Infarct Size as Predictor of Systolic Functional Recovery after Myocardial Infarction

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Abstract

Background: The effects of modern therapy on functional recovery after acute myocardial infarction (AMI) are unknown.

Objectives: To evaluate the predictors of systolic functional recovery after anterior AMI in patients undergoing modern therapy (reperfusion, aggressive platelet antiaggregant therapy, angiotensin-converting enzyme inhibitors and beta-blockers).

Methods: A total of 94 consecutive patients with AMI with ST-segment elevation were enrolled. Echocardiograms were performed during the in-hospital phase and after 6 months. Systolic dysfunction was defined as ejection fraction value < 50%.

Results: In the initial echocardiogram, 64% of patients had systolic dysfunction. Patients with ventricular dysfunction had greater infarct size, assessed by the measurement of total and isoenzyme MB creatine kinase enzymes, than patients without dysfunction. Additionally, 24.5% of patients that initially had systolic dysfunction showed recovery within 6 months after AMI. Patients who recovered ventricular function had smaller infarct sizes, but larger values of ejection fraction and E-wave deceleration time than patients without recovery. At the multivariate analysis, it can be observed that infarct size was the only independent predictor of functional recovery after 6 months of AMI when adjusted for age, gender, ejection fraction and E-wave deceleration time.

Conclusion: In spite of aggressive treatment, systolic ventricular dysfunction remains a frequent event after the anterior myocardial infarction. Additionally, 25% of patients show functional recovery. Finally, infarct size was the only significant predictor of functional recovery after six months of acute myocardial infarction. (Arq Bras Cardiol. 2014; 102(6):549-556)

Keywords: Myocardial Infarction; Heart Failure; Ventricular Dysfunction; Recovery of Function.

Introduction

Many factors determine the outcome of patients after an Acute Myocardial Infarction (AMI)[1,2]. Among these prognostic factors, heart failure is highlighted due to left ventricular dysfunction. In fact, cardiac dysfunction after AMI increases the risk of death by three to four-fold[3].

Epidemiological studies report that signs and symptoms of heart failure after infarction occur in approximately 25% of patients with AMI. Additionally, large clinical trials report that approximately 40% of AMI cases are accompanied by left ventricular systolic dysfunction, suggesting that functional deterioration is a common event after AMI[4].

An important aspect to be considered, however, is that a considerable percentage of patients with systolic dysfunction in the acute phase of myocardial infarction show functional recovery over time. However, the current prevalence and risk factors for prediction of functional recovery are not completely understood.

Thus, this study aimed to evaluate the prevalence and predictors of systolic functional recovery after AMI in patients undergoing modern therapy after anterior myocardial infarction.

Methods

Design

The present was a prospective, observational study carried out in the coronary care unit of our institution. Consecutive patients of both genders that had the first episode of anterior AMI from December 2008 to December 2010 were included in the study.

The diagnosis of anterior AMI was established by a history of chest pain lasting more than 20 minutes and the presence of ST-segment elevation in at least two contiguous precordial leads (V1-V4) or the presence of new complete left bundle branch block at the electrocardiogram. Exclusion criteria were: congenital heart disease, significant primary valve disease, atrial fibrillation, inadequate

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condition for the completion of first echocardiogram during hospitalization, inadequate echocardiographic window, cancer, autoimmune disease, chronic renal failure (creatinine clearance ≤ 30 mL/min), liver failure and chronic immunosuppressive therapy.

The study protocol was approved by the Ethics Committee of our institution and patients were enrolled after signing the free and informed consent form. During hospitalization, patients were evaluated daily and submitted to the first echocardiogram; the time of follow-up after hospital discharge was 6 months and at 6 months, patients underwent clinical reassessment and a new echocardiogram.

Clinical variables

Data related to the clinical profile of patients were obtained from patient history and physical examination on admission. Blood samples were obtained according to the routine of the Coronary Care Unit. Electrolytes, renal function and blood count were measured on admission and measurement of blood glucose and lipids was performed on samples obtained after a 12-hour fast. The levels of total (CPK) and isoenzyme MB creatine phosphokinase (CK-MB) were assessed at admission and every 6 hours until levels started to decrease. Two measurements of troponin I were performed (on admission and 90 minutes after patient arrival).

