WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

	Date Submitted for review:
Mailing address:	**Phone:**
	Email:

2. Clinical question:

[NOTE – ALL ITALICIZED TEXT IS SAMPLE TEXT – PLEASE DELETE IT AND REPLACE IT BEFORE SUBMITTING YOUR WORKSHEET]
In patients with suspected ACS in various settings (e.g. prehospital, emergency or in-hospital) and normal oxygen saturations (P), does the use of supplemental oxygen (I), compared with room air (C), improve outcomes (e.g. chest pain resolution, infarct size, ECG resolution, survival to discharge, 30/60 d mortality) (O) ?

3. Conflict of interest specific to this question:

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?

4. Search strategy (including electronic databases searched):

4a. Databases

-MEDLINE via PUBMED (1950 to May 2009) (performed on August 28th 2010)
1. myocardial infarction
2. acute coronary syndromes
3. unstable angina
4. chest pain
5. oxygen therapy

1 and 5: 22 relevant hits out of 2180 total hits
2 and 5: 1 additional relevant hit
3 and 5: no additional relevant hits
4 and 5: no additional relevant hits

-CAB (1910 to Feb 2011) (performed on August 11th 2010)
Report as for Medline

4b. Other sources

-GOOGLE SCHOLAR (performed on August 5th 2010)
Report as for Medline

-In addition all references of identified articles and in particular the references of the following relevant review articles were checked: (Nicholson 2004), (Beasley, Aldington et al. 2007) and (Wijesinghe, Perrin et al. 2009)

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

Inclusion criteria

Use of oxygen therapy in patients with ST elevation myocardial infarction or acute coronary syndromes

Exclusion criteria

Intracoronary oxygen, Hyperbaric oxygen. Abstracts only. Editorials

4d. Number of articles/sources meeting criteria for further review: 13

-Two randomized trials were identified: (Rawles and Kenmure 1976) and (Wilson and Channer 1997)

-Five relevant human (mechanistic) studies were identified: (Thomas, Malmcrona et al. 1965), (Kenmure, Murdoch et al. 1968), (Foster, Casten et al. 1969), (Horvat, Yoshida et al. 1972) and (Madias, Madias et al. 1976).

-Six relevant animal studies were identified: (Maroko, Radvany et al. 1975), (Malm, Arborelius et al. 1977),(Ribeiro, Louie et al. 1979) (Weisse, Moore et al. 1982),(Ishikawa, Kanamasa et al. 1986) and (Kelly, Hursey et al. 1995)

5. Summary of evidence

Evidence Supporting Clinical Question

Good						
Fair					*Madias 1974; E=ischemic injury by ST segment*	*Horvat 1972; E=angina threshold Maroko 1975; E=infarct size Ribeiro 1979; E=myocardial blood flow Ishikawa 1986; E= myocardial contractile force Kelly 1995; E=infarct size*
Poor	*Wilson 1997; E=severe hypoxemia*					
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

Evidence Neutral to Clinical question

Good						
Fair	*Nicholson 2004 systematic review Rawles 1976; E=mortality, incidence of arrhythmias*					*Weisse 1982; E=infarct size*
Poor						
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

Evidence Opposing Clinical Question

Good						
Fair	*Rawles 1976; C E=infarct size Wijesinghe 2009; C*					*Kenmure 1968; E=cardiac output Foster 1969; E=cardiac output*
Poor						*Thomas 1965; E=cardiac output Malm 1977; E=infarct size*
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Oxygen has been used in the treatment of myocardial infarction and acute coronary syndromes for many years. Evidence in support of this approach is primarily derived from animal models, in which the administration of oxygen during and/or after experimental coronary artery occlusion reduces the extent of myocardial necrosis in some (Maroko 1975, Ribeiro 1979, Kelly 1995, Ishikawa 1986), but not all studies (Malm 1977, Weisse 1982). Few human studies conducted in small number of patients suffering a myocardial infarction reported diminished cardiac output during oxygen therapy (Thomas 1965, Kenmure 1968, Foster 1969). One human case study found improvement in ST changes with the use of oxygen (Madias 1976). Rawles and Kenmure conducted a blinded randomized controlled trial in 157 patients suffering myocardial infarction (oxygen versus room air inhalation). Aspartate aminotransferase levels, as surrogate for infarct size, were higher in the oxygen group (P<0.05). There were 11.3% deaths in the oxygen group and 4% in the air group, relative risk of death 2.9 (95% CI 0.8-10.3, P=0.08). Ventricular tachycardia occurred in 13.8% of the oxygen group and 6.5 % of the air groups, relative risk 2.1 (0.8-5.8, P=0.13). The authors concluded that there was suggestive evidence of a deleterious effect of oxygen. This study lacked statistical power to detect clinically important outcomes. Wilson and Channer conducted a parallel-group, non-blinded controlled study of oxygen therapy. Fifty patients with myocardial infarction treated with streptokinase were randomized to oxygen or room air for 24h. The study was not designed to compare outcomes measured by infarct size or mortality. Ventricular tachycardia occurred in 23% of the oxygen group and 25% of the air group (P=NS). Also there was no significant difference in opiate use. Severe hypoxemia occurred in 8 patients (1 in the oxygen group versus 7 in the air group, P<0.05)

