pre-diabetic and were given metformin, as the first line anti-diabetic medication in HFpEF.[2]

Several studies have been conducted to investigate effective treatments in reducing mortality and hospitalization due to heart failure in HFpEF. Several of the studies found significant results. However, this is in contrast to many studies on HFrEF where mortality dropped significantly.[2]

Current ongoing study on HFpEF treatment is PARAGON-HF, comparing valsartan and sacubitril/valsartan or angiotensin receptor-neprilysin inhibitor (ARNI), primarily to examine the effects of sacubitril itself. Another consideration from the researchers to compare those drugs is that the majority of patients in the study and the general population have already used ARBs. The result was no significant difference in hospitalization for heart failure and cardiovascular mortality in the valsartan and ARNI groups with p = 0.059. Statistically, the effect of ARNI was not significant, but in subgroup analysis it was found that ARNI provided better results in the female population and also patients with LVEF below 57% or the median EF in this study.[11]

Conclusion

A man and woman with HFpEF and HHD, came to the emergency room with signs and symptoms of congestion. Additional examination was performed to support the diagnostic criteria, namely ECG, NTproBNP and echocardiography. HFA-PEFF scores of the first and second patient was 3 and 4 respectively. During hospitalization, diuretics was given to overcome congestion according to guidelines, as well as ACE-inhibitor and beta-blocker. Both patients were also screened for cardiovascular and non-cardiovascular comorbidities, and were given appropriate therapy. The diagnosis of HFpEF does not have a gold standard yet, meanwhile the HFA-PEFF scoring can be used. Recommended HFpEF therapy includes diuretics for congestion and management of comorbidities. Several studies of HFpEF treatment are ongoing.

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Case Reports

The de Winter Pattern as Pre-Anterior ST-Elevation-Myocardial-Infarction. "An Evolution Sequence": A Case Report

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Abstract

Background: The de Winter pattern (dWP) was first described by de Winter and colleagues in 2008 as a static pattern associated with anterior myocardial infarction. A recent study showed the evolution sequence of this pattern into typical ST-elevation myocardial infarction (STEMI). This case discussed dWP who present as pre-anterior STEMI.

Case Illustration: A-56-year old Male arrived in the emergency room complained of chest pain for about 3 hours. The patient also complained of diaphoresis, nausea, and fatigue. The patient has a previous history of hypertension. The vital signs were stable with an unremarkable physical examination. The initial electrocardiogram (ECG) revealed sinus rhythm with j-point depression followed by prominent T wave in precordial leads, slight ST-segment elevation in aVR, and loss of precordial R-wave progression. The initial troponin T was 31 pg/mL. Follow-up 1-hour after initial ECG showed typical ST-segment-elevation in V1-V4. The patient undergoing thrombolytic, followed by angiography that showed subtotal occlusion in the proximal left anterior descending (LAD) artery, occlusion in the proximal circumflex artery, and stenosis in the proximal right coronary artery, echocardiography revealed regional wall motion abnormality in the septal and anterior segments and preserved ejection fraction 58%, the patient was discharged after 8-days treated in the intensive cardiac care unit.

Conclusion: dWP has been shown as a static and dynamic pattern in some conditions and is associated with acute LAD occlusion. In this case, we showed dWP as early anterior STEMI, recognition of this pattern leads to early reperfusion and better myocardial salvage as anterior STEMI has a poor outcome.

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Keywords: de Winter pattern; left anterior descending occlusion; STEMI equivalent

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Background

Acute myocardial ischemia caused by coronary artery occlusion causes electrophysiological changes of the cardiac cell that lead to the appearance of a characteristic pattern in surface electrocardiogram (ECG). The de Winter pattern (dWP) was first described by de Winter and colleagues in 2008 as a static pattern of ECG that is associated with anterior myocardial infarction associated with left anterior descending (LAD) artery occlusion.[1] The ECG characteristics including upsloping ST-segment depression at the J-point in precordial leads followed by a prominent positive symmetrical T wave, other additional characteristics including slight ST-segment elevation in aVR and loss of precordial R wave progression.[1]

The prevalence of this pattern was 2% in the patient with anterior myocardial infarction with considerable loss of myocardium despite successful reperfusion procedure.[1-4] The mechanism of this ECG pattern was still unclear, and the early report state that the ECG pattern was static, but later, there are reports of the dynamic characteristics of this pattern into typical anterior ST-elevation myocardial infarction (STEMI).[1,5-7] Recognition of this ECG characteristic leads to early management and better prognosis.

