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Anesthetic Propofol Enhances Plasma γ-Tocopherol Levels in Patients Undergoing Cardiac Surgery

Viviana Cavalca, Ph.D., Susanna Colli, Ph.D.,† Fabrizio Veglia, Ph.D.,‡ Sonia Eligini, Ph.D.,§ Lorenzo Zingaro, Ph.D.,‖ Isabella Squellerio, Ph.D.,‖ Nicola Rondello, M.D.,# Giuliana Cighetti, Ph.D.,** Elena Tremoli, Ph.D.,†† Erminio Sisillo, M.D.‡‡*

Background: **Propofol (2,6-diisopropylphenol) is an anesthetic drug with antioxidant and antiinflammatory properties, documented both *in vitro* and in experimental models of ischemia–reperfusion injury and septic shock. These properties have been related to the similarity of its chemical structure to that of endogenous tocopherols, which are phenol-containing radical scavengers. This study evaluated the effects of propofol on α- and γ-tocopherol (α- and γ-T) levels and on selected markers of oxidant–antioxidant and inflammatory status in patients undergoing cardiac surgery.**

Methods: **Patients were randomly assigned for anesthesia with either propofol (propofol group, n = 22) or sevoflurane (control group, n = 21). Plasma levels of α- and γ-T, individual antioxidant capacity, malondialdehyde, and interleukin 10 were measured before, during, and after anesthesia. In addition, levels of the proinflammatory prostaglandin E_2 as a marker of cyclooxygenase-2 activity and those of interleukin 10 were measured in whole blood cultured with bacterial lipopolysaccharide.**

Results: **γ-T levels increased significantly during surgery in propofol group ($P < 0.0001$ *vs.* control group). By contrast, α-T similarly decreased in both groups. Malondialdehyde and interleukin 10 increased markedly and individual antioxidant capacity decreased, without differences between groups. Prostaglandin E_2 levels measured 24 h after anesthesia induction were significantly lower in the propofol than in the control group. *In vitro* studies highlighted the different capacity of γ- and α-T to impair prostaglandin E_2 synthesis by human monocytes challenged with bacterial lipopolysaccharide.**

Conclusions: **The antiinflammatory properties of propofol that may be linked to its effect on γ-T levels could be relevant in controlling the inflammatory response that accompanies tissue injury during reperfusion.**

PROPOFOL (2,6-diisopropylphenol) is an anesthetic drug widely used intravenously in surgical procedures.[1] Several studies, both *in vitro* and in animal models, have reported for this drug a scavenging activity against a broad range of free radicals, including peroxynitrite.[2–4] Whether this effect applies in patients is still controversial.[3] The antioxidant profile of propofol has been related to its chemical structure, which is similar to that of phenol-based scavengers such as the endogenous tocopherols.[5] α-Tocopherol (α-T), the major isoform in the tocopherol pool in human plasma, is the main lipid-soluble chain-breaking antioxidant preventing lipid peroxidation in biologic membranes.[6] Conversely, γ-tocopherol (γ-T) is far more active than α-T in quenching peroxynitrite,[7–9] which plays a critical role in cell or tissue damage associated with inflammation, shock, and ischemia–reperfusion injury.[10] Moreover, γ-T, unlike α-T, reduces proinflammatory eicosanoids through inhibition of cyclooxygenase (COX)-2 activity, *in vitro* and *in vivo*, in animal models of inflammation.[11,12]

Besides its antioxidant properties, propofol has antiinflammatory effects.[13] At clinically relevant concentrations, it impairs neutrophil and macrophage functions[14–16] and reduces the levels of proinflammatory cytokines *in vitro*[17] and *in vivo*, in experimental models of inflammation[18,19] and in patients undergoing coronary artery bypass grafting.[20,21] In addition, it increases the levels of the antiinflammatory and immune regulatory cytokine interleukin (IL)-10 when added *in vitro* in cultured human whole blood (WB).[22]

Ischemia–reperfusion oxidative injury occurs during cardiac surgery requiring an on-pump procedure. Increased production of reactive oxygen species can rapidly overcome endogenous antioxidant defenses and cause membrane injury and mitochondrial dysfunction.[23–27] Higher levels of proinflammatory cytokines, *e.g.*, IL-6 and IL-8, also contribute to organ dysfunction and morbidity,[28] whereas an increase of IL-10 is thought to counterbalance the effect of proinflammatory cytokines.[29] Moreover, *in vivo* data indicate that endogenous IL-10 is an important regulator of eicosanoid production in response to bacterial lipopolysaccharide.[30]

Propofol has been shown to reduce the levels of proinflammatory cytokines in patients undergoing coronary artery bypass grafting,[20,21] but whether this anesthetic drug influences the oxidant–antioxidant balance and other inflammatory components of myocardial reperfusion injury in patients undergoing cardiac surgery is unknown.

This study was designed to evaluate the effect of propofol, at doses used to induce and maintain anesthesia, on the plasma oxidant–antioxidant profile and on the inflammatory status in patients undergoing cardiac surgery. In addition, the mechanism by which propofol

* Assistant Professor, Institute of Cardiology, ‡ Temporary Professor, Unit of Biostatistics, ‖ Research Fellow, Laboratory of Cellular Biology and Biochemistry of Atherothrombosis, # Resident in Anesthesiology and Intensive Care Unit, ‡‡ Chief of Anesthesiology and Intensive Care Unit, Centro Cardiologico Monzino, Istituto di Ricovero e Cura a Carattere Scientifico (I.R.C.C.S.), University of Milan. † Associate Professor, § Assistant Professor, †† Full Professor, Department of Pharmacological Sciences, University of Milan. ** Full Professor, Department of Preclinic Sciences, Laboratorio Interdisciplinare di Tecnologie Avanzate, Vialba, University of Milan.

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Address correspondence to Dr. Cavalca: Institute of Cardiology, Centro Cardiologico Monzino I.R.C.C.S., Via Parea, 4–20138 Milan, Italy. viviana.cavalca@unimi.it.

exerts its antiinflammatory effect has been explored by *in vitro* studies in human adherent monocytes.

