

REBEL Cast July 2015 Show Notes

Topic #1: The AVOID Trial - Oxygen versus Room Air for STEMI

Question: Does the administration of supplemental oxygen benefit patients who are normoxic with ST-Elevation Myocardial Infarction (STEMI)?

What Specific Article Will We Be Covering?

Stub D et al. Air Versus Oxygen in ST-Segment Elevation Myocardial Infarction. Circulation May 2015 [[epub ahead of print](#)]

Details of the Study

Background: The first report for supplemental oxygen for angina was in 1900, and since then oxygen therapy has been a commonly used treatment of patients with ST-Elevation Myocardial Infarction (STEMI). The reason for this is the belief that supplemental oxygen will increase oxygen delivery to ischemic myocardium and help reduce myocardial injury. This belief is based off lab studies and older clinical trials, but there have been other studies that suggest potential adverse physiologic effects of supplemental oxygen (i.e reduced coronary blood flow, increased coronary vascular resistance, and production of reactive oxygen species) causing vasoconstriction and reperfusion injury. Ultimately, there are no studies evaluating the effects of supplemental oxygen therapy involving STEMI patients who are undergoing percutaneous coronary intervention.

Taking all this information together there is a lot of uncertainty over the utility of routine supplemental oxygen therapy in acute myocardial infarction with no clear recommendations in normoxic patients in the most recent American Heart Association (AHA) STEMI guidelines. Despite this most patients with acute STEMI still have supplemental oxygen administered.

What They Did:

- Compare supplemental oxygen therapy (face mask at 8 L/min) vs NO oxygen therapy in normoxic patients with STEMI (if O₂ sat fell <94% received 4L/min nasal cannula or facemask 8L/min)
- Multicenter, Prospective, Open Label, Randomized Trial
- Conducted by Ambulance Victoria and 9 Metropolitan Hospitals in Melbourne, Australia
- Individuals involved with the delivery of oxygen therapy pre-hospital and in-hospital were not blinded to treatment, but 6 month follow up coordinator and investigators undertaking data analysis were masked to treatment assignment

Patient Population:

- **Inclusion Criteria**
 - Age ≥ 18 years

- Chest Pain < 12 hours
- Prehospital ECG evidence of STEMI (STE of ≥ 0.1 mV in 2 contiguous limb leads, or ≥ 0.2 mV in 2 contiguous chest leads, or new LBBB)
- **Exclusion Criteria**
 - Oxygen saturation <94%
 - Bronchospasm requiring nebulized beta₂ agonist therapy using oxygen
 - Oxygen administration prior to randomization
 - Altered mental status
 - Planned transport to a non-participating hospital
 - Deemed not to have STEMI after physician assessment at hospital

Outcomes:

- **Primary Endpoint**
 - Myocardial injury (measured by peak cTnl and CK)
- **Secondary Endpoints (At Hospital Discharge & 6 Months)**
 - ECG ST-segment resolution
 - Mortality
 - Major Adverse Cardiac Events (Death, recurrent MI, repeat revascularization, and stroke)
 - Myocardial infarct size on Cardiac Magnetic Resonance Imaging (CMR) at 6 months

Results:

- 638 patients randomized for study → 441 with confirmed STEMI included in analysis
- Primary Outcomes:
 - Mean Peak Troponin I: 57.4 mcg/L (Oxygen Group) vs 48.0 mcg/L (No Oxygen Group) [p = 0.18]
 - Mean Peak CK: 1948 U/L (Oxygen Group) vs 1543 U/L (No Oxygen Group) [p = 0.01]
- Secondary Outcomes:
 - Mortality at Hospital Discharge: 1.8% (Oxygen Group) vs 4.5% (No Oxygen Group) [p = 0.11]
 - In-Hospital Recurrent MI: 5.5% (Oxygen Group) vs 0.9% (No Oxygen Group) [p = 0.006]
 - In-Hospital Cardiac Arrhythmias: 40.4% (Oxygen Group) vs 31.4% (No Oxygen Group) [p = 0.05]
 - CMR performed on 139 patients (32%) at 6 months
 - Median Infarct Size: 20.3g (Oxygen Group) vs 13.1g (No Oxygen Group) [p = 0.04] → Expressed as proportion of left ventricular mass = 12.6% vs 9.0% respectively [p = 0.08]

Limitations:

