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Short term (In-Hospital) outcomes of patients suffering from acute myocardial infarction in relation to presence of pre-infarction angina (Adults & Elderly)

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Abstract
Background: The mortality rate from coronary artery disease is greater in elderly than in young patients. In experimental studies, ischemic preconditioning affords an endogenous form of protection against ischemia–reperfusion injury in adult but not in senescent hearts. Angina before myocardial infarction, a clinical equivalent of experimental ischemic preconditioning, has a protective effect in adult patients. It is not known whether angina before myocardial infarction is also protective elderly patients.
Objectives: The present study examined whether angina 48 hour before acute myocardial infarction provides protection in adults and elderly patients.
Methods: This study was conducted at cardiac care unit in Ibn-Sina hospital. A case series study started at 1st of September till 31st of December 2011 involving 126 patients in two groups:
1-Patients with pre-infarction angina: (n= 68, 38 of them < 65 years old and 30 of them ≥ 65 years old).
2-Patients without pre-infarction angina: (n= 58, 35 of them < 65 years old and 23 of them ≥ 65 years old).
Results: In-hospital death was more frequent in adult patients without than in those with previous angina (11.4% vs. 2.6%; p <0.01), as were congestive heart failure or shock (11.4% vs. 2.6%; p < 0.01) and the combined end points (in-hospital death and congestive heart failure or shock) (22.8% vs. 5.2%; p < 0.0003). In contrast, the presence or absence of previous angina before acute myocardial infarction in elderly patients seems not to influence the incidence of in-hospital death (13.3% vs. 13.0%; p = 0.97), congestive heart failure or shock (16.6% vs. 13.0%; p = 0.92) and the combined end points (29.9% vs. 26.0%; p = 0.83). Analysis models for in-hospital end points show that previous angina is a positive predictor in adult but not in elderly.
Conclusions: The presence of angina before acute myocardial infarction seems to confer protection against in-hospital outcomes in adults; this effect seemed to be less obvious in elderly patients. This study suggests that the protection afforded by angina in adult patients may involve the occurrence of ischemic preconditioning, which seems to be lost in senescent hearts.

Keywords: acute mi, pre-infarction angina, in-hospital outcomes

Introduction

According to the report of the World Health Organization (WHO), coronary artery disease annually is the most important cause of death of more than 3.8 million males and 3.4 million females all over the world. Despite the optimal therapies, coronary artery disease mortality is still significantly high [1].In some studies, the existence of anginal attack before acute myocardial infarction (MI) has efficient effects on left ventricle function after acute MI, but its effects on reperfusion of coronary artery creation are unknown [2]. Many experimental laboratories have shown that brief attacks of ischemia immediately before sustained coronary occlusion significantly reduce myocardial infarct size [3], this phenomenon termed as "preconditioning". There is strong evidence that this phenomenon occurs in the heart of humans as recently reviewed [4]. Murry *et al* demonstrated it also in dogs, rats, rabbits, and pigs [5]. Recent clinical studies suggest that preconditioning could occur in patients with repetitive balloon inflations in angioplasty and with intermittent aortic cross-clamping during bypass procedures of coronary artery [6]. In addition, the experimental, as well as, clinical studies reported that myocardial ischemic preconditioning preserves the anatomic microvasculature, functional vascular reactivity, and myocyte function [7]. Preconditioning occurs in patients before acute MI is not known, but a history of previous angina or angina occurring immediately before MI (unstable angina) might serve as a "marker" for patients who have experienced a concise phase of ischemia (and therefore may have been "preconditioned") before MI [8].Death due to coronary artery disease increases progressively with age [9]. In America, 80% of deaths from coronary artery disease occur among patients ≥ 65 years. The incidence of deaths increased among elderly patients as an outcome of the reduction of the thrombolytic therapy due to a higher frequency of the complicating illness, absence of the pain on admission, and the nonspecific electrocardiographic (ECG) abnormalities [10]. Maggioni *et al*. demonstrated that age is an independent dominant predictor of mortality rates (for both in-hospital and post-discharge) in patients with a first MI who received thrombolytic therapy, and they excluded a correlation between age-related higher mortality for MI and more extensive coronary artery disease. They found that the number and degree of the critical coronary stenosis did not

