Advances in Therapy® | *Volume 24 No. 1*
January/February 2007

Can Hyperbaric Oxygen Be Used as Adjunctive Heart Failure Therapy Through the Induction of Endogenous Heat Shock Proteins?

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ABSTRACT

Heart failure (HF) is a chronic condition that is expected to increase in incidence along with increased life expectancy and an aging population. As the incidence of HF increases, the cost to national healthcare budgets is expected to run into the billions. The costs of lost productivity and increased social reliance on state support must also be considered. Recently, acute myocardial infarction (AMI) has come to be seen as the major contributing factor to HF. Although thrombolysis may restore coronary perfusion after an AMI, it may also introduce ischemic reperfusion injury (IRI). In an attempt to ameliorate sustained protein damage caused by IRI, endogenous chaperone proteins known as heat shock proteins (HSPs) are induced as a consequence of the stress of IRI. Recently, hyperbaric oxygen has been shown to induce the production of HSPs in noncardiac tissue, with a resultant protective effect. This current opinion review article suggests a possible role for hyperbaric oxygen, as a technologically modern drug, in augmenting the induction of endogenous HSPs to repair

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and improve the function of failing hearts that have been damaged by AMI and IRI. In addition, this simple, safe, noninvasive drug may prove useful in easing the economic burden of HF on already overextended health resources.

Keywords: hyperbaric oxygen; heat shock protein; heart failure

HEART FAILURE: A CONDITION WITH A POOR PROGNOSIS AND A CRIPPLING ECONOMIC BURDEN

Heart failure (HF) is a chronic, progressive disease that causes substantial morbidity and mortality.[1,2] In the United States, approximately 10 of every 1000 people older than age 65 are affected by HF[3]; it is the most common diagnosis made in this age group,[4] accounting for about 1% to 3% of the adult population.[5] In-hospital mortality associated with HF occurs at a rate of almost 5%.[6] In all, 50% of patients with HF require subsequent hospitalization within 6 mo of discharge from their first admission,[2] and approximately one third of patients with HF die within the first year of hospitalization.[7] The Framingham Heart Study[8] showed that overall 1-y and 5-y survival rates following the diagnosis of HF were 57% and 25% in men and 64% and 38% in women, respectively.

The cost of treating HF in the United States during the year 2000 was estimated at $23 billion, or 1.5% of the total healthcare expenditure, for hospitalization, outpatient visits, physician consultations, nursing home care, drugs, and community nursing.[9] An additional $2 billion was estimated for the indirect costs associated with HF, or loss of productivity due to morbidity and mortality.[9] The socioeconomic burden of HF in the United States is rising; according to the American Heart Association (AHA) Heart Disease and Stroke Statistics—2006 Update, the direct and indirect costs of HF in 2006 were estimated at $29.6 billion.[3]

Recent studies have identified acute myocardial infarction (AMI) as the principal cause of HF (36%-58%).[10-13] The AHA Heart Disease and Stroke Statistics—2006 Update[3] has revealed that, in the United States, about 22% of men and 46% of women who experience an MI will be disabled by HF within 6 y of the infarction. Although the myocardial ischemia that occurs after coronary occlusion results in well-documented cellular injury leading to infarction and apoptosis, reperfusion of the coronary vasculature and the myocardium after thrombolytic therapy has been shown to exert deleterious cellular consequences.[14] The myocardial and vascular injury that results from ischemia followed by reperfusion is known as ischemic reperfusion injury (IRI). The components of this injury and subsequent cellular degradation eventually lead to HF.

The drive to manage HF cost effectively has given the impetus to an explosion of anti–heart failure therapies ranging from diuretics, inotropic agents, intravenous vasodilators, natriuretic peptides, and investigational agents such as tezosentan and levosimendan.[15] Although these drugs have produced symptomatic and prognostic improvement, they are not without adverse effects and contraindications. It is imperative, therefore, that other simple, safe, noninvasive, cost-effective drugs that are technologically novel continue to be developed to be combined with current anti-HF regimens. The use of the most up-to-date technology to enhance drug delivery for the improvement of HF is not a new concept. Yacoub and Zeitlin[16] reported

in 1965 that the use of hyperbaric oxygen (HBO) in the postoperative treatment of patients with low cardiac output syndrome results in satisfactory clinical outcomes. To date, this is the only human case report in the English medical literature that has documented the use of a drug, oxygen, augmented by technology, a hyperbaric chamber, to improve the symptoms of HF. Despite the fact that this is an interesting report, no further advancement has been made to verify this report or to attempt to hypothesize and elucidate how HBO may prove beneficial in the treatment of patients with HF.