Materials and Methods

All chemicals were obtained from Sigma Chemical Co. (Milan, Italy) if not otherwise specified. Propofol was administered using a commercially available target-controlled infusion system (Diprifusor; AstraZeneca S.p.A, Milan, Italy).

Patients and Study Design

Patients scheduled to undergo elective cardiac surgery with cardiopulmonary bypass (CPB) were enrolled in this prospective, randomized, controlled study after approval from the institutional review board (Centro Cardiologico Monzino, Milan, Italy) and written informed consent. Inclusion criteria were stable angina, left ventricular ejection fraction greater than 40%, and age 60–80 yr. Exclusion criteria were aortic valve stenosis, angina on arrival in the operating room, and acute myocardial infarction during the past 7 days. Preanesthetic medication included morphine (0.1 mg/kg) and atropine (0.07 mg/kg), administered intramuscularly 1 h before surgery. Intravenous cefazolin (30 mg/kg) was administered before instrumentation. Monitoring was performed by five-lead electrocardiography with continuous ST-segment analysis (leads II and V5), radial artery catheter, pulse oximetry, and triple-lumen catheter or pulmonary artery catheter (Swan-Ganz) inserted through the right internal jugular vein. Patients were assigned to one of two groups by means of a random computer-generated list. Anesthesiologists were unaware of the due treatment until the morning of surgery, after patient enrollment. In the propofol group, anesthesia was induced by propofol and remifentanil, simultaneously administered according to a target-controlled infusion protocol (2.5–4 μg/ml propofol, 10–12 ng/ml remifentanil). Anesthesia was maintained with propofol (1.5 μg/ml) and remifentanil (8–12 ng/ml), decreasing to 1.2 and 4 ng/ml, respectively, during CPB. In the control group, anesthesia was induced by thiopental (4–6 mg/kg) and maintained with inhalation of sevoflurane (1–2%) in an oxygen–air mixture and remifentanil (8–12 ng/ml, target-controlled infusion) for the entire procedure, with the exception of CPB, during which midazolam (50–100 $\mu g \cdot kg^{-1} \cdot h^{-1}$) was administered intravenously and remifentanil was reduced (4 ng/ml). During the procedure, the control group also received the propofol vehicle (100 ml Intralipid®; Fresenius Kabi Italia S.r.l., Verona, Italy), because it contains tocopherols. In both groups, tracheal intubation was facilitated by succinylcholine (0.1 mg/kg) and pancuronium (0.1 mg/kg). Lungs were ventilated at normocapnia in an air–oxygen mixture (fraction of inspired oxygen [F_{IO_2}] = 0.5). Patients received 300 U/kg heparin before cannulation, and activated clotting time was kept above 450 s during the extracorporeal procedure. CPB was performed with a roller or centrifugal pump and a hollow-fiber oxygenator in mild hypothermia (32°–34°C). The circuit was primed with 1.0 l Normosol® (Abbott Laboratories, North Chicago, IL), 5% glucose (500 ml), 18% sodium bicarbonate solution (100 ml), and 18% mannitol solution (100 ml), given just before the opening of the aortic cross clamp. Blood flow in the bypass was titrated to ensure a mean arterial blood pressure between 55 and 75 mmHg (at least 2.4 $l \cdot min^{-1} \cdot m^{-2}$). Additional boluses of norepinephrine and nitroglycerin were used to maintain the pressure within the range. Hematocrit was kept between 18% and 25%. The myocardium was protected by administration of cold antegrade and retrograde multidose blood cardioplegia. At the end of the procedure, all patients received an intravenous bolus of morphine (0.1 mg/kg) and were transferred to the intensive care unit without reversal of muscle relaxation. Here, both groups were ventilated in mandatory minute ventilation (Dräger Evita 4; Drägerwerk AG & Co., Lübeck, Germany) and extubated when they fulfilled the following criteria: adequate response to verbal stimuli, body temperature greater than 36°C, blood loss less than 100 ml/h, hemodynamic stability, respiratory rate between 10 and 15 breaths/min, partial pressure of carbon dioxide less than 45 mmHg, and arterial oxygen saturation greater than 96% with an F_{IO_2} of 0.5. Postoperative analgesia was obtained by remifentanil perfusion (0.1–0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) until extubation, and with tramadol if required (visual analog score >3).

Blood Sampling

Blood was collected from the radial artery into pyrogen-free EDTA before induction of anesthesia (T_0, baseline), 30 min after the beginning of CPB (T_1), after protamine administration and on-pump weaning (T_2), at arrival in the intensive care unit (T_3), and 24 h after anesthesia induction (T_4). Plasma was obtained by centrifugation at 4°C and stored at −80°C until analysis. For studies with cultured WB, additional blood samples from a subgroup of patients (14 in propofol group and 15 in control group) were collected in heparin at T_0 and T_4.

Whole Blood Experiments

Aliquots of WB were cultured for 24 h at 37°C with or without 10 μg/ml bacterial lipopolysaccharide (*Escherichia coli* 0111:B4). Acetylsalicylic acid (30 μM) was added to samples to prevent COX-1 activity. After centrifugation (700*g* for 15 min), prostaglandin E_2 (PGE_2) and IL-10 levels were determined by commercially available enzyme immunoassays (Prostaglandin E_2 EIA Kit-Monoclonal; Cayman Chemical, Spi-bio, Montigny le Bretonneux, France, and Endogen Human IL-10 ELISA Kit; Pierce Bio-

technology Inc., Rockford, IL, respectively). All samples were determined in duplicate.

