The Etiology of ‘Smoker’s Paradox’ in Acute Myocardial Infarction With Special Emphasis on the Association With Inflammation

Toshiro KATAYAMA,¹ MD, Yoshihiro IWASAKI,¹ MD, Naoya SAKODA,¹ MD,
and Masato YOSHIOKA,¹ MD

SUMMARY

Despite increased risk for coronary artery disease and acute myocardial infarction (AMI), prior studies have found that smokers with AMI have lower mortality rates than nonsmokers, a phenomenon often termed ‘smoker’s paradox’. The present study was designed to examine the etiology of ‘smoker’s paradox’, especially with respect to the association with inflammation.

The subjects included 528 consecutive AMI patients who were admitted within 24 hours of onset and underwent successful coronary intervention. Of the 528 subjects, 232 (44%) were smokers.

The cardiac mortality rates over a 6 month period was significantly lower in the smoking group than the nonsmoking group (3% versus 9%, $P = 0.01$). There were significantly more male patients in the smoking group, and the smoking group was significantly younger than the nonsmoking group ($P < 0.0001$). The value of high sensitivity C-reactive protein (hs-CRP) on admission and 24 hours after onset, and serum amyloid A protein (SAA) were significantly higher, and acute phase BNP was significantly lower (hs-CRP on admission 1.36 ± 1.03 mg/dL versus 0.75 ± 0.82 mg/dL, $P = 0.02$, hs-CRP at 24 hours 3.86 ± 4.32 mg/dL versus 2.90 ± 3.46 mg/dL, $P = 0.008$, SAA; 288 ± 392 μ g/dL versus 176 ± 206 μ g/dL, $P < 0.05$, BNP; 248 ± 342 pg/mL versus 444 ± 496 pg/mL, $P = 0.0002$) in the smoking group than in the nonsmoking group. The early ST-segment resolution rate was higher in the smoking group compared with the nonsmoking group (80% versus 66%, $P = 0.003$).

The reason why smokers with AMI have lower mortality rates than nonsmokers, the so-called ‘smoker’s paradox’, is believed to be because smoking induces inflammation and smokers may have less damage to microvascular function after primary percutaneous coronary intervention. (Int Heart J 2008; 49: 13-24)

Key words: Myocardial infarction, Smoking, Inflammation

EVEN though many epidemiologic studies have shown that cigarette smoking is associated with higher rates of myocardial infarction and death from coronary

From the ¹ Department of Cardiology, Nagasaki Kouseikai Hospital, Nagasaki, Japan.

Address for correspondence: Toshio Katayama, MD, Department of Cardiology, Nagasaki Kouseikai Hospital, 1-3-12 Hayama, Nagasaki, Nagasaki 852-8156, Japan.

Received for publication September 28, 2007.

Revised and accepted December 3, 2007.

artery disease,¹⁻³⁾ considerable evidence in the literature suggests that habitual cigarette smokers have lower unadjusted mortality rates following acute myocardial infarction (AMI), a phenomenon often termed 'smoker's paradox'.⁴⁻⁷⁾ Some investigators have shown that cigarette smokers, suffering an acute myocardial infarction, tend to be younger with less diffuse coronary artery disease and fewer comorbidities compared to nonsmokers and these differences have been invoked to explain many of the differences in early mortality.⁶⁻⁸⁾

On the other hand, there is now increasing evidence that acute coronary syndrome (ACS) is an inflammatory condition.⁹⁻¹¹⁾ It is likely that smoking induces inflammation, an atherogenic lipid profile, and a propensity to thrombosis, thereby promoting the development of coronary atherothrombosis. However, it is uncertain if chronic inflammation, which is provoked by smoking, plays an etiologic role in 'smoker's paradox'.

The present study was designed to examine the etiology of 'smoker's paradox', particularly its association with inflammation.

