Early detection of myocardial viability by hyperbaric oxygenation in patients with acute myocardial infarction treated with thrombolysis

Milica Dekleva[1], Miodrag Ostojic[2], Aleksandar Neskovic[3], Sanja Mazic[4], Alja Vlahovic[3], Jelena Suzic Lazic[1] and Nikola Dekleva[†]

[1] *University Clinical Centre "Dr. Dragiša Mišović-Dedinje", Belgrade, Serbia*
[2] *Institute for Cardiovascular Diseases, Clinical Center of Serbia, Serbia*
[3] *Clinical-Hospital Center Zemun, Belgrade, Serbia*
[4] *Institute of Medical Physiology, Faculty of Medicine, University of Belgrade, Serbia*

Abstract. Hyperbaric oxygen treatment (HBO) could transiently reverse hypoxia during acute myocardial infarction (AMI). In order to evaluate whether early HBO can identify viable segments after AMI, improvement of wall motion score index (WMSI) after HBO was compared to dobutamine stress echocardiography (DSE). Thirty-one patients with first AMI treated with thrombolysis received 100% oxygen at 2 technical atmospheres for 1 h within 24 h of the onset of chest pain. All patients underwent echocardiography before and after HBO and during DSE. Improvements in WMSI after HBO, as well as during DSE were considered as proof of viability. Total of 186 akinetic segments were detected before HBO. Functional recovery was defined at 73 after HBO and 113 segments were fixed. Eighty-one segments improved contraction with DSE. WMSI improved before HBO compared to the one after HBO (1.79 vs. 1.65, $p = 0.024$) and DSE (1.79 vs. 1.60, $p < 0.001$). Close relationship between WMSI after HBO and DSE was found ($r = 0.417$, $p = 0.022$). Sensitivity and specificity of HBO for viability were 73% and 85%, respectively. HBO may identify viable myocardium as early as day one after AMI. The highest number of responding segments was detected in patients who received HBO within shortest intervals following the onset of chest pain.

Key words: Myocardial viability — Hyperbaric oxygenation — Acute myocardial infarction

Introduction

In the setting of myocardial infarction treated with thrombolysis loss of myocardial contractile function may be due to myocardial necrosis, stunning or hibernation. Whereas myocardial necrosis usually suggests irreversible myocardial dysfunction, stunning and hibernation reflect reversibility of myocardial function (Braunwald and Rutherford 1986; Rahimtoola 1989). In the case of hibernating myocardium, coronary revascularization may reduce heart failure symptoms and improve left ventricular (LV) function and survival (Rahimtoola 1998; Bax et al. 1999; Schinkel et al. 2002). The improvement is directly related to the number of dysfunctional, but viable segments (Bax et al. 1997; Wijns et al. 1998). It has been hypothesized that acute, as well as chronic hypoperfusion may result in down regulation of myocardial contractile function to preserve myocardial integrity and this process may be reversed after adequate restoration of myocardial perfusion.

The hibernating myocardium has been demonstrated to have several characteristics: cell membrane integrity, preserved glucose metabolism and inotropic reserve. Various techniques that are currently available for assessment of myocardial viability are based on the evaluation of these characteristics (Wijns et al. 1998). Currently, most frequently used are scintigraphic imaging with either positron emission tomography (PET) for intact metabolism, thalium, contrast or single photon emission computer tomography (SPECT) for intact microvascular circulation

Correspondence to: Jelena Suzic Lazic, Department of Echocardiography, University Clinical Centre "Dr. Dragiša Mišović-Dedinje", Milana Tepića 1, 11000 Belgrade, Serbia
E-mail: jsuzic@eunet.rs; mildek@sbb.rs

and echocardiography during stepwise infusion of dobutamine for intact inotropic reserve. None of the available techniques for the identification of myocardial viability can be considered unequivocally superior to the others. By far most widely used is one with low dose dobutamine stress echocardiography (LDSE) as the preferred stressor for assessing myocardial viability.

The hallmark for viability using LDSE (5–20 μg/kg/m) is the improvement of contractility of asynergic segment after adrenergic stimulation. Enhanced inotropic state, heart rate and blood pressure require increased myocardial oxygen consumption (VO_2). In the absence of myocardial ischemia, myocardial contractility in akinetic, but viable segments will enhance resulting in improvement of myocardial thickening during LDSE. The most specific indicator of myocardial viability in setting of hibernation is deterioration of this zone showing initial augmentation in response to increasing dose of dobutamine referred to as the biphasic response. Hibernating myocardium may be identified by DSE with highest specificity (81%) and with an accuracy of 80% in prediction functional recovery (Geleijnse et al. 1997; Wijns et al. 1998; Sicari et al. 2008).

