versity of geography and population in the United States, lawmakers throughout the country need the freedom and flexibility to apply gun regulations that are appropriate to their jurisdictions. The Court's decision in *District of Columbia v. Heller* may greatly reduce the latitude that legislators have had in setting firearm regulations for their localities.

With the Supreme Court's decision and the expectation of a substantial reduction in gun regulation, we are poised to witness another epidemiologic study of the effect of regulation on gun violence. With this experiment, which may play out in many American cities, we will know in the coming years whether the overturned laws reduced death and injury from handguns. The Court has heard the arguments and made its decision; we will now learn the human ramifications of this landmark case.

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Time to Take Myocardial Reperfusion Injury Seriously

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Every year, 500,000 people in the United States have an ST-elevation myocardial infarction.[1] Timely and effective reperfusion with the use of either primary percutaneous coronary intervention (PCI) or thrombolytic therapy remains the most effective treatment strategy for limiting the size of the myocardial infarct, preserving left ventricular ejection fraction, and improving the clinical outcomes in such patients. However, despite optimal reperfusion therapy, morbidity and mortality remain substantial, with about 5 to 6% of patients having a subsequent cardiovascular event by 30 days.[2]

One treatment strategy that might reduce the size of the infarct and improve the clinical outcomes in these patients is to protect the heart from the detrimental consequences of myocardial reperfusion. The abrupt reperfusion of ischemic myocardium can itself inflict injury on the myocardium — a phenomenon termed myocardial reperfusion injury.[3] Experimental studies indicate that this form of myocardial injury accounts for up to 50% of the final size of the infarct,[3] providing an important potential target for protection of the heart. However, previous attempts to individually target known mediators of myocardial reperfusion injury in patients with the use of antioxidant therapy, calcium-channel blockers, sodium–hydrogen exchange inhibitors, and antiinflammatory drugs have been largely disappointing, leading to calls for a reevaluation of the current procedure for translating experimental interventions into clinical therapy.[3]

Against this tide of disappointment, recent experimental studies have identified new strategies to protect the heart during myocardial reperfusion. One such approach is termed ischemic postconditioning.[4] This method, in which myocardial reperfusion in patients undergoing primary PCI is interrupted with several low-pressure inflations of the angioplasty balloon to temporarily reocclude the coronary artery, has been shown to reduce the size of the myocardial infarct, as determined by single-photon-emission computed tomography, by 40% at 6 months and to improve left ventricular ejection fraction, as determined by echocardiography, by 7% at 1 year.[5] These findings strongly support the existence of myocardial reperfusion injury in humans and demonstrate that an intervention that is applied at the onset of myocardial reperfusion has the ability to confer long-term beneficial effects. However, ischemic postconditioning is restricted to patients with ST-elevation myocardial infarction who are receiving PCI and require an invasive intervention.

The cardioprotective signal-transduction pathway that underlies ischemic postconditioning has been linked to the activation of endogenous prosurvival protein kinases of the reperfusion-injury salvage kinase pathway.[6] This finding suggests that the effects of ischemic postconditioning on limiting the size of the infarct can be reproduced by pharmacologic manipulation of these signaling components. Preliminary clinical studies suggest that pharmacologic agents that are known to activate the reperfusion-injury salvage kinase pathway (adenosine and atrial natriuretic peptide) are beneficial when they are administered as adjunctive therapy during primary PCI.[3]

Interestingly, both ischemic postconditioning and the reperfusion-injury salvage kinase pathway mediate their cardioprotective actions by acting on the mitochondrial permeability-transition pore.[7,8] Under certain pathologic conditions, the inner mitochondrial membrane can undergo an abrupt transition in permeability, rendering it freely permeable to protons and solutes that are less than 1500 daltons in size, collapsing the mitochondrial membrane potential, and uncoupling oxidative phosphorylation. These changes can lead to the depletion of ATP and to cell death.[7] This mitochondrial permeability transition was first characterized in the late 1970s by Hunter and Haworth[9] and was attributed to the opening of a proteinaceous pore in the inner mitochondrial membrane. Experimental studies by Crompton and colleagues[10] in the late 1980s first identified the immunosuppressant cyclosporine as an inhibitor of the opening of the mitochondrial permeability-transition pore and first implicated the mitochondrial permeability-transition pore as a major factor in ischemia–reperfusion injury.

The initial observations by Crompton et al. have been subsequently confirmed in several ways. Experimental studies indicate that the mitochondrial permeability-transition pore remains closed during myocardial ischemia and only opens in the first few minutes of reperfusion, when factors required for inducing its opening, such as an overload of mitochondrial calcium and phosphate, depletion of ATP, oxidative stress, and the rapid restoration of physiologic pH, are present.[11] Inhibiting the opening of the mitochondrial permeability-transition pore with the use of cyclosporine at the onset of myocardial reperfusion has been shown in studies in animals to reduce the size of the myocardial infarct by 50%,[12] improve left ventricular ejection fraction,[13] and reduce mortality.[13] In addition, cyclosporine has been demonstrated to improve postischemic contractile function in human atrial muscle that is subjected to simulated ischemia–reperfusion injury.[14] Transgenic mice that lack cyclophilin D, a regulatory component of the mitochondrial permeability-transition pore, have been shown to have smaller myocardial infarcts than wild-type mice.[15] Finally, the suppression of the opening of the mitochondrial permeability-transition pore appears to underpin the effects of both ischemic preconditioning and postconditioning on limiting the infarct.[8]

In this issue of the *Journal*, Piot and colleagues[16] report the results of a small proof-of-concept clinical study involving 58 patients. Their study proposes that the mitochondrial permeability-transition pore may be a new target for reducing the size of a myocardial infarct in the clinical setting. A single intravenous bolus of cyclosporine (2.5 mg per kilogram of body weight), administered immediately before primary PCI, significantly reduced the release of serum creatine kinase by 44%; troponin I was reduced by 13% (a nonsignificant reduction). In a subgroup of 27 patients, the absolute size of the infarct (as measured by delayed gadolinium-enhanced cardiac magnetic resonance imaging [MRI]) was reduced by 20% in patients who received cyclosporine therapy. Patients who had smaller infarcts appeared to benefit less from cyclosporine therapy than patients who had larger infarcts. This finding is consistent with that of clinical studies that showed that the cardioprotective benefits of adenosine, hyperoxemia, and therapeutic hypothermia are restricted to patients who have larger, anterior myocardial infarcts. Of note, no adverse effects were seen in the patients who received acute intravenous cyclosporine therapy; this observation is to be expected, since many of the recognized side effects of cyclosporine therapy are manifested with long-term therapy. However, more specific and safer inhibitors of mitochondrial permeability-transition pores would be preferable and need to be developed.

The findings from the study by Piot and colleagues confirm the existence of myocardial reperfusion injury in humans and suggest that the mitochondrial permeability-transition pore is a new target for protecting the heart against this form of injury and reducing the size of the myocardial infarct in patients who are undergoing pri-

mary PCI. Large, multicenter studies are required to determine whether this new treatment strategy is able to influence the clinical outcomes after ST-elevation myocardial infarction. Targeting the opening of the mitochondrial permeability-transition pore may also offer protection in other clinical contexts, such as stroke, cardiac surgery, and organ transplantation. We believe it is now time to take myocardial reperfusion injury seriously, since it provides a new target for reducing the size of a myocardial infarct and potentially improving the clinical outcomes in patients with ST-elevation myocardial infarction.

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