ANESTHESIOLOGY

Hyperoxia and Antioxidants for Myocardial Injury in Noncardiac Surgery: A 2 × 2 Factorial, Blinded, Randomized Clinical Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Myocardial injury after noncardiac surgery is associated with significantly increased morbidity and mortality.
- *Post hoc* analyses of several previous trials suggest that intraoperative hyperoxia may associate with increased postoperative acute coronary syndrome and mortality in noncardiac surgical patients.

What This Article Tells Us That Is New

- This is a 2 × 2 factorial, randomized, clinical trial (VIXIE [VitamIn and oXygen Interventions and cardiovascular Events] trial) designed to determine whether perioperative administration of 0.80 F_{IO_2} *versus* 0.30 F_{IO_2}, as well as perioperative administration of antioxidants (vitamin C and N-acetylcysteine) *versus* placebo, significantly impacted degree of myocardial injury after noncardiac surgery. Myocardial injury was assessed by measurement of high-sensitivity troponin.
- The VIXIE trial found no association between increased perioperative F_{IO_2} or administration of antioxidants and degree of myocardial injury after noncardiac surgery.

ABSTRACT

Background: Hyperoxia and oxidative stress may be associated with increased risk of myocardial injury. The authors hypothesized that a perioperative inspiratory oxygen fraction of 0.80 *versus* 0.30 would increase the degree of myocardial injury within the first 3 days of surgery, and that an antioxidant intervention would reduce degree of myocardial injury *versus* placebo.

Methods: A 2 × 2 factorial, randomized, blinded, multicenter trial enrolled patients older than 45 yr who had cardiovascular risk factors undergoing major noncardiac surgery. Factorial randomization allocated patients to one of two oxygen interventions from intubation and at 2 h after surgery, as well as antioxidant intervention or matching placebo. Antioxidants were 3 g IV vitamin C and 100 mg/kg N-acetylcysteine. The primary outcome was the degree of myocardial injury assessed by the area under the curve for high-sensitive troponin within the first 3 postoperative days.

Results: The authors randomized 600 participants from April 2018 to January 2020 and analyzed 576 patients for the primary outcome. Baseline and intraoperative characteristics did not differ between groups. The primary outcome was 35 ng · day/l (19 to 58) in the 80% oxygen group; 35 ng · day/l (17 to 56) in the 30% oxygen group; 35 ng · day/l (19 to 54) in the antioxidants group; and 33 ng · day/l (18 to 57) in the placebo group. The median difference between oxygen groups was 1.5 ng · day/l (95% CI, −2.5 to 5.3; $P = 0.202$) and −0.5 ng · day/l (95% CI, −4.5 to 3.0; $P = 0.228$) between antioxidant groups. Mortality at 30 days occurred in 9 of 576 patients (1.6%; odds ratio, 2.01 [95% CI, 0.50 to 8.1]; $P = 0.329$ for the 80% *vs.* 30% oxygen groups; and odds ratio, 0.79 [95% CI, 0.214 to 2.99]; $P = 0.732$ for the antioxidants *vs.* placebo groups).

Conclusions: Perioperative interventions with high inspiratory oxygen fraction and antioxidants did not change the degree of myocardial injury within the first 3 days of surgery. This implies safety with 80% oxygen and no cardiovascular benefits of vitamin C and N-acetylcysteine in major noncardiac surgery.

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Supplemental oxygen is given to all patients during general anesthesia and excess oxygen can result in hyperoxia. Hyperoxia can reduce coronary artery blood flow in healthy individuals, but the clinical impact is unknown.[1] However, some studies associate a high perioperative inspiratory oxygen fraction (F_{IO_2}) during general anesthesia with long-term increased risks of mortality and acute coronary syndrome.[2,3] Therefore, patients with cardiac disease may be at particular risk when exposed to hyperoxia. Myocardial injury after noncardiac surgery is a serious and often overlooked postoperative complication that

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is strongly associated with 30-day morbidity and mortality.[4,5] The surgical stress response may lead to a formation of excess reactive oxygen species that exceed the body's own antioxidant capacity and can cause cell damage and cardiovascular events such as myocardial injury.[6] The body's own antioxidants help to mitigate damage by transforming oxidants into less reactive compounds or even removing them completely.[7,8] Antioxidant supplements may relieve oxidative stress by scavenging free radicals.[7] N-acetylcysteine is a widely used therapeutic drug with antioxidant properties and may act directly by scavenging reactive oxygen species and indirectly by replenishing gluthathione.[9] Vitamin C also scavenges reactive oxygen species, and indirectly inhibits lipid peroxidation through regeneration of vitamin E.[10] These antioxidants may therefore protect against oxidative stress that may otherwise be a feature in the atherothrombotic process,[8] and antioxidant supplements have shown benefits in critically ill patients and patients with cardiovascular diseases.[11–14]

Myocardial injury has not been assessed in previous randomized clinical trials of hyperoxia or antioxidants. Most cases of myocardial injury after noncardiac surgery are diagnosed within the first 2 days of surgery by measurement of high-sensitive cardiac troponin level.[5] The degree of myocardial injury is quantified by calculating the area under the curve (AUC) of troponin within the first days of surgery.[15]

In a 2×2 factorial randomized clinical trial, the aim of the VIXIE (Vitamin and Oxygen Interventions and Cardiovascular Events) trial was to determine the association between perioperative 0.80 F_{IO_2} (the 80% oxygen group) *versus* 0.30 F_{IO_2} (the 30% oxygen group), as well as antioxidants *versus* placebo, on the degree of myocardial injury when given to patients at cardiovascular risk during major noncardiac surgery. We hypothesized that hyperoxia (0.80 F_{IO_2}) will increase the degree of myocardial injury as compared to normoxia (0.30 F_{IO_2}), and separately, that antioxidants will reduce the degree of myocardial injury as compared with placebo.

Materials and Methods

The VIXIE trial was a 2×2 factorial, randomized, blinded, clinical trial. The trial was conducted in four centers at three hospitals in the Capital Region of Denmark. Before inclusion of the first patient, the trial was registered at clinicaltrials.gov (NCT03494387; principal investigator Cecilie Holse; first posted April 11, 2018) and approved by the Danish Medicines Agency (Journal No. 2017064658), the Regional Research Ethics Committee (Journal No. H-17039073), and the Danish Data Protection Agency (Journal No. 2012-58-0004). The trial protocol has been published.[16]

Patients

Eligible patients had significant cardiovascular risk factors (either coronary artery disease, stroke, peripheral artery disease, vascular surgery, or two minor risk factors), were age 45 yr or older, and were undergoing elective or emergent surgery in general anesthesia with an estimated duration of 1 h or more (Supplemental Digital Content 1, http://links.lww.com/ALN/C768). Exclusion criteria included: pregnancy; inability to give informed consent; preoperative peripheral oxygen saturation (Spo_2) less than 90% without supplementary oxygen; drug allergy involving any of the interventional drugs; surgery within the last 30 days; or previous treatment with bleomycin. An investigator screened the surgery schedule for eligible patients and included patients after obtaining oral and written informed consent.

