

# World Journal of *Cardiology*

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## Nifekalant in the treatment of life-threatening ventricular tachyarrhythmias

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effective antiarrhythmic agent for refractory ventricular tachyarrhythmias. Further clinical studies are required before nifekalant is routinely used in the emergency care setting.

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**Key words:** Nifekalant; Ventricular tachycardia; Ventricular fibrillation; Cardiac arrest; Acute coronary syndrome

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### Abstract

The aim of the present study is to review the literature and discuss nifekalant's potential use as a first aid drug in an emergency care setting. The PubMed database was used to identify papers, using keywords nifekalant, MS-551, amiodarone and lidocaine. Nifekalant hydrochloride, formally known as MS-551, is a class III antiarrhythmic agent which acts only by increasing the time course of myocardial repolarization. It was developed and is currently being used only in Japan for the treatment of ventricular tachyarrhythmias. It is a non-selective K<sup>+</sup> channel blocker without any  $\beta$ -blocking actions. Administration of nifekalant suppressed sustained ventricular tachyarrhythmias in acute coronary syndrome patients, and in cardiac arrest victims as well as during or after cardiac surgery. The major adverse effect of nifekalant is QT interval prolongation and occurrence of torsades de pointes which requires frequent monitoring of the QT interval during nifekalant infusion with adequate dose adjustment. Nifekalant is a possible

### INTRODUCTION

Intravenous amiodarone is considered to be the drug of choice for the treatment of ventricular tachycardia/fibrillation (VT/VF) in emergency care medicine<sup>[1]</sup>. However, amiodarone does not have a prompt onset of effect; its onset of action is 6-8 h after administration. Furthermore, its intravenous use is occasionally accompanied by adverse effects such as hypotension and bradycardia<sup>[2]</sup>. These effects make its use as rescue medication in life-threatening situations difficult.

On the other hand, lidocaine is a class I b antiarrhythmic drug with a modest negative inotropic effect on cardiac function. Although it has been widely used for the treatment of ventricular tachyarrhythmias it was excluded from the list of drugs that can be used to treat such arrhythmias in acute coronary syndrome (ACS) patients because there was no evidence to support its antiarrhythmic effect on sustained VT/VF, according to the guidelines for “the management of patients with ST-elevation myocardial infarction”<sup>[3]</sup> or “cardiopulmonary resuscitation and emergency cardiovascular care”<sup>[1]</sup>.

Recently, researchers have focused on newer class III antiarrhythmic agents such as nifekalant hydrochloride, which act only by increasing the time course of myocardial repolarization. Nifekalant is available only for intravenous injection for the treatment of ventricular tachyarrhythmias and was approved in Japan in June 1999. It was developed and is currently being used only in Japan. The purpose of this paper is to review the literature and discuss its potential use as a first aid drug in an emergency care setting.

## LITERATURE SEARCH

The PubMed database was used to identify papers, using keywords: nifekalant hydrochloride, MS-551, amiodarone, lidocaine. Articles published between January 1, 1993 and January 31, 2011 were retrieved. Reference lists of papers were searched to identify relevant publications. Forty-nine articles were found to be relevant and included in this non-systematic review.

## NIFEKALANT HYDROCHLORIDE

Nifekalant hydrochloride, which was formerly known as MS-551, is a class III antiarrhythmic agent having a pirimidinedione structure<sup>[4]</sup>. It differs from the other class III antiarrhythmic agents such as dofetilide and d-sotalol by having a nitro group instead of a methanesulfonamido group at the 4-para position on the benzene ring. It also differs in that nifekalant blocks the transient outward K<sup>+</sup> current, the inward rectifier K<sup>+</sup> current and the adenosine triphosphate (ATP)-sensitive K current in addition to the rapid component of the delayed rectifier K<sup>+</sup> current, which results in significant prolongation of the duration of the action potential. It affects neither the Na<sup>+</sup> current nor does it possess  $\beta$ -adrenergic activity<sup>[5-7]</sup>. Furthermore, it does not affect the slowly activating delayed rectifier K<sup>+</sup> channel in rabbit and guinea pig ventricular myocytes<sup>[5,7]</sup>. Nifekalant interacts with the cardiac M2 and the peripheral M3 receptors with a Ki value of 27 and 74 mmol/L, respectively. It dose dependently blocks HERG channels with an IC50 value of 7.9 mmol/L, but it does not block minK currents in the *Xenopus* oocyte expression system. It blocks HERG channels mainly in their open state in a frequency dependent manner<sup>[6]</sup>. As a pure K<sup>+</sup> channel blocker, it does not have negative inotropic effects which amiodarone has *via* a  $\beta$ -blocking action and does not af-

fect cardiac conduction. The negative inotropic effect of amiodarone is disadvantageous, particularly when amiodarone is administered rapidly to a failing heart<sup>[8]</sup>.

Regarding the pharmacokinetics of nifekalant, only the unchanged form is active. It has a prompt onset of action, its half-life is relatively short (1.5-2.1 h) and its volume of distribution is 0.14 L/kg. The urinary excretion ratio for the unchanged form is approximately 30%. The remaining nifekalant undergoes glucuronate conjugation in the liver which may be influenced by the impaired hemodynamics<sup>[9]</sup>.

The major adverse effect of nifekalant is QT interval prolongation and occurrence of Torsades de pointes (TdP) owing to an increase in transmural dispersion of repolarization<sup>[10]</sup>.

## NIFEKALANT IN ACS PATIENTS

Life-threatening ventricular tachyarrhythmias such as VT or VF are likely to develop during the acute phase of ACS, and the occurrence of these arrhythmias has important effects on the prognosis of these patients<sup>[11]</sup>.

Nifekalant may be useful for ischemia-induced VT/VF because it inhibits ATP-sensitive potassium channels under ischemic and hypoxic conditions<sup>[6,12]</sup>. Ohashi *et al*<sup>[13]</sup> evaluated the VT/VF-controlling effect of continuous intravenous infusion of nifekalant in 16 ACS patients with refractory VT/VF and 14 patients with chronic structural heart disease and refractory VT/VF. VT/VF was considered refractory when it appeared in patients pretreated with oral amiodarone or sotalol or when VT/VF did not disappear after intravenous administration of class I a and I b drugs, or was refractory to shock. The mean dose level of nifekalant was  $0.19 \pm 0.14$  mg/kg body weight per hour. Treatment was successful in controlling VT/VF in 12 of the 16 patients (75%) with ACS, and 9 of the 14 patients with chronic structural heart disease. None of these patients experienced worsening of their hemodynamic status. The incidence of TdP after administration of nifekalant occurred in 5 of the 30 patients (17%), but it disappeared soon after nifekalant administration was discontinued, without any additional treatment<sup>[13]</sup>. The high incidence of TdP should not be attributed only to the increase in transmural dispersion of repolarization caused by nifekalant, but also to the fact that patients were pretreated with other anti-arrhythmic drugs that enhance QT prolongation<sup>[14]</sup>.

Another study included 41 ACS patients who presented with sustained VT/VF (refractory to shock) that was producing circulatory failure in the patients. Nineteen of these patients failed to respond to a bolus dose of 1.0 mg/kg followed by a continuous intravenous infusion of 1.0-2.0 mg/kg per hour of lidocaine prior to administration of nifekalant. Nifekalant was given first as an intravenous bolus injection (0.2 mg/kg) and then as a continuous intravenous infusion at a relatively low dose level (0.2 mg/kg per hour) to all patients. Sustained VT/VF was successfully inhibited in 34 patients (83%). In



subgroup analysis, nifekalant achieved VT/VF inhibition in 79% of patients who received lidocaine and in 86% of patients who received only nifekalant. There were no significant changes in systolic blood pressure or heart rate following nifekalant therapy and TdP developed in only 1 patient<sup>[15]</sup>.

Survival until hospital discharge was significantly higher when nifekalant was administered in 30 patients with ischemic heart disease and VT/VF resistant to first shock. The control group consisted of 33 patients with ischemic heart disease and VT/VF resistant to first shock. The rates of death within 48 h and the rates of cardiac death during hospitalization were significantly lower in the nifekalant group than in the control group (7% *vs* 27% and 40% *vs* 67%, respectively). When a multivariate analysis of all 63 patients was performed, nifekalant administration was a factor that significantly improved mortality rates<sup>[16]</sup>.

When lidocaine and/or procainamide were unable to control ventricular tachyarrhythmias developing 48-72 h following acute myocardial infarction in patients with single vessel disease for which percutaneous transluminal coronary angioplasty (PTCA) was performed, nifekalant was administered. All patients had severely depressed left ventricular function. Nifekalant was administered in lower doses than usually used (loading dose of 0.05-0.15 mg/kg and a maintenance dose of 0.05-0.20 mg/kg per hour) but effectively suppressed tachyarrhythmias in all patients<sup>[17]</sup>.

A very interesting case report was that of a 47-year-old man who presented ST segment elevation in leads II, III and lead aVF after being resuscitated from cardiac arrest. Sustained VT appeared immediately after PTCA. Since lidocaine failed to prevent the recurrent VT after electrical cardioversion, a loading dose (0.3 mg/kg every 5 min) followed by maintenance dose (0.4 mg/kg per hour) of nifekalant was administered. Just after the loading injection of nifekalant, the next electrical cardioversion successfully defibrillated the sustained VT which was never again recorded in the ECG monitor in the catheter laboratory<sup>[18]</sup>.

## NIFEKALANT AND PERI-OPERATIVE VENTRICULAR TACHYARRHYTHMIAS

Ventricular tachyarrhythmias are potentially fatal or serious complications occurring during or after cardiac surgery. Usually they are treated with class I antiarrhythmic agents, but these drugs often induce heart failure due to their negative inotropic effect. As nifekalant prolongs the refractory period without having a negative inotropic effect, researchers hypothesized that it would be safer to administer nifekalant in such patients.

In fact, when 5 patients with peri-operative VT and 2 patients with peri-operative VF were treated with nifekalant, the recurrence of these arrhythmias was inhibited in 3 of the 5 cases with VT and in both cases with VF. None of the patients exhibited changes in heart rate, cardiac output or QTc interval and no TdP was observed<sup>[19]</sup>.

Intravenous administration of nifekalant in a dose of 0.3 mg/kg, was also effective against peri-operative VT in two patients with impaired left ventricular function (left ventricular ejection fraction: 26.9% and 16%, respectively)<sup>[20]</sup>.

Furthermore, in 2 patients with pre-operatively decreased cardiac function due to old myocardial infarction, who presented with sustained VT/VF after coronary artery bypass grafting, nifekalant ceased the life-threatening arrhythmias without producing hypotension. Previous infusion of lidocaine was totally ineffective in controlling the arrhythmias<sup>[21]</sup>.

Moreover, in a 52-year-old male with ischemic cardiomyopathy and severe ventricular dysfunction who presented with incessant VT early after he underwent coronary artery bypass grafting and left ventricular reconstruction, nifekalant at a loading dose (0.3 mg/kg every 5 min), followed by an intravenous infusion (0.4 mg/kg per hour), controlled the arrhythmia<sup>[22]</sup>.

Nifekalant completely suppressed VT and ventricular premature contractions in a patient with 3-vessel coronary artery disease and left ventricular aneurysm who underwent coronary artery bypass grafting combined with the Dor approach. Class I b antiarrhythmics, like lidocaine and mexiletine, were unable to control VT<sup>[23]</sup>.

## NIFEKALANT IN CARDIOPULMONARY RESUSCITATION

Cardiac arrest patients, both in- and out-of-hospital, have a poor prognosis for survival. When a rhythm check reveals VT or VF, prompt electrical defibrillation is most effective for terminating these arrhythmias during cardiopulmonary resuscitation. If life-threatening VT or VF persists despite repeated defibrillation attempts, an additional antiarrhythmic drug is required.

The "2010 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care" of the American Heart Association and the International Liaison Committee on Resuscitation, recommend antiarrhythmic drugs such as amiodarone and lidocaine as "acceptable" and "probably helpful" in the treatment of VT/VF that persists after three or more external defibrillation shocks<sup>[1,24]</sup>.

Researchers in Japan performed a lot of studies in order to compare nifekalant with lidocaine and amiodarone in cardiac arrest victims with persistent VT/VF (Table 1).

In a study that involved 32 out-of-hospital cardiac arrest victims with refractory VT/VF, 11 patients were treated with nifekalant 0.15-0.3 mg/kg followed by intravenous infusion of 0.3-0.4 mg/kg per hour as antiarrhythmic therapy. VT/VF was considered refractory when it appeared in patients pretreated with high dose epinephrine infusion, a bolus dose of lidocaine (1-2 mg/kg) and was refractory to direct current shocks. The remaining 21 patients were treated with one more dose of lidocaine (1-2 mg/kg). Sinus rhythm was restored in 9 patients (82%) treated with nifekalant and only 4 patients (19%) treated with lidocaine. QT interval was not prolonged

**Table 1 Efficacy of antiarrhythmic drugs in cardiac arrest victims with persistent ventricular tachycardia/fibrillation**

| First author                          | Type of study   | n   | Drug used   | Termination of arrhythmia                          | Other complications  | TdP         | Survival  |
|---------------------------------------|---|-----|---|--|--|-------------|---|
| Human studies                         |   |     |   |  |  |             |   |
| Amino <i>et al</i> <sup>[25]</sup>    | Out of hospital cardiac arrest with refractory VT/VF to epinephrine and lidocaine | 32  | 11 nifekalant<br>21 lidocaine   | 9 (82%)<br>4 (19%)                                 |  | 0<br>0      | 2 (18%)<br>0  |
| Yoshioka <i>et al</i> <sup>[26]</sup> | Out of hospital cardiac arrest with refractory VT/VF to epinephrine and lidocaine | 36  | 12 nifekalant<br><br>24 lidocaine and magnesium and procainamide if necessary | 9 (75%)<br><br>4 (17%)                             | 4 sinus suppression (sinus bradycardia and sinus pause)              | 0           | 2 (17%) (24 h)  |
|                                       | In hospital cardiac arrest with refractory VT/VF to epinephrine and lidocaine     | 29  | 9 nifekalant<br><br>20 lidocaine and magnesium and procainamide if necessary  | 8 (89%)<br><br>15 (75%)                            | 0 sinus suppression (sinus bradycardia and sinus pause)              | 1           | 4 (44%) (24 h)  |
| Tahara <i>et al</i> <sup>[27]</sup>   | Out of hospital cardiac arrest with refractory VF to epinephrine                  | 120 | 55 nifekalant<br><br>65 lidocaine   |  |  | 0<br>0      | 37 (67%) (hospital admission)<br>29 (53%) (24 h)<br>24 (37%) (hospital admission)<br>20 (31%) (24 h)                                |
| Igarashi <i>et al</i> <sup>[28]</sup> | Out of hospital cardiac arrest (VF)   | 22  | 8 nifekalant<br>14 lidocaine  | 5 (61.5%)<br>2 (14.3%)                             |  |             |   |
| Yasuda <i>et al</i> <sup>[29]</sup>   | Out of hospital cardiac arrest with refractory VT/VF to epinephrine               | 14  | 14 nifekalant   | 12 (86%)   |  | 1           | 11 (79%) (hospital admission)   |
| Shiga <i>et al</i> <sup>[30]</sup>    | In hospital cardiac arrest with refractory VT/VF                                  | 55  | 27 nifekalant<br><br>28 lidocaine   | 22 (81%)<br><br>15 (54%)                           | 0 Asystole<br>2 PEA<br>1 QT>0.55<br>7 Asystole<br>1 PEA<br>0 QT>0.55 | 0<br>0      | 13 (48%) (1-mo survival)<br>12 (44%) (survival to discharge)<br>9 (32%) (1-mo survival)<br>8 (29%) (survival to discharge)          |
| Amino <i>et al</i> <sup>[31]</sup>    | Out of hospital cardiac arrest with refractory VF                                 | 30  | 15 nifekalant<br><br>15 amiodarone  | 7 (47%)<br><br>10 (67%)                            | 0 Thyroid dysfunction<br>1 Thyroid dysfunction                       | 0<br>0      | 7 (47%) (hospital admission)<br>4 (27%) (survival to discharge)<br>10 (67%) (hospital admission)<br>8 (53%) (survival to discharge) |
| Animal studies                        |   |     |   |  |  |             |   |
| Ji <i>et al</i> <sup>[32]</sup>       | 4 min of untreated VF   | 36  | 12 saline<br>12 nifekalant<br>12 amiodarone                                   | 7 (58.3%) ROSC<br>12 (100%) ROSC<br>12 (100%) ROSC |  | 0<br>1<br>0 | 2 (17%) (24 h)<br>8 (67%) (24 h)<br>9 (75%) (24 h)  |

VT/VF: Ventricular tachycardia/fibrillation; TdP: Torsades de pointes.

and no TdP was observed. Two patients finally survived in the nifekalant group, while no patient survived in the lidocaine group. Interestingly, most patients in the nifekalant group died from sinus arrest in comparison with the lidocaine group in which most patients died from persistent VT/VF<sup>[25]</sup>.

