

Oxygen in heart attacks: a long-standing belief changes

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Dr. Dion Stub is interested in studying treatments for emergencies related to heart attacks. Here he discusses his research interests and his recent scientific input to the controversy between the benefits versus adverse effects of supplemental oxygen therapy in heart attack cases.



To start, can you tell the readers how did your career start in cardiology and what are your research interests?

I graduated from Monash University, Australia, in 2003 and undertook cardiology training at The Alfred Hospital. In 2013, I was awarded a PhD for my research on developing a unique treatment pathway for patients with refractory cardiac arrest, through combined research at the Baker IDI Heart and Diabetes Institute and The Alfred Hospital. Afterwards, I spent two years in the US and Canada as a post-doctoral fellow, working alongside international leaders in researching cardiac emergency care and transcatheter heart interventions. I have a particular interest in researching and treating emergencies related to coronary disease and cardiac arrest, whilst specializing in coronary and structural heart interventional procedures.

Your research is mainly focused on cardiovascular diseases, what are their impacts on public health and patient's lifestyle?

Cardiovascular diseases account for almost 30% of the disease burden around the world. In Australia, heart diseases and stroke cause over 50,000 deaths per year, which is only expected to increase over the coming decades due to our ageing population. The major risk factors for cardiovascular diseases include high blood pressure, high cholesterol, diabetes and smoking. Other key lifestyle features increasing the risk of cardiovascular disease are obesity and a sedentary lifestyle. Accordingly, patients suffering cardiovascular diseases or individuals at high risk are required to adapt their lifestyle habits such as diet, smoking, alcohol consumption and physical exercise in order to avert or reduce the critical lack of blood supply to the heart and the brain. Failure to do so

might cause life-threatening outcomes.

Given the old-age belief in the therapeutic benefit of supplemental oxygen in cases of heart attacks, do you expect the findings of your 'AVOID' study, which recommend the opposite, to change the current international treatment guidelines?

The AVOID trial specifically aimed to investigate the effects of supplemental oxygen therapy on heart injury, in patients with suspected heart attack. Although oxygen is beneficial in complicated cases where patients develop hypoxia, evidence supporting its routine use in patients with normal blood oxygen levels is not strong. Recent mechanistic studies have highlighted the potential adverse effects of supplemental oxygen to the heart. Simply, our bodies respond to excess of oxygen by decreasing the blood flow to the various organs. During a heart attack, this response may further reduce blood flow through the coronary arteries. Additionally, excessive oxygen can promote the generation of destructive molecules known as free radicals in the cells, which can further aggravate the damage of the heart muscle.

The AVOID study, together with these recent physiological studies, does not demonstrate any significant benefit of routine oxygen therapy in alleviation of heart attacks or their symptoms. Instead, the AVOID trial identified a signal for increased heart muscle injury with the routine use of supplemental oxygen in patients with normal blood oxygen levels. Oxygen should be treated like all other medical therapies, balancing efficacy versus side effects. Based on the findings of the AVOID trial - the largest so far - we would recommend that pre-hospital and hospital care providers review their current practice regarding supplemental oxygen. Until

larger studies are available, international guidelines should consider updating recommendations, highlighting the lack of benefit of oxygen therapy and its potential harm in cases of heart attacks, unless blood oxygen saturation is below 94%.

Was the AVOID study done in collaboration with other research groups or institutes? The study was led and conducted by Ambulance Victoria in collaboration with nine metropolitan hospitals that provide 24 hour cardiac intervention services in Melbourne, Australia, between October 2011 and July 2014. Important contributions were also made by Baker IDI Heart and Diabetes Institute and Monash University.

Are you planning to extend your research on oxygen therapy further? What might be the scope of the next step?

Further trials are needed to confirm the potential harmful effects of excess oxygen during acute heart attacks and more importantly, its effect on patient survival. Currently a trial is running in Sweden, based on registered records of patients with acute heart attack to investigate the possible adverse effects of oxygen therapy. The trial is statistically designed to provide evidence for the effects of supplemental oxygen on cardiovascular survival. Also, the AVOID investigators together with the Australian Resuscitation Outcomes Consortium is planning a similar trial in patients with out-of-hospital heart arrest to investigate the potential cardiac and neurological outcomes of high flow oxygen following heart arrest.

