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Preinfarction Angina Protects Against Out-of-Hospital Ventricular Fibrillation in Patients With Acute Occlusion of the Left Coronary Artery

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OBJECTIVES The goal of this study was to evaluate the effect of preconditioning on out-of-hospital ventricular fibrillation (VF) in patients with acute myocardial infarction (AMI).

BACKGROUND More than half of the deaths associated with AMI occur out of the hospital and within 1 h of symptom onset. In humans, preinfarction angina (PA), which can serve as a surrogate marker for preconditioning, reduces infarct size, but the protective effect against out-of-hospital VF has not been investigated.

METHODS Preinfarction angina status and acute coronary angiographic findings of 72 consecutive patients with AMI complicated by out-of-hospital VF were compared with 144 matched controls without this complication.

RESULTS Preinfarction angina is associated with a lower risk for VF (odds ratio [OR]: 0.40, 95% confidence interval [CI]: 0.18 to 0.88). In patients with acute occlusion of the left coronary artery (LCA) (n = 136), the risk reduction is pronounced (OR: 0.25, 95% CI: 0.10 to 0.66), whereas, in patients with acute occlusion of the right coronary artery (RCA) (n = 67), the protective effect of PA on VF was not observed (OR: 2.25, 95% CI: 0.45 to 11.22). Subgroup and multivariate analyses show that the protective effect is independent of cardiovascular risk factors, preinfarction treatment with beta-adrenergic blocking agents or aspirin, the presence of collaterals or residual antegrade flow or the extent of coronary artery disease.

CONCLUSIONS Preinfarction angina protects against out-of-hospital VF in patients with acute occlusion of the LCA. This protection is independent of risk factors or coronary anatomy. A larger study is needed to examine the apparently different effect in patients with acute occlusion of the RCA. (J Am Coll Cardiol 2001;38:1369–74) © 2001 by the American College of Cardiology

When the heart is subjected to a transient nonlethal period of ischemia, it quickly adapts itself to become more resistant to infarction due to a subsequent ischemic insult. This adaptation is called preconditioning. In animal experiments, preconditioning both reduces myocardial infarct size and protects against life-threatening ventricular arrhythmias (1–4). Although protective effects of preconditioning are clearly demonstrated in humans (5), for both logistic and ethical reasons, no clinical study can meet the strict conditions of experimental studies on preconditioning with infarct size or life-threatening arrhythmias as the end point. Clinical studies on infarct size have demonstrated that preinfarction angina (PA) can serve as a "marker" for preconditioning (2,6), reduce infarct size (6–8) and protect against ventricular arrhythmias after reperfusion therapy (9). To our knowledge, the effect of preconditioning or PA against life-threatening arrhythmias during the out-of-hospital phase of acute myocardial infarction (AMI) has not been studied in humans.

The demonstration of a beneficial effect of preconditioning in humans could have several important clinical implications (5,10,11) and provide a mandate for further study of the cellular mechanisms and the translation into therapeutic strategies (2). Because the most important cause of death associated with AMI is out-of-hospital ventricular fibrillation (VF), a key question would be whether preconditioning or PA can also protect against this lethal complication.

We previously reported a large case-control study of survivors of out-of-hospital VF related to acute coronary occlusion (12). In the present study we use this patient series to test the hypothesis that PA protects against out-of-hospital VF during AMI. Since we demonstrated that patients with acute occlusion of the left coronary artery (LCA) have a significantly higher risk for out-of-hospital VF compared with patients who have acute occlusion of the right coronary artery (RCA), we also analyzed the effect of PA according to the site of occlusion.