The authors concluded that one of the reasons for the sinus arrest was the acidotic condition of the patients. Therefore, another study investigated the differences in the effect of nifekalant in out-of-hospital cardiac arrest patients with acidosis ( $n = 36$ ) and in-hospital cardiac arrest patients without acidosis ( $n = 29$ ). According to the

protocol patients with persistent or recurrent VT/VF after administration of epinephrine (1 mg iv), lidocaine (1 mg/kg iv) and direct current defibrillation attempts were divided in two groups: a lidocaine group, in which additional lidocaine up to 3 mg/kg plus magnesium sulfate and procainamide were administered if necessary; and a nifekalant group in which 0.15 mg/kg of nifekalant was slowly injected in combination with direct current shocks. Additional nifekalant was administered for persistent or recurrent VT/VF as needed. Sinus rhythm was restored in 43% (19/44) of the lidocaine group and 81% (17/21) of the nifekalant group. The successful defibril-

lation rate of out-of-hospital cardiac arrest patients was significantly lower than that of in-hospital cardiac arrest patients ( $P < 0.05$ ) in the lidocaine group. On the other hand, in the nifekalant group, the successful defibrillation rate was more than 75% in both out-of-hospital and in-hospital cardiac arrest patients. This means that the VT/VF-controlling effect of nifekalant was maintained even with acidosis. However, sinus bradycardia in out-of-hospital cardiac arrest patients and TdP in in-hospital cardiac arrest patients were occasionally observed<sup>[26]</sup>.

A bigger study which included 120 out-of-hospital cardiac arrest victims with VF persistent to shocks from an external defibrillator and intravenous epinephrine, found that patients treated with nifekalant had significantly higher rates of survival to hospital admission. They also had a significantly higher 24 h survival<sup>[27]</sup>.

Nifekalant's efficacy was also studied in 8 out-of-hospital cardiac arrest victims who presented to the hospital with VF. Sinus rhythm returned in 5 of 8 patients in comparison with only 2 out of 14 patients treated with lidocaine (control group) ( $P < 0.05$ )<sup>[28]</sup>.

A recent multicenter study enrolled 14 patients with out-of-hospital VF refractory to 3 or more precordial shocks and intravenous epinephrine. Nifekalant was intravenously administered at a dose of 0.15-0.30 mg/kg body weight and then an additional shock was delivered. If VF persisted, an additional dose of nifekalant was administered. The rate of return of spontaneous circulation was 86% and the rate of survival to hospital admission was 79%. Only one patient developed TdP<sup>[29]</sup>.

When 55 patients with in-hospital VT/VF resistant to at least two defibrillation attempts were treated with either lidocaine or nifekalant, nifekalant was more effective in terminating the arrhythmias. Half of the patients treated with nifekalant showed termination of VT/VF after intravenous infusion alone. Patients with nifekalant were more likely to achieve return of spontaneous circulation but no difference was observed in 1-mo survival or survival to hospital discharge between the two groups. No Tdp was observed<sup>[30]</sup>.

The only human study to compare nifekalant with amiodarone, in 30 patients with first defibrillation failure or VF recurrence, treated half with amiodarone and the rest with nifekalant. Defibrillation success was achieved in 67% of patients treated with amiodarone and 47% of patients treated with nifekalant. The hospital discharge survival rate was 53% in the amiodarone and 27% in the nifekalant group ( $P = 0.06$ ). Compared to the amiodarone group, patients treated with nifekalant achieved faster defibrillation success. This may be the reason that all 4 survivors in the nifekalant group could take up normal daily life, in comparison with only 2 patients from the 11 survivors in the amiodarone group<sup>[31]</sup>.

These results were further supported by a porcine model of VF treated with either amiodarone or nifekalant. Restoration of spontaneous circulation and 24 h survival rate were comparable for nifekalant and amiodarone<sup>[32]</sup>.

A very interesting study by Amino *et al.*<sup>[33]</sup> demonstrated that the combination of intravenous nifekalant and left stellate ganglion block can be useful for patients with VT/VF resistant to lidocaine and nifekalant. In fact sinus rhythm was restored in 7 out of 11 patients refractory to lidocaine and nifekalant VT/VF when left stellate ganglion block was performed.

## NIFEKALANT IN PATIENTS WITH IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

Electrical storm defined as 3 shocks per day is reported in 10%-30% of patients with an implantable cardioverter-defibrillator (ICD)<sup>[34]</sup>. Recurrent episodes of VF are associated with intracellular calcium overload<sup>[35]</sup> which results in progressive left ventricular dysfunction<sup>[36]</sup> and re-initiation of VF<sup>[35]</sup>. In addition, multiple shocks from ICD increase cardiac troponin levels and thus lead to myocardial injury<sup>[37,38]</sup>.

When 10 patients with a mean number of  $18 \pm 12$  ICD discharges/h were treated with a combination of deep sedation (thiamylal or propofol) and  $\beta$ -blockade, the electrical storm was treated in 4 patients while the remaining 6 patients were stabilized after intravenous administration of nifekalant. In 1 of these 6 patients, VT ceased during the administration of the loading dose of nifekalant and did not re-occur. No hemodynamic deterioration was evident during the administration of nifekalant in these 6 patients although 4 of them had left ventricular ejection fraction  $< 0.40$ <sup>[39]</sup>.

## COMPARISON OF NIFEKALANT WITH OTHER ANTIARRHYTHMIC DRUGS

A study that compared the effects of nifekalant to sotalol in humans showed that both drugs had similar effects on inducible ventricular tachyarrhythmias. The comparison was made with programmed electrical stimulation, in 14 patients with sustained ventricular tachyarrhythmia, after nifekalant and after sotalol administration. The response of inducible ventricular tachyarrhythmia to nifekalant could predict the clinical efficacy of sotalol. In fact, in 4 out of 5 patients whose ventricular tachyarrhythmia became non-inducible by nifekalant, subsequent treatment with sotalol also suppressed the inducible tachyarrhythmias. On the other hand, in all of the 9 patients not responding to nifekalant, tachyarrhythmias remained inducible during sotalol treatment<sup>[40]</sup>.

A comparison between nifekalant and procainamide was performed by Igawa *et al.*<sup>[41]</sup> in 30 patients with inducible sustained VT (programmed ventricular stimulation of up to three extra stimuli). Nifekalant suppressed VT in 4 of 15 patients while procainamide suppressed VT in 6 of 15 patients but the difference was not statistically significant. QT interval was significantly increased in the nifekalant group.

## DISCUSSION

Effective control of recurrent ventricular tachyarrhythmias can be expected with an antiarrhythmic drug that has prompt onset of effect and that does not alter hemodynamic status variables such as blood pressure. It is difficult to use a drug that takes time until the onset of its effect, such as amiodarone, in the emergency care of patients suffering frequent episodes of VT/VF.

Amiodarone is a multiple-channel blocker with complex pharmacologic properties, affecting  $\beta$ -adrenergic receptors, calcium channels, sodium channels, and potassium channels. A lot of patients with ACS as well as cardiac arrest victims with refractory to direct current shock tachyarrhythmias, are likely to have cardiac dysfunction. Antiarrhythmic drugs with negative inotropic activity can negatively affect the outcome of such patients.

Nifekalant seems to have some important advantages. It does not have negative inotropic effects<sup>[42,43]</sup>, it lowers the defibrillation threshold<sup>[44-46]</sup> and even if adverse reactions develop, they are transient because nifekalant has a short half-life<sup>[47]</sup>. It is clearly demonstrated that nifekalant is also effective against peri-operative ventricular tachyarrhythmias, especially in patients with impaired left ventricular function.

Of course the reviewed articles had some limitations that should be kept in mind. For example, in Tahara's paper<sup>[27]</sup>, the lidocaine group was a historical control. Shiga's paper<sup>[30]</sup> was a prospective multicenter study, but was not randomized and most of the studies were retrospective evaluations in single centers. In addition, in many of the studies included in this review, nifekalant was administered in patients with refractory VT/VF, in which other anti-arrhythmic drugs had already been given. Therefore the possibility of possible cumulative effects needs to be ruled out. However, despite these limitations the results of these studies did not differ from the results of a multicenter cohort post-marketing study<sup>[48]</sup> which demonstrated that intravenous administration of nifekalant successfully terminated VT/VF in around 50% of the patients studied and prevented the recurrence of refractory VT/VF in about 60%. Most of the patients for whom nifekalant was effective were refractory to lidocaine or other antiarrhythmic drugs. In patients who failed to terminate VT, even after single administration of nifekalant, their heart rate during VT significantly decreased and of course this property of nifekalant should be considered therapeutically beneficial. It was also demonstrated that nifekalant enhances the defibrillating effect of direct current by lowering the defibrillation threshold of myocardium, in contrast to class I anti-arrhythmic agents which usually increase the defibrillation threshold by blocking sodium channels<sup>[48]</sup>.

Needless to say that nifekalant may exhibit significant side-effects which may limit its use. Because excretion in the urine is an important pathway for elimination of nifekalant, dosages must be adjusted and it must be administered cautiously in patients with renal failure.

Myoishi *et al.*<sup>[9]</sup> demonstrated that in patients with im-

paired left ventricular function and chronic renal failure, half of the dose administered in patients with normal renal function and stable hemodynamics (0.15 mg/kg BW per hour) achieved almost the same therapeutic concentration in the plasma. They also reported that concentration did not change significantly before or after hemodialysis, even under continuous infusion. A possible explanation is that nifekalant binds strongly to protein and it may not be dialyzed.

It has been demonstrated that higher doses of nifekalant have resulted in higher rates of VT termination accompanied by QT dispersion prolongation<sup>[14]</sup>. Occurrence of TdP due to the development of QT interval prolongation should always be taken into account. It is considered important to monitor QT interval frequently during nifekalant infusion with adequate dose adjustment. Another important factor that can induce TdP while administering nifekalant is hypokalemia. It has been proposed that serum levels of potassium concentration should be maintained above 4.0 mmol/L<sup>[14]</sup>.

It is also important to note that nifekalant has a reverse use-dependent blocking action. It causes less action potential prolongation with an increasing heart rate and inversely, action potential prolongation is enhanced with a decreasing heart rate<sup>[47]</sup>. Furthermore, it has been reported that the QTc interval shows diurnal variation that is influenced by autonomic activity and that its variation reaches a peak shortly after awakening, which suggests that the action of nifekalant may be weakened not only by an increased heart rate but also by increased sympathetic activity<sup>[49]</sup>. Needless to say such considerations may support the usefulness of combination therapy using nifekalant and a  $\beta$ -blocker.

As amiodarone has not yet been approved in Japan, to the best of our knowledge, only one animal study and one human study have compared the effects of nifekalant with those of amiodarone in an emergency care setting<sup>[31]</sup>. From these reports, it seems that amiodarone is borderline superior over nifekalant but further studies are needed for extraction of safer conclusions.

On the other hand, lot of studies have demonstrated that nifekalant has a much greater inhibitory effect on ventricular tachyarrhythmias than lidocaine, but again it is difficult for conclusions to be made as nifekalant is not yet available in USA and Europe and no European or American study has ever been conducted.

## CONCLUSION

Nifekalant is a possible effective antiarrhythmic agent for refractory ventricular tachyarrhythmias. Further clinical studies are required before nifekalant is used as a first aid drug in the emergency care setting.

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## Transcatheter aortic valve implantation: Current status and future perspectives

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### Abstract

Although surgical aortic valve replacement is the standard therapy for severe aortic stenosis (AS), about one third of patients are considered inoperable due to unacceptable surgical risk. Under medical treatment alone these patients have a very poor prognosis with a mortality rate of 50% at 2 years. Transcatheter aortic valve implantation (TAVI) has been used in these patients, and has shown robust results in the only randomized clinical trial of severe AS treatment performed so far. In this review, we will focus on the two commercially available systems: Edwards SAPIEN valve and CoreValve Revalving system. Both systems have demonstrated success rates of over 90% with 30-d mortality rates below 10% in the most recent transfemoral TAVI studies. Moreover, long-term studies have shown that the valves have good haemodynamic performance. Some studies are currently exploring the non-inferiority of TAVI procedures vs conventional surgery in high-risk patients, and long-term clinical results of the percutaneous valves. In this article we review the current status of TAVI including selection of patients, a comparison of available prostheses, results and complications of the procedure, clinical outcomes, and future perspectives.

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### INTRODUCTION

Degenerative aortic stenosis (AS) is the most frequent acquired heart valve disease, with a prevalence of 4.6% in adults aged 75 years or more, and is the most common indication for valve surgery<sup>[1-3]</sup>. Surgical aortic valve replacement (SVR) is the current treatment of choice in symptomatic AS. There is a huge worldwide experience with SVR, which has resulted in improved survival in historical comparisons with a low rate of mortality in low-risk patients<sup>[4-6]</sup>. However, about one third of patients with AS referred for surgery are rejected, mainly because of their high surgical risk<sup>[7,8]</sup>.

Transcatheter aortic valve implantation (TAVI) was developed as an alternative for those patients, and consists of a conventional aortic valvuloplasty followed by

the implantation of a biological prosthetic valve stitched to a metallic stent and crimped on a catheter. The implantation is performed inside the native valve, rejecting the native leaflets between the stent and the walls, instead of the surgical technique of replacing the diseased valve with a prosthetic valve, with the advantage of not requiring open-heart surgery.

Since the first-in-man TAVI in 2002, this technology has grown to currently become a true alternative to surgery in patients with severe AS rejected for surgery<sup>[9,10]</sup>. Moreover, transfemoral TAVI has become the first therapy for AS to demonstrate improved survival and non-inferiority compared to surgery in a randomized trial<sup>[11,12]</sup>. This trial randomized patients with unacceptable surgical risk to medical treatment including valvuloplasty *vs* transfemoral TAVI, and showed an absolute reduction in mortality of 20% at 1 year. The other arm of the trial showed non-inferiority when compared to SVR<sup>[12]</sup>. It is noteworthy that TAVI technology was developed on an extremely high-risk population, and this should be taken into account when analyzing the initial outcomes of TAVI procedures.

In this review, we will focus on TAVI procedures using the two commercially available systems: Edwards SAPIEN (ES) and Medtronic CoreValve ReValving System (CS). We will review the current status of TAVI procedures: selection of candidates, a comparison of available prostheses, results and complications of the procedure, clinical outcomes, and future perspectives.

## CURRENT TRANSCATHETER VALVES

There are two commercially available valves for transcatheter implantation (Figures 1 and 2). The main characteristics and differences between these valves are shown in Table 1. The Edwards-SAPIEN (Edwards Lifesciences, Irvine, USA) system uses a bovine pericardial valve sutured to a metallic stent frame which is balloon-expandable. From the early Cribier-Edwards model this device evolved to the THV valve and finally, to the current XT model, which is delivered in the new, low profile, NovaFlex catheter system. Conversely, the CoreValve ReValving system (Medtronic Inc., Minneapolis, USA) uses a porcine pericardial valve in a larger and self-expandable nitinol frame which covers both the left ventricular outflow tract (LVOT) and the aortic root. Currently, the third generation CS system is commercially available. Prostheses sizes are different: ES uses 23 mm valves for aortic annulus (measured from hinge to hinge of the leaflets) of 18-21.5 mm and 26 mm from 21.5-25 mm, whereas CS uses 26 mm valves for 20-23 mm annulus and 29 mm valves for annulus of 24-27 mm. A larger (29 mm) ES valve is expected for the transapical approach in 2011, and the release of new CS 23 mm and ES 20 mm sizes is anticipated.

