Inhibition of mitochondrial permeability transition improves functional recovery and reduces mortality following acute myocardial infarction in mice

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Gomez L, Thibault H, Gharib A, Dumont J-M, Vuagniaux G, Scalfaro P, Derumeaux G, Ovize M. Inhibition of mitochondrial permeability transition pore (mPTP) opening by cyclosporin A or ischemic postconditioning attenuates lethal reperfusion injury. Its impact on major post-myocardial infarction events, including worsening of left ventricular (LV) function and death, remains unknown. We sought to determine whether pharmacological or postconditioning-induced inhibition of mPTP opening might improve functional recovery and survival following myocardial infarction in mice. Anesthetized mice underwent 25 min of ischemia and 24 h (protocol 1) or 30 days (protocol 2) of reperfusion. At reperfusion, they received no intervention (control), postconditioning (3 cycles of 1 min ischemia-1 min reperfusion), or intravenous injection of the mPTP inhibitor Debio-025 (10 mg/kg). At 24 h of reperfusion, mitochondria were isolated from the region at risk for assessment of the Ca2+ retention capacity (CRC). Infarct size was measured by triphenyltetrazolium chloride staining. At 30 days of reperfusion, mortality and LV contractile function (echocardiography) were evaluated. Postconditioning and Debio-025 significantly improved Ca2+ retention capacity (132 ± 13 and 153 ± 31 vs. 53 ± 16 mmol Ca2+/mg protein in control) and reduced infarct size to 35 ± 4 and 32 ± 7% of area at risk vs. 61 ± 6% in control (P < 0.05). At 30 days, ejection fraction averaged 74 ± 6 and 77 ± 6% in postconditioned and Debio-025 groups, respectively, vs. 62 ± 12% in the control group (P < 0.05). At 30 days, survival was improved from 58% in the control group to 92 and 89% in postconditioned and Debio-025 groups, respectively. Inhibition of mitochondrial permeability transition at reperfusion improves functional recovery and mortality in mice.

ischemic postconditioning; left ventricular contractile function; mitochondrial permeability transition pore

MYOCARDIAL INFARCTION (MI) remains the leading cause of cardiac death in Western countries. Heart failure is an increasingly common outcome of MI and a frequent cause of cardiovascular morbidity and mortality (22, 40, 44). Survival 5 yr after the diagnosis of heart failure is poor, as low as 25–35% (33).

Infarct size is a major determinant of mortality (10). Besides treatment of heart failure per se, initial limitation of infarct size appears, in theory, to be the best strategy to prevent postschismic heart failure and improve survival.

Postconditioning might offer major hope to improve postinfarction outcome. Zhao et al. (54) reported that three episodes of 30 s of reperfusion-30 s of ischemia immediately after a prolonged 60-min ischemic insult in the dog heart dramatically attenuate irreversible myocardial injury. This observation has been confirmed in several experimental preparations and, more recently, in humans (4, 9, 32, 35, 38, 47).

Since all patients with ongoing acute MI cannot be treated with ischemic postconditioning by angioplasty, identification of a pharmacological mimetic to postconditioning is obviously required. Potential molecular targets have been identified, along with signaling pathways involved in postconditioning, including adenosine A2A or A1 receptors, mitochondrial ATP-sensitive K+ channels, and several kinases, including phosphatidylinositol 3-kinase, Akt, endothelial nitric oxide synthase, PKC-ε, ERK1/2, and glycogen synthase kinase-3β (11, 14, 17, 37, 48, 52, 53). These signal transduction pathways seem to converge to mitochondria and, more specifically, implicate a function called “mitochondrial permeability transition” (12, 15, 50, 55). Convincing evidence indicates that mitochondrial permeability transition plays a crucial role in lethal myocardial reperfusion injury (16, 27, 28, 31, 36). Argaud et al. (4, 5) demonstrated in the in vivo rabbit heart that ischemic postconditioning inhibits mitochondrial permeability transition pore (mPTP) opening and pharmacological inhibition of mPTP opening by cyclosporin A (CsA) and its analog NIM-811, administered at the onset of reperfusion, reduced infarct size to an extent similar to that caused by ischemic postconditioning.