Randomization and Blinding

Patients were randomized by unblinded trial personnel who also prepared the intervention. The randomization was centralized with concealed allocation using computer-generated allocation sequence with blocks of varying sizes. The randomization was stratified by center and previous myocardial infarction (MI) or angina. We randomized patients in a 1:1:1:1 allocation ratio to receive: 0.80 F_{IO_2} and antioxidants; 0.80 F_{IO_2} and placebo; 0.30 F_{IO_2} and antioxidants; or 0.30 F_{IO_2} and placebo. Only the unblinded trial personnel not involved in the allocation of patients to the trial had access to the allocation in the trial database. Investigators and clinical personnel administered the intervention drugs. The patient, surgeons, and sponsor were blinded for the oxygen intervention; the investigators, anesthetists, anesthesia nurses, and postanesthesia care unit (PACU) nurses were not blinded for the oxygen intervention. The patient, investigators, and all clinical personnel were blinded for the antioxidant intervention, which was prepared in formulations of identical appearance.[16]

Medical investigators collected study data and outcomes,[16] which was managed using REDCap electronic data capture tools hosted at the Capital Region of Denmark.[17] The statistical analyses were performed with the statistician blinded to allocation and interventions. To further minimize bias, the article, including the Discussion and Conclusion, was written in two versions; one was based on the assumption that Treatment A was 0.80 F_{IO_2}, Treatment B was 0.30 F_{IO_2}, Treatment C was antioxidants, and Treatment D was placebo; the other version was written based on the reverse assumptions. All authors approved both versions before unmasking the allocation.

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*Members of the VIXIE (VitamIn and oXygen Interventions and cardiovascular Events) trial group are listed in the appendix.

Procedure and Interventions

Patients in the VIXIE trial were anaesthetized *via* adherence to trial protocol and local guidelines. Induction commenced after preoxygenation with 1.00 F_{IO_2} and the oxygen intervention was initiated immediately after tracheal intubation or laryngeal mask insertion. F_{IO_2} could be increased from the allocated concentration if clinically required to achieve an Spo_2 greater than or equal to 94%, except for patients with chronic obstructive pulmonary disease or a body mass index greater than or equal to 40 kg/m^2, in which case, an 88 to 92% Spo_2 target was used. A positive end-expiratory pressure of 5 cm H_2O was kept during anesthesia and was increased to 8 cm H_2O if the patient was obese (body mass index greater than or equal to 30 kg/m^2). If clinically significant atelectasis was suspected intraoperatively, an alveolar recruitment maneuver was performed. Oxygen administration was increased to, or kept at, 0.80 in the minutes before extubation.[16] During transportation from the operating room to the PACU, all patients received oxygen *via* a nonrebreathing mask (high-concentration oxygen mask; Intersurgical Limited, United Kingdom) with a flow of 15 l/min O_2 (the 80% oxygen group) or 10 l/min O_2 (the 30% oxygen group). Upon PACU arrival, the flow was changed to a mixture of 14:2 l/min oxygen:air in the 80% oxygen group and 2:14 l/min oxygen:air in the 30% oxygen group and was continued for 2 h.

The antioxidant intervention consisted of an injection of 30 ml vitamin C solution containing 3 g ascorbic acid given 0 to 4 h before induction of anesthesia, and an infusion of 500 ml containing 100 mg/kg N-acetylcysteine started after the induction of anesthesia and administered during 4 h. Matching placebos (saline) of both drugs were administered in packages of identical appearance. When patients had a high-sensitive troponin I value greater than 41 ng/l or an absolute high-sensitive troponin T value of greater than or equal to 65 ng/l, or a change in high-sensitive troponin T of 5 ng/l or more with a value of greater than or equal to 20 ng/l, they were clinically assessed by a medical doctor and had an electrocardiogram done.[5]

Follow-up was performed 30 days after surgery. A serious adverse event was defined as any untoward medical occurrence that resulted in prolonged hospital stay, significant disability, or death. We collected all serious adverse events and adverse events by reviewing medical records with verification *via* telephone interview or visit. Serious adverse events were reported to the trial sponsor in accordance with the International Conference on Harmonization of Good Clinical Practice. The regional Good Clinical Practice unit monitored the trial in collaboration with the sponsor. The monitoring plan adhered to the International Conference on Harmonization of Good Clinical Practice standards and informed consent was verified for all patients. Protocol adherence, as well as primary and secondary outcomes, were verified in selected patients.

Primary and Secondary Outcomes

The primary outcome was degree of myocardial injury as assessed by the AUC for high-sensitive troponin T (Cobas 8000 e801 module; Roche Diagnostics, Switzerland) or high-sensitive troponin I (ADVIA Centaur XP; Siemens, Germany) in nanograms per liter in absolute plasma concentrations measured during the first 3 in-hospital postoperative days on morning rounds.[16] High-sensitive troponin T and I react similarly, although not with identical concentrations, so we calculated AUC as a robust measure as it includes the baseline value. Secondary outcomes were all-cause mortality, nonfatal MI as defined by the fourth universal definition,[18] and nonfatal serious adverse event within 30 days, defined according to the International Conference on Harmonization of Good Clinical Practice as any untoward medical occurrence that is life-threatening, requires prolonged hospitalization, or results in persistent disability.