Both systems utilize the arterial retrograde access to the aortic root and require a conventional aortic valvuloplasty prior to final implantation of the valve<sup>[13]</sup>. Initially,

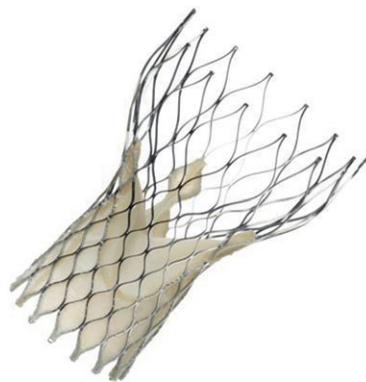


Figure 1 Corevalve Revalving System.

ES catheters were bigger (22-24 French), but currently both systems have comparable 18-19 F transfemoral delivery systems. For patients with inadequate diameters in the femoral arteries, CS has developed the surgical subclavian approach, and ES the transapical access. There are also isolated case reports of implants through a surgical approach using the ascending aorta or the retroperitoneal iliac artery as entry points<sup>[14]</sup>. Recommended medical treatment after implantation is aspirin indefinitely and clopidogrel for 1 to 3 mo **after the procedure**.

## PATIENT SELECTION

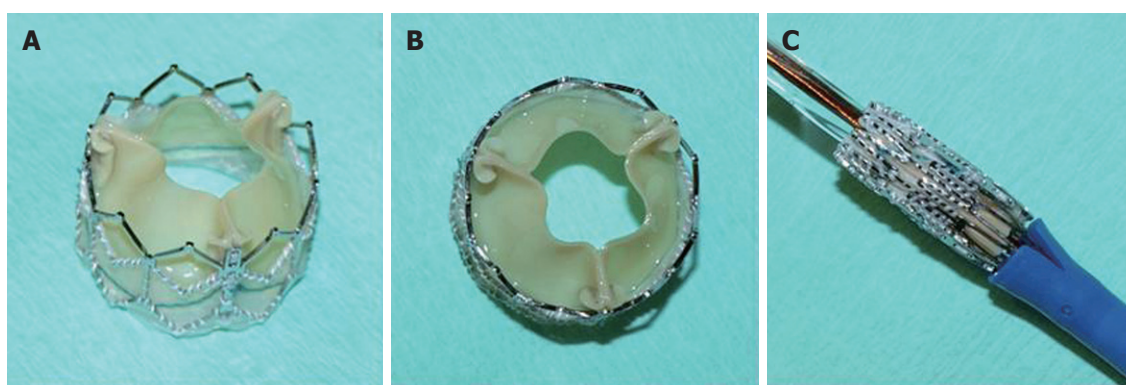
The selection of candidates for TAVI is crucial for the success of the TAVI programme. A team of clinical cardiologists, interventional cardiologists, heart surgeons and anaesthesiologists is needed. The multidisciplinary approach to these patients is essential to the success of the programme<sup>[15]</sup>. Patients should have severe tri-leaflet native-valve AS with an area  $< 1 \text{ cm}^2$  or  $< 0.6 \text{ cm}^2/\text{m}^2$ . Unsuitability for surgery is established by a predicted mortality in EuroSCORE  $> 20\%$  or STS Score  $> 10\%$ , or other conditions that preclude conventional SVR such as porcelain aorta, frailty, advanced liver or renal disease, or previous patent left internal mammary artery grafts<sup>[16,17]</sup>. The decision on each patient's surgical risk should be individualized, but basically, any contraindication for sternotomy, cardiopulmonary bypass, cardioplegic cardiac arrest or aortic clamping may be indications for TAVI.

The patient assessment protocol used at our institution includes three main tests. (1) **Catheterization:** Coronary angiography is performed to exclude significant coronary disease and aortography and femoral angiography are also performed<sup>[18]</sup>. If significant coronary lesions are present, they should be revascularized percutaneously and the TAVI procedure is usually deferred for  $\geq 1$  mo; (2) **Echocardiography:** The aortic valve annulus diameter measured by echocardiography should fall into the available prosthesis size range (Table 1). Transesophageal echocardiography is more accurate in sizing the aortic annulus than transthoracic echocardiography; and (3) **Computed tomography:** vascular computerized tomography with three-dimensional reconstructions of the infrarenal



**Table 1** Comparative characteristics of the Edwards SAPIEN and Corevalve ReValving System valves

| Features                                | Edwards SAPIEN XT     | Medtronic core valve               |
|---|-----------------------|------------------------------------|
| Manufacturer                            | Edwards Lifesciences  | Medtronic                          |
| Stent                                   | Cobalt Chromium       | Nitinol                            |
| Valve leaflets                          | Bovine pericardium    | Porcine pericardium                |
| Implantation                            | Balloon-expandable    | Self-expandable                    |
| Repositionable                          | No                    | Partially (prior to release)       |
| Retrievable                             | No                    | No                                 |
| Fixation                                | Aortic annulus        | Aortic annulus and ascending aorta |
| Available diameters (mm)                | 23, 26                | 26, 29                             |
| Recommended annulus diameter (mm)       | 18-25                 | 20-27                              |
| Delivery system diameter                | 18F (23) and 19F (26) | 18 F                               |
| Minimum required arterial diameter (mm) | 6                     | 6                                  |
| Alternative to transfemoral             | Transapical           | Trans-subclavian                   |
| Permanent pacemaker implantation        | < 10%                 | 25%-35%                            |

**Figure 2** Edwards SAPIEN XT valve, 23 mm. A and B: Two views of the valve before implantation, in the final, deployed position; C: View of the valve crimped on the delivery catheter (18F).

aorta to the femoral arteries is performed, and those patients with diameters < 6 mm, or excessive calcification and/or tortuosity are excluded from the trans-femoral approach. Other authors also propose computerized tomography of the aortic root and the whole aorta, but the usefulness of this test is not well-established<sup>[19]</sup>. Exclusion criteria for TAVI, other than inadequate femoral access or apical thrombus for the transapical approach, are recent myocardial infarction, congenital bicuspid valve (although there are some reports of successful cases<sup>[20]</sup>) and very severe impairment in left ventricular ejection fraction (LVEF ≤ 20%).

## TRANSFEMORAL PROCEDURE

TAVI is performed in a hybrid or interventional cardiology room in a sterile environment, and under general anaesthesia (although some groups perform TAVI under sedation without general anaesthesia and intubation). Fluoroscopic, angiographic and transesophageal echocardiographic monitoring is needed. The retrograde, transarterial route is currently preferred over the initial transvenous and transeptal antegrade approach<sup>[13]</sup>. Arterial access can be accomplished by surgical cutdown of the femoral artery, or now typically by true percutaneous puncture. Further arterial access is needed for blood

pressure monitoring and aortic root angiography. A transvenous pacemaker is placed in the right ventricle to perform rapid (around 200 bpm) pacing, needed to avoid prosthesis displacement during implantation. A conventional balloon valvuloplasty is performed, and immediately afterwards the prosthesis is released (inflating the balloon in the ES system or withdrawing the sheath in the CS). Angiography, echocardiography and/or direct gradient measuring verify the success of the implant. All catheters are removed and the access site is closed surgically or with percutaneous suture closure devices. The pacemaker is left in position because delayed auriculoventricular (AV) blocks have been described. In our centre, with the ES valve, the pacemaker is removed after monitoring for 24 h when no new bundle branch or AV block has occurred. CS usually needs a longer monitoring time.

## NON-FEMORAL APPROACHES

The most common is the transapical approach, designed initially for the ES valve<sup>[21]</sup>, although the first-in-man transapical implantation of a CS valve has also been reported<sup>[22]</sup>. The left ventricular apex is directly punctured through a left lateral mini-thoracotomy, a high-support guidewire is placed across the aortic valve, and a 26 F catheter is inserted in the left ventricle, after which the

procedure is similar to the transfemoral access but with a different delivery catheter<sup>[22]</sup>. The subclavian access for CS consists of a direct surgical dissection of the subclavian artery and insertion of the catheter, after which the procedure follows the transfemoral approach<sup>[23]</sup>. The subclavian approach is still considered off-label, similar to the direct transaortic surgical approach. Following reduction in the profile of the catheters, non-femoral access is needed in around 30% of patients. One advantage of these approaches is more direct handling of the catheter due to the shorter distance to the target, however, as it is more invasive, the results are still slightly poorer at medium-term follow-up. However, it must be taken into account that patients referred for transapical access are systematically described as a higher risk compared to the transfemoral population across studies.

## COMPLICATIONS OF THE PROCEDURE

### Valve malapposition and/or embolization

Valve malapposition or embolization rates were  $\leq 2\%$  in the most recent studies. The ES valve is not repositionable once expanded, whereas the CS is partially repositionable as some adjustment of the final position is possible when only the distal half of the prosthesis is released. These figures will probably remain stable until a fully retrievable valve is developed. Prevention of this complication is crucial and fine measurements of the aortic annulus, as well as the calcifications, which are frequently asymmetrical, of the aortic root are necessary<sup>[24,25]</sup>. On the other hand, the operator has to be extremely cautious during positioning and implantation of the valve.

### Aortic regurgitation

Aortic regurgitation is frequently found after the procedure. The mechanism of aortic regurgitation is usually due to the presence of small paravalvular leaks because of incomplete apposition of the valve, due to severe nodular calcifications. In most cases, the grade is trace or mild, with minimal clinical consequences. Only 5% of procedures result in severe aortic regurgitation, which may be treated by a second, valve-in-valve procedure or with conventional surgery. With the ES system, aortic regurgitation is frequently improved with a second, higher volume, balloon inflation within the valve. Deaths due to severe aortic regurgitation (probably associated with significant valve malapposition) were more frequent in CS than in ES (10% *vs* 0%,  $P = 0.03$ ) in a recent pooled analysis<sup>[26]</sup>. In follow-up studies, no increase in the degree of aortic regurgitation was found, remaining stable or improving after the procedure.

### Conversion to open heart surgery

The rate of conversion to open heart surgery or the need for haemodynamic support is also  $\leq 2\%$  across published data. Currently it is not recommended that these procedures be performed in centres without cardiac surgery backup. Both complications are predictors of higher

mortality across published series<sup>[24,27]</sup>.

### Access site complications

Access site complications are the most frequent complications in transfemoral procedures. These complications reach 40% in some series, with a great variety of severity, from small haematomas to severe bleedings, tears or even avulsions of the femoral vessels. While most of the data comes from series with larger delivery systems (RetroFlex 22-24 F for ES), the impact of the reduction in the gauge of delivery catheters is assumed but still needs to be determined<sup>[28]</sup>. The ES valve has higher reported rates of these complications than the CS, and are linked to higher mortality<sup>[26]</sup>, however, most of the data on ES come from the early, larger systems. Currently both systems use comparable sizes of catheters (Table 1), and data from the last generation of devices concerning this issue are awaited. Careful selection of patients, with comprehensive analysis of the femoral and iliac anatomy, and identification of size, calcification and tortuosity decrease these complications. Patients with inappropriate femoral anatomy should be directed towards transapical or subclavian approaches. It is advisable to have experience in peripheral interventions and/or to have the backup of vascular surgeons to help solve incidental problems with the access site. In the Placement of AoRTic TraNscathetER Valve Trial (PARTNER) trial (ES valve randomized *vs* SVR), there were more major bleedings (19.5% *vs* 9.3%,  $P < 0.01$ ) but fewer major vascular site complications (3.2% *vs* 11%,  $P < 0.01$  in the SVR group at 1 mo<sup>[12]</sup>.

### Stroke

Cerebrovascular event rates are reported to be below 5% in most series; these figures are fairly low bearing in mind the advanced age and high prevalence of atherosclerosis in the TAVI population (Stroke rates in SVR are usually reported to be over 5% in the elderly). Studies with magnetic resonance before and after a TAVI procedure showed that subclinical cerebrovascular ischemia occurs frequently (73%-84%) during TAVI<sup>[29]</sup>. These results have also been reported with SVR, at a rate of 40%-50% and are mostly clinically silent, with unknown long-term consequences<sup>[30]</sup>. Some studies have suggested that the transapical approach, avoiding manipulation of catheters along the aorta, is related to a lower rate of stroke compared to transfemoral access, but results are inconclusive<sup>[31]</sup>. An embolic deflection device deployed through radial access has been tested in humans as a protection device<sup>[32]</sup>. In the recently presented PARTNER trial, TAVI was associated with a higher rate of the composite outcome "all stroke or transient ischemic attack" (5.5% *vs* 2.4%,  $P = 0.04$ ) compared with SVR at 1 mo; with no differences in the individual components of the outcome<sup>[12]</sup>.

### Myocardial infarction and coronary obstruction

The incidence of myocardial infarction during TAVI is highly variable, ranging from 0.2%-18%, however, this information is biased by the absence of a common defi-



**Table 2** Clinical outcomes across the most recent published studies

|  | Year published | Patients         | Valve | Access       | Procedural success (%) | 30-d mortality (%) | 1-yr mortality (%) |
|--|----------------|------------------|-------|--------------|------------------------|--------------------|--------------------|
| PARTNER EU <sup>[55]</sup>               | 2010           | 61               | ES    | TF           | 91                     | 8.1                | 21.3               |
| SOURCE Registry <sup>[56]</sup>          | 2010           | 463              | ES    | TF           | 95.2                   | 6.3                | -                  |
| PARTNER cohort B <sup>[111]</sup>        | 2010           | 179              | ES    | TF           | -                      | 5                  | 30.7               |
| Rodés-Cabau <i>et al</i> <sup>[24]</sup> | 2010           | 168              | ES    | TF           | 90.5                   | 9.5                | 25                 |
| PARTNER cohort A <sup>[12]</sup>         | 2011           | 244              | ES    | TF           | -                      | 3.3                | 22.2               |
| PARTNER EU <sup>[55]</sup>               | 2010           | 69               | ES    | TA           | 91                     | 18.8               | 51.7               |
| SOURCE Registry <sup>[56]</sup>          | 2010           | 575              | ES    | TA           | 92.7                   | 10.3               | -                  |
| Rodés-Cabau <i>et al</i> <sup>[24]</sup> | 2010           | 177              | ES    | TA           | 96.1                   | 11.3               | 23                 |
| Wong <i>et al</i> <sup>[45]</sup>        | 2010           | 60               | ES    | TA           | 98.3                   | 18.3               | -                  |
| PARTNER cohort A <sup>[12]</sup>         | 2011           | 104              | ES    | TA           | -                      | 3.8                | 29                 |
| Grube <i>et al</i> <sup>[43]</sup>       | 2008           | 102 <sup>2</sup> | CS    | TF           | 91.2                   | 10.8               | -                  |
| Piazza <i>et al</i> <sup>[57]</sup>      | 2008           | 646              | CS    | TF           | 97.2                   | 8                  | -                  |
| Avanzas <i>et al</i> <sup>[58]</sup>     | 2010           | 108              | CS    | 103 TF/5 TS  | 98.1                   | 7.4                | 17.7               |
| Tamburino <i>et al</i> <sup>[27]</sup>   | 2011           | 663              | CS    | 599 TF/64 TS | 98                     | 5.4                | 15                 |

<sup>1</sup>Dr. Wong and Dr. Rodés-Cabau are from the same centre, probably patients overlapped in these two studies; <sup>2</sup>Results referred to the third generation Corevalve ReValving System (CS) device only. ES: Edwards SAPIEN; TF: Transfemoral; TA: Transapical; TS: Trans-subclavian.

nition for myocardial infarction after TAVI. The question of which rise in cardiac markers after a TAVI procedure should be “acceptable” is still unanswered. To ensure a more reliable outcome definition, the reported rates of coronary ostia obstruction are always below 1%. The usual mechanism of the obstruction is not due to jailing of the ostia, but rather displacement of the native aortic valve leaflets, severely calcified and distorted, over the coronary ostia. Manufacturers and independent investigators recommend measuring the distance between the aortic annulus and the coronary ostia, but there are no specific recommendations to prevent this complication<sup>[33]</sup>.

### Acute kidney injury

The reported incidence of acute kidney injury ranges from 12%-28%<sup>[34]</sup>. This complication has been identified as a predictor of mortality in several studies<sup>[27,35]</sup>. The need for haemodialysis after TAVI ranges from 2.5%-7.4%. Acute kidney injury in patients undergoing a TAVI procedure can be due to a combination of several factors: the injection of contrast media needed for angiography, severe hypotension during certain procedures, manipulation of large catheters in atherosclerotic aortas resulting in microembolization of cholesterol crystals, and an important prevalence of chronic kidney disease in this population.