There is insufficient evidence to support the use of oxygen in the treatment of uncomplicated myocardial infarction (Nicholson 2004, Wijesinghe 2009). The routine use of oxygen in this situation may increase infarct size and possibly increase the risk of mortality. There is a need for randomized controlled trials of the use of oxygen therapy in uncomplicated myocardial infarction that are sufficiently powered and performed in the current reperfusion era.

7. Conclusion

DISCLAIMER: Potential possible wording for a Consensus on Science Statement. Final wording will differ due to other input and discussion.

CONSENSUS ON SCIENCE: One human case study (LOE 5) (Madias 1976 p411) reported improvement of ST changes if oxygen therapy was applied in 17 patients suffering myocardial infarction. In one randomized trial (LOE 1) (Rawles 1976 p1121), conducted before the introduction of reperfusion therapy, the amount of aspartate aminotransferase released in the circulation was increased in patients who received oxygen therapy. There was no significant difference in mortality, incidence of arrhythmias, use of analgesics between the two groups. Another randomized study (LOE 1) (Wilson 1997 p657) involving myocardial infarction patients treated with streptokinase showed no impact of oxygen on the occurrence of ventricular tachycardia. As the studies were small and lacked statistical power to detect a true influence on clinical outcomes, it may be concluded that, although there is no definite proof of a harmful effect of oxygen therapy, there is absolutely no hint of a beneficial role in patients with myocardial infarction not complicated by heart failure.

8. Acknowledgement

9. Citation list

Beasley, R., S. Aldington, et al. (2007). "Oxygen therapy in myocardial infarction: an historical perspective." J R Soc Med 100(3): 130-3.
It is over 100 years since the use of oxygen to relieve angina pectoris was first described by Steele. More importantly, it is over 50 years since Russek and colleagues cautioned that the administration of 100% oxygen may actually be contraindicated in patients with myocardial infarction or angina pectoris in whom the arterial oxygen saturation is normal. Since this warning, there have been numerous reports of potentially harmful effects of high flow oxygen in the treatment of myocardial infarction, yet it is routine clinical practice to administer oxygen to virtually all patients in this situation. In this essay we have considered, from an historical perspective, the findings from the key studies of the effects of oxygen therapy in patients with myocardial infarction. We propose that randomized controlled trials are urgently required.
Level 1, neutral, funding: none sought or received
Key points: historical overview including the randomized trial from Rawles and Kenmure. The authors stress the need for randomized controlled trials.

Foster, G. L., G. G. Casten, et al. (1969). "The effects of oxygen breathing in patients with acute myocardial infarction." Cardiovasc Res 3(2): 179-89.
AUTHORS' SYNOPSIS. Haemodynamic and biochemical studies while breathing four different concentrations of oxygen showed increases in peripheral resistance and arterial pressure without an appreciable change in cardiac output. The patients with low cardiac outputs had lower arterial pO2 values. Lactate and pyruvate levels declined with time rather than the concentration of oxygen.
Level 6, opposing, funding: NIH USA grant
Key point: small study 14 pts acute myocardial infarction and 4 volunteers receiving 4 combinations of oxygen. Effects on hemodynamics studied.

