and the ability to reverse those morphological changes was not explored.

Certainly, this article does not completely answer the question of the safe timing for redosing del Nido cardioplegia in adult patients, but the authors need to be congratulated on providing a morphologic timeline of the changes of mitochondria ultrastructure. Their observations provide the foundation for additional studies where form, function, and ability to recover after reperfusion are examined.

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Commentary: del Nido cardioplegia—the jury is still out and a new trial is needed

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A major area of concern when using del Nido cardioplegia (DNC) in adult cardiac surgery is when and how much additional cardioplegia should be administered after the initial dose. DNC appears to be safe for low-risk, elective patients with minimal comorbidities when undergoing isolated coronary artery bypass grafting or aortic valve replacement procedures during which the crossclamp time is no longer than 60 minutes. However, in more complex procedures when the crossclamp time exceeds 60 minutes, the margin of safety after a single dose of DNC is unknown.

In this edition of the *Journal*, Jung and colleagues¹ report the results of their study, which sought to determine the safe

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CENTRAL MESSAGE

The margin of safety after a single dose of del Nido cardioplegia in adult cardiac surgery has not been determined.

period of ischemia after a single dose of DNC in 7 hearts extracted from patients undergoing heart transplantation. After an initial 1-liter infusion of DNC, hearts were extracted and placed in a water bath filled with normal saline to maintain a myocardial temperature of 18°C. Serial biopsies of the left ventricle (LV) were obtained every 30 minutes for 180 minutes. Irreversible ischemic injury in the myocardial mitochondria and nuclei were first detected 90 minutes after the initial DNC infusion and increased in a significant linear correlation over the next 90 minutes. The authors concluded that irreversible injury begins to occur 90 minutes following

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the initial dose of DNC in adult human hearts and that additional doses of DNC are required after this time period to avoid permanent myocardial injury.

As noted by the authors, there are several important limitations with this study. Since the hearts were kept in vitro in an iced saline bath after the initial dose of DNC, the effects of in vivo blood reperfusion, or an additional dose of DNC given at 90 minutes, could not be determined. The pathophysiology of hearts with end-stage disease undergoing transplantation differs from hearts requiring surgery for coronary and valvular disease and may be more susceptible to ischemic injury after longer periods of cardioplegic arrest. In this study, myocardial temperature was maintained at 18°C, which is considerably lower than the temperature in standard surgical procedures and may have afforded additional protection and extended the time before ischemic injury occurred in these DNC hearts. Only small, discrete areas of the LV could be studied from these biopsies. Furthermore, the authors could not correlate the degree of mitochondrial injury seen in these isolated tissue sections with actual indices of LV contractility and compliance in an intact myocardial model. Finally, and most importantly, no comparator group is provided, ie, a group of transplanted hearts protected with multidose blood cardioplegia (MBC) given every 20 minutes after the initial arresting dose.

Unfortunately, these limitations prevent us from determining what the optimal period of myocardial protection is after the initial dose of cardioplegia in DNC-protected hearts. In a recent retrospective, nonrandomized study of patients undergoing complex, aortic root surgery in patients receiving both DNC and MBC, Lenoir and colleagues² found that patients receiving DNC had no difference in postoperative morbidity or mortality when an additional dose of DNC was given 60 minutes after the initial DNC dose in those patients in whom the crossclamp time exceeded 90 minutes. Although the incidence of myocardial infarction was twice as great in the DNC group (18% vs 9%), this was not statistically significant ($P = .16$). However, in those patients in whom the crossclamp time was >180 minutes, creatine kinase-MB levels were significantly

greater in the DNC group, although there was no difference in morbidity or mortality.

The results from the study by Jung and colleagues and the experience of Lenoir and colleagues strongly suggest that in those patients receiving DNC who may require 90 minutes of aortic crossclamping, an additional dose of DNC will be required to avoid ischemic injury. However, infusing multiple doses of DNC may result in increased myocardial concentration of lidocaine, resulting in lidocaine toxicity, which is associated with peripheral vasodilation, negative inotropy, ventricular arrhythmias, and seizures.³ If patients receiving DNC require crossclamp times exceeding 60 minutes, it may be prudent to switch to MBC for the rest of the crossclamp period to avoid lidocaine toxicity and further ischemic injury.

The safe application of DNC in adult cardiac surgery for patients requiring more complex procedures, and in whom crossclamp times exceed 60 minutes, remains unknown. This information will only be derived from multicenter, prospectively randomized, adequately powered trials including all types of adult cardiac surgery procedures, elective, urgent, and emergent, with established protocols for delivering MBC and DNC when crossclamp times exceed 60 minutes. This could be best performed in a Cardiothoracic Surgery Network-sponsored trial.^{4,5} The jury has not been able to reach a verdict on the safe application of DNC in those adult cases when the crossclamp time exceeds 60 minutes based on the current, available data. Therefore, a new trial is needed.

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