Category II fetal heart tracings are defined by the National Institute of Child Health and Human Development as a broad class of electronic fetal monitoring observed in more than 80% of laboring patients.[1,2] Although indeterminate in its ability to predict neonatal acidemia, the presence of category II fetal heart tracings often results in intrauterine resuscitation maneuvers aimed at improving fetal oxygenation. Maternal oxygen administration is 1 such technique; it is commonly performed in more than 60% of patients in labor in an attempt to reverse perceived fetal hypoxemia and prevent resultant acidemia.[3] Use of oxygen as recommended by several governing bodies[3,4] has unproven benefit, with some concern for harm, given evidence that in utero and postnatal hyperoxemia is associated with increased neonatal morbidity.[5-10] Given data linking hyperoxygenation with increased respiratory and neurologic morbidity in infants, the American Academy of Pediatrics now recommends against initial neonatal resuscitation with oxygen.[11]

In a recent review of intrapartum maternal oxygen administration, Hamel et al[3,12] concluded that the evidence for routine oxygen administration is insufficient and that such administration may even harm the fetus through production of free radicals. Likewise, a 2012 Cochrane review found limited evidence supporting the use of oxygen for intrapartum fetal distress.[13] The 3 clinical trials comparing oxygen administration with room air in patients in labor did not show neonatal benefit with oxygen exposure.[14-16] Importantly, none of these studies assessed the population in which oxygen is most commonly used—those with category II fetal heart tracings. In the absence of evidence that oxygen improves fetal metabolic status, the liberal use of oxygen on labor and delivery units requires further careful evaluation.

We performed a randomized clinical trial to test the hypothesis that room air for category II fetal heart tracings is noninferior to oxygen in improving fetal metabolic status as represented by umbilical artery lactate, a marker of metabolic acidosis and neonatal morbidity.[17-19]

Key Points

Question Is room air comparable with maternal oxygen supplementation for intrauterine fetal resuscitation in labor?

Findings In this randomized noninferiority trial of 114 pregnant patients with category II fetal heart tracings in labor, room air was noninferior to oxygen for the reduction of umbilical artery lactate, a cord gas marker of metabolic acidosis. There were no differences in mode of delivery or other cord gases between groups.

Meaning Room air may be an acceptable alternative to oxygen for category II fetal heart tracings in labor.

Methods

Study Design

This was a randomized clinical noninferiority trial of patients in labor who had category II fetal heart tracings at a single, tertiary care center from June 2016 through June 2017. A noninferiority approach was chosen on the basis of biologic plausibility because it is unlikely that room air is superior to oxygen in improving fetal metabolic status. Therefore, the null hypothesis was that room air for category II fetal heart tracings is associated with an increase in umbilical artery lactate by more than a prespecified noninferiority margin.

The study was approved by the Washington University School of Medicine Human Research Protection Office and was registered on ClinicalTrials.gov (NCT02741284). Patients completed informed consent at the time of their presentation to the labor and delivery unit. The full trial protocol is available in Supplement 1.

Study Population

Pregnant patients at 37 weeks' gestation or greater who were presenting in spontaneous labor or for an induction of labor were enrolled on admission to the labor and delivery unit. Patients with major fetal anomalies, multiple gestations, and maternal hypoxia (maternal oxygen saturation <97%) were excluded.

Randomization and Intervention

Consented patients were randomized at any point in the active phase of labor (defined as 6 cm of cervical dilation or more) if and when they developed category II fetal heart tracings requiring any form of intrauterine resuscitation (ie, maternal repositioning, intravenous fluid bolus, or decrease in or discontinuation of oxytocin infusion). Patients were randomized in a 1:1 ratio using a computer-generated random sequence in blocks of 6 that were individually sealed in opaque envelopes and opened by the primary nurse at time of randomization. Patients were assigned to receive either room air without a facemask or oxygen via a nonrebreather facemask at a rate of 10 L/min (fraction of inspired oxygen: approximately 0.80)[20] until delivery. Study participants otherwise received standard obstetric and intrapartum care. Alternative intrauterine resuscitation maneuvers for both groups was left to the discretion of the medical team and recorded.

Outcomes and Data Collection

Per institutional protocol, arterial and venous blood samples were collected from a clamped segment of umbilical cord by trained technicians immediately after delivery of the infant. These samples were analyzed in the hospital laboratory using the ABL825 benchtop gas analyzer (Radiometer America). The coefficient of variation of lactate using this analyzer ranges from 3.0% to 3.4%.

