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doi:10.1016/j.jtcvs.2004.01.029

Reply to the Editor:

In response to the comments of Bloch and Mehlhorn on the effects of poly-adenosine diphosphate-ribose polymerase (PARP) inhibition after cardioplegic arrest and reperfusion, we agree that the PARP enzyme family has a complex regulatory role under several physiologic and pathologic conditions. After a decade of intensive research, we reported on the role of PARP in general¹ and focusing on ischemia-reperfusion injury.^{2,3} To date, the role of PARP in physiologic DNA repair, apoptosis, and necrosis can be summarized as follows: depending on the severity of DNA damage, genotoxic stimuli can trigger three different pathways. In the case of mild DNA damage, PARP facilitates DNA repair and thus survival. However, the exact physiologic role of PARP still remains to be clarified; many authors have suggested that PARP is an abundant enzyme with limited role under physiologic conditions. More severe DNA damage induces apoptotic cell death, during which caspases, the main executor enzymes of apoptotic process, inactivate PARP, cleaving it into two fragments (p89 and p24) and thus PARP *cleavage* by caspases is a marker of *apoptotic* cell death. This pathway allows cells with irreparable DNA damage to become eliminated in a safe way. Much of the cell death related literature focuses on PARP *cleavage* (as opposed to PARP *activation*). The most severe DNA damage may cause excessive PARP activation, depleting oxidized nicotinamide adenine dinucleotide (NAD⁺) and adenosine triphosphate stores. NAD⁺/ATP depletion blocks apoptosis and results in necrosis. This pathway, which we proposed in the article under discussion, has no relationship to the PARP cleavage pathway. As mentioned previously, the cleaved form of PARP is catalytically inactive; PARP cleavage has been considered as an endogenous mechanism that serves to prevent PARP-dependent metabolic suppression and necrosis.

Considering the previously mentioned mechanisms, the cited study of Fischer and colleagues⁴ is not contrary to but supportive of our results. They found caspase activation but *no* apoptotic cell death and *no* PARP *cleavage* in a similar model of car-

diopulmonary bypass and cardiac arrest. On the basis of these findings, Bloch and Mehlhorn criticized our study, suggesting that pharmacologic PARP inhibition may be detrimental by inhibiting physiologic DNA repair and promoting apoptosis.

We do believe that the fact they did not find apoptotic cell death and PARP *cleavage* (inactivated PARP) after cardioplegic arrest indicates that the primary form of cell damage is the necrotic (or preneurotic) pathway, with concomitant PARP *activation* instead of PARP *cleavage*. It is also evident that cardioplegic arrest leads to adenosine triphosphate depletion, and therefore it is not surprising that no or negligible apoptosis occurs during reperfusion, because apoptosis is an adenosine triphosphate-dependent process. The loss of the ability of the cells to undergo apoptosis results in missing PARP *cleavage* and turns the cells toward PARP *activation* and metabolic suppression. Indeed, there is immunohistochemical evidence of PARP *activation* in different models of cardioplegic arrest and reperfusion.^{2,5} It is also important to note that cellular PARP activation does not always need to culminate in full-fledged cellular necrosis (complete breakdown of cell membrane integrity and release of cellular content into the extracellular space); a partial, and reversible suppression of cellular energetic pools can be associated with reversible cell dysfunction. These phenomena are sometimes termed *pre-necrosis* or *cytopathic hypoxia* and are reversible by PARP inhibition.^{6,7}

The questions raised about additional functions of PARP, its potential toxicity, and its role in aging were far beyond the scope of our study; however, we refer to a previous review article in which they were discussed and considered in detail.¹ We note, nevertheless, that in addition to participating in the NAD depletion/pre-necrosis/necrosis pathway PARP *activity* plays an active role in the transcription of various proinflammatory genes. Suppression of this process thus may provide additional cardioprotective benefits during and after cardioplegia.

The reference made by Bloch and Mehlhorn to stroke and NAD depletion does not have any direct relationship to our current work, but for the record we note that the vast majority of studies (more than 20 published reports, reviewed in Virág and Szabó¹) demonstrate the marked protective effect of PARP inhibitors and genetic PARP deficiency in various models of stroke. In most experimental models of

stroke (similar to myocardial ischemia) a preneurotic/necrotic pathway of cell death (as opposed to apoptosis or PARP *cleavage*) appears to play the dominant role and can be beneficially affected by PARP inhibition.

Whether inhibition or scavenging of upstream effectors of apoptosis or necrosis, such as reactive oxygen species, would be more effective by reduction of endogenous PARP activation in addition to the inhibition of DNA damage and subsequent cell death remains to be clarified. We have pre-clinical experience with the novel porphyrinic peroxynitrite decomposition catalyst FP15,^{8,9} which shows beneficial effects during regional ischemia/reperfusion^{8,9} and after cardioplegic arrest (unpublished observations).