Clinical variables were obtained: age, gender, ethnicity, symptoms at admission, duration of chest pain (between the onset of pain and the first assessment in the emergency room), prior coronary revascularization, heart rate, systemic blood pressure and signs of pulmonary and systemic congestion[5-8].

The following cardiovascular risk factors were investigated: systemic arterial hypertension (SAH), Diabetes Mellitus (DM), dyslipidemia, smoking, obesity and family history of coronary artery disease[5-8].

Patients that reported a previous diagnosis of SAH and that had at least one measurement of systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, or routinely used antihypertensive drugs were considered hypertensive. Patients that reported a previous diagnosis of DM and were receiving regular treatment, or patients that had two fasting glucose levels ≥ 126 mg/dL or a casual plasma glucose ≥ 200 mg/dL associated with classic symptoms of DM were considered as diabetics. Dyslipidemia was considered in patients on regular use of lipid-lowering medication or the presence of serum Low Density Lipoprotein levels (LDL-C) ≥ 160 mg/dL and/or serum levels of high density lipoprotein (HDL-c) ≤ 40 mg/dL (men) or ≤ 50 mg/dL (women) and/or serum triglycerides ≥ 150 mg/dL.

Patients that smoked daily, regardless of the number of cigarettes, were considered smokers. Patients with first-degree relatives with premature coronary artery disease (men < 55 years and women < 65 years) were considered as having a positive family history for CAD. Finally, obesity was diagnosed by the presence of Body Mass Index (BMI) ≥ 30 kg/m^2 and central obesity by the presence of waist circumference > 102 cm for men and > 88 cm for women. Weight and height were measured on a Welmy Brazil scale, with a maximum capacity of 200 kg and fixed stadiometer. The waist circumference was measured with an inelastic tape in the mid-distance between the iliac crest and the last rib.

Weight, height and waist circumference were measured in the morning, after fasting, 48 hours after admission with patients wearing the standard hospital gown[5-8].

Regarding the treatment of AMI, reperfusion strategy and the following drugs prescribed during the in-hospital phase were evaluated: acetylsalicylic acid (ASA), Clopidogrel, heparin (unfractionated or low-molecular weight), Glycoprotein IIb/IIIa receptor inhibitor (IGP IIb/IIIa) inhibitors, angiotensin-converting enzyme inhibitors (ACEI), beta-blockers, calcium-channel blockers, nitrates, intravenous positive inotropic agents, diuretics, digitalis, statins, spironolactone and warfarin[5-8].

The post-AMI clinical complications that occurred in the in-hospital phase were defined as follows: post-AMI ischemia as the occurrence of chest pain during appropriate drug therapy and/or acute ischemic alterations in the electrocardiogram (ECG) after the second day of evolution after AMI; arrhythmia with occurrence of sustained ventricular tachycardia or ventricular fibrillation; heart failure as clinical or radiological pulmonary congestion that required intravenous diuretic treatment, presence of hypotension as SBP < 90 mmHg for a period > 30 minutes in euvolemic patients with no signs of tissue hypoperfusion; cardiogenic shock, as SBP < 90 mmHg for a period > 30 min and signs of peripheral hypoperfusion (cold extremities, oliguria, sweating, pallor, restlessness or drowsiness) associated with pulmonary congestion and pericarditis, as occurrences of characteristic chest discomfort and associated with pericardial friction or the presence of diffuse ST-segment elevation on the electrocardiogram[5-8].

Echocardiographic assessment

Morphological and functional evaluation of the left ventricle (LV) was performed by echocardiography. The examinations were performed by three echocardiographists blinded to patients' clinical characteristics and treatment. Echocardiograms were performed during the in-hospital phase and 6 months after the AMI by the same examiner. In our service, the interobserver variability is < 5% for one-dimensional measurements and < 10% for two-dimensional measurements and Doppler-derived time variables; intraobserver variability is <5% for all variables.

Examinations were performed in a Philips HDI-5000 equipment according to standard technique[9]. Systolic dysfunction was defined as ejection fraction < 50% assessed by Simpson's method[10]. Recovery of left ventricular systolic function was defined as an increase in LV ejection fraction > 50% in those patients with dysfunction detected between the first and second echocardiograms.