### Need for permanent pacemaker implantation

TAVI is highly associated with new intraventricular conduction abnormalities and the need for permanent pacemaker insertion. The underlying mechanism is trauma over the AV node and the bundle of His generated by the radial forces of the stent<sup>[36]</sup>. The need for a permanent pacemaker is clearly different between the two systems: < 10% with ES *vs* near 30% with CS. The proposed explanation for this is that the CS is longer and is usually situated lower in the LVOT. There is no identified strategy to prevent this complication, but some predictors of the need for permanent pacemaker implantation have been identified, such as small aortic annulus, use of CS over

ES and the development of transient AV block during implantation<sup>[37]</sup>. Interestingly, in the recently reported results from the PARTNER trial with ES valves, no differences in new pacemaker implantations were found (3.8% TAVI *vs* 3.6% SVR at 1 mo,  $P = 0.89$ )<sup>[12]</sup>.

### Cardiac tamponade

This complication is usually related to a perforation in the left ventricle wall due to the guidewire or in the right ventricle due to the temporary pacemaker lead. In a recent study, cardiac tamponade was reported more frequently as a cause of death with the CS valves, probably linked to the higher rate of AV block and longer time with a temporary pacemaker lead after the procedure<sup>[26]</sup>. Rupture of the aortic annulus has been reported but it is a rare complication.

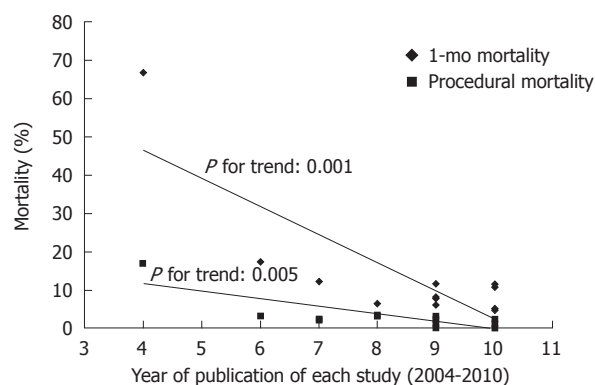
## PATIENT OUTCOMES

Reported procedural success and available mortality rates at 30 d and 1 year are shown in Table 2. We have chosen studies published only in the past 2 years to show the results of the latest generation of valves and after the learning curve. They are mostly registries, and most have a relatively selected population. Globally, the success rate is above 90%, whereas mortality rate at 30 d is below 10% for transfemoral and around 15% for transapical. Mortality rates at 1 year are still highly variable (Table 2). A recent German registry including 697 patients in a real-world population, mixing CS and ES valves (84% CS) and 96% by femoral access resulted in a mortality rate of 12.4% at 30 d<sup>[38]</sup>.

The PARTNER trial is the first randomized trial of TAVI. The remarkable results of cohort B (transfemoral TAVI with ES valve *vs* medical treatment including valvuloplasty in patients rejected from surgery) showed an absolute reduction in mortality at 1 year of 20% (50.7% in medical treatment *vs* 30.7% in TAVI group,  $P < 0.05$ )<sup>[11]</sup>. In cohort A, 699 patients with high surgical risk were as-

**Table 3** Future valves under development

| Name          | Manufactured by                   | Country | Advantages and published experience  |
|---------------|-----------------------------------|---------|--|
| AorTx™        | Hansen Medical                    | USA     | Fully retrievable  |
| Direct Flow™  | Direct Flow Medical Inc           | USA     | Fully retrievable, inflatable fabric cuff around the valve that seals the aortic annulus. 6 patients implanted <sup>[59]</sup>             |
| Engager™      | Medtronic                         | USA     | Specifically designed for transapical access. Easy positioning, better fixation (hooks). 30 implants in tricuspid position <sup>[53]</sup> |
| HLT™          | Heart Leaflet Technologies        | USA     | "Flow-through" configuration that does not create obstruction. No need for rapid pacing  |
| JenaValve™    | JenaValve                         | Germany | Repositionable, clipping of the native leaflets. No need for rapid pacing. First-in-man  |
| Lotus™        | Sadra Medical / Boston Scientific | USA     | Fully repositionable, self-centring, early leaflet function before final release. First-in-man <sup>[60]</sup>                             |
| Paniagua™     | Endoluminal technology Research   | USA     | Low profile catheter. First retrograde implantation in the world <sup>[61]</sup>   |
| St Jude™      | St Jude Medical                   | USA     | Additional binding in the ascending aorta. Early stages. No human implants yet   |
| ValveXchange™ | ValveXchange Inc                  | USA     | Permanent support frame and exchangeable leaflet set. Early stages. No human implants yet  |

**Figure 3** Decrease in 1-mo and procedural mortality observed through the years (from studies published in 2004 to 2010) in patients undergoing transcatheter aortic valve implantation. From Moreno *et al*<sup>[26]</sup>.

sessed for transfemoral access and then randomized 1:1 to transfemoral TAVI *vs* SVR (492 patients) or transapical TAVI *vs* SVR (207 patients). The primary endpoint, non-inferiority of TAVI with ES valve in all-cause mortality at 1 year, was met (24.2% *vs* 26.8%,  $P = 0.001$  for non-inferiority). The transfemoral TAVI subgroup was also non-inferior to SVR. TAVI was associated with more strokes and major vascular complications, whereas SVR had more major bleedings and new onset atrial fibrillation<sup>[12]</sup>.

Left ventricular ejection fraction improves after TAVI in patients with impaired function prior to the procedure<sup>[39]</sup>. Moreover, the increase in LVEF is higher in TAVI patients when compared to SVR patients<sup>[40]</sup>. In addition, left ventricular mass decreased and diastolic dysfunction improved after TAVI<sup>[41]</sup>. Mitral regurgitation, which is usually present in some degree, remains unchanged in most patients (61% in one study), although some may experience a change<sup>[42]</sup>. Severe mitral regurgitation has been identified as a poor prognostic factor and we think that it should be considered as an exclusion criterion for the procedure.

In less than 10 years of the use of this technique we

have seen a remarkable drop in procedure failure and mortality rates. This rapid mastering of the procedure is mainly explained by two factors. One is the development of a new generation of devices with reduction in catheter sizes and better deliverability. Studies comparing the first and last generation of the devices have demonstrated a significant reduction in procedure failure and mortality rates<sup>[43,44]</sup>. The other factor is the training of interventional cardiologists or surgeons who want to start a TAVI programme, which usually involves a course at an experienced centre, followed by surveillance of the first cases by a proctor. This approach has largely contributed to shortening the learning curve and rapidly improving the results of TAVI procedures in naïve centres. Also, the learning curve has contributed to improving the selection of candidates for the procedure.

The importance of the learning curve has been highlighted by some groups, making a comparison between early and late experience, and obtaining a relative reduction in death and complications of 50%-70%<sup>[43,45,46]</sup>. Figure 3 shows the improvement in outcomes from studies published during the last 5 years<sup>[26]</sup>.

Some authors have tried to identify predictors of procedure success. In a two-centre, German experience with 168 patients, good pre-procedure functional status (Karnofsky index) was identified as the only independent predictor of in-hospital survival<sup>[47]</sup>. In a large (663 patients) multicentre Italian series, conversion to open heart surgery, cardiac tamponade, major access site complications, LVEF < 40%, prior balloon valvuloplasty, and diabetes mellitus were independent predictors of mortality at 30 d. In addition, prior stroke, postprocedural paravalvular leak  $\geq 2$ , prior acute pulmonary edema, and chronic kidney disease were independent predictors of mortality between 30 d and 1 year<sup>[27]</sup>. The Canadian experience identified pulmonary hypertension, severe mitral regurgitation and the need for haemodynamic support as 30-d mortality predictors with the ES valve<sup>[24]</sup>. Periprocedural acute kidney injury is also proposed as a 30-d and 1-year predictor of mortality<sup>[35]</sup>.

The long-term durability of these valves has been addressed only in small studies, due to the newness of the technique. Theoretically, and accordingly to the manufacturer's wear test, both CS and ES valves are designed to last  $\geq 10$  years. All published studies agree with their good durability and preserved haemodynamic function with effective orifice areas over  $1.5 \text{ cm}^2$  and no significant change in gradients or new aortic regurgitation at 3 years<sup>[48,49]</sup>.

## OFF-LABEL INDICATIONS

As with other new devices, some experienced centres have tried to explore the outer limits of the current indications for these valves. The "valve-in-valve" procedures were developed to avoid redo cardiac surgery in elderly, high-risk patients with degenerated bioprostheses, usually in the aortic position, with acceptable results<sup>[50]</sup>. It is also a common last-resource technique for unsuccessful TAVI procedures with severe paravalvular leaks<sup>[51]</sup>. Isolated case reports of valve-in-valve procedures of mitral bioprostheses have also been published<sup>[52]</sup>. Another proposed procedure is the valve-in-ring, in which a transcatheter prosthesis is inserted inside a failed annuloplasty. In addition, transcatheter valves have been successfully implanted in tricuspid or pulmonary positions<sup>[53,54]</sup>. Further investigations in this field are warranted.

## FUTURE VALVES AND PERSPECTIVES

Several new valves are in different phases of experimental, clinical, or feasibility investigation. Most of the new models have the self-expanding technology. These will improve delivery of the valve, minimize paravalvular leaks, and allow for reposition or recovery of the implanted valve. Unfortunately, there is still a paucity of information and clinical data for these valves. Table 3 shows the potential advantages and published experience of the valves that are currently under development.

In the next few years we will probably see a drop in the "high risk" threshold of patients selected for TAVI, possibly in direct competition with SVR. With the accumulated experience, risk scores for mortality and morbidity in TAVI procedures will be developed. New valves will probably come onto the market, reducing the costs of the procedure and providing advantages such as simplification of the procedure, widening of the valve size range, reduction in catheters (albeit a balance between catheter gauge and quality of the stent/leaflets will closely follow) and a further fall in complication rates. Off-label indications, such as valve-in-valve procedures and implantation in other valve rings will generate more literature. Cost-effectiveness studies will also clarify the final position of the TAVI procedure in modern cardiology. Results from many ongoing studies like the pivotal trials of CS *vs* SVR (one ongoing in the US and the SURTAVI trial in preparation in Europe), a small study of valve-in-valve in failing aortic bioprostheses with CS (REDO study),

and some post market registries from both systems are eagerly awaited.

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## Ischemia/reperfusion injury and cardioprotective mechanisms: Role of mitochondria and reactive oxygen species

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### Abstract

Reperfusion therapy must be applied as soon as possible to attenuate the ischemic insult of acute myocardial infarction (AMI). However reperfusion is responsible for additional myocardial damage, which likely involves opening of the mitochondrial permeability transition pore (mPTP). In reperfusion injury, mitochondrial damage is a determining factor in causing loss of cardiomyocyte function and viability. Major mechanisms of mitochondrial dysfunction include the long lasting opening of mPTPs and the oxidative stress resulting from formation of reactive oxygen species (ROS). Several signaling cardioprotective pathways are activated by stimuli such as preconditioning and postconditioning, obtained with brief intermittent ischemia or with pharmacological agents. These pathways converge on a common target, the mitochondria, to preserve their function after ischemia/reperfusion. The present review discusses the role of mitochondria in cardioprotection, especially the involvement of adenosine triphosphate-dependent potassium channels, ROS signaling, and the mPTP. Ischemic postconditioning has emerged as a new way to

target the mitochondria, and to drastically reduce lethal reperfusion injury. Several clinical studies using ischemic postconditioning during angioplasty now support its protective effects, and an interesting alternative is pharmacological postconditioning. In fact ischemic postconditioning and the mPTP desensitizer, cyclosporine A, have been shown to induce comparable protection in AMI patients.

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**Key words:** Adenosine triphosphate-dependent potassium channels; Cardioprotection; Ischemia-reperfusion injury; Mitochondrial permeability transition pore; Reactive oxygen species

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### INTRODUCTION

Acute myocardial infarction (AMI) is responsible for the death of millions of persons worldwide each year, with a mortality rate of about 10%, and is the leading cause of chronic heart failure<sup>[1]</sup>. Notwithstanding, marked improvements in the strategy to reduce infarct size and to reduce all manifestations of postischemic injury, with subsequent improvement in prognosis, have been developed in recent years. Although early reperfusion is the

only way to salvage an ischemic organ, during the crucial early moments of reperfusion, significant reversible and irreversible organ damage is initiated, and is referred to as reperfusion injury. Reperfusion injury include arrhythmias, transient mechanical dysfunction of the heart or “myocardial stunning”, microvascular injury and “no-reflow”, as well as inflammatory responses. In reperfusion, cell death can occur due to apoptosis, necrosis, and autophagy<sup>[2-8]</sup>. Given that recent data indicate that the different forms of cell death are probably interrelated<sup>[6,7]</sup>, a better strategy to develop cardioprotective agents is not to define the mode of cell death and its proportion occurring during ischemia/reperfusion, but to identify mediators active in all forms of cell death. In this context, the variation in mitochondrial membrane permeability appears to be one of the major regulators of all forms of cell death.

## REPERFUSION INJURY: CENTRAL ROLE OF MITOCHONDRIA

During normal perfusion mitochondria generate adenosine triphosphate (ATP), consume large amounts of O<sub>2</sub> and contribute to a balanced generation and scavenging of reactive oxygen species (ROS). Mitochondria are also involved in cellular ion homeostasis, including calcium homeostasis.

During ischemia, the lack of O<sub>2</sub> inhibits electron flow, and myocardial ATP utilization becomes inefficient. The proton-translocating F<sub>0</sub>F<sub>1</sub>ATP synthase, which normally produces ATP, switches into reverse mode, i.e. becomes an F<sub>0</sub>F<sub>1</sub>ATPase, and consumes ATP to pump protons from the matrix into the intermembrane space<sup>[9,10]</sup>. In prolonged ischemia, Na<sup>+</sup>/K<sup>+</sup> ATPase is inhibited (because of the drop in ATP levels) and the intracellular acidification (induced by lactate production and the hydrolysis of ATP) activates the Na<sup>+</sup>/H<sup>+</sup> exchanger (NHE), i.e. the cell tries to restore the intracellular pH; the resulting increase in intracellular Na<sup>+</sup> concentration activates the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCE), which lead to Ca<sup>2+</sup> overload. Elevated cytosolic Ca<sup>2+</sup> concentrations may contribute to cellular damage by activation of degrading enzymes such as nucleases, phospholipases and proteases culminating in the destruction of the membrane integrity and leading to cell death if the ischemic period is of sufficient duration<sup>[11,12]</sup>.

At reperfusion, intracellular and mitochondrial events such as Ca<sup>2+</sup> overload, inadequate resynthesis of ATP, loss of membrane phospholipids, low production of nitric oxide (NO) and oxidative stress by ROS contribute to reperfusion injury<sup>[13-16]</sup>. Yet, when an increase in ATP concentration occurs, it paradoxically contributes to reperfusion injury, leading to hyper-contracture of cardiomyocytes, membrane disruption and subsequent band necrosis<sup>[16,17]</sup>. Clearly the recovery of pH, oxidative stress and Ca<sup>2+</sup> overload can induce the abrupt opening of the mitochondrial permeability transition pores (mPTP), a large conductance pore in the inner mitochondrial membrane (IMM), which strongly contributes to cardiomyo-

cyte hyper-contracture, apoptosis and necrosis<sup>[18-22]</sup>.

