ELSEVIER

International Journal of Cardiology 110 (2006) 415 – 416

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Letter to the Editor

# Elevated hydroperoxide levels as a prognostic predictor of mortality in a cohort of patients with cardiovascular disease

Cristina Vassalle *, Claudio Boni, Pietro Di Cecco, Patrizia Landi

*CNR Institute of Clinical Physiology, Pisa, Italy*

Received 11 August 2005; accepted 20 August 2005
Available online 15 November 2005

**Abstract**

The aim of this study was to evaluate whether hydroperoxide levels, an index of oxidative stress, predict cardiac and total death in patients with cardiovascular disease.

Serum hydroperoxide levels were measured in 157 consecutive inpatients, followed during a mean follow-up of 20 ± 0.3 months.

Elevated oxidative stress resulted in an independent predictors for cardiac death, suggesting that hydroperoxide evaluation could provide an adjunctive estimate in the evaluation of prognosis in the cardiovascular clinical setting.
© 2005 Elsevier Ireland Ltd. All rights reserved.

*Keywords:* Hydroperoxide; Oxidative stress; Cardiovascular disease

Oxidative stress has been involved as a crucial factor in the pathogenesis and development of a variety of chronic and degenerative diseases, including aging, cancer and cardiovascular disease. Moreover, disorders tightly associated to the atherosclerotic process, such as diabetes, hypertension and dyslipidemia, have all been related with elevated oxidative stress [1]. However, only few data on prognostic impact of elevated oxidative stress in the clinical outcome of cardiovascular patients are available.

Accordingly, the aim of this study was to evaluate the value of serum hydroperoxides, as index of oxidative stress, for prediction of cardiac and total death, in an initial cohort of 166 consecutive cardiovascular inpatients, investigated in a clinical cardiology setting.

At the time of the blood sampling, all subjects gave a complete history which included cardiovascular risk factors such as smoking habits, hypertension, diabetes and dyslipidemia. No patient was receiving vitamins and/or antioxidant therapies.

Venous blood samples were collected and immediately centrifuged (3000×*g* for 10 min). After adding butylated hydroxytoluene (5 mmol/l), serum samples were stored at −80 °C for less than 2 weeks before hydroperoxide measurements by using D-Roms test (Diacron, Italy) [2]. Intra- and inter-run coefficient of variation (%CV) resulted always <6%.

Data were expressed as mean ± S.E.M. Statistical analysis performed included Student's *t* test, $\chi^2$ test, (Statview statistical package, version 5.0.1, SAS Institute). Statistical analysis also included Kaplan–Meier survival curves and Cox proportional hazard models. Differences between survival curves were compared with the log-rank test. A $p$ value $\leq 0.05$ was considered statistically significant.

Follow-up (cardiac-related death, total mortality and nonfatal myocardial infarction) was available in 157 patients (94%; 112 were males, age = 66 ± 1 years) at a mean duration of 20 ± 0.3 months, accounting for total 15 events, which included 7 non-cardiac-related deaths and 8 deaths attributed to cardiac cause. When patients were divided into two groups, subsets according to 75th percentile of hydroperoxides which correspond 482.6 AU (group A if hydroperoxides <75th percentile and B if >75th percentile), total mortality account for 8 death (6.7%) in group A and 7

* Corresponding author. Istituto di Fisiologia Clinica, Area di ricerca CNR, Via Moruzzi 1, I-56124, Pisa, Italy. Tel.: +39 050 3152199; fax: +39 050 3152166.

*E-mail address:* cristina.vassalle@ifc.cnr.it (C. Vassalle).

0167-5273/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2005.08.046

(18.4%) in group B ($\chi^2=4.6$, $p=0.03$). When considering cardiac mortality, there were 2 deaths (1.7%) in patients from group A and 6 (15.8%) from group B ($\chi^2=11.8$, $p=0.0006$). Kaplan–Meier survival estimates for cardiac and total mortality are reported in Fig. 1.

Variables that predicted univariate risk were entered into Cox regression analysis, thus indicating that ejection fraction <40% and hydroperoxides >75th percentile were independent predictors for cardiac death (Table 1).

The principal finding of this study is that hydroperoxides are strongly and independently associated with cardiac mortality, incremental to other already known prognostic parameters. Previous data indicate that oxidative DNA damage and repair markedly increased in human atherosclerotic plaques [3]. Accordingly, we have evidenced elevated levels of oxidative DNA damage in patients with angiographically documented coronary artery disease (CAD) [4]. Moreover, we and others have demonstrated that isoprostanes, markers of lipid peroxidation, and reduced antioxidant capacity are related to increased risk for cardiovascular disease and correlated with the number of cardiovascular risk factors [5,6]. Other evidences indicate that thiobarbituric acid-reactive substances (TBARS, lipid peroxidation indicators) levels correlated with endothelial dysfunction and coronary artery disease [7,8]. In addition, a recent study, conducted in a large cohort of patients with stable CAD, indicate that TBARS levels represent strong and independent prognostic predictors of cardiovascular events [9]. All these data jointly support the hypothesis of a major role for markers of oxidative stress in the atherosclerotic process, and provide evidence as how their evaluation might help in the prediction of the risk for cardiovascular events, suggesting that the estimate of hydroperoxides might represent an adjunctive prognostic parameter and a possible target of pharmacological treatments to positively influence the progression of the cardiovascular disease.

