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COMMENTARY

Myocardial ischaemia/reperfusion injury and preconditioning: effects of hypercholesterolaemia/hyperlipidaemia

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There appears to be a controversy in the literature, whether experimental hyperlipidaemia influences the severity of myocardial ischaemia/reperfusion injury, and if it interferes with the cardioprotective effect of preconditioning. In this issue of *Br. J. Pharmacol*., Wang *et al*. (2002) described that experimental hyperlipidaemia induced by an 8-week hyperlipidaemic diet increased infarct size and apoptotic cell death, and they showed for the first time in the literature that this can be inhibited by a pharmacological blockade of the caspase-1 cascade in a rabbit open-chest coronary occlusion/reperfusion model. Golino *et al*. (1987) showed that acute hypercholesterolaemia *per se* (2% cholesterol-enriched diet for 3 days), independently from its atherogenic effect, increased the extent of myocardial infarct size in rabbits after 30 min coronary occlusion followed by 5.5 h reperfusion. Infarct size was also increased in rabbits fed a high-cholesterol diet for 8 weeks (Ma *et al*., 1996), 4 weeks (Jung *et al*., 2000), or 4 days (Hoshida *et al*., 1996). We have also shown that cholesterol-enriched diet for 8 weeks led to an increased ST-segment elevation in response to rapid pacing-induced ischaemia in conscious rabbits (Szilvassy *et al*., 1995). Hearts of apolipoprotein E and low-density lipoprotein receptor double-knockout mice (ApoE/LDLr−/−) fed an atherogenic diet for 6–8 months had worse post-ischaemic function and increased infarct size and troponin T release as compared to genetic controls (Li *et al*., 2001). These studies clearly show that hyperlipidaemia leads to a significant aggravation of myocardial ischaemia/reperfusion injury.

An interesting study by Girod *et al*. (1999) showed that 2 weeks of high cholesterol diet increased infarct size in LDLr−/− mice as compared to wild-types after 30 min ischaemia and 120 min reperfusion, however, high cholesterol diet for 12 weeks resulted in a significant decrease in infarct size in both wild-type and LDLr−/− mice. Ischaemia/reperfusion resulted in a deterioration of cardiac contractile function in isolated hearts of rabbits fed 2% cholesterol-enriched diet for 2–3 weeks when compared to rabbits fed the same diet for a longer duration (5–16 weeks) or rabbits fed normal diet (Tilton *et al*., 1987). These data suggest that a short-term cholesterol feeding renders the myocardium more susceptible to ischaemia-reperfusion injury, whereas a long-term hypercholesterolaemia may confer cardioprotection. We have shown that in hearts isolated from rats fed 2% cholesterol-enriched diet for 24 weeks, baseline left ventricular end-diastolic pressure was elevated, however, ischaemic and post-ischaemic cardiac functional parameters were not significantly deteriorated (Ferdinandy *et al*., 1997; 1998a). Others have shown that in hearts isolated from rabbits after a 6-week feeding with 2% cholesterol, although pre-ischaemic cardiac contractile function was significantly lower, no significant differences were observed upon reperfusion when compared to controls (Le Grand *et al*., 1995). The reason why in some *ex vivo* rat and rabbit heart models and in LDLr−/− mice, hyperlipidaemic diet may not significantly deteriorate or may even improve recovery of post-ischaemic contractile function especially after a long-term cholesterol diet is not known. It should be noted that long term cholesterol diet, due to the development of severe atherosclerosis and liver failure, may lead to several extracardiac pathologies in animal models which may further influence the susceptibility of the myocardium to ischaemia.

We have observed for the first time in the literature, that the cardioprotection conferred by classical preconditioning against myocardial stunning and electrophysiological changes was lost when rabbits developed hypercholesterolaemia and atherosclerosis after 8 weeks of exposure to 1.5% dietary cholesterol. When these animals were re-exposed to normal diet, the normalization of serum lipid levels resulted in the recapture of preconditioning in the presence of constant degree of intimal lesions indicating that atherosclerosis itself without hyper-cholesterolaemia does not significantly interact with preconditioning (Szilvassy *et al*., 1995). The loss of early preconditioning was subsequently confirmed in hearts isolated from rats exposed to dietary cholesterol without development of atherosclerosis (Ferdinandy *et al*., 1997). Hyperlipidaemia without atherosclerosis has been also shown to prevent the protective effect of early preconditioning on the contractility and responsiveness to phenylephrine in rat papillary muscle (Kocic *et al*., 1999). The infarct size limiting effect of early preconditioning was also attenuated in rabbits fed 1% cholesterol (Ueda *et al*., 1999). The loss of the anti-ischaemic effect of preconditioning in hyperlipidaemia has been confirmed also in patients undergoing repeated balloon inflations during coronary angioplasty (Kyriakides *et al*., 2002). In this study, the loss of the anti-ischaemic effect of early preconditioning was correlated with plasma cholesterol

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and LDL levels. Very few studies examined the interaction of hyperlipidaemia with late preconditioning, but it seems that late preconditioning can be induced in hyperlipidaemia using a preconditioning stimulus stronger than that used in normal animals (Szekeres *et al*., 1997). These studies show that hyperlipidaemia leads to an inhibition of cardiac stress adaptation (see for review: Ferdinandy *et al*., 1998b).

In contrast to the aforementioned studies, in rabbits fed a cholesterol enriched diet for 8 weeks (Li *et al*., 2001) or 4 weeks (Jung *et al*., 2000) and in ApoE/LDLr−/− double-knockout mice fed an atherogenic diet for 6–8 months (Kremastinos *et al*., 2000), the infarct size limiting effect of acute preconditioning was not attenuated.

The mechanism by which hyperlipidaemia may influence the severity of myocardial ischaemia and preconditioning is not exactly known, however, accumulation and redistribution of tissue/membrane cholesterol and the resulting changes in sarcolemmal and mitochondrial membrane microviscosity rather than the direct effect of high serum lipoprotein levels and coronary atherosclerosis may account for this (Haukur & Leeson, 1975; Hexeberg *et al*., 1993; Venter *et al*., 1991). Previous studies suggest that membranes can sense environmental changes and the resulting modulation of their phase state and microdomain organization regulates the expression of several genes including heat shock proteins (see for review: Vigh *et al*., 1998). Accordingly we have recently reported that the expression of the cardioprotective 70 kDa heat shock protein (Hsp70) in response to ischaemic and heat stress is markedly attenuated in hearts of hyperlipidaemic rats (Csont *et al*., 2002). A decrease in cardiac NO bioavailability (Ferdinandy *et al*., 1997; Hoshida *et al*., 1996) and ecto-5′-nucleotidase activity (Ueda *et al*., 1999), an inhibition of the mevalonate pathway (Ferdinandy *et al*., 1998a), as well as enhanced apoptotic cell death (Wang *et al*., 2002) have been also shown to contribute to increased ischaemia/reperfusion injury and loss of preconditioning in hyperlipidaemic animal models.

In summary, the majority of the studies show that hyperlipidaemia, independently from the development of coronary atherosclerosis, worsens the outcome of ischaemia/reperfusion injury and attenuates the cardioprotective effect of preconditioning, however, existing data in the literature are still somewhat contradicting. These findings emphasize the necessity of lipid lowering therapy and promote the development of new cardioprotective drugs that are capable to reverse the increased susceptibility of hearts to ischaemic stress and to recapture cardiac stress adaptation in hyperlipidaemia.

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