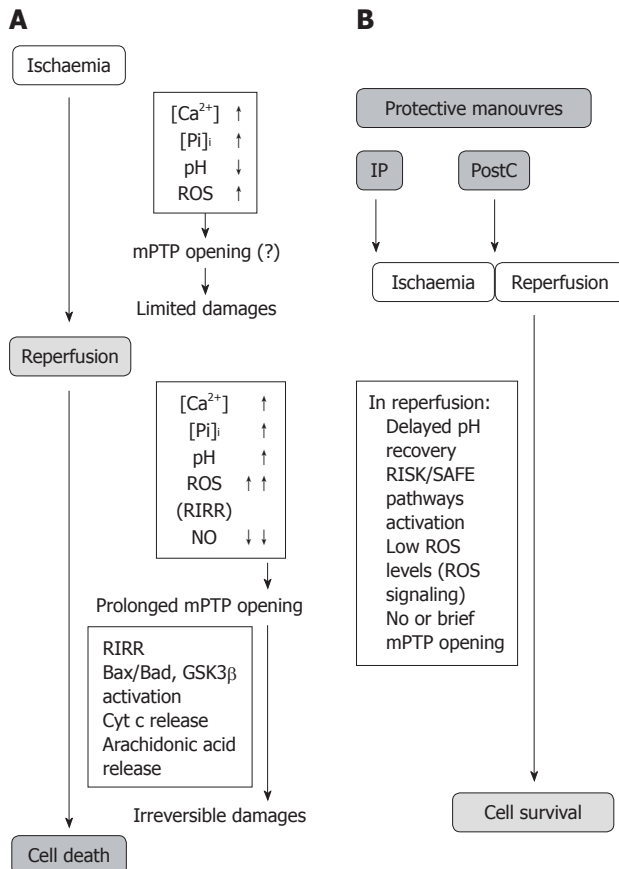
### mPTP

This pore is a high conductance megachannel, which builds up at the contact sites between the mitochondrial outer and inner membranes. When the mPTP is formed, it permits communication between the cytoplasm and mitochondrial matrix<sup>[23]</sup>. The molecular identity of the protein(s) forming this pore is still unknown. It has been suggested that the mPTP is formed by the voltage-dependent anion channel in the outer mitochondrial membrane (OMM), the adenine nucleotide transporter in the IMM, and cyclophilin D (Cyp D) in the matrix of mitochondria. mPTP opening seems to be facilitated by binding of the matrix protein Cyp D to the IMM in a process regulated by both Ca<sup>2+</sup> and inorganic phosphate (Pi)<sup>[19]</sup> (Figure 1). However, even experiments with transgenic mice in each of the putative components of mPTP reached controversial results<sup>[24-31]</sup>.

**mPTP opening:** The oxidative opening of mPTP is central in reperfusion injury (Figure 2A). Many studies have indeed revealed an important contribution of mPTP opening and have correlated cell death with the release of cytochrome c (Cyt c) after Bax and enhanced ROS levels<sup>[22,32-35]</sup>.

Importantly, the opening probability of mPTP of the de-energized mitochondria is drastically reduced below pH 7.4, a condition occurring during sufficiently prolonged ischemia<sup>[36]</sup>. Low pH also reduces mitochondrial calcium uptake and favors calcium extrusion from the mitochondrial matrix, due to the activation of mitochondrial NHE and subsequent NCE<sup>[37]</sup>. However, low pH may activate uncoupling proteins (UCPs), IMM carriers of H<sup>+</sup> that uncouple ATP synthesis from oxygen consumption<sup>[38]</sup>. For the role of UCPs in cardioprotection see below<sup>[39-41]</sup>. Low pH may also inhibit glycolysis and pyruvate production, resulting in a slower feeding of the respiratory complex chain. Therefore low pH mainly prevents mPTP opening in ischemia (Figure 1A).

On reperfusion, quite different conditions are created depending on whether or not the mitochondrial membrane potential rapidly recovers. In the case of energized respiring mitochondria, a low pH can stimulate Pi uptake increasing its intra-mitochondrial content, thus acting as an mPTP opener<sup>[42]</sup>. In contrast, in the presence of mitochondrial membrane depolarization, long-lasting opening of the mPTP take places when rapid normalization of tissue pH occurs in the presence of Ca<sup>2+</sup> overload, Pi, ROS formation, and/or lower levels of NO<sup>•</sup><sup>[32,43-46]</sup>. The latter condition (i.e. membrane depolarization and rapid pH normalization) is the more common scenario upon abrupt reperfusion. In fact, the probability of this pore being open is facilitated by several factors including high pH, Ca<sup>2+</sup> overload, and burst of ROS at the onset of reperfusion. Apart from its direct action on mitochondria, the opening effect of Ca<sup>2+</sup> is also due to indirect effects, such as phospholipase A<sub>2</sub> and calpain activation<sup>[47-50]</sup> (Figure 1A).



**Figure 1** Flowchart depicting the variations of pH, ROS and mPTP opening during ischaemia and reperfusion phases in the control hearts, and in hearts protected by preconditioning or postconditioning. **A:** In the control hearts reactive oxygen species (ROS) production slightly increases during the initial part of ischaemia until the O<sub>2</sub> is exhausted. Then sharply increases in reperfusion. Formation of mitochondrial permeability transition pores (mPTP) had been limited during ischaemia by the low pH despite increased cellular levels of ROS, Ca<sup>2+</sup> and Pi overload. But as pH returns to its baseline level and ROS formation increases prolonged opening occurs. The limited damages occurring during ischaemia are exacerbated by the prolonged mPTP opening which mediates irreversible cell damages in reperfusion. The opening effect, besides Ca<sup>2+</sup> overload, is also due to indirect effects, such as phospholipase A2 (PLA2) and calpain activations and consequent arachidonic acid release after membrane phospholipids degradation. A part membrane depolarisation also inorganic phosphate (Pi), lower levels of nitric oxide (NO) contribute to mPTP opening. Other factors which regulate pore formation are Bcl-2-associated X protein (Bax)/Bcl-2-associated death promoter (Bad), B-cell lymphoma 2 (Bcl-2) and glycogen synthase kinase 3 β (GSK-3β). Pore opening leads to cell-death through the release of pro-apoptotic factors as cytochrome c (Cyt c) and via ROS-induced ROS release (RIRR); **B:** The pre/postconditioned hearts are characterized by delayed pH recovery, ROS signalling and activation of protective pathways (e.g. Reperfusion Injury Salvage Kinases (RISK)/Survivor Activating Factor Enhancement (SAFE)). These conditions contribute to reduce mPTP opening and consequent cell death limitation. The details of the protective signalling (RISK/SAFE) can be seen in Figure 2 and Figure 3. For further explanations see the text.

**Consequences of mPTP opening:** Depending on the complex balance between cellular inducers and antagonists, mPTP can undergo transient or intermediate/long-lasting opening<sup>[51]</sup>. mPTP opening of short duration is likely to generate reversible cellular changes, so that this transient opening has been suggested to be involved in physiological processes and cardioprotection, such as intracellular NAD<sup>+</sup> traffic, and transient formation of

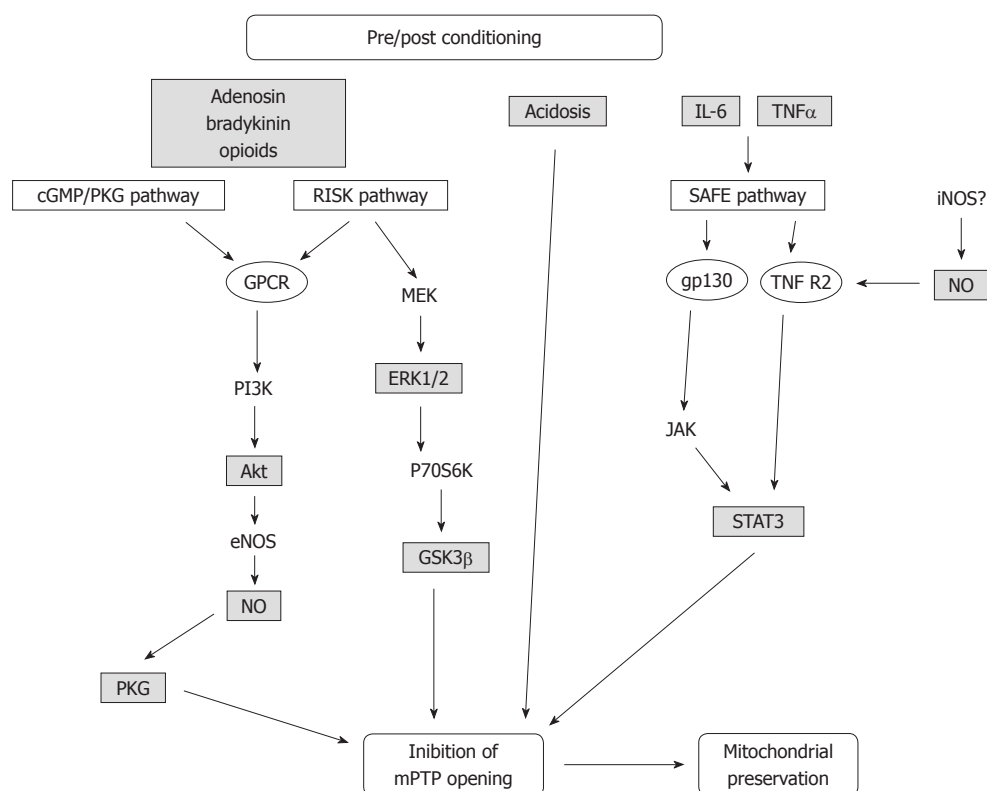
ROS (see also below)<sup>[52-55]</sup>. Actually, the transient increase in the opening probability of mPTP is involved in ROS-dependent triggering of cardioprotection by preconditioning<sup>[56,57]</sup> (see below).

While a transient/intermediate pore opening may or may not lead to apoptosis, long-lasting pore formation is followed by profound alterations of cellular bioenergetics that are considered irreversible; it results in increased mitochondrial permeability to ions and solutes with molecular weights of up to 1.5 kDa, matrix swelling and loss of critical electrochemical gradients. In this condition the F<sub>0</sub>F<sub>1</sub>ATPase actively hydrolyzes rather than synthesizes ATP, leading to inevitable cell death<sup>[11,12,33,58,59]</sup>. Actually, the mandatory consequence of long-lasting mPTP opening is the collapse of mitochondrial membrane potential. This is rapidly followed by ATP and NAD<sup>+</sup> depletion, mitochondrial release of accumulated Ca<sup>2+</sup>, matrix swelling and rupture of the OMM leading to loss of pyridine nucleotides and release of pro-apoptotic factors such as Cyt c, which triggers apoptosis and thus also inhibits electron flow through the electron transport chain<sup>[11,19,20,32,60-62]</sup>. Many have postulated that long-lasting mPTP formation is the event that leads to irreversible changes in cellular function and cell death<sup>[13,59,62,63]</sup>. Di Lisa *et al.*<sup>[62]</sup> were among the first to observe that addition of Ca<sup>2+</sup> to mitochondria causes organelle swelling and profound decreases in NAD<sup>+</sup> content.

At least two mechanisms which are not mutually exclusive have been proposed to explain mitochondrial membrane permeabilization and apoptosis. Apart the mPTP, which involves the participation of both the IMM and the OMM, a mechanism of mitochondrial death which involves only the OMM and the formation of channels across the membrane has been described. Although there is controversy concerning the structure, the regulation and the definite role of these two putative different channels, strong evidence indicates that proteins of the Bcl-2 family may contribute to both mechanisms<sup>[64,65]</sup>.

**Prevention of prolonged mPTP opening:** All these opening factors are counteracted by “physiological” mPTP antagonists, such as adenine nucleotides (mainly ADP), elevated concentrations of protons (i.e. pH below 7.4), increased mitochondrial membrane potential, and magnesium ions, as well as by physiological levels of nitric oxide<sup>[19,66]</sup>. The pore is rapidly closed if Ca<sup>2+</sup> is chelated<sup>[19,60]</sup>. Promotion of mPTP opening is also prevented by some drugs, including cyclosporine A (CsA), which at nM concentrations is a mPTP desensitizer<sup>[36,58,67]</sup>. Notably, in the absence of Pi the desensitizing effects of CsA are no longer present<sup>[58,67]</sup>.

Since mPTP formation is likely to be a causative event in reperfusion injury and a major proportion of cell death results from mPTP formation, it is not a surprise that cardioprotective strategies demonstrated that inhibition of mPTP is the end-effector of cardioprotection (Figures 1B and 2). In fact the importance of mPTP closure as a target for myocardial protection has been described in several studies<sup>[58,68-70]</sup>. The mechanisms of cardioprotec-



**Figure 2** Flowchart depicting the main factors involved in cardioprotective pathways triggered by pre and postconditioning. Activation of cell-surface receptors in response to an ischaemic conditioning stimulus recruits cGMP/PKG, RISK and SAFE pathways. In particular, iNOS seems to be involved in SAFE pathway<sup>[77]</sup>. These signal transduction pathways, together with acidosis, activated at the time of reperfusion will crosstalk and will terminate on mitochondria to activate protective pathways. Akt: Serine/threonine protein kinase; cGMP/PKG: Cyclic guanosin monophosphate/protein kinase G; eNOS: Endothelial NO synthase; ERK1/2: Extracellular regulated kinase 1/2; gp130: Glycoprotein 130; GPCR: G-protein-coupled receptor; GSK3β: Glycogen synthase kinase 3 β; IL-6: Interleukin 6; iNOS: Inducible NO synthase; JAK: Janus kinase; MEK: Mitogen-activated protein kinase kinase; mPTP: Mitochondrial permeability transition pore; NO: Nitric oxide; P70S6K: p70 ribosomal S6 protein kinase; PI3K: Phosphoinositide 3-kinase; PKG: Protein kinase G; RISK: Reperfusion injury salvage kinases; SAFE: Survivor activating factor enhancement; STAT-3: Signal transducer and activator of transcription 3; TNFα: Tumour necrosis factor α; TNF-R2: Tumour necrosis factor receptor 2.

tion and mPTP closure in reperfusion are described in the following section.

## CARDIOPROTECTIVE STRATEGIES TARGETING MITOCHONDRIA

Lethal reperfusion injury appears to represent from 20 to 70% of the total amount of irreversible myocardial damage according to the studied species and therefore constitutes a major therapeutic target<sup>[2,71-75]</sup>.

### Preconditioning and postconditioning

Over the last decades ischemic preconditioning and postconditioning have been recognized as protective phenomena and have been confirmed in humans; they share certain signaling elements in experimental analyses<sup>[2,76-78]</sup> (Figure 2). In 1986, Murry *et al.*<sup>[79]</sup> reported that four 5 min circumflex occlusions, each separated by 5 min of reperfusion, followed by a sustained 40 min occlusion (index ischemia = infarcting ischemia) in the dog heart dramatically attenuated ischemia/reperfusion injury. This phenomenon was named ischemic Preconditioning (PreC). In 2003, Zhao *et al.*<sup>[73]</sup> reported that three episodes of 30 s of

reperfusion/30 s of ischemia performed immediately after index ischemia (60 min coronary occlusion) in the dog heart drastically attenuated reperfusion injury. This phenomenon was named ischemic Postconditioning (PostC). It was soon clear that the later the application of the first postconditioning ischemia, the lower the protection.

The recognition of the ischemic PostC phenomenon put an end to any discussion on the existence of reperfusion injury<sup>[80]</sup>. The term “PostC” has also highlighted the importance of intervening at the beginning of myocardial reperfusion to protect the post-ischemic heart; a clinically more relevant time-point for intervention in patients presenting with an AMI. As such, its clinical application has been rapid for both ST-elevation AMI patients undergoing primary percutaneous coronary intervention (PCI)<sup>[81,82]</sup> and for patients undergoing on-pump cardiac surgery<sup>[83]</sup> (see also below).

The protective effects observed with PostC are comparable to those observed with the powerful PreC<sup>[2,73,84,85]</sup>. In fact, PostC may reduce apoptosis, necrosis, and endothelial dysfunction/activation, thus leading to a reduced endothelium/leukocyte interaction and to reduced ROS inflammatory formation<sup>[5,73]</sup>. PostC also reduces the incidence of reperfusion arrhythmias<sup>[86-90]</sup>.