Peripheral Blood Mononuclear Leukocyte Isolation and Monocyte Culture

Peripheral blood mononuclear leukocytes (PBMLs) were isolated by density gradient centrifugation over Ficoll-Paque (Amersham Biosciences Europe GmbH, Milan, Italy), as previously described,[31] from aliquots of blood collected in heparin at T_0 and T_4 from a randomly selected subgroup of 11 patients. After isolation, PBMLs were rinsed with phosphate-buffered saline supplemented with 0.5% bovine serum albumin and 2 mM EDTA and were counted. The pellet was stored at −20°C until analysis. For *in vitro* studies, PBMLs obtained from venous blood of healthy donors were suspended in medium-199 supplemented with 10% human AB serum (5×10^6/ml) and plated in tissue culture dishes for 90 min at 37°C.[32] Adherent cells were 85–90% monocytes, as determined by nonspecific esterase staining. Monocytes were incubated for 18 h with α- or γ-T, dissolved in ethanol. Lipopolysaccharide (100 ng/ml) was then added, and incubation was continued for further 24 h. For the evaluation of COX-2 activity in terms of PGE_2 synthesis, monocytes were washed and incubated for 30 min in Hank's buffer (pH 7.4) containing 1 mg/ml bovine serum albumin and 10 μM arachidonic acid. Adherent monocytes were then harvested in lysis buffer, pH 6.8, and Western blot analysis was performed as described.[32]

Determination of α- and γ-Tocopherol Levels

α-Tocopherol and γ-T concentrations were measured by high-performance liquid chromatography.[33] Plasma samples and PBMLs, resuspended in lysis buffer, were extracted with organic solvents, injected into a Discovery C18 reversed-phase column (250 × 4.6 mm, 5 μm; Supelco/Sigma-Aldrich, Bellefonte, PA), and eluted with methanol (100%), as mobile phase.

Determination of Malondialdehyde

Plasma total malondialdehyde was detected by high-performance liquid chromatography with a method modified from Carbonneau *et al.* [34] Briefly, plasma (200 μl) was subjected to alkaline hydrolysis (1 M NaOH, pH 13) at 60°C for 1 h. After acidification (2 M $HClO_4$, pH 1) and centrifugation (13,000*g* for 10 min), supernatants were treated with 2-thiobarbituric acid (0.2% wt/vol) for 1 h at 100°C. After cooling, the samples were centrifuged at 13,000*g* for 10 min. Supernatants were injected into XBridge C18 reversed-phase column (150 × 4.6 mm, 5 μm; Waters Co., Milan, Italy) and eluted with 10 mM phosphate buffer (30% MeOH, pH 7), as mobile phase, at a flow rate of 1 ml/min. Malondialdehyde levels were measured by a fluorometer (Jasko FP1520; Tokyo, Japan: λ_{Ex} 515 nm, λ_{Em} 553 nm). The peak areas were integrated using commercial software (EZStart; ESA Biosciences, Chelmsford, MA). The sample concentrations were calculated from calibration curves using 1,1,3,3-tetraethoxypropane as standard. Calibration of the analytical procedure gave a linear signal over the malondialdehyde range of 0.25–4 μM ($r = 0.9992$), with a quantification and detection limits of 0.15 and 0.05 μM, respectively. The intraassay and interassay coefficient of variations were 2.4% and 9.2%.

Measurement of Individual Antioxidant Capacity

Plasma individual antioxidant capacity (IAC), a parameter that provides a measure of the overall protection against oxidative damage, was measured by a commercially available spectrophotometric assay (OXY-Adsorbent Test Diacron®; Diacron International, Grosseto, Italy). Samples were tested for their capacity to neutralize massive oxidation by hypochlorous acid, and IAC values were determined by reading the absorbance at 505 nm.

Measurement of Interleukin 10

Interleukin-10 levels were determined in plasma by a commercially available enzyme immunoassay, as described for WB experiments. All samples were determined in duplicate.

Statistical Analysis

Sample size was calculated from a pilot study on the primary outcome (effect of propofol on γ-T levels in patients who underwent cardiac surgery). Twenty-one subjects per group allowed a 90% statistical power to detect a between-group difference of 0.15 μg/ml in peak levels of γ-T, with an α error of 0.05. Results are expressed as mean ± SD, unless otherwise stated. Variables whose distribution was markedly skewed (IL-10 levels, both in plasma and in WB, PGE_2 levels in WB, European System for Cardiac Operative Risk Evaluation [EuroSCORE], duration of intubation, and blood loss) were $\log_{10}$ transformed before analyses. All other variables were nearly normally distributed.

Baseline data were compared between the two groups by Student *t* test or Fisher exact test, when appropriate. To minimize the intersubject variability, individual variations of analytes in plasma, during and after surgery, were analyzed as delta *versus* baseline. However, absolute values were also analyzed to check the consistency of the results. The time course of the analytes was compared between groups by a repeated-measures analysis of covariance with a group × time factorial design. The group effect, the time effect, and the group × time interaction were assessed. As *post hoc* analyses, we tested the within-group difference of each time point *versus* baseline, controlling for multiple testing by the Bonferroni method. The association between PGE_2 production and γ-T was assessed by the Pearson correlation on log-transformed data. The *in vitro* effect of increasing doses of α- or γ-T on PGE_2 synthesis by monocytes was

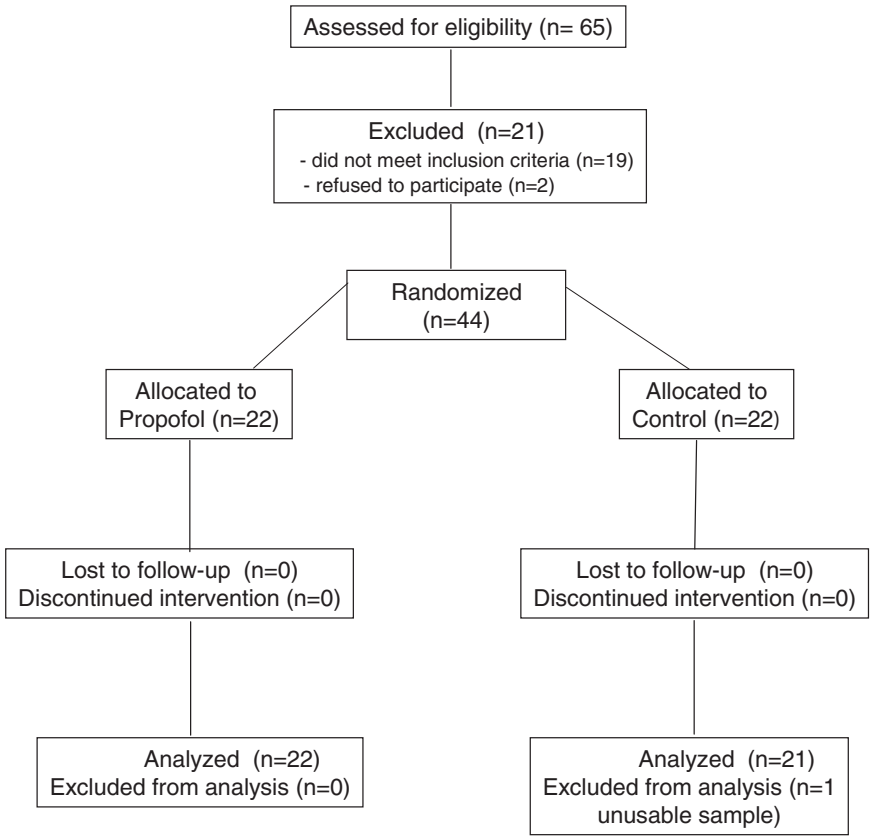

Fig. 1. Diagram showing the flow of patients undergoing cardiac surgery through each stage of the randomized trial.