METHODS

In De Weezenlanden Hospital, Zwolle, and in the University Hospital, Ghent, primary angioplasty is the treatment of choice for complicated and uncomplicated AMI as long as patients present within 6 h after symptom onset, have electrocardiographic criteria for AMI (presence of ST segment elevation of more than 0.1 mV in at least two adjacent leads of a 12-lead ECG or presence of a presumed new left bundle branch block) and, for AMI cases complicated by

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CAD = coronary artery disease
CI = confidence interval
IRA = infarct-related coronary artery
LCA = left coronary artery
MI = myocardial infarction
OR = odds ratio
PA = preinfarction angina
RCA = right coronary artery
VF = ventricular fibrillation

out-of-hospital VF, have a reasonable chance to survive without major neurological sequelae. Between January 1995 and December 1998, 72 survivors of out-of-hospital VF fulfilled these criteria and were candidates for primary angioplasty. Clinical and angiographic data were compared with that of 144 controls matched for age, gender, admission hospital (Gent or Zwolle) and primary or secondary admission (referred by a local community hospital after diagnosis of AMI) as previously reported (12). In summary, univariate analysis showed that patients with an acute occlusion of the LCA (left anterior descending artery or circumflex artery) had a higher risk for out-of-hospital VF compared with patients with an acute occlusion of the RCA (odds ratio [OR] and 95% confidence interval [CI], respectively, 4.82 [2.35 to 9.92] and 4.92 [2.34 to 10.39]). Multivariate analysis showed that only acute occlusion of the LCA was significantly associated with out-of-hospital VF. Flow grade in the infarct-related artery (IRA) or presence of an additional (chronic) occlusion in a non-IRA were both of borderline significance as predictors of out-of-hospital VF. In this study, we further specify preinfarction medication and medical history including family history of coronary artery disease (CAD) and history of hypertension, diabetes mellitus, hypercholesterolemia and current smoking. The timing of onset of angina before MI in relation to outcome is unknown in humans (13). In previous clinical studies, the timing ranged between 24 h and one month (8,14–18). In a prospective temporal analysis of onset of PA and its effect on outcome, angina that occurred within 24 h was more protective than PA occurring later than 24 h (13). In an experimental study, the optimal interval between ischemic preconditioning stimulus and the prolonged episode occurred between 24 h and 72 h (19). Therefore, in this study, we arbitrarily defined PA by the presence of at least one period of chest pain occurring within the 72 h preceding the AMI. Chronic angina is defined as documented symptomatic CAD or typical chest pain occurring at least one month remote from the AMI. These data were entered prospectively for the patients of De Weezenlanden Hospital (n = 150) and were retrospectively collected by reviewing the medical records for the patients of University Hospital, Ghent (n = 66).

Table 1. Clinical Characteristics of Patients With and Without Out-of-Hospital VF

	Patients With Out-of-Hospital VF (n = 66)	Patients Without Out-of-Hospital VF (n = 137)	p Value*
Men	51 (77.3%)	107 (78.1%)	1.00
Age	55.7 (± 10.2)	56.7 (± 10.3)	0.52
Family history	30 (46.9%)	63 (46.0%)	1.00
Current smoking	30 (46.9%)	65 (52.0%)	0.54
Hypertension	17 (26.2%)	30 (21.9%)	0.60
Hypercholesterolemia	11 (17.2%)	27 (20.3%)	0.70
Diabetes mellitus	5 (7.7%)	4 (2.9%)	0.15
Chronic angina	9 (13.6%)	17 (12.7%)	0.83
Preinfarction angina	9 (13.6%)	39 (28.5%)	0.02
History of MI	5 (7.6%)	11 (8.1%)	1.00
Medication before MI			
Beta-blocker	5 (7.7%)	16 (12.0%)	0.46
Aspirin	4 (6.2%)	14 (10.5%)	0.43

*According to two-tailed Fisher exact test. Data presented are number (%) of patients or mean ± SD.
MI = myocardial infarction; VF = venticular fibrillation.

Statistical analysis. Univariate analysis of categorical variables was carried out by a two-tailed Fisher exact test. Descriptive variables with a normal distribution were given by mean and SD, and means were compared using *t* test. Tests for heterogeneity of subgroups were carried out by Breslow-Day test. Multivariate analysis for prediction of out-of-hospital VF was carried out using logistic regression analysis (SPSS release 7.5).

RESULTS

Relation between PA and VF. Data on PA status were documented in 66 of the 72 patients with VF (91.6%) and in 137 of the 144 controls (95.2%). Patients with undocumented PA status were excluded from further analysis. Preinfarction angina is associated with a lower risk for VF (OR: 0.40, 95% CI: 0.18 to 0.88). Preinfarction angina was present in 13.6% of patients with VF compared with 28.5% of controls (p = 0.02) (Table 1).