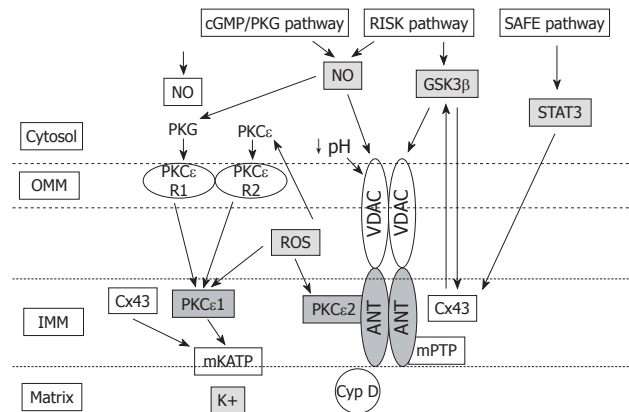
Intensive investigation of the signaling pathways underlying PreC and PostC have identified a number of signal transduction pathways conveying the cardioprotective signal from the sarcolemma to the mitochondria, some of which overlap for PreC and PostC. In fact, both PreC and PostC induce activation of signaling elements during the early reperfusion following the index ischemia<sup>[91]</sup> (Figure 2). Great attention has focused on the cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG)-pathway<sup>[92-94]</sup>, on the Reperfusion Injury Salvage Kinases (RISK) pathway<sup>[95,96]</sup>, which involves the kinases Akt and ERK1/2, and more recently on the Survivor Activating Factor Enhancement (SAFE) pathway that has been suggested to contribute to PostC protection through the activation of tumor necrosis factor (TNF)- $\alpha$ , its receptor type 2, Janus kinase (JAK) and signal transducer and activator of transcription (STAT)-3<sup>[78,97]</sup>. All these pathways in preconditioning and postconditioning converge on the mitochondria *via* the modulation of several kinases including glycogen synthase kinase-3 $\beta$ , Bax/Bad and the  $\epsilon$  isoform of protein kinase C (PKC) (for reviews see<sup>[10,78]</sup>). The modalities of mitochondrial control by cytosolic kinases depicted in Figures 2 and 3 are still controversial and are beyond the aims of this editorial.

Nevertheless, ROS signaling and acidosis in early reperfusion are two cardioprotective processes operating in early reperfusion in both preconditioning and postconditioning (Figures 2 and 3). They may act, first, directly on mPTP components to limit their opening and, then, may activate signaling pathways that have been suggested to converge again on mitochondria to decrease the susceptibility to mPTP opening and mediate protection (Figures 2 and 3). These two processes are discussed in the next sections.

### ROS signaling and acidosis in early reperfusion

Before considering the beneficial role of ROS signaling, let us consider the forms and the detrimental effects of ROS within the heart.

**Forms of ROS:** ROS are generated in different cellular compartments and by several enzymes, including NADPH oxidases at the plasma membrane<sup>[98,99]</sup> and cytosolic xanthine oxidases<sup>[100]</sup>. Although ROS are produced by several extracellular and intracellular processes, in cardiomyocytes the mitochondria represent the most relevant site for ROS formation<sup>[101-105]</sup>. Within the mitochondria, most of the oxygen is reduced to water at respiratory complex IV. The mitochondrial formation of ROS might be modulated by NO<sup>[106-108]</sup> which reversibly inhibits cytochrome oxidase<sup>[105,109-112]</sup>. This inhibition can be transformed into irreversible alterations of the respiratory chain when NO $\cdot$  reacts with O $_2$  to generate a large amount of peroxynitrite, which can produce the irreversible nitration of proteins<sup>[113]</sup>. Even nitric oxide synthases can become “uncoupled” resulting in the generation of O $_2$  $\cdot$  and OH $\cdot$ , instead of NO $\cdot$  under certain conditions, such as scarcity of substrate and/or cofactors<sup>[112,113]</sup>. Apart from the electron transport chain, ROS can also be produced by



**Figure 3 Extra- and intra-mitochondrial signalling: interactions among Cx43, mKATP, PKC $\epsilon$ , ROS, and mPTP.** The mPTP is believed to be composed of the adenine nucleotide transporter (ANT) in the inner membrane (IMM), the voltage-dependent anion channel (VDAC) of the outer membrane (OMM), and cyclophilin D (Cyp D) in the matrix. Signals arising from RISK and SAFE pathways are delivered to mitochondrial permeability transition pore (mPTP) via nitric oxide (NO)/glycogen synthase kinase 3  $\beta$  (GSK3 $\beta$ ) and signal transducer and activator of transcription 3 (STAT-3), respectively, and then to connexin 43 (Cx43) on the IMM. Signals arising from cGMP/PKG are delivered to mitochondria via the terminal protein kinase G (PKG). PKG phosphorylates an unknown OMM receptor, “R1”, whereas PKC $\epsilon$  act in conjunction to activate a distinct OMM receptor, “R2”. These OMM receptors transmit the signal by an unknown mechanism to PKC $\epsilon$ 1 located at the IMM. The activated PKC $\epsilon$ 1 phosphorylates and opens mitochondrial ATP-sensitive potassium (mKATP). Also Cx43 located at the IMM regulated mKATP opening. The mKATP opening via PKC $\epsilon$ 1 causes K $^+$  uptake and increased ROS production from respiratory chain. ROS produced by mKATP activation now diffuses and activates both PKC $\epsilon$ 1 and PKC $\epsilon$ 2 on the IMM and PKC $\epsilon$  in the cytosol. ROS signalling may represent the link between mitochondria and cytosol. mPTP opening is prevented by cytosolic pH lowering, ROS signalling and PKC $\epsilon$ 2 activation.

monoamine oxidases (MAOs) in the OMM. MAOs transfer electrons from amine compounds to oxygen to generate hydrogen peroxide<sup>[102,114,115]</sup>. Within the mitochondria, p66Shc oxidizes reduced Cyt c, which induces the partial reduction of oxygen to peroxide<sup>[116-118]</sup>.

Besides being a relevant site for ROS formation, mitochondrial function and structure are profoundly altered by oxidative stress<sup>[34]</sup>, especially when mPTPs have long-lasting opening. In fact, mPTPs play a central role in the so-called ROS-induced ROS release (RIRR)<sup>[61,119,120]</sup>; excessive ROS facilitate mPTP opening which in turn favors ROS formation by inhibiting the respiratory chain because of mPTP-induced loss of Cyt c and pyridine nucleotides<sup>[12,34]</sup>. This vicious cycle is likely to be established at the onset of a rapid reperfusion when a large increase in ROS formation occurs along with pH recovery, and Ca $^{2+}$  overload, thus inducing injury amplification, as discussed above and below (Figure 1).

**Detrimental effects of excessive ROS:** Various detrimental processes can result from an imbalance between the excess formation of ROS and limited antioxidant defenses (referred to as ‘oxidative stress’). For instance, excessive ROS indiscriminately react with DNA, lipids and proteins<sup>[113,120-123]</sup>. The lack of protection of mitochondrial DNA by histones, the limited capacity of repair mecha-



nisms and the proximity of mitochondrial DNA to the production site of ROS by RIRR render the mitochondrial DNA highly susceptible to increased oxidative stress<sup>[124]</sup>. Excessive oxidative stress, besides contributing to irreversible myocardial injury, induces long-lasting mPTP opening leading to cellular dysfunction and cell death, and may also induce reversible injury during ischemia and reperfusion<sup>[105,125-128]</sup>. The reversible contractile dysfunction following myocardial ischemia/reperfusion (“stunning”) is clearly a manifestation of excessive oxidative stress<sup>[129,130]</sup>. Whether stunning is due to RIRR has not yet been investigated.

On the other hand, as mentioned above, low levels of reactive species may act as secondary messengers, modulating cardioprotective signaling pathways by covalent modification of target molecules, referred to as ‘redox signaling’ or ‘ROS signaling’, which is the main topic of the next section.

### **Beneficial effects of ROS signaling and acidosis - focus on early reperfusion**

It has been proposed that reintroduction of oxygen after transient ischemia induces ROS production, but it does not protect against reperfusion injury because mPTPs open and trigger RIRR before the activation of endogenous survival pathways.

The key event for cardioprotection may be prolongation of cellular acidosis by cardioprotective phenomena during early reperfusion (Figure 2B). In fact acidic perfusion in early reperfusion or PostC, delaying pH normalization, could inhibit mPTP during the first minutes of reflow and allow for endogenous protective signaling pathways to be activated by ROS signaling. The delivery of oxygen during acidic perfusion or the brief intermittent reperfusion of PostC would promote mitochondrial ROS formation which has been proposed to activate isoforms of PKC through redox signaling<sup>[131]</sup>. Different isoforms of PKC appear as critical kinases in the signaling cascade leading to a reduced probability of mPTP opening after pH normalization<sup>[131-134]</sup> (see Figure 3 and below).

Not only mPTPs may be inhibited by a limited ROS production and acidosis, but also, as mentioned above, a transient or short duration opening of the mPTP has been suggested to induce a slight, transient formation of ROS that might be relevant for cardioprotection<sup>[51-54,56,57,135]</sup>. Supporting this concept, pharmacological and genetic inhibition of Cyp D was reported to attenuate both preconditioning-induced ROS formation and protection<sup>[136,137]</sup>. In brief, in protected reperfusion, low levels of ROS may act directly on mPTP components or activate signaling pathways that have been suggested to act on mitochondria decreasing their susceptibility to prolonged mPTP opening.

Redox signaling by transient/reduced formation of ROS is also included among the triggers of PostC<sup>[138]</sup>. In fact, we were the first to show that the ROS scavengers N-acetylcysteine (NAC)<sup>[132]</sup> and N-2-mercaptopyrionyl glycine (MPG) prevent the protective effects of ischemic or pharmacological PostC<sup>[94,132,139,140]</sup>, and the same ROS

scavenger has been shown to block the protection afforded by acidic reperfusion<sup>[141]</sup>. In our laboratory isolated rat hearts were subjected to ischemia and reperfusion. While PostC significantly reduced infarct size, protection by PostC was lost in hearts perfused with NAC for the entire reperfusion period. Infarct size was still reduced when, in postconditioned hearts, perfusion with NAC was initiated after the first 3 min of reperfusion, demonstrating an essential role of ROS formation during early reperfusion in PostC protection<sup>[132]</sup>. Cardioprotection, induced with acidic buffer for the first 2 min of reperfusion, was blocked by MPG applied for 20 min in reperfusion<sup>[141]</sup>, suggesting the involvement of ROS signaling in acidosis-induced protection. Infarct size reduction by either ischemic PostC, 1.4% isoflurane or 10 mg/kg of delta-opioid receptor agonist SNC-121 in mouse hearts *in vivo* were attenuated by the ROS scavenger MPG when administered a few minutes before but not 10 min after the postconditioning stimulus<sup>[140]</sup>. NAC in the first minutes of reperfusion also abolished postconditioning by bradykinin or sevoflurane in isolated rat hearts<sup>[94,139]</sup>. Importantly, in the human myocardium, desflurane-induced postconditioning was mediated by adenosine and bradykinin receptors *via* ROS signaling<sup>[115]</sup>. These studies support a central role for ROS signaling during early reperfusion in the protection by ischemic postconditioning and in the protection by acidosis in early reperfusion.

### **Mitochondrial ATP-sensitive potassium channels**

Mitochondrial ATP-sensitive potassium (mK<sub>ATP</sub>) channels in the mitochondrial inner membrane are considered targets of protective cascades, and play a pivotal role in ROS production, mainly superoxide anion derived from complex I of the electron transport chain<sup>[21,76,138,142,143]</sup>. Opening of the mK<sub>ATP</sub> channels and subsequent generation of ROS is considered to be a pivotal step in the mechanisms of pre- and postconditioning<sup>[3,21,76]</sup>. We found evidence that ROS signaling is downstream of mK<sub>ATP</sub> channel opening in isolated rat hearts subjected to ischemia/reperfusion with an intermittent infusion of diazoxide or diazoxide plus MPG at the onset of reperfusion, since MPG attenuated diazoxide-induced protection. However, while ROS scavenging attenuates infarct size reduction by postconditioning or diazoxide, increasing exogenous ROS formation with purine/xanthine oxidase at the onset of reperfusion does not confer protection<sup>[94]</sup>. It is likely that the type, the concentration, and/or the compartmentalization of reactive species may play a pivotal role in triggering protection at reperfusion. Nevertheless, we cannot rule out that a different ROS generator could trigger PostC protection.

In the context of cardioprotection, it has been reported that PKG- and/or Akt-dependent phosphorylation induces the opening of mK<sub>ATP</sub> promoting K<sup>+</sup> entry into mitochondria with consequent alkalinization of the mitochondrial matrix and generation of ROS with a protective signaling role. Indeed, PKG phosphorylates a protein on the OMM, which then causes the mK<sub>ATP</sub> on

the IMM to open. This implies that the protective signal is transmitted from the OMM to the IMM. This is accomplished by a series of intermembrane signaling steps that includes PKC $\epsilon$  activation. The resulting ROS then activate a second PKC pool which, through another signal transduction pathway causes inhibition of the mPTP (the end effector) and reduction in cell death<sup>[3,76,144-146]</sup> (Figure 3). Pharmacological opening of mK<sub>ATP</sub> channels by diazoxide contributes to the formation of small amounts of ROS<sup>[147]</sup>. Also, NO $\cdot$  donors can activate mK<sub>ATP</sub> channels in rabbit ventricular myocytes and can potentiate the protective effect of the mK<sub>ATP</sub> opener diazoxide<sup>[143]</sup>. Besides cGMP/PKG-dependent phosphorylation, mK<sub>ATP</sub> could be opened by direct reaction of NO $\cdot$  and derivatives (S-nitrosylation), as well as by the action of H<sub>2</sub>S *via* S-sulphydration<sup>[4]</sup>. However, controversy exists on the nature, existence and opening of mK<sub>ATP</sub> channels, which may also be a toxic process<sup>[145,148]</sup>. PKC activation leading to the opening of mK<sub>ATP</sub> channels has been challenged by the Halestrap group: they demonstrated that preconditioning inhibits opening of the mPTP *in situ*, by an indirect mechanism probably involving decreased ROS production and Ca<sup>2+</sup> overload at reperfusion<sup>[11,148]</sup>.

### Mitochondrial uncoupling

Mitochondrial uncoupling, i.e. proton influx into the mitochondrial matrix without phosphorylation of ADP, contributes to ROS formation<sup>[39,40]</sup>. Although controversy exists on the cardioprotective role of uncoupling, mild uncoupling secondary to activation of UCPs has been described to confer cardioprotection under several conditions, including myocardial reperfusion, likely by decreasing ROS production<sup>[41]</sup>. Intriguingly, it has been suggested that transient complex I inhibition during reperfusion is cardioprotective *via* attenuated ROS production<sup>[149,150]</sup>. Nevertheless, experimental evidence supporting the involvement of these changes in PostC protection has yet to be provided. Whether UCPs play a deleterious or protective role in ischemia tolerance is controversial<sup>[39-41]</sup>.

### Mitochondrial connexin-43

Mitochondrial connexin-43 (Cx43) has also been implicated in ROS-signaling, though its role is not completely defined<sup>[121,151,152]</sup>. Actually, within cardiomyocytes Cx43 is mainly localized at gap junctions, but it is also present in other organelle membranes, including the IMM of sarcolemmal mitochondria<sup>[152-154]</sup> where Cx43 regulates mitochondrial potassium flux<sup>[155,156]</sup>. It seems that Cx43 translocates to the IMM, with cardioprotection *via* the intervention of heat shock protein 90-TOM (translocation of the outer membrane) import pathway<sup>[154]</sup>.

Mitochondrial Cx43 has been described to be essential for preconditioning protection<sup>[154,157,158]</sup>, but a recent study in mice heterozygous for Cx43 (Cx43<sup>+/-</sup>) indicates that it does not play a significant role in PostC protection. Actually, Cx43 is a target of several protein kinases, and mitochondrial Cx43 is highly phosphorylated under physiological conditions<sup>[159]</sup>; it seems that in the IMM of

a subset of cardiomyocyte mitochondria, subsarcolemmal mitochondria, the phosphorylated portion of Cx43 increases with ischemia<sup>[152]</sup> and decreases with PostC<sup>[138]</sup>. Since a decrease in the mitochondrial Cx43 content is sufficient to abolish the cardioprotection by diazoxide preconditioning, i.e. reduces ROS formation<sup>[147]</sup>, one can speculate that Cx43 reduction in PostC may be one of the mechanisms to reduce excessive ROS production in the reperfusion phase. Recently it has been suggested that genetic ablation or pharmacological inhibition of mitochondrial Cx43 confers resistance to mK<sub>ATP</sub> channel opening in response to diazoxide in patch-clamped mitochondria (mitochondria devoid of the OMM). However, the open-probability of the mK<sub>ATP</sub> channel was not affected under baseline conditions; thus it is likely that Cx43 regulates this channel activity rather than constituting the pore forming unit of the mK<sub>ATP</sub> channel<sup>[156]</sup>.