Horvat, M., S. Yoshida, et al. (1972). "Effect of oxygen breathing on pacing-induced angina pectoris and other manifestations of coronary insufficiency." Circulation 45(4): 837-44.
SUMMARY
Eleven patients with arteriographically confirmed coronary artery disease and normalarterial oxygen saturation were studied. The angina threshold was determined first by successive elevation of heart rate at increments of 10 and 5 beats/min by right atrial pacing while the patients were breathing air via a close-fitting mask. The mask was then connected to an oxygen tank without the patient's knowledge. After 5 min of oxygen breathing, the heart rate was again raised to the previously determined threshold level. In nine of 11 patients angina did not recur. The absence of angina was associated with improvement in myocardial lactate extraction from -17 15 to +18 10% (P < 0.025), in S-T abnormalities in six of seven patients, and in pulsus alternans in three of five patients. The pacing rate was then raised at increments of 5 beats/min until angina recurred. With oxygen breathing, angina developed at higher pacing rates (129 7 beats/min with air and 137 6 beats/min with oxygen, on the average; P < 0.005), at higher rate-pressure product (18.0 0.8 and 19.5 0.9 x 103 mm Hg/min, respectively;P < 0.01), and at higher left ventricular oxygen consumption (21.3 1.1 and 24.6 1.1 ml/min, respectively; P <0.005). The results indicate that oxygen breathing permits the heart to do more work before coronary insufficiency develops.
Level 6, supporting. funding: NIH USA grant
Key points: small study, 11 patients with CAD, right atrial pacing to determine angina threshold, when oxygen was given (patients were unaware) the threshold was higher.

Ishikawa, K., K. Kanamasa, et al. (1986). "The beneficial effects of 40% and 100% O2 inhalations on acutelyinduced myocardial ischemia in dogs." Tohoku J Exp Med 149(2): 107-17.

The effectiveness of O2 inhalation on the acutely-induced ischemic myocardium in dogs was investigated. In 22 open-chest mongrel dogs, the left anterior descending coronary artery was partially occluded to reduce coronary flow. The regional coronary vein accompanying the artery was cannulated to obtain coronary venous blood. Switching of inspiratory gas from room air to 40% O2 produced an elevation of coronary venous O2 saturation from 35.8 +/- 12.7 (S.D.) to 41.1 +/- 11.9% and shifting of myocardial lactate production to utilization (from -0.9 +/- 36.9 to 5.0 +/- 36.7%), indicating that 40% O2 inhalation ameliorated ischemia. Application of 100% O2 inhalation caused even more beneficial effects; coronary venous O2 saturation was elevated to 50.6 +/- 12.6% and myocardial lactate extraction was improved to 7.8 +/- 40.5%. The present study indicated that 40% O2 inhalation was effective and 100% O2 inhalation even more effective in ameliorating acutely-induced myocardial ischemia. Decreases in myocardial contractile force and left ventricular size and suppression of sympathoadrenal activity might be possible mechanisms for these beneficial effects.
Level 6, supporting, funding: not clear
Key points: animal experiment 22 dogs, LAD occlusion , oxygen 40% improved coronary saturation and shifted myocardial lactate production to utilization, also ST segment elevation on epicardial ecg improved

Kelly, R. F., T. L. Hursey, et al. (1995). "Effect of 100% oxygen administration on infarct size and left ventricular function in a canine model of myocardial infarction and reperfusion." Am Heart J 130(5): 957-65.
High oxygen concentrations reduced infarct size in prereperfusion era studies; however, with reperfusion therapy, high oxygen tension carries the theoretical risk of exacerbating reperfusion injury by increasing toxic oxygen-derived free radicals. In this study, two groups of dogs underwent 90 minutes of coronary occlusion and 72 hours of reperfusion. The oxygen group (n = 16) received 100% inspired oxygen from 20 minutes before reperfusion through 3 hours of reperfusion, whereas the room-air group (n = 19) was ventilated with room air. Infarct size (as a percentage of risk area) was reduced by 38% in the oxygen group (26.7% +/- 4.7% vs 43.3% +/- 4.3%; p = 0.017). This benefit was independent of underlying variability in collateral blood flow in individual dogs (p = 0.016 by analysis of covariance [ANCOVA]). Left ventricular ejection fraction was significantly improved in the oxygen group (43% +/- 3% vs 33% +/- 2%; p = 0.008), as was regional function in the infarct zone (p < 0.05). These data suggest that high concentrations of inspired oxygen may also benefit patients with acute myocardial infarction who undergo reperfusion therapy.
Level 6, supporting, funding: academic Rush Medical College
Key points: dogs underwent 90 minutes coronary occlusion , one group received room air, the other group oxygen. Infarct size (histochemical staining technique) was lower and EF better in the oxygen group.

