

Epicardial Adipose Tissue Thickness and Body Mass Index as Early Predictors of Thrombolysis Success in Patients with Elevated ST-Segment Myocardial Infarct

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ABSTRACT

Introduction: Early intravenous thrombolysis in elevated ST-segment myocardial infarcted patients reduces morbidity/mortality, however in non-responsive patients, it can delay the endovascular revascularization process. Increased epicardial adipose tissue thickness (EATT) is associated with adverse cardiovascular events and artery patency. Our aim was to evaluate if EATT influences the response to thrombolytic therapy in patients with acute myocardial infarction.

Material and Method: This prospective cohort study included fifty patients (40 males and 10 females) with a mean age of 60 ± 9 years old and a presumptive acute myocardial infarct diagnosis. All the patients were hospitalized in the intensive care coronary unit. According to ESC and ACC guidelines, the diagnosis of acute myocardial infarct was corroborated. Patients were treated with 0.5 mg/kg IV bolus of the specific recombinant plasminogen activator Tenecteplase. The transthoracic 2-dimensional echocardiography was performed to recognize EAT from the parasternal long-axis view.

Results: The time lapse between initial symptoms and thrombolysis was 227 ± 43 mm. Sixteen patients showed positive reperfusion less than 90 minutes after thrombolysis, and the remaining 34 required a percutaneous coronary intervention. The mean EATT value of thrombolysis-responding patients was 2.4 ± 0.4 mm vs 6.5 ± 0.6 mm of the non-responders ($p = 0.001$). In responders, the percentage of body mass index (BMI) was $26.1 \pm 0.02\%$ vs $29.1 \pm 0.02\%$ (kg/m^2) in non-responders ($p = 0.001$). Interestingly, an EATT value > 2.5 mm and a BMI > 26 showed a highly significant inverse correlation response to thrombolysis and positive myocardial reperfusion ($r = -0.71$ y 0.55 , $p = 0.001$ respectively). These values had a prognostic sensitivity of 93% and specificity of 84%.

Conclusion: EATT and BMI could be useful serve as early decision indicators to determine the possible response to thrombolysis and positive myocardial reperfusion in acute myocardial infarcted patients, although there is a need for studies with larger sample sizes.

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Introduction

Epicardial adipose tissue (EAT) is located between the myocardium and the visceral pericardium. It is made up mainly of adipocytes, inflammatory and immune cells, thus they have local and systemic effects (1, 2). Its main function is to serve as a source of energy and release anti-inflammatory adipokines to the myocardium (3). When it is enlarged it contributes to atherosclerotic cardiovascular disease mediated by the secretion of pro-inflammatory adipokines (IL-1, IL-6, TNFa) that go directly into the coronary lumen (2-4) and have angiocrine and vasomotor effects that regulate blood flow to the coronary arteries (5). EAT is measured using the coronary artery calcium score (6), or through transthoracic echocardiography (7).

Acute myocardial infarction results from an atheroma plaque fracture within a coronary vessel that triggers a coagulation cascade that ends in platelet aggregation and thrombus formation, thus obstructing coronary blood flow (8). Early intravenous thrombolysis reduces morbidity/mortality, but some patients do not respond thus delaying the endovascular intervention (9). Well recognized risk factors such as type 2 diabetes mellitus (10), high blood pressure, (11) white cell count (12), body mass index (13), or malnutrition (14) are implicated in a deficient response to thrombolysis. It has recently emerged that EAT thickness is related to adverse cardiovascular events (15) or enhanced cardiovascular risk (16). Interestingly, EAT has also been associated with infarct artery patency (17), defines the flow through the infarcted artery, and may affect cardiac electrical stability (18) thus reinforcing the relevance of a successful early thrombolysis event. The aim of this project was to evaluate if the response to thrombolytic therapy in patients with acute myocardial infarction is associated to epicardial adipose tissue thickness.

Material and Methods

The study was approved by the Local Committees of Research, Ethics and Biosafety of the Centro Médico Nacional '20 de Noviembre' ISSSTE, Mexico City (Protocol ID

No. 611.2019) and All participants gave their written informed consent.

