Cochrane corner

Hyperbaric oxygen therapy for acute coronary syndrome: a systematic review of randomised controlled trials

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Key words
Hyperbaric oxygen therapy, cardiovascular, evidence, Cochrane library, review article

Abstract
(Bennett MH, Jepson N, Lehm J. Hyperbaric oxygen therapy for acute coronary syndrome: a systematic review of randomised controlled trials. *Diving and Hyperbaric Medicine*. 2006; 36: 201-7.)
Background: During an ischaemic event, hyperbaric oxygen therapy (HBOT) will improve oxygen supply to the threatened heart and may reduce the volume of heart muscle that will perish. This may reduce death rate and other major adverse outcomes following acute coronary syndrome (ACS). This review assesses the randomised clinical evidence for benefit or harm from HBOT in this setting.
Methods: We performed a systematic search of the literature and made a pooled analysis of predetermined outcomes where possible.
Results: There was a trend towards a decrease in the risk of death with HBOT (relative risk 0.64, 95% CI 0.38 to 1.06, P = 0.08). There was evidence from individual trials of reductions in the risk of major adverse coronary events (MACE) (RR 0.12, 95% CI 0.02 to 0.85, P = 0.03; NNT 4, 95% CI 3 to 10) and some dysrhythmias (RR 0.59, 95% CI 0.39 to 0.89, P = 0.01; NNT 6, 95% CI 3 to 24) following HBOT. The time to relief of pain was reduced with HBOT (mean difference 353 minutes shorter, 95% CI 219 to 488, P < 0.0001).
Conclusions: For people with ACS, the addition of HBOT reduced the risk of MACE and some dysrhythmias, and reduced the time to relief from ischaemic pain, but did not significantly reduce mortality. The review was hampered by modest numbers of patients, methodological shortcomings and poor reporting. More research is needed. The routine application of HBOT to these patients cannot be justified from this review.

Introduction

Cardiovascular disease remains the leading cause of death in developed countries, and is predicted to become the disease with the greatest global burden by 2020.[1] In the United Kingdom, coronary heart disease is the most common cause of premature death, causing 125,000 deaths from approximately 274,000 episodes in 2000 at a community cost of around £10 billion.[2,3] Because myocardial infarction (the presence of two out of three of: chest pain, ECG changes and cardiac enzyme rise) is not always diagnosable during an acute event, unstable or persisting ischaemic heart pain (angina) with or without infarction is described as acute coronary syndrome (ACS).

The main underlying problem in coronary heart disease is atherosclerosis – a degenerative process characterised by the formation of plaques comprising platelets, cells, matrix fibres, lipids, and tissue debris in the vessel lumen. While such plaques are often complicated by ulceration of the vessel wall with obstruction to blood flow, such ulceration is not necessary for plaques to be problematic.[4] An unstable plaque (coronary atheroma vulnerable to rupture and fissure, and associated with thrombus formation) can lead to an acute coronary syndrome without the artery being totally occluded, and infarction may follow.[5] A significant proportion of patients admitted with acute myocardial infarction (AMI) will suffer a major morbidity or mortality, even when thrombolysis or angioplasty is used to relieve the obstruction.[6]

Hyperbaric oxygen therapy (HBOT) has been proposed as an adjunctive measure to improve outcome following ACS, being first reported in a canine experimental model in 1958,[7] and in a human in 1964.[8] Several uncontrolled human studies have been published since, generally with indications of benefit measured as a reduction in mortality or improvements in haemodynamic or metabolic parameters.[9,10]

The administration of HBOT is based on the argument that the myocardium is hypoxic, and that HBOT can reverse that hypoxia in areas that are marginally perfused. This effect is achieved by greatly increasing the diffusion gradient down which oxygen moves from the blood to the myocyte. Improved oxygen availability may also improve outcome through the effects of oxygen as a modulator of tissue repair. Oxygen has been shown to increase the expression of antioxidant enzymes in both tissues and plasma through an increase in glutathione levels,[11,12] to reduce the degree of lipid peroxidation[13] and to prevent the activation of neutrophils in response to endothelial damage, thus modifying ischaemia-reperfusion injury.[14]

Despite over 40 years of interest in the delivery of HBOT in

these patients, relatively little clinical evidence exists for the assertion that such an intervention improves outcome.