Explorative Outcomes

Exploratory outcomes were defined in the trial protocol[16]: surgical site infection and pneumonia, as defined by Centers for Disease Control and Prevention; sepsis as defined by the Joint Task Force by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine; acute respiratory failure defined as the need for controlled ventilation or the presence of a peripheral oxygen saturation of 90% or less, despite oxygen therapy; acute kidney injury as defined by the Kidney Disease Improving Global Outcomes guidelines; myocardial injury after noncardiac surgery as defined by any postoperative high-sensitive troponin T of greater than or equal to 20 ng/l with a change of 5 ng/l, or a single measurement of greater than or equal to 65 ng/l, or a high-sensitive troponin I measurement of greater than or equal to 40 ng/l in patients where the medical record reported no signs of significant extracardiac cause of troponin elevation (*e.g.,* renal insufficiency, pulmonary embolism, or severe sepsis).[5]

Statistical Analysis

The sample size was based on an expected myocardial injury where the AUC troponin mean was 34 ng · day/l in the control group (SD = 34 ng · day/l).[16] A total of 420 patients was needed to detect a 33% change in myocardial injury with 90% power and a 5% significance level. This was also accentuated by data from the AVOID (Air *versus* Oxygen in Myocardial Infarction) trial,[15] from which it can be calculated that 578 patients are needed to detect a 33% reduction from the 3-day AUC for cardiac troponin of 1,996 ng/l (SD = 2,440 ng/l),[16] although troponin release in high-risk surgical patients is much less than in patients with ongoing MI. We decided to include 600 patients to compensate for the uncertainty of the SD in our trial population, as well as for patients who did not have postoperative

troponins measured. The trial was designed and analyzed as a 2 × 2 factorial trial; this was possible since there are no documented interactions between FIO_2 and antioxidants. Our trial was therefore not sufficiently powered for the test of interaction itself.

The modified intention-to-treat population included patients who were randomized, had surgery performed, and did not withdraw consent, and for whom data on the primary outcome was obtained (*i.e.,* troponins measured postoperatively). Perioperative characteristics and outcomes are described with numbers (frequencies) and medians [interquartile range]. The primary outcome was continuous and analyzed with analysis of covariance in which the mean difference of median AUC troponin was adjusted for 80% oxygen (Yes/No), antioxidants (Yes/No), center (No. 1, 2, 3, or 4), previous MI/angina (Yes/No), and interaction between 80% oxygen and antioxidants as fixed effects, with the baseline value of troponin as a covariate. We also performed tests of interaction for the interventions. Analyses of secondary outcomes were done in the modified intention-to-treat population, plus patients without postoperative troponin measurement. Secondary outcomes were analyzed with multivariate logistic regression with adjustment for center, previous MI/angina, and antioxidant intervention. We performed subgroup analyses of the primary outcome (based on center, previous MI/angina, and per-protocol compliance), as well a sensitivity analysis for lower detection threshold.[16] Statistical analyses were performed in SAS Studio 3.8 (SAS Institute Inc., USA) and a two-sided $P < 0.05$ was considered statistically significant.

Results

We screened 2,296 patients between April 4, 2018, and January 21, 2020, of which 1,061 were eligible and 600 patients were randomized (fig. 1). Five patients had their surgeries cancelled, two withdrew consent, and 17 had no postoperative troponin measured; hence, the modified intention-to-treat population for the primary outcome was 576 patients (fig. 1). Baseline characteristics were similar in the groups: the mean age was 72 yr; 76% of patients were active or previous smokers; 70% had hypertension; and 10% had previous MI (table 1). The most common type of surgery was laparoscopic abdominal surgery and the median duration of anesthesia was 205 min (table 2).

Primary Outcome

Median peak troponin was 16 ng/l after surgery (fig. 2, A and B). The degree of myocardial injury was not significantly different between the 80% and 30% oxygen groups (median AUC troponin, 35 ng · day/l [19 to 58] *vs.* 35 ng · day/l [17 to 53]; estimated median difference, 1.5 ng · day/l [95% CI, −2.5 to 5.3]; $P = 0.202$) (fig. 2A). The median difference in AUC troponin was −0.5 ng · day/l (95% CI, −4.5 to 3.0; $P = 0.228$) between the antioxidant and placebo groups (fig. 2B).

Secondary and Explorative Outcomes

All-cause mortality within 30 days was 2.0% in the 80% oxygen group, 1.0% in the 30% oxygen group, 1.3% in the antioxidants group, and 1.7% in the placebo group (adjusted odds ratio for difference between 80% and 30% oxygen, 2.01 [95% CI, 0.50 to 8.1]; $P = 0.329$; adjusted odds ratio, 0.79 [95% CI, 0.214 to 2.99]; $P = 0.732$ for patients given antioxidants *vs.* placebo) (table 3). Nonfatal MI occurred in 1.3%, 2.0%, 1.3%, and 2.0% of patients allocated to 80% oxygen, 30% oxygen, antioxidants, and placebo, respectively, with no statistical differences between the groups. Nonfatal serious adverse events within 30 days were reported in 160 patients (table 3): 28% in the 80% oxygen group, 26% in the 30% oxygen group, and 27% in the antioxidant and placebo groups (80% *vs.* 30% oxygen: adjusted odds ratio, 1.15 [95% CI, 0.78 to 1.61]; $P = 0.54$; antioxidants *vs.* placebo: adjusted odds ratio, 0.97 [95% CI, 0.68 to 1.40]; $P = 0.885$). The most common type of serious adverse event was reoperation, occurring in 10% of patients, and adverse events occurred in 54% of patients (table 4). There was no difference in surgical site infection, which was diagnosed in 11% of patients in both oxygen groups. Acute kidney injury did not occur in patients in the antioxidants group, but did occur in three patients (1.0%) in the placebo group (table 3). Intraoperative erythrocyte transfusion was needed in 9.0% *versus* 5.4% of patients in the antioxidant and placebo groups, respectively (table 2), and major bleeding, according to International Society of Thrombosis and Hemostasis, occurred in 3.7% *versus* 2.4% of patients given antioxidants or placebo (table 4).

Ancillary Analyses

The per-protocol analysis of patients who received the intended interventions included 559 patients for oxygen interventions and 561 patients for antioxidant interventions; results were comparable to the results in the modified intention-to-treat population (AUC troponin, 35 ng · day/l [19 to 57] *vs.* 35 ng · day/l [17 to 53] *vs.* 33 ng · day/l [17 to 57] *vs.* 35 ng · day/l [19 to 53] in the 80% oxygen, 30% oxygen, antioxidants, and placebo groups, respectively ($P = 0.213$ for oxygen interventions; $P = 0.238$ for antioxidant interventions). The primary outcome was further evaluated in subgroup and sensitivity analyses including trial sites, previous MI/angina, and types of troponin measurements without statistically significant differences (Supplemental Digital Content 2, http://links.lww.com/ALN/C769). Logarithm transformation of troponin values did not result in significant differences between the groups either (Supplemental Digital Content 3 [http://links.lww.com/ALN/C770] and Supplemental Digital Content 4 [http://links.lww.com/ALN/C771]). The test of