Table 1
Multivariate Cox predictive model of cardiac and total mortality

| | Cardiac mortality | | | Total mortality | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% CI | *p* | Odds ratio | 95% CI | *p* |
| Age | | | | 1.1 | 1.0–1.2 | 0.09 |
| Prior infarction | 1.66 | 0.5–9.1 | 0.56 | 1.6 | 0.5–5.2 | 0.42 |
| Hydroperoxides (75th percentile) | 8.6 | 1.5–50.2 | 0.016 | 2.8 | 0.8–9.3 | 0.1 |
| Ejection fraction <40% | 5 | 1–25.9 | 0.05 | 3.4 | 1.1–11.2 | 0.036 |
| Diabetes | 2.4 | 0.5–9 | 0.55 | 2.3 | 0.7–7.6 | 0.11 |

CI=confidence interval.

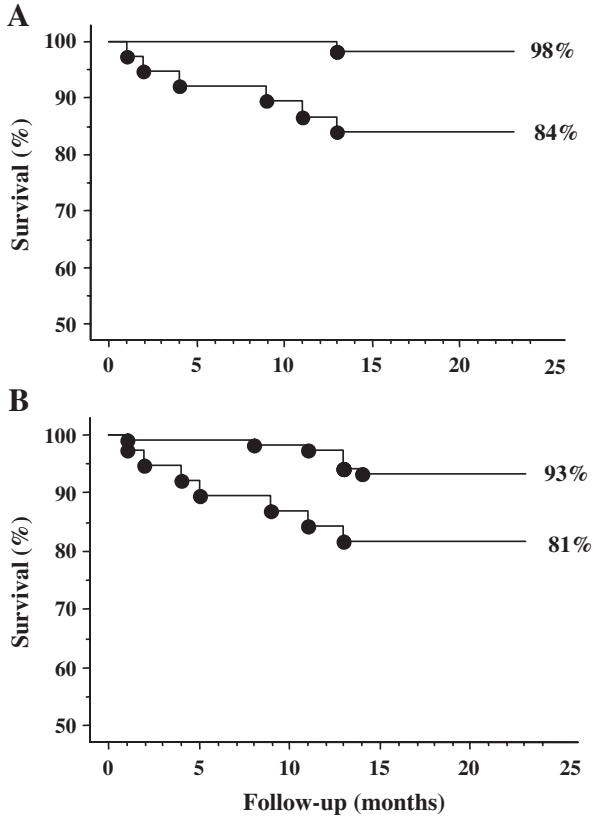


Fig. 1. Kaplan–Meier survival curves according to 75th hydroperoxide percentiles, considering cardiac death (A) and total mortality (B) as end points.

## References

[1] Madamanchi NR, Vendrov A, Runge MS. Oxidative stress and vascular disease. Arterioscler Thromb Vasc Biol 2005;25:29–38.
[2] Cornelli U, Terranova R, Luca S, Cornelli M, Alberti A. Bioavailability and antioxidant activity of some food supplements in men and women using the D-Roms test as a marker of oxidative stress. J Nutr 2001;131:3208–11.
[3] Martinet W, Knaapen MWM, De Meyer GRY, Herman AG, Kockx MM. Elevated levels of oxidative DNA damage and DNA repair enzymes in human atherosclerotic plaques. Circulation 2002;106:927–32.
[4] Botto N, Masetti S, Petrozzi L, Vassalle C, Manfredi S, Andreassi MG. Elevated levels of oxidative DNA damage in patients with coronary artery disease. Coron Artery Dis 2002;13:269–74.
[5] Vassalle C, Petrozzi L, Botto N, Andreassi MG, Zucchelli GC. Oxidative stress and its association with coronary artery disease and different atherogenic risk factors. J Intern Med 2004;256:308–15.
[6] Schwedhelm E, Bartling A, Lenzen H, et al. Urinary 8-*iso*-prostaglandin $F_{2\alpha}$ as a risk marker in patients with coronary heart disease: a matched case-control study. Circulation 2004;109:843–8.
[7] Sakuma N, Hibino T, Sato T, et al. Levels of thiobarbituric acid-reactive substance in plasma from coronary artery disease patients. Clin Biochem 1997;30:505–7.
[8] Penny WF, Ben-Yehuda O, Kuroe K, et al. Improvement of coronary artery endothelial dysfunction with lipid-lowering therapy: heterogeneity of segmental response and correlation with plasma-oxidized low density lipoprotein. J Am Coll Cardiol 2001;37:766–74.
[9] Walter MF, Jacob RF, Jeffers B, et al. PREVENT Study. Serum levels of thiobarbituric acid reactive substances predict cardiovascular events in patients with stable coronary artery disease: a longitudinal analysis of the PREVENT study. J Am Coll Cardiol 2004;44:1996–2002.