Patients

This prospective cohort study included fifty patients (40 males and 10 females) with a mean age of 60 ± 9 years old and a presumptive acute myocardial infarct diagnosis. Following referral by their health-care units all the patients were hospitalized in the intensive care coronary unit, National Medical Center '20 de Noviembre' ISSSTE, Mexico City, Mexico. An echocardiography was performed and the diagnosis of acute myocardial infarct according to the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) guidelines (> 3 mm elevation of the ST-segment, elevated cardiac troponin above the 99th percentile URL, and 2-fold increase of creatine phosphokinase MB) (19-21) was corroborated. Patients with pericardial effusion, peripheral artery disease, mitral valve insufficiency, or left ventricle wall rupture were excluded, as were patients who had undergone coronary artery bypass grafting or aortic and mitral valve repair or replacement. The Body Mass Index (BMI) was calculated, after the height and body weights were measured using the $BMI = \text{kg}/\text{m}^2$ formula; 5 ml blood samples were obtained for a 28 parameters blood chemistry analysis at arrival at the Intensive Care Unit.

Echocardiographic evaluation

Patients were treated with 0.5 mg/kg IV bolus of the specific recombinant plasminogen activator Tenecteplase and the transthoracic echocardiography was simultaneously performed using the Phillips EPIQ 7 ultrasound machine with a PureWave transducer (Philips N.V., USA). One well-trained cardiologist who was blind to the original patient characteristics according to a standardized protocol, performed the echocardiographic examination.

Measurement of EAT thickness

EATT was recognized as an echo-free space located between the visceral pericardium and the outer wall of the myocardium on 2-

dimensional echocardiography. To standardize the measuring point, the aortic annulus was used as an anatomical reference. From the parasternal long axis view, EAT thickness was measured perpendicularly on the free wall of right ventricle at end-systole for 3 consecutive cardiac beats (22).

Statistical analysis

Results are presented as the mean \pm standard deviation of the mean. Pearson & Rho Spearman to correlation analysis. Logistic and linear regression to independence effect. Chi square and Students T test were used to determine the difference between responders and non-responders to thrombolysis treatment and ROC curve test was used for prognostic value of EATT and BMI percentage to positive response of thrombolysis, for a p value < 0.05 was considered as statistically significant. SPSS v 28 software was used to analyze the information.

Results

The table 1 shows the risk factors, left ventricular area affected of patients possessing myocardial infarction and the heart failure severity proposed by Killip and Kimball classification. An elevated

percentage had type 2 diabetes mellitus (66%) and high blood pressure (60%); almost half had dyslipidemia or were smokers; fifty-eight percent were overweight (BMI >25 but <30) and thirty-two were obese (BMI >30); the inferior wall of the left ventricle was the most frequent affected area followed by the anterior and lateral walls and 33 of the patients belonged to class I which conveys no clinical signs of heart failure, 7 were classified as class II which conveys mild heart failure, 2 were classified as class III which conveys severe heart failure with pulmonary edema and 8 were classified as class IV that include cardiogenic shock and severe heart.

The time lapse between initial symptoms and thrombolysis was 227 ± 43 min. Sixteen patients showed positive reperfusion in less than 90 minutes after thrombolysis, whereas 34 didn't, thus requiring a percutaneous coronary intervention (PCI). No significant differences between risk factors on the efficacy of thrombolysis were observed (Table 2). The 30-day follow-up showed NYHA functional class I in 40 patients (80%) and NYHA II in 7 patients (14%). Three male patients classified as class IV Killip Kimball index requiring ICP (6%) died, although none was due to the consequence of the procedure.

Table 1. Cardiovascular disease risk factors and Killip Kimball stratification of patients*.

| Risk Factors | | N |
|-----------------------------------|------------|----|
| Diabetes Mellitus | | 33 |
| Hypertension | | 30 |
| Dyslipidemia | | 24 |
| Smoking | | 24 |
| Body Mass Index | Normal | 5 |
| | Overweight | 29 |
| | Obese | 16 |
| Left Ventricular area affected | Anterior | 22 |
| | Lower | 24 |
| | Lateral | 4 |
| Killip and Kimball classification | I | 33 |
| | II | 7 |
| | III | 2 |
| | IV | 8 |

* Parameters determined before the thrombolysis procedure was performed.

