CARDIOVASCULAR
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MEDICINE

Hyperbaric oxygen preconditioning improves myocardial function, reduces length of intensive care stay, and limits complications post coronary artery bypass graft surgery[☆],[☆☆],[★]

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Abstract

Objective: The objective of this study was to determine whether preconditioning coronary artery disease (CAD) patients with HBO_2 prior to first-time elective on-pump cardiopulmonary bypass (CPB) coronary artery bypass graft surgery (CABG) leads to improved myocardial left ventricular stroke work (LVSW) post CABG. The primary end point of this study was to demonstrate that preconditioning CAD patients with HBO_2 prior to on-pump CPB CABG leads to a statistically significant ($P<.05$) improvement in myocardial LVSW 24 h post CABG.

Methods: This randomised control study consisted of 81 (control group=40; HBO_2 group=41) patients who had CABG using CPB. Only the HBO_2 group received HBO_2 preconditioning for two 30-min intervals separated 5 min apart. HBO_2 treatment consisted of 100% oxygen at 2.4 ATA. Pulmonary artery catheters were used to obtain perioperative hemodynamic measurements. All routine perioperative clinical outcomes were recorded. Venous blood was taken pre HBO_2, post HBO_2 (HBO_2 group only), and during the perioperative period for analysis of troponin T.

Results: Prior to CPB, the HBO_2 group had significantly lower pulmonary vascular resistance ($P=.03$). Post CPB, the HBO_2 group had increased stroke volume ($P=.01$) and LVSW ($P=.005$). Following CABG, there was a smaller rise in troponin T in HBO_2 group suggesting that HBO_2 preconditioning prior to CABG leads to less postoperative myocardial injury. Post CABG, patients in the HBO_2 group had an 18% ($P=.05$) reduction in length of stay in the intensive care unit (ICU). Intraoperatively, the HBO_2 group had a 57% reduction in intraoperative blood loss ($P=.02$). Postoperatively, the HBO_2 group had a reduction in blood loss (11.6%), blood transfusion (34%), low cardiac output syndrome (10.4%), inotrope use (8%), atrial fibrillation (11%), pulmonary complications (12.7%), and wound infections (7.6%). Patients in the HBO_2 group saved US$116.49 per ICU hour.

Conclusion: This study met its primary end point and demonstrated that preconditioning CAD patients with HBO_2 prior to on-pump CPB CABG was capable of improving LVSW. Additionally, this study also showed that HBO_2 preconditioning prior to CABG reduced

myocardial injury, intraoperative blood loss, ICU length of stay, postoperative complications, and saved on cost, post CABG.

1. Introduction

Hyperbaric means relating to, producing, operating, or occurring at pressures higher than normal atmospheric pressure [1]. In hyperbaric oxygen (HBO_2) therapy, the patient breaths pure oxygen (100%) at a pressure greater than atmospheric pressure while in a steel or polymer chamber. HBO_2 therapy is known mainly for its use as the treatment of choice in carbon monoxide poisoning, gas embolism, and decompression sickness. The experience of hyperbaric medicine specialist and, to a certain extent, the scientific literature also support the use of HBO_2 as an adjuvant treatment for a number of other medical conditions, such as complex refractory wounds [2], intracranial abscess, radiation tissue injury, crush injuries, compartment syndrome, acute traumatic peripheral ischemia, burns, and other tissue damage resulting from ischemic reperfusion injury (IRI) [3]. At present, there are no standard protocols for specific medical conditions. The therapeutic procedures vary according to the condition (acute or chronic) and the treatment centre. The treatment can be administered on a one-time basis and varies in duration by way of several daily or twice daily sessions of predetermined duration. The pressure at which HBO_2 is administered depends on several factors such as the medical condition, the patient's characteristics, the type of chamber, and the centre's practices.

Hyperbaric oxygen results in an oxidative stress that is capable of increasing reactive oxygen species (ROS) generation [4–6]. It has been previously suggested that part of the therapeutic effect of HBO_2 may originate from the generation of ROS [7] and that this ROS initiates a cascade of events that may lead to myocardial protection. This is paradoxical to the traditional premise that ROS plays an important role in IRI-mediated cellular damage [8,9]. In a study involving IRI conducted by Sterling et al. [10], it was demonstrated that the animals exposed to HBO_2 during ischemia only, reperfusion only, or ischemia and reperfusion had significantly smaller myocardial infarct sizes compared to the control animals, indicating they had been protected by HBO_2. This study suggested that HBO_2 compared to normobaric hyperoxia was capable of inducing myocardial protection. Furthermore, it also provided one of the first experimental evidences that pretreatment with HBO_2 (also known as HBO_2 preconditioning) prior to a reperfusion injury was capable of inducing myocardial protection. The specific ability for HBO_2 preconditioning prior to IRI to reduce myocardial infarct size in animals has also more recently been demonstrated by Kim et al. [11] and Han et al.

[12]. The work by Kim et al. [11] furthermore suggests that part of the protective effect of HBO_2 preconditioning may involve ROS and its effects on antioxidants. Moreover, it has also been suggested [7,13] that the cellular protective effects of HBO_2 may stem from production of nitric oxide synthase (NOS) and heat shock proteins (Hsp). Both NOS [14] and Hsp [15] are known to be cardioprotective and have been shown to be induced by ROS [16,17], thus implicating their possible roles in HBO_2-induced myocardial protection via ROS.