Statistical analysis

Continuous variables are shown as mean and standard deviation or median and 25% and 75% percentiles in case of non-normal distribution. Proportional variables were analyzed by chi-square test or the Fisher exact test for comparison between groups. Continuous variables were tested for

normality; continuous variables with normal distribution were compared by Student's *t* test, while non-normal continuous variables were compared using the Mann-Whitney test.

Existing associations between the variables and functional recovery after AMI were analyzed by multivariate logistic regression. The occurrence of functional recovery was included as the dependent variable. Variables that showed statistically significant differences in the univariate analysis, plus age and gender, were included as independent variables. The ROC (Receiver Operating Characteristic) curve was used to determine the best infarct size cutoff. The SigmaStat statistical package for Windows 3.5 (Systat Software Inc. - San Jose, CA – USA) was used or statistical analysis. The level of significance was set at 5% for all tests.

Results

During the observation period, 94 patients with anterior AMI were evaluated. However, eight patients died before the second echocardiogram and three patients were lost to follow-up. Thus, our final sample consisted of 83 patients. Of these, 73% were males, mean age of 58 ± 12 years.

In the initial echocardiogram, 64% of the patients had systolic dysfunction. As expected, patients with ventricular dysfunction had larger infarct sizes, assessed by CPK and CPK-MB enzymes, than patients without dysfunction (Table 1). No differences were found for the other analyzed variables.

Regarding baseline echocardiographic data, patients with ventricular dysfunction had higher LV diameters, associated with lower ejection fractions. There were no other differences between patients with or without dysfunction (Table 2).

Regarding functional recovery, 24.5% of patients with initial systolic dysfunction showed recovery within 6 months after AMI. Patients that recovered ventricular function had smaller infarct sizes than patients without recovery. There were no differences in relation to other clinical variables (Table 3).

Regarding the echocardiographic data, patients that had functional recovery showed higher EDT and ejection fraction than those without recovery. No differences were found for other variables (Table 4).

Multivariate analysis showed that infarct size was the only independent predictor of functional recovery 6 months after AMI, when adjusted for age, gender, ejection fraction, and EDT (Table 5). The ROC curve was used to determine the best cutoff for infarct size as assessed by the MB isoform, which determines LV function recovery, with the following result for the area under the curve: 0.814; 95% confidence interval (95% CI): 0.698 to 0.929, p <0.001, with a cutoff of 521U/L (Figure 1).

Discussion

This study aimed to evaluate the prevalence and predictors of systolic functional recovery after AMI in patients

Table 1 – Clinical, demographic and treatment data of 83 patients with anterior-wall acute myocardial infarction

Variables	Ventricular dysfunction		p value
	Yes (n = 53)	No (n = 30)	
Age (years)	57.9 ± 11.7	59.2 ± 13.1	0.632
Male, % (n)	75.5 (40)	70.0 (21)	0.777
SAH, % (n)	50.9 (27)	73.3 (22)	0.078
DM, % (n)	24.5 (13)	33.3 (10)	0.545
Dyslipidemia, % (n)	75.5 (40)	80.0 (24)	0.842
BMI (kg/m^2)	26.9 (23.6-28.9)	28.9 (24.8-32.0)	0.116
WC (cm)	94.1 ± 9.8	98.1 ± 12.6	0.113
CPK (U/L)	4421 (1.453-7.658)	1.491 (683-4.116)	0.018
CPK-MB (U/L)	445.0 (180.8-734.5)	178.5 (111.0-324.0)	0.002
Primary angio, % (n)	69.8 (37)	66.7 (20)	0.960
Reperfusion, % (n)	84.9 (45)	86.7 (26)	1.000
ASA, % (n)	100 (53)	100 (30)	-
Clopidogrel, % (n)	100 (53)	100 (30)	-
ARB, % (n)	1.9 (1)	6.7 (2)	0.295
ACEI, % (n)	92.5 (49)	93.3 (28)	1.000
Beta-blocker, % (n)	94.3 (50)	100 (30)	0.550
Spironolactone, % (n)	22.6 (12)	13.3 (4)	0.386

SAH: systemic arterial hypertension; DM: diabetes mellitus; BMI: body mass index; WC: waist circumference; CPK: creatine phosphokinase; CPK-MB: creatine phosphokinase-MB fraction; ASA: acetylsalicylic acid; ARB: angiotensin-II receptor blocker; ACEI: angiotensin-converting enzyme inhibitor. Data expressed as mean ± SD or median (including 25th and 75th percentiles).