Methods

Using specific search strategies for a wide range of sources, we aimed to locate all randomised controlled trials that investigated the effect of HBOT for ACS. Any trial administering HBOT between 1.5 ATA and 3.0 ATA with treatment times between 30 minutes and 120 minutes on at least one occasion was eligible.

Each reviewer independently assessed the electronic search results and selected potentially relevant studies. Disagreements were settled by examination of the full paper and consensus. To assess methodological quality and detect potential sources of bias we used the methods detailed in section six of the *Cochrane handbook for systematic reviews of interventions*.[15] To allow an intention-to-treat analysis we extracted the data reflecting the original allocation group where possible. Disagreements were again settled by consensus.

Important clinical outcomes were predetermined and each trial accepted into the review must have reported at least one of the following: death, major adverse coronary events (MACE – this includes death, recurrent MI or need for urgent revascularisation by coronary artery bypass graft (CABG) or percutaneous coronary angioplasty), significant dysrhythmia, onset of cardiac failure, time to relief of cardiac pain, size of infarct area, magnitude of cardiac enzyme changes, left ventricular function, length of stay, myocardial perfusion, quality of life (QOL), re-admission, costs for the delivery of care or adverse effects of therapy.

STATISTICAL ANALYSIS

Following agreement, the data were entered into Review Manager® 4.2.1. (Cochrane Collaboration, Oxford, UK). For dichotomous outcomes such as mortality, we calculated relative risk (RR) with 95% confidence interval (CI). A statistically significant difference from control was assumed when the 95% CI of the RR did not include the value 1.0. For continuous outcomes such as the mean time to pain relief for each group, we calculated the mean difference (MD) between groups with 95% CI. We used a fixed-effects model where problematic heterogeneity between the studies was not likely, and a random-effects model where such heterogeneity was likely. Heterogeneity was deemed problematic if the I^2 analysis suggested more than 30% of the variability in an analysis was due to systematic differences between trials rather than chance alone.[16] Consideration was then given to the appropriateness of pooling and meta-analysis. Number needed to treat (NNT) with 95% CI was calculated when the relative risk estimates were statistically significant.

We planned sensitivity analyses for missing data using best-case and worst-case scenarios for imputing outcome. We also considered subgroup analysis based on the inclusion or otherwise of thrombolysis in both arms of the trial, the nature of comparator treatment modalities, the dose of oxygen received, the presence or absence of cardiogenic shock and the site of the myocardial infarction.

Results

THE INCLUDED STUDIES

The initial search produced ten possible relevant randomised comparative trials. After appraisal of the full publications, five of these reports were accepted into the review.[17-21] Shandling 1997 and Stavitsky 1998 are reports from the same study, the Hyperbaric Oxygen Therapy for Myocardial Infarction (HOTMI) Study, but they report different outcomes and so have both been included. These trials included a total of 425 participants, 210 receiving HBOT and 215 control (see Table 1 for a summary of the characteristics of these studies).

All studies involved the administration of 100% oxygen at a pressure of 2 atmospheres absolute (ATA) for between 30 and 120 minutes; however, the total number of treatment sessions varied between studies. The lowest number administered was a single session (Stavitsky 1998; Swift 1992), while the highest was a maximum of 16 treatments within 48 hours (Thurston 1973). All trials included participants with acute myocardial infarction and Sharifi et al 2004 also included individuals presenting with unstable angina. Only Swift 1992 described allocation concealment and blinded subjects to allocation with a sham HBOT session. The time from presentation to enrolment varied from 'within one week' (Swift 1992) to 'within 24 hours' (Thurston 1973) and 'within six hours' (Stavitsky 1998; Shandling 1997). Sharifi 2004 did not state any time. The primary purpose of three of these reports was the treatment of AMI with HBOT, while for Swift 1992 it was the use of HBOT in AMI patients to identify myocardial segments capable of functional improvement, and for Sharifi 2004 the effect of HBOT on re-stenosis following percutaneous coronary interventions.

All trials excluded those unfit for HBOT, but in addition Stavitsky 1998 and Shandling 1997 excluded subjects who were not suitable for thrombolysis (e.g., recent stroke), those with previous transmural AMI and those in cardiogenic shock, while Swift 1992 excluded those with uncontrolled heart failure and/or significant ongoing angina. Thurston 1973 excluded subjects over 70 years old and those presenting when there was no HBOT chamber available. Sharifi 2004 excluded those who continued to show evidence of ischaemia after 30 minutes of medical treatment.

