Early age of onset of unstable angina is associated with major oxidative stress

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Introduction

The process of coronary atherosclerosis (ATS) develops over several decades. Sequences of events for early atherogenesis include retention of lipoproteins in the vascular wall, that then will trigger formation of foam cells in the subintimal space[1,2]. It has been proved that the peroxidation of lipids initially trapped in the vascular wall is a critical component for the progression of early and advanced ATS in experimental models of atherosclerosis[3]. ATS in humans is associated with increased production of free radicals: particularly, an accelerated lipid peroxidation and lipoxidative aging of proteins in the vascular wall has been demonstrated in patients with ATS[4,5]. This is consistent with the result showing that younger subjects, compared to older subjects, are better protected from oxidative attacks. Early clinical onset of coronary ATS recognizes environmental and genetic factors. Because lipid abnormalities explain no more than 50% of the early and accelerated atherosclerosis, mechanisms behind this early clustering may include other environmental or genetic factors. We hypothesized that an impaired oxidative balance due to increased lipoxidative reactions and/or to reduced defenses to oxidative attacks may be associated with early coronary ATS. Therefore, aim of this study was to determine plasma levels of malondialdehyde, which is widely used as an index of oxidative damage, in a group of patients with recent onset of unstable angina (UA), separated only for age of onset of coronary symptoms. A cohort of age-matched control subjects was also enrolled. Because an increased incidence of known cardiovascular risk factors might be associated with the early onset of UA, we have also measured them in the two groups of patients.

Methods

Patients and blood sampling. A total of 40 male patients with new-onset UA (Braunwald classification class II/III) who performed coronary angiography at our center were recruited for this study. All patients had a stenosis (≥ 70%) of at least one major epicardial vessel. Patients with UA were divided into two groups: early UA group, including 20 consecutive patients with UA of age < 56 years at the time of the diagnosis; and late UA group, that included 20 patients of age > 64 years at the time of the diagnosis. Exclusion criteria included presence of diabetes mellitus and of other chronic comorbidities (cancer, chronic renal failure, etc.) likely to affect the measurements. Twenty control subjects, without overt history of ischemic heart disease, were also selected for the study.

Peripheral venous blood samples in the fasting state were taken at the time of hospital (patients) and outpatient cardiac clinic (controls) admission. Blood samples were collected in EDTA tubes, centrifuged at 3000 g for 15 min at room temperature within 1 hour of collection; plasma was then stored at -80°C until analysis.

Biochemical determinations. Plasma levels of malondialdehyde, a product of lipid peroxidation, was determined by high-performance liquid chromatography assay following the method of Young and Trimble[6].

Plasma fibrinogen (Clauss), von Willebrand factor and total number of white cells were measured by an automated analyzer.

Total cholesterol, and HDL cholesterol levels were measured enzymatically with commercial kits (Boehringer Mannheim Italia, Monza-MI, Italy) with an automated analyzer (Boehringer Mannheim Diagnostics/Hitachi 704 Italia, Monza-MI, Italy). LDL cholesterol was calculated using the formula: LDL cholesterol = total cholesterol - HDL cholesterol - triglycerides/5, according to the formula of Friedewald[7].

Statistical analysis. Data are reported as the mean ± standard error. Comparisons among the three groups were made using ANOVA (Statview 4, Abacus Concepts, Berkeley, CA, USA) on an IBM computer. A p value < 0.05 was considered statistically significant.

Results

Table I shows the clinical characteristics of the two groups of the patients and of the control subjects. The number of subjects having hypertension, hyperlipidemia, family history of vascular disease and who were active smokers was similar between the two groups of patients with UA.

Plasma levels of malondialdehyde were significantly higher in patients with UA than in controls (1.50 ± 0.07 vs 1.1 ± 0.04 nmol/ml, p < 0.001; Fig. 1). In addition, malondialdehyde levels in patients with early-onset UA were higher than those of patients with late-onset UA (1.63 ± 0.09 vs 1.34 ± 0.07, p < 0.05; Fig. 2).

Compared with controls, patients with UA had lower HDL cholesterol levels and higher plasma values of fibrinogen. Moreover, white blood counts were significantly higher in early-onset UA patients compared to controls, while von Willebrand factor was significantly more elevated in early than in late-onset UA patients. Plasma levels of total cholesterol in early-onset UA patients and in control subjects were very similar, but in late-onset UA patients they were significantly lower than in control subjects, probably reflecting the contribution of drugs (statins).