### Timing and targets of ROS signaling in cardioprotection

In the context of cardioprotection, reactive species with a signaling role are suggested to be formed during three time points: (1) during preconditioning-ischemia and/or (2) during reperfusion that follows the brief preconditioning-ischemia; and (3) in the initial part of reperfusion that follows the index ischemia; both in the postconditioning and in the preconditioning context.

**During preconditioning-ischemia:** A wide body of evidence exists demonstrating that appreciable formation of ROS occurs during ischemia<sup>[126,128,160-162]</sup>. In fact, mitochondrial ROS formation is favored by a decrease in electron flow resulting from respiratory chain inhibition, and is counteracted by uncoupling that is generally produced by an increased IMM permeability to protons. Therefore, the inhibition of the electron transport chain caused by insufficient oxygenation facilitates the escape of electrons that can react directly with the scarce available oxygen resulting in ROS formation.

**During reperfusion that follows brief preconditioning-ischemia:** Small amounts of ROS may be formed during reperfusion following a short period of preconditioning ischemia. To support this viewpoint, the group of Downey<sup>[163]</sup> used MPG (a cell-permeant ROS scavenger<sup>[164]</sup>) to test whether the ROS that triggers protection are produced during the ischemic or the reperfusion phases of the preconditioning maneuvers. These authors concluded that protective redox signaling occurs when molecular O<sub>2</sub> is reintroduced following the brief preconditioning coronary occlusion.

**In the initial part of reperfusion that follows the index ischemia in postconditioning:** The above observations were done in the preconditioning phase, i.e. before the index ischemia, and extended to PostC itself. In fact, as reported above, the protective effect of PostC was attenuated by infusing, during early reperfusion, large spectrum ROS scavengers, making the oxygenated perfusate

alkaline during the early reperfusion phases or making the early reperfusion buffer hypoxic<sup>[50,94,131,132,142,165]</sup>.

### Early reperfusion events in preconditioned heart:

Clearly, both PreC and PostC, besides sharing a number of signaling elements, induce activation of signaling elements (RISK and SAFE) during early reperfusion following the prolonged index ischemia<sup>[78,91,166]</sup> (Figure 2). It is now thought that, after a triggering phase in the pre-ischemic period, the actual protection by PreC occurs in the reperfusion rather than in the ischemic phase, with the repopulation of sensitized G-protein-coupled receptors at the beginning of myocardial reperfusion following the index ischemia<sup>[167]</sup>. Hence, reintroduction of O<sub>2</sub> at the beginning of reperfusion permits generation of signaling ROS, which will activate the PKC-dependent signaling cascade. In fact the PreC protective effect was also attenuated by infusing, during early reperfusion, large spectrum ROS scavengers, making the oxygenated perfusate alkaline during the early reperfusion phase or making the early reperfusion buffer hypoxic<sup>[56,166,167]</sup>.

**Targets of ROS signaling:** Reactive species function as trigger molecules of protection by activating protein kinases such as PKC within and outside the mitochondria<sup>[3,146,147,168,169]</sup>, as well as the mitogen-activated protein kinase p38 and/or JAK/STAT<sup>[170,171]</sup>. Several mitochondrial components are targeted by reactive species *via* oxidative/nitrosative processes<sup>[4,10]</sup>. Accordingly, many large spectrum scavengers of ROS, such as ascorbic acid, MPG or NAC, attenuate infarct size reduction by ischemic or pharmacological PreC or PostC, in several animal species<sup>[2-4,132,145,169,172]</sup>. Since a target of ROS in redox signaling is the PKC, hearts can be preconditioned by simply infusing free radicals into the coronary arteries, and that protection can be blocked by a PKC antagonist<sup>[76,167]</sup>. Evidence exists that ROS-activated PKC will also protect the reperfused heart<sup>[132,169]</sup>. This sequence would explain the observation that a PKC activator could rescue hearts experiencing acidic and hypoxic reperfusion<sup>[131]</sup>. Moreover, chelerythrine, a non-specific PKC antagonist, blocks PostC protection<sup>[132-134]</sup>.

Indeed, it has been reported that ROS can activate PKC *in vitro* by reacting with thiol groups associated with the zinc finger region of the molecule<sup>[173]</sup>. Reactive nitrogen species-dependent activation of PKC, possibly *via* a redox-sensitive S-nitrosylation process, has been also suggested; a process which also occurs within mitochondria<sup>[4,174,175]</sup>. Recently, we have observed in an *ex vivo* study that PostC induces downregulation of superoxide dismutase (SOD), whereas catalase activity does not change in the early reperfusion phase. Moreover, PostC reduces 3-nitrotyrosine and increases S-nitrosylated protein levels, thus contributing to cardioprotection triggering<sup>[176]</sup>. The persistence of acidosis<sup>[50,68,131,141,165]</sup> and the NO<sup>•</sup> augmentation (enzymatic and non-enzymatic production)<sup>[132]</sup> in early reperfusion of postconditioned hearts, together with SOD downregulation may favor nitrosylation and/or may limit protein de-nitrosylation. In fact SOD is a de-nitrosylating

enzyme<sup>[177]</sup>. Intriguingly, exogenous-SOD prevents PostC-triggering, whereas exogenous-catalase does not interfere with PostC protection. That is, the addition of exogenous-SOD during PostC maneuvers does not allow the early reduction in overall SOD activity, usually induced by PostC.

### Preservation of functional and morphological integrity of mitochondria

Preconditioning and postconditioning activate cardioprotective pathways that are protective against reperfusion injury *via* preservation of the functional and morphological integrity of mitochondria. The protection of PostC against apoptosis is mediated by reduced generation of superoxide anions, lowered activity of c-Jun-N-terminal kinases/p38, lowered levels of caspases 3 and 8, reduced release of TNF $\alpha$ , and by the modulation of the Bax/Bcl-2 ratio<sup>[178]</sup>. PostC increases the levels of anti-apoptotic markers, including the cardioprotective kinase Pim-1, decreases pro-apoptotic markers, e.g. Cyt c, and preserves the mitochondrial structure. In fact, at the onset of reperfusion, mitochondria undergo profound structural alterations. In particular, post-ischemic mitochondria are characterized by disruption of membranes, broken cristae and the appearance of dense granules within the mitochondrial matrix, which are caused by massive accumulation of Ca<sup>2+</sup>, generating insoluble calcium phosphate precipitate<sup>[179]</sup>. These mitochondrial damages are reduced by PostC<sup>[138]</sup>. Carbonylation of mitochondrial proteins was prevented and aconitase activity was preserved in the PostC hearts suggesting that mitochondrial integrity was associated with a diminution in oxidative stress<sup>[180]</sup>. However, PostC does not influence mitochondrial respiration<sup>[181]</sup>. In particular, PostC does not affect basal state 4 or ADP-stimulated state 3 respiration, excluding uncoupling or inhibition of the respiratory chain as a mechanism of mPTP inhibition<sup>[182]</sup>. Nevertheless, while basal respiration was not affected, ADP-stimulated respiration was increased after pharmacological PostC with morphine<sup>[183]</sup>. This is in line with many reports showing that a mild degree of mitochondrial dysfunction confers protection against ischemia/reperfusion injury<sup>[175,184]</sup>.

In summary, ROS signaling before index ischemia, i.e. during brief preconditioning ischemia and/or during the following reperfusion, is clearly involved in the triggering of preconditioning protection. Excessive ROS formation during reperfusion, following infarcting ischemia, enhances cell death, but ROS signaling during early reperfusion is essential for protection of ischemic and some pharmacological preconditioning and postconditioning against reperfusion injury. In early reperfusion, opening of mK<sub>ATP</sub> channels may be upstream of ROS signaling. Cardioprotective procedures delay the post-ischemic recovery of intracellular pH that may prevent mPTP opening directly and indirectly (i.e. by inhibiting calpain activation). In addition, mPTP opening may be further prevented by a ROS signaling that appears to depend on acidosis and by a decrease in intracellular Ca<sup>2+</sup>. ROS signaling triggers a protective kinase cascade starting from PKC and converging on mPTPs.



Thus, mPTP closure may be dependent on ROS signaling effects, both upstream, together with an acidotic effect, and downstream, dependent on kinase effects. Therefore, mitochondria are involved in at least four different steps to limit reperfusion injury: (1) as the target of acidosis (i.e. prevention of mPTP opening); (2) as triggers or signal amplifiers (i.e. activation of mK<sub>ATP</sub> channels and resulting formation of small amounts of ROS); (3) as the target of signaling pathways and end-effectors (i.e. inhibition of mPTP opening and of release of pro-apoptotic factors into the cytosol); and (4) as targets of damage and protection from it (i.e. functional and morphological integrity).

## THERAPEUTIC IMPLICATIONS

The signaling role of ROS in early reperfusion must be kept in mind for successful treatment in reperfusion. Clearly, the mPTP is a major factor in determining cell death, and mPTP inhibition affords significant cardioprotection<sup>[12,32,185,186]</sup>, a concept that has been successfully translated into the clinical setting<sup>[81,82,187,188]</sup>. In particular, postconditioning transition to the clinical setting has proven the existence of lethal myocardial reperfusion injury in man, and the clinical studies suggest that 40%-50% of the final reperfused infarct in humans may be attributable to myocardial reperfusion injury<sup>[189]</sup>.

In AMI patients the involved coronary artery may be opened by either angioplasty or thrombolysis, with or without application of a stent. The ischemic postconditioning, though reserved for patients reperfused by primary angioplasty, may provide impressive results when the no-reflow phenomenon, the infarct size and the myocardial contractile function are considered, raising great hopes for potential clinical benefits. Feasible in every patient, the pharmacological postconditioning, including CsA infusion, would allow the expansion of postconditioning protection to almost all ST-elevation AMI patients. Obviously restoring reperfusion to the ischemic myocardium is the definitive strategy in reducing infarct size. However, blood flow may not be restored to all segments of the microvasculature in the post-ischemic myocardium<sup>[190]</sup>, a situation that is associated with the no-reflow phenomenon as a predictor of adverse long-term outcomes in patients<sup>[191]</sup>. The obvious implication of low- or no-reflow is that the blood supply is inadequate to sustain contractile function, and the decrease may be severe enough to induce cell death of the involved myocardium. Reducing the no-reflow area may lead to smaller infarcts, less adverse remodeling and less severe heart failure. Post-ischemic blood flow in a small group of patients undergoing PCI for AMI was studied by Laskey<sup>[192]</sup>. Patients were assigned to receive standard care *vs* an “ischemic conditioning” stimulus. While the control group (standard care) had a 90-s balloon inflation only before withdrawal of the catheter, the conditioned group had a 90-s inflation followed by 3-5 min of balloon deflation, and after that the balloon was advanced distal to the stenosis. These conditioned patients have shown an improved post-ischemic coronary blood

flow as revealed by an increased peak coronary blood flow velocity, diastolic/systolic velocity ratio and blood flow velocity reserve (evaluated with Doppler flow wire) compared to the control group. Staat *et al*<sup>[81]</sup> used blush grade, the speed by which contrast is washed out of the myocardium at risk, as a marker of myocardial reperfusion after the initial period of reflow in patients subjected to standard angioplasty or postconditioning, which consisted of four cycles of 60-s deflation/inflation of the angioplasty balloon in the target vessel. In postconditioned patients the blush grade was 25% greater than that of control patients. Also Ma *et al*<sup>[193]</sup> found that post-ischemic coronary blood flow in the target vessel was greater in AMI patients who received postconditioning treatment. This was associated with lower markers of lipid peroxidation by ROS and lower plasma levels of myocardial creatine kinase. Moreover, brachial arterial endothelium-mediated (flow-dependent) relaxation in response to transient cuff occlusion applied 24 h after PCI was better in the postconditioned patients. Although flow-dependent vasodilator effects in the brachial artery do not directly reflect physiology of the coronary vascular endothelium, it may be reflective of a “remote” protection to the endothelium of other organs, which then becomes a surrogate measure of the coronary vascular endothelium. Actually remote ischemic postconditioning (conditioning stimuli applied to a distant organ during reperfusion of the target organ) induced by transient episodes of ischemia of distant organs, including kidney, arms and legs, is a clinically feasible method for protecting the heart against injury at the time of reperfusion. Recently, it has been observed in rats that remote ischemic preconditioning may reduce infarct size, and that repeated remote postconditioning further reduces adverse remodeling of the left ventricle and may improve survival in a dose-dependent fashion<sup>[194]</sup>. Indeed, remote postconditioning has been reported experimentally<sup>[194,195]</sup>, and correlated with endothelial protection in humans<sup>[196,197]</sup>. Thus, although these data suggest that local and remote ischemic postconditioning have favorable effects on recovery of microvascular perfusion following relief of ischemia, further experimental and clinical studies are needed to establish whether postconditioning attenuates microvascular injury and the extent of no-reflow.

As mentioned above, a pharmacological approach may be more suitable. In fact, initial progress has been made with novel approaches for preventing myocardial reperfusion injury by administering drugs in the first minutes of reperfusion; preliminary clinical data indicate that drugs targeting mPTPs or RISK may confer benefits to patients with AMI, with and without comorbidities, above that provided by myocardial reperfusion alone. Very good results are obtained with drugs such as CsA as an mPTP desensitizer<sup>[81,187,188]</sup>, as well as with other drugs targeting RISK, such as erythropoietin and its analogs<sup>[198,199]</sup>. Importantly, similar cardioprotective effects were obtained with other drugs acting on mPTP, confirming the relevance of this approach. For instance, derivatives of CsA, such as [N-methyl-ala<sup>6</sup>]CsA, [N-methyl-Val<sup>7</sup>]CsA, Debio 025,



NIM811, or sanglifehrin A<sup>[11,12,56,58,59,68,71,136,189]</sup> also prevented myocardial ischemia/reperfusion injury in an experimental setting. Importantly, in small, proof-of-concept trials<sup>[81,82,187,189]</sup>, the administration of CsA in patients with AMI at the time of reperfusion has been associated with smaller infarct size. The efficacy of treatment has been assessed measuring the release of the cardiac biomarkers creatine kinase and troponin I and by measuring the area of late hyperenhancement of the reperfused myocardium on magnetic resonance imaging (MRI). In one of this studies<sup>[187]</sup>, the area under the curve for the creatine kinase concentration suggested that the administration of cyclosporine induced a reduction in infarct size of approximately 40%. This result was confirmed by a reduction in the area of late hyperenhancement on MRI. However, the area under the curve for the troponin I concentration was not significantly reduced by the administration of cyclosporine. Mewton *et al.*<sup>[188]</sup> recently examined whether CsA modified left ventricle remodeling in patients. Cardiac MRI was performed at day 5 and after 6 mo. The authors reported that CsA did not exert any deleterious effect on left ventricle remodeling, and confirmed that infarct size reduction persisted after 6 mo. In addition, infarct size reduction by CsA was associated with a lower left ventricle dilatation at day 5, which was maintained at 6 mo. These data require confirmation in larger clinical trials.

## CONCLUSION

It appears that many different signals can induce (and inhibit) mPTP formation, strictly linking ischemia/reperfusion stress and damage to the mitochondria. This highlights the capacity of mitochondria to function as general cell death sensors and to integrate many lethal signals. Clearly, mitochondria and ROS are attractive mechanistic targets for cardioprotection. Indeed, proof-of-concept studies demonstrated beneficial effects of the mPTP desensitizer CsA during early reperfusion in patients with AMI. Patient-tailored treatment to either prevent mPTP formation or the upstream events leading to mPTP opening may be achievable in the next future.

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## Conventional risk factors among newly diagnosed coronary heart disease patients in Delhi

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### Abstract

**AIM:** To analyze the conventional risk factors among newly diagnosed cases of coronary heart disease (CHD) admitted to a hospital in Delhi, India.

**METHODS:** This hospital-based prospective study included 276 consecutive newly diagnosed cases of CHD in the Coronary Care Unit of a tertiary care hospital in Delhi.

**RESULTS:** The mean age of the cases was  $49.7 \pm 9.5$  years, with the youngest case aged 27 years. The two risk factors present most frequently among the cases were inadequate physical activity and abnormal lipid profile. Just about 3.6% of cases in our study had a physical activity level (PAL) that could be termed as "active", with a large proportion (96.4%) having a PAL suggestive of a sedentary lifestyle. A majority of patients were found to be current tobacco smokers

(53.3%) and 188 (68.1%) subjects were lifetime ever smokers. There was not a single case who did not have one or more of the risk factors. More than one-quarter ( $n = 76$ ) had six or more of the studied risk factors.