differ according to age group in 20% of patients who died during the hospital period and underwent autopsy [11]. Experimental studies demonstrated that preconditioning acts through brief ischemic attacks before a prolonged coronary occlusion, to protect the heart by delaying lethal injury, including the post-ischemic electrical and mechanical dysfunction [12]. Patients with MI presenting with prodromal angina have a significantly minor infarct size [13], and a better in-hospital outcome than patients without prodromal symptoms [14].Although the presence of chronic angina before MI may be an indicator of more extensive coronary collateral circulation, our reports suggest that ischemic preconditioning (due to recent angina) has played an important task in the better prognosis of patients with acute MI [15].

Patients and Methods

From 1st of September 2011 till 31st of December 2011, patients with an acute MI were admitted to our coronary care unit; 76 were < 65 years old, and 60 were ≥ 65 years old. Patients were enrolled in our study if they had two criteria from the following:

1. Typical chest pain
2. ECG changes with the evolution of Q waves
3. Elevation of serum troponin levels.

We recorded data from the history, physical examination, laboratory results, echocardiographic variables, and the ECG. Family history was considered positive when symptomatic coronary artery disease occurred before age 60 in siblings, parents, parents' siblings, or grandparents.

Patients with documented systolic blood pressure more than 140 mm Hg and/or diastolic blood pressure more than 90 mm Hg and those taking antihypertensive drugs were regarded as hypertensive. A previous MI was diagnosed by ECG or hospital records. Other historical variables included the history of CHF (exertional dyspnea associated with either orthopnea or paroxysmal nocturnal dyspnea), the history of diabetes, hypercholesterolemia (> 200 mg/dl), and smoking. History of administration of nitrates, angiotensin-converting enzyme inhibitors, clopidogrel, beta-adrenergic blocking agents, aspirin, and the lipid-lowering agents was recorded at admission. All the patients were given thrombolytic therapy except those with complicating illness and lack of chest pain at the time of admission or presented with abnormal nonspecific ECG. The age of ≥ 65 years was not considered a contraindication for this therapy. All patients ≥ 65 years old with an acute MI were admitted to our coronary care unit regardless of functional status. Patients with an advanced illness such as cerebrovascular disease and neuropsychiatric disorders as dementia and delirium were not included in the study. In particular, among patients < 65 years old, one (1.4%) with a terminal illness and two (2.8%) with the cerebrovascular disease were excluded. Among patients ≥ 65 years old, 2 (3%) with a terminal illness, 2 (3%) with the cerebrovascular disease, and 3 (5%) with dementia were excluded.

The following ECG variables were determined:

Presence or absence of ventricular tachycardia and fibrillation; atrial fibrillation and flutter; atrial and junctional tachycardia; bundle branch block; intraventricular conduction delay; and first, second or complete heart block. We also used continuous ECG monitoring to analyze complex ventricular arrhythmias when present and defined them as frequent ventricular beats (> 1 beat/min or 60 beats/h), multiform ventricular premature beats, couplets, and ventricular tachycardia (> 3 premature ventricular beats). These ECG variables had been monitored during the full clinical course. The assays of S.troponin levels were done using blood samples taken on admission. The maximum value of the normal range in our laboratory is < 0.01 IU/L.

Major in-hospital outcomes in the coronary care unit were death, CHF, and cardiogenic shock, while the minor endpoints were the extension of infarction, continual chest pain, S.troponin level, ventricular fibrillation and tachycardia, the atrioventricular block of high grade, left ventricular dysfunction, indicated by the presence of S3 gallop, rales or radiographic evidence of pulmonary congestion or as extensive left ventricular injury in the absence of clinical heart failure. We collected a detailed clinical history for all patients. Patients who had not experienced chest pain (ischemic chest pain, exertional, central, left or right shoulder pain, jaw pain, epigastric pain or upper back pain), chest discomfort, or left arm and jaw pain 48 h before the episode leading to admission were defined as having "no previous angina." Patients showing angina lasting < 30 min 48 h before the acute MI were defined having "previous angina." Patients that had independently a history of previous angina any time 48 hours before the acute MI were labeled as "chronic angina.