Oxygen for Heart Attack Victims: Friend or Foe?

Dr. Stub and his fellow researchers have recently completed a clinical study that addresses the concerns over the adverse effects of supplemental oxygen therapy in patients with heart attack who exhibit normal blood oxygen levels.

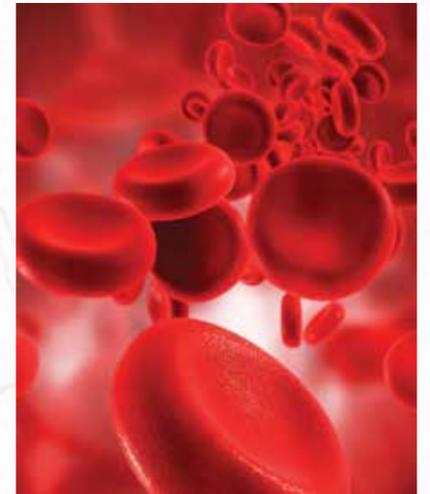
THE STORY OF HEART ATTACKS AND OXYGEN

Each year some 19 million people around the globe experience cardiac emergencies such as heart attack and heart arrest. The majority of heart attacks occur as a result of disease conditions causing severe occlusion of one or more of the coronary arteries that nourishes the heart. These conditions commonly include coronary artery disease and coronary thrombosis. As a result of coronary occlusion, some parts of the heart musculature (myocardium) suffer a lack of blood flow, leading to heart muscle injury, a condition known as myocardial infarction. At this point, the victim might suffer symptoms of a heart attack, which include pain and discomfort in the chest and upper body parts such as the jaws, neck, arms and shoulders and shortness of breath.

Following the first report of supplemental oxygen for heart disease in 1900, oxygen therapy has been commonly used in the initial treatment of patients with heart attack. This was based on the belief that supplemental oxygen may increase oxygen delivery to the heart muscles lacking blood supply and hence, reduce myocardial injury. 'Until recently giving supplemental oxygen to all patients with suspected heart attack was considered a fundamental first aid response and was part of all international medical guidelines, taught to paramedics, medical and nursing staff', Says Dr. Stub.

ALARMS AGAINST ROUTINE OXYGEN THERAPY

Oxygen therapy can in fact be beneficial in complicated cases of heart attacks, where a patient concurrently suffers a significant decrease in blood oxygen saturation levels. However, a combined analysis of the data obtained from three independent small clinical trials suggested a possible increase in adverse outcomes of supplemental oxygen administration in patients with normal blood oxygen. Similarly, a combined analysis of the



findings from two clinical trials where novel techniques were used for additional oxygen delivery to the parts of the myocardium lacking sufficient blood supply indicated that this treatment caused a significant reduction in coronary blood flow, an increase in coronary resistance to blood flow (coronary constriction), and a significant reduction in myocardial oxygen consumption. 'These data appear to suggest that supplemental oxygen may be harmful', says Dr. Stub.

THE 'AVOID' STUDY

With the growing concerns over the potential adverse effects of supplemental oxygen therapy in patients with heart attack showing normal blood oxygen levels, Dr. Stub and his research team have conducted a larger clinical trial to compare supplemental oxygen therapy with no oxygen therapy in these patients to determine the effects of the treatment on the size of myocardial damage. The trial which has been given the title The Air Versus Oxygen in Myocardial Infarction is better known in the scientific community as 'AVOID'.

The AVOID trial was conducted by Ambulance Victoria and nine metropolitan hospitals across Melbourne, between October 2011 and July 2014. The study involved 441 adults of ≥ 18 years of age, who complained chest pain commencing

less than 12 hours prior to assessment, and who were later confirmed to suffer a serious type of heart attacks known as ST-segment elevation myocardial infarction. Importantly, all of the selected patients showed normal blood oxygen saturation levels, while patients with saturation levels of $\geq 94\%$ were excluded from the study since withholding oxygen therapy may be unsafe for them. Supplemental oxygen therapy was randomly assigned to half of the patients (218), while the other half received no oxygen (referred to as Air). Paramedics were given a 'randomisation envelope' to open at the scene, informing them to provide or withhold oxygen therapy in each case. Patients assigned to supplemental oxygen therapy continued to receive oxygen during the in-hospital care.