assessed by analysis of covariance with isoform (α- or γ-T) × concentration factorial design. The different effect of the two isoforms was assessed by testing the isoform × concentration interaction. Analyses were performed using SAS statistical package version 8.2 (SAS Institute, Cary, NC). All *P* values reported are two-sided and are considered statistically significant at less than 0.05.

Results

Characteristics of the Patients

Sixty-five patients undergoing cardiac surgery were assessed for eligibility (fig. 1). Two patients refused to participate and 19 did not meet the inclusion criteria. After randomization, the baseline blood sample from one patient was unusable, and therefore, it was excluded from data analysis. Patients assigned to the propofol or control group were comparable for age, body mass index, risk factors, and type of surgical procedures (table 1). A nonsignificant imbalance was observed for sex distribution. The biochemical values in plasma did not significantly differ between the two groups (table 2). The two treated groups were also comparable for PGE_2 and IL-10 levels measured in WB cultured with or without lipopolysaccharide for 24 h (table 3). Changes in blood cellular profile assessed at baseline and 24 h after anesthesia induction were similar in the two groups

Table 1. Demographic and Clinical Characteristics of the Patients

	Propofol, n = 22	Controls, n = 21	*P* Value
Age, yr	67.7 ± 7.4	65.2 ± 10.7	0.29
Men, n (%)	10 (48)	18 (78)	0.06
BMI, kg/m^2	24.6 ± 3.3	25.6 ± 2.8	0.35
Hypertension, n (%)	13 (52)	15 (65)	0.82
Diabetes, n (%)	2 (10)	4 (19)	0.45
Hypercholesterolemia, n (%)	18 (86)	18 (78)	0.37
Creatinine, mg/dl	1.0 ± 0.3	1.0 ± 0.2	1
Ejection fraction, %	60.6 ± 7.1	61.1 ± 8.1	0.87
EuroSCORE	4 (3–6)*	4 (0–5)*	0.75†
NYHA I/II, n (%)	20	20	1.0‡
NYHA III/IV, n (%)	2	1	
Previous MI, n (%)	2	5	0.24‡
COPD, n (%)	2	4	0.41‡
Type of surgery			
Aortic valve + ascending aorta replacement	1	2	0.35‡
Coronary artery bypass graft	14	16	
Aortic + mitral valve replacement	0	1	
Mitral valve replacement	6	2	
Myxoma excision	1	0	

Values are mean ± SD. The two groups were compared by two-sample *t* test.

* Values are median (interquartile range). † Data were log transformed before analysis. ‡ Data were compared by Fisher exact test.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction; NYHA = New York Heart Association Classification.

Table 2. Patients' Biochemical Values in Plasma at Baseline

	Propofol, n = 22	Controls, n = 21	*P* Value
Malondialdehyde, nmol/ml	1.38 ± 0.41	1.30 ± 0.20	0.53
IAC, μmol HClO/ml	300 ± 52.9	271 ± 39.9	0.06
α-T, μg/ml	12.1 ± 2.5	11.6 ± 2.1	0.49
γ-T, μg/ml	0.26 ± 0.1	0.29 ± 0.1	0.39
IL-10, pg/ml*	46.3 (30.6–59.8)	33.0 (25.3–119.2)	0.9†

Values are mean ± SD. The two groups were compared by two-sample *t* test.

* Values are median (interquartile range). † Data were log transformed before analysis.

α-T = α-tocopherol; γ-T = γ-tocopherol; IAC = individual antioxidant capacity; IL-10 = interleukin 10.

Table 4. Perioperative and Postoperative Clinical Outcomes

	Propofol, n = 22	Controls, n = 21	*P* Value
Surgery time, h	4.7 ± 1.5	4.7 ± 0.9	0.9
Cross clamp time, min	84 ± 55.0	77.1 ± 27.6	0.69
CPB time, min	108.9 ± 64	107.3 ± 30	0.69
Intubation time, h*	6 (5–7)	7 (6–12)	0.05†
Total blood loss, ml*	615 (410–840)	600 (400–830)	0.87†
ICU stay, days	2.3 ± 1.3	2.1 ± 0.5	0.86
Deaths, n	0	0	—
Major complications,‡ n	0	0	—

Values are means ± SD. The two groups were compared by two-sample *t* test.

* Values are median (interquartile range). † Data were log transformed before analysis. ‡ Acute respiratory distress syndrome, myocardial infarction, cerebral accidents, cardiogenic or septic shock.

— = No test performed; CPB = cardiopulmonary bypass; ICU = intensive care unit.

(*P* = 0.22, 0.34, and 0.67 for leukocytes, erythrocytes, and platelets, respectively). No significant differences between the two groups were found in the perioperative course or in the outcomes, except for a borderline statistical difference in the time of intubation (table 4). No patients died or experienced major complications (myocardial infarction, acute respiratory distress syndrome, cerebral accidents, or cardiogenic or septic shock; table 4).

Time Course of α- and γ-Tocopherol Levels

The α- and γ-T levels in plasma measured before (T_0), during (T_1, T_2), and after surgery (T_3, T_4) are shown in figures 2A and B. α-T levels decreased significantly in both groups 30 min after ischemia induction and on pump start (T_1), and remained low during and after surgery (T_2, T_3) and the first postoperative day (T_4). No significant difference between groups was observed (fig. 2A). In contrast, the two groups differed markedly in γ-T levels, which progressively and significantly increased in the propofol group, returning to basal values 24 h after surgery (fig. 2B). In the control group, γ-T levels remained roughly unchanged during and after surgery.