This current opinion review article attempts to provide some perspective on how HBO may pharmacologically induce and trigger cellular mechanisms after AMI and IRI to improve myocardial function and possibly delay the progression to HF.

HEAT SHOCK PROTEINS IN SUPPORT OF FAILING HEARTS

When a heart starts to fail, several adaptive mechanisms are initiated. The composition of contractile proteins within the heart muscle is modified, their mass is increased, and the heart becomes enlarged.[17,18] The myofibrillar composition of skeletal muscle changes[19,20] and the neurohumoral system is chronically activated.[21,22] These mechanisms, which are ontogenically developed as a stress reaction, may be useful in the short term, but, over the long term, they may be detrimental, thereby affecting the evolution of disease.[23,24]

Among many proteins expressed within the heart during the stress reaction is the inducible form of heat shock protein (HSP) 70 known as HSP 72. Stress conditions known to induce the expression of HSP 72 consist of acute cardiac overload,[25] HF,[26] ischemia,[27] and hypoxia.[28] These proteins play a role in protecting cells from subsequent stresses and are involved in recovery from various injuries.[29,30] They act as chaperones, preventing protein aggregation, and they participate in the refolding of damaged proteins following stress. In animal models, overexpression of HSP 70 protects the heart against the damaging effects of ischemia.[31] Furthermore, it has been shown that stretch and decreased myocyte shortening result in increased expression of HSP in the isolated perfused rabbit heart.[32] It is conceivable that HSP 70 represents a protective mechanism, not only in acute settings (eg, those associated with ischemia and reperfusion following coronary artery bypass grafting),[33] but also in cases of chronic stress, as occurs in HF.[34] Increased expression of HSP 70 may represent an innate protective mechanism developed to restore physiologic conditions.[32]

MECHANISM OF MYOCARDIAL PROTECTION BY HEAT SHOCK PROTEIN

After AMI and thrombolysis occur, the resultant vascular reperfusion is associated with an oxidative burst that generates reactive oxygen species (ROS). When the production of ROS exceeds the capacity of endogenous detoxification mechanisms, myocardial cells are damaged, by ROS directly or by the ROS-dependent triggering of a cascade of proinflammatory events. Directly deleterious effects of ROS are mediated by an abnormal electrolyte milieu, in particular, the shift of intracellular potassium toward the extracellular milieu, which is associated with increased intracellular calcium concentrations and depletion of adenosine triphosphate stores.

These abnormalities lead to significant depression of myocardial contractility[35] and eventually to HF. HSPs may favorably interfere with these ROS-induced phenomena through their role as biological molecular chaperones. Because ROS-mediated damage mainly affects the structure of macromolecules such as lipids, DNA, and proteins, HSPs are strategically positioned within the cytoplasm, mitochondria, peroxisomes, and endoplasmic reticulum, providing an organized network for quality control of protein folding in major subcellular compartments.[36-38] Under conditions of redox metabolism shifted toward oxidative stress, levels of HSPs closely parallel the activity of antioxidant enzymes such as catalase; this finding indirectly confirms that the heat shock response pathway is activated to counteract ROS-dependent cellular and tissue damage.[39-41]

Recent studies have focused on HSPs as immunodominant molecules that interact with proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interferon-γ, and interleukin (IL)-1α, -1β, and -6, which, in turn, may induce HSP expression.[42] It has been suggested that after HSPs have been released into the extracellular milieu, they may act as signaling molecules that downregulate the production of cytokines by other cell types. Dybdahl and colleagues[33] proposed that the receptor implicated in the modulation of this HSP signaling activity may be the CD14 antigen or the toll-like receptor 4. Furthermore, HSPs may interfere with the signaling pathway of the transcription factor NF-κB. This pathway is involved in the transcription of several proinflammatory genes. It has been shown that the heat shock response inhibits activation of the NF-κB pathway, resulting in suppression of the cellular inflammatory response. At a molecular level, the crucial aspect of this suppression is probably the phosphorylation of the inhibitory κBa by the inhibitory κB kinase complex.