METHODS

Patient population: The study population consisted of 528 consecutive (232 smokers, 296 nonsmokers, mean age, 69 ± 10 years, range, 34-97) patients with AMI who were admitted and reperfused by primary coronary intervention (PCI) within 24 hours after onset and enrolled between January 2001 and December 2006. The study protocol was approved by the hospital ethics committee, and informed consent was obtained from each patient by one of the investigators before entry into the study. Diagnosis of AMI was made on the basis of the following criteria; (1) complaint of chest pain and/or discomfort; (2) electrocardiographic ST segment elevation of ≥ 0.1 mV in two or more limb leads, or ≥ 0.2 mV in two or more precordial leads, or new left bundle branch block; and (3) elevated total serum creatine kinase more than twice the upper limit of the normal range. We excluded patients found to have renal failure on admission (defined as serum creatinine levels > 3.0 mg/dL), and those who were former smokers and had quit within one year before admission. Of the 528 patients, 232 were current smokers and 296 were nonsmokers. We distinguished between angina pectoris occurring within 24 hours before onset of AMI from overall angina pectoris in order to take into account the existence of ischemic preconditioning. All patients were followed-up for 6 months. The endpoint of the study was a major complication during this period, such as a reinfarction, coronary artery bypass grafting (CABG) and/or target vessel revascularization (TVR), and cardiac mortality.

Definitions: Information about smoking status was obtained from the patient or a representative at the time of admission. Current smokers were considered to be

those who reported smoking cigarettes at the time of entry into the study. Non-smokers were defined as patients who had never smoked and former smokers as those who had quit over one year before admission. Former smokers who had quit within one year before admission were excluded. Restenosis was defined as 50% or more diameter stenosis at 6 months follow-up angiography. In the chronic phase, an indication for TVR or PCI to another coronary artery which had remaining significant stenosis was confirmed by symptoms, an electrocardiogram, or scintigraphic evidence of ischemia at rest or during exercise.

Treatment strategy: Following oral administration of 200 mg of aspirin and 200 mg of ticlopidine, all patients successfully underwent direct PCI therapy within 24 hours of the onset of symptoms. Our strategy for direct PCI therapy was revascularization to only an infarct related artery in acute phase. In 76 patients, conventional balloon angioplasty was deemed sufficient, while the remaining 452 all underwent coronary stent implantation. For 72 hours after reperfusion therapy, patients received intravenous administration of heparin (10,000 units/day). All patients received either an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker beginning the day after onset. The frequency of other pharmacological therapy, such as calcium-channel blockers, diuretics, β -blockers, nitrates, nicorandil, and HMG-CoA reductase inhibitors did not differ between the smoker and nonsmoker groups.

Blood sampling: Twenty-four hours after onset, blood samples were taken from all subjects while in the supine position. Brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), and serum amyloid A protein (SAA) were all assessed from the same blood samples. SAA assay by latex agglutination nephelometric immunoassay (LA-NIA) was contracted out to BML (BioMedical Laboratories) Inc. Highly sensitive C-reactive protein (hs-CRP) was evaluated on admission, and 24 hours after onset. Creatine kinase (CK) was serially determined every 4 hours after admission for a period of 3 days. The peak values of the CK levels (peak-CK) were taken to reflect infarct size.

Measurement of hemodynamics and cardiac function: Left ventriculograms were taken for all subjects, from a single-plane with a right anterior deviation of 30° at the acute (soon after recanalization) and chronic (6 ± 1 months after onset) phases to evaluate left-ventricular ejection fraction (LVEF) and the left-ventricular end-diastolic volume index (LVEDVI), using the area-length method. We excluded posterior infarctions from our evaluation because of the associated issue of inaccuracy. We also evaluated left ventricular end-diastolic pressure (LVEDP) at two separate stages. We used the Thrombolysis In Myocardial Infarction (TIMI) classification to evaluate epicardial coronary flow. On admission, we used the Killip classification to assess the severity of the patient's condition.

