Preventing Atrial Fibrillation After Cardiac Surgery
A New Method Using an Old Tool
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A trial fibrillation (AF) after cardiac surgery remains a common problem, resulting in prolonged hospital stays and added morbidity for a substantial proportion of patients.\(^1\) Although traditional therapies with antiarrhythmic agents can suppress this common arrhythmia in nearly half of all cases, generally \(>1\) in 10 of all cardiac surgery patients will have AF despite the best available therapies, and amiodarone, the most potent conventional agent, carries the risk of numerous toxicities.\(^2\)

Recent studies have sought to address more directly the pathophysiology of AF in this setting, building on data that the arrhythmia may occur as a result of surgically induced inflammation.\(^3\) A randomized trial of atorvastatin versus placebo initiated 7 days before surgery demonstrated a 22\% absolute risk reduction and an adjusted 61\% reduction in the odds of developing AF.\(^4\) However, 35\% of subjects in the treated arm still developed AF postoperatively. In addition, although this study provided an important proof of principle, it is unlikely that it will radically change clinical practice because most cardiac surgery patients will still undergo therapy with statins because of their coronary disease. In an attempt to test the antiinflammatory hypothesis even more directly, investigators in Finland performed a placebo-controlled, randomized clinical trial of hydrocortisone in cardiac surgery patients and demonstrated a 46\% reduction in the risk of AF.\(^5\) Once again, however, 30\% of those in the treatment arm exhibited AF. Although no major complications were observed, trepidation regarding the administration of high-dose steroids in the immediate postoperative setting may prevent widespread adoption of this method.

In this issue of Circulation, Cavalli et al\(^6\) present data that a 60-minute infusion of nitroprusside during reperfusion may significantly reduce the risk of AF after coronary artery bypass grafting in another important double-blind, randomized, placebo-controlled trial. During 5 days of follow-up, 27\% of those in the placebo arm developed AF compared with 12\% of those who received nitroprusside. As with the previous studies of novel agents for the prevention of postoperative AF, this study is important for 2 reasons. First, from a clinical standpoint, it offers an additional strategy to combat this common condition using a familiar, relatively inexpensive, and easy-to-administer medication. An advantage is that a 1-time infusion, given intraoperatively under the direct supervision of both the cardiac anesthesiologist and cardiac surgeon in a controlled environment, may be all that is needed. Second, from a research standpoint, this finding may offer new clues to the mechanisms underlying AF after cardiac surgery, potentially motivating new directions for future investigation.

Before recommending the routine use of this strategy in the clinical realm or delving into research projects aimed at elucidating potential underlying mechanisms, we should critically review the limitations of the present study. First, the study was relatively small, with 50 patients in each arm, representing a pilot study as stated in the title. With smaller numbers, randomization may not be adequate to guarantee an equal distribution of potential confounders between the 2 groups. Thus, it is possible that the baseline characteristics favored less AF in the treatment arm. Although not statistically significant, left atrial size was on average slightly larger in the control arm; a value of \(P=0.053\) in such a small study may not be negligible. Although a large number of clinical characteristics for each group are presented, it is not an exhaustive list. For example, a history of AF, a potentially important confounder, is not described for each group. In addition, cointerventions that may have been given are not described in a comprehensive fashion. For example, it is surprising that the mean blood pressure during rewarming (and therefore during the nitroprusside infusion) was not at all different between the 2 groups, suggesting that, even if the investigators were blinded, other cardiovascular agents may have been administered differentially between the 2 groups. Finally, there was a highly statistically significant difference in the number of intraoperative defibrillations between the 2 groups, with 9 nitroprusside patients and 24 control patients requiring defibrillation. This may reflect the fact that those randomly assigned to nitroprusside happened by chance alone to have healthier hearts that were less prone to arrhythmias; in such a circumstance, the magnitude of this difference may have been sufficient to completely explain the difference in outcomes between the 2 arms. Alternatively, the difference in defibrillation may have been due to a beneficial effect of the nitroprusside, demonstrating either a general antiarrhythmic property or an important intermediate step that facilitated the prevention of postoperative AF. Larger studies with more complete data collection are necessary to provide more definitive answers.
Assuming that nitroprusside does indeed reduce AF after cardiac surgery, what are the possible mechanisms? By measuring C-reactive protein (CRP) levels preoperatively and daily postoperatively, the authors provide useful insight into the potential process at play. Although there were no significant differences between baseline CRP levels, CRP was consistently lower in the nitroprusside group on postoperative days 1 through 5, regardless of whether AF developed. In fact, nitroprusside has previously been shown to have anti-inflammatory effects, resulting in a reduction in interleukin-6 and interleukin-8. This effect is particularly important because interleukin-6 has been implicated as a direct actor in the development of both postoperative and spontaneous AF.

The mechanism by which nitroprusside would exert such an anti-inflammatory effect is not known. Because an elevated left ventricular end-diastolic pressure has been shown to be associated with a higher CRP, the nitroprusside-anti-inflammatory connection may simply reflect a benefit on hemodynamics. However, it is of interest that the reduction in CRP persisted for several days, fitting very well with the delayed onset of postoperative AF observed clinically and in the study. This brings up the possibility of a lasting effect resulting from this transient change in hemodynamics such as a reduction in ischemia or atrial stretch that might have minimized atrial remodeling over the ensuing few days.

Finally, the authors postulate that the beneficial effect stems from the fact that nitroprusside acts as a nitric oxide (NO) donor. Although studies to date have suggested that AF may result in a reduction in NO, there have been limited data from animal work and/or bench research suggesting that NO might influence the risk of AF. Primarily, it is thought that NO exerts an anti-inflammatory action by reducing oxidative stress and apoptosis. However, other mechanisms also may be important. For example, NO has been shown to increase vagal tone, potentially providing some protection against postoperative AF driven by sympathetic activation. NO also has been shown to block potassium currents, potentially leading to a prolongation of the atrial effective refractory period and therefore decreasing the likelihood that AF will develop. Other electric effects of NO include an inhibition of intracellular calcium-induced calcium release, potentially reducing the electric remodeling that may make the atria more prone to fibrillate.

In short, this initial investigation should motivate larger studies that can validate the primary findings while providing comprehensive data collection to answer several lingering questions. In addition to offering a simple method that may help to address the important problem of AF after cardiac surgery, investigating this novel therapy may lead to a better understanding of the pathophysiology underlying this pervasive disease.

**Disclosures**

None.

**References**

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