In the Hyperbaric Oxygen Therapy in Percutaneous Coronary Intervention (HOT-PI) study [18], following stabilization with medical therapy, resolution of chest pain, and normalization of ST-segment changes, patients who presented with unstable angina or acute myocardial infarction (AMI) were randomized to a group treated with HBO_2 or a group which was not treated with HBO_2. The results demonstrated that patients who received adjunctive HBO_2 in the early peri-percutaneous coronary intervention period had a lower clinical restenosis rate. Significantly fewer patients ($P<003$) in the HBO_2 group required revascularization of the target lesion, and the number of patients with recurrence of late angina symptoms was also less frequent ($P<05$) in this group. In addition, composite adverse cardiac events [death, myocardial infarction, coronary artery bypass graft surgery (CABG), or revascularization of target lesion] at 8 months were significantly higher in the control group compared to the HBO_2 group ($P=.001$). The results of this study also suggest that HBO_2 preconditioning may have the capacity to reduce vascular ischemic events by perhaps limiting the pathological progression of atherosclerosis. This concept has been corroborated by animal findings [19,20] demonstrating that HBO_2 treatment halted the progress of atherosclerosis and appeared to facilitate it regression.

In the Hyperbaric Oxygen Therapy in Myocardial Infarction (HOT-MI) study [21], patients with an AMI who received recombinant tissue plasminogen activator (rTPA) were randomized to treatment consisting of HBO_2 combined with rTPA or rTPA alone. In this study, the group that was also treated with HBO_2 experienced an improvement in post MI ejection fraction, a 35% reduction in mean creatinine phosphokinase (CK) at 12 and 24 h post MI, a reduction in time to pain relief, and ST-segment resolution post MI. The authors of this study concluded by suggesting that adjunctive HBO_2 was a feasible and safe treatment for AMI.

Based on the available clinical evidence [18,21], the hypothesis of this clinical study was that HBO_2 preconditioning in patients with CAD, prior to first-time elective on-

pump cardiopulmonary bypass (CPB) CABG, would be capable of improving myocardial function. The objective of this study was to determine whether preconditioning CAD patients with HBO_2 prior to first-time elective on-pump CPB CABG leads to improved myocardial left ventricular stroke work (LVSW) post CABG.

The primary end point of this study was to demonstrate that preconditioning CAD patients with HBO_2 prior to on-pump CPB CABG leads to a statistically significant ($P<.05$) improvement in myocardial LVSW 24 h post CABG. The secondary end points of this study were to assess the effects of HBO_2 preconditioning on

a) the other measured parameters of cardiovascular hemodynamics which included:
   i. Heart rate (HR)
   ii. Mean arterial pressure (MAP)
   iii. Stroke volume (SV)
   iv. Cardiac output (CO)
   v. Cardiac index (CI)
   vi. Mean pulmonary artery pressure (MPAP)
   vii. Pulmonary capillary wedge pressure (PCWP)
   viii. Pulmonary vascular resistance (PVR)
   ix. Pulmonary vascular resistance index (PVRI)
   x. Systemic vascular resistance (SVR)
   xi. Systemic vascular resistance index (SVRI)
   xii. Left ventricular stroke work (LVSW)
   xiii. Left ventricular stroke work index (LVSWI)
   xiv. Right ventricular stroke Work (RVSW)
   xv. Right ventricular stroke work index (RVSWI)
b) serum troponin T
c) myocardial NOS and Hsp
d) serum soluble adhesion molecules (sPSGL-1, sP-selectin, sE-selectin, sICAM-1)
e) post CABG length of intensive care unit (ICU) stay
f) the incidence of the following post CABG complications:
   i. low cardiac output syndrome (defined as difficulty in maintaining intra- and postoperative mean arterial pressure above 70 mmHg)
   ii. inotrope usage
   iii. atrial fibrillation
   iv. intra- and postoperative blood loss
   v. postoperative blood transfusion
   vi. pulmonary, renal, gastrointestinal, and neurological complications
   vii. infections
   viii. perioperative MI
   ix. reoperations for bleeding
   x. mortality

A post hoc analysis was also done to determine the cost-effectiveness of HBO_2 preconditioning in this study. This article will focus on the primary end point and all the secondary end points apart from the serum adhesion molecules and the myocardial NOS and Hsp, which will be reported on later.

2. Methods and materials

2.1. Research approval, study design, and statistical analysis

Prior to commencing this study, ethical and hospital approval was obtained from the Hull and East Riding Local Research Ethics Committee (approval number: 04/Q1104/26) and the Hull and East Yorkshire NHS Trust (approval number: R0047), respectively. This study is registered on ClinicalTrials.gov (http://clinicaltrials.gov/ct2/show/NCT00623142?term=hyperbaric+oxygen&rank=1) with the registration number NCT00623142 and conforms with the Declaration of Helsinki.

Sample size calculations were based on detecting differences between treatment groups in the percentage change of LVSWI from initial to final measurement points, as was done in another study involving pharmacological preconditioning and myocardial protection [22]. Based on a previous clinical study [23] involving HBO_2 and CABG, a within-group standard deviation of 6.25% was assumed. A two-sided 5% significance level and a 90% power were specified. Allowing for a 7.5% detection of an interaction between the two possible treatment combinations and allowing for increased variance of interaction and estimates relative to the main effect [24], it was determined that a minimum of 60 patients would be required to show statistical significance. Patients were randomised by pulling out sealed envelopes in sequence from a box. The random treatment allocations were contained within the envelope. The random treatment allocation list was prepared by the study statistician.

Repeated measures ANOVA was used to analyse the hemodynamic data, clinical outcomes, and perioperative serum troponin T. Data were analysed in accordance with the principles of intention-to-treat (ITT) basis [25,26]. Where data were missing, no imputation of data was done. Where the data were skewed, log transformation was performed to normalise the data for statistical analysis. Where relevant, data from logged results were transformed back into original estimates as the geometric mean of the ratio of the HBO_2 group to control group values [27].

2.2. Patient selection

From January 2005 to July 2006, 774 consecutive patients were admitted to the hospital for first-time elective CABG surgery with the use of CPB. From this cohort of patients, 81 matched the study criteria.