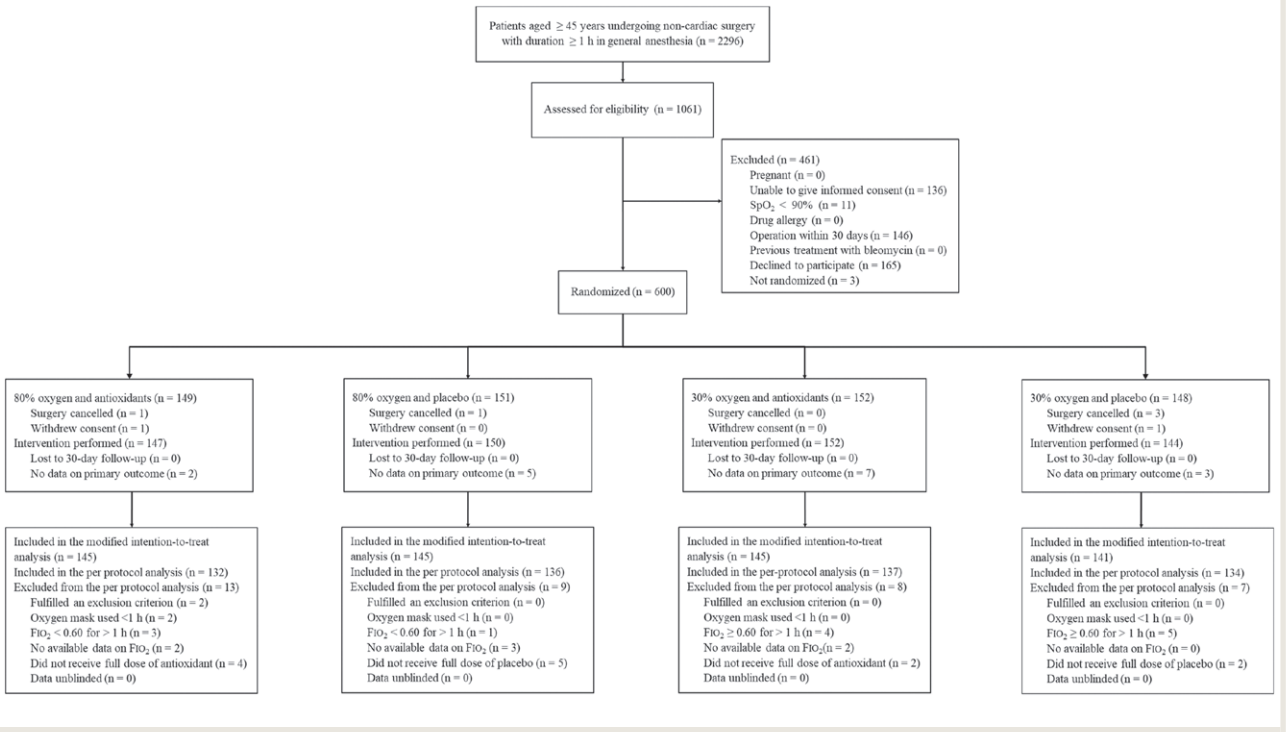

Figure 1. Patient enrollment, randomization, and treatment. F_{IO_2}, inspiratory oxygen fraction; S_{PO_2}, peripheral oxygen saturation.

interaction between the two oxygen interventions and the antioxidant/placebo interventions revealed no statistically significant interaction on the primary outcome ($P = 0.296$).

Discussion

In patients with cardiovascular risk factors who underwent noncardiac surgery in general anesthesia, we found no significant difference in occurrence of myocardial injury between patients receiving 0.80 F_{IO_2} or 0.30 F_{IO_2} both intraoperatively and for 2 h postoperatively. The combination of perioperative vitamin C and N-acetylcysteine did not affect degree of myocardial injury either. There was no significant difference in the occurrence of MI, serious adverse events, and mortality.

Postoperative high-sensitive troponin T elevations greater than 65 ng/l are associated with a 30-day mortality of 9.1%.[5] The 30-day mortality in patients without myocardial injury after noncardiac surgery has been reported to be 0.6%, whereas 30-day mortality in patients with myocardial injury (with or without ischemic symptoms) is between 2.9 and 8.5%.[5]

We found a relatively low median troponin (AUC, 35 ng · day/l) in the study groups and a median peak troponin of 16 ng/l. Despite this, 23% of our patients fulfilled the myocardial injury after noncardiac surgery criteria; however, the frequency of myocardial injury in the groups were similar.

An F_{IO_2} of 1.00 reduces cardiac output in young, healthy individuals and reduces coronary blood flow by 29%.[1,19,20] The clinical implications of the effect of hyperoxia on coronary blood flow in the perioperative setting have been sparsely investigated.

In the VIXIE trial, mortality was 2.0% in the 80% oxygen group and 1.0% in the 30% oxygen group. Mortality rates have diverged in previous studies, and although some observational studies and long-term follow-up studies of randomized clinical trials have indicated increased mortality with high F_{IO_2}, other studies have found no statistically significant differences in 30-day mortality.[21–23] Some trials of hyperoxia have reported MIs as secondary outcomes or analyses. The PROXI (PeRioperative OXygen fraction – effect on surgical site Infection and pulmonary complications after abdominal surgery) trial included 1,400 abdominal surgery patients and found a 4.4% mortality within 30 days in the group who received 80% oxygen compared to 2.9% in the group who received 30%,[21] and at long-term follow-up, the hazard ratios for mortality was 1.30 (95% CI, 1.03 to 1.64) and 2.86 (95% CI, 1.10 to 7.44) for MI with 80% oxygen.[2,3] Other trials have reported similar frequencies of MI: the ENIGMA (Nitrous oxide anesthesia and morbidity after major surgery) trial included 2,050 patients undergoing major noncardiac surgery and found an adjusted odds ratio of 0.58 (95% CI, 0.22 to 1.50) for MI within 30 days when comparing 0.80 F_{IO_2} (and nitrous oxide–free anesthesia) with 0.30 F_{IO_2} (with nitrous

Table 1. Baseline Characteristics of 593 Surgical Patients Randomized to 80% or 30% Oxygen and Antioxidants or Placebo