- This study was not powered for clinical endpoints (i.e. in-hospital recurrent myocardial infarctions, major cardiac arrhythmias, and mortality) but instead looked at surrogate cardiac biomarker and LV infarct size
- Treatment allocation not blinded to paramedics, patients or in-hospital cardiology teams, but the 6 month follow up coordinator, statistician, and investigators undertaking data analysis were masked to treatment assignment
- There was a very low mortality rate in this trial.
- There were a lot of patients enrolled in the pre-hospital setting, who were excluded later by physicians which could cause a selection bias
- At 6-months approximately 1/3 of randomized patients had cardiac MRI, and this was due to contraindications to MRI, and availability at a single center site making it difficult for patients to travel
- There was a portion of the no oxygen arm that did receive oxygen therapy (7.7%), which may dilute the differences quoted in this study.

Discussion:

- Many believe that routine administration of supplemental oxygen in normoxic patients with STEMI reduces psychological and physiological stresses, but in this study there was no difference in chest pain scores or the requirement for additional opioid analgesics.
- Only 7.7% of patients in this study allocated to the no oxygen arm required oxygen by the time they arrived to the catheterization lab.
- This study was also not designed to assess the impact of lower concentrations of supplemental oxygen (i.e. <8L/min)
- It is important to remember that oxygen is a drug, and just like any drug we prescribe to patients it has possible significant side effects. Unfortunately, to date there is a paucity of clinical trial data to support routine use of supplemental oxygen in normoxemic patients with STEMI to help with guidance.

Study Conclusion: This study does not demonstrate any significant benefit of routine use of supplemental oxygen therapy for reducing myocardial infarct size, improving patient hemodynamics, or alleviating symptoms.

Stay Tuned for DETO2X Trial: <http://www.deto2x.se/english/>

The DETO₂X-AMI trial is a RCT designed and powered to evaluate effects of oxygen in acute cardiac ischemia by looking at hard endpoints (i.e. morbidity & mortality) as well as surrogate endpoints using modern biochemistry, angiographic and imaging techniques. The study design and a description of a 3-months pilot study is published in the [American Heart Journal](#) and [clinicaltrials.gov \(NCT01787110\)](https://clinicaltrials.gov/ct2/show/study/NCT01787110).

Clinical Take Home Point: This study does not demonstrate any significant benefit of routine use of supplemental oxygen therapy for reducing myocardial infarct size, improving patient hemodynamics, or alleviating symptoms, but we still need some studies with clinical endpoints before changing practice.

Topic #2: The FLORALI Trial: High-Flow Oxygen Through Nasal Cannula in Acute Hypoxemic Respiratory Failure

Clinical Question: In patients with acute hypoxemic respiratory failure does oxygen through high-flow nasal cannula compared to standard oxygen delivered through a facemask or non-invasive positive-pressure ventilation help prevent intubation?

Article: Frat JP et al. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. NEJM 2015 [epub ahead of print]. [PMID: 25981908](#)

Background: It is a well-known fact that Non-Invasive Positive Pressure Ventilation (NIPPV) reduces the need for intubation and mortality in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) or cardiogenic pulmonary edema. The reason for this is a decrease in work of breathing and improvement of gas exchange. On the other hand in patients with acute hypoxemic respiratory failure the use of NIPPV with respect to intubation and mortality are conflicting. Thus far the literature does not conclusively support the use of NIPPV in patients with non-hypercapnic acute hypoxemic respiratory failure. Oxygen through High-Flow Nasal Cannula (HFNC) can produce low levels of positive pressure ventilation due to the high flow rates, which may also decrease physiological dead space. To date, the effect of oxygen through HFNC on mortality and intubation rates of patients admitted to the intensive care unit (ICU) with acute hypoxemic respiratory failure has never been studied until now.

What They Did:

- Prospective, Multicenter, Open-Label, Randomized, Controlled Trial from 23 ICUs in France and Belgium of patients without hypercapnia who had acute hypoxemic respiratory failure
- Patients randomized to HFNC (50LPM & FiO₂ of 1.0 at initiation), standard oxygen therapy through a facemask (≥10 LPM), or NIPPV (Pressure-support level to obtain TV of 7 – 10 mL/kg of predicted body weight, Initial PEEP 2 – 10 cmH₂O)

Inclusion Criteria:

- Consecutive patients who were ≥18 years of age who met the following four criteria:
 1. Respiratory rate of >25 breaths per minute