The inclusion criteria were:

a) patients undergoing first-time elective CABG surgery using CPB.

The exclusion criteria were:

b) age <20 and >85 years
c) ejection fraction <30%

d) unstable angina
e) 1 month post myocardial infarction
f) cardiac disease other than coronary artery disease (CAD)
g) organ failure
h) history of chronic obstructive pulmonary disease (COPD), pneumothorax, pulmonary bullae, convulsions, malignancy, myopia, or intraocular lens
i) current use of $K_{(ATP)}^+$ channel openers, oral hypoglycemics, opioid analgesics, or catecholamines

2.3. Randomisation

Of the 81 fully informed patients who volunteered and consented to participate in this study, 40 were randomised to the control group (not receiving HBO_2 preconditioning) and 41 were randomised to the HBO_2 preconditioning group. In this study, the patients were aware of their randomisation groups but none of the surgeons, anaesthetist, perfusionists, or nursing team was aware of the treatment allocation groupings of the study patients. Following randomisation,

there were five drop outs from the control group and seven from the HBO_2 group. Fig. 1 shows the CONSORT flow diagram of patients recruited to this study.

2.4. Hyperbaric oxygen preconditioning protocol

The pressure and duration for HBO_2 preconditioning were based on the optimum effect noted in a previous clinical study [23]. On the morning prior to CABG, patients randomised to the HBO_2 group were treated with HBO_2. The HBO_2 preconditioning treatment consisted of pressurisations over 10 min from 1 to 2.4 ATA. During this pressurisation period, the patients were breathing air. Once at 2.4 ATA, patients placed a clear plastic hood over their heads. One hundred percent oxygen was supplied into this hood which the patients breathe for 30 min. This period was followed by a 5-min interval out of the hood at 2.4 ATA. During this period out of the hood, patients were only breathing air. After this interval, the hood was placed on again for a further 30 min and the patients again breathe 100% oxygen at 2.4 ATA. Subsequent to this, the hood was removed again and the
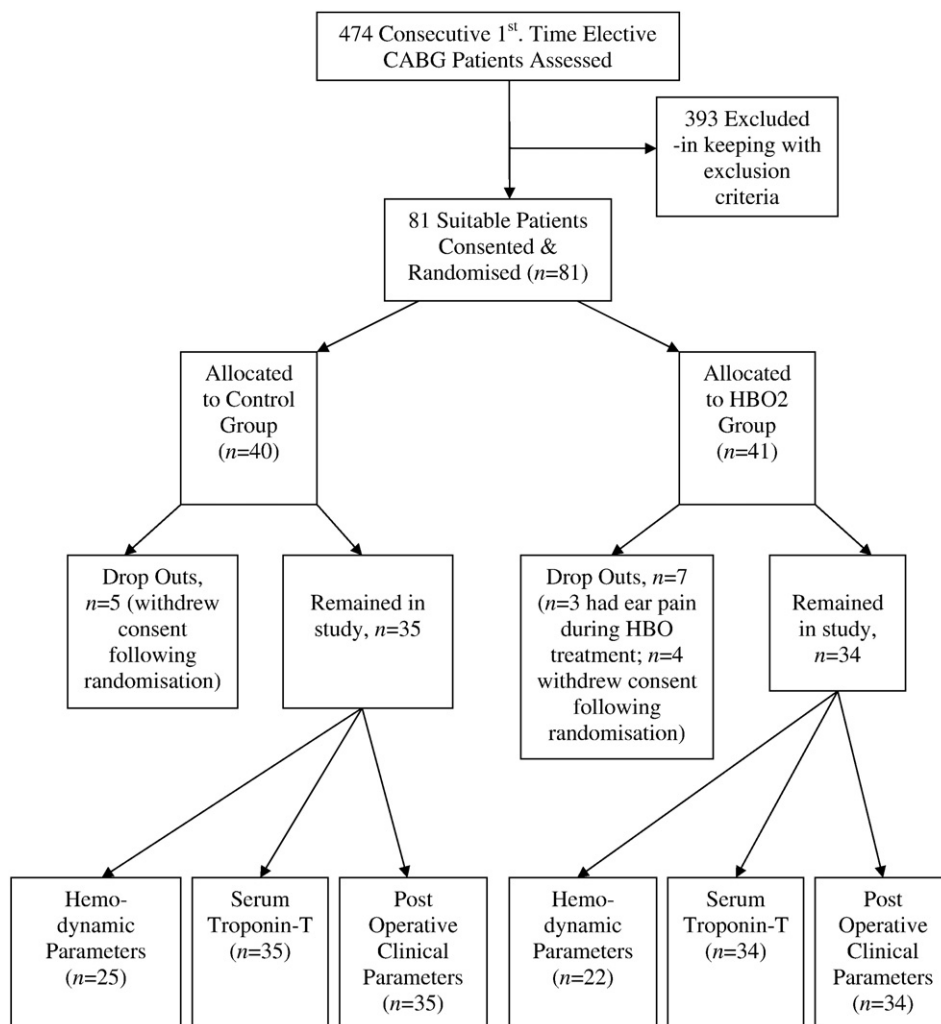

Fig. 1. Consort flow diagram of study.

chamber is depressurised over 25 min back to 1 ATA. During this depressurisation period, patients were again only breathing air. Treatment with HBO_2 preconditioning was completed approximately 4 h prior to CPB.

2.5. Surgical protocol

There were two surgeons and seven anaesthetists who were part of this single-centre, randomised control study. All of them adhered to the same surgical technique. Intermittent cross clamp fibrillatory arrest was used as means of intraoperative myocardial protection. A Stockert SIII roller pump (Stockert Instrumente, Germany) with a hollow fibre membrane oxygenator and an integral hard shell venous cardiotomy reservoir (Avant Phisio/M-Dideco, Italy) was used for CPB together with a 38-μm arterial line filter (Affinity352 Medtronic, USA). Moderate systemic hypothermia of 32°C was maintained during CPB. Rewarming of the patient was commenced during the distal anastomosis of the final CABG.