It has been shown that activation of the inhibitory κB kinase complex is inhibited by the heat shock response, and this is associated with enhanced intracellular phosphatase activity.[43] Downregulation of cytokine production mediated by HSPs may account for HSP-dependent protection of the myocardium during experimental ischemia and reperfusion; this has been supported by Grunenfelder and colleagues,[44] who proved that the myocardial protection provided by upregulation of HSP 70 is strongly associated with suppression of inflammatory cytokines in a model of ischemia and reperfusion. AMI is now recognized as the main cause of HF and it is associated with an inflammatory response,[45] so it is not difficult to perceive the beneficial role of HSPs in inducing myocardial protection in failing hearts.

Additionally, the myocardial protection provided by HSP may be linked to mechanisms involving nitric oxide (NO) and NO synthase (NOS), particularly because the 3 known isoforms of NOS (neuronal NOS [nNOS], endothelial NOS [eNOS], and inducible NOS) have been detected in the human myocardium.[46] Appreciation of the beneficial role of NO in failing hearts[47] has resulted mainly from an appraisal of the favorable effects of NO on cardiac energetics[48] and on left ventricular diastolic distensibility.[49] Although the exact mechanism involved in the interaction between NO and HSPs remains unknown, evidence suggests that HSP 70 expression is paralleled by an increase in NO production. Thus, NO may trigger HSP 70 synthesis and expression; this seems to ultimately protect myocardial cells against the cytotoxic effects of TNF-α, a cytokine with a central role in inflammation.[50]

Recently, it has been shown that increased activity of the inducible macrophage isoform of NOS is beneficial in an animal model of myocardial ischemia. This protective effect was paralleled by an elevated expression of HSP 70, with reduced activity of both NF-κB and activator protein 1.[51] These protective effects of NO mediated by HSP again highlight the role that HSPs may play in supporting failing hearts, particularly following the inflammatory response of an AMI.

HYPERBARIC OXYGEN TREATMENT IN MYOCARDIAL MODELS LEADING TO HEART FAILURE

Evidence is slowly emerging regarding the potential for HBO to function as a drug used concomitantly with other pharmacologic regimens in the treatment of patients with organ failure. This is nowhere more evident than in the central and peripheral nervous systems.[52] HBO has been successfully used as an adjunct in the treatment of patients with ischemic stroke, brain trauma, spinal cord lesions, and a few neurologic conditions (eg, carbon monoxide poisoning, cerebral palsy, facial palsy, multiple sclerosis, migraine headache). Although clinical evidence is lacking in other organ systems, the pharmaceutical benefits of HBO therapy, alone or in conjunction with other drugs, in halting, repairing, or even reversing multiple organ failure in animal models are compelling.[53-55]

In examining the potential for adjunctive use of HBO to support failing hearts, it is possible to assess the benefits of this drug in models of myocardial ischemia and reperfusion (ie, models that are known to result in MI and HF). One of the earliest studies undertaken to assess the ability of HBO to provide myocardial protection in the setting of IRI was carried out by Sterling et al,[56] who used an open chest rabbit model. A branch of the left coronary artery was occluded for 30 min; this was followed by 3 h of reperfusion, and the resultant area of infarction was measured. During this surgery, "untreated" rabbits were ventilated with 100% oxygen at 1 absolute atmosphere (ATA); "treated" rabbits were exposed to 100% oxygen at 2.5 ATA (one of the many possible HBO treatment regimens). Animals exposed to HBO during ischemia only, reperfusion only, or ischemia and reperfusion had significantly smaller infarcts compared with control animals, indicating that some degree of myocardial protection was provided by HBO. When HBO was begun 30 min after the onset of reperfusion, no myocardial protection was seen. This animal study highlighted the possible therapeutic potential of inhaled 100% oxygen, enhanced by delivery within a pressurized chamber, to limit myocardial damage prior to or during a traumatic cellular insult (ie, ischemic reperfusion).