Although postconditioning by ischemia or mPTP inhibition can reduce infarct size, it remains unknown whether both interventions provide a persistent beneficial outcome following acute MI. Using the mouse model of MI, with a 30-day follow-up period, we questioned whether inhibition of mPTP opening at the time of reperfusion, by ischemic postconditioning or a pharmacological intervention (i.e., 2 realistic clinical interventions), would enhance recovery of contractile function and improve survival.

METHODS

The investigation conformed with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1996) and performed under a license (No. 69.388.0502) from the French government (veterinary department) to conduct animal research.

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Surgical Preparation

Seven- to 8-wk-old male OF1 mice (Charles River Laboratories, L’Arbresle, France) were anesthetized by intraperitoneal injection of 0.3 ml/10 g body wt of a 1:1 mixture of fentanyl citrate (0.011 mg/ml) and midazolam (0.4 mg/ml), as previously described (23). The animals were orally intubated using a 22-gauge vinyl catheter and ventilated via a rodent ventilator (model 687, Harvard Apparatus), with a tidal volume of 0.2 ml and a breath rate of 160 beats/min. A left thoracotomy was performed in the fourth left intercostal space. The pericardium was opened, and the heart was exposed. An 8-0 polypropylene suture attached to a small curved needle was passed around the left anterior descending coronary artery. Ischemia was confirmed by ST segment shift on the ECG (78534C monitor, Hewlett Packard) and the appearance of myocardial pallor. Body temperature was monitored via a rectal thermometer and maintained at 36–37°C with a heating pad. After surgery, the animals were allowed to recover from anesthesia, and the endotracheal tube was removed once spontaneous breathing resumed.

Experimental Design

All animals underwent 25 min of coronary artery occlusion followed by reperfusion (Fig. 1). Postconditioning consisted of three cycles of 1 min of reperfusion and 1 min of ischemia performed immediately after reflow. In the Debio-025 group, 5 min before reperfusion, mice received a slow (over 3 min) injection of Debio-025 (10 mg/kg iv). Control mice received the vehicle for Debio-025 (a mixture of Solutol and 94% ethanol) (46) under similar conditions. At the end of the surgical procedure, the chest was closed, and the animal was returned to the animal facility until the end of the reperfusion period.

Protocol 1: infarct size and mitochondrial permeability transition. After 24 h of reperfusion, a first subset of mice were euthanized under deep anesthesia, and the heart was excised for determination of infarct size (n = 28) or assessment of Ca2+-induced mitochondrial permeability transition (n = 21).

Protocol 2: recovery of LV function and survival. An additional subset of mice (n = 57) underwent 30 days of reperfusion. During the 30-day study period, the cages were inspected daily to identify any deceased animal. At the end of the 30-day period (i.e., just before euthanasia), echocardiography was performed under light intraperitoneal anesthesia.

Techniques

Area at risk and infarct size determination. At the end of the 24-h reperfusion, the coronary artery was briefly reoccluded, and Unisperse blue pigment (0.5 mg/kg iv; Ciba-Geigy, Hawthorne, NY) was injected to delineate the in vivo area at risk, as previously described (23). With this technique, the previously nonischemic myocardium appears blue, whereas the previously ischemic myocardium (area at risk) remains unstained.

The heart was excised and cut into four to five 1-mm-thick transverse slices, parallel to the atrioventricular groove. After removal of right ventricular tissue, each heart slice was weighed. The basal surface of each slice was photographed for later measurement of the area at risk. Each slice was then incubated for 15 min in a 1% solution of triphenyltetrazolium chloride at 34°C to differentiate infarcted (pale) from viable (brick red) myocardial area (49). The slices were then rephotographed. Enlarged projections of these photographs were utilized to estimate the area at risk and area of necrosis. Extent of the area at risk and area of necrosis was quantified by computerized planimetry and corrected for the weight of the tissue slices.

Total weights of the area at risk and the area of necrosis were then calculated and expressed in grams and as percentage of total LV or area at risk weight, respectively.