2.6. Hemodynamic monitoring

In order to monitor hemodynamic parameters, a pulmonary artery (PA) catheter (Edward Life Sciences, Germany) was inserted following anaesthetic induction. Hemodynamic parameters were measured post anaesthetic induction; 5 min post CPB; and 2, 4, 8, 12, and 24 h post CPB. The hemodynamic parameters that were measured were HR, MAP, SV, CO, CI, MPAP, PCWP, PVR, PVRI, SVR, SVRI, LVSW, LVSWI, RVSW, and RVSWI.

2.7. Venous blood sampling

Venous blood was taken pre HBO_2 preconditioning from all patients in the HBO_2 group. At this same time point, a venous blood sample was also taken from all patients in the control group. Further venous blood samples were taken within 1 h post HBO_2 preconditioning (HBO_2 group only), 5 min following the onset of CPB (both groups), 5 min post IRI (following the final period of clamping and unclamping of the aorta—both groups), 2 h post CPB (both groups), and 24 h post CPB (both groups). The blood was collected into a yellow top BD Vacutainer Tube (SST ll Advance) and used to analyse the presence of serum troponin T. This analysis was done by the Department of Biochemistry at the Hull and East Yorkshire NHS Trust, within 4 h of collection using an immunochemiluminescent sandwich assay performed on the Roche Elecsys 2010 analyser (Roche Diagnostics, Germany) in accordance with the manufacturer's recommendations.

3. Results

Table 1 shows the perioperative data of the patients recruited to this study. In this study, patient ages and gender

Table 1
Comparison of perioperative factors

Variable	Control group (n=40)	HBO₂ group (n=41)
Age	68.8	64.7
Men	29 (72.5%)	33 (80.5%)
BMI	28.8	28.2
Preoperative Euroscore	3.78 (1.95)	2.83 (1.88)
Unstable angina	3 (7.5%)	1 (2.5%)
Previous MI	20 (51.3%)	16 (41.0%)
Left main stem disease	13 (32.5%)	13 (31.7%)
One diseased coronary artery	0 (0%)	1 (2.4%)
Two diseased coronary arteries	7 (17.5%)	8 (19.5%)
Three diseased coronary arteries	33 (82.5%)	32 (78.0%)
Left ventricular function		
≥50%	31 (79.5%)	33 (82.5%)
30–50%	7 (17.9%)	7 (17.5%)
Hypertension	30 (75.0%)	25 (62.5%)
Diabetes mellitus	5 (12.5%)	3 (7.5%)
Peripheral vascular disease	1 (2.5%)	3 (7.5%)
CABG×1	1 (2.5%)	2 (5.0%)
CABG×2	13 (32.5%)	13 (32.5%)
CABG×3	20 (50.0%)	22 (55.0%)
CABG×4	5 (12.5%)	3 (7.5%)
CABG×5	1 (2.5%)	0 (0%)
Myocardial ischemia time (min)	29.2	27.6
Cardiopulmonary bypass time (min)	65.8	62.5

Values are means except when otherwise labelled.

between the groups were similar. The control group had a slightly higher mean preoperative risk score with a mean preoperative Euroscore of 3.78, while the HBO_2 group had a mean preoperative Euroscore of 2.83. The control group had a higher number of diabetic patients ($n=5$; 12.5%) compared to the HBO_2 group ($n=3$; 7.5%). There were more patients with peripheral vascular disease in the HBO_2 group ($n=3$; 7.5%) than in the control group ($n=1$; 2.5%). The majority of patients in the control group and HBO_2 group had CABG×3 (50% vs. 55%). More patients in the HBO_2 group had CABG×1 ($n=2$; 5% vs. $n=1$; 2.5%) and CABG×3 ($n=22$; 55% vs. $n=20$; 50%) compared to the control group. However, the control group had more patients who had CABG×4 ($n=5$; 12.5 vs. $n=3$; 7.5%). The control group had a slightly longer mean myocardial ischemic time (29.2 vs. 27.6 min) and a slightly longer CPB time (65.8 vs. 62.5 min).

3.1. Hemodynamic outcomes

The hemodynamic results are shown in Table 2. Only 25 patients in the control group and 22 patients in the HBO_2 group had PA catheters inserted. This was due to the insufficient numbers of monitoring equipment required for measuring hemodynamic readings. This insufficiency occurred because the hemodynamic monitor-