ECG analysis: ST-segment elevation was measured 0.08 seconds after the J

point. The sum of ST-segment elevations (Σ ST) was obtained from leads I, aVL, and V1 through V6 for left anterior descending artery occlusions and from leads II, III, aVF, V5, V6 and reciprocal ST segment depressions in V1 and V2 for right coronary artery and left circumflex artery occlusions. Σ ST was calculated from two separate 12-lead ECG recordings, one just prior to and one at the conclusion of coronary intervention. ST segment analysis was performed by a single observer blinded to the clinical data. A reduction of at least 50% in the Σ ST segment elevation between the pre- and post-PCI ECGs was considered to constitute significant ST segment resolution.

Statistical analysis: Values are expressed as the mean $\pm$ standard deviation (SD). All statistical tests were two-tailed, and a P value < 0.05 was considered to be statistically significant. The cut off points of the concentrations of cardiovascular peptides, peak hs-CRP, and peak-CK were chosen based on tertiles in the overall sample. Univariate and multivariate logistic regression analyses were performed, with the independent variables assessed including age, gender, diabetes mellitus, culprit lesion location, the number of vessels involved, Killip classification on admission ($\geq$ II, on admission), elapsed time, spontaneous recanalization, ANP, BNP, peak-hs-CRP, and peak-CK value. The odds ratios and 95% confidence intervals were also calculated.

RESULTS

The clinical characteristics and laboratory findings for the smoking group and the nonsmoking group are summarized in Table I. There were significantly more males in the smoking group (91% versus 50%, $P < 0.0001$), and the smoking group was significantly younger than the nonsmoking group (64 ± 11 years old versus 74 ± 10 years old, $P < 0.0001$). The value of high sensitivity C-reactive protein (hsCRP) on admission and 24 hours after onset, and serum amyloid A protein (SAA) were significantly higher, and acute phase BNP was significantly lower (CRP on admission 1.36 ± 1.03 mg/dL versus 0.75 ± 0.82 mg/dL, $P = 0.02$, CRP at 24 hours 3.86 ± 4.32 mg/dL versus 2.90 ± 3.46 mg/dL, $P = 0.008$, SAA; 288 ± 392 μ g/dL versus 176 ± 206 μ g/dL, $P < 0.05$, BNP; 248 ± 342 pg/mL versus 444 ± 496 pg/mL, $P = 0.0002$) in the smoking group than in the nonsmoking group.

Hemodynamic data at the time of admission are shown in Table II. There were no significant differences in heart rate and systolic blood pressure between the two groups. In terms of the clinical severity of heart failure on admission, there were no significant differences in Killip classification between the two groups.

Table III presents the coronary anatomy, electrocardiographic results, and

Table I. Baseline Patient Characteristics and Laboratory Findings

	Smoking group (n = 232)	Nonsmoking group (n = 296)	P
Age (years)	64 ± 11	74 ± 10	< 0.0001
Sex (male)	211 (91)	148 (50)	< 0.0001
Hypertension	125 (54)	172 (58)	NS
Diabetes mellitus	72 (31)	110 (37)	NS
Hyperlipidemia	100 (43)	124 (42)	NS
Family history	88 (38)	89 (30)	NS
Within 24h AP	123 (53)	139 (47)	NS
Time from onset to arrival (hours)	4.6 ± 9.5	4.8 ± 9.7	NS
Time from onset to reperfusion (hours)	5.8 ± 9.7	6.0 ± 10.1	NS
Prior MI	30 (13)	50 (17)	NS
BNP (pg/mL)	248 ± 342	444 ± 496	< 0.001
ANP (pg/mL)	47 ± 70	75 ± 80	< 0.01
Peak-CK (IU/L)	3088 ± 3111	2160 ± 2172	< 0.01
hs-CRP on admission (mg/dL)	1.36 ± 1.03	0.75 ± 0.82	0.02
hs-CRP at 24 hours since onset (mg/dL)	3.86 ± 4.32	2.90 ± 3.46	< 0.01
SAA (μg/dL)	288 ± 392	176 ± 206	< 0.05
Peak CK time from onset (hours)	12.8 ± 8.6	16.4 ± 9.6	< 0.05

(); %. Continuous values are the mean ± SD. Within 24h AP indicates existence of angina within 24 hours prior to onset of AMI; Prior MI, prior myocardial infarction; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide; Peak CK, maximum value of creatine kinase; hsCRP, high sensitivity C-reactive protein; and SAA, serum amyloid A protein.