Table 2 – Echocardiographic data of 83 patients with anterior-wall acute myocardial infarction

Variables	Ventricular dysfunction		p value
	Yes (n = 53)	No (n = 30)	
LA (mm)	41.2 ± 4.6	40.9 ± 4.8	0.776
LVEDD (mm)	51.2 ± 5.6	48.7 ± 4.2	0.037
LVESD (mm)	35.7 ± 5.4	31.0 ± 4.0	< 0.001
PW (mm)	10.5 ± 1.4	10.9 ± 1.8	0.309
E/A	0.76 (0.64-0.92)	0.79 (0.71-0.88)	0.624
IVRT (ms)	116 (100-124)	114 (104-128)	0.943
EDT (ms)	215.3 ± 64.5	228.8 ± 60.1	0.360
HR (bpm)	76.4 ± 13.5	74.9 ± 13.4	0.621
EF	0.41 ± 0.05	0.58 ± 0.05	< 0.001

LA: left atrium; LVEDD: left ventricular-end diastolic diameter; LVESD: left ventricular-end systolic diameter; PW: left ventricular posterior wall thickness; IVRT: isovolumetric relaxation time; EDT: E-wave deceleration time; HR: heart rate; EF: ejection fraction. Data expressed as mean ± SD or median (including 25th and 75th percentiles).

Table 3 – Clinical, demographic and treatment data of patients with ventricular dysfunction

Variables	Functional recovery		p value
	Yes (n = 13)	No (n = 40)	
Age (years)	63.4 ± 12.3	56.2 ± 11.1	0.061
Male, % (n)	69.2 (9)	77.5 (31)	0.712
SAH, % (n)	38.5 (5)	55.0 (22)	0.473
DM, % (n)	15.4 (2)	27.5 (11)	0.480
Dyslipidemia, % (n)	84.6 (11)	72.5 (29)	0.480
BMI (kg/m^2)	25.7 ± 3.5	26.8 ± 3.7	0.356
WC (cm)	92.4 ± 9.9	94.6 ± 9.8	0.483
CPK (U/L)	1.351 (841-4.167)	5.587 (2.125-8.269)	0.002
CPK-MB (U/L)	168 (80-273)	579 (254-807)	< 0.001
Primary angio, % (n)	69.2 (9)	70.0 (28)	1.000
Reperfusion, % (n)	76.9 (10)	87.5 (35)	0.389
ASA, % (n)	100 (13)	100 (40)	-
Clopidogrel, % (n)	100 (13)	100 (40)	-
ARB, % (n)	7.7 (1)	0 (0)	0.245
ACEI, % (n)	84.6 (11)	95.0 (38)	0.249
Beta-blocker, % (n)	92.3 (12)	95 (38)	1.000
Spironolactone, % (n)	7.7 (1)	27.5 (11)	0.147

SAH: systemic arterial hypertension; DM: diabetes mellitus; BMI: body mass index; WC: waist circumference; CPK: creatine phosphokinase; CPK-MB: creatine phosphokinase-MB fraction; ASA: acetylsalicylic acid; ARB: angiotensin-II receptor blocker; ACEI: angiotensin-converting enzyme inhibitor. Data expressed as mean ± SD or median (including 25th and 75th percentiles).

undergoing modern therapy after anterior myocardial infarction. Our data suggest that systolic ventricular dysfunction remains a frequent event after AMI, with approximately 25% of patients showing functional recovery. Additionally, infarct size was the only significant predictor of functional recovery 6 months after the acute coronary event.

The first information from our study to be considered is that systolic dysfunction was a common event. In fact, approximately 65% of patients had ventricular dysfunction. Therefore, some factors are worth mentioning.