Hyperbaric oxygen improves ventricular function and reduces tissue injury when administrated during evolving myocardial infarction (Jain 1990). Experimental and clinical data suggest that this effect is mediated by decreasing tissue edema, reducing formation of lipid peroxide radicals, altering nitric oxide syntheses, expression and inhibition of leukocyte adherence and plugging in the microcirculation. (Cameron et al. 1966; Thomas et al. 1990; Stavitsky et al. 1998; Dekleva et al. 2004; Sharifi et al. 2004; Vlahovic et al. 2004). Hyperbaric oxygenation can produce hyperoxia in ischemic tissue and reveal hibernating myocardium in the setting of recent myocardial infarction (Swift et al. 1992).

The aim of this study was to evaluate by two-dimensional echocardiography whether hyperbaric oxygen treatment (HBO) early after acute myocardial infarction (AMI) can identify viable segments and compare these finding to changes in segmental wall motion to myocardial viability determined by dobutamine stress echocardiography (DSE) as a clinically relevant method for viability detection.

Materials and Methods

Study population

The study population was selected from 37 consecutive patients admitted to our coronary care unit who satisfied the following criteria: first AMI diagnosed on the basis of typical ischemic chest pain >20 min in duration, acute ST segment elevation >2 mm in two contiguous electrocardiographic (ECG) leads, a significant rise and fall in serum troponin and creatine kinaze and MB isoenzyme levels and demonstrable wall motion abnormality on routine TTE. Exclusion criteria were: presence of uncontrolled heart failure, arrhythmias or significant postinfarction angina and presence of serious non-coronary disease that might preclude dobutamine echocardiography. Further exclusions to HBO were the inability to equilibrate pressure in the middle ear space secondary to thinitis or otitis, severe claustrophobia and chronic obstructive pulmonary disease. Study patients were treated with 1.5 million IU of streptokinase by rapid infusion (over 30 to 60 min) followed by infusion of heparin after six hours (25,000 IU) and aspirin (300 mg). All patients were treated with HBO after thrombolysis. After one week they underwent DSE. However, 5 patients with serious ventricular arrhythmia and one with severe hypertension at rest were contraindicated for DSE.

HBO

After thrombolytic therapy, within first 24 h, patients were treated in monoplace hyperbaric chamber. Under medical supervision, each patient was treated with 100% oxygen pressurized at 2 AT for 45 min followed by 15 min of decompression breathing the same gas mixture. Inside the chamber 3-lead ECG were recorded before hyperbaric exposure, during bottom time and during decompression.

Coronary angiography

Coronary angiography was performed after hospital discharge. Perfusion of the infarct-related artery was assessed by using criteria from the Thrombolysis in Myocardial Infarction (TIMI) trial (TIMI Study Group 1985, see References). Successful reperfusion was coded as TIMI grade 3.

Echocardiography

Two-dimensional echocardiography was obtained with commercially available imaging system using Acuson 128 XP system (Acuson Corp., Mountain View, California USA) with a 2.5 MHz transducer and images acquired in parasternal long and short axis and apical 4 and 2 chamber views. The complete echocardiographic studies were recorded for subsequent playback analysis performed on day one of AMI before and after HBO and during LDSE. Left ventricular ejection fraction (LVEF) was determined from apical two and four chamber views by using Simpson's biplane formula according to the recommendations of American Society of Echocardiography (Schiller et al. 1989; Cheitlin et al. 2003). Tracing of endocardial borders in the endsystole and enddiastole was performed in the technically best cardiac cycle.

Two independent, well-trained experienced observers performed blind analysis of regional wall motion thickening after the patients had received HBO. Interobserver agreement was 96%. Presence of viability has been defined by improvement at least one grade in two or more LV segments after HBO or DSE. Segments with unchanged wall motion were considered non viable (Pellikka et al. 2007).

DSE

Two dimensional (2D) echocardiograms and 12-lead ECG monitoring were performed during LDSE. The protocol used dobutamine infusion at two low dose stages (5 and 10 μg/kg/min) with each stage lasting 3 min. The benefit of proceeding to higher doses (20, 30, 40 μg/kg/min) of dobutamine even if contractile reserve is demonstrated at lower doses is to observe a "biphasic response" (Geleijnse et al. 1997; Sicari et al. 2008). In present study we obtained high DSE according to the 3 min increment protocol in all patients who did not have contraindications. DSE was scheduled within one week of the hyperbaric study and all study procedures were performed between one and ten days after AMI. All antianginal medications were withheld before DSE (nitrates 24 h and B blockers and calcium antagonists 48 h before the test). Non echocardiographic end points requiring test interruption were the following: severe chest pain or significant ST segment changes, symptoms of intolerance, blood pressure > 240/120 mmHg, decrease in blood pressure >30 mmHg, and significant arrhythmia.