Table II. Hemodynamic Data on Admission

	Smoking group (n = 232)	Nonsmoking group (n = 296)	P
HR (beats/min)	80 ± 22	82 ± 19	NS
Systolic BP (mmHg)	119 ± 34	122 ± 32	NS
Killip classification			NS
I	144 (62)	158 (53)	
II	44 (19)	53 (18)	
III	12 (5)	41 (14)	
IV	32 (14)	44 (15)	

(); %. Continuous values are expressed as the mean ± SD.

HR indicates heart rate; and Systolic BP, systolic blood pressure.

Other abbreviations are as shown in Table I.

left-ventricular function of the patients. There were no significant differences in terms of culprit vessel, the existence of spontaneous recanalization (TIMI II or III) before coronary angioplasty, or the rate of use of coronary stents between the two groups. However, there was a significantly lower incidence of patients with multivessel disease in the smoking group than in the nonsmoking group (38% versus 46%, $P = 0.04$). We observed significantly more patients who got TIMI 3

Table III. Coronary Anatomy and Electrocardiographic Results

	Smoking group (<i>n</i> = 232)	Nonsmoking group (<i>n</i> = 296)	<i>P</i>
Culprit vessel			NS
LMT	4 (2)	6 (2)	
LAD	109 (47)	148 (50)	
RCA	77 (33)	86 (29)	
LCx	42 (18)	56 (19)	
Spontaneous recanalization	86 (37)	107 (36)	NS
TIMI grade pre PCI			NS
TIMI 0	93 (40)	133 (45)	
TIMI I	56 (24)	53 (18)	
TIMI II	72 (31)	95 (32)	
TIMI III	11 (5)	15 (5)	
TIMI grade post PCI			0.03
TIMI 0	2 (1)	6 (2)	
TIMI I	2 (1)	9 (3)	
TIMI II	7 (3)	21 (7)	
TIMI III	221 (95)	260 (88)	
Multivessel disease	88 (38)	136 (46)	0.04
Stent use	206 (89)	246 (83)	NS
LVEDP on the acute phase (mmHg)	14 ± 7	15 ± 6	NS
LVEDVI on the acute phase (mL/m ²)	65 ± 17	67 ± 18	NS
LVEF on the acute phase (%)	52 ± 10	50 ± 12	NS
LVEF on the chronic phase (%)	58 ± 16	52 ± 12	0.02
ST resolution	186 (80)	195 (66)	0.003

(); %. Culprit vessel indicates culprit coronary artery of acute myocardial infarction; LMT, left main trunk coronary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCX, left circumflex coronary artery; TIMI, Thrombolysis in Myocardial Infarction classification; Spontaneous recanalization, existence of spontaneous recanalization (TIMI II or III); Stent use, use of coronary stenting; LVEDP, left ventricular end diastolic pressure; LVEDVI, left ventricular end diastolic volume index; LVEF, left-ventricular ejection fraction; and ST resolution, A reduction of at least 50% in the Σ ST segment elevation between the pre- and post-PCI ECGs was considered significant ST segment elevation resolution. Other abbreviations as in Table I.

flow after primary coronary angioplasty in the smoking group than in the non-smoking group (95% versus 88%, $P = 0.03$). Furthermore, in terms of ST segment elevation resolution, there were significantly more patients who showed significant ST segment resolution in the smoking group than in the nonsmoking group (80% versus 66%, $P = 0.003$). In terms of left-ventricular function, in the acute stage (soon after recanalization), there were no significant differences in LVEDP, LVEDVI, or LVEF either. In the chronic stage (6 ± 1 month after onset), however, LVEF was significantly better in the smoking group than in the non-smoking group (58 ± 16% versus 52 ± 12%, $P = 0.02$).