The patient's primary nurse and research personnel monitored adherence to the study protocol during labor. Trained research staff blinded to intervention abstracted demographic information, medical and antepartum history, fetal monitoring data, and neonatal outcomes from medical records and forms filled by the patient's primary nurse. Umbilical cord gas results were abstracted by staff who were blinded to the intervention. An independent data and safety monitoring board monitored adverse maternal and neonatal events.

The primary outcome was umbilical artery lactate at delivery. The rationale for umbilical artery lactate as the primary outcome was 2-fold. First, umbilical artery lactate is a

direct product of anaerobic metabolism and precedes pH changes in the setting of fetal hypooxygenation.[17,21] Second, elevated umbilical artery lactate is a sensitive predictor of hypoxia-associated neonatal morbidity.[18] Prespecified secondary outcomes were cesarean delivery for nonreassuring fetal status, operative vaginal delivery, and other umbilical artery gas components including pH, partial pressure of oxygen, partial pressure of carbon dioxide, and base deficit.

Statistical Analysis

Based on our institutional data, we estimated a baseline umbilical artery lactate mean (SD) of 31.5 (14.4) mg/dL in patients with category II fetal heart tracings that receive oxygen per current practice on the institution's labor and delivery unit. Using a 1-sided α of .025, a sample size of 98 patients was required to detect a noninferiority margin of 30% (mean umbilical artery lactate difference of 9.0 mg/dL [1.0 mmol/L] between groups) with 90% power. A noninferiority margin of 30% was selected because it corresponds to an upper umbilical artery lactate cutoff value of 40.5 mg/dL, above which there is an increased risk of neonatal morbidity.[18,22,23] To accommodate 15% loss to unattainable paired cord gases, we planned to enroll 114 patients.

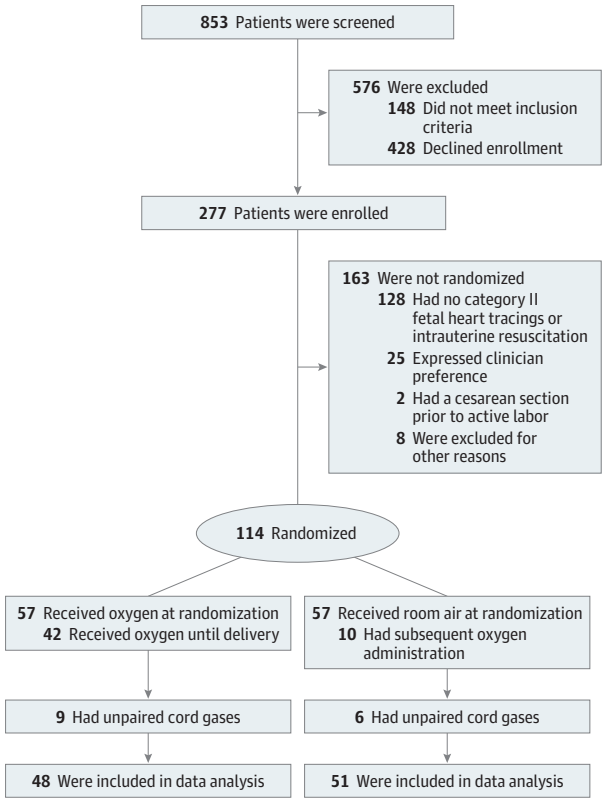
Data analysis was blinded and performed using the modified intention-to-treat principle. All patients with paired umbilical artery and vein cord gases were included in the final analysis. Univariable statistics were used to compare baseline characteristics between groups. Continuous outcomes were compared using the *t* test or Mann-Whitney U test as appropriate. Categorical outcomes were compared using the χ^2 or Fisher exact test. Noninferiority for the primary outcome was determined by whether the upper bound of the 95% confidence interval for umbilical artery lactate in the room air group crossed the noninferiority margin.

We performed 1 prespecified subgroup analysis of the primary outcome in patients with recurrent late or recurrent variable decelerations at time of randomization. Univariate log-binomial models were conducted to estimate relative risks for the secondary outcomes. A secondary per-protocol analysis was performed of all patients who received the assigned intervention without interruption. Post hoc multiple imputation was performed for the primary outcome in a sensitivity analysis to account for missing cord gases. Missing paired gases were assumed to be missing at random. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Of the 853 patients screened for eligibility, 148 individuals (17.4%) did not meet inclusion criteria, and 428 (51.2%) declined to participate, resulting in a total of 277 enrolled patients (32.5%). Of these 277 women, 128 (46.2%) were not randomized because of lack of category II fetal heart tracing requiring resuscitation, 25 (9.0%) because of provider preference, 2 (0.7%) because of cesarean deliveries performed prior to active labor, and 8 (2.9%) because of other, miscellaneous reasons. The remaining 114 patients (41.2%) were randomized to either 10 L/min oxygen by facemask (57 [20.6%]) or room air (57 [20.6%]). All patients received their assigned intervention; however, 15 of 57 patients (26.3%) in the oxygen group were subsequently taken off oxygen and 10 of 57 patients (17.5%) in the room air group subsequently received oxygen. A total of 99 patients (86.8% of 114 randomized participants; 48 of 57 women on oxygen [84.2%] and 51 of 57 women on room air [89.4%]) with paired umbilical cord gases were included in the primary modified intention-to-treat analysis (**Figure 1**).

