

Oral presentation

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## Nitrate-induced tolerance, toxicity and preconditioning: a rationale for reconsidering the use of these drugs

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Although organic nitrates have been clinically used for more than a century, findings in the last decade have radically challenged our traditional view concerning the mechanism(s) of their clinical effects. This presentation will make four separate points.

1. There is no doubt that when given acutely, they relieve cardiac ischemia and can reduce pulmonary congestion. Unfortunately when given chronically, without nitrate – free intervals, these beneficial effects are lost.
2. There is now strong evidence that chronic therapy is associated with increased bioavailability of reactive oxygen species and that this phenomenon may result in both tolerance and adverse effects on endothelial function.
3. There continues to be no evidence that these widely used drugs improve long-term outcome in patients with angina or congestive heart failure (except when given in combination with hydralazine in patients with congestive heart failure).
4. Paradoxically there is now clear evidence that short-term administration of nitroglycerin and other organic nitrates are potent pharmacologic preconditioning agents and that short-term exposure (generally 2 hours) protects from the impact of ischemia reper-

fusion injury up to 48 hours later. We will also discuss the mechanism of this preconditioning effect.

While their hemodynamic properties are well known, the knowledge that nitrates possess previously unexpected nonhemodynamic effects is a unique opportunity of which clinicians should be aware. Our group believes that tolerance, increased free radical bioavailability and their ability to precondition are likely all interrelated. A PDF of a recent editorial from our group is attached.