Regional wall motion was assessed according to the recommendation of the American Society of Echocardiography with 16 segment model (Schiller et al. 1989). In all studies segmental wall motion was semi quantitatively graded from 1 to 4 as follows: 1 – normal motion at rest with normal wall motion after HBO or increased wall motion during dobutamine infusion, 2 – hypokinetic (marked reduction in endocardial motion and thickening), 3 – akinetic (absence of inward motion and thickening), 4 – dyskinetic (paradoxical wall motion away from the center of the left ventricle in systole). The wall motion score index (WMSI) was derived by dividing the sum of individual segment scores with the number of interpretable segments calculated for baseline, after HBO and during DSE. Myocardial segments were considered normal in cases when regional wall motion was normal or mild hypokinetic. Only dysfunctional segments (segments with severe hypokinesia, akinesia or dyskinesia at resting echocardiography) were evaluated for myocardial viability.

Statistical analysis

All continuous data are expressed as mean ± SD; percentages are rounded. Continuous variables were compared by means of the Student's *t*-test for paired samples. Relationships between examined variables included echocardiographic parameters before and after HBO and during DSE were compared using Pearson's correlation test. Sensitivity, specificity and accuracy were evaluated using standard definitions and expressed as percentage points. Statistical significance was defined as $p < 0.05$.

Results

Demographic, clinical and angiographic data

Patient's demographic, clinical and angiographic data are listed in Table 1. The study population was predominantly male (29/8) aged 55 ± 7 years. There were more patients with acute inferior (23 patients, 62%) than with anterior (14 patients, 38%) myocardial infarction. As shown in Table 2,

Table 1. Patient's demographic, clinical and angiographic characteristics

Characteristic	Patients
Mean age (years)	55 ± 7
Female/male	8/29
Hypertension (%)	14 (38)
Diabetes mellitus (%)	8 (22)
Cigarette smoking (%)	30 (81)
Killip class > 2 (%)	2 (5)
Time to STK (h)	2.4 ± 1.6
Localization, anterior (%)	14 (38)
Peak value CK (U/l)	989 ± 643
Multivessel CAD (%)	19 (51)
TIMI 3 flow (%)	22 (59)
Collaterals (%)	9 (24)
Cardiac mortality (%)	0 (0)

Table 2. Pharmacological therapies during hospital stay and at discharge

Medications	Patients (%)
Heparin	37 (100)
Aspirin	36 (97)
Oral anticoagulation	5 (14)
Nitroglycerin IV	7 (19)
Long-acting nitrates	30 (81)
Calcium channel blockers	1 (3)
β-blockers	26 (70)
Digitalis	1 (3)
Diuretics	3 (8)
ACE inhibitors	8 (22)

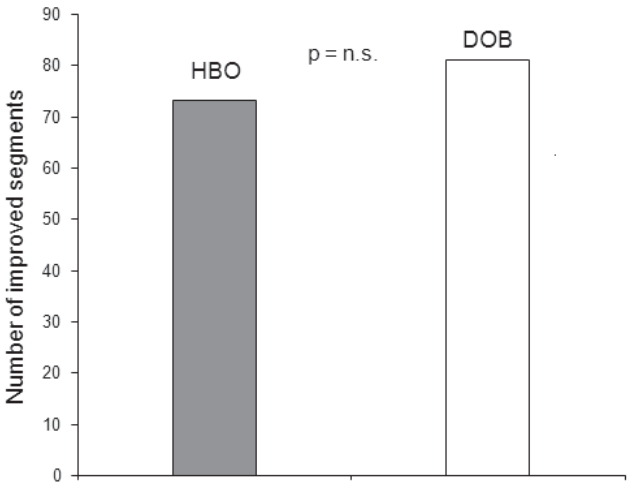

Figure 1. Contractile response of LV segments during DSE and after hyperbaric oxygen treatment (HBO). DOB, dobutamine; n.s., non-significant.