Preparation of isolated mitochondria. At the end of the 24-h reperfusion period, hearts were excised while still beating and immediately placed in cold buffer, and area at risk myocardium was harvested for mitochondria isolation. Preparation of mitochondria was adapted from a previously described procedure (23). All operations were carried out in a cold room at 4°C. Myocardial area at risk biopsies (20–30 mg) were placed in isolation buffer containing 70 mM sucrose, 210 mM mannitol, and 1 mM EDTA in 50 mM Tris·HCl (pH 7.4). The tissue was finely minced with scissors and then homogenized in the same buffer (10 µl buffer/mg tissue) with a Kontes tissue grinder and then with a Potter-Elvehjem. The homogenate was centrifuged at 1,300 g for 5 min and the supernatant was centrifuged to determine the boundaries of the area at risk and area of necrosis. Extent of the area at risk and area of necrosis was quantified by computerized planimetry and corrected for the weight of the tissue slices.

Ca2+ retention capacity. Extramitochondrial Ca2+ concentration was measured with a Hitachi F2500 spectrophotometer in the presence of 0.5 µM Calcium Green-5N, with excitation and emission wavelengths set at 500 and 530 nm, respectively. Briefly, isolated mitochondria (100 µg of protein) were suspended in 2 ml of buffer [150 mM sucrose, 50 mM KCl, 2 mM KH2PO4, and 5 mM succinic acid in 20 mM Tris·HCl (pH 7.4)] in a polystyrene cuvette. Mitochondria were gently stirred for 90 s. At the end of the preincubation period, 5-nmol CaCl2 pulses were administered every 60 s. Each 5-nmol CaCl2 injection causes a peak of extramitochondrial Ca2+ concentration; then extramitochondrial Ca2+ concentration spontaneously returns to near-baseline level as Ca2+ enters the mitochondrial matrix via the Ca2+ uniporter (7) (see Fig. 3A). After sufficient Ca2+ loading, extramitochondrial Ca2+ concentration abruptly increased, indicating a massive release of Ca2+ by mitochondria due to mPT opening, as previously described (23, 24). Ca2+ retention capacity (CRC) was defined as the amount of Ca2+ required to trigger this massive Ca2+ release (3, 34); it is used here as an indicator of the mPT sensitivity to Ca2+ and expressed as nanomoles of CaCl2 per milligram of mitochondrial proteins (n = 5–6/group).

The in vitro effect of Debio-025 had so far only been assessed in rat brain mitochondria; we then addressed its ability to inhibit transition pore opening assessed using mitochondria isolated from sham hearts.
We first performed an in vitro study to determine the capacity of Debio-025 (10–1,000 nM, i.e., from no detectable effect to plateau effect) to inhibit mPTP opening in sham mouse hearts; in this case, mitochondria were isolated from the whole sham LV. CRC was also assessed after 24 h of reperfusion in sham, control, postconditioned, and Debio-025 mice. In all four groups, mitochondria were isolated from the area at risk within the anterior wall of the LV. Care was taken to clearly identify, by visual inspection, the boundaries of the area at risk during ischemia.

**Recovery of LV contractile function.** At the end of the 30-day period (i.e., just before euthanasia), echocardiography was performed under light anesthesia (ketamine, 80 mg/kg ip). Images were acquired using a 13-MHz linear-array transducer with a digital ultrasound system (Vivid 7, GE Medical Systems). Conventional measurements [LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD)] were obtained from gray-scale M-mode traces at the level of the papillary muscles. LV ejection fraction (EF) was calculated from the two-dimensional parasternal long-axis view by the prolate-ellipsoid method (18, 43). After echocardiography, the area at risk was measured using blue dye injection (see above; n = 5 mice/group).

**Treatment with Debio-025.** Debio-025 (a gift from Debiopharm) is a nonimmunosuppressive cyclosporin that inhibits cyclophilin D within the mitochondrial matrix and has been shown in isolated rat brain mitochondria to be a potent inhibitor of mPTP opening (30). Debio-025 was dissolved in a mixture of Solutol and 94% ethanol (46). Debio-025 was injected over 3 min into the caudal vein at 10 mg/kg 5 min before coronary artery reperfusion.

**Statistical Analysis**

Comparison between groups was performed using one-way ANOVA. When a significant F value was obtained, means were compared using Tukey’s test. Differences in the relationship between infarct size and area at risk were evaluated by analysis of covariance and Tukey’s post hoc test, with infarct size as the dependent variable and area at risk as the covariant. Survival was analyzed using Kaplan-Meier curves, and differences among groups were evaluated using the log-rank test. Values are means ± SE. Statistical significance was defined as P < 0.05.