Table 2
Hemodynamic measurements

		SV		CO		PVR		PVRI		LVSW		LVSWI	
		Control group $(n=25)$ [b]	HBO$_2$ group $(n=22)$ [b]	Control group $(n=25)$ [b]	HBO$_2$ group $(n=22)$ [b]	Control group $(n=25)$ [b]	HBO$_2$ group $(n=22)$ [b]	Control group $(n=25)$ [b]	HBO$_2$ group $(n=22)$ [b]	Control group $(n=25)$ [b]	HBO$_2$ group $(n=22)$ [b]	Control group $(n=25)$ [b]	HBO$_2$ group $(n=22)$ [b]
Postinduction	Mean value (S.D.)	61.8 (16.4)	64.5 (15.2)	4.38 (1.0)	4.60 (1.0)	158 (74.2)	115 (77.6)	292 (120)	228 (154)	58.3 (19.3)	60.1 (18.1)	30.6 (9.4)	30.4 (8.1)
	Geometric mean estimate and 95% confidence interval (p-value) [a]	Not significant		Not significant		1.55; 1.05–2.29 ($P=.03$)		1.49; 1.01–2.19 ($P=.05$)		Not significant		Not significant	
5 min post CPB	Mean value	59.9 (12.8)	66.1 (13.8)	4.85 (1.2)	5.22 (0.9)	147 (164)	105 (55.8)	214 (85.1)	208 (113)	50.1 (11.2)	56.0 (11.9)	25.8 (5.2)	28.3 (5.1)
	Geometric mean estimate and 95% confidence interval (P value) [a]	1.13; 1.03–1.25 ($P=.01$)		Not significant		Not significant		Not significant		1.28; 1.05–1.31 ($P=.005$)		1.122; 1.019–1.235	
2 h post CPB	Mean value	57.2 (15.8)	65.0 (9.9)	4.76 (1.5)	5.54 (1.5)	140 (68.4)	150 (93.0)	263 (128)	297 (198)	59.4 (20.2)	76.1 (20.0)	31.1 (10.0)	38.7 (11.3)
	Geometric mean estimate and 95% confidence interval (P value) [a]	1.13; 1.03-1.25 ($P=.01$)		Not significant		Not significant		Not significant		1.28; 1.05–1.31 ($P=.005$)		1.122; 1.019–1.235	
4 h post CPB	Mean value	58.1 (13.4)	60.0 (12.5)	5.41 (1.5)	5.74 (1.4)	157 (121)	152 (89.5)	306 (254)	298 (172)	54.4 (14.4)	62.0 (16.9)	29.4 (6.7)	31.2 (8.5)
	Geometric mean estimate and 95% confidence interval (P value) [a]	1.13; 1.03-1.25 ($P=.01$)		Not significant		Not significant		Not significant		1.28; 1.05–1.31 ($P=.005$)		1.122; 1.019–1.235	
8 h post CPB	Mean value	58.2 (15.5)	71.5 (22)	5.20 (1.6)	5.98 (1.7)	130 (73.5)	115 (62.6)	274 (131)	226 (121)	57.7 (16.3)	69.7 (23.4)	29.8 (6.9)	35.0 (11.3)
	Geometric mean estimate and 95% confidence interval (P value) [a]	1.13; 1.03-1.25 ($P=.01$)		Not significant		Not significant		Not significant		1.28; 1.05–1.31 ($P=.005$)		1.122; 1.019–1.235	
12 h post CPB	Mean value	67.8 (15.8)	68.0 (11.9)	5.48 (1.1)	5.75 (1.0)	121 (55.6)	123 (64.3)	230 (99.9)	245 (128)	65.7 (14.5)	67.7 (15.4)	33.8 (6.5)	34.2 (7.8)
	Geometric mean estimate and 95% confidence interval (P value) [a]	1.13; 1.03-1.25 ($P=.01$)		Not significant		Not significant		Not significant		1.28; 1.05–1.31 ($P=.005$)		1.122; 1.019–1.235	
24 h post CPB	Mean value	63.1 (13.9)	74.6 (19.7)	5.16 (1.0)	5.89 (1.4)	150 (85.8)	106 (49.4)	270 (117)	210 (98.9)	67.2 (14.6)	79.6 (26.5)	35.1 (8.0)	40.5 (15.0)
	Geometric mean estimate and 95% confidence interval (P value) [a]	1.13; 1.03–1.25 ($P=.01$)		Not significant		Not significant		Not significant		1.28; 1.05–1.31 ($P=.005$)		1.122; 1.019–1.235	

[a] Ninety-five percent confidence intervals are only given where the result is statistically significant; the mean estimates and confidence intervals provided are obtained following translation of logged results back into estimates of the geometric mean of the ratio of the HBO group to control.

[b] This is an ITT analysis.

Table 3
Comparison of post CABG ICU stay

Length of ICU stay (h)	Control group $(n=40)$ [†]	HBO$_2$ group $(n=41)$ [b]
Total	1051	850
Mean	26	21
Range	21-76	6-28
Geometric mean estimate and 95% confidence interval (P value) [a]	1.18 and 0.02–7.96 (P=.05)	

[a] Geometric mean estimates and confidence intervals provided are obtained following translation of logged results back into estimates of the geometric mean of the ratio of the HBO group to control.

[b] This is an ITT analysis.

ing equipment was required for the management of more critical ICU patients.

From the hemodynamic measurements obtained, we found that prior to CPB, the control group had a 55% higher PVR (P=.03) (estimate and 95% confidence interval: 1.550 and 1.05–2.29) and a 49% higher PVRI (P=.05) (estimate and 95% confidence interval: 1.492 and 1.017–2.188) compared to the HBO$_2$ group. At all time points post CPB, the HBO$_2$ group had SV that was 13% higher (P=.01) (estimate and 95% confidence interval: 1.134 and 1.03–1.25) compared to the control group. Furthermore, at all time points post CPB, the LVSW and the LVSWI in the HBO$_2$ group was 28% (P=.005) (estimate and 95% confidence interval: 1.275 and 1.05–1.31) and 12% (P=.02) (estimate and 95% confidence interval: 1.122 and 1.019–1.235) higher than in the control group. The HBO$_2$ group had an 11% improvement in CO post CPB compared to the control group, but this was not statistically significant (P=.06) (estimate and 95% confidence interval: 1.11 and 0.996–1.24). The other measured hemodynamic parameters revealed no clinically or statistically significant findings.

3.2. Clinical outcomes

Our results show that patients in the HBO$_2$ group spent 24 min longer on mechanical ventilation (P=.2) and had 36 min longer endotracheal intubation time (P=.2). However, patients in the HBO$_2$ group had an 18% reduction in length of post CABG ICU stay (P=.05) (estimate and 95% confidence interval for the difference: 1.18 and 0.02–7.96) which equated to a geometric mean of 4 less in ICU length of stay post CABG (Table 3). Apart from gastrointestinal complications, which had similar incidences in both groups post CABG (Table 4), the HBO$_2$ group had a 10.4% reduction in low cardiac output syndrome (P=.4), an 8% reduction in inotrope usage (P=.1), an 11% reduction in atrial fibrillation (P=.6), a 12.7% reduction in pulmonary complications (P=.8), and a 7.6% reduction in infections (P=.4). Furthermore, the HBO$_2$ group had no incidences of renal and neurological complications of which there was an incidence of 5% and 2.5%, respectively, in the control group. The results also showed that the HBO$_2$ group of patients had a

57% reduction in intraoperative blood loss (P=.02), 11.6% reduction in postoperative blood loss (P=.09), and a 34% reduction in postoperative blood transfusion (P=.4) (Table 5).