Figure 1. Flowchart of Study Participants



Baseline characteristics were similar between groups, including maternal age, race/ethnicity, body mass index (calculated as weight in kilograms divided by height in meters squared), and chronic comorbidities (**Table 1**). Baseline characteristics of those with unpaired cord gases were not significantly different from those with paired cord gases (eTable 1 in Supplement 2). Additional measures of intrauterine resuscitation after randomization were similar between groups, including intravenous fluid administration, discontinuation or decrease in oxytocin, and rates of amnioinfusion. Time from randomization to delivery was similar between the room air and oxygen groups (**Table 2**). Specific fetal heart rate patterns under the broader category II fetal heart tracing classification were similar between groups in the 60 minutes prior to randomization (eTable 2 in Supplement 2).

The primary outcome of umbilical artery lactate was similar between groups with a mean lactate of 30.6 mg/dL (95% CI, 27.0-34.2 mg/dL) in the oxygen group and 31.5 mg/dL (95%

Table 1. Baseline Characteristics of Study Participants

Characteristic	No. (%) Oxygen (n = 48)	Room Air (n = 51)
Maternal age, mean (SD), y	27.3 (6.3)	27.8 (5.3)
Race/ethnicity		
African American	36 (75.0)	40 (78.4)
White	5 (10.4)	9 (17.6)
Hispanic	3 (6.3)	1 (2.0)
Asian	3 (6.3)	0 (0.0)
Other	1 (2.1)	1 (2.0)
Prepregnancy BMI, mean (SD)	26.9 (6.5)	27.7 (7.3)
Gestational age at delivery, mean (SD), wk	39.2 (1.1)	39.1 (1.1)
Nulliparity	5 (10.4)	6 (11.8)
Chronic hypertension	3 (6.3)	6 (11.8)
Preeclampsia	0 (0.0)	3 (5.9)
Pregestational diabetes	0 (0.0)	0 (0.0)
Tobacco use	6 (12.5)	8 (15.7)
Illicit drug use	12 (25.0)	8 (15.7)
Alcohol	0 (0.0)	2 (3.9)
Induction of labor	34 (70.8)	36 (70.6)
Oxytocin	43 (89.6)	45 (88.2)
Chorioamnionitis	0 (0.0)	0 (0.0)
Epidural	44 (91.7)	50 (98.0)
Hematocrit on admission, mean (SD), %	32.8 (3.5)	32.5 (3.2)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

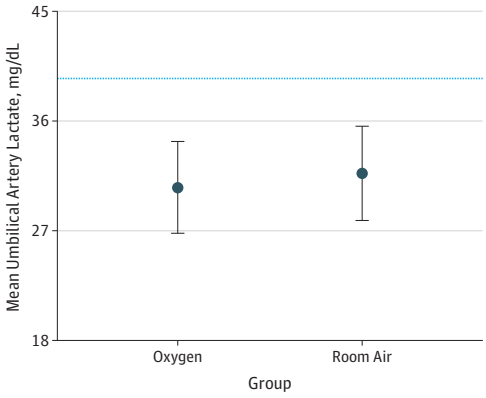
Table 2. Alternate Methods of Intrauterine Resuscitation and Interventions After Randomization

Intrapartum Intervention	No. (%) Oxygen (n = 48)	Room Air (n = 51)	*P* Value
Intravenous fluid bolus	9 (18.8)	9 (17.7)	.89
Total intravenous fluids, median (IQR), mL	234.0 (114.5-708.0)	438.0 (125.0-867.0)	.27
Oxytocin discontinued or decreased	21 (43.8)	18 (35.3)	.39
Maternal repositioning	39 (81.3)	45 (88.2)	.33
Times repositioned, median (IQR), No.	3 (2-5)	3 (2-4)	.40
Amnioinfusion	13 (27.1)	10 (19.6)	.38
Time from randomization to delivery, median (IQR), min	96 (47-176)	109 (53-279)	.34

Abbreviation: IQR, interquartile range.