Relation between PA and VF according to the site of acute coronary occlusion. In patients with acute occlusion of the LCA (n = 136), PA protected against VF (OR: 0.25, 95% CI: 0.10 to 0.66) (Fig. 1). In patients with acute occlusion of the RCA (n = 67), PA was not significantly associated with VF (OR: 2.25, 95% CI: 0.45 to 11.22). The effect of PA against VF differed significantly according to the site of occlusion (Breslow-Day test for heterogeneity: p = 0.014) (Fig. 1). Coronary history (chronic angina or prior MI) and coronary risk factors of patients with acute occlusion of the LCA were comparable to those with acute occlusion of the RCA; however, the latter were significantly older and had more preinfarction hypertension (Table 2).

Clinical characteristics and coronary anatomy of patients with PA. Preinfarction angina was not associated with the presence of risk factors, the extent of CAD (multivessel disease or jeopardy score), the history of MI or the presence

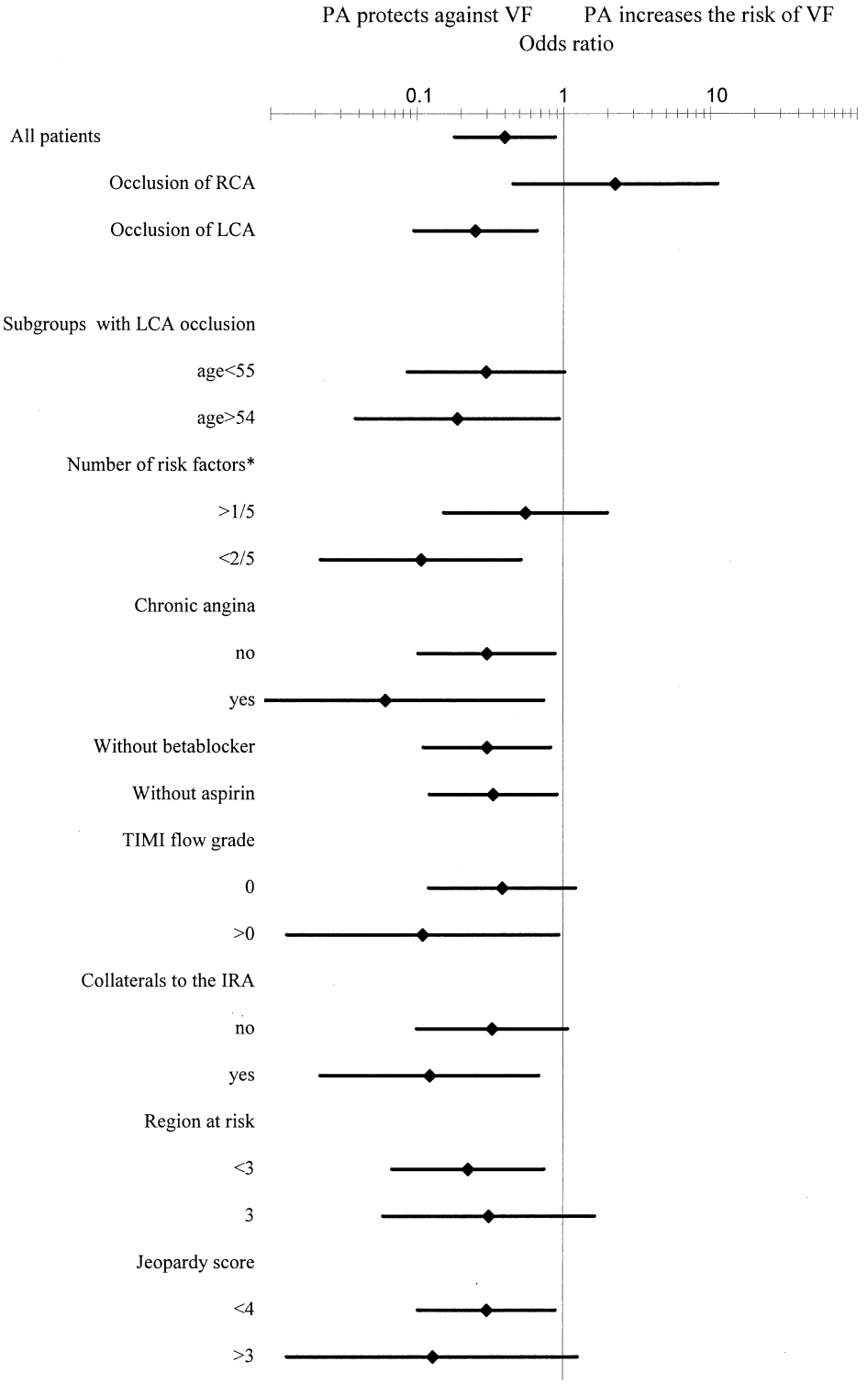

Figure 1. Graph showing on a logarithmic scale the odds ratios and 95% confidence intervals for out-of-hospital ventricular fibrillation associated with preinfarction angina in various subgroups. *Hypertension, hypercholesterolemia, diabetes mellitus, current smoking and family history. IRA = infarct-related coronary artery; LCA = left coronary artery; PA = preinfarction angina; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction; VF = ventricular fibrillation.

of chronic occlusions (Table 3). Patients with PA had more chronic angina (22.9% vs. 9.9%, p = 0.03) and used beta-adrenergic blocking agents and aspirin more frequently (respectively, 16.7% vs. 8.7% and 18.8% vs. 6.0%). The IRA of patients with PA had antegrade flow more frequently (Thrombolysis In Myocardial Infarction [TIMI] flow