3.3. Serum troponin T results

At approximately 1 h post HBO$_2$ preconditioning, the HBO$_2$ group had no clinically significant change in serum troponin T levels and these results at this time point were reported as "<0.02 ng/ml" by the laboratory. Intra- and postoperatively, there were no statistically significant changes in serum troponin T in either group. Clinically, we observed that, in both groups, the concentration of serum troponin T appeared to rise from the onset of CPB to 24 h post CPB (Fig. 2). This rise, however, was greater in the

Table 4
Post CABG complications

Variable	Control group (n=41; intention to treat)	HBO group (n=40; intention to treat)	P value [a]
Low cardiac output	10 (25%)	6 (14.6%)	.4
Inotrope usage	10 (25%)	7 (17%)	.1
1. Adrenaline	2	1	
2. Dopamine	3	3	
3. Noradrenaline	0	2	
4.Adrenaline+dopamine	1	0	
5. Adrenaline+noradrenaline	2	1	
6. Adrenaline+milrinone	1	0	
7.Adrenaline+noradrenaline+ milrinone	1	0	
Atrial fibrillation	10 (25%)	6 (14%)	.6
Pulmonary complications	9 (22.5%)	4 (9.8%)	.8
1. Pneumothorax	1	0	
2. Pleural effusion	2	0	
3. Chest infection	4	2	
3. Atelectasis requiring BiPAP/CPAP	1	0	
4. Chest infection+ pleural effusion	0	1	
5. Other	1	1	
Renal complications (creatinine >200 mmol/l)	2 (5%)	0	.5
Neurological complications	1 (2.5%)	0	1.0
1. Confusion+blurred vision	1	0	
Gastrointestinal complications	1 (2.5%)	1 (2.4%)	
1. *Clostridia difficile* diarrohea	1	0	
2. Other	0	1	
Infections	4 (10%)	1 (2.4%)	.4
1. Superficial sternal	3	0	
2. Deep sternal	1	0	
3. Leg	0	1	
Perioperative myocardial infarction	0	0	
Reoperation for bleeding	0	0	
Mortality	0	0	

BiPAP=Biphasic positive pressure ventilation; CPAP=continuous positive airway pressure.

[a] This is an ITT analysis.

Table 5
Comparison of blood loss and blood transfusion

Variable	Control group (*n*=40)	HBO$_2$ group (*n*=41)	% Reduction in HBO$_2$ group	*P* value[a] (independent sample *t* test)	95% Confidence intervals
Intraoperative blood loss (ml)			[(309−133)/309]×100=57	.02	−318 to −32
Mean	309	133			
Range	0–1528	0–961			
Postoperative blood loss (ml)			[(727−643)/727]×100=11.6	.1	−31 to 200
Mean	727	643			
Range	255–1295	325–1330			
Total blood transfusion (ml)			[(138−91)/138]×100=34	.4	−63 to 159
Mean	138	91			
Range	0–612	0–610			

[a] Intention-to-treat analysis.

control group than in the HBO$_2$ group. Furthermore, 2 h post CPB, in the HBO$_2$ group, the rise in serum troponin T appeared to plateau off, while in the control group, it appeared to continue to rise.

3.4. Cost

During the post hoc cost-effectiveness analysis of this study, the HBO$_2$ treatment as a whole was estimated to be about US$402.75 per patient. The cost for the ICU bed per day in our hospital was estimated as US$4000.00. Using these cost estimates, we calculated (Table 6) that patients treated with HBO$_2$ preconditioning prior to CABG saved US$582.45 per patient, in terms of ICU cost. This means an estimated savings of US$116.49 per saved ICU hour. As a study, the 34 patients treated with HBO$_2$ preconditioning saved an estimated US$19,803.67, in terms of ICU cost, when compared to the control group.

4. Discussion

4.1. The effects of HBO$_2$ preconditioning and clinical outcomes and hemodynamic parameters

Our study demonstrated that, despite the slightly longer post CABG ventilation and intubation time, the patients who

Changes in Serum Troponin-T

Fig. 2. Comparison of changes in serum troponin T in HBO$_2$ and control group.

were preconditioned with HBO$_2$ had a significantly (*P*=.05) shorter stay in ICU (5 h less). Age, CPB time, and pre CABG COPD are known to affect ICU length of stay [28,29]. The ages of patients and CPB times of both groups in this study were similar (Table 1). Patients with COPD were excluded from this study as they are at risk of developing a pneumothorax, and this risk is increased in an HBO$_2$ chamber where there are changes in pressure during the pressurisation and depressurisation stages of the HBO$_2$ treatment. As such, it is reasonable to deduce that HBO$_2$ preconditioning was, in part, the cause for the shorter ICU stay observed in the HBO$_2$ group.