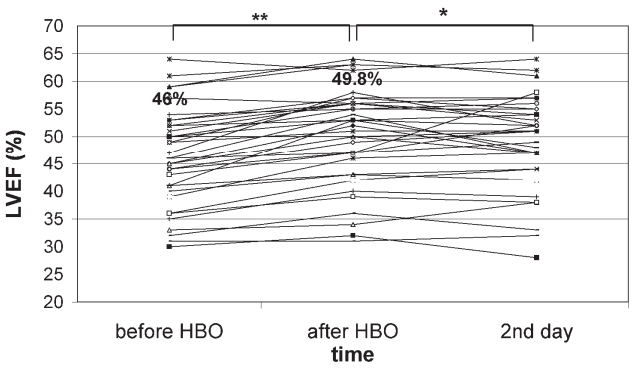

Figure 2. Global LV systolic function before and after hyperbaric oxygen treatment (HBO). LVEF, left ventricular ejection fraction;* $p < 0.001$, * p = non-significant.

all patients received similar therapy during their hospital stay and at discharge including β blockers, ACE inhibitors, long acting nitrates, calcium channel inhibitors, digitalis and diuretics.

From 419 detectible segments, 186 segments were defined as akinetic or severe hypokinetic in 31 patients by rest echocardiograms after cessation of thrombolytic therapy and before HBO, during day one of AMI. There were no dyskinetic segments.

Functional recovery was defined at 73 segments after HBO (38.9%) and other 113 segments remained unchanged, there were no deteriorated segments. In 6 patients no changes were found compared to rest echocardiogram. During DSE there were only 6 patients with biphasic response and other wall motion improvements were detected by LDSE. Patients with biphasic response obtained DSE with dobutamine infusion 20–30 μg/kg/min. Eighty-one segments (43.5%) of resting wall motion abnormality showed improved contraction with DSE. Thus, positive predictive value for improvement of WMSI by HBO compared to DSE was 90%. Resting asynergy was associated with no improvement in contraction with HBO in 113 segments of which 105 during DSE were also unchanged (negative predictive value 92%). Wall motion response during DSE and after HBO was without significant difference ($t = 1.56$, $p = 0.32$; Fig. 1). Score indices significantly improved from rest echocardiogram before HBO to echocardiogram after HBO exposure (1.79 ± 0.32 vs. 1.65 ± 0.21, $p = 0.024$) and from rest echocardiogram to DSE (1.79 ± 0.32 vs. 1.60 ± 0.22, $p < 0.001$). The level of functional regional systolic LV function, measured by score indices improvement, calculated after HBO and during LDSE was similar (1.65 vs. 1.60, $t = 1.30$, $p = 0.22$). There was close relationship between the number of improved segments calculated by 2D echocardiography immediately after HBO and during DSE ($r = 0.417$, $p = 0.022$). Sensitivity and specificity of HBO for detection of viability were 73% and 85 %, respectively. Global systolic function obtained from LVEF after HBO significantly increased compared to basal values of LVEF after thrombolysis (46.0 ± 8.8 vs. 49.78 ± 8.7%, $t = 7.47$; $p < 0.001$; Fig. 2).

The number of improved LV segments in the infarction zone after HBO or during DSE was not closely related to TIMI flow of the infraction related artery ($r = 0.74$, p = non-significant). Therefore, in our study, the number of viable segments was not predictable for its patency.

The interval at which patients received HBO within the 24 h of AMI ranged from 3 to 20 h, averaging 13 h. There was significant negative correlation between the level of functional recovery or contractile improvement of LV wall segments and time from the onset of chest pain to HBO exposure ($r = -0.557$, $p = 0.002$), and also between the time from thrombolysis to HBO ($r = -0.499$, $p = 0.007$; Fig. 3). The response of viable segments was optimal in cases when the HBO was performed during the first 10 h from the onset of the chest pain ($r = 0.498$, $p = 0.003$).

Discussion

The ability to distinguish myocardial hibernation from necrosis in early phase of AMI may be important in the selection of patients for mechanical or surgical intervention (Smart et al. 1997). Furthermore, following thrombolytic therapy for AMI, viable myocardium in reperfused zone may remains ischemic and can be at risk of progression to necrosis if not salvaged by early mechanical intervention (Lew et al. 1990).