In order to evaluate the possible adverse outcomes of supplemental oxygen therapy in patients with heart attack, a set of primary and secondary clinical measures relevant to cardiac health was assessed. The primary measure was the size of the myocardial damage, as indicated by the blood levels of two enzymes, troponin and creatine kinase. These enzymes are known to be synthesized in the muscle cells of the heart and are found in the blood in high concentrations when a significant myocardial damage occurs. Secondary measures included abnormal heart rhythm, as indicated by electrocardiogram and repeated heart attacks. Also, after 6 months, the researchers reevaluated the size of myocardial damage in about one-third of the participants by cardiac magnetic resonance imaging.

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The findings of the AVOID study provide evidence for an increase in myocardial damage in patients with heart attacks as a result of supplemental oxygen therapy

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A CENTURY-OLD PRACTICE DOING MORE HARM THAN GOOD

The findings of the AVOID study have further confirmed the suggested adverse effects of supplemental oxygen therapy in heart attack patients, who exhibit normal blood oxygen saturation. Dr. Stub and his colleagues have found that supplemental oxygen therapy can significantly contribute to increasing the size of the myocardial damage. According to

the abstract presented to the American Heart Association Scientific Sessions in November of last year, a 25 percent increase in blood levels of troponin and creatine kinase was recorded in the patient group receiving oxygen compared to the no oxygen group. Even more, a significantly higher percentage of the oxygen-treated patients developed more dangerous heart rhythms or experienced subsequent heart attacks compared to the patients received no oxygen. Among the subgroup of patients who returned after 6 months for magnetic resonance imaging of the heart, the oxygen-treated patients showed a 30 percent increase in the size of myocardial damage compared to the no oxygen group. Additionally, supplemental oxygen therapy made no difference in symptoms felt by the patients during the study, which is rather surprising since supplemental oxygen has been commonly believed to help relieve the chest pain.

TIME TO AVOID SUPPLEMENTAL OXYGEN?

Although the findings of the AVOID study clearly demonstrate the potential adverse outcomes of supplemental oxygen therapy in cases of heart attacks, it does not give a full insight on the influence of the practice on patients' survival. In the course of the AVOID study, no statistically significant differences in mortality were found among oxygen-treated and non-oxygen-treated patient groups. However, with the relatively low overall mortality observed during the study, such differences might have been missed. Therefore, larger studies are necessary to circumvent these limitations. 'An outcomes-based study would require much larger numbers of patients', says Dr. Stub.

So far, AVOID is the largest available study, in terms of the number of participants. Therefore, in light of the evidences provided by AVOID, the community of cardiologists and cardiac care providers should revise the current practices in treatment of heart attacks patients, particularly those with normal blood oxygen saturation.

In response to the recommendations of the AVOID trial, a growing number of hospitals, not only in Australia, but also in other countries, instruct the ambulance crew to check the blood oxygen levels of patients suspected with heart attacks before any supplemental oxygen is given. Additionally, the findings of Dr. Stub and his research team have been applauded by independent cardiology experts.

Researcher Profile



Dr. Dion Stub
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Dr. Dion Stub is a cardiologist investigating new ways of managing people with cardiac arrest and heart attack. He was awarded his PhD in 2013, through his work at Monash University and the Baker IDI Heart and Diabetes Research Institute. He is also a coronary and structural interventional cardiologist at the Alfred Hospital and Western Health in Melbourne. Dion spent 2 years overseas as a post doctorate fellow, with the support of the prestigious Victoria Fellowship and Australian Cardiac Society Award. He worked first at the University of Washington, Seattle and then spent 12 months at St Paul's Hospital, Vancouver working alongside Prof. John Webb, an international expert at transcatheter aortic valve replacement. His ongoing research is supported by joint NHMRC and National Heart foundation grants.

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LINKS

<http://globalnews.ca/news/1690465/watch-study-could-change-how-heart-attack-patients-are-treated/>
<http://www.medscape.com/viewarticle/835297>

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