Nitroglycerin-induced preconditioning: interaction with nitrate tolerance

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PRECONDITIONING IS CHARACTERIZED by a remarkable ability to adapt to ischemic stress in a variety of organs (or tissues) with the highest clinical impact in the heart and brain (10, 24). Preconditioning can be induced by several interventions such as ischemia (blockade of blood supply), rapid pacing (increased oxygen demand), or administration of pharmacological agents (pharmacological preconditioning) before a severe ischemic event causing cell death and organ dysfunction (10). Clinically, pharmacological preconditioning is the most relevant in patients with coronary heart disease. The application of ischemic preconditioning in patients is less relevant, since ischemic interventions should be performed before the onset of the ischemic event that is rather difficult to predict (25). Accumulating evidence shows, however, that several risk factors, pathological conditions, or pharmacological agents interact with the protective mechanisms of preconditioning both in animal models and humans (10, 15, 22). Nitroglycerin has been previously shown to exert preconditioning-like and direct anti-ischemic effects in several studies (8, 12, 13, 14). Moreover, organic nitrates including nitroglycerin are the oldest and most frequently prescribed drugs to prevent ischemic events in coronary heart disease (18). However, a rapid development of tolerance to the hemodynamic effects of nitroglycerin due to continuous administration limits its clinical applicability (7, 18).

In the American Journal of Physiology-Heart and Circulatory Physiology, Gori and colleagues (11) have investigated in healthy human subjects whether the previously described (12) preconditioning-like effect of nitroglycerin on endothelial dysfunction induced by forearm ischemia-reperfusion can be maintained during prolonged exposure. The authors elegantly demonstrated that not only a continuous nitroglycerin administration that leads to the development of tolerance but also repeated short-term nitroglycerin treatments (2 h/day for 6 days) before the forearm ischemia-reperfusion results in a loss of the preconditioning effect of nitroglycerin on the endothelium (11). The deleterious effect of continuous nitroglycerin on preconditioning has already been reported in animal models (21). However, the finding that repeated nitroglycerin dosing without the development of tolerance interacts with endothelial preconditioning suggests that patients with stable coronary artery disease taking nitroglycerin may have deteriorated adaptive responses to ischemia. On the other hand, a recent cohort study concluded that chronic nitrate treatment beneficially affects the severity of myocardial injury in response to an acute coronary event (1). It is also demonstrated in the present study by Gori et al. (11) that a single high dose of vitamin C administered intraarterially just before ischemia-reperfusion dramatically improved endothelial function both before and after ischemia-reperfusion in subjects receiving continuous nitroglycerin (11). This finding is in line with previous observations by others showing that antioxidant treatment may attenuate tolerance development in the vasculature (2, 23). The finding that a single dose of vitamin C is able to restore normal endothelial function in nitrate tolerance may have potential clinical relevance, suggesting the benefit of vitamin C coadministration in patients receiving nitroglycerin (7). However, further studies are needed to explore whether vitamin C attenuates tolerance development or ischemia-reperfusion injury (19), since the effect of vitamin C was not examined in placebo-treated subjects in the present work. Gori et al. (11) have also reported by using human umbilical vein endothelial cells that a single dose of nitroglycerin increased mRNA level for heme oxygenase-1; however, this effect was abolished when treatment with nitroglycerin was repeated four times (11), suggesting that the induction of heme oxygenase-1 might be an important step in the molecular mechanism of nitroglycerin-induced preconditioning of the endothelium.

Nevertheless, there are several limitations of the present study. Whether these findings can be applied to other tissues or organs (such as coronary arteries, cardiac tissue, and brain, etc.) and whether other organic nitrates act similarly remain to be elucidated. Also, the definite molecular mechanisms of nitroglycerin-induced preconditioning, nitrate tolerance, and their interaction remain unresolved in this study. More importantly, the hypothesis has not been tested in patients with coronary artery disease. Thus the conductance of future studies is essential to address these issues.

The exact molecular mechanism of the development of tolerance to the vasodilator effect of nitroglycerin is likely multifactorial and still not entirely clear despite more than a century of research. Several hypotheses have been implicated in the last couple of decades including alterations in the metabolism of nitroglycerin, nitric oxide, and cGMP signaling, depletion of sulphhydryl groups, increased oxidative stress, and systemic counterregulatory neurohormonal activation just to mention a few (7, 17). In recent years, a number of studies have emphasized the importance of mitochondrial aldehyde dehydrogenase and oxidative/nitrosative stress in the development of vascular tolerance to nitroglycerin (5, 17) and suggested that nitroglycerin should be avoided in the clinical use. The molecular link, however, between tolerance development and nitroglycerin-induced preconditioning is unclear. Also, the importance of the duration, frequency, and dose of nitroglycerin treatment to induce preconditioning is incompletely understood. Since the second window of protection elicited by preconditioning may last for 24–72 h (10); therefore, it seems feasible that a less frequent administration of nitroglycerin may remain effective. The present results of Gori et al. (11) raised several additional questions to be answered in future studies. For instance, there is a need to investigate the interaction between nitroglycerin-induced preconditioning and repeated nitroglycerin treatment in patients with an increased risk for...
coronary heart disease, since different risk factors such as hyperlipidemia, diabetes, ageing, etc., may have a severe impact on preconditioning (3, 10). Another issue to be addressed is whether the effect of repeated nitrate treatment results in a loss of preconditioning effect in cell types other than endothelial cells, because some studies have shown the beneficial effects of nitroglycerin without detrimental oxidative/nitrosative stress in cardiac tissue when nitrate tolerance has been developed in the vasculature (6, 8, 13). Moreover, some novel research directions already initiated by this group and others are also supported. Such directions include finding appropriate treatment regimens for neutralization of the detrimental effect of prolonged nitroglycerin pretreatment. As it was originally demonstrated by Kojda et al. (16), long-term treatment with some organic nitrates, such as pentaerythrityl tetranitrate, may not lead to the development of significant vascular nitrate tolerance. Therefore, the development and the preclinical and clinical assessment of novel organic nitrates (or nitric oxide donors) not sharing the problems of nitroglycerin treatment are of great importance (4, 20). Finally, testing whether the adaptation to ischemia-reperfusion injury triggered by either ischemic or pharmacological postconditioning interacts with prolonged nitrate treatment is a promising future direction (9). This latter issue is especially interesting, because postconditioning is clinically more relevant than preconditioning, since in the case of an acute coronary occlusion, intervention should be applied just on the beginning of reperfusion, which is a frequent situation in patients undergoing percutaneous coronary intervention (10, 25).

In conclusion, there are still many unanswered questions regarding the clinical effectiveness of nitroglycerin-induced preconditioning during prolonged application. Thus well-designed randomized large-scale clinical trials are urged to determine whether nitroglycerin pretreatment (alone or in combination with antioxidants) is able to precondition the heart toward a subsequent ischemic episode, thereby reducing the extent of myocardial infarction and mortality.

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DISCLOSURES
T. Csont is involved in the management of a pharmaceutical/biotechnological company.

REFERENCES