	80% Oxygen (n = 297)	30% Oxygen (n = 296)	Antioxidants (n = 299)	Placebo (n = 294)
Age, yr	72 ± 9	72 ± 9	72 ± 9	72 ± 9
Female sex	120 (40)	124 (42)	129 (43)	115 (38)
Body mass index, kg/m²	27 [23–30]	27 [24–30]	27 [23–30]	27 [24–31]
American Society of Anesthesiologists physical status				
I	6 (2.0)	2 (0.7)	6 (2.0)	2 (0.7)
II	123 (41)	143 (48)	133 (44)	133 (45)
III	165 (56)	148 (50)	156 (52)	157 (53)
IV	3 (1.0)	3 (1.0)	4 (1.3)	2 (0.7)
Emergent surgery	30 (10)	26 (8.8)	29 (9.7)	27 (9.2)
Previous or current daily smoker	234 (79)	217 (73)	229 (77)	222 (76)
Excessive alcohol consumption*	54 (18)	49 (17)	44 (15)	59 (20)
History				
Stroke	27 (9.1)	39 (13)	29 (9.7)	37 (13)
Transient cerebral ischemia	10 (3.4)	7 (2.4)	2 (0.7)	15 (5.1)
Hypertension	209 (70)	208 (70)	202 (68)	215 (73)
Atrial fibrillation	37 (12)	48 (16)	44 (15)	41 (14)
Coronary artery disease including angina	51 (17)	52 (18)	52 (17)	51 (17)
Myocardial infarction	31 (10)	29 (9.8)	34 (11)	26 (8.8)
Aortic stenosis	13 (4.4)	8 (2.7)	8 (2.7)	13 (4.4)
Percutaneous coronary intervention or coronary artery bypass grafting	34 (11)	34 (11)	37 (12)	31 (11)
Congestive heart failure	17 (5.7)	20 (6.8)	24 (8.0)	13 (4.4)
Pulmonary embolus or deep vein thrombosis	18 (6.0)	14 (4.7)	14 (4.7)	18 (6.1)
Peripheral arterial disease	39 (13)	48 (16)	43 (14)	44 (15)
Chronic obstructive pulmonary disease	38 (13)	41 (14)	40 (13)	39 (13)
Renal failure requiring dialysis or plasma creatinine >175 μM	8 (2.7)	6 (2.0)	7 (2.3)	7 (2.3)
Diabetes type 1 or 2	63 (21)	55 (19)	58 (19)	60 (20)
Active cancer	70 (24)	71 (24)	74 (25)	67 (23)
Infection within 3 months	19 (6.4)	19 (6.4)	24 (8.0)	14 (4.8)
Other significant noncardiovascular disease	53 (18)	55 (19)	59 (20)	49 (17)
Medications taken within 7 days of surgery				
Beta-blocker	74 (25)	80 (27)	83 (28)	71 (24)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	143 (48)	149 (51)	152 (51)	140 (48)
Calcium channel blocker	72 (24)	86 (30)	72 (24)	86 (29)
Diuretics	106 (36)	114 (39)	106 (35)	114 (39)
Statins	146 (49)	158 (54)	149 (50)	155 (53)
Steroids	24 (8.1)	20 (6.8)	19 (6.4)	25 (8.5)
Antithrombotic therapy	150 (51)	166 (56)	160 (54)	156 (53)
Oral antioxidant supplements	165 (56)	170 (58)	175 (59)	160 (54)

Data are number (%), mean ± SD, or median [interquartile range].

* >12 g alcohol/day for women and >24 g alcohol/day for men.

oxide).[23] A subanalysis of a large alternating intervention trial of 80% *versus* 30% intraoperative oxygen measured troponins on the first in-hospital days of 1,647 patients after colorectal operations.[24] Myocardial injury after noncardiac surgery was diagnosed in 58 patients (80% *vs.* 30% oxygen: relative risk, 0.70 [95% CI, 0.43 to 1.15]).

There is no formal consensus in perioperative medicine that high concentrations of oxygen cause cardiovascular harm, but systematic reviews and guidelines in emergency medicine and critical care state that liberal oxygen therapy increases mortality and should be avoided.[25,26] This was based, in part, on a trial of patients with acute MI that found supplemental oxygen given to nonhypoxemic patients was associated with a larger infarct size at 6 months and a difference in median AUC troponin of 15%.[15] In contrast, a larger clinical trial found no significant difference in mortality in nonhypoxic acute coronary syndrome patients when given 6 l of supplemental oxygen by facemask compared with ambient air.[27] The World Health Organization suggests using 0.80 F_{IO_2} in intubated patients to reduce surgical site infections[28]; however, the apparent beneficial effect is exclusively measurable in the subgroup of endotracheally intubated patients (relative risk, 0.80 [95% CI, 0.64 to 0.99]).[28] In the current trial, the numbers of surgical wound–related complications as well as serious surgical site infections within 30 days were similar in the 80% oxygen group and the 30% oxygen group.

One in eight patients in our trial had chronic obstructive pulmonary disease, and the overall occurrence of pneumonia and respiratory failure was 15% and 1.5%, respectively. There was a higher point estimate for pneumonia and acute respiratory failure in the 30% oxygen group compared with

Table 2. Intraoperative Characteristics of 597 Surgical Patients Randomized to 80% or 30% Oxygen and Antioxidants or Placebo

	80% Oxygen (n = 297)	30% Oxygen (n = 296)	Antioxidants (n = 299)	Placebo (n = 294)
Surgery				
Open abdominal surgery	49 (16)	37 (13)	45 (15)	41 (14)
Laparoscopic abdominal surgery	101 (34)	114 (39)	108 (36)	107 (36)
Vascular surgery	60 (20)	64 (22)	61 (20)	63 (21)
Orthopedic surgery	83 (28)	79 (27)	83 (28)	79 (27)
Other	4 (1.3)	2 (0.7)	2 (0.7)	4 (1.4)
Type of anesthesia				
Total intravenous anesthesia	242 (81)	242 (82)	247 (83)	237 (81)
Inhalational	54 (18)	51 (17)	48 (16)	57 (19)
Regional anesthesia	1 (0.3)	3 (1.0)	4 (1.3)	0
Epidural analgesia	44 (15)	45 (15)	34 (11)	55 (19)
Duration of anesthesia, min	200 [105–404]	210 [96–397]	200 [152–277]	209 [157-272]
Duration of surgery, min	127 [52–303]	137 [54–316]	123 [88–179]	139 [93-189]
Intraoperative mean arterial pressure, mmHg	69 [58–85]	69 [57–81]	68 [63–73]	69 [65-75]
Dose of ephedrine, mg	20 [0–50]	20 [0–50]	20 [10–30]	20 [10-30]
Dose of phenylephrine, mg	0.1 [0–7.4]	0.2 [0–6.3]	0.1 [0–1.3]	0.2 [0-1.6]
Requiring other vasopressors	19 (6.4)	25 (8.4)	24 (8.0)	20 (6.8)
Intraoperative fluid management				
Estimated blood loss, ml	100 [0–300]	100 [0–300]	100 [0–350]	100 [0-300]
Crystalloid infused, ml	1,533 [1,116–2,121]	1,701 [1,104–2,214]	1,612 [1,108–2,167]	1593 [1117-2164]
Colloid infused, ml	0	0	0	0
Patients receiving blood transfusion	21 (7.1)	22 (7.4)	27 (9.0)	16 (5.4)
Erythrocyte transfusion, ml	490 [245–500]	490 [250–980]	485 [245–735]	520 [490-980]