In this paper, we discussed a case 56-year-old male with dWP ECG in first medical contact followed by a typical anterior STEMI pattern with a review of the mechanism.

Case Illustrations

A 56-year old Male arrived in the emergency room complained of a heavy pressure sensation in the chest for about 3 hours. The patient also complained of diaphoresis, nausea, and fatigue. The patient has a previous history of hypertension about 3 years and was treated with amlodipine, and has no history of smoking and family history with premature coronary heart disease.

The vital signs revealed blood pressure 130/90 mmHg, heart rate 60x/m, respiration rate 18x/m, temperature 36.7ºC, and SpO2 97% in room air with an unremarkable physical examination. The initial

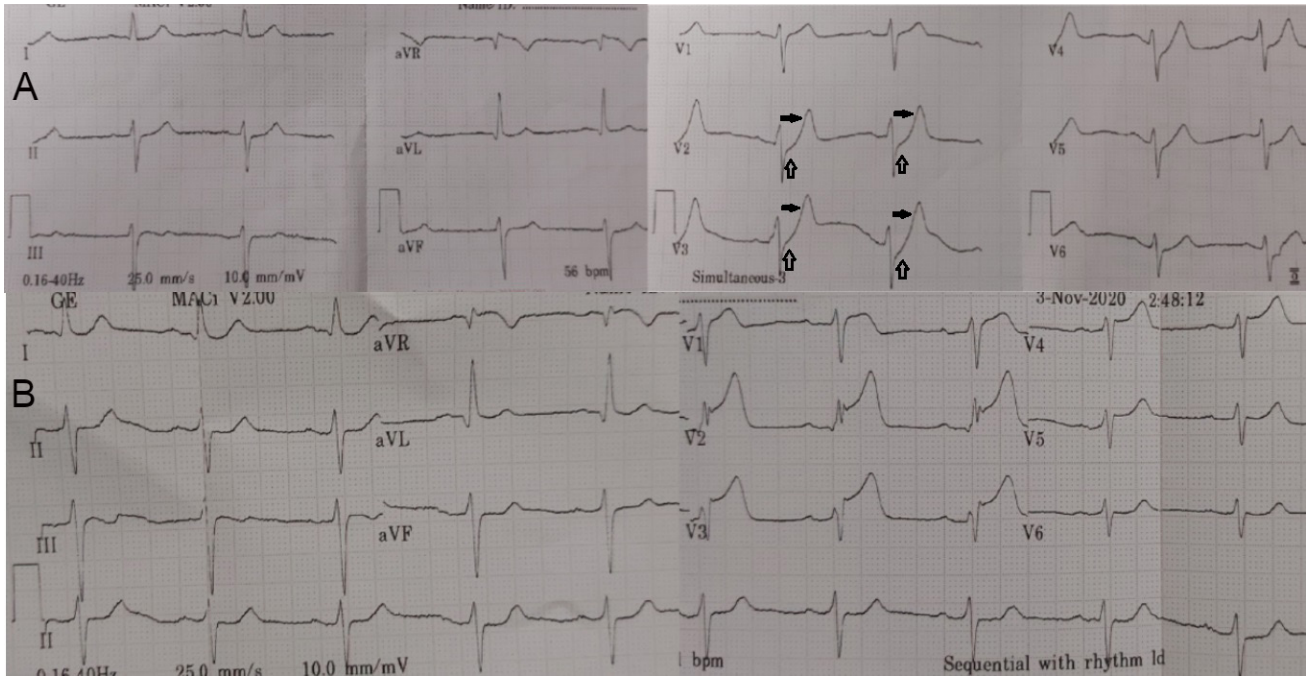

Figure 1. Electrocardiogram (ECG) in Emergency Department. (A) Initial ECG showed sinus rhythm with j-point depression upsloping pattern (non-fill-arrow) followed by prominent T wave in precordial leads (black-fill-arrow), slight ST-segment elevation in aVR, and loss of precordial R-wave progression. (B) Follow-up ECG 1-hour after the initial ECG showed typical ST-segment elevation in V1-V4.