CI, 27.9-36.0 mg/dL) in the room air group (a mean difference of 0.9 mg/dL [95% CI, −4.5 to 6.3 mg/dL]; *P* = .69). The 95% CI of umbilical artery lactate in the room air group did not cross the prespecified noninferiority margin of 40.5 mg/dL (**Figure 2**). In an imputation analysis that included patients with unpaired or missing umbilical artery gases, there was no difference in umbilical artery lactate between the room air group (median [interquartile range], 30.6 [27.0-33.3] mg/dL) and the oxygen groups (median [interquartile range], 31.5 [27.9-35.1] mg/dL; *P* = .57).

Figure 2. Mean Umbilical Artery Lactate in Patients Randomized to Oxygen and Room Air



The blue line indicates the noninferiority margin; black dots mark the mean and error bars the 95% CIs. SI conversion factors: to convert lactate to mmol/L, multiply by 0.111.

In the subgroup analysis of patients with recurrent late or recurrent variable fetal heart rate decelerations at time of randomization, umbilical artery lactate remained similar in room air and oxygen groups with no evidence of modification by the presence or absence of recurrent decelerations (room air group: presence: mean, 29.7 mg/dL [95% CI, 25.2-42.3 mg/dL] vs absence: 32.4 mg/dL [95% CI, 20.7-48.6 mg/dL] and oxygen group: presence: mean, 26.1 mg/dL [95% CI, 18.9-36.0 mg/dL] vs absence: 26.1 mg/dL [95% CI, 21.6-37.8 mg/dL]; *P* for interaction = .85) (eTable 3 in Supplement 2).

There were no significant differences in other umbilical artery gas components, including pH, base deficit, partial pressure of oxygen, and partial pressure of carbon dioxide, between room air and oxygengroups. Mode of delivery, including cesarean delivery for nonreassuring fetal status and operative vaginal delivery, did not differ between groups (**Table 3**). One neonate in the oxygen group received hypothermia treatment. There were no other adverse neonatal outcomes or neonatal deaths.

Among patients who received room air or oxygen per protocol, there was no difference in umbilical artery lactate between groups (mean, 31.5 mg/dL [95% CI, 27.0-36.9 mg/dL] vs 28.8 mg/dL [95% CI, 25.2-32.4 mg/dL]; *P* = .36). Secondary outcomes were also similar between oxygen and room air groups (eTable 4 in Supplement 2).

Discussion

The results of this randomized clinical trial of room air vs oxygen for intrapartum category II fetal heart tracings show that room air is noninferior to oxygen for the reduction of umbilical artery lactate, a marker of fetal metabolic acidosis. Umbilical artery lactate remained similar between room air and oxygen groups even among patients with recurrent fetal heart rate decelerations in labor. Room air did not change other umbilical artery gas components, nor did it increase

Table 3. Secondary Outcomes in Patients Randomized to Oxygen or Room Air

Characteristic	Mean (95%CI)		Mean Difference (95% CI)	Relative Risk (95% CI)[a]
	Oxygen (n = 48)	Room Air (n = 51)		
Umbilical artery gas				
pH	7.25 (7.23 to 7.27)	7.26 (7.24 to 7.28)	0.01 (−0.01 to 0.03)	NA
Base deficit	−3.6 (−4.3 to −2.9)	−3.6 (−4.3 to −2.9)	0.0 (−1.0 to 1.0)	NA
pO_2, mm Hg[b]	24.4 (20.0 to 28.8)	19.7 (17.5 to 22.0)	−4.7 (−9.6 to 0.1)	NA
pCO_2, mm Hg[b]	57.4 (54.2 to 60.6)	55.9 (53.5 to 58.2)	−1.5 (−5.4 to 2.4)	NA
Mode of delivery, No. (%)				
Cesarean delivery	6 (12.5)	2 (3.9)	NA	0.32 (0.07 to 1.48)
Cesarean delivery for nonreassuring fetal status	2 (4.2)	0 (0.0)	NA	NA
Operative vaginal delivery	1 (2.1)	6 (11.8)	NA	5.65 (0.71 to 45.20)

Abbreviations: NA, not applicable; pO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide.

[a] Relative risks determined for categorical outcomes.

[b] SI conversion factors: to convert partial pressure of oxygen and partial pressure of carbon dioxide to kPa, multiply by 0.133.

rates of cesarean delivery for nonreassuring fetal status or operative vaginal delivery.