All patients required a clinical diagnosis of AMI for enrolment in these studies except in Sharifi 2004, who also enrolled subjects with unstable angina. All patients in that study had presumed coronary arterial lesions where a percutaneous stent was indicated and so were a more highly selected subset of ACS patients.

Table 1
Characteristics of included studies (AMI – acute myocardial infarct ; LVEF – left ventricular ejection fraction; MACE – major adverse coronary events; RCT – randomised controlled trial; TOE – transoesophageal echo)

Study	Methods	Participants	Interventions	Outcomes
Stavitsky 1998[18]	Multicentre RCT. No blinding. 16 were excluded after randomisation.	138 patients enrolled in emergency room with clinical diagnosis of AMI and eligible for thrombolysis.	Control: Thrombolysis, aspirin, heparin and IV nitroglycerine. HBO: Same plus 2 ATA O_2 for two hours.	Death, time to pain relief, enzyme changes, LVEF.
Shandling 1997[19]	As for Stavitsky 1998.	82 patients.	As for Stavitsky 1998.	Length of stay.
Sharifi 2004[17]	RCT, no blinding. 5 crossed after allocation.	69 patients with AMI or unstable angina. Excluded if pain or S-T segments unresolved after 30 min.	Control: Stenting, aspirin, heparin and clopidogrel. HBOT: Same plus 2 ATA O_2 for 90 minutes at 1 and 18 hours.	MACE, adverse events.
Swift 1992[20]	RCT with 2 active-arm patients for each control. No loss to follow-up. Subject and assessor blinding.	34 patients with a clinical diagnosis of AMI within one week, plus abnormal wall motion on TOE.	Control: Echo, followed by 2 ATA air for 30 mins and repeat echo. HBOT: Same but 2 ATA O_2.	Improved LV function on echo.
Thurston 1973[21]	RCT, no blinding after allocation.	221 patients with strong clinical suspicion of AMI at admission. 13 later excluded.	Control: "Coronary care including oxygen by mask." HBOT: 48 hours of cycling from 2 ATA O_2 for 2 hours, then 1 ATA air for 1 hour.	Death, significant dysrhythmia, adverse effects.

The follow-up period varied from the period immediately following HBOT (Swift 1992), to three weeks (Thurston 1973) and eight months (Sharifi 2004). Stavitsky 1998 reported mortality to discharge from hospital. Study quality was generally assessed as low and quality was not used as a basis for sensitivity analysis.

Swift 1992 reported no losses to follow up or any violation of treatment protocol. Stavitsky 1998 and Shandling 1997 reported 16 subjects withdrawn from analysis after allocation to groups (four became unstable, four generated incomplete data, three were enrolled after six hours in violation of inclusion criteria, two showed no cardiac enzyme rise, two received an incorrect treatment protocol and one refused to have HBOT). Thurston 1973 similarly did not report data on 13 subjects who were withdrawn for misdiagnosis or being aged more than 70 years in violation of inclusion criteria. The group allocation was not indicated for any of the withdrawn patients in either of these studies.

Sharifi 2004 excluded nine subjects allocated to HBOT from the analysis, five of whom were crossed over to the control arm after declining to receive HBOT. The other four participants required CABG or did not have a lesion suitable for stent, while there were also four subjects excluded from the control group for the same reasons. None of the included studies specifically indicated an intention-to-treat approach, and such an approach was not possible for Sharifi 2004 as five subjects crossed from HBOT to control for analysis.

CLINICAL OUTCOMES

Statistical pooling was not possible for the majority of pre-planned outcome measures due to lack of suitable data. Problems included the small number of studies, modest number of patients, and the variability in outcome measures employed.

Three trials reported the number of subjects who died at any time after enrolment (Sharifi 2004; Stavitsky 1998; Thurston 1973), involving 391 subjects, with 186 (48%) allocated to standard treatment plus HBOT and 205 (53%) to standard therapy alone (Figure 1). Fewer subjects died following HBOT, but the difference was not statistically significant (18 (9.7%) versus 29 (14.1%), RR 0.64, 95% CI 0.38 to 1.06, P = 0.08), nor was there any statistically significant reduction on subgroup analysis for those presenting in cardiogenic shock (RR with cardiogenic shock 0.57, 95% CI 0.3 to 1.09,

P = 0.09, RR without cardiogenic shock 0.65, 95% CI 0.35 to 1.2, P = 0.17). The overall comparison was sensitive to the allocation of withdrawals (best-case RR of death with HBOT is 0.42, 95% CI 0.26 to 0.70, P = 0.0008).