Firstly, we observed that our patients received the recommended treatment for patients with AMI[11]. Thus, more

Table 4 – Initial echocardiographic data of patients with ventricular dysfunction

Variables	Functional recovery		p value
	Yes (n = 13)	No (n = 40)	
AE (mm)	39.9 ± 3.0	41.6 ± 5.0	0.239
LVEDD (mm)	50.8 ± 3.5	51.4 ± 6.2	0.737
LVESD (mm)	34.7 ± 3.9	36.0 ± 5.8	0.467
PW (mm)	10.0 (10.0-11.0)	10.7 (9.4-11.4)	0.827
E/A	0.75 (0.64-0.86)	0.77 (0.62-0.93)	0.844
IVRT (ms)	120 (109-126)	116 (98-125)	0.443
EDT (ms)	250.9 ± 77.6	203.5 ± 55.7	0.020
HR (bpm)	70.8 ± 12.0	78.2 ± 13.6	0.097
EF	0.44 ± 0.06	0.40 ± 0.05	0.006

LA: left atrium; LVEDD: left ventricular-end diastolic diameter; LVESD: left ventricular-end systolic diameter; PW: left ventricular posterior wall thickness; IVRT: isovolumetric relaxation time; EDT: E-wave deceleration time; HR: heart rate; EF: ejection fraction. Data expressed as mean ± SD or median (including 25th and 75th percentiles).

Table 5 – Logistic regression for predicting left ventricular function recovery 6 months after AMI

Patient characteristics	Odds Ratio	95%CI	p value
Gender	1.719	0.236-12.509	0.593
Age (years)	1.062	0.986-1.144	0.114
EF (%)	1.137	0.895-1.445	0.294
EDT (ms)	1.002	0.982-1.002	0.845
CPK-MB (U/L)	0.995	0.990-0.999	0.015

95%CI: 95% confidence interval; EF: ejection fraction; EDT: E-wave deceleration time; CPK-MB: creatine phosphokinase-MB fraction.

