Should Stroke Victims Routinely Receive Supplemental Oxygen?
A Quasi-Randomized Controlled Trial

Ole Morten Rønning, MD; Bjørn Guldvog, MD, PhD

Background and Purpose—We sought to test the hypothesis that breathing 100% oxygen for the first 24 hours after an acute stroke would not reduce mortality, impairment, or disability.

Methods—Subjects admitted to the Central Hospital of Akershus, Norway, with stroke onset <24 hours before admittance were allocated to 2 groups by a quasi-randomized design using birth numbers. All patients with acute stroke admitted to hospital within 24 hours after a stroke were included and enrolled. Patients were allocated to a group that received supplemental oxygen treatment (100% atmospheres, 3 L/min) for 24 hours (n=292) or to the control group, which did not receive additional oxygen. Main outcome measures were 1-year survival, neurological impairment (Scandinavian Stroke Scale), and disability (Barthel Index) 7 months after stroke.

Results—One-year survival was 69% in the oxygen group and 73% in the control group (OR 0.82; 95% CI 0.57 to 1.19; \( P=0.30 \)). Impairment scores and disability scores were comparable 7 months after stroke. Among patients with Scandinavian Stroke Scale (SSS) scores of \( \geq 40 \), 82% in the oxygen group and 91% in the control group survived (OR 0.45; 95% CI 0.23 to 0.90; \( P=0.023 \)). For patients with SSS scores of \( <40 \), 53% in the oxygen group and 48% in the control group survived (OR 1.26; 95% CI 0.76 to 2.09; \( P=0.54 \)).

Conclusions—Supplemental oxygen should not routinely be given to nonhypoxic stroke victims with minor or moderate strokes. Further research is needed to give conclusive advice concerning oxygen supplementation for patients with severe strokes. (Stroke. 1999;30:2033-2037.)

Key Words: oxygen ▪ stroke management ▪ stroke outcome

In both Norwegian and international guidelines for management of patients with acute ischemic stroke, the role of supplemental oxygen is questioned, although such treatment for hypoxic patients is recommended.\(^1\)\(^2\) Paramedics and staff in emergency clinics routinely give such treatment to all patients with acute stroke. Treatment is often continued within the hospital, regardless of whether the patient is hypoxic or not. There exists no empirical evidence for the benefit of this practice. Hyperoxia increases the formation of oxygen free radicals\(^3\)\(^-\)\(^6\) and induces cerebral vasoconstriction, which may reduce cerebral blood flow.\(^7\) Conflicting evidence exists about cerebral damage after ischemia caused by free radical formation and lipid peroxidation. Animal studies evaluating hyperbaric oxygen therapy have not been conclusive concerning recovery after cerebral ischemia.\(^8\)\(^-\)\(^11\) Two studies\(^12\)\(^,\)\(^13\) showed increased mortality among animals exposed to oxygen-enriched atmospheres.

Early mobilization is paramount in treatment of stroke patients,\(^14\)\(^,\)\(^15\) and thus it is important to reduce the number of procedures that prevent such mobilization. We hypothesized that supplemental oxygen was not effective to increase survival among stroke patients, nor to reduce impairment or disability. In particular, we hypothesized that patients with less-severe strokes would not benefit from supplemental oxygen, because ventilation among these patients is rarely impaired.

The study was performed to compare supplemental oxygen with no such treatment in patients with acute stroke of various severity, assessing the effect on survival, impairment, and disability.

Subjects and Methods

Patients referred to the Central Hospital of Akershus, Norway, within 24 hours after onset of a stroke were prospectively enrolled in the study. The hospital serves a population of about 300 000. The study began March 1, 1994, and ended December 31, 1995. Stroke was defined according to WHO guidelines.\(^16\) Exclusion criteria were age \(<60\) years and symptomatic onset of acute stroke \(>24\) hours before admittance to hospital. Patients with subdural hematoma, subarachnoid hemorrhage, and transient ischemic attacks were excluded. Of all 570 patients admitted to the hospital with acute stroke in the study period, 550 patients (mean age 74.6 years; 53% men) were enrolled (Figure 1). The 20 patients excluded from the study did not comply with 1 or more of the inclusion criteria. Patients were allocated to