MACE were reported only by Sharifi at eight months (61 subjects), with one subject (4%) suffering a MACE following HBOT versus eight subjects (35%) in the control group (RR 0.12, 95% CI 0.01 to 0.61, P = 0.01). This result was also sensitive to the allocation of withdrawals (worst-case RR 0.56, 95% CI 0.23 to 1.40, P = 0.22). The number needed to treat (NNT) to avoid one extra MACE was 4, (95% CI 3 to 10).

Thurston (1973, 208 subjects) reported the incidence of significant dysrhythmia (complete heart block, ventricular fibrillation or asystole). It is not clear if the numbers reported reflect individuals who suffered these events, or the number of events in total. Overall there were 25 such events reported in the patients receiving HBOT versus 43 such events in the control group, and patients receiving HBOT were significantly less likely to suffer one of these dysrythmias (RR 0.59, 95% CI 0.39 to 0.89, P = 0.01; NNT 6, 95% CI 3 to 24). Again, this result was sensitive to the allocation of withdrawals (worst-case RR 0.73, 95% CI 0.50 to 1.06, P = 0.10). Separate analyses for each of the three dysrythmias suggested HBOT patients were significantly less likely to suffer with complete heart block (RR 0.32, 95% CI 0.12 to 0.84, P = 0.02), but not ventricular fibrillation (RR 0.78, 95% CI 0.36 to 1.71, P = 0.54) or asystole (RR 0.73, 95% CI 0.73 to 1.56, P = 0.42) (Figure 2).

Stavitsky (1998, 81 subjects) reported a statistically shorter mean time to pain relief in the HBOT group (261 minutes versus 614, MD 353 minutes, 95% CI 219 to 488, P < 0.0001) but not significantly lower creatine phosphokinase (CPK) level at 12 and 24 hours, nor the maximum CPK level recorded (e.g., maximum CPK in HBOT group 1,698 units versus 2,111 units with control, MD 413, 95% CI -982 to 156, P = 0.15).

Two trials reported improvements in left ventricular (LV) function; however, pooling was not appropriate. Swift 1992 reported the number of individuals in whom improved function could be demonstrated on echocardiography following HBOT. Twelve out of 24 (50%) showed improved function in at least one segment following HBOT versus 0 with control (RR 0.09, 95% CI 0.01 to 1.4, P = 0.09). Stavitsky 1998 reported left ventricular ejection fraction (LVEF) at discharge (mean LVEF with HBOT 51.7% versus 48.4% with control therapy, MD 3.3%, 95% CI -1.1 to 7.6, P = 0.14).

Shandling 1997 reported the length of stay in the first 63 subjects of the HOTMI study. The mean days' stay in hospital for the HBOT group was 7.4 days versus 9.2 days for the controls. This difference was not statistically significant (MD 1.8 days, 95% CI 3.7 to -0.1, P = 0.06).

With regard to the adverse effects of therapy, two trials (Sharifi 2004, Thurston 1973), involving 269 subjects, reported that one patient suffered tympanic membrane rupture in the HBOT group versus none of the controls (RR with HBOT 4.56, 95% CI 0.19 to 107.54, P = 0.35). Three trials (Sharifi 2004, Shandling 1997, Thurston 1973) involving 335 subjects reported a zero incidence of neurological oxygen toxicity in all arms. Thurston reported a significant incidence of claustrophobia in the monoplace setting, 15 subjects (15%) with claustrophobia requiring cessation of therapy in the HBOT group versus none in the control group (RR 31.6, 95% CI 1.92 to 521, P = 0.02).

ECONOMIC ANALYSIS

None of the included trials made any attempt at economic analysis. Using the effectiveness estimates from this review, combined with data reported by Gomez-Castillo,[22] the cost of avoiding a single extra episode of MACE by using HBOT is estimated at $AUD6,080 (95% CI $4,560 to $15,200) assuming five treatments, and $AUD18,240 (95% CI 13,680 to 36,480) assuming 15 treatments (in fact, Sharifi used only two treatments). This estimate should be interpreted with caution given the paucity of data from which it is drawn.