Because an association between sex and tocopherol levels have been reported,[33] the time course of tocopherols was reanalyzed, after adjusting for sex, to control for the excess of women in the propofol group. Similar results for the treatment effects were obtained ($F = 0.72$, $P = 0.40$ for α-T and $F = 41.4$, $P \leq 0.0001$ for γ-T).

γ-Tocopherol levels measured at T_4 in PBMLs from a subgroup of patients were higher in the propofol group (1.42 ± 0.72 ng/10^3 PBMLs [mean ± SD], n = 4 in propofol group and 0.67 ± 0.37, n = 7 in control group; $P = 0.045$). An analogous significant difference between groups was not observed in α-T levels (7.15 ± 6.52 ng/10^3 PBMLs in propofol group and 5.00 ± 4.23 ng/10^3 PBMLs in control group; $P = 0.51$). The small sample size, however, limits the statistical power of this comparison.

Time Course of Oxidant–Antioxidant Balance

The different effect of the two anesthesia regimens on γ-T levels in plasma was not mirrored by changes in the oxidative status (figs. 2C and D). Measurement of malondialdehyde, as an index of lipid peroxidation, showed no appreciable difference between the two groups of treatment. Malondialdehyde levels markedly increased during surgery with a progressive decline after ischemia induction and on-pump beginning (T_1) in both groups (fig. 2C). As a reflection of the increase in malondialdehyde, IAC levels significantly declined during surgery, again with no difference between the two groups (fig. 2B). After surgery, IAC levels remained lower than at baseline, although a trend toward baseline values was detected (fig. 2D).

Table 3. Prostaglandin E_2 and Interleukin-10 Levels at Baseline in Whole Blood Cultured with or without Bacterial Lipopolysaccharide

	Propofol, n = 14	Controls, n = 15	*P* Value
IL-10, pg/ml	26.1 (20.4–66.9)	29.1 (14.1–57.8)	0.24
Lipopolysaccharide-induced IL-10, pg/ml	757 (707–790)	727 (700–757)	0.92
PGE_2, ng/ml	0.12 (0.03–0.63)	0.16 (0.09–1.64)	0.36
Lipopolysaccharide-induced PGE_2, ng/ml	24.8 (20.3–38.8)	23.7 (18.9–41.3)	0.92

Values are expressed as median (interquartile range). The two groups were compared by two-sample *t* test. Data were log transformed before analysis. Lipopolysaccharide = 10 μg/ml.

IL-10 = interleukin 10; PGE_2 = prostaglandin E_2.