None of the 3 prior randomized clinical trials investigating cord gas outcomes in laboring patients with so-called reassuring fetal heart tracings randomized to oxygen or room air have demonstrated benefit to neonatal acid-base status with maternal oxygen supplementation. In a trial of 86 patients in the second stage of labor, Thorp et al[14] observed no difference in umbilical artery pH between room air and oxygen groups. Rather, there was a significantly higher rate of neonatal acidemia (umbilical artery pH <7.20) in the oxygen group.[14] Similar suggestion of harm was found in another trial of 56 patients, which noted a higher rate of delivery room resuscitation in neonates born to oxygen-exposed mothers with no differences in pH or other cord gases between room air and oxygen groups.[15] The largest trial thus far (of 443 patients) also found no differences in umbilical artery pH between patients with and without low-flow oxygen exposure.[16] Our results corroborate the negative findings of these 3 trials. However, unlike preceding trials, our study included patients with category II fetal heart tracings, suggesting that maternal oxygen supplementation even in the setting of putatively abnormal tracings is unlikely to improve neonatal acid-base status. We evaluated umbilical artery lactate, rather than pH, as it is a surrogate cord gas marker associated with hypoxia-associated neonatal morbidity and is superior to pH in the prediction of such morbidity.[18]

The ineffectiveness of maternal oxygen supplementation may be explained by the oxygen-hemoglobin dissociation curve. In a patient with normal oxygen saturations, the addition of supplemental oxygen increases maternal partial pressure of oxygen but only by clinically insignificant amounts.[16] Prior studies and our results demonstrate either minimal or no increase in fetal partial pressure of oxygen with maternal oxygen supplementation, thereby making prevention or reversal of fetal anaerobic metabolism and subsequent acidosis less plausible.[14,15] Hyperoxygenation may not only be futile, but may also be harmful, because excess oxygen exposure is associated with vasoconstriction,[24,25] which may negatively impact placental oxygen delivery and tissue perfusion. Furthermore, reoxygenation of the fetus after a period of hypoxia is associated with free radical production that may have detrimental sequelae.[3,26]

Limitations

This trial has several limitations. First, patients and clinicians were not blinded to the intervention arms. Lack of blinding in this setting may have introduced bias in subsequent labor management. However, there were no differences in other measures of intrauterine resuscitation or mode of delivery between groups. Additionally, outcome assessment and analysis was performed in a blinded fashion. Second, the noninferiority design of this study does not allow for conclusions regarding superiority of 1 intervention vs the other. Although the noninferiority of room air to oxygen raises suspicion for the futility of a widely practiced intrapartum resuscitation technique, our sample size limits conclusions regarding neonatal outcomes or the safety of oxygen vs room air. Third, our study did not include any patients with category III fetal heart tracings, the group at highest risk for fetal acidemia. However, category III tracings are observed infrequently (in 0.1% of patients in labor).[2] Therefore, this trial investigated oxygen use in the population of patients it is most commonly administered to: patients with category II fetal heart tracings in labor. Last, although we used broad inclusion criteria, this trial was performed in a single center. This may reduce generalizability.

Conclusions

Among patients with category II fetal heart tracings in labor, room air is noninferior to maternal oxygen supplementation for the improvement of umbilical artery lactate, a marker of fetal metabolic acidosis. Use of room air, instead of oxygen, did not affect other components of an umbilical artery gas or mode of delivery. These findings challenge a widely practiced intrauterine resuscitation technique. The results of this randomized clinical trial suggest that room air may be an acceptable alternative and establish equipoise for future investigation into the safety and utility of intrapartum oxygen administration.

ARTICLE INFORMATION

Accepted for Publication: April 10, 2018.

Published Online: July 23, 2018. doi:10.1001/jamapediatrics.2018.1208

Author Contributions: Dr Raghuraman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Raghuraman, Temming, Macones, Tuuli, Cahill.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Raghuraman, Wan.
Critical revision of the manuscript for important intellectual content: Raghuraman, Temming, Woolfolk, Macones, Tuuli, Cahill.
Statistical analysis: Raghuraman, Wan, Temming, Woolfolk, Macones, Tuuli.
Obtained funding: Raghuraman, Cahill.
Administrative, technical, or material support: Temming, Cahill.
Supervision: Macones, Tuuli, Cahill.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was funded by the Thrasher Research Fund (grant 14084, Dr Raghuraman).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Meeting Presentation: Presented at the Society for Maternal-Fetal Medicine Annual Pregnancy Meeting; February 1, 2018; Dallas, Texas.

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