Data are number (%) or median [interquartile range].

the 80% oxygen group, but the trial was not powered to detect differences in these outcomes. Most concerns about high F_{IO_2} have been related to pulmonary complications; a large, 70,000-patient, observational study found that high intraoperative F_{IO_2} was associated with major pulmonary complications.[22] In that study, the frequency of reintubation,

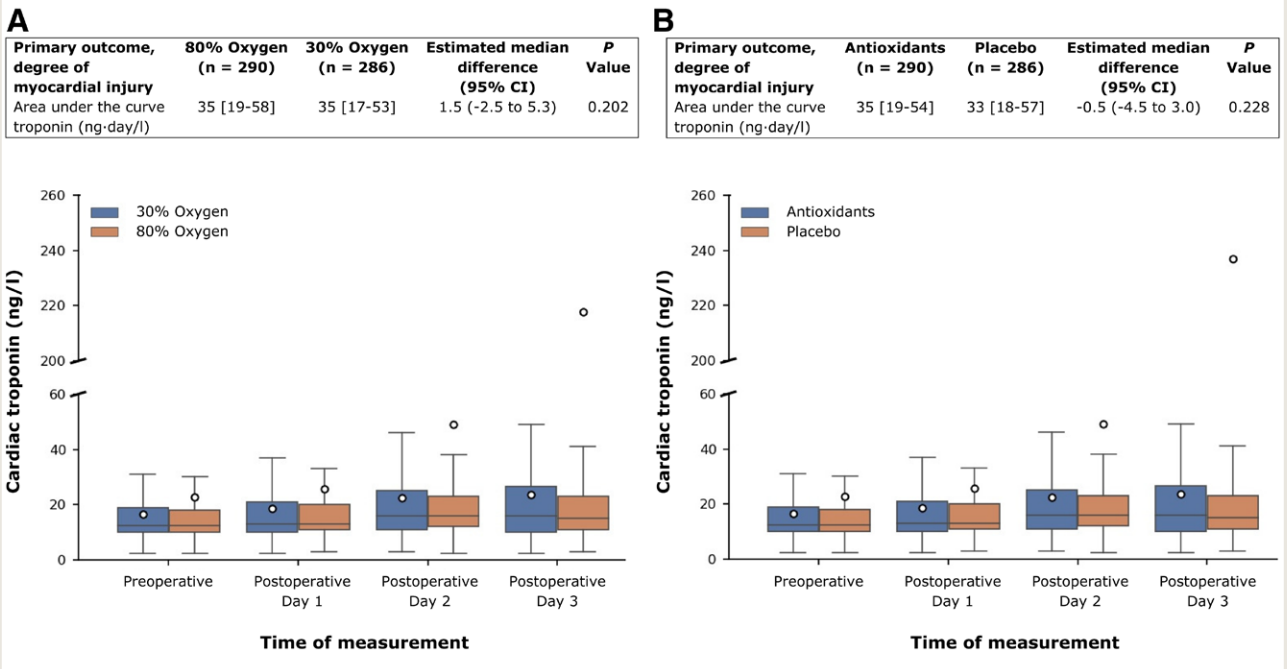

Figure 2. Primary outcome and boxplot of troponins according to oxygen and antioxidant intervention. *(A)* Comparison of 80% oxygen and 30% oxygen. *(B)* Comparison of antioxidants and placebo. Data are median [interquartile range].

Table 3. Secondary and Exploratory Outcomes of 593 Surgical Patients Randomized to 80% or 30% Oxygen and Antioxidants or Placebo

	80% Oxygen (n = 297)	30% Oxygen (n = 296)	Antioxidants (n = 299)	Placebo (n = 294)	80% *vs.* 30% Oxygen Odds Ratio	*P* Value	Antioxidants *vs.* Placebo Odds Ratio	*P* Value
Secondary outcomes								
All-cause mortality	6 (2.0)	3 (1.0)	4 (1.3)	5 (1.7)				
Unadjusted odds ratio					2.01 (0.50–8.1)	0.325	0.78 (0.211–2.95)	0.718
Adjusted odds ratio					2.01 (0.50–8.1)	0.329	0.79 (0.214–2.99)	0.732
Nonfatal myocardial infarction	4 (1.3)	6 (2.0)	4 (1.3)	6 (2.0)				
Unadjusted odds ratio					0.66 (0.184–2.36)	0.523	0.65 (0.183–2.33)	0.509
Adjusted odds ratio					0.65 (0.183–2.35)	0.515	0.65 (0.180–2.31)	0.502
Nonfatal serious adverse event	83 (28)	77 (26)	80 (27)	80 (27)				
Unadjusted odds ratio					1.10 (0.77–1.59)	0.596	0.98 (0.68–1.40)	0.901
Adjusted odds ratio					1.12 (0.78–1.61)	0.545	0.97 (0.68–1.40)	0.885
Exploratory outcomes								
Surgical site infection	32 (11)	32 (11)	30 (10)	34 (12)				
Pneumonia	15 (5.0)	22 (7.4)	18 (6.0)	19 (6.5)				
Sepsis	3 (1.0)	7 (2.4)	6 (2.0)	4 (1.4)				
Acute respiratory failure	4 (1.3)	5 (1.7)	2 (0.7)	7 (2.4)				
Acute kidney injury	0	3 (1.0)	0	3 (1.0)				
Myocardial injury after noncardiac surgery	64 (22)	72 (24)	73 (24)	63 (21)				

Adjusted odds ratio is adjusted for center, previous myocardial infarction/angina, and oxygen/antioxidant intervention. Data are number (%) or odds ratio (95% CI).

respiratory failure, pulmonary edema, and pneumonia within 7 days of surgery was increased (adjusted odds ratio, 1.99 [95% CI, 0.72 to 2.31]).