**RESULTS**

**Ca2+-Induced Mitochondrial Permeability Transition**

**In vitro effects of Debio-025.** Although Hansson et al. (30) demonstrated that Debio-025 can inhibit mitochondrial permeability transition in isolated rat brain mitochondria, no data were available concerning its effects on cardiac mitochondria. In mitochondria isolated from sham mouse hearts, CRC averaged 336 ± 34 nmol Ca2+/mg mitochondrial proteins (Fig. 2). Debio-025 dose dependently inhibited mPTP opening and significantly increased CRC (482 ± 26 nmol Ca2+/mg mitochondrial proteins) at a concentration as low as 50 nM. It appeared slightly (although not significantly) more potent than the reference mPTP inhibitor CsA (Fig. 2).

**CRC.** In 21 mice (5 sham, 6 control, 5 postconditioned, and 5 Debio-025), CRC was assessed in mitochondria isolated at the end of the 24-h reperfusion period. In sham hearts, mitochondrial CRC averaged 271 ± 32 nmol Ca2+/mg mitochondrial proteins (Fig. 3). As expected, prolonged ischemia-reperfusion resulted in a significant decrease in CRC: 53 ± 16 nmol Ca2+/mg mitochondrial proteins in control (P < 0.001 vs. sham). Postconditioning and Debio-025 improved CRC: 132 ± 13 and 153 ± 31 nmol Ca2+/mg mitochondrial proteins, respectively [P < 0.05 vs. control, P = not significant (NS) in postconditioning and Debio-025; Fig. 3].

**Area at Risk and Infarct Size**

Twenty-nine mice (11 control, 9 postconditioned, and 9 Debio-025) were included in the area at risk and infarct size
Area at risk was comparable among the three groups: 41 ± 7, 41 ± 6, and 53 ± 4% of the LV weight in control, postconditioning, and Debio-025 groups, respectively (P = NS among groups). Ischemic postconditioning significantly reduced infarct size: 35 ± 4% vs. 61 ± 6% of the area at risk in the control group (P < 0.05; Fig. 4A). The extent of infarct size reduction induced by Debio-025 was similar to that induced by postconditioning: 32 ± 7% of the risk region (P < 0.05 vs. control, P = NS vs. postconditioning). These results were confirmed when infarct size was plotted vs. its major determinant in the mouse model, i.e., area at risk. As shown in Fig. 4B, most data points for the postconditioning and Debio-025 groups lie below the control line, indicating that, for any size of area at risk, postconditioning and Debio-025 hearts developed significantly smaller infarcts than controls.

**Recovery of LV Contractile Function**

At 30 days post-MI, area at risk was comparable among the three groups: from 29 ± 4% to 32 ± 1% of the LV weight (P = NS among groups). The two-dimensional and M-mode measurements were interpretable in all animals that completed the 30 day follow-up period (5 sham, 10 control, 12 postconditioned, and 13 Debio-025; Fig. 5). Control hearts exhibited a significant LV dilatation and impairment in LV global function (EF; Fig. 6). LVEDD and LVESD averaged 4.2 ± 0.4 and 2.5 ± 0.5 mm, respectively in the control group and 3.6 ± 0.2 and 1.6 ± 0.3 mm, respectively, in the sham group (P < 0.05 for both). Postconditioned hearts displayed a significant reduction in LVEDD and LVESD: 3.9 ± 0.3 and 2.1 ± 0.2 mm, respectively (P < 0.05 vs. control). This reduced LV dilatation was even more pronounced (although not significantly) in Debio-025-treated hearts with LVEDD and LVESD: 3.8 ± 0.3 and 1.8 ± 0.5 mm, respectively (P < 0.05 vs. control).

LV function was significantly improved in postconditioned hearts, with a shortening fraction of 46 ± 4% vs. 41 ± 7% in controls and EF of 74 ± 6% vs. 62 ± 12% in controls (P < 0.05). Similar improvement was observed in Debio-025-treated hearts, with a shortening fraction of 54 ± 9% vs. 41 ± 8% in controls (P < 0.05) and EF of 77 ± 6% vs. 62 ± 12% in controls (P < 0.05; Fig. 6). These differences existed, although heart rate was comparable among treated groups and not different from that expected in normal unsedated mice, indicating that anesthesia was light and did not interfere with assessment of contractile function.