Discussion

There is limited evidence that HBOT reduces the incidence of both MACE and complete heart block, and reduces the time to relief from angina when administered to patients with ACS. Although there was a trend toward favourable outcomes, there were no reliable data from these trials to confirm or refute any effect of HBOT on mortality, length of stay or LV contractility. Only four trials with 425 participants were available for evaluation using our planned comparisons, and meta-analysis was not appropriate or possible for a number of these. Other problems for this review were the poor methodological quality of most of these trials, variability in entry criteria and the nature and timing of outcomes, and poor reporting of both outcomes and methodology. In particular, there is a possibility of bias due to different anatomical locations and extent of myocardial damage on entry to these small trials, as well as from non-blinded management decisions in all except Swift 1992.

Patient inclusion criteria were not standard, and poorly reported in some trials. Only Stavitsky and Swift clearly indicated the time at which the inclusion criteria were applied. There was significant variation both in oxygen dose during an individual treatment session, and in the number of sessions administered to each patient. While all trials used some form of 'standard' cardiac therapy in a dedicated unit designed to maximise outcome, these comparator therapies were generally poorly described and could not form the basis of a meaningful subgroup analysis.

Pooling of data for clinical outcomes of interest could

Figure 1
Forest plot of the risk of death with HBOT; subgroup analysis by presence or absence of cardiogenic shock

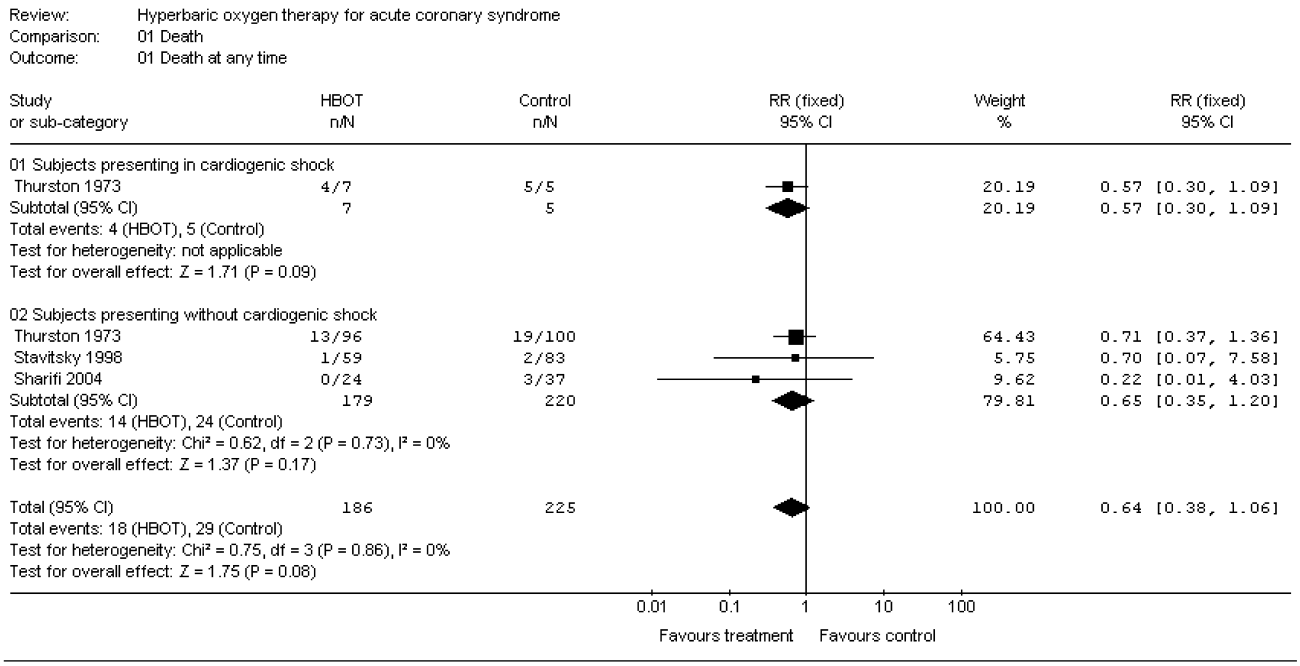
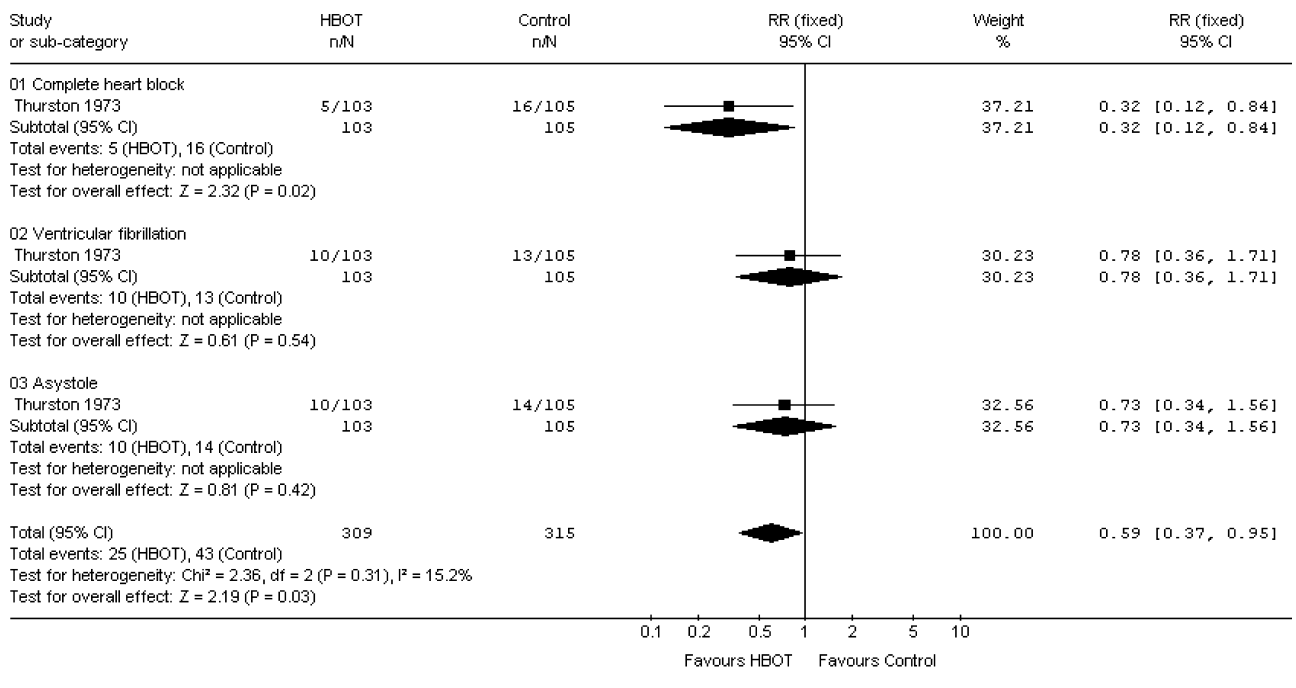