Antioxidant therapy is often given in relation to coronary artery disease, stroke, peripheral vascular disease, hypertension, and heart failure. This is mainly because of the effect of antioxidants on atherosclerosis.[7] One study found immediate effects of vitamin C through elimination of vasoconstriction in the left anterior descending coronary artery during inhalation of 100% oxygen.[1] Vitamin C reduced myocardial injury after percutaneous coronary intervention from 18% to 11%,[29] and although patients in our trial received a similar vitamin C dose, coronary interventions can provoke a larger myocardial supply–demand mismatch than noncardiac surgery. A recent systematic review indicated a 26% risk reduction in mortality of perioperative patients receiving antioxidants, but was graded as low-quality evidence.[12] Vitamin C and N-acetylcysteine did not result in significant benefits in our trial, but we cannot reject a clinically relevant reduction of myocardial injury in the subgroup of patients with a previous MI since the 95% CI of the estimated median difference was wide: from −3.0 ng · day/l to 29 ng · day/l. The kidneys are also susceptible to oxidative stress, and N-acetylcysteine, in particular, has been studied for its potential to reduce risk of acute kidney injury.[12,30] Our trial had no cases of acute kidney injury in the antioxidants group and only three cases in the placebo group. Preoperative vitamin C depletion is common and may be associated with postoperative bleeding, even in the presence of normal coagulation parameters.[31–33] The point estimates for intraoperative transfusion and major perioperative bleeding were, however, higher in our antioxidant group.

The number of nonfatal serious adverse event was similar in all intervention groups and there were no serious adverse drug reactions. We used doses of vitamin C and N-acetylcysteine that have been tested in multiple trials and the N-acetylcysteine dosage was approximately half of initial standard treatment of acetaminophen poisoning.

Strengths and Limitations

The primary strength of this trial is the unique and detailed assessment of myocardial injury in much higher numbers than previous oxygen trials. We included a broadly generalizable group of 600 major noncardiac surgical patients with cardiovascular risks and adequate power to refute significant benefits of antioxidants and harms of high perioperative F_{IO_2} on the myocardium. We assessed the degree of myocardial injury by AUC troponin, instead of peak troponin, because AUC troponin is more sensitive and provides better information about the severity of myocardial injury. We completed 30-day follow-ups of all serious adverse events and mortality *via* close monitoring from the Good Clinical Practice unit (Copenhagen University Hospital, Denmark).

Our trial also has some limitations. First, none of the investigators or anesthesia personnel were blinded for the oxygen intervention and data on oxygen exposure was not collected after discharge from PACU, but there were specific instructions to not inform colleagues (*e.g.,* surgeons) of the allocation. Second, a possible interaction between antioxidants and oxygen cannot be excluded, even though no previous trial has shown a direct interaction between the two. Third, we had 17 patients without postoperative troponin measurement, but the numbers were similar

Table 4. Adverse and Serious Adverse Events of 593 Surgical Patients Randomized to 80% or 30% Oxygen and Antioxidants or Placebo

	80% Oxygen (n = 297)	30% Oxygen (n = 296)	Antioxidants (n = 299)	Placebo (n = 294)
Serious adverse events				
Patients with any serious adverse events or fatality	89 (30)	80 (27)	84 (28)	85 (29)
Respiratory	16 (5.4)	18 (6.1)	15 (5.0)	19 (6.5)
Circulatory	20 (6.7)	16 (5.4)	15 (5.0)	21 (7.1)
Major bleeding*	11 (3.7)	7 (2.4)	11 (3.7)	7 (2.4)
Gastrointestinal	16 (5.4)	12 (4.1)	15 (5.0)	13 (4.4)
Serious surgical site infection	18 (6.1)	22 (7.4)	20 (6.7)	20 (6.8)
Reoperation	32 (11)	28 (9.5)	31 (10)	29 (9.9)
Other	29 (9.8)	28 (9.5)	28 (9.4)	29 (9.9)
Adverse events				
Patients with any adverse events	164 (54)	159 (55)	168 (56)	157 (53)
Respiratory	12 (4.0)	20 (6.8)	14 (4.7)	18 (6.1)
Circulatory	19 (6.4)	23 (7.8)	18 (6.0)	26 (8.8)
Gastrointestinal	39 (13)	32 (11)	44 (15)	27 (9.2)
Surgical wound–related	46 (15)	46 (16)	46 (15)	55 (19)
Postoperative nausea and vomiting	20 (6.7)	18 (6.1)	24 (8.0)	14 (4.8)
Urinary tract infection	15 (5.1)	18 (6.1)	13 (4.4)	20 (6.8)
Other infection	14 (4.7)	14 (4.7)	14 (4.7)	16 (5.4)
Other	70 (24)	62 (21)	81 (27)	88 (30)
Withdrawal from intervention due to adverse events	0	1 (0.3)	3 (1.0)	1 (0.3)

Data are number (%).

*Fulfilling International Society of Thrombosis and Hemostasis criteria.

in the groups. Eleven of these patients were discharged without complications on the day of surgery or on the first postoperative day, indicating that troponin levels most likely were low and patients were asymptomatic. Fourth, our trial was not powered to detect differences in mortality, MI, or serious adverse event, and these trial findings should therefore be combined with other trial results.

All biomarker outcomes classify as surrogate outcomes, but postoperative troponin measurements are the only way to detect myocardial injury after noncardiac surgery, a primarily asymptomatic complication that occurs in almost 20% of patients after noncardiac surgery.[5] The degree of myocardial injury (AUC) can therefore evaluate clinical decisions and potential interventions that are commonly used but may be harmful (*e.g.,* supplemental oxygen). The AUC troponin was similar in the oxygen groups and the 95% CI for difference was narrow and within the clinically relevant limits of 10 ng/l. Even though there is a pathophysiologic rationale for a possible harmful effect of oxygen in patients with cardiac risk factors,[1,19,20] our trial excludes a short-term adverse effect on the myocardium. This must, however, be conformed in other studies, and the international literature is far from conclusive regarding benefits and harms of hyperoxia on intermediate outcomes such as surgical site infection and respiratory complications, as well as long-term outcomes like mortality and cancer recurrence.

Conclusions

This blinded, randomized, clinical trial found no statistically or clinically significant differences in degree of myocardial injuries when comparing perioperative 0.80 F_{IO_2} to 0.30 F_{IO_2} and antioxidants to placebo in patients with cardiac risk factors.

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Dr. Holse received departmental funding and grants from The Danish Society of Anaesthesiology and Intensive Care Medicine (Copenhagen, Denmark) and the Bispebjerg and Frederiksberg Hospital Research Foundation (Copenhagen, Denmark). Dr. Christensen is funded by a core grant to his institution from the Oak Foundation Denmark (Copenhagen, Denmark). Dr. Meyhoff received a grant from The Scandinavian Society of Anesthesiology and Intensive Care Medicine (Copenhagen, Denmark). Other support was provided solely from institutional sources.