**30-Day Survival**

Fifty-seven mice (20 control, 14 postconditioned, 18 Debio-025, and 5 sham) were followed up for 30 days to address mortality following acute MI. Two mice died during the surgical preparation: one control and one postconditioned. During the 30 day follow-up period, 11 mice (8 controls, 1 postconditioned, and 2 Debio-025) died.

As shown by the Kaplan-Meier curves in Fig. 7, 30 days after acute MI, the survival rate was significantly better in the postconditioned and Debio-025 groups: 92% and 89%, respectively, vs. 58% in the control group (log-rank test, P < 0.05).

**DISCUSSION**

This study demonstrates that inhibition of mitochondrial permeability transition at the time of reperfusion by ischemic postconditioning or Debio-025 can enhance recovery of LV contractile function and improve 30-day survival in the mouse model.

Postconditioning dramatically reduced infarct size in the in vivo mouse heart, with average reduction of 44%, which is as pronounced as in other animal species (4, 32, 35, 38, 47, 54). Debio-025, which specifically binds to the mitochondrial cyclophilin D and reduces the sensitivity of the mPTP to Ca²⁺, reduced infarct size to a similar extent (i.e., 48%). Mitochondria isolated from postconditioned and Debio-025-treated hearts displayed similar enhanced CRC. This finding is consistent with a preliminary report from our group that postconditioning improved CRC of isolated mitochondria and increased the total and free mitochondrial Ca²⁺ concentration (6). These data further suggest that mitochondrial Ca²⁺ concentration is likely not the only

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Fig. 4. **A**: area at risk (AR) and infarct size. All 3 groups displayed comparable AR. Area of necrosis (AN), expressed as a function of area at risk weight, was significantly reduced in postconditioned and Debio-025 groups. *P < 0.05 vs. control. **B**: infarct size as a function of area at risk. There was a significant correlation between infarct size and area at risk in the control group. Most data points for postconditioned or Debio-025-treated hearts lie below control line, indicating that, for any size of area at risk, these hearts developed significantly smaller infarcts.
signal that regulates mPTP opening upon reperfusion. These results are in agreement with previous reports suggesting that mitochondrial permeability transition plays a key role in lethal reperfusion injury and may be a good candidate for future pharmacological postconditioning in patients (27, 31, 36). Because Debio-025 was administered 5 min before reflow, one might question whether it may also have limited ischemia-induced injury. This is, however, unlikely; previous studies using other inhibitors of transition pore opening administered only 1 min before reperfusion showed comparable infarct size limitation (4, 5). It might be questioned whether the increased CRC in the treated groups could simply be the consequence of more viable mitochondria being harvested from less infarcted tissue. This hypothesis appears, however, unlikely for the following reasons. 1) The isolation procedure eliminates dead cardiomyocytes and ruptured mitochondria; the latter fragile organelles are more abundant in the control group, and remaining mitochondria harvested from this group are, in fact, the...
least damaged. 2) The same final amount of mitochondrial proteins is used in each group. 3) In our previous study using shorter ischemic insult (10 min, i.e., unable to induce any necrosis), pre- and postconditioning increased CRC in a fully viable tissue (i.e., in the absence of potential selection bias during the mitochondria isolation procedure) (3). Although the increased CRC in postconditioned and Debio-025 groups does not demonstrate a causal link between the inhibition of mPTP opening and infarct size reduction, it strongly suggests that it is the case.

After acute MI, a patient’s prognosis has been shown to be influenced by recovery of LV function (41, 45). We therefore sought to determine whether inhibition of mPTP opening, by ischemic postconditioning or Debio-025, may alter this predictor of outcome. We have demonstrated for the first time that inhibition of mPTP opening can ameliorate recovery of cardiac contractile function after MI. Persistence of a reduced LV dilatation and enhanced global contractile function at 30 days suggest a likely long-lasting protection. How inhibition of mitochondrial permeability transition might improve functional recovery remains to be determined.