Dekleva et al[57] conducted a randomized controlled study to assess the benefits of HBO after thrombolysis for left ventricular function and remodeling in patients with AMI. A total of 74 consecutive patients with first time AMI were randomly assigned to treatment with HBO combined with streptokinase (HBO+) or streptokinase alone (HBO–). A significant decrease in end-systolic volume index was noted from the first day to the third week in HBO+ patients compared with HBO– patients. This was accompanied by no change in end-diastolic volume index in the HBO+ group and increased values in the HBO– group. The ejection fraction significantly improved in the HBO+ group but decreased in the HBO– group 3 wk after AMI. This study concluded that adjunctive HBO after thrombolysis in AMI has a favorable effect on left ventricular function and the remodeling process. It showed that HBO, used as

an adjunct to thrombolysis, is capable of improving systolic function while simultaneously arresting any further deterioration in diastolic function after AMI. Furthermore, it showed that in the absence of adjunctive use of HBO with thrombolysis, the HBO– group went on to show no improvement in systolic and diastolic function after AMI. This finding was further verified by a similar study conducted by Vlahovic et al.[58] Both of these studies clinically demonstrated that HBO, by positively affecting ventricular function and remodeling, is capable of limiting the deleterious effects of IRI after AMI and thrombolysis, while inhibiting the development of HF over the short term.

The HOT MI (Hyperbaric Oxygen and Thrombolysis in Myocardial Infarction) study[59] was undertaken to assess the safety and feasibility of treating patients with HBO after an acute MI. In this randomized controlled study, patients were randomly assigned to receive recombinant tissue plasminogen activator (25 patients) or recombinant tissue plasminogen activator + HBO after AMI (26 patients). Patients in the HBO group were treated with 100% oxygen at 2 ATA for 60 min. This study found that in the group treated adjunctively with HBO, post-AMI ejection fraction improved, and a 35% reduction in mean creatinine phosphokinase was observed at 12 and 24 h post AMI, along with a reduction in time to pain relief and ST-segment resolution post MI. Investigators concluded that adjunctive HBO was a feasible and safe drug when included in the pharmaceutical regimen used for the management of AMI. These findings were later validated by a similar but larger randomized controlled study conducted by this same group.[60] These studies show that HBO, as an adjunct in the management of AMI, is a drug that is capable of limiting myocardial damage and improving myocardial function.

The effect of HBO on the infarct size of human hibernating myocardium has been investigated. Swift et al[61] conducted a study to characterize hibernating myocardium in post-MI patients by combining echocardiography with HBO and relating changes in segmental wall motion to myocardial viability, as determined by single photon emission computed tomography thallium-201 exercise scintigraphy. To evaluate the potential for HBO to produce transient improvement in function in areas of myocardium that are ischemic at rest (hibernating myocardium), investigators studied 24 patients within 1 wk of an AMI. Echocardiography demonstrated improved contraction following HBO in 20 of 62 damaged left ventricular segments in 12 of 24 patients. Thirteen of 28 segments and 9 of 14 patients with reversible ischemia on single photon emission computed tomography imaging showed improvement with HBO. In all, 8 segments with apparently normal resting contractions showed a reversible thallium defect after HBO. This imaging study was not only capable of clinically and objectively visualizing the improved functional response of an ischemic area of myocardium after treatment with HBO, it also further strengthened the pharmacologic premise that HBO is a drug that has the potential to stimulate myocardial recovery after AMI and IRI, and to at least delay the onset of HF.

Thurston et al[62] carried out a randomized controlled study to examine the effects of HBO on mortality after a recent AMI. Patients were younger than 70 y of age; 103 were recruited to the HBO group, and 105 were recruited to the control group. Both groups of patients were treated with the units protocol used for AMI. Patients in the HBO group, however, also received 100% oxygen at 2 ATA for 2 h, followed by air for 1 h, with the cycle repeated day and night for 48 h. Investigators observed a reduction in mortality in the HBO group compared with the control group 3 wk

after an AMI, as well as a reduction in significant dysrhythmias (ie, complete heart block, ventricular fibrillation, and asystole). They concluded that this reduction in major adverse coronary events after an AMI in the HBO group justified the routine use of HBO in selected cases of AMI.