The mean EATT value in all patients was 5.8 ± 2.1 mm, however significant difference between responders and non-responders was observed (2.8 ± 0.4 mm vs 6.5 ± 0.6 , $p = 0.001$). Patients that responded positively to thrombolysis had a mean EATT value of 2.4 ± 0.4 mm and a BMI of $26.1 \pm 0.02\%$ as opposed to patients who did not respond to thrombolysis and required an PCI, with values of 6.5 ± 0.6 mm for EATT and $29.1 \pm 0.02\%$ for BMI ($p = 0.001$ for each). These values had a prognostic sensitivity of 93% and specificity of 84% (Figure. 1). It was very interesting to observe that an EATT value >2.5 mm and a BMI higher than 26 showed a highly significant inverse correlation ($r = -0.71$ y 0.55 , $p = 0.001$ respectively), as well as, with an independent effect ($p = 0.001$) on positive response to thrombolysis and positive myocardial reperfusion (Table 3).

Discussion

Epicardial adipose tissue (EAT) is a fat depot localized between the myocardial surface and the visceral layer of the pericardium (23). In normal conditions epicardial adipose tissue is a unique buffering pool in the homeostasis of the myocardium

(24) that protects against hypothermia and mechanical stress. In obese individuals EAT promotes the development of cardiovascular diseases (25). The median epicardial adipose tissue thickness (EATT) values varies enormously from 9 ± 2.96 mm, in cardiological outpatients with similar anthropometric parameters to our population (6) to 1.36 ± 0.7 mm in healthy Hispanic adolescent controls (26). EAT thickness is regulated by age, gender, ethnicity (27, 28) and most importantly body mass index (13). Although EATT correlates significantly with BMI, the thickness is not secondary to hypertrophy of the epicardial tissue adipocytes but to epicardial remodeling via adipocyte proliferation (29). Enhanced adipocyte proliferation decreases adiponectin secretion and boosts leptin secretion increasing local inflammation, oxidative stress and adhesion of monocytes and macrophages (30) thus destabilizing atherosclerotic plaques. It has been recently recognized that local inflammation influences coronary microvascular dysfunction and that EATT can discriminate between the presence or the absence of dysfunction (31).

Table 2. Differential analysis of cardiovascular disease risk factors upon the success of the thrombolysis procedure.

| | Thrombolysis therapy | | P value |
|----------------------------------|----------------------|----------------|---------|
| | Responders* | Not responders | |
| Smoking (years) | 24±15 | 21±12 | 0.87** |
| Diabetes Mellitus (years) | 9±2 | 10±3 | 0.54*** |
| Glycosylated hemoglobin % | 6±3 | 7±3 | 0.22** |
| Dyslipidemia (years) | 5±1 | 7±2 | 0.43*** |
| Low-Density Lipoprotein (mg/dl) | 174±15 | 182±15 | 0.14*** |
| High-Density Lipoprotein (mg/dl) | 58±9 | 48±10 | 0.29*** |
| Triglycerides (mg/dl) | 160±9 | 178±12 | 0.16*** |
| Cholesterol (mg/dl) | 210±12 | 152±11 | 0.09*** |

* Responders are those patients that showed a positive reperfusion response less than 90 minutes after thrombolysis, not responders were those patients that 6 h after thrombolysis did not show a reduction in the ECG ST segment and/or a reduction in troponin or CPK mb serum values and had to have an ICP.

** P value was calculated using Chi2 .

*** The student's T test.

In this study, it is clearly established that an EATT value greater than 2.4 mm together with a BMI greater than 26% tags the outcome of the infarcted patient; these values are strong indicators that the early thrombolytic procedure in patient having both abnormal values will not be successful >90% of the occasions. These results emphasize that EATT is a parameter that needs to be considered along BMI as a prognostic marker for the outcome of myocardial infarcted patients with an elevated ST segment that require a reperfusion process, either thrombolysis or PCI. As the EATT/BMI association proved to be highly significant when in-hospital mortality was evaluated we had to consider the Killip-Kimball classification, which is a cornerstone in the evaluation and prognosis of patients suffering an acute myocardial infarction (32).

It has been clearly established that in-hospital mortality for patients with myocardial infarction and an ST-segment elevation increases from 9.9% in class I Killip patients to nearly 95% in class IV patients and a BMI > 30 kg/m² is a significant contributor to the bad prognosis (33). Similar tendencies are observed in patients treated in more optimal conditions (34, 35). The results confirmed the prognostic value of the Killip classification. But most importantly our results demonstrate that the evaluation of BMI and EATT, two simple parameters easily determined in an acute coronary unit or an emergency room, should always be

contemplated before ascertaining the success of a reperfusion procedure especially in individuals with a Killip class III or IV.