Major complications in the first 6 months are shown in Table IV. In terms of clinical severity, there were significantly less patients with heart failure (26% ver-

Table IV. Clinical Outcomes Over the 6-Month Follow-up Period

	Smoking group (<i>n</i> = 232)	Nonsmoking group (<i>n</i> = 296)	<i>P</i>
Cardiac rupture	5 (2)	5 (2)	NS
Subacute thrombosis	6 (3)	4 (2)	NS
Acute closure	1 (0.4)	1 (0.3)	NS
IABP use	14 (6)	18 (6)	NS
Postinfarctional angina	9 (4)	18 (6)	NS
Q wave infarction	155 (67)	204 (69)	NS
CABG	21 (9)	33 (11)	NS
VT and/or Vf	77 (33)	98 (33)	NS
Heart failure	60 (26)	118 (40)	0.01
Cardiac death	7 (3)	27 (9)	0.01

(); %. Cardiac rupture indicates patients with cardiac rupture; Subacute thrombosis, as thrombotic stent closure, which was confirmed angiographically, from 24 hours to 30 days after the procedure; Acute closure, patients with abrupt vessel closure within 24 hours after primary PCI therapy; IABP use, use of intra aortic balloon pumping; CABG, patients required coronary artery bypass grafting; VT and/or Vf, patients with ventricular tachycardia (≥ 3 consecutive beats) and/or ventricular fibrillation; Cardiogenic shock, patients with cardiogenic shock; and Heart failure, patients with heart failure, NYHA classification ≥ 2 . Other abbreviations are as shown in Table I.

Table V. Predictors of Cardiac Death by Multivariate Analysis Over the 6-Month Follow-up Period

	Odds ratio	95% C.I.	<i>P</i>
Killip class. on admission	7.5	1.7-21.2	0.006
H-peak CK	4.9	1.6-22.5	0.03
H-BNP	4.4	1.3-5.7	0.04
H-hs-CRP at 24 hours	1.5	0.9-2.0	0.07
H-age	1.4	0.8-1.8	0.07
DM	1.3	0.9-2.0	0.08
Female gender	1.2	0.6-1.8	NS
Smoker	0.7	0.4-1.5	NS

95% C.I. indicates 95% confidence interval; Killip class. on admission, Killip classification on admission; H-hs-CRP at 24 hours, hs-CRP at 24h since onset levels in the upper tertile; H-BNP, BNP levels in the upper tertile; H-Peak-CK, peak-CK levels in the upper tertile; and H-age, patients who were over 70 years old. Other abbreviations as in Tables I to IV.

sus 40%, $P < 0.05$) in the smoking group compared with the nonsmoking group. Thirty-four patients suffered mortality from cardiovascular causes during the follow-up period; heart failure was the cause in 25 cases, cardiac rupture in 5 cases,

and sudden death out of hospital in 4 cases. Only 7 of these patients were in the smoking group. This constitutes a significantly lower mortality rate for the smoker group than the nonsmoker group (3% versus 9%, $P = 0.01$).

Table V shows the predictors of cardiac death in our AMI patients during the first 6 months following onset. According to multivariate analysis, Killip classification at admission, peak-CK value, and the value of BNP were identified as independent predictors of cardiac death, however, smoking was not identified as an independent predictor.

DISCUSSION

There are large amounts of data that support the association between smoking and cardiovascular morbidity, including increased risk of myocardial infarction and sudden cardiac death,¹⁻³⁾ however, the precise mechanism by which smoking contributes to these events has not yet been established. Smoking cessation is associated with a substantial reduction in risk of all-cause mortality among patients with coronary heart disease.¹²⁾

With respect to acute myocardial infarction, however, several large clinical trials have demonstrated that smokers have a better prognosis than nonsmokers. It has been proposed that this paradox occurs because smokers who present with myocardial infarction differ with regards to the extent of coronary vessel disease and have lesions that are more thrombogenic than atherogenic.¹³⁾