Hemodynamically, the results of this study showed that (Table 2) prior to the onset of CPB, the HBO$_2$ group had a significantly lower PVR compared to the control group. This reduction in PVR suggests that HBO$_2$ preconditioning is capable of improving pulmonary vascular blood flow prior to the CABG and IRI. Post CPB, the HBO$_2$ group had significantly increased SV and LVSW. CO post CPB was improved in the HBO$_2$ group, but this was not a statistically significant finding though clinically important. These results appear to suggest that HBO$_2$ preconditioning prior to CABG has the capacity to enhance myocardial mechanical performance post CABG and IRI. An indirect measure of support for our findings comes from the study by Dekleva et al. [30]. They conducted a randomized control study to assess the benefits of HBO$_2$ after thrombolysis on the left ventricular function and remodelling in patients who had suffered from an AMI. They observed that there was a significant decrease in end-systolic volume index from the first day to the third week in HBO$_2$ patients compared with the control patients. This was accompanied with no changes in end-diastolic volume index in the HBO$_2$ group with increased values in the control group. The ejection fraction was also significantly improved in the HBO$_2$ group and decreased in the control group of patients 3 weeks after AMI. Their study concluded that adjunctive HBO$_2$ after thrombolysis in AMI has a favorable effect on left ventricular function and the remodelling process. Furthermore, it showed that, in the
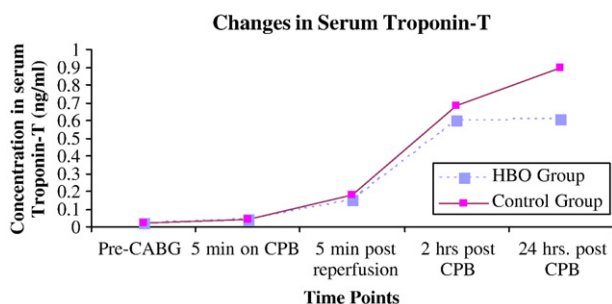
Table 6
Summary of Cost

Item	Cost (US dollars)
HBO$_2$ treatment	402.75
HBO$_2$ treatment for 34 patients	13,693.50
ICU bed per day	4000.00
ICU bed per hour	166.67
ICU stay for 35 control patients (A)	166.67×1051=175,166.67
ICU stay for 34 HBO$_2$ patients	166.67×850=141,669.50
HBO$_2$ treatment+ICU stay for 34 patients (B)	13,693.50+141,669.50=155,363.00
Total savings for HBO$_2$ patients (A−B)=C (savings made by 34 HBO$_2$ patients who spent a total of 1051−850=201 h less in ICU; see Table 3)	175,166.67−155,363.00=19,803.67
Savings per HBO$_2$ patient in ICU	582.45
Savings per ICU hour saved in each HBO$_2$ patient	116.49

absence of HBO$_2$ to adjunct thrombolysis, the control group went on to develop systolic and diastolic disimprovement post AMI. Further support comes from the HOT-MI study [21] which showed an improvement in post MI ejection fraction. In another study, Swift et al. [31] evaluated the potential for HBO$_2$ to produce improvement in myocardial function in the hibernating myocardium. In that study, they found that patients who were also treated with HBO$_2$ following an AMI had improved myocardial contraction as observed by echocardiography and demonstrated reversible ischemia as determined by SPECT imaging compared to those patients who were not treated with HBO$_2$ post AMI. More recently, Aparci et al. [32] also found that, in diabetic patients who were being treated for nonhealing lower extremity ulcers, after 10 HBO$_2$ treatment sessions, these patients had an improved diastolic function. These clinical studies suggest that HBO$_2$ has the clinical potential to stimulate and improve myocardial function.

Over the years, other investigators have also observed the clinically beneficial effects of HBO$_2$ treatment. Where low cardiac output is concern, Yacoub and Zeitlin [33] reported in 1965 that post cardiac surgery (and therefore post IRI) treatment of low cardiac output syndrome with HBO$_2$ resulted in satisfactory clinical outcome. In our study, we found that preconditioning with HBO$_2$ prior to IRI was also capable of reducing the incidence of low cardiac output syndrome (Table 4). In 1973, Thurston et al. [34] conducted a randomised control study to examine the effects of HBO$_2$ on mortality following recent AMI. This group observed that, in the HBO$_2$ group, there was a reduction in mortality 3 weeks after an AMI and a reduction in significant dysrrhythmias (complete heart block, ventricular fibrillation, and asystole). In the clinical study conducted by us, we also found that HBO$_2$ preconditioning was beneficial by way of lowering the incidence of post CABG inotrope usage, atrial fibrillation, and general pulmonary, renal, and neurological complications (Table 4). With respect to sternal wound

infection, there are a number of studies [35–38] that have shown that HBO$_2$ is a useful adjunct to promote sternal wound healing following postoperative sternal wound breakdown. The reduction in the incidence of wound infection observed in our study (Table 4) appears to also suggest that HBO$_2$ preconditioning prior to median sternotomy may have a prophylactic antimicrobial effect that is capable of reducing both superficial and deep sternal wound infections post CABG. Perhaps this may be linked to the antimicrobial properties of oxygen and HBO$_2$ [39]. Where cost was concerned, we found that the significantly shorter length of ICU stay among patients preconditioned with HBO$_2$ was associated with savings in hospital cost (Table 6).

With respect to blood loss, our results (Table 5) showed that HBO$_2$ preconditioning prior to CABG and IRI appears to result in a reduction in intraoperative and postoperative blood loss, and postoperative blood transfusion. Presently, there is only one case report that has documented the successful use of HBO$_2$ to stop hematuria in a patient following ischemic haemorrhagic cystitis [40]. In a recent animal study [41], HBO$_2$ treatment following occlusion and reperfusion of middle cerebral artery was shown to be useful in reducing hemorrhagic transformation after this focal transient cerebral ischemia. These results suggest that HBO$_2$ prior to IRI (our study) and post IRI [40,41] may be a useful pharmacological therapy, at least as an adjunct, in efforts to limit perioperative blood loss and conserve blood. This may partly result from the ability of HBO$_2$ to reduce vascular permeability [41,42].