In conclusion, we maintain that PARP inhibition is a promising concept for reducing cell damage during ischemia and reperfusion. Even if alternative cardiac surgical techniques such as beating-heart surgery minimize ischemia-reperfusion injury, PARP inhibition may improve postoperative outcome in those cases in which cardioplegia is still necessary.

Gábor Szabó, MD, PhD^a

Csaba Szabó, MD, PhD, DSc^b

Department of Cardiac Surgery^a

University of Heidelberg

Im Neuenheimer Feld 110

69120 Heidelberg, Germany

Inotek Pharmaceuticals Corporation^b

Beverly, MA 01915

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doi:10.1016/j.jtcvs.2004.02.004

Interventional atrial incision in the Fontan operation: Novel prophylaxis or iatrogenic substrate for intra-atrial reentrant tachycardia?

To the Editor:

In the March 2004 issue of the *Journal*, Collins and colleagues¹ published short-term results of their interesting prospective, randomized, blinded trial to assess the feasibility, safety, and efficacy of an interventional atrial incision placed at the time of the Fontan operation to reduce the development of intra-atrial reentrant tachycardia (IART). Although the idea sounds clever, there are serious concerns about the long-term efficacy of their modification.

Staged palliation culminating in a successful Fontan procedure is the current surgical goal for most patients with a functional single ventricle. Since its introduction in 1968, the Fontan procedure has undergone many modifications.² At present, two modifications in common use are the lateral tunnel and extracardiac conduit.³ The incidence of late supraventricular tachycardia after a lateral tunnel procedure varies from 0% to 22%, and that after an extracardiac conduit operation varies from 0% to 8%.³ These figures definitely do not justify undertaking a prophylactic procedure for IART in all patients who undergo Fontan operation in the modern era. It is extremely difficult to predict with accuracy the patients who will definitely have IART.

An even more important concern is the high incidence of early sinus node dysfunction among the study patients. Early sinus node dysfunction may carry long-term im-

plications because it predicts late sinus node dysfunction,⁴ which in turn is associated with late supraventricular tachycardia.⁵ Although Collins and colleagues¹ attributed this high incidence to a "broad definition" of sinus node dysfunction, I think that the interventional atrial incision may be partially if not wholly responsible for this phenomenon. There is a consensus of opinion that the presence of a region of structural or functional block within the atria is a substrate for atrial muscle reentry.⁵ The Fontan operation results in regions of structural block as a result of atrial incisions and multiple suture lines, as well as functional block from relative right atrial hypertension with right atrial dilation and hypertrophy.⁵ The "prophylactic atrial incision" not only will act as region of structural block in the long term but probably interferes with the blood supply of the sinus node in the short term. This could well explain the high incidence of early sinus node dysfunction in the study.

In conclusion, the high prevalence of atrial arrhythmias is a result of extensive atrial surgical procedures, elevated atrial pressures, and atrial enlargement. Until modifications aimed at avoiding atrial manipulation are discovered, earlier identification of sinus node dysfunction with early institution of atrial pacing may be the best prophylaxis to decrease the incidence of IART in this group of patients. My message for Collins and colleagues in particular and readers in general is that any "prophylactic atrial incision" made with the best of intentions will act as nothing but a substrate for IART.

Shahzad G. Raja, MRCS

Department of Paediatric Cardiac Surgery

Alder Hey Hospital

Eaton Rd

Liverpool L12 2AP, United Kingdom

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doi:10.1016/j.jtcvs.2004.03.043

Reply to the Editor:

The Fontan population is heterogeneous in terms of the underlying anatomy and number and nature of surgical interventions before the Fontan operation. Many factors are thought to be associated with the development of atrial arrhythmias in this group. Animal studies have suggested that surgical incision and extended suture lines are particularly likely to create an arrhythmogenic substrate.¹⁻³ The more recent versions of the Fontan procedure (lateral tunnel or the extracardiac conduit) have had lower reported incidences of late atrial arrhythmias than the older types of Fontan operations.⁴ Long-term follow-up of the extracardiac conduit Fontan operation has not yet been reported with respect to arrhythmia, but Stamm and colleagues⁴ have recently shown that the lower incidence of atrial tachycardia in the lateral tunnel Fontan procedure persisted through a mean 10-year follow-up.⁴ One can interpret this finding to mean that the current Fontan techniques are in fact less arrhythmogenic than was initially projected when our study was undertaken. If so, placement of an interventional atrial incision to the lateral tunnel Fontan may not be warranted in every case, only for patients deemed at higher risk (eg, with a preoperative history of atrial tachycardia).

Although avoiding atrial manipulation and suture lines altogether has theoretic benefits, it is not practical in all cases. If atrial suture lines are required for the surgical intervention, then choosing to place or extend them in such a way to reduce the likelihood of atrial arrhythmias is warranted. Our interventional atrial incision to the lateral tunnel Fontan procedure was designed to transect potential arrhythmia circuits around the atriotomy or the right atrioventricular valve, the primary areas where atrial arrhythmias typically develop. It was designed to be simple, to be feasible in patients with varied anatomy, and to have low added risks for the patient. The location of the incision is inferior to the