Cigarette smoking is a major risk factor for ACS and there is now increasing evidence that ACS is an inflammatory disease. Current thinking suggests systemic inflammation is associated with ischemic heart diseases, including AMI.^{14,15)} Previous some studies have demonstrated that CRP, an acute phase representative protein, is associated with various complications including cardiac events in AMI.^{16,17)} SAA, also an important acute phase inflammatory protein, has an expanded dynamic range with different kinetics compared with CRP and is reported to be a more sensitive indicator of inflammation in some noncardiovascular inflammatory conditions.¹⁸⁾ When in vivo inflammation occurs, synthesis of SAA, as well as CRP, in the liver is accelerated by inflammatory cytokines. We have reported that acute-phase elevated plasma SAA concentrations, like CRP concentration,¹¹⁾ might be suggestive of a poor prognosis in patients with AMI. In this study, the value of hs-CRP on admission and 24 hours after onset, and SAA were significantly higher in the smoking group than in the nonsmoking group. It is thus possible that smoking induces inflammation, thereby promoting rupture of plaque, which is initiated by endothelial injury and dysfunction. Yasue, *et al* showed that inflammation markers, such as the blood levels of CRP, fibrinogen, and leukocytes, which are a manifestation of chronic inflammation, are elevated

in current smokers compared with subjects who have never smoked.¹⁹⁾ Furthermore, it was also reported that smokers have increased levels of several inflammatory biomarkers.^{20,21)} It is thus quite probable that smoking induces inflammation, an atherogenic lipid profile, and a propensity to thrombosis, thereby promoting the development of coronary atherothrombosis.

In previous studies, older age has been consistently regarded as the most important factor influencing the early prognosis after acute myocardial infarction.²²⁻²⁴⁾ In accordance with previous studies, we also noticed that cigarette smokers were significantly younger. In our study, the smokers were 10 years younger than the nonsmokers. This difference in age between the smokers and nonsmokers could be one of the reasons for the better prognosis for smokers.

Cigarette smokers were most likely to be males. The independent influence of gender on early mortality after AMI has been well documented. We have also previously shown that females have a significantly higher mortality.²⁵⁾ By multivariate analysis, however, female gender was not an independent predictor of cardiac mortality. Therefore, we concluded the gender difference between smokers and nonsmokers in this study did not influence survival advantage.

In this study, peak-CK time from onset was significantly earlier in the smoking group than in the nonsmoking group. Previously, we reported that the time delay to peak-CK after primary PCI in AMI patients had a close relation to damage to the microvascular circulation.²⁶⁾ In other words, AMI patients who are smokers might have less damage to the microvascular circulation compared with nonsmokers.

It was reported that smoking provoked endothelial dysfunction and precipitated agglutination of platelets.^{27,28)} It was also reported that nicotine induced coronary vasospasm. Lavi, *et al* reported that smokers had more epicardial vasoconstriction in response to intracoronary acetylcholine, and were more likely than nonsmokers to have epicardial endothelial dysfunction.²⁹⁾ That is to say, smokers have acute coronary syndrome slightly more often in spite of less atherosclerosis in the coronary arteries.

We observed significantly more patients who failed to show ST-segment resolution among the nonsmokers than smokers. Some reports^{30,31)} have suggested that the absence of early ST-segment resolution after successful primary PCI identifies patients who are less likely to benefit from the recanalization of the infarct-related artery, since these patients are likely to have sustained greater microvascular injury and consequently have less salvageable myocardium. There may indeed be a close relationship between smoking and less microvascular injury. The present results revealed the left ventricular ejection fraction (LVEF) in the chronic phase was significantly better in the smoking group. LV systolic dysfunction in the nonsmoker group may be provoked by microcirculatory dys-

function in spite of subsequent successful recanalization.

Heeschen, *et al* reported that in a mouse model of hind-limb ischemia, nicotine increased capillary and collateral growth, and enhanced tissue perfusion.³²⁾ This effect of nicotine was mediated through nicotinic acetylcholine receptors at nicotine concentrations that are pathophysiologically relevant. Ruixing, *et al* reported intramuscular administration of nicotine was capable of significantly promoting intramyocardial angiogenesis.³³⁾ Nicotine treatment increased the number of endothelial progenitor cells in the bone marrow and spleen, and increased their incorporation into the vasculature of ischemic tissue.³⁴⁾ In the short term, nicotine promotes angiogenesis and arteriogenesis in the setting of ischemia.³⁵⁾ Thus, smoking might increase collateral circulation and prevent microvascular injury after PCI therapy. This may be the reason there were significantly less patients with heart failure in the smoking group.