4.2. The effects of HBO$_2$ preconditioning and serum troponin T

In our study, we observed that 1 h following HBO$_2$ treatment, serum from patients in the HBO$_2$ group did not show any clinically valuable change in serum troponin T levels. This suggests that 1 h following the oxidative stress of HBO$_2$, this modality of treatment does not cause any clinically detectable myocardial injury and is a safe modality of treatment. While there have been no other experimental or clinical studies involving HBO$_2$ and troponin T, the HOT-MI study [21] found that, in the HBO$_2$ group, there was a 35% reduction in mean CK at 12 and 24 h post MI and concluded that adjunctive HBO$_2$ was a feasible and safe treatment for AMI. Clinical studies have yet to find any correlation between oxidative stress, myocardial injury, and troponin T release [43–45]. In our study, we observed that, following CPB, the HBO$_2$ group showed a smaller increase in serum troponin T. Moreover, in the HBO$_2$ group, the rise in serum troponin T stopped 2 h post CPB and the levels plateaued off, while in the control group serum troponin T appeared to continue to rise. This suggests that the oxidative stress of HBO$_2$ preconditioning prior to the oxidative stress of IRI during CABG induces a myocardial protective mechanism that limits the degree of myocardial necrosis and the subsequent troponin T release. This implies that precondi-

tioning with HBO_2 prior to on-pump CPB CABG and IRI may have the ability to attenuate myocardial injury post CPB.

Essentially, HBO_2 preconditioning prior to ischemia and reperfusion, as utilised in this study, functions as a mode of ROS preconditioning. Both HBO_2 therapy [6] and ischemia and reperfusion [46] generate ROS. It is possible that, by preconditioning patients with HBO_2 and exposing them to the nonlethal controlled dose of ROS that results from HBO_2, a complex set of biological protective pathways are initiated. As such, when patients are subsequently exposed to a further burst of ROS, as occurs during ischemia and reperfusion, which normally lead to cellular injury and clinical dysfunction [47], there is already a protective mechanism that has been initiated to enable better tolerance to this insult. Various studies have demonstrated that low doses of ROS [48–50] and ROS preconditioning [51–53] lead to myocardial protection. Additionally, Yaguchi et al. [54] demonstrated that ROS preconditioning leads to better myocardial protection than just ischemic preconditioning alone.

5. Conclusion

This single-centre randomised control study in patients with CAD was designed to determine whether precondition-ing these patients with one session of HBO_2, prior to first-time elective on-pump CPB CABG, was capable of further improving myocardial function during ischemia and reperfusion post CABG. In this clinical study, the primary end point was met. It demonstrated that preconditioning CAD patients with HBO_2 prior to on-pump CPB CABG was capable of improving LVSW ($P=.005$) 24 h post CPB. However, this study only met with some of its secondary hemodynamic end points. In this study, prior to the onset of CPB, the HBO_2 group had a lower PVR ($P=.03$) and PVRI ($P=.05$). Furthermore, this study also showed that, at all time points post CPB, only SV ($P=.01$) and LVSWI ($P=.02$) increased in the HBO_2 group. Additionally, it was observed that there was an 18% reduction in ICU stay following HBO_2 precondi-tioning and CABG ($P=.05$) and a 57% reduction ($P=.02$) in intraoperative blood loss. While none of the other clinical secondary end points reached significance, there were some interesting improvements in clinical outcomes in the HBO_2 group of patients. Postoperatively, the HBO_2 group had a reduction in blood loss (11.6%), blood transfusion (12.7%), low cardiac output syndrome (10.4%), inotrope use (8%), atrial fibrillation (11%), pulmonary complications (12.7%), and wound infections (7.6%).

This small clinical study provides some evidence that preconditioning CAD patients with HBO_2 prior to first-time elective on-pump CPB CABG was capable of improving myocardial function post CABG while also improving pulmonary vascular flow prior to CABG. It also attenuated the degree of myocardial injury and troponin T release post CABG. Additionally, following CABG, it reduced post-operative complications and the length of ICU stay, and was

cost effective. While the results are encouraging, the strength of the evidence from this study is still weak. This is a consequence of the major limitation of this study, which was that the total number of patients was small. Furthermore, the cohort of patients recruited to this study was a relatively low-risk group and, as such, the actual impact of HBO_2 preconditioning may not have been easily appreciated. As the centre where this study was carried out did not regularly perform CABG without the use of CPB (i.e., off-pump CABG), no comparison was made with a group of CAD patients who had CABG without the use of CPB. Additionally, no comparison was made with a group of patients who were treated with a controlled ischemia and reperfusion protocol prior to the multiple variable periods of ischemia and reperfusion that occurred during this clinical study involving CABG and IRI.

The trend for HBO_2 preconditioning to demonstrate beneficial clinical, biological, and economic effects in low-risk CABG patients, as observed in this study, also provides encouragement for its use in more high-risk patients who are about to undergo on-pump CPB CABG. Surgeons and anaesthetists may wish to consider this modality of treatment to further optimise the clinical condition of more high-risk patients prior to embarking on complex cardiac surgical procedures involving prolonged periods of ischemia and reperfusion that traditionally are associated with poor postoperative clinical outcomes.

Despite promising results, the future of HBO_2 precondi-tioning medicine remains unclear as this modality of treatment is not found in the vicinity of every acute hospital and, where available, it is not of appropriate design and lacks the facilities to accommodate an unwell post cardiac surgical ICU patient. For this modality of treatment to become a recognised and more frequently used modality of treatment, more translational studies are required to facilitate the transition from bench research to the bedside clinical therapy. More HBO_2 units are required in major acute hospitals with a design that is capable of caring for critically ill ICU patients such as in various centres in the USA, Sweden, Norway, and Australia. Furthermore, more well-conducted multicentre randomised control studies are required, not only to validate laboratory findings, but to also to address the clinical issues in the 'real world' and provide an evidence-based platform for its use in day-to-day clinical care.

Acknowledgments

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