Although Thurston's findings showed the favorable use of HBO post AMI in reducing mortality, the results were not significant. Recently, however, Sharifi et al[63] conducted a randomized controlled study to assess whether use of HBO as an adjunct to percutaneous coronary intervention could reduce clinical restenosis. This study examined 33 patients in the HBO group and 36 in the control group. All patients presented with unstable angina or AMI and were treated according to the units protocol for AMI. Patients randomly assigned to the HBO group received HBO treatment 2 h before or immediately after percutaneous coronary intervention, followed by another treatment given less than 18 h after the first HBO treatment. HBO treatment consisted of 100% oxygen given at 2 ATA for 90 min. Investigators showed that 8 mo after treatment for AMI, the group that was also treated with HBO exhibited a significant reduction in composite adverse cardiac events, which included mortality, MI, coronary artery bypass, and revascularization of the target lesion; a significant reduction in coronary restenosis and recurrent angina was noted as well. Collectively, a statistically significant reduction in composite adverse cardiac events occurred, but the reduction in mortality on its own was not statistically significant, despite a reduction in mortality in the HBO group. This suggests that not only did HBO as a drug demonstrate a tendency to reduce mortality after AMI, but, by halting the progression of coronary atherosclerosis and stenosis in this group of patients, it may have reduced the recurrence of AMI that would otherwise have led to the progression of HF. This suggestion that HBO may halt or even reverse the progression of atherosclerosis is not new and has been demonstrated in animal models.[64-66]

Despite a number of small-scale human studies that have illustrated the potential for HBO to be used as a drug in the treatment of patients with IRI,[61-66] a meta-analysis conducted by the Cochrane Collaborative led by Bennett[67] failed to significantly conclude that routine HBO could prove beneficial in the treatment of patients with a relatively common clinical condition such as acute coronary syndrome (ACS). Researchers reviewed and compared all studies of ACS treatment regimens that included HBO with those that did not include HBO. This meta-analysis comprised 4 trials consisting of 462 patients. Investigators found no significant decrease in the risk of death with ACS treatment regimens that included HBO (P=.08), although they noted a trend toward such a decrease. Evidence from individual trials revealed reductions in the risk of major adverse coronary events (P=.03) and some dysrhythmias (P=.01), particularly complete heart block (P=.02), following HBO. The Cochrane review also showed that HBO treatment after ACS reduced time to pain relief after the onset of angina (P<.0001). The Cochrane Collaborative concluded that, despite the fact that HBO treatment provided after ACS resulted in no statistically significant reduction in mortality, study flaws, such as modest patient numbers, methodologic shortcomings, and poor reporting, may have affected these results. Thus, they stated that appropriately powered, randomized controlled studies of high methodologic rigor were required to objectively identify patients who would benefit from this new treatment.

HYPERBARIC OXYGEN–INDUCED HEAT SHOCK PROTEIN: A TECHNOLOGICALLY MODERN ADJUNCTIVE DRUG IN ANTI–HEART FAILURE THERAPY?

Although significant clinical evidence for the routine use of HBO as a drug in conditions that evolve from IRI is lacking, findings at least suggest that HBO is capable of attenuating myocardial ischemic reperfusion injury, MI, and, thus, the development of HF. It remains to be elucidated, however, how, at a molecular level, this novel drug leads to such myocardial tolerance and protection. Evidence currently suggests that the mechanism for this may involve ROS activation of NOS,[68] and that resultant NO production prevents neutrophil adhesion by inhibiting the function of CD11a/18[69] and ICAM-1 (intercellular adhesion molecule-1).[70] Although this may contribute to the capacity of HBO to attenuate ischemic reperfusion injury within the myocardial microvasculature, the protective effects exerted on cardiomyocytes are not so clear.