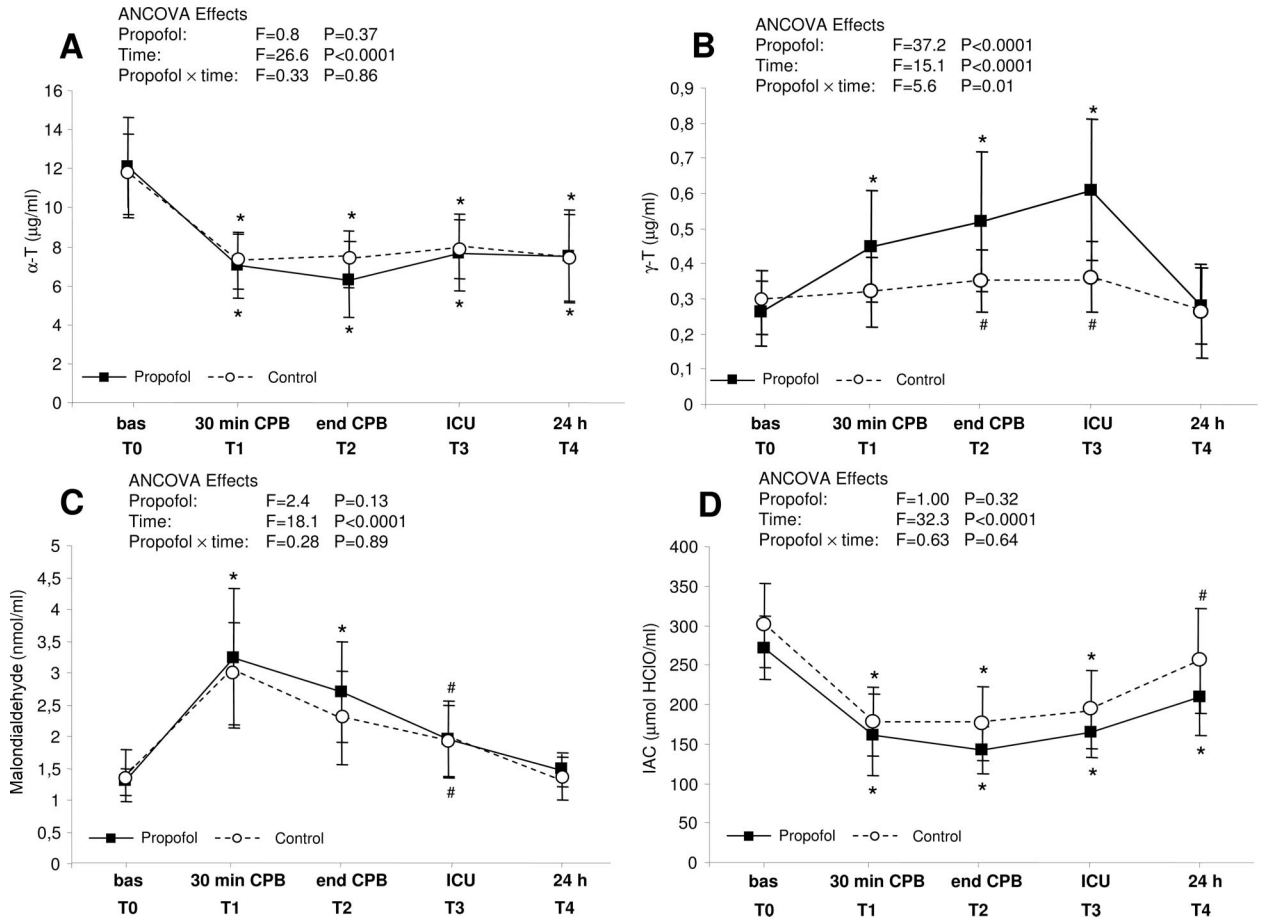

Fig. 2. Time course of α-tocopherol (α-T; *A*), γ- tocopherol (γ-T; *B*), malondialdehyde (*C*), and individual antioxidant capacity (IAC; *D*) plasma levels, during and after surgery. Blood was collected before induction of anesthesia (bas, T_0), 30 min after the beginning of cardiopulmonary bypass (30 min CPB, T_1), after protamine administration and on-pump weaning (end CPB, T_2), at arrival in the intensive care unit (ICU, T_3), and 24 h after anesthesia induction (24 h, T_4). Data are mean and SD. * $P < 0.001$ and # $P < 0.05$ *versus* baseline, after controlling for multiple testing. Data were analyzed as delta values *versus* baseline and compared between the two anesthesia regimens by repeated-measures analysis of covariance (ANCOVA) with a group × time factorial design.

Time Course of Interleukin-10 Levels

Changes of plasma IL-10 levels in the propofol and control groups before, during, and after surgery are shown in figure 3. IL-10 increased during surgery, with no significant difference between groups. A complete return to baseline values was observed at T_4.

The time courses of α- and γ-T, malondialdehyde, IAC, and IL-10 were also analyzed using actual instead of delta values, and superimposable results were obtained: Specifically, the effect of propofol on γ-T levels was associated with a *P* value of 0.005.

Prostaglandin E_2 and Interleukin-10 Production in Whole Blood Cultured Ex Vivo

Prostaglandin E_2 production, as an index of COX-2 activity, was measured in WB collected at T_0 and T_4 and then cultured for 24 h either in the absence or in the presence of 10 μg/ml lipopolysaccharide. The reduction of lipopolysaccharide-induced PGE_2 production, relative to preoperative levels, was significantly more marked in the propofol group than in the control group (fig. 4A). In contrast, no significant difference between groups was detected when IL-10 levels were measured in the same experimental system (fig. 4B).

Of interest, significant negative correlations between PGE_2 production induced by lipopolysaccharide in WB at T_4 and γ-T levels were found, both in plasma at the end of surgery (T_3; $r = -0.44$, $P = 0.04$) and in PBMLs ($r = -0.65$, $P = 0.04$).

Different Effects of α- and γ-Tocopherol on Prostaglandin E_2 Synthesis in Human Adherent Monocytes

To assess the effect of α- and γ-T on COX-2 activity, we performed *in vitro* experiments (n = 10) on adherent monocytes exposed to lipopolysaccharide (100 ng/ml) in the presence or absence of α- or γ-T. Lipopolysaccharide markedly increased PGE_2 synthesis from 0.30 ± 0.34 to 4.8 ± 1.2 ng/ml. The increase was dependent on COX-2 induction (figs. 5A and B). γ-T, preincubated with monocytes for 18 h before lipopolysaccharide addition,

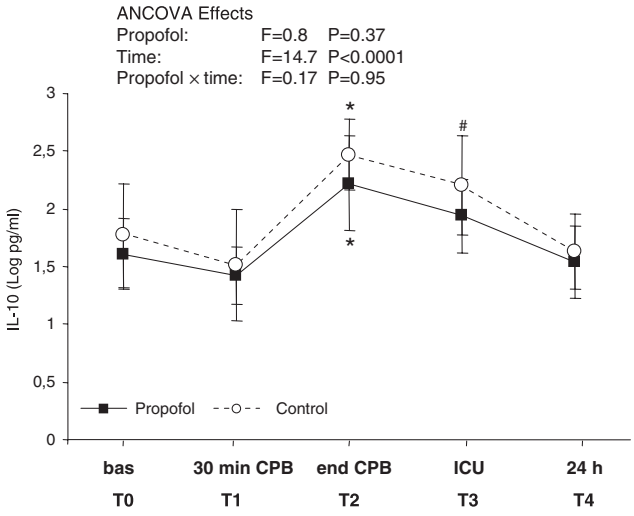

Fig. 3. Time course of log_{10}-transformed plasma interleukin-10 (IL-10) levels during and after surgery. Blood was collected before induction of anesthesia (bas, T_0), 30 min after the beginning of cardiopulmonary bypass (30 min CPB, T_1), after protamine administration and on-pump weaning (end CPB, T_2), at arrival in the intensive care unit (ICU, T_3), and 24 h after anesthesia induction (24 h, T_4). Data are mean and SD. * $P < 0.001$ and # $P < 0.05$ *versus* baseline, after controlling for multiple testing. Data were analyzed as delta values *versus* baseline and compared between the two anesthesia regimens by repeated-measures analysis of covariance (ANCOVA) with a group × time factorial design.

concentration-dependently reduced PGE_2 levels (fig. 5A), without affecting COX-2 expression (fig. 5B). The effect of the same concentrations of α-T on COX-2 activity was less apparent (fig. 5A): The slopes of COX-2 activity inhibition *versus* tocopherol concentration were significantly different for the α- and γ-T isoforms ($P = 0.016$ for the interaction term).

Discussion

This study shows, for the first time, that propofol selectively enhances the levels of γ-T in the plasma of patients undergoing cardiac surgery and that this effect may account for the reduction of PGE_2 synthesis observed in their WB cultured with lipopolysaccharide. This finding is reinforced by the *in vitro* observation that γ-T inhibits lipopolysaccharide-induced PGE_2 synthesis in human adherent monocytes.