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From the Foundation for Health Services Research, Central Hospital of Akershus, Nordbyhagen, Norway.
Correspondence and reprint requests to Ole Morten Rønning, Foundation for Health Services Research, HELTEF, Central Hospital of Akershus, 1474 Nordbyhagen, Norway. E-mail bguldvog@sia.pilot.akershus-f.kommune.no
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Stroke is available at http://www.strokeaha.org
supplemental oxygen treatment or to no treatment (control group) by a quasi-randomized design that was based on the date of birth in the month. Patients with uneven digits in their date of birth within the month (e.g., 1, 3, 5–27, 29, 31) were allocated to the control group and patients with even digits to the treatment group. Stroke patients in the treatment group received 100% oxygen at atmospheric pressure at a rate of 3 liters per minute through a nasal catheter for 24 hours after they entered the hospital. Separate parts of the stroke study, evaluating the effect of a stroke unit and a hospital-based rehabilitation unit with respect to survival and disability, are described elsewhere.17,18

The study was analyzed on an intention-to-treat basis. No patients were excluded from the study because they withdrew or because of pulmonary diseases or other conditions that could interfere with oxygen treatment. We chose to use intention-to-treat analysis because we were aware of the theoretical possibility that quasi-randomization based on birth digits could violate the requirement of a proper randomized study that all patients should have the same chance of receiving each treatment. Therefore, the protocol did not allow the admitting clinician to exclude patients with acute stroke from the study for any reason. If a patient was hypoxic or suffered from serious chronic obstructive lung disease, the physician responsible for the patient was instructed to give supplemental oxygen or not, as he found necessary, independent of the treatment to which the patient was allocated. Hence, we avoided introduction any systematic bias in this study. Informed consent regarding participation in this study was obtained from each patient or the next of kin. The experimental protocol was approved by the regional ethics committee. The research protocol contained ethical considerations stating that documentation of a benefit of oxygen therapy was lacking for stroke patients without respiratory insufficiency and that experiment was justified on this basis. A physician who was engaged in the investigation was involved when informed consent was obtained. Both the patients and the physician responsible for treatment could at any time withdraw the patient from the study or adjust the treatment. All of the patients (or the next of kin) who were asked accepted inclusion of the patient in the study.

Information on death was collected until March 1, 1997, through the National Register, an official register containing name, date of birth, address, and date of death. This register is continually updated. Impairment was assessed by Scandinavian Stroke Scale (SSS) score on admission and after 7 months. Disability was assessed by Barthel Index (BI) the first day after admittance and after 7 months. The initial assessment on admission was performed by the practitioner on duty, who also carried out the inclusion, assignment, and initiation of treatment. One of the investigators (O.M.R.) evaluated

![Figure 1. Trial profile.](http://stroke.ahajournals.org/)

### Table 1. Baseline Data for Stroke Victims in Treatment and Control Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Strokes</th>
<th></th>
<th>Moderate or Minor Strokes (SSS ≥40)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxygen Group (n=292)</td>
<td>Control Group (n=258)</td>
<td>P</td>
<td>Oxygen Group (n=159)</td>
</tr>
<tr>
<td>Mean (SD) age, y</td>
<td>76.7 (7)</td>
<td>76.1 (8)</td>
<td>0.60</td>
<td>75.5 (7)</td>
</tr>
<tr>
<td>Male</td>
<td>166 (56.8)</td>
<td>126 (48.9)</td>
<td>0.06</td>
<td>94 (59.1)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>37 (12.7)</td>
<td>29 (12.7)</td>
<td>0.60</td>
<td>12 (7.5)</td>
</tr>
<tr>
<td>Time from onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3 h</td>
<td>49 (19.0)</td>
<td>57 (19.5)</td>
<td>0.96</td>
<td>20 (12.6)</td>
</tr>
<tr>
<td>3–6 h</td>
<td>72 (27.9)</td>
<td>73 (25.0)</td>
<td>0.70</td>
<td>39 (24.5)</td>
</tr>
<tr>
<td>6–12 h</td>
<td>38 (14.7)</td>
<td>49 (16.8)</td>
<td>0.73</td>
<td>29 (18.2)</td>
</tr>
<tr>
<td>12–24 h</td>
<td>50 (19.4)</td>
<td>52 (17.8)</td>
<td>0.86</td>
<td>34 (21.4)</td>
</tr>
<tr>
<td>&lt;24 hours (i.e., during sleep)</td>
<td>49 (19.0)</td>
<td>61 (20.9)</td>
<td>0.42</td>
<td>37 (23.3)</td>
</tr>
<tr>
<td>Barthel Index (range)*</td>
<td>45 (0–79)</td>
<td>50 (15–85)</td>
<td>0.04</td>
<td>70 (50–90)</td>
</tr>
<tr>
<td>SSS score (range)*</td>
<td>42 (23–49)</td>
<td>43 (26–51)</td>
<td>0.14</td>
<td>48 (44–53)</td>
</tr>
<tr>
<td>Treated in stroke unit</td>
<td>135 (46.2)</td>
<td>136 (52.7)</td>
<td>0.13</td>
<td>76 (50.3)</td>
</tr>
<tr>
<td>Length (SD) of stay, d</td>
<td>8.6 (6)</td>
<td>8.7 (7)</td>
<td>0.80</td>
<td>7.0 (5)</td>
</tr>
<tr>
<td>Prior medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior stroke</td>
<td>66 (22.6)</td>
<td>63 (24.4)</td>
<td>0.24</td>
<td>27 (17.0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>48 (16.4)</td>
<td>44 (17.1)</td>
<td>0.99</td>
<td>26 (16.4)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>46 (15.8)</td>
<td>48 (18.6)</td>
<td>0.80</td>
<td>18 (11.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>127 (43.5)</td>
<td>107 (41.5)</td>
<td>0.25</td>
<td>76 (47.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38 (13.0)</td>
<td>44 (17.1)</td>
<td>0.11</td>
<td>20 (12.6)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>26 (8.9)</td>
<td>25 (9.7)</td>
<td>0.85</td>
<td>14 (8.8)</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean±SD. Categorical data are expressed as number of patients with/without a given characteristic and also in percentages (in parentheses).