ECG that was recorded within 10 minutes of arrival showed sinus rhythm with j-point depression followed by prominent T wave in precordial leads, slight ST-segment elevation in aVR, and loss of precordial R-wave progression (Figure 1a). The initial laboratory showed troponin-T 31 pg/mL and elevated creatinine (Table 1). Chest X-ray showed cardiomegaly with clear lung. The point of care ultrasound showed regional wall motion abnormality in the septal and anterior segments. The patient was initially treated with oral aspirin 180 mg, clopidogrel 300 mg, and sublingual isosorbide dinitrate 5 mg.

Follow-up 1-hour after initial ECG, the serial ECG showed typical ST-segment-elevation in V1-V4 (Figure 1b). The patient received intravenous fondaparinux 2.5 mg followed with subcutaneous administration, nitroglycerin drip 20 mcg/minute, oral atorvastatin 40 mg, and although the patient arrives in percutaneous coronary intervention (PCI) center, because of the expected delay time to primary PCI, the patient undergoing streptokinase thrombolytic. The patient develops hypotension during thrombolytic therapy and is stabilized by dobutamine and norepinephrine drip. The chest pain was resolve after the thrombolytic therapy. The ECG 1-hour after thrombolytic therapy showed typical ST-segment elevation in the precordial area with marked loss of R wave progression (Figure 2).

The patient undergoing angiography that showed three-vessel disease including subtotal occlusion in the proximal left anterior descending artery, occlusion in the proximal left circumflex artery, and stenosis in the proximal right coronary artery (Figure 3). Follow-up 24 hours troponin-T showed marked elevation (10.000 pg/mL), echocardiography revealed regional wall motion abnormality in the septal and anterior segments and preserved ejection fraction 58%, the patient was stable during hospitalization and discharged after-8 day treated in the intensive cardiac care unit.

Discussion

This case showed the evolution of dWP to a typical anterior STEMI pattern, leading this pattern may also have a dynamic sequence rather than only a static. From the early of the de Winter and colleagues introducing this pattern, some electrophysiological hypotheses were proposed, and the characteristic of this pattern now has been studied.

A study from de Winter et. al. in 2008, recognize a static pattern of dWP in a minority (2%) of anterior myocardial infarction patients. The ECG was obtained with an average of 1.5 hours from the onset.[1] The ECG pattern was persisted from initial ECG to pre-procedural ECG. Although with a successful revascularization procedure, the peak of creatine kinase-myocardial band (CKMB) was still high.[1,2,4] In our case, we obtained the initial ECG about 3 hours from the onset, and the evolution was prominent 1 hour later. The follow-up of our cardiac marker (Troponin-T) was also high. A report from Barbati and colleagues also reporting the high peak of troponin-I despite adequate revascularization of proximal LAD occlusion, with the evolution of pathological Q waves and the appearance of cardiogenic shock during hospitalization.[3]

In contrast to the previous study, another study showed evolved cases into typical ST elevation patterns in the majority of patients with dWP.[6-8] In one study the prevalence of dWP was more common (3.4%) in anterior myocardial infarction, and 86.7% of the patient initially with dWP evolved into typical anterior STEMI pattern, with time from onset to ECG recording was 108 minutes, and time from dWP to ST-segment elevation evolution was 114 minutes, and mostly involved multi-vessel disease.[6] In a systematic review the dWP has a high positive predictive value (PPV) (95.2%, 100%, and 100% in the three respective studies) of acute LAD occlusion.[9] In our case the time from dWP to ST elevation was shorter and also involved LAD and multi-vessel disease.