Although limited research involving HBO has proved its ability to induce the production of myocardial HSPs, Cabigas et al[71] explored the use of various concentrations of oxygen and pressure in a rat heart model of IRI. Rats were treated for 1 h with normoxia + normobaric oxygen (21% O_2 at 1 ATA), hyperoxia + normobaric oxygen (100% O_2 at 1 ATA), normoxia + hyperbaric oxygen (21% O_2 at 2 ATA), and hyperoxia + hyperbaric oxygen (100% O_2 at 2 ATA). After each of these regimens was given, isolated rat hearts were made ischemic for 25 min; this was followed by 180 min of reperfusion. The investigators discovered that preconditioning with hyperoxia + hyperbaric oxygen resulted in the greatest decrease in myocardial infarct size and increased recovery of left ventricular diastolic pressure. A 4-fold increase in the association of HSP 90 with eNOS was noted in the hyperoxia + hyperbaric oxygen group, in addition to an increase in eNOS and nitrite + nitrate content in the hearts of this group of rats. The investigators found that the myocardial protective effects of hyperoxia + hyperbaric oxygen were reversed by L-NAME (N[G]-nitro-L-arginine methyl ester; a NO inhibitor). Although they did not detect a significant increase in total HSP 90 content in the hyperoxia + hyperbaric oxygen group, investigators believed that this increased association of HSP 90 with eNOS supports the notion that HSP 90 helps eNOS to produce NO (as shown in their experiments), and this is responsible for the observed myocardial protection against IRI seen in the hyperoxia + hyperbaric oxygen group. To date, this study by Cabigas et al[71] is the only published English language research that has examined the effects of HBO and HSP on myocardial protection.

Shyu and colleagues[72] investigated the effects of HBO on HSP 70 expression in mouse neuroblastoma cell lines. They showed that HBO administration resulted in a time- and dose-dependent increase in HSP 70 expression at mRNA and protein levels. Thom and colleagues[73] investigated the impact of elevated partial pressures of oxygen on levels of NO, nNOS, eNOS, and HSP 90 within the cerebral cortex. They determined that treatment with hyperoxia and elevated partial pressures of oxygen causes an increase in NO synthesis as part of a response to oxidative stress, and that the mechanisms for nNOS activation include augmentation in association with HSP 90. According to this brain study, however, HBO did not change the association of eNOS with HSP 90; this contrasts with the heart findings of Cabigas et al.[71]

Dennog and colleagues,[74] in their investigation into the adaptive protection against DNA damage provided by HBO, found that synthesis of HSP 70 was significantly induced in the lymphocytes of human subjects after a single treatment with HBO. This suggested an important role for HSP 70 in cellular protection against oxidative stress—a role that may be used to blunt the oxidative burst associated with myocardial ischemic reperfusion injury. Wada and associates[75] investigated the effects of repeated HBO treatment on ischemic tolerance in the gerbil hippocampus. HBO was administered for 1 h to gerbils for a single session or every other day for 5 sessions. Two days after HBO pretreatment, gerbils were subjected to 5 min of forebrain ischemia produced by occlusion of both common carotid arteries under anesthesia. Immunohistochemical staining for HSP 72 in the gerbil hippocampus 2 d after pretreatment revealed that 5-session HBO pretreatment increased the amount of HSP 72 present over that seen in the ischemic control group and in the single HBO pretreatment group. Investigators concluded that tolerance against ischemic neuronal damage induced by repeated HBO pretreatment occurred through induction of HSP 72 synthesis.

DISCUSSION

It has been established that HSPs play a role in myocardial protection by attenuating ischemic reperfusion injury. They achieve this in part by limiting the inflammatory response, metabolic derangements, infarct size, and apoptosis. Although at present, clinical data on the protective effects of HBO are limited, available research into the effects of HBO on the myocardium and other tissues has shown that HBO is also capable of preserving cellular energy requirements,[76-78] reducing infarct size,[56] and limiting apoptosis[79] and the proinflammatory response.[80,81] These findings highlight a possible role for HBO in functioning as a drug to protect the myocardium against IRI and eventually HF. It is possible that part of the myocardial protection provided by HBO involves a mechanism that upregulates the production of HSPs. To explore this, however, dedicated laboratory research and human randomized controlled multicenter studies involving HBO and the myocardium are required. Elucidating the possible cardioprotective role of HBO is crucial because HBO is a drug that is pharmacologically simple, safe, and noninvasive with limited adverse effects and contraindications. Furthermore, due to the increased construction of large, rectangular hyperbaric chambers that can be placed at various sites, HBO is not an expensive "one pill per patient" drug. Because such chambers are capable of holding multiple patients who have chronic disease or who are bedridden by critical illness, HBO may be capable of offering cost-effective treatment to multiple patients during a single session. Although much clinical work is needed to examine the practicality of using HBO as an adjunct to routine anti-HF treatment, this treatment represents a new frontier in the pharmacologic battle to retard, halt, or even reverse progression of disease toward HF in the aging global community.

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