*Median value and interquartile range.
improvement and disability after 7 months (±1 month), without knowledge of the date of birth (and hence the treatment group) before the scoring. It has been recommended⁵¹ that outcome after stroke should be measured at 6 months because most significant recovery will be completed by that time.

We performed a subgroup analysis on patients with SSS ≥40 on admission, in corroboration with our hypothesis that patients with particularly moderate or minor strokes did not benefit from supplemental oxygen. This analysis was prespecified, but we chose 40 as the SSS score cutoff point after the start of the study.

Thirty-three patients in the treatment group did not receive supplemental oxygen as prescribed. They were either not given such treatment or they received the treatment for <24 hours. Sixty-six patients in the control group were given oxygen treatment, but most of these patients were treated for considerably <24 hours. Eight of these patients had severe strokes and clinically impaired respiration and hence were offered supplemental oxygen.

**Statistical Analysis**

The associations between the normally distributed continuous variables and treatment group were examined by using the unpaired t test. The χ² test was used to investigate the association between the categorical variables and the treatment group. Survival curves were plotted with the Kaplan-Meier method. The log-rank test was used for calculations of survival. Neurological and functional scores were analyzed by the Mann-Whitney test. The study had 75% power in analysis, survival was still in favor of the control group (12 of 129 and 25 of 122, respectively; P=0.030). For patients with severe stroke, there was a tendency for higher 1-year survival among the patients who received oxygen supplementation (53%) than among the control patients (48%), but the difference was not statistically significant (P=0.60).

Figure 2 shows survival curves for the 2 treatment groups with all patients included; Figure 3 shows survival curves for patients with mild or moderate strokes and patients with severe strokes, by treatment group.

**Discussion**

The study shows that oxygen supplementation given as routine treatment does not appear to be of benefit for stroke victims. On the contrary, our study raises the hypothesis that oxygen supplementation to nonhypoxic patients with mild or moderate strokes may increase mortality. This is the first study of its kind to assess the effect of supplemental oxygen given routinely to patients with acute stroke and the first to show that oxygen supplementation to an unselected population of acute stroke patients does not seem to improve outcome. In our opinion, the practical consequence of our study is that nonhypoxic patients with moderate or minor strokes should not routinely receive supplemental oxygen after admission to the hospital. Our study is not conclusive regarding oxygen supplementation for patients with severe strokes. There was a tendency among these patients toward a benefit of oxygen supplementation, but the differences were statistically insignificant.

How could oxygen possibly contribute to worsening the prognosis for patients with moderate or minor strokes? We do

**Table 2. One-Year Survival, Neurological Impairment, and Disability at 7 Months for Treatment and Control Groups**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Oxygen Group (n=292)</th>
<th>Control Group (n=258)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survived</td>
<td>201 (68.8%)</td>
<td>188 (72.9%)</td>
<td>0.30</td>
<td>0.82 (0.57–1.19)</td>
</tr>
<tr>
<td>SSS score (range)*</td>
<td>54 (48–58)</td>
<td>55 (48–58)</td>
<td>0.674</td>
<td></td>
</tr>
<tr>
<td>Barthel Index score (range)*</td>
<td>95 (70–100)</td>
<td>100 (80–100)</td>
<td>0.070</td>
<td></td>
</tr>
</tbody>
</table>

*Median value and interquartile range.