Statistical analysis

Categorical data were compared with chi-square analyses. We assess the role of previous angina in death, CHF, and cardiogenic shock and the combined endpoints unadjusted and simultaneously adjusted for thrombolytic therapy, antianginal treatment and demographic variables (age, gender, family history, smoking, chronic angina, previous MI, CHF, hypertension, diabetes, and cholesterolemia). Risk or protection assessment of any parameter, done by calculating of Odd ratio (OR). The p-value of < 0.05 was considered significant.

Results

Baseline characteristics: Table (1) demonstrates frequencies of baseline characteristics of adults (< 65 years old) and elderly patients (≥ 65 years old) with acute MI and reveals that there significant difference in elderly over the adults (p-value =0.01), male gender is highly significant more affected among adults than elderly (p-value=0.0001), similarly findings regarding smoking and hypercholesterolemia (p-value=0.001) and (p-value=0.0000) respectively.

Table 1: Baseline characteristics of adults and elderly patients with acute MI.

Parameters	Adult patient (n=73)	Elderly patient (n=53)	P-value
Age	52.7 ± 9.2	74.2 ± 7.1	0.01
Male	63 (86.3%)	32 (60.3%)	0.0001
Family history	21 (28.7%)	14 (26.4%)	0.75
Chronic angina	25 (34.25%)	17 (32.1%)	0.77

Previous MI	18 (24.65%)	12 (22.6%)	0.52
Smoking	60 (82.0%)	27 (50.9%)	0.001
Hypertension	26 (35.6%)	23 (43.3%)	0.10
CHF	9 (12.3%)	7 (13.2%)	0.95
Diabetes	20 (27.3%)	16(30.1%)	0.49
Hypercholesterolemia	24 (32.85%)	7 (13.2%)	**0.000**
Nitrates	12 (16.4%)	11 (20.7%)	0.12
Beta-blockers	4 (5.4%)	2 (3.7%)	0.36
Calcium blockers	15 (20.5%)	14 (26.4%)	0.18
Aspirin and/or clopidogrel	9 (12.3%)	9 (17.05%)	0.25

In-hospital outcome: Table (2) shows the In-hospital outcomes of adult patients with or without previous angina 48 hours before acute myocardial infarction and displays that, in-hospital deaths and Congestive heart failure/shock are more frequent in the adult patients without previous history of angina (11.4%) than in those with (2.6%) with significant difference (p-value=0.01). The mean level of Troponin I with SD is (0.007 ± 0.004) in patient previous angina comparing to (0.013 ± 0.005) without, which is significant at (p-value= 0.01). LV dysfunction in patients without previous angina (22.8%) is significantly (p-value=0.04) differ from those with previous attacks (13.1%).

Table 2: In-hospital outcomes of adult patients with or without previous angina 48 hours before acute myocardial infarction.

		Previos angina		**P-value**
In-Hospital End Points		**Yes (n=38)**	**No(n=35)**	
In-hospital death		1 (2.6%)	4 (11.4%)	0.01
CHF		1 (2.6%)	4 (11.4%)	0.01
Lytic therapy		18 (47.3%)	14 (40.0%)	0.40
Time to lytic therapy	≥ 4 h	15 (39.4%)	12(34.3%)	0.85
	< 4 h	3 (7.9%)	2 (5.7%)	0.10
In-hospital reinfarction		4 (10.4%)	2 (5.7%)	0.71
Recurrent ischemic pain		5 (13.1%)	3 (8.5%)	0.36
Q wave MI		24 (63.1%)	26 (74.3%)	0.14
Troponin I		0.007 ± 0.004	0.013 ± 0.005	0.01
Ventricular fibrillation		1 (2.6%)	3 (8.5%)	0.06
Ventricular tachycardia		11 (28.9%)	13 (37.1%)	0.16
High grade AV block		2 (5.2%)	3 (8.5%)	0.37
LV dysfunction		5 (13.1%)	8 (22.8%)	0.04

Table (3) displays the frequencies of elderly patients according to presence or absence of previous angina before an acute myocardial infarction seems not to influence the occurrence of in-hospital death, and shows that the lytic therapy presents in 33.3% of elderly patients with angina against (13.0%) in patients without angina, with a very highly statistical significant difference in between (p-value=0.003). Moreover, time to lytic therapy whether ≥ 4 h or < 4 h show (23.3%) and (10.0%) of patients with previous angina in comparison with (8.6%) and (4.3%) in those without angina, with significant differences for both (p-value=0.04) and (p-value=0.01) in that order.