Our study reconfirmed that smokers with AMI have lower mortality rates than nonsmokers, the so-called 'smoker's paradox'. However, smoking was not identified as an independent predictor of cardiac survival. The etiology of 'smoker's paradox' was considered to be less damage to the microvascular function after primary coronary intervention, and smokers have a slightly higher incidence of AMI with a higher grade of inflammation, without severe coronary atherosclerosis.

Conclusion: The etiology of 'smoker's paradox', in which smokers have a better prognosis than nonsmokers in AMI, is believed to be due to less damage to microvascular function after primary coronary intervention, and smokers have a slightly higher incidence of AMI with a higher grade of inflammation, without severe coronary atherosclerosis.

REFERENCES

1. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *Br Med J* 1976; 2: 1525-36.
2. Doyle JT, Dawber TR, Kannel WB, Kinch SH, Kahn HA. The relationship of cigarette smoking to coronary heart disease. *JAMA* 1964; 190: 886-90.
3. LaCroix AZ, Lang J, Scherr P, *et al*. Smoking and mortality among older men and women in three communities. *N Eng J Med* 1991; 324: 1619-25.
4. Weisz G, Cox DA, Garcia E, *et al*. Impact of smoking status on outcomes of primary coronary intervention for acute myocardial infarction -- the smoker's paradox revisited. *Am Heart J* 2005; 150: 358-64.
5. Angeja BG, Kermgard S, Chen MS, *et al*. The smoker's paradox: insights from the angiographic substudies of the TIMI trials. *J Thromb Thrombolysis* 2002; 13: 133-9.
6. Andrikopoulos GK, Richter DJ, Dilaveris PE, *et al*. In-hospital mortality of habitual cigarette smokers after acute myocardial infarction; the "smoker's paradox" in a countrywide study. *Eur Heart J* 2001; 22: 776-84.
7. Barbash GI, Reiner J, White HD, *et al*. Evaluation of paradoxical beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: mechanism of the "smoker's paradox" from the GUSTO-I trial, with angiographic insights. Global utilization of streptokinase and tissue-plasminogen activator