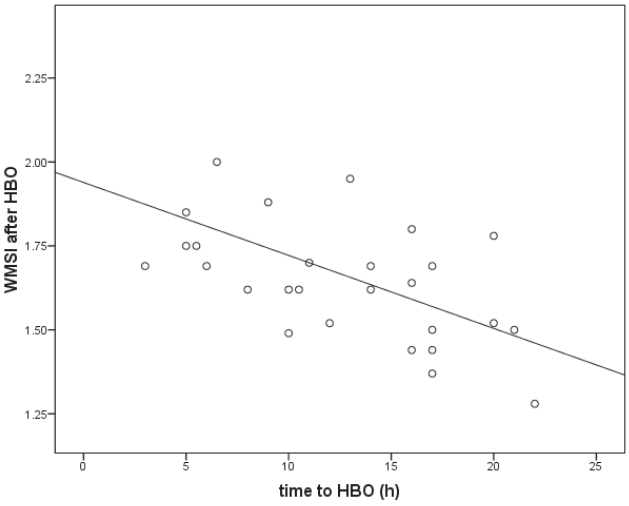

Figure 3. Relationship between time to hyperbaric oxygen treatment (HBO) and wall motion score index (WMSI) after oxygen exposure.

Mechanism of functional recovery of hibernating myocardium with HBO

Administrating of 100% oxygen at 2 AT increases the amount of oxygen dissolved in the blood and tissue by 10-fold and is more than enough to meet the resting cellular requirements without any contribution from hemoglobin-bound oxygen (Jain 1990). At least three different mechanisms are responsible for favorable changes in myocardial oxygen supply and demand during HBO: increase in total barometric pressure, direct increase in oxygen partial pressure in arterial blood, significant increase in oxygen content of arterial blood, interstitial fluids and tissues especially plasma dissolved fraction. All mechanisms produce different oxygen transport regimens in specific conditions and increase effective cellular oxygenation at very low rates of blood flow by achieving high arterial O_2 pressure. The net effect is an approximately 25% enhanced oxygen blood content and consumption with 3 to 4 times increased tissue oxygen diffusion distance. In case of critical coronary stenosis, the difference in high oxygen tension pressure between ischemic and non-ischemic tissue, improves penetration of oxygen into hypoxic tissue (Jain 1990; Rochitte et al. 1998; Dekleva et al. 2004).

During AMI there are structural changes in coronary microcirculation followed by decreased density and disturbed perfusion in capillary bed (Rochitte et al. 1998; Wu et al. 1998). In ischemic and hypoxic tissues, the capillaries are often partially occluded by microthrombi, and the transport of red blood cells along the capillary may be compromised or halted. In certain circumstances only plasma with large amount of dissolved oxygen under hyperbaric condition can flow through the suffering blood vessel. This phenomenon is known as "plasma skimming" and can be of vital importance as the only vehicle to assure adequate oxygen transport to the areas beyond the capillary subobstruction and also may represent the way to discover hibernating myocardium (Wu et al. 1998). Oxygenation occurs in "local blood flow" in "supply" dependent tissues, in which oxygen transport in normobaric condition falls below 8–10 ml/O_2/kg/min. Regional myocardial function may remain abnormal unless transmural ischemia is almost completely reversed by reperfusion (Yogaratnam et al. 2008). Therefore wall motion analysis after HBO may indicate a more relevant improvement of wall contraction without functional-perfusion mismatch.

Recent studies have shown that treatment with HBO postischemia and reperfusion ameliorated myocardial ischemia-reperfusion injury by stimulating the endogenous production of nitric oxide (Cabigas et al. 2006; Yogaratnam et al. 2008). Favorable circumstances of hyperoxic and hyperbaric actions of HBO induced cardio-protection and functional recovery by activation of nitric oxide synthetase, which is directly dependent of oxygen availability (Cabigas et al. 2006).

In condition of recent myocardial infarction the capacity of transporting hemoglobin-bind oxygen to the sites of utilization is severely decreased. During DSE, adrenergic stimulation enhances oxygen demand, provoking the tense contractile reserve to detect the viable myocardium. Contrary to this, hyperbaric oxygen enables favorable oxygen tension and functional recovery of hibernating myocardium.

Previous studies

According to previous studies the role of HBO in patients with AMI was controversial ranging from not beneficial to a favorable effect (Cameron et al. 1966; Thomas et al. 1990). Recent studies suggested that adjunctive HBO in patients with AMI treated with thrombolysis or with percutaneous coronary interventions is a safe and beneficial therapy. These studies, in addition to showed feasibility of use HBO, demonstrated that HBO, as an adjunct to the management of AMI, pharmacologically limits myocardial damage and improves myocardial function (Stavitsky et al. 1998; Dekleva et al. 2004; Sharifi et al. 2004; O'Neil et al. 2007). Similar to present results, improved myocardial salvage after adjunctive use of HBO after thrombolysis was documented by improving of global systolic function measured by higher value of LVEF after HBO (Stavitsky et al. 1998; Dekleva et al. 2004).