Table 3: In-hospital outcomes of elderly patients with or without previous angina 48 hours before acute MI.

		Previous angina		**P-value**
In-Hospital End Points		**Yes (n=30)**	**No(n=23)**	
In-hospital death		4 (13.3%)	3 (13.0%)	0.97
CHF		5 (16,6%)	3 (13.0%)	0.92
Lytic therapy		10 (33.3%)	3 (13.0%)	0.003
Time to lytic therapy	≥ 4 h	7 (23.3%)	2 (8.6%)	0.04
	< 4 h	3 (10.0%)	1 (4.3%)	0.01
In-hospital reinfarction		2 (6.6%)	2(8.6%)	0.93
Recurrent ischemic pain		4 (13.3%)	3 (13.0%)	0.59
Q wave MI		20 (16.0%)	16 (69.5%)	0.59
Troponin I		0.003 ± 0.005	0.005 ± 0.009	0.88
Ventricular fibrillation		2 (6.6%)	2 (8.6%)	0.79
Ventricular tachycardia		8 (26.4%)	7 (30.4%)	0.51
High grade AV block		4 (13.2%)	3 (13.0%)	0.92
LV dysfunction		5 (16.6%)	4 (17.2%)	0.95

Logistic regression models for death and CHF or shock Table (4) demonstrates unadjusted logistic regression models for death and CHF or shock in the adults and elderly patients as dependent variables for the protective role of a ngina 48 hours before acute MI in adults and elderly, and depicts the protective role of previous angina in adult but not in elderly patients, with (p-value= 0.01) in both.

Table 4: Unadjusted regression models for in-hospital death and CHF or shock.

	ADULT			ELDERLY		
	Chi-square	**OR (95% CI)**	**P-value**	**Chi square**	**OR(95% CI)**	**P-value**
Death	5.69	0.24 (0.07-0.81)	0.01	0.00	0.94 (0.42-2.16)	0.97
CHF or Shock	5.26	0.28 (0.09-0.86)	0.01	0.00	0.91 (0.36-2.32)	0.92

Table (5) demonstrates unadjusted logistic regression models for death and CHF or shock in the adults and elderly patients 48 hours before acute MI, and shows that, after simultaneously adjustment for thrombolytic therapy, antianginal therapy and several variables, including age, gender, family history, smoking, chronic angina, previous MI, CHF, hypertension, diabetes and cholesterolemia. Therefore, we perform analysis with simultaneous adjustment for lytic therapy, antianginal drugs and demographic variables to evaluate the protective role of angina regardless of these possible confounding variables.

Table 5: Adjusted regression models for in-hospital death and CHF or shock.

	Adult			Elderly		
	Chi-square	**OR (95% CI)**	**P-value**	**Chi-square**	**OR (95% CI)**	**P-value**
Death	9.27	0.04 (0.005-0.32)	0.002	1.48	0.49 (0.15-1.90)	0.22
CHF or Shock	4.95	0.20 (0.04-0.82)	0.02	0.00	0.42 (0.11-1.48)	0.18

Table (6) demonstrates the multivariate analysis including all variables for in-hospital mortality in adult (< 65 years old) and elderly patients (≥ 65 years old), and confirms the protective role (OR= 0.04) of previous angina in adult (p-value= 0.002), but not elderly patients, whereas only age is risky (OR= 1.17) in elderly patients (p-value= 0.001).

Table 6: Multivariate analysis including all variables for in-hospital mortality in adult and elderly patients.