The increase of γ-T after propofol infusion observed in this study is in accordance with data obtained in animal models of ischemia–reperfusion and septic shock.[35,36] The comparison with control patients, who received the vehicle only, ruled out the possibility that this increase was dependent on the tocopherol content of the propofol vehicle.[37]

γ-Tocopherol was still raised in mononuclear leukocytes 1 day after the induction of anesthesia, which suggests that these cells may represent a suitable compartment for γ-T accumulation, as already observed for other tissues.[12,38] This feature may account for the lower PGE_2 levels observed in cultured WB from propofol patients 1 day after the intervention. The antiinflammatory effect of γ-T observed *ex vivo* is supported by the results obtained *in vitro*, in adherent monocytes. In these cells, in agreement to what has been shown in murine macrophages and Caco2 cells,[11,39] γ-T counter-

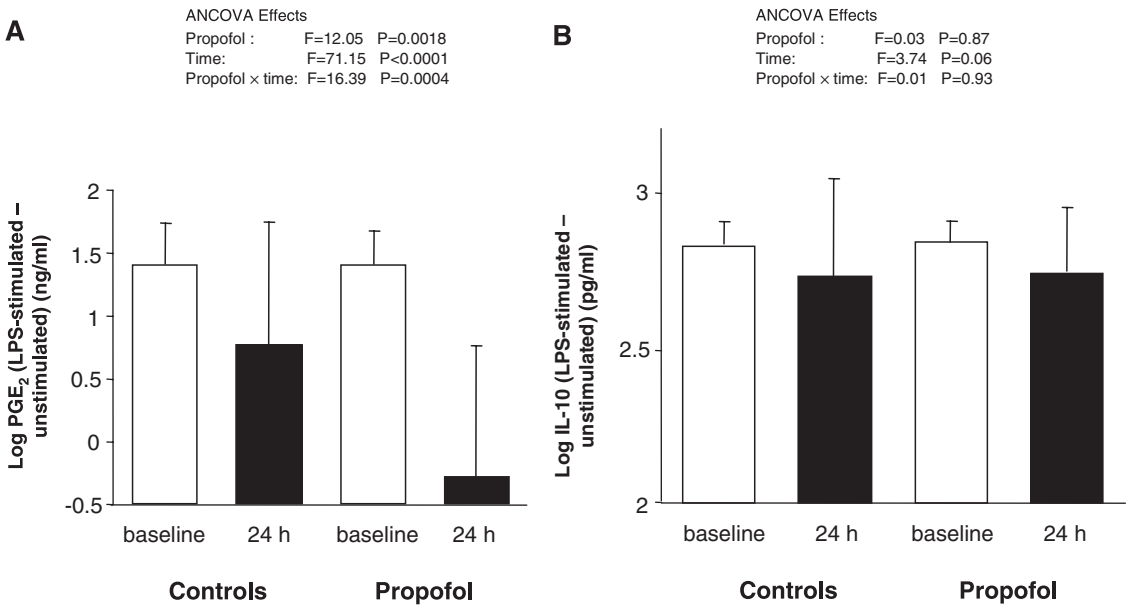

Fig. 4. Effect of the two anesthesia regimens on *ex vivo* prostaglandin E_2 (PGE_2; *A*) and interleukin-10 (IL-10; *B*) production by lipopolysaccharide (LPS)–stimulated whole blood. Blood was collected at baseline (*empty columns*) and 24 h after anesthesia induction (*black columns*), and cultured for 24 h either in the absence or in the presence of 10 μg/ml bacterial lipopolysaccharide. Data are mean and SD, expressed as log-transformed values of LPS-stimulated samples subtracted from that of unstimulated samples. Data were compared between the two anesthesia regimens by repeated-measures analysis of covariance (ANCOVA) with a group × time factorial design.

