Editorial

Treatment of myocardial damage past the coronary intervention—what can be salvaged?

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In the report by Li *et al.* in this issue of *Journal of Xiangya Medicine* (*JXYM*), 80 rats underwent either permanent ligation of the left anterior descending coronary artery or a sham operation. The animals that underwent ligation, and therefore developed an acute myocardial infarction, were subsequently treated with either placebo, low-dose salidroside or high dose salidroside. Treatment with salidroside has been previously reported to be beneficial in cerebral ischemia (1) and cancer (2). These effects are partly attributed to the anti-apoptotic properties of salidroside. Li *et al.* studied whether this effect could also be beneficial in the heart, following myocardial infarction after 2 weeks. Using a combination of TUNEL staining and immunoblotting and myocardial mitochondria isolation, the authors elegantly show that treatment with salidroside significantly improves survival rates and limits myocardial cell apoptosis, 2 weeks after myocardial infarction. Furthermore, Li *et al.* deliver evidence that this effect could be attributed to alterations in expression of genes that are known to be involved in cell apoptosis, such as Bcl-2 and cytochrome-c. Besides this they show also that salidroside limits the release of cleaved caspase-3 and -9. These two proteins play an important role in the caspase cascade, which leads to apoptosis (3). Taken together, treatment with salidroside seems to be beneficial in preserving myocardial tissue following myocardial infarction by limiting ischemia and induced cell death.

Ischemia-reperfusion damage is still a major problem in the current treatment of acute myocardial infraction. In the past decades therapy strategies have developed rapidly. Today, the mortality of an ST-elevated myocardial infarction is less than 5%, mainly due to fast restoration of epicardial flow by percutaneous coronary intervention. However, treatment with percutaneous coronary intervention has introduced the phenomenon of no reflow. Although revascularization is paramount for acute restoration of blood flow to the affected ischemic myocardium, reperfusion after a period of ischemia is not entirely beneficial. First reported by Jennings over 50 years ago, ischemia-reperfusion potentially leads to additional cell death in the myocardium (4). Since then ischemia-reperfusion damage (I-R damage) has been a topic of research, and it has become apparent that I-R damage is very complex and influenced by many factors. Among others, suggested mechanisms are the formation of oxygen radicals, an overload in intracellular calcium-ions, inflammation and many more (5). Disappointingly, the vast amount of research has not lead to the development of an adequate therapy for I-R damage; at least in humans that is. Some studies have shown some promising results in a clinical setting, such a post-conditioning, a form of therapy in which the blood flow is not restored suddenly, but rather graded in course of several minutes (6). However, recently a large randomized study with more than 1,200 patients showed no improvement in clinical outcomes with post-conditioning, suggesting some of responsible mechanisms act at a later stage of reperfusion (7). Also it could be postulated that the cascade that leads to reperfusion damage is actually already initiated during ischemia. In a rat-model of ischemia-reperfusion using a combination of *in vivo* and *ex vivo* reperfusion however, this theory is refuted; showing that reperfusion not merely unveils ischemic damage, but

causes major additional damage itself (8).

One of the factors that have gained more and more interest in the past decade is the role of apoptosis, which is thought to play a major role in I-R damage (9). When apoptosis is initiated is still under debate. Some reports mention that apoptosis can be initiated by ischemia, but that the level of apoptosis is determined by the duration of reperfusion (10). Others claim programmed cell death only occurs when reperfusion takes place (11). Either way, the majority of cell death that is caused by apoptosis occurs after relief from ischemia, and limiting the effects of apoptosis is therefore an interesting approach in limiting I-R damage, especially considering the unfavorable correlation between apoptosis and clinical outcomes (12).

In the study of Li *et al.*, the role of salidroside in the inhibition of cardiac apoptosis is studied (13). It is already shown that salidroside limits I-R damage in the brain (1), and now for a first time a similar effect is demonstrated in a cardiac ischemia-reperfusion model. Although these findings still have to be translated to the clinical field, they give hope for the future treatment of ischemia-reperfusion injury and the optimization of post-infarction myocardial salvage.

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