- for occluded coronary arteries. *J Am Coll Cardiol* 1995; 26: 1222-9.
8. Gourlay SG, Rundle AC, Barron HV. Smoking and mortality following acute myocardial infarction: results from the National Registry of Myocardial infarction 2 (NRM1 2). *Nicotine Tob Res* 2002; 4: 101-7.
9. Berton G, Cordiano R, Palmieri R, Pianca S, Pagliara V, Palatini P. C-reactive protein in acute myocardial infarction: association with heart failure. *Am Heart J* 2003; 145: 1094-101.
10. Sano T, Tanaka A, Namba M, *et al*. C-reactive protein and lesion morphology in patients with acute myocardial infarction. *Circulation* 2003; 108: 282-5.
11. Katayama T, Nakashima H, Takagi C, *et al*. Prognostic value of serum amyloid A protein in patients with acute myocardial infarction. *Circ J* 2005; 69: 1186-91.
12. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA* 2003; 290: 86-97. (Review)
13. Barbash GI, White HD, Modan M, *et al*. Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction. Experience gleaned from the International Tissue Plasminogen Activator/Strep-tokinase Mortality Trial. *Circulation* 1993; 87: 53-8.
14. Stefanadis C, Diamantopoulos L, Dornellis J, *et al*. Heat production of atherosclerotic plaques and inflammation assessed by the acute phase proteins in acute coronary syndromes. *J Mol Cell Cardiol* 2000; 32: 43-52.
15. Kosuge M, Kimura K, Ishikawa T, *et al*. Relation between white blood cell counts and myocardial reperfusion in patients with recanalized anterior acute myocardial infarction. *Circ J* 2004; 68: 526-31.
16. Berton G, Cordiano R, Palmieri R, Pianca S, Pagliara V, Palatini P. C-reactive protein in acute myocardial infarction: association with heart failure. *Am Heart J* 2003; 145: 1094-101.
17. Sano T, Tanaka A, Namba M, *et al*. C-reactive protein and lesion morphology in patients with acute myocardial infarction. *Circulation* 2003; 108: 282-5.
18. Malle E, De Beer FC. Human serum amyloid A (SAA) protein: a prominent acute-phase reactant for clinical practice. *Eur J Clin Invest* 1996; 26: 427-35. (Review)
19. Yasue H, Hirai N, Mizuno Y, *et al*. Low-grade inflammation, thrombogenicity, and atherogenic lipid profile in cigarette smokers. *Circ J* 2006; 70: 8-13.
20. Karimi K, Sarir H, Mortaz E, *et al*. Toll-like receptor-4 mediates cigarette smoke-induced cytokine production by human macrophages. *Respir Res* 2006; 7: 66.
21. Reynolds PR, Cosio MG, Hoidal JR. Cigarette smoke-induced Egr-1 upregulates proinflammatory cytokines in pulmonary epithelial cells. *Am J Respir Cell Mol Biol* 2006; 35: 314-9.
22. Lee KL, Woodlief LH, Topol EJ, *et al*. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation* 1995; 91: 1659-68.
23. Greenland P, Reicher-Reiss H, Godbout U, Behar S. In-hospital and 1-year mortality in 1,524 women after myocardial infarction. Comparison with 4,315 men. *Circulation* 1991; 83: 484-91.
24. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. *N Eng J Med* 1999; 341: 217-25.
25. Katayama T, Iwasaki Y, Yamamoto T, *et al*. Clinical manifestations and outcome of acute myocardial infarction in young adults treated with primary coronary angioplasty. *J Cardiol* 2006; 48: 1-7. (Japanese)
26. Katayama T, Nakashima H, Takagi C, *et al*. Prognostic significance of time-delay to peak creatine kinase after direct percutaneous coronary intervention in acute myocardial infarction patients. *Int Heart J* 2005; 46: 771-81.
27. Nowak J, Murray JJ, Oates JA, FitzGerald GA. Biochemical evidence of a chronic abnormality in platelet and vascular function in healthy individuals who smoke cigarettes. *Circulation* 1987; 76: 6-14.
28. Choudhury M, Marsh JD. Myocardial infarction in young patients. *Am J Med* 1999; 107: 254-61. (Review)
29. Lavi S, Prasad A, Yang EH, *et al*. Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. *Circulation* 2007; 115: 2621-7.
30. Matetzky S, Novikov M, Gruberg L, *et al*. The significance of persistent ST elevation versus early resolution of ST segment elevation after primary PTCA. *J Am Coll Cardiol* 1999; 34: 1932-8.
31. Claeys MJ, Bosmans J, Veenstra L, Jorens P, De Raedt H, Vrints CJ. Determinants and prognostic implications of persistent ST-segment elevation after primary angioplasty for acute myocardial infarction: importance of microvascular reperfusion injury on clinical outcome. *Circulation* 1999; 99: 1972-7.

32. Heeschen C, Jang JJ, Weis M, *et al*. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. *Nat Med* 2001; 7: 833-9.
33. Ruixing Y, Qi B, Tangwei L, Jiaguan L. Effects of nicotine on angiogenesis and restenosis in a rabbit model. *Cardiology* 2007; 107: 122-31.
34. Heeschen C, Chang E, Aicher A, Cooke JP. Endothelial progenitor cells participate in nicotine-mediated angiogenesis. *J Am Coll Cardiol* 2006; 48: 2553-60.
35. Heeschen C, Weis M, Cooke JP. Nicotine promotes arteriogenesis. *J Am Coll Cardiol* 2003; 41: 489-96.