Study limitations

The results of this study with 50 patients clearly established a specific value of EATT (Greater than 2.4 mm) combined with a BMI greater than 26% in infarcted patient exist a strong possibilities (>90%) failure of the early thrombolytic procedure, condition that can contribute to making therapeutic decisions, especially when the patient's condition is critical. However, we also consider that a study with a larger sample size is necessary to confirm the findings of this study. On the other hand, our findings suggest that it is necessary to study the coronary inflammatory scenery conditioned by EATT, to understand the thrombolytic effect better and look for the use of other alternatives therapeutics for acute infarcted patients, because this cardiological pathology continues to represent the principal mortality.

Conclusion

EATT and BMI could serve as early decision indicators to determine the possible response to thrombolysis and positive myocardial reperfusion in acute myocardial infarcted patients, although there is a need for studies with larger sample sizes.

Table 3. Association between Epicardial Adipose Tissue Thickness and Thrombolytic Therapy response.

| | r | P | Multivariate P |
|--------------------------|---------|-----------|----------------|
| EATT (mm) | -0.72** | 0.001**** | 0.001 |
| Body Mass Index | -0.55** | 0.001**** | 0.001 |
| Diabetes Mellitus | 0.14* | 0.32*** | 0.40 |
| Hypertension | 0.05* | 0.71*** | 0.21 |
| Dyslipidemia | 0.25* | 0.68*** | 0.70 |
| Smoking | 0.23* | 0.10*** | 0.18 |

- **EEAT:** Epicardial Adipose Tissue Thickness.

* Rho Spearman test .

**Pearson test were used to evaluate correlation .

***The multivariate analysis with logistic.

**** linear regression.

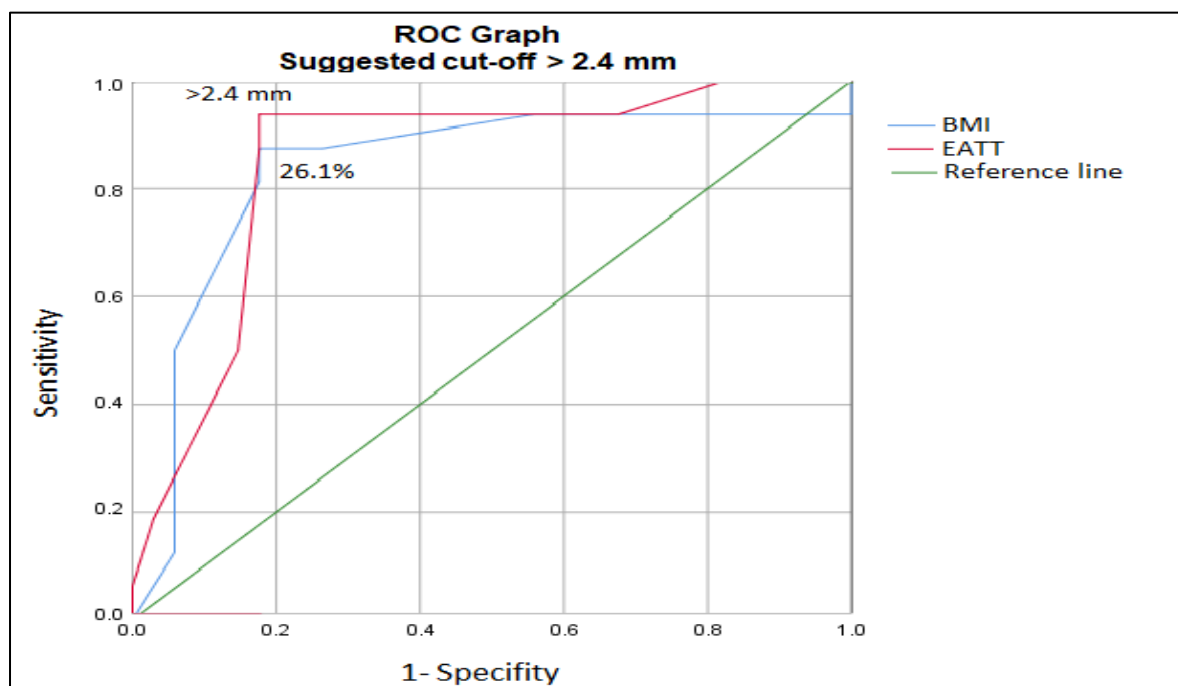


Figure 1. ROC graph suggested cut off >2.4 mm .Predictive ROC Curve of not response to thrombolysis therapy using epicardial adipose tissue thickness and body mass index.

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