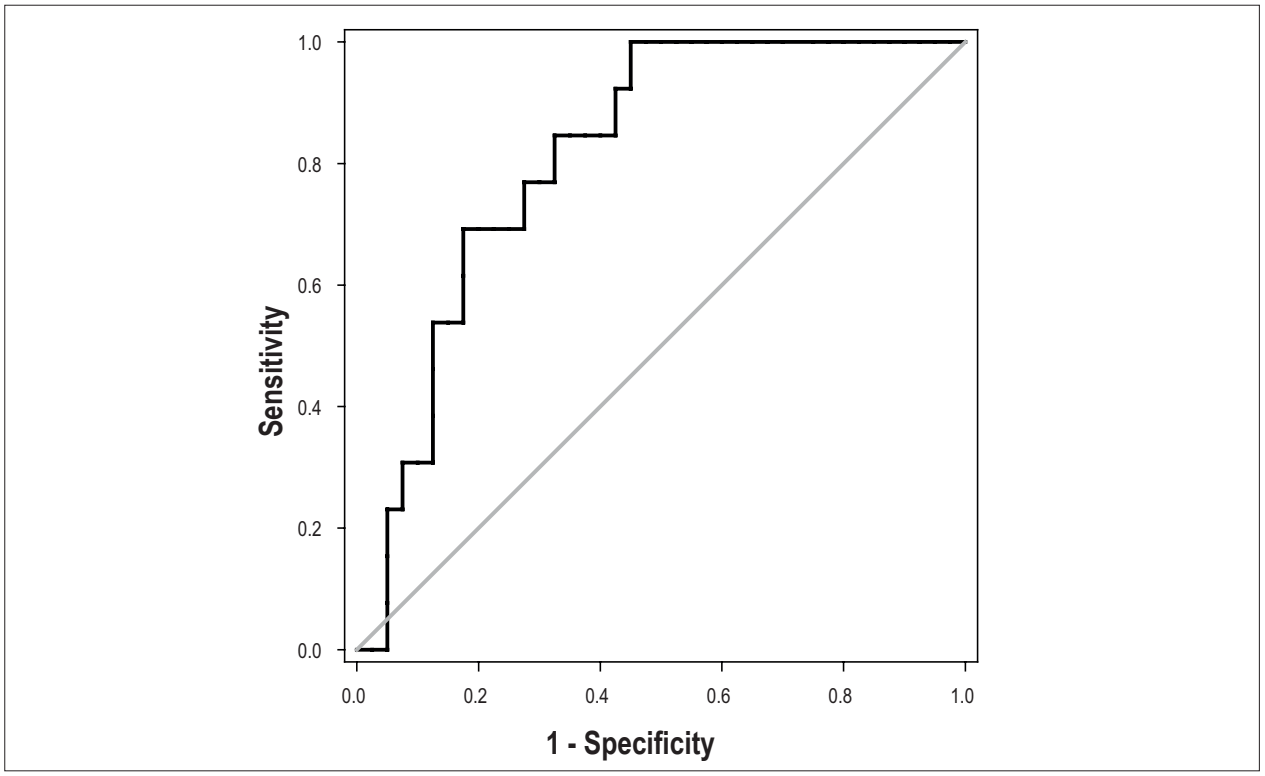

Figure 1 – *ROC curve of the infarct size measured by peak CK-MB isoform, which determines left ventricular function recovery. Area under the curve: 0.814, 95% confidence interval: 0.698 to 0.929, p value < 0.001, and cutoff of 521U / L.*

than 85% of patients were submitted to reperfusion therapy - most by primary angioplasty - 100% of patients received dual antiplatelet therapy and over 90% received beta-blockers and ACE inhibitors. However, we concluded that in most of our patients, this aggressive treatment was not capable of preventing the occurrence of ventricular dysfunction.

Another fact to be considered refers to the fact that the definition of systolic dysfunction is controversial, with different values of ejection fraction (≤ 35%, <40% or <45%) being considered in clinical trials. Our study determined that only patients with ejection fraction > 50% were considered as having completely normal systolic function, in agreement with a recent guideline[10]. This might have contributed to the high prevalence of dysfunction in our analysis.

To better understand functional recovery after AMI, one must consider the potential mechanisms of dysfunction after infarction. After the ischemic injury, the main physiopathological mechanisms that explain ventricular dysfunction include: loss of contractile capacity dependent on the affected amount of muscle, hearts affected by other comorbidities, mechanical complications, stunned myocardium and cardiac remodeling process[4].

However, of the aforementioned mechanisms, the stunned myocardium is the one that best explains functional recovery over time[12,13]. Corroborating this hypothesis, we consider that currently, a significant number of patients with AMI are submitted to reperfusion therapy, which increases the likelihood of stunned myocardium and functional recovery[14-17]. Therefore, our study assumes that the stunned myocardium plays a crucial role in functional recovery after coronary occlusion. However, questions remain about the impact of more contemporary therapy on functional improvement and what the predictors of functional recovery are.

In the most recent study, which assessed patients from the HEART study, more than 50% of patients showed functional improvement after reperfusion and 24% had complete recovery within 2 weeks. It is important to emphasize that in this study, 65% of patients underwent thrombolytic therapy, whereas only 15% were submitted to primary angioplasty[18]. In our study, more than 65% of patients underwent primary angioplasty. However, our rate of complete functional recovery was similar to that observed in the HEART study. Thus, one can infer that our more aggressive treatment strategy had little additional impact on functional recovery of patients with AMI.

Finally, our study, in agreement with a previous one[18], suggests that infarct size is the only predictor of functional recovery, therefore being superior to functional variables. Additionally, our study suggests that CPK-MB levels < 521U/L, a simple method for assessing infarct size, could be incorporated into clinical practice to predict functional recovery in patients after anterior wall AMI with ST elevation.

Conclusion

In conclusion, our study indicates that, despite aggressive treatment, systolic ventricular dysfunction remains a frequent event after AMI with ST-segment elevation. Additionally, 25% of patients show functional recovery. Finally, infarct size is the only significant predictor of functional recovery 6 months after the acute coronary event.

Author contributions

Conception and design of the research: Zornoff LAM; Acquisition of data: Fusco DR, Cogni AL, Azevedo PS, Okoshi K, Zanati SG, Paiva SAR, Zornoff LAM; Analysis and interpretation of the data: Fusco DR, Cogni AL, Azevedo PS, Okoshi K, Zanati SG, Paiva SAR; Obtaining financing: Zornoff LAM; Statistical analysis: Zornoff LAM; Writing of the manuscript: Zornoff LAM; Critical revision of the manuscript for intellectual content: Azevedo PS, Paiva SAR, Zornoff LAM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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