2. A ratio of the partial pressure of arterial oxygen to the FiO₂ of 300mmHg or less while breathing oxygen at 10 liters/minute for at least 15 minutes
3. A partial pressure of arterial carbon dioxide not higher than 45mmHg
4. An absence of clinical history of underlying chronic respiratory failure

Exclusion Criteria:

- Partial pressure of arterial carbon dioxide of > 45mmHg
 1. Exacerbation of asthma or chronic respiratory failure
 2. Cardiogenic pulmonary edema
 3. Severe neutropenia
 4. Hemodynamic instability
 5. Use of vasopressors
 6. A Glasgow Coma Scale Score of <12 points
 7. Contraindications to non-invasive ventilation
 8. Urgent need for endotracheal intubation
 9. A do-not-intubate order
 10. Decision not to participate

Outcomes:

- **Primary**
 - Proportion of patients who required intubation within 28 days after randomization
- **Secondary**
 - Mortality in the ICU
 - Mortality at 90 days
 - Number of ventilator free days in 1st 28 days
 - Duration of ICU stay

Results:

- 2506 patients with acute hypoxemic respiratory failure → 525 eligible for inclusion → 313 underwent randomization → 3 withdrew consent → 310 patient included in analysis (94 standard oxygen therapy, 106 HFNC, and 110 NIPPV)
- The main cause of acute respiratory failure was community-acquired pneumonia (CAP) in 75.5% of patients
- Primary Outcomes:
 - Intubation rate at day 28 (p= 0.18)
 - 38% in HFNC
 - 47% in Standard Oxygen Group
 - 50% in NIPPV
- Secondary Outcomes:
 - In ICU Mortality (p = 0.047)
 - 11% in HFNC
 - 19% in Standard Oxygen Group
 - 25% in NIPPV

- 90 Day Mortality (p = 0.02)
 - 12% in HFNC
 - 23% in Standard Oxygen Group
 - 28% in NIPPV
 - HR Standard Oxygen vs HFNC 2.01
 - HR NIPPV vs HFNC 2.50
- Ventilator Free Days (p = 0.02)
 - 24 +/- 8 in HFNC
 - 22 +/- 10 in Standard Oxygen Group
 - 19 +/- 12 in NIPPV
- Ventilator Free Days in Patients with P/F Ratio ≤ 200 mmHg (p <0.001)
 - 24 +/- 8 in HFNC
 - 21 +/- 10 in Standard Oxygen Group
 - 18 +/- 12 in NIPPV

Strengths:

- Multicenter, randomized trial, which makes the results more generalizable.
- Sealed randomization to assigned strategies of oxygen delivery
- Complete follow-up at 90 days

Limitations:

- This was a small patient population which underpowered study to detect a significant between-group difference in the intubation rate in the overall population, but a reduced intubation rate was seen in the post hoc analysis in the subgroup of patients with a P/F ratio of ≤ 200 mmHg

Discussion:

- Although there was not a statistical difference in the primary outcome (i.e. intubation rate) due to the small patient population enrolled, there is obviously a very real clinical difference: HFNC 37% vs 47% O₂ via facemask vs 50% in NIPPV (Absolute difference of 10% and 13%)
- This trial does not tell us if HFNC is beneficial or NIPPV is harmful and ultimately is NIPPV better than early intubation in these patients? A study by Kang BJ et al in Intensive Care Med 2015 showed that failure of HFNC causing delayed intubation might have worse clinical outcomes in patients with respiratory failure (i.e. Overall ICU mortality 39.2 vs 66.7% and extubation success 37.7 vs 15.6% in patients intubated <48hr vs >48hrs respectively)
- Given this small population, it is hard to have a definitive take away point, but as with most initial studies on a new topic that are not powered well, more studies are needed to validate these initial findings, but HFNC is definitely not inferior to NIPPV in this patient population

Study Conclusion: Treatment with high-flow oxygen improved the survival rate among patients with acute hypoxemic respiratory failure, even though no difference was seen in the intubation rate (i.e. primary outcome).

Clinical Take Home Point: HFNC is non-inferior to NIPPV, in patients with hypoxemic respiratory failure, but further studies are needed to determine whether these initial findings of benefit are practice changing.

Upcoming Conferences:

1. The Teaching Course New York (Nov. 10th – 13th, 2015): Registration at www.theteachingcourse.com
2. Blood and Sand – Resuscitation, Airway, and Ultrasound (Dec. 6th – 10th, 2015): Registration at www.cmevacations.com