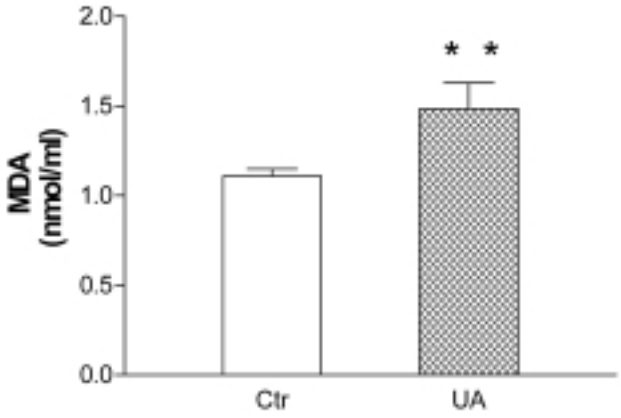

Figure 1. *Plasma levels of malondialdehyde (MDA) in controls (Ctr) and in patients with unstable angina (UA). ** = p < 0.001 vs controls.*

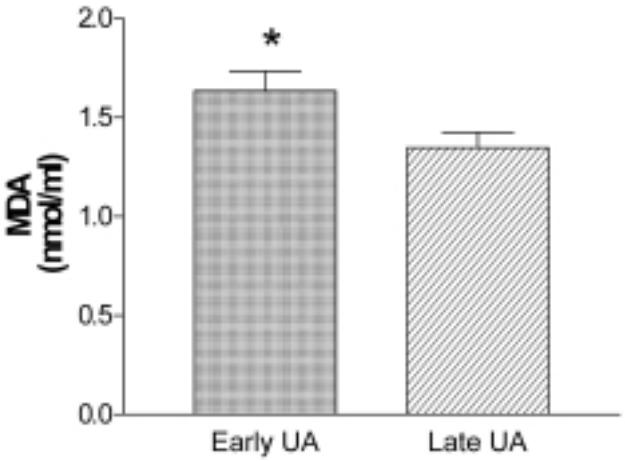

Figure 2. *Plasma levels of MDA in patients with early-onset UA and in patients with late-onset UA. Abbreviations as in figure 1. * = p < 0.05 vs late-onset UA.*

Table I. Clinical characteristics of the study patients.

	Early UA	Late UA	Controls
BMI (kg/m^2)	27.2 ± 0.7	27.2 ± 0.7	25.5 ± 0.6
Total cholesterol (mg/dl)	203.6 ± 14.2	191.2 ± 9.1*	221.3 ± 10.8
HDL (mg/dl)	38.8 ± 1.9*	38.8 ± 1.5*	43.8 ± 1.9
LDL (mg/dl)	131.2 ± 10.6	132.9 ± 9.1	153.8 ± 9.4
von Willebrand factor (%)	143.3 ± 20.7**	191.3 ± 38.2	120.4 ± 16.8
Fibrinogen (mg/ml)	401.7 ± 30.4*	402.0 ± 23.1*	317.5 ± 16.4
Total WBC (10^3/μl)	7.85 ± 4.19*	7.01 ± 3.79	6.17 ± 2.76
Current smokers (%)	56	56	31
Family history of ATS (%)	31	23	18
Hyperlipidemia (%)	87	62	57
History of hypertension (%)	69	56	47

ATS = atherosclerosis; BMI = body mass index; UA = unstable angina; WBC = white blood cell count. * = p < 0.05 vs controls; ** = p < 0.05 vs late UA.

Discussion

The present study shows a strong association between plasma levels of lipid peroxidation and coronary artery disease.

Moreover plasma levels of malondialdehyde were significantly higher in the early-onset UA group than in the late-onset UA group. A key feature of our observations is the similar prevalence of most of the risk factors for ATS between patients with early and patients with late-onset UA.

Taken together these data seems to imply a free radical excess in early UA patients not buffered by defense systems, results that are particularly surprising since oxidative damage accumulates during aging. Impaired oxidative balance in young patients with UA is more likely to be due to genetic factors than to environmental or lifestyle factors. We suggest that a genetic predisposition to generate free radicals or to determine a lower antioxidant protection may be responsible for the link between early onset of coronary ATS and increased oxidative damage in these patients. Accordingly, we are developing studies to identify genes predisposing to early ATS in patients with ischemic heart disease.

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