Competing Interests

All authors have completed the Unified Competing Interest form (available on request from the corresponding author). Dr. Christensen reports grants from public and private foundations, companies, and private individuals to his institution, which is also supported by a core grant from the Oak Foundation Denmark (Copenhagen, Denmark). Dr. Christensen is a founding member of the Technical Advisory Group of OMERACT (Outcome Measures in Rheumatology; Toronto, Canada), an organization that develops outcome measures in rheumatology and receives arms-length funding from 12 companies. Drs. Meyhoff and Aasvang are cofounders of the WARD (Wireless Assessment of Respiratory and circulatory Distress; Copenhagen, Denmark) project and a start-up

company, WARD247 ApS (Copenhagen, Denmark), aiming to pursue regulatory and commercial activities of the WARD-project. WARD247 ApS has finalized terms for license agreement for any WARD project software and patents and have one patent filed (WARD – Clinical Support System [CSS], which is an automated clinical support system to improve patient safety and outcomes). Dr. Meyhoff also reports direct and indirect research funding from Merck, Sharp and Dohme Corp. (Copenhagen, Denmark), and Boehringer Ingelheim (Ingelheim, Germany), as well as lecture fees from Radiometer (Copenhagen, Denmark). None of the aforementioned entities have influence on the study design, conduct, analysis or reporting. All other authors report no conflicts.

Reproducible Science

Full protocol available at: christianmeyhoff@gmail.com. Raw data available after 6 months to researchers who provide a methodologically sound proposal, and pending approval from regulatory bodies in Denmark. Proposals should be directed to: christianmeyhoff@gmail.com.

Correspondence

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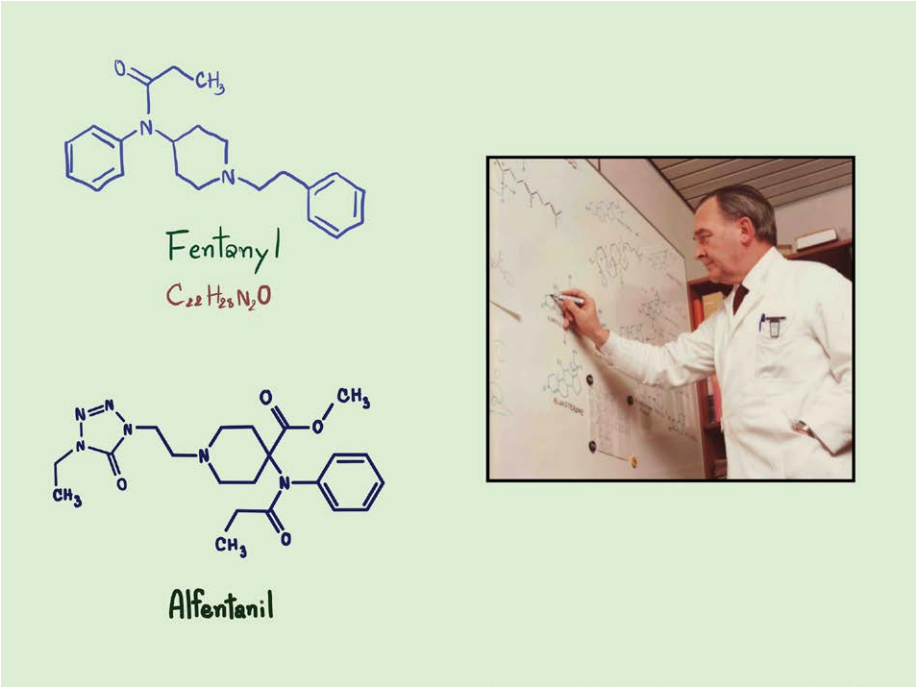
Appendix: VIXIE Trial Group Collaborators

The following VIXIE Trial Group collaborators do not meet all authorship criteria but contributed substantially to the work reported in the article: research nurse Marlene Søgaard, R.N., research assistant Zacharias D. Holm, M.B., and research fellow Sine A. N. Eriksen, R.N., contributed as investigators to the inclusion of 376 patients from the Department of Anaesthesia and Intensive Care, Bispebjerg and Frederiksberg Hospital, University of Copenhagen (Copenhagen, Denmark); research assistant Emilie Sigvardt, M.B., and research nurse Marlene E. Madsen, R.N., contributed to the inclusion of 134 patients from the Department of Anaesthesia, Center for Cancer and Organ Diseases, Rigshospitalet, University of Copenhagen (Copenhagen, Denmark); research assistant Casper D. Tvarnø, M.B., and research assistant Jannick B. Hansen, M.B., contributed as investigators to the inclusion of 51 patients from the Herlev Anaesthesia Critical and Emergency Care Science Unit (ACES), Department of Anaesthesiology, Copenhagen University Hospital Herlev-Gentofte (Herlev, Denmark); and research assistant Mo H. Larsen, M.B., research assistant Laurits Elgaard, M.B., research assistant Christina Drægert, M.B., and research assistant Cecilie M. B. Jensen, M.B., contributed as investigators to the inclusion of 42 patients from the Department of Anaesthesia, Center of Head and Orthopaedics, Rigshospitalet, University of Copenhagen (Copenhagen, Denmark).

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Dr. Paul Janssen: Making Piperidine Dreams Come True



The son of a physician-entrepreneur, young Paul Janssen (1926 to 2003, *right*) dreamed of creating a company that would profit from its own research efforts. When Germany occupied Belgium during World War II, Janssen secretly enrolled in college, where his love for chemistry grew. While in medical school, Janssen traveled to the United States, seeking exposure to advanced pharmacology research and winning chess matches to fund his trip. After obtaining his medical degree, he worked with several European scientists, including Nobel laureate Corneille Heymans. In 1953, "Dr. Paul" set out to achieve his childhood dream. He started his first laboratory within his father's company building. Constantly drawing novel compounds, Janssen manipulated known structures to enhance specific physiological effects. Synthesizing more than 1,100 new drugs in the first 3 years (and hundreds of thousands thereafter), Janssen Pharmaceutica would gain renown for haloperidol, droperidol, and etomidate. Dr. Paul's fascination with the piperidine ring, the fundamental structure of morphine and meperidine, also led to the development of fentanyl (*upper left*) and its derivatives sufentanil and alfentanil (*lower left*). (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

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