Table 2. Clinical Characteristics According to Site of Acute Occlusion

	Occlusion of LCA (n = 136)	Occlusion of RCA (n = 67)	p Value*
Men	109 (80.1%)	49 (73.1%)	0.28
Age	55.1 (± 10.2)	58.9 (± 10.0)	0.01
Family history	60 (44.4%)	33 (50.0%)	0.55
Current smoking	63 (48.8%)	32 (53.3%)	0.64
Hypertension	25 (18.5%)	22 (32.8%)	0.03
Hypercholesterolemia	22 (16.8%)	16 (24.2%)	0.25
Diabetes mellitus	6 (4.4%)	3 (4.5%)	1.00
Chronic angina	18 (13.5%)	8 (11.9%)	0.83
Preinfarction angina	30 (22.1%)	18 (26.9%)	0.48
History of MI	11 (8.2%)	5 (7.5%)	1.00
Medication before MI			
Beta-blocker	11 (8.3%)	10 (15.2%)	0.15
Aspirin	12 (9.1%)	6 (9.1%)	1.00

*According to two-tailed Fisher exact test. Data presented are number (%) of patients or mean ± SD.

LCA = left coronary artery; MI = myocardial infarction; RCA = right coronary artery; VF = ventricular fibrillation.

grade > 0, p = 0.02) and had more collaterals (p = 0.04) than patients without PA (Table 3).

Relation of PA to out-of-hospital VF in subgroups of patients with occlusion of the LCA. Preinfarction angina also reduces the risk of VF in predefined subgroups of patients with occlusion of the LCA (Fig. 1). The protective effect of PA against VF is observed in patients with or without collaterals to the IRA, in patients with or without antegrade flow in the IRA, in patients with a large area at risk (region at risk = 3) and in patients with and without extensive CAD (respectively, jeopardy score >3 or <4). The protective effect was also present in patients who were not treated with beta-blockers or aspirin before the onset of MI, in patients with multiple coronary risk factors, in patients younger or older than 55 years and in patients with or without chronic angina.

Table 3. Clinical and Angiographic Characteristics of Patients With and Without Preinfarction Angina