		ADULT			ELDERLY	
	Chi-square	**OR (95% CI)**	**P-value**	**Chi-square**	**OR (95% CI)**	**P-value**
Previous angina	9.27	0.04 (0.005-0.32)	**0.002**	1.47	0.49 (0.15-1.56)	0.225
age	0.04	0.97 (0.90-1.06)	0.620	16.02	1.17 (1.08-1.27)	**0.001**
Chronic angina	0.07	0.80 (0.15-4.12)	0.789	0.02	1.08 0.39-2.95)	0.882
Gender	1.48	0.33 (0.05-1.93)	0.223	0.24	1.28 (0.48-3.39)	0.622
Previous MI	2.19	3.71 (0.65-21.07)	0.138	0.44	0.60 (0.13-2.67)	0.505
Thrombolytic therapy	0.10	0.77 (0.16-3.53)	0.741	0.56	0.57 (0.13-2.42)	0.452
CHF	2.98	5.28 (0.79-35.03)	0.084	0.00	0.98 (0.20-4.74)	0.982
Hypertention	2.59	5.18 (0.28-11.44)	0.107	0.01	1.07 (0.35-3.27)	0.899
DM	0.39	1.80 (0.28-5.78)	0.531	1.05	1.75 (0.60-5.10)	0.304
Family history	0.10	1.28 (0.30-6.33)	0.745	0.05	0.87 (0.28-2.72)	0.819
Smoking	0.00	1.00 (0.48-2.11)	0.986	0.97	1.42 (0.71-2.85)	0.325
Nitrates	0.14	0.62 (0.05-6.94)	0.704	0.12	0.79 (0.21-2.91)	0.718
Beta-blockers	0.06	1.47 (0.07-28.11)	0.796	0.07	0.70 (0.06-7.99)	0.777
Calcium ch. Blockers	1.35	2.81 (0.49-16.12)	0.245	0.87	1.85 (0.51-6.73)	0.350
Aspirin	0.00	1.08 (0.09-12.90)	0949	0.01	0.92 (0.27-3.22)	0.899
Cholesterol (10 mg increase)	0.70	0.95 (0.30-2.95)	0.402	0.02	0.99 (0.99-1.01)	0.882

Discussion

The current study proposed that in adult patients, previous angina 48 h before acute MI is responsible for the lower rate of in-hospital mortality, CHF or shock, and combined endpoints when judged against the patients without previous angina [16]. The protective effect of previous angina was not related to the administration of thrombolytic therapy and anti-anginal drugs and the demographic variables such as a previous MI [17]. Unexpectedly, previous angina gives the impression to lose its protective effect in elderly patients [20]. S.troponin level, number of Q wave MI, ventricular fibrillation, and left ventricular dysfunction was significantly higher in adult patients without than in those with angina before acute MI. These results display that in adult patients, the absence of angina before acute MI represents a risk factor for MI-induced electromechanical modifications.In elderly patients, Previous angina loses to various degrees its protective role [20]. The incidence of in-hospital mortality, CHF or shock, and combined endpoints were analogous in elderly with and without previous angina. S.troponin level, number of Q wave IMs, ventricular fibrillation, and left ventricular dysfunction were also like to the elderly patients with and without previous angina [21]. Results obtained from adult patients confirm published reports that previous angina plays a protective role in patients with acute MI. Patients with pre-infarction angina had enhanced survival, less heart failure, minor arrhythmias, and diminished peak of cardiac serum enzyme levels. The results of our study support the beneficial, protective role of pre-infarction angina when it is experienced during the 48 hours before acute MI. Pre-infarction angina was correlated with reduced infarct size, which is in accordance with the results of other authors [17]. Hirai *et al* [18] confirmed that the ejection fraction of the left ventricle, was higher and the abnormalities of wall motion rarer in patients with angina less than one week before acute MI than in those without angina. In addition, left ventricular performance is better in patients with a history of angina before acute MI [19, 21]. A history of angina was interrelated with fewer episodes of re-occlusion after thrombolytic therapy and a reduced