Table 3 shows the outcomes separately for stroke patients with SSS <40 and SSS ≥40. One-year survival was higher in the control group than the treatment group for these patients (P=0.023), but the groups did not differ in other outcomes. If patients with hemorrhagic stroke were excluded from the analysis, survival was still in favor of the control group (12 of 129 and 25 of 122, respectively; P=0.030). For patients with severe stroke, there was a tendency for higher 1-year survival among the patients who received oxygen supplementation (53%) than among the control patients (48%), but the difference was not statistically significant (P=0.60).

**Table 3. One-Year Survival, Neurological Impairment, and Disability at 7 Months in Study Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Moderate or Minor Strokes*</th>
<th>Severe Strokes†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxygen Group (n=159)</td>
<td>Control Group (n=151)</td>
</tr>
<tr>
<td>Survival</td>
<td>130 (81.8%)</td>
<td>137 (90.7%)</td>
</tr>
<tr>
<td>SSS score (range)‡</td>
<td>57 (54–58)</td>
<td>57 (52–58)</td>
</tr>
<tr>
<td>Barthel Index score (range)‡</td>
<td>100 (95–100)</td>
<td>100 (95–100)</td>
</tr>
</tbody>
</table>

*SSS score of ≥40 on admission.
†SSS score of <40 on admission.
‡Median value and interquartile range.
not know the cause of these findings, even though there are some reports of a possible harmful effect of oxygen therapy. One small controlled study did not show any effect of hyperbaric oxygenation after stroke whereas another study found that such treatment might worsen outcome.22,23 Controlled clinical studies of the effect of breathing an oxygen-enriched atmosphere has not been performed. One study of gerbils12 supports the hypothesis of damaging effects of oxygen supplementation. Several factors could contribute to this result. Free radicals of oxygen or reactive oxygen species and xanthine oxidase occur during reperfusion following ischemia.3–5,24 Mitochondrial respiration is impaired after ischemia, 25 and an increase in molecular oxygen could theoretically result in an increase in reactive oxygen species, which could further result in tissue injury.26 In addition, oxygen supplementation by nasal catheter theoretically could reduce the opportunity of early mobilization in the treatment group, but we did not find differences in onset of mobilization between the groups.

Why could supplemental oxygen be of less harm among the patients with severe strokes? Some patients with severe strokes may have impaired respiration that is clinically undetectable and obviously could have benefited from supplemental oxygen. Further, such patients may have insufficient reperfusion of ischemic areas of the brain to allow a harmful effect of oxygen treatment, while the stroke patients who are less disabled on admission are those who have reperfusion of these areas. One possible damaging effect of supplemental oxygen could be dependent on this reperfusion, because reoxygenation of ischemic brain is a prerequisite for oxygen products that may participate in a posts ischemic neuronal damage. Because this is the first study of its kind, we recommend that the results be interpreted with caution. However, we have reason to believe that the possible damaging effect of supplemental oxygen may be even more pronounced than shown in our study, because some patients (n = 33; 11%) allocated to the treatment group did not receive such treatment for a full 24 hours. In addition, some patients in the control group (n = 66; 26%) were offered oxygen by paramedics before arrival at the hospital and/or in the emergency room.

Could our study be biased? The number of patients with odd and even birth numbers in the month admitted, and hence the number in the treatment group (n = 292) and control group (n = 258), were different. This difference in the occurrence of odd and even birth numbers among stroke patients admitted to hospital must have happened by chance. All patients who complied with the criteria were enrolled in the study, no referring doctor in the area knew about the randomization methods of the study, and the professional guidelines used by the primary health care and paramedics recommended that all patients with acute stroke should immediately be admitted to the hospital. Although we acknowledge the theoretical possibilities of bias with allocation based on the date of birth, we maintain that the allocation method in this case practically equals full randomization.

Through further investigation we intend to analyze the causes of death in the 2 groups, but a complete list of causes of death is not yet available. We do not know the duration or the threshold of the possible deleterious effect of breathing 100% oxygen through a nasal catheter. We recommend that further studies be performed to assess the effects of supplemental oxygen on patients with severe strokes. We believe, however, that our study probably gives sufficient documentation to recommend that supplemental oxygen should not be given routinely to patients with mild and moderate strokes.

References


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