	Patients With PA (n = 48)	Patients Without PA (n = 155)	p Value*
Men	37 (77.1%)	121 (78.1%)	0.85
Age	57.0 (± 9.9)	56.1 (± 10.4)	0.59
Family history	27 (56.3%)	66 (43.1%)	0.14
Current smoking	18 (40.9%)	77 (53.1%)	0.17
Hypertension	14 (29.2%)	33 (21.4%)	0.33
Hypercholesterolemia	13 (27.1%)	25 (16.8%)	0.14
Diabetes mellitus	2 (4.2%)	7 (4.5%)	1.00
Chronic angina	11 (22.9%)	15 (9.9%)	0.03
History of MI	4 (8.3%)	12 (7.8%)	1.00
Beta-blocker	8 (16.7%)	13 (8.7%)	0.18
Aspirin	9 (18.8%)	9 (6.0%)	0.02
Multivessel disease	23 (47.9%)	60 (38.7%)	0.31
Jeopardy score > 3	11 (22.9%)	31 (20.0%)	0.69
Chronic occlusion	10 (6.5%)	4 (8.3%)	0.75
Proximal occlusion	18 (37.5%)	58 (37.4%)	1.00
TIMI flow grade > 0	23 (47.9%)	45 (29.0%)	0.02
Collaterals	20 (41.7%)	39 (25.2%)	0.04

*According to two-tailed Fisher exact test. Data presented are number (%) of patients or mean ± SD.

MI = myocardial infarction; PA = preinfarction angina; TIMI = Thrombolysis In Myocardial Infarction; VF = ventricular fibrillation.

Multivariate analysis of the effect of PA against VF in patients with acute occlusion of the LCA. We included all clinical and angiographic variables in a multivariate model to predict VF in patients with acute occlusion of the LCA. Variables included were: PA, age, gender, chronic angina, previous MI, hypertension, diabetes mellitus, hypercholesterolemia, current smoking, family history, number of diseased vessels, jeopardy score, acute occlusion of the LAD, proximal acute occlusion, region at risk, TIMI flow grade >0 and presence of collaterals. In the model, PA was the only significant predictor of VF (adjusted OR = 0.20, p = 0.007), which demonstrates that in patients with acute occlusion of the LCA, PA has a protective effect on VF independent of the former clinical and angiographic variables.

DISCUSSION

In this case-control study, we confirm the hypothesis that PA protects against out-of-hospital VF during AMI (OR: 0.40, 95% CI: 0.18 to 0.88). Absence of PA is significantly associated with out-of-hospital VF. Moreover, we found the protective effect of PA to depend on the site of occlusion. In patients with acute occlusion of the LCA, there is a strong protective effect of PA against VF (OR: 0.25, 95% CI: 0.10 to 0.66). In patients with acute occlusion of the RCA, the effect of PA is significantly different (p = 0.014). Due to the low number of patients with VF and acute occlusion of the RCA (n = 7), a larger study is needed to specify the effect of PA in this subgroup.

Protective effect of PA against out-of-hospital VF in patients with acute occlusion of the LCA. To our knowledge, this is the first study that tests the hypothesis that PA protects against VF during the out-of-hospital phase of MI in humans. Patients with angina during 48 h preceding their AMI have lower rates of in-hospital VF after thrombolytic treatment (9,15). Previous studies have also shown a protective effect of preconditioning on the occurrence of complex ventricular premature beats during acute coronary occlusion in the setting of percutaneous transluminal coronary angioplasty (20) or during ST segment elevation in patients with variant angina (21).

Animal experiments have confirmed that preconditioning protects against VF during acute coronary occlusion (3,4,22–24). The confirmation of this protective effect during acute coronary occlusion in humans invites further research as early VF is the major cause of death in patients with AMI. The case fatality of AMI is still between 25% and 55%, the proportion of out-of-hospital death varies between 67% and 91% (inversely related to age [25]), and out-of-hospital death during AMI is mainly related to early VF (26). Moreover, at this point, preconditioning can also be simulated or inhibited by pharmacologic interventions in humans (5,11). For instance, sulphonylureas for patients

with diabetes or methylxanthines inhibit the preconditioning pathways and, therefore, could be deleterious in patients who are at risk for AMI. The increased mortality from cardiovascular causes observed in diabetic patients on sulphonylureas in the UGDP trial (27) and the worse outcome at the time of AMI (28) might be due to blockade of preconditioning. Otherwise, preconditioning mechanisms can pharmacologically be simulated by adenosine A1-receptor agonists and K^+ ATP channel openers (5).

The protective effect of PA can theoretically be mediated by preconditioning mechanisms, formation of collaterals or better preservation of antegrade flow in the IRA (5). Subgroup and multivariate analyses (Fig. 1) indicate that the protection against VF does not depend on the presence of collaterals or antegrade flow rate in the IRA. Therefore, our data strongly support animal (3,4,22–24) and human (20,21) studies in which preconditioning exerted an antiarrhythmic effect during prolonged coronary occlusion.