The hypothesis that transitory hyperoxia in dysfunctional myocardium would be followed by transitory improvement in contraction of viable segments has been proved by Swift et al (1992). These authors tried to detect viable myocardium in postinfarction patients by immediate transthoracic (TTE) and transesophageal echocardiography (TEE) after

HBO and compared results with thallium-201 SPECT exercise scintigraphy. They demonstrated that TTE and TEE are complementary in their ability to define improvement in myocardial contraction after HBO. Swift et al. (1992) showed that there was no improvement of wall motion abnormality in patients receiving hyperbaric room air after AMI. According to their results, from the non contracting segments at rest (62), 20 segments (32%) improved with HBO and 29 segments (47%) had evidence of viability on thallium SPECT. From the 20 segments with improvement of contraction after HBO, 18 segments were viable by SPECT. In our study also close relationships between improved segments with HBO and DSE was established. Similar to our results, positive predictive value of improvement by HBO for viability on thallium scintigraphy was 90%. Swift et al. (1992) reported that fixed contraction abnormalities were obtained in 42 segments after HBO, of which 30 segments showed a fixed defect in SPECT (negative predictive value 71%). To describe myocardium with reversible thallium defects with no improvement of contractility after HBO, those authors proposed term "covert hibernation". Because rapid improvement in O_2 delivery to myocardium is not always followed by an immediate improvement of contractile function, even though, tissue oxygen tension remained elevated for several hours after cessation of HBO and tissue remained oxygenated.

The study conducted by Veselka et al. (1999) examined the possibility of using echocardiography after HBO to detect viable myocardium. Results from 17 patients were compared with DSE. Patients enrolled in that study had LV dysfunction and heart failure. This study suggested that the number of segments with improved contraction after HBO (36–17.6%) was lower than in DSE at 10 μg/kg/min (82–40.2%) but higher than DSE at an infusion rate of 5 μg/kg/min (31–15.2%). Thus HBO echocardiography was statistically equivalent to low dose, but inferior to higher dose during DSE, so authors presumed that sensitivity of HBO for detection of myocardial viability might be about 70% which is similar to our results. According to the present study, Veselka et al. (1999) showed that there was no significant difference between improved segments detected by HBO and low rate of dobutamin during DSE (5 μg/kg/min). This study suggested that HBO is capable of detecting viable myocardium in patients with LV dysfunction, but authors proposed that a combination of DSE and HBO could have greater accuracy than just DSE or HBO.

Limitation of the study

This study is limited by the small number of patients. There is no follow up of patients with viable myocardium. Confirmation of myocardial viability in stress echocardiography remains the eyeballing interpretation of regional wall motion in black and white cine-loops. New echocardiographic technologies proposed to establish the viability on a more quantitative basis, but are not completely validated in their clinical meaning. In the present study we didn't used the new technologies applied to DSE.

Tissue characteristics in setting of the acute infarction are dynamic, but there was no possibility to obtain HBO and DSE at the same time. All coronary angiograms were obtained more than one month after AMI.

Because HBO requires additional logistic support, we excluded from the study patients with severely impaired left ventricle and severe heart failure who may, in fact, have benefited the most from detection of viable segments by HBO for further treatment and survival.

Conclusions

Different forms of radionuclide myocardial perfusion imaging for detection of myocardial viability, utilizing thallium rest or stress-redistribution SPECT, FDG-PET scanning or technetium-sestamibi SPECT take time exposure for active uptake or passive diffusion of the agent. Interpretation of radionuclide myocardial distribution takes high quality of gamma camera imaging characteristics, making these techniques less accessible and more expensive. There are several side effects of radionuclide techniques such as long lasting physical half life, presence of gamma and mercury rays, high proton energy or transient hepatic uptake. Prolongation and repetition of the perfusion procedures are not proper for the early phase of AMI.

Our data indicate that HBO and echocardiography can identify hibernating myocardium as early as day one after AMI. Oxygen supply under hyperbaric condition could detect viability within one hour, by functional recovery of the infarcted segments without adrenergic or any other harmful stimulation, producing only ameliorate effects Therefore, clinical application of HBO as a test of myocardial viability after AMI is rational and can further expand therapeutic application of HBO. On the other hand, DSE provides in viable segments prospective improvement of contractility. The combination of these two methods possibly reflects more completely the functional properties of viable segments following myocardial infarction.

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