Figure 2
Forest plot of the risk of significant dysrhythmias with HBOT; subgroup analysis by the nature of dysrhythmia



be performed only with respect to the risk of death and adverse effects. While the risk of dying was not significantly improved following HBOT, there was some trend in that direction (RR 0.64, P = 0.08) and the absolute risk difference of 3.2% suggested an NNT of around 31 patients in order to save one life by the addition of HBOT. Only one trial (Thurston 1973) reported the fate of those presenting in cardiogenic shock, and while there was no statistically significant difference between groups in this small sample, it is worth noting that all survivors were from the HBOT group (three from seven subjects versus none from five). The one small study that reported MACE rather than death alone (Sharifi 2004) also suggested better outcome with the use of HBOT. This possible treatment effect would be of

great clinical importance and deserves further investigation. At present, given the small numbers and the sensitivity of the risk of both death and MACE to the allocation of withdrawals, this result should be interpreted with caution. The routine adjunctive use of HBOT in these patients cannot yet be justified by the clinical evidence.

Given the indicative findings of improved outcomes with the use of HBOT in these patients, however, there is a case for large randomised trials of high methodological rigour in order to define the true extent of benefit (if any) from the administration of HBOT. Specifically, more information is required on the subset of disease severity and timing of therapy most likely to result in benefit. Given the activity of HBOT in modifying ischaemia-reperfusion injury, attention should be given to combinations of HBOT and thrombolysis in the early treatment of acute coronary events and the prevention of re-stenosis after stent placement.

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