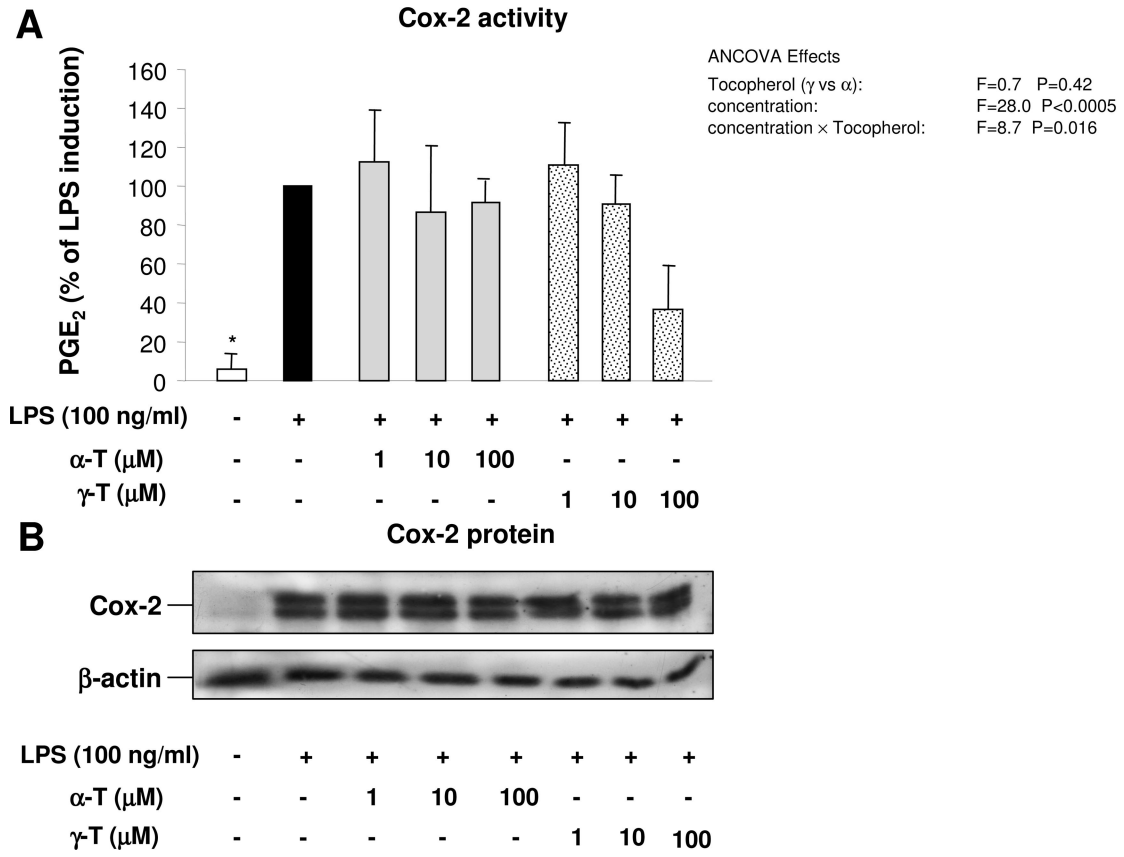

Fig. 5. Different effect of α-tocopherol (α-T) and γ-tocopherol (γ-T) on cyclooxygenase-2 (COX-2) activity (*A*) and protein expression (*B*) in lipopolysaccharide (LPS)–stimulated human adherent monocytes. Monocytes were incubated with different concentrations of α- or γ-T for 18 h and subsequently challenged with bacterial lipopolysaccharide for 24 h. Prostaglandin E_2 (PGE_2) levels were determined in monocyte incubation medium after the addition of arachidonic acid. Results are expressed as mean ± SD of 10 experiments performed with different monocyte cultures. * $P = 0.004$ *versus* LPS. Data were compared between the two tocopherol isoforms regimens by analysis of covariance (ANCOVA) with a concentration × isoform factorial design (*A*). COX-2 protein levels determined by Western blot. β-Actin was used as internal standard for control of protein load. Blots are representative of three different experiments performed with different monocyte cultures (*B*).

acts the synthesis of PGE_2 mediated by COX-2 induction. γ-T acts posttranscriptionally on COX-2 activity, leaving COX-2 protein levels unaltered, as already reported for other cell types.[39]

Plasma levels of malondialdehyde, a marker of peroxidative stress, sharply increased 30 min after the beginning of bypass surgery, reflecting the switch of reactive oxygen species and isoprostane production during ischemia–reperfusion.[24,26] Along with the increased pro-oxidant status, antioxidant defenses declined, as shown by the time course levels of IAC, an index of the overall protection against oxidative damage. The elevation of systemic malondialdehyde and the decrease of IAC levels during bypass surgery were similar under the two anesthesia regimens, despite the selective and marked increase of γ-T occurring in the propofol group. Therefore, our findings do not support a greater antioxidant effect of propofol, at the doses used in this study, with respect to the control treatment. We cannot, however, exclude the possibility that propofol infused at higher doses for a longer time period would exert an antioxidant effect, as reported by others.[21,40]

Of interest, γ-T is characterized by selective antioxidant properties that are not shared by α-T and that may result in distinct biologic effects.[7] Although the biologic or clinical significance of our findings is far to be clear (indeed our study was not powered to assess differences in clinical outcomes), indications exist that a walnut diet, resulting in increased γ-T levels, improves endothelium-dependent vasodilation in hypercholesterolemic patients[41] and in healthy subjects.[42] In addition, a 6-week supplementation of γ-T (800 mg/day), resulting in doubled plasma levels of γ-T (similarly to what observed in propofol treated patients), reduced biomarkers of inflammation, *i.e.*, plasma C-reactive protein and urine nitrotyrosine, in subjects with metabolic syndrome.[43]

Our data show that IL-10 levels increase in plasma during surgery, as observed in patients undergoing elective major surgery and coronary artery bypass graft surgery.[44,45] The increase of IL-10 may be due to a counterregulatory response to the proinflammatory status

induced during and after the surgical intervention. Increased levels of proinflammatory cytokines such as tumor necrosis factor α, IL-6, and IL-8 play a key role in the inflammatory cascade that follows cardiac surgery and that can lead to adverse perioperative events,[46] whereas antiinflammatory cytokines such as IL-10 significantly limit these complications.[47] It has been reported that propofol reduces the release of proinflammatory cytokines both *in vitro*[48] and in patients undergoing abdominal and coronary artery bypass graft surgery.[20,49] With respect to control anesthesia, propofol did not significantly suppress the increase of plasma IL-10 during surgery or affect its production in lipopolysaccharide-cultured WB, an experimental condition in which the synthesis of PGE_2 is, conversely, markedly reduced. This finding suggests that propofol, by increasing γ-T levels in cells, selectively targets the proinflammatory PGE_2, sparing the capacity of WB to synthesize IL-10. The positive effect of propofol on the balance between antiinflammatory and proinflammatory cytokines has been highlighted also in surgical settings that do not require CPB and that, therefore, are not associated with ischemia–reperfusion injury.[50–52]

The increased γ-T levels observed in the propofol group could be attributed to the interaction of propofol with CYP3A4, for propofol is mostly eliminated by CYP3A4-mediated catabolism,[53] and tocopherols are metabolized by side-chain ω-oxidation and consecutive β-oxidation through a CYP3A-dependent mechanism.[54,55] The selective effect of propofol on γ-T levels may be explained by the different turnover and metabolic rates of the two tocopherol isoforms, possibly related to their chemical structure.[55,56]

It should be mentioned that potential limitations may have affected the results of our study. Basic hemodynamic parameters could not be measured continuously in all patients because, according to the clinical practice of our institution, only selected patients had a Swan-Ganz catheter in place. Therefore, the influence of these parameters on γ-T or other analytes cannot be excluded. In addition, differences in anesthetic regimens other than propofol may have affected γ-T levels. To our knowledge, however, a specific effect of any of the drugs administered in the control treatment on γ-T has never been documented. Although a protective effect of sevoflurane against reperfusion injury has been reported,[57] this could be hardly put in relation with a decrease, or even with a lesser increase, of plasma γ-T.

Moreover, the sample size of the study did not allow enough statistical power to detect small differences in several of the comparisons reported. Specifically, the lack of significance in the comparison performed on α-T levels in PBMLs and on IL-10 production in WB should be considered with due caution.

The use of delta values in the statistical analysis also deserves some clarifications. Our approach was adopted *a priori* to control the intersubject variability. In addition, when the analysis was performed using actual values, similar results were obtained: As expected from the reduced statistical power, *P* values were generally higher (data not shown), but the significance of the main findings was unchanged.

In conclusion, our data show that γ-T levels are significantly increased in patients treated with propofol, compared with patients treated with the control anesthetic regimen. This effect was detected both in plasma and in mononuclear leukocytes and is associated with reduced COX-2 activity. These findings suggest for propofol a novel antiinflammatory effect, which may be relevant in controlling the inflammatory response related to tissue injury after reperfusion. Whether this antiinflammatory effect translates into a clinically significant outcome remains to be determined on the basis of properly powered clinical trials.

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