incidence of in-hospital mortality [22]. In another study [35], patients with prodromal phase of angina had a significantly lesser infarct size than those without. More in recent times, Kloner *et al*. [35] reported that previous angina has a valuable effect on in-hospital outcomes after acute MI. At last, Nakagawa *et al*. [23] reported the protective effect of anginal attacks in patients with re-perfused anterior wall MI. It is not recognized how previous angina manipulates its protective role. Experimental studies have reported that short attacks of ischemia trigger adaptive changes that protect the myocardium from the effects of a subsequent, prolonged ischemic insult. This phenomenon, now known as "ischemic preconditioning" [12, 24], has been extended to humans. Ischemic preconditioning in humans is defined as "unstable angina before acute MI, percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery with intermittent cross-clamp inflation episodes" [25]. Generation of stress protein [26, 27], prostacyclin [28], adenosine release [29], activation of adenose triphosphate–regulated K1 channels [30], and more recently, norepinephrine [31] have been involved as mediators of ischemic preconditioning. Recently demonstrated [15] that ischemic preconditioning does not take place in isolated hearts from older animals, whereas exogenous norepinephrine creates preconditioning in both adults and senescent hearts. Therefore, in the senescent heart, the lack of ischemic preconditioning may result from the absence of a mediator that activates this protective endogenous system [15]. This hypothesis agrees with studies showing a diminution of norepinephrine release from cardiac adrenergic terminals after ischemia and reperfusion in the senescent animals [32, 33]. In addition, Nitta *et al*. [34] suggested that the more susceptibility of aged hearts to ischemia may be due to damaged protective mechanisms offered by heat shock proteins. Ischemic preconditioning has been related to the induction of stress proteins [26, 27]; therefore, the age-related absence of ischemic preconditioning could be due to the reduction of heart shock protein synthesis observed in old hearts during myocardial ischemia. The absence of this endogenous mechanism may explain why the aging heart is more sensitive to electromechanical dysfunction induced by myocardial ischemia [15]. In our study, in elderly patients, the presence or absence of previous angina before an acute MI appears not to affect the rate of in-hospital mortality ($p = 0.97$), CHF, or shock ($p = 0.92$). Whereas, in adult patients, the in-hospital mortality was common among those without angina than in patients with a recent history of angina (11.4 % vs. 2.6%; p-value= 0.01). CHF or shock (11.4 % vs. 2.6%; p-value= 0.01) were more common in adult patients without than in those with previous angina before acute MI. One probability why elderly patients did not gain from pre-infarction angina is that they were less probable to have reperfusion. Kloner *et al*. [35] reported that a history of angina before a non thrombolyzed acute MI is a marker of increased risk of infarct extension, recurrent ischemic pain, and mitral regurgitation. However, spontaneous thrombolysis was correlated with a trend in the direction of minor infarct size in patients who had a history of previous angina [35]. Spontaneous thrombolysis was connected with S. troponin, which was lower in adults than in elderly patients with previous angina. However, both values were obtained within 15 h, suggesting that both adult and senescent patients had similar reperfusion. Thrombolytic therapy resulted in more rapid reperfusion and smaller infarct size in patients with an acute MI preceded by unstable angina than in those without pre-infarction angina [36]. The protective effect of previous angina could have been lost in the group of elderly patients because fewer of them received thrombolytic therapy than did adult patients. In other words, if the protective effect of pre-infarction angina is related to the rapidity of coronary reperfusion in patients receiving thrombolytic therapy, the age-related absence of angina-induced protection must be due to the decline in the quantity of elderly patients after administrating thrombolytic therapy. Previous angina appears in our logistic regression analysis, as a protective factor in adults rather than in elderly patients, even independent of thrombolytic therapy [36].

Limitations of the study

In general, data from case-series studies should be viewed with caution [37]. We established criteria for patient inclusion before studying the patient record. In addition to the biased recall of events, data obtained from hospital records may be incomplete. However, the major limitation of this study is the number of patients. The significance of our results should be considered in view of these findings. In addition, in the adjusted model, the odds ratio of death in elderly patients becomes 0.49, suggesting that there is a 50% improvement in outcome in elderly patients who have pre-infarction angina. Coronary angiography had not been performed in most of the patients, and therefore the hypothetic difference in epicardial collateral arteries between patients with and without angina was not investigated. Another limitation of this study is the quantification of ischemic episodes. Ambulatory ECG monitoring was not performed in our study cohort before acute myocardial infarction, and therefore episodes of silent ischemia, which are particularly frequent in elderly patients, were not taken into account in patient stratification.

Conclusions

Previous angina before acute MI seems to confer protection against in-hospital outcomes, such as death, CHF, or shock in adult patients, regardless of thrombolytic therapy, anti-anginal drug use, and demographic variables, such as previous myocardial infarction; this effect seemed to be less evident in elderly patients.

Recommendations

Prospective studies are needed to verify the protective role of previous angina before acute myocardial infarction and the hypothetic loss of preconditioning in elderly patients.

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