The effect of PA on out-of-hospital VF depends on site of occlusion. The significantly different effect of PA against VF in patients with acute occlusion of the RCA is an unexpected finding (Fig. 1 and Breslow-Day test, $p = 0.014$). It would be overly cautious to deduce from this finding that PA does not have a protective effect against out-of-hospital VF, because only seven of the 67 patients with out-of-hospital VF presented with acute occlusion of the RCA. The different effect of PA against VF in these patients (OR: 2.25, 95% CI: 0.45 to 11.22) has to be confirmed in larger studies. To our knowledge, this finding was not reported in animal experiments. One hypothesis to explain this finding is that PA attenuates the vagal reflexes associated with the occlusion of the RCA and, therefore, aborts the vagal-mediated protection against VF during acute occlusion of the RCA. Inferior-wall infarctions induce vagal reflexes more often than infarctions located at other sites (29), and vagal tone protects against VF during AMI (30–32). Brief periods of ischemia attenuate extreme autonomic reactions (33), and patients with angina have attenuated vagal tone (34) and less severe bradyarrhythmias compared with those without PA (35). Therefore, PA might abort the vagal-mediated protection against VF that specifically occurs during occlusion of the RCA. Another hypothesis to explain this finding is that there is an age-related reduction of ischemic preconditioning (36). Patients with acute occlusion of the RCA in this study are older compared with patients with acute occlusion of the LCA (58.9 vs. 55.1 years, $p = 0.01$).

Study limitations. The major limitation of retrospective studies of survivors of out-of-hospital VF is the possibility of information bias. In survivors of out-of-hospital VF, the presence of PA could be under-reported due to retrograde anamnesia or due to the possibly lower sensitivity of heteroanamnesis for the detection of PA. However, it is very unlikely, and there are no theoretical grounds that under-reporting of PA occurs significantly more frequently in VF patients with occlusion of the LCA than in VF patients with occlusion of the RCA. We found a significantly different effect according to the site of occlusion. Therefore, the lower incidence of PA in survivors of out-of-hospital VF with occlusion of the LCA cannot be attributed to under-reporting.

The second limitation is the relatively low number of patients. Although this is the largest consecutive series of survivors of out-of-hospital VF with angiography during AMI, there are too few patients to study the effect of the time interval between the last period of PA and the onset of MI and the effect of PA on out-of-hospital VF in patients with acute occlusion of the RCA.

The third limitation of this study is the potential for selection bias. Every study on out-of-hospital VF in humans with AMI is threatened by potential selection bias. The study group (out-of-hospital VF) does not include patients with VF in whom resuscitation was not successful. The control group does not include victims of AMI complicated by sudden cardiac death not related to out-of-hospital VF (asystole, severe bradyarrhythmias and electromechanical dissociation). In order to explain our first finding (PA protects against VF) by selection bias only, one had to assume that PA reduces the success rate of resuscitation for VF. To the best of our knowledge, there are no data supporting this assumption. Moreover, in our study, the presence of PA was not associated with more severe CAD (jeopardy score, number of diseased vessels) or larger region at risk for infarction. On the contrary, it was associated with more collaterals and better flow in the IRA. Therefore, the effect of selection bias on our first finding is very unlikely. In order to explain our second finding (the effect of PA against VF differs according to the site of occlusion) by selection bias only, one had to assume that PA increases the success rate of resuscitation for VF in patients with occlusion of the RCA. Although there are no data directly supporting this assumption, it is known that PA in patients with RCA occlusion protects against right ventricular infarction and is associated with lower in-hospital mortality (35). Therefore, the effect of selection bias on our second finding cannot be excluded.

Conclusions. This is the first study in humans that has addressed the effect of PA on VF during acute coronary occlusion. Preinfarction angina protects against out-of-hospital VF in patients with acute occlusion of the LCA. This protection is independent of cardiovascular risk factors, presence of collaterals or flow in the IRA or the extent of CAD. To determine the specific effects of PA in patients with acute occlusion of the RCA, a larger study is needed.

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