Mitochondrial permeability transition is responsible for the F1F0-ATPase breaking down, rather than building, ATP (13). Inhibition of mPTP opening might therefore preserve energy levels in a population of ischemic but still viable cardiomyocytes, which might eventually result in better resumption of LV contraction. Whether pharmacological inhibition of mPTP opening might have unspecific side effects on LV remodeling cannot be ruled out. However, in contrast to CsA, which binds to the cytosolic cyclophilin A and acts on the calcineurin-nuclear factor of activated T cells (NFAT) pathway, Debio-025 is a cyclophilin D inhibitor that does not act on the calcineurin-NFAT pathway and has no known action on cardiac hypertrophy that would influence cardiac remodeling (28). The role of other mechanisms that play a role in ischemia-reperfusion damage, including altered function of the sarcoplasmic reticulum or spread of injury via gap junctions, cannot be ruled out (21, 42).

Since postconditioning and Debio-025 treatments were performed at one single time point (i.e., reperfusion) and had comparable impact on lethal reperfusion injury, it appears likely that the limitation of LV dilatation and improvement of contractile function correspond to an unspecific consequence of infarct size limitation (51). This is in agreement with clinical reports indicating that peak creatine kinase value, a surrogate marker for infarct size, is an independent predictor of LV remodeling (8).

Another major observation of the present study is that postconditioning and inhibition of the mPTP by Debio-025 significantly reduced the mortality rate within the first 30 days after acute MI. The mechanism of this major outcome remains to be determined. Most deaths in the control group occurred during the first 2 days after reperfusion. This pattern is different from that usually observed in permanent coronary artery ligation studies in mice, in which mortality incidence is more scattered over the 1st wk after infarction (1, 20, 26). In the mouse model of reperfused MI, most early deaths may be due to lethal ventricular arrhythmias or acute heart failure.

The present study does not allow us to determine which of these two types of events was affected by Debio-025 and postconditioning. One cannot exclude the possibility that both treatments had antiarrhythmic effects. Galagudza et al. (19) and Halkos et al. (29) reported that ischemic postconditioning reduces the incidence of ventricular arrhythmias, although the benefit they reported was not statistically significant. Recently, Kloner et al. (39) reported that postconditioning significantly inhibits reperfusion arrhythmias after a 5-min ischemic insult in the rat heart. Although it has recently been proposed that mitochondria may play a role in postischemic arrhythmias, inner membrane depolarization and activation of inner membrane anion channel, rather than opening of the mPTP, appeared involved (2). To our knowledge, there is no evidence in the literature that inhibition of mPTP opening might per se be antiarrhythmic. One may, however, speculate that inhibition of mPTP opening could limit ventricular arrhythmias by limiting cytosolic Ca2+ oscillations and overload or by attenuating ATP breakdown and secondary opening of the sarcolemmal ATP-sensitive K+ channel and proarrhythmic shortening of action potential duration. Early death after reperfusion may also result from acute heart failure. Zhao et al. (54) did not find that postconditioning attenuates myocardial stunning in the dog heart. However, their follow-up of contractile function was limited to the first 3 h after reperfusion, and it cannot be ruled out that postconditioning or Debio-025 may limit acute LV dilatation and prevent acute heart failure, or even the related stretch-induced arrhythmias, within the first 48 h after reperfusion. Further studies are needed to specifically address these important issues.

Limitations of the Study

This study has several limitations. 1) Mortality following acute MI was assessed only over 30 days and in a relatively small cohort of animals. 2) Although Debio-025 and postconditioning provided very comparable benefits in terms of infarct size reduction and improvement in contractile function, as well as in mitochondrial CRC, this does not demonstrate that the mechanism of these effects was the same. Further studies are needed to demonstrate a causal relationship between inhibition of mitochondrial permeability transition and infarct size reduction in postconditioned hearts.
Conclusion

Using a mouse model of reperfused MI, we have demonstrated that ischemic postconditioning and pharmacological inhibition of the mPTP enhanced the recovery of LV contractile function and improved survival. Since recent reports indicate that postconditioning can protect the human heart, the present data represent an encouraging background for the search for new pharmacological agents aimed at inhibiting the mPTP at the time of reperfusion in patients undergoong acute MI.

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REFERENCES