Kenmure, A. C., W. R. Murdoch, et al. (1968). "Circulatory and metabolic effects of oxygen in myocardial infarction." Br Med J 4(5627): 360-4.
Summary: The circulatory and metabolic effects of inhalation of oxygen in high concentration were investigated in 50 patients with acute myocardial infarction. The heart rate, arterial blood pressure, cardiac output, blood gas tensions, pH, and lactate and pyruvate levels were measured. In general, oxygen inhalation produced a fall in cardiac output and stroke volume and a rise in blood pressure and systemic vascular resistance. In a small number of patients with very low cardiac outputs there was a rise in output. A substantial rise in arterial oxygen tension was obtained even in patients with low initial values. The raised arterial blood lactate levels which were frequently present were reduced after oxygen. The therapeutic implications of these effects are discussed.
Level 6, opposing, funding: British Heart Foundation
Key points: myocardial infarction patients were treated with oxygen, CO and SV diminished, vascular resistance and BP increased.

Madias, J. E., N. E. Madias, et al. (1976). "Precordial ST-segment mapping. 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction." Circulation 53(3): 411-7.

Precordial ST-segment mapping was serially applied in the Coronary Care Unit for the study of the effect of oxygen inhalation on the ischemic injury in 17 patients with acute anterior transmural myocardial infarction. A 49-lead ECG system was used. The sum of all ST elevations (sigmaST) recorded was taken as an index of magnitude of ischemic injury and the number of recording sites showing ST elevation (NST) was taken as an index of extent of ischemic damage. Stability of the precordial maps was observed over a period of one hour while the patients were on ambient air. Oxygen inhalation for a mean of 66 min resutled in a fourfold increase of PaO2 and a mean of 16% reduction of both sigmaST and NST. When the patients were returned to ambient air breathing, a mean of 13% increase of sigmaST and 19% of NST from the levels recorded during oxygen inhalation were observed. Levels of sigmaST and NST on ambient air following discontinuation of oxygen inhalation were not significantly different from the corresponding values from maps recorded before onset of oxygen breathing. Blood pressure and heart rate remained unchanged throughout the study. Clinical status of the patients was unchanged during the study period save for two patients who showed changes in intensity of their chest pain.
Level 5, supporting, funding: USPHS and AHA grants
Key points: 17 patients with acute anterior myocardial infarction admitted to the CCU. Measurement of blood gasses and ST segment monitoring during ambient air and 66 minutes oxygen. Sum of ST elevation and number of sites showing elevation was lower with oxygen. PaO2 was higher. Clinical status remained unchanged.

Malm, A., M. J. Arborelius, et al. (1977). "Effects of oxygen on acute myocardial infarction: a thermographic study in the dog." Cardiovasc Res 11(6): 512-8.
An acute myocardial infarction was created in a series of dogs by ligation of a branch from the left anterior descending coronary artery. The effects on the infarction with 100% oxygen were studied by thermography in 23 animals. The changes in the infarction size were registered on polaroid photographs. In 10 dogs the infarction showed a uniform cool area, permitting accurate measurement by cutting out and weighing the black, infarcted area from the photographs. During oxygen administration 2 dogs showed a considerable increase in the cool area and 6 other dogs a moderate but significant increase. The remaining 2 dogs in this group showed non-significant change in the infarcted area. In the other 13 animals the cool area was not sufficiently uniform to allow accurate measurement. However, all the dogs in this group, except one, presented a visible increase of the cool area of varying degree. High oxygen supply does not seem to have a favourable effect on an experimentally induced acute myocardial infarction. It is known to promote a lowering of the coronary artery perfusion pressure. In addition to this, it may somehow decrease the arterial supply from the vascular bed round the ischaemic area.
Level 6, opposing, funding: swedish medical research council
Key points: 23 dogs, LAD ligation induced medium sized infarction, infarct size measurement with thermography, ventilation with 100% oxygen during 15 minutes. Control series of 4 dogs. the infarcted area under the influence of oxygen did not diminish in size in any cases.