Some possible mechanisms of this pattern were proposed. In 2008, de Winter and colleagues were proposed probable mechanisms that cause static patterns include myocardial conduction delay as a result of Purkinje fiber variance and lack of activation of sarcolemmal adenosine triphosphate (ATP) sensitive potassium channels that cause the absence of ST-segment elevation.[1] Later, a recent study showed the dynamic characteristic from dWP, that proposed some new probable mechanisms including subendocardial ischemia during the appearance of dWP that resulting from ischemic behavior of the subendocardial action potentials (AP) compared to the normal subepicardial AP, that progress to transmural ischemia that results in typical STEMI pattern in later.[5,6]

According to the theory of the transmembrane action potential (TAP) summation, the normal ECG can be explained by summing up the subendocardial plus the subepicardial TAP.[10] The QRS complex and T wave in the normal ECG is generated by voltage difference because the subendocardial AP starts earlier but ends later than the epicardial AP. The lack of voltage difference between subendocardial and subepicardial areas during the plateau phase of the AP resulting in a normal isoelectric ST segment. The mechanism of ST-segment depression in dWP would be related to the negative voltage difference between the ischemic subendocardial and the normal subepicardial action potentials during the plateau phase (phase 2 of AP) caused by subendocardial ischemia, this negative voltage difference is based on the theory of the TAP summation causing ST depression in the surface ECG. The peaked T waves in dWP were generated because of the shorter time duration between the ischemic subendocardial and normal subepicardial repolarization, causing both areas to repolarize within the almost same time, so generate more peaked T waves.[5,10,11] The change in the TAP shape would be resulting from repolarization delay in the subendocardial area because of hypoxia driven-alteration in ATP-dependent potassium channels.[11]

The repolarization abnormalities of the ischemic subendocardium area would be associated with interstitial accumulation of K+ (ie. opening of ATP-sensitive K channels (iK-ATP)), catecholamines, and other metabolites caused by depletion of ATP and lactic acid accumulation. The Na+/H + exchanger was activated because of increased intracellular H+, resulting in H+ extrusion in exchange for Na+ entry, which in turn results in calcium overload because of activation of the Na+/Ca++ exchanger. These processes causing the hallmark electrophysiological changes of ischemic myocardium include depolarization, inactivation of Na+ channel (causing a reduction in peak inward Na+), and slow conduction.[12] If these ischemic cells are located in the subendocardium, based on the theory of the ischemic vector, this will produce the ST depression of the surface ECG because the ischemic vector toward the less electronegative area (ischemic area) or away from the surface lead during the systole (systolic current of injury), and elevation of TP segment causing ST depression because adjusted by AC amplifier because during diastole the vector toward normal myocardium because the partially depolarized ischemic cell during diastole compared with normal cell (diastolic current of injury).[10,13] The shape of the ST depression may denote the difference of severity and extent of myocardial ischemia, anatomical different, and myocardial protection with the upsloping pattern was the most severe form than non-upsloping (horizontal and downsloping) for the dWP.[14]

Subendocardial ischemia in the early time results dWP to appear, when ischemia is progressed into transmural ischemia the STEMI pattern will appear with classic diastolic and systolic current of injury mechanism. It can be hypothesized that there was a time when the ischemia expanded from the subendocardium to the epicardium that showed the evolution of the ST-segment.[6,13]

Conclusion

In this case, we showed the dWP in the presentation that evolves into typical anterior STEMI. The dWP has been shown as a static and dynamic pattern in some conditions and associated with acute LAD occlusion, and may involve multivessel lesions, some proposed mechanisms of this ECG pattern have been there to describe this phenomenon. The serial ECG is mandatory to show the evolution of dWP, and the most important, the recognition of this pattern in the "first look" ECG to avoid delay in the treatment and lead to early reperfusion and better myocardial salvage as anterior STEMI has a poor outcome in the short and longterm period.

List of Abbreviations

ALT=Alanine transaminase
AP=action potential
AST=aspartate transaminase
ATP=adenosine triphosphate
CKMB=creatine kinase-myocardial band
dWP=de Winter pattern
ECG=electrocardiogram
LAD=left anterior descending
PCI=percutaneous coronary intervention
PPV= positive predictive value
STEMI=ST-elevation myocardial infarction
TAP=transmembrane action potential

Conflict of Interest

None.

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