**CONCLUSION:** Indians have among the CHD highest mortality rates amongst all ethnic groups studied so far. It is important to study the regional epidemiology of the cardiovascular events to allow for location-specific prevention and control programs.

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**Key words:** Risk factors; Coronary heart disease; Geographical-distribution; Epidemiology

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Bhasin SK, Dwivedi S, Dehghani A, Sharma R. Conventional risk factors among newly diagnosed coronary heart disease patients in Delhi. *World J Cardiol* 2011; 3(6): 201-206 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v3/i6/201.htm> DOI: <http://dx.doi.org/10.4330/wjc.v3.i6.201>

### INTRODUCTION

Studies show that at the beginning of the 20th century, coronary heart disease (CHD) accounted for less than 10% of all deaths worldwide. At the beginning of the 21st century, CHD accounts for nearly 50% of all deaths in the developed world and 25% in developing countries, such as India<sup>[1]</sup>. Currently, cardiovascular diseases are the leading cause of mortality in the developing world and their incidence rate in India is now 4-fold higher than that in the



United States<sup>[2]</sup>. Mortality due to CHD in India is 24.2% and CHD accounts for 8.1% of disability<sup>[3]</sup>.

Cardinal features of CHD among Indians compared to other populations are higher prevalence, incidence, hospitalization and mortality, with 5-10 years earlier onset of first myocardial infarction (MI)<sup>[4]</sup>. Since the early 1960s, many countries have been able to reduce the rate of CHD, and subsequently mortality, by implementing preventive and control measures along with better treatment. In contrast, India still has the highest CHD mortality rates amongst all ethnic groups studied so far. The most worrying part of the whole scenario is its rapid spread in younger people. We therefore planned to study the major risk factors among CHD subjects presenting to a large tertiary care hospital in Delhi.

## MATERIALS AND METHODS

We conducted a hospital-based prospective study and collected data of all subjects newly diagnosed with coronary artery disease admitted to the Coronary Care Unit (CCU) of Guru Tegh Bahadur (GTB) Hospital in Delhi. GTB Hospital is one of the larger tertiary care hospitals located in Delhi, the capital of India. It caters to patients mostly belonging to the lower and middle socioeconomic strata, who come from all over Delhi and also from other neighboring states of India. The present study was part of an ongoing larger study of the CHD patients admitted for care to the CCU of the hospital. We did a comprehensive analysis of the conventional risk factors for CHD among 276 consecutive newly diagnosed cases of CHD admitted from May 2008 to July 2009.

Permission was taken from the institutional ethics committee before carrying out the study. The enrolled subjects gave informed consent after a full explanation of the purpose of study and liberty to drop out. This was done in both Hindi and English languages for easy comprehension. Study subjects were male and female newly diagnosed cases of CHD in the age group 25-65 years. CHD patients were diagnosed as per the Monica criteria: (1) two or more ECG showing specific changes; (2) an ECG showing probable changes plus abnormal cardiac injury enzymes; or (3) typical symptoms such as retrosternal pain plus abnormal enzymes<sup>[5]</sup>. Pregnant women, known CHD patients, and patients suffering from dementia and/or severe psychiatric illness were excluded. A descriptive analysis was used to assess the demographic and risk profile. The risk factors studied included the conventional ones as mentioned by the World Health Organisation<sup>[6]</sup>, and other studies<sup>[7-11]</sup>.

Data collection was performed using a pre-tested, semi open-ended questionnaire. Anthropometric measurements (weight, height, waist circumference, hip circumference), blood pressure and laboratory investigations, such as fasting and post-prandial blood sugar, glycosylated hemoglobin, lipid profiles were performed using standard accepted techniques. The lipid profile values were classified as per the National Cholesterol Education Program-Adult

Treatment Panel III Guidelines that are endorsed by the American Heart Association<sup>[12,13]</sup>. Body mass index (BMI) and waist circumference were classified as per the new national consensus guidelines for India<sup>[14]</sup>. The subject was classified as obese if the BMI was 25 kg/m<sup>2</sup> or higher, and abdominal obesity was defined as a waist circumference > 90 cm in males and > 80 cm in females. The occupation was classified as per the Kuppuswami classification<sup>[15]</sup>.

We measured depression, anxiety and stress based on Depression Anxiety Stress Scale (DASS, 42 items)<sup>[16]</sup>. Physical activity level (PAL) was calculated using the validated proforma by Bharathi *et al.*<sup>[17]</sup> according to which an individual is classified as sedentary if the PAL is less than 1.40<sup>[18]</sup>. The data collected through the questionnaires, clinical examination and investigations was fed into a spreadsheet and analyzed using SPSS software.

## RESULTS

The study consisted of an analysis of 276 consecutive cases of newly diagnosed CHD, presenting to the CCU of GTB Hospital during the study period. The age of the patients ranged from 27 to 66 years (mean, 49.7 ± 9.5 years) and 44 (15.9%) were below the age of 40 years. Of the 276 subjects 222 (80.4%) were male and 54 (19.6%) were female. The mean age among males was 49.1 ± 9.4 years and among females was 52.3 ± 9.8 years, a significant difference ( $t = 2.27$ ,  $df = 274$ ,  $P = 0.02$ ). Most of the subjects (234; 84.8%) were from an urban background. Of the total, 195 (70.7%) were Hindu by religion, 77 (27.9%) were Muslim, three were Christian and one was Sikh. A large proportion (246; 89.1%) were currently married. Regarding type of family, 141 (51.1%) came from a nuclear family and 135 (48.9%) belonged to a joint family.

While 46 (16.7%) were currently unemployed, 87 (31.5%) were unskilled, 81 (29.3%) were semi-skilled, and only 51 (18.5%) were a skilled worker or higher. Eleven (4.0%) were retired from work. The education level of the cases too were skewed towards a lower level, with the majority (78; 28.3%) being illiterate, 52 (18.8%) having a primary education, 123 (44.6%) having middle to higher levels of schooling and only 23 (8.3%) being college graduates. Among the cases, the clinical diagnosis was established as ST wave elevation MI (STEMI) in the vast majority (209; 75.7%), as non-STEMI type MI in 53 (19.2%) and as angina pectoris in 14 (5.1%).

The predominant diet for 114 (41.3%) of the cases was vegetarian while 162 (58.7%) were non-vegetarian by habit. Two-thirds (187; 67.8%) were using predominantly mustard oil for cooking at home, 11 (4.0%) sunflower oil, 62 (22.4%) soybean oil while the remaining 16 (5.8%) had been using other types of cooking oil. The 24-h recall method was used for dietary assessment. The majority (248; 89.8%) of the respondents had a calorie deficit, mean deficit being 734 ± 409 Calories per day from the recommended calorie intake. A few of the subjects (33; 11.9%) had an excess fat intake daily, with the mean excess intake being 26.8 ± 30.2 g/d above the recommended total daily fat intake.



**Table 1 Results of hematological investigations of the cases**

| Investigation           | <i>n</i> | Mean  | Median | Minimum | Maximum | SD    |
|-------------------------|----------|-------|--------|---------|---------|-------|
| Lipid profile (mg/dL)   |          |       |        |         |         |       |
| Total cholesterol       | 276      | 159.3 | 152.0  | 65      | 424     | 48.47 |
| Triglycerides           | 268      | 135.4 | 115.5  | 39      | 556     | 80.0  |
| HDL                     | 267      | 36.5  | 36.0   | 13      | 57      | 7.73  |
| LDL                     | 257      | 94.8  | 90.0   | 19      | 312     | 41.66 |
| Glycosylated hemoglobin |          |       |        |         |         |       |
| HbA1c (%)               | 68       | 10.1  | 10.2   | 4.5     | 13.2    | 1.73  |
| Blood sugar (mg/dL)     |          |       |        |         |         |       |
| Fasting                 | 212      | 112.6 | 98.0   | 63      | 322     | 43.46 |
| Post-prandial           | 208      | 163.4 | 141.0  | 68      | 547     | 69.75 |

*n*: No. of cases for which a value was available; LDL: Low density lipoprotein cholesterol; HDL: High density lipoprotein cholesterol.

Only 10 (3.6%) had a PAL of 1.40 or more and could be termed as active. The other 266 (96.4%) had a PAL of < 1.40 and were classified as sedentary. Among the 54 female patients in the present study, 11 were currently menstruating whereas the majority (43) were post-menopausal. Among the female patients, none was currently taking oral contraceptive pills.

A set of questions were asked regarding their lifestyle habits. Among the subjects, 73 (26.4%) were current alcohol users with a total of 89 (32.2%) being lifetime ever users of alcohol, i.e. either current users or regular users in the past. Among the total, 188 (68.1%) were lifetime ever smokers with 154 (55.8%) of the subjects being current smokers. Of the current smokers (*n* = 154), the majority (126; 81.8%) smoked "beedis", 16 (10.4%) smoked cigarettes and 12 (7.7%) smoked both. The current smokers had been smoking for a mean of  $21.7 \pm 12.2$  years. If we consider only the male cases (*n* = 222), the proportion of current smokers was 149 (67.1%) and the proportion of "beedi" smokers was 122 (55.0%).

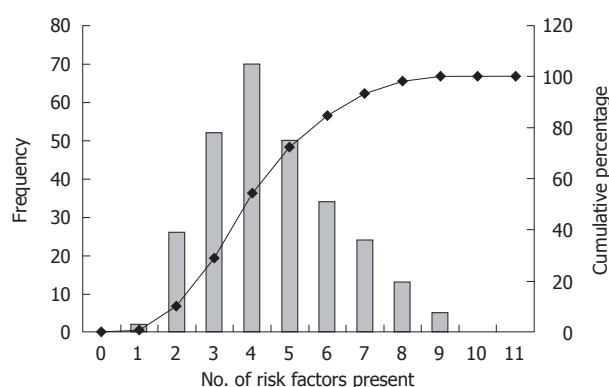
The medical history of the patients was also elicited. Among the 276 cases of CHD, 92 (33.3%) were known hypertensives, 134 (48.6%) were not hypertensive and the status of the remaining 50 (18.1%) was not known. Among the known hypertensives, only 39 (42.4%) were taking medication for it regularly, 45 (48.9%) were taking medication but not regularly, while 08 (8.7%) were not taking any medication at all. Of the total, 50 (18.1%) were known diabetics, 191 (69.2%) had no history of diabetes and the status of 35 (12.7%) was not known. Anthropometric measurements were recorded as part of the study. BMI ranged from 13.8 to 33.7 kg/m<sup>2</sup> (mean,  $23.2 \pm 3.8$  kg/m<sup>2</sup>). Waist circumference was studied separately by gender. As per the new Indian consensus guidelines, waist circumference was found to be raised in 157 (56.9%) of the subjects.

The results of the hematological investigations are presented in Table 1. Taking the standard cutoffs for dyslipidemia, it was seen that 44 (15.9%) had raised total cholesterol (> 200 mg/dL), 80 (29.9%) had raised triglycerides (> 150 mg/dL), 80 (39.3%) had raised low density lipoprotein (LDL) cholesterol (> 100 mg/dL) and 188

**Table 2 Presence of conventional risk factors among the newly diagnosed coronary heart disease patients in our study (*n* = 276)**

| Risk factor                  | No. for which value was available | Proportion having the risk factor |
|------------------------------|-----------------------------------|-----------------------------------|
| Inadequate physical activity | 276                               | 266 (96.4)                        |
| Reduced HDL cholesterol      | 267                               | 188 (70.4)                        |
| Raised waist circumference   | 276                               | 157 (56.9)                        |
| Current smoker               | 276                               | 154 (55.8)                        |
| Raised LDL cholesterol       | 257                               | 101 (39.3)                        |
| Hypertension                 | 276                               | 92 (33.3)                         |
| Obesity <sup>1</sup>         | 276                               | 91 (33.0)                         |
| Raised triglyceride          | 268                               | 80 (29.9)                         |
| Diabetes                     | 276                               | 50 (18.1)                         |
| Raised total cholesterol     | 276                               | 44 (15.9)                         |
| Stress                       | 276                               | 38 (13.8)                         |

<sup>1</sup>Classified by the new guidelines for obesity among Indians. LDL: Low density lipoprotein cholesterol; HDL: High density lipoprotein cholesterol.

**Figure 1 Distribution of cases by the number of conventional risk factors present (*n* = 276).**

(70.4%) had reduced high density lipoprotein (HDL) cholesterol (< 40 mg/dL among males and < 50 mg/dL among females). The percentages are of the number of subjects for whom each investigation result was available. Only 50 (18.1%) of the cases had a clear family history of CHD, 180 (65.2%) had a negative family history while the family history of 46 (16.7%) was not known. The depression, anxiety and stress levels among the cases were assessed using the DASS questionnaire. Using the normative cut-offs for the subscales of the DASS scale, 55 (19.9%) of the cases had depression, 73 (26.4%) had anxiety, while 38 (13.8%) had stress.

Table 2 summarizes the presence of the conventional risk factors that we studied among the cases. Based on this, a further analysis was carried out to study the distribution of the conventional risk factors among the CHD cases. The distribution by the number of risk factors is shown in Figure 1. There was not a single case that did not have one or more of the risk factors studied.

## DISCUSSION

CHD is a rising epidemic of the modern world. A com-

prehensive study of the demographic and epidemiological profile of 276 consecutive cases with newly diagnosed CHD, admitted to a large tertiary care hospital in Delhi, India was carried out. It was seen that the mean age of the cases was  $49.7 \pm 9.5$  years, with the youngest case of an acute coronary event occurring at the age of 27 years. The mean age in our study is much lower than that found in the Iran study (60.6 years)<sup>[7]</sup>. The INTERHEART study had found the mean age among the Indians ( $53.0 \pm 11.4$  years) to be significantly lower than in other countries<sup>[8]</sup>. The mean age was also lower than that reported in Kerala, India ( $58.3 \pm 15.6$  years)<sup>[19]</sup>. The INTERHEART study had found the proportion of cases below 40 years to be 11.7%, compared with 15.9% in the current study.

The proportion of males in our study was 80.4%, with females comprising only 19.6% of the total. This concurs with previous findings that males predominate among the coronary event cases presenting to hospital<sup>[7,8,19,20]</sup>. The mean age was found to be significantly lower among males compared with females, again in line with international experience<sup>[7,8,19]</sup>. In our study, most of the patients were illiterate (28.3%), with others having done various levels of schooling, and only 8.3% being college graduates. Gupta *et al.*<sup>[21]</sup> had found a link between the prevalence of CHD and lower education status of the patients.

In our study, a majority of the cases (58.7%) were predominantly non-vegetarian by habit. It has been observed earlier that a diet rich in plant foods is associated with a lower risk of cardiovascular diseases<sup>[9]</sup>. A large scale systematic review of the association between diet and CHD concluded that the beneficial substances in a vegetarian diet have a big role in reducing risk of CHD<sup>[22]</sup>. Most of the patients were found to have a calorie deficit (89.8%) rather than a calorie excess, on eliciting dietary history by a 24-h recall method. A few of the subjects (11.9%) had a daily fat intake that exceeded the recommended upper limit. While the dietary recall method is subject to limitations, and particularly taking a single 24-h recall period, the results that we obtained still point to the fact that CHD occurs in a majority of Indian patients, despite no evident over-nutrition.

A significant factor can be the sedentary lifestyle, especially of the urban population. This was evident by the finding that just about 3.6% of the cases in our study had a PAL that could be termed as “active”, with a large proportion (96.4%) having a PAL suggestive of a sedentary lifestyle. A low level of physical activity has been noted to be a significant risk factor for premature CHD in Indians<sup>[23]</sup>.

A majority of the female patients in our study were post-menopausal (43 out of 54) which reinforces the observation by Rissam *et al.*<sup>[11]</sup> that post-menopausal females need special attention as they constitute a distinct subgroup at a high risk for CHD.

A majority of the patients were found to be current tobacco smokers (53.3%), and a total of 188 (68.1%) subjects were lifetime ever smokers. The proportion was higher than the Iran study where 32% had a history of

smoking<sup>[7]</sup>, but matched the results among South Asians found in the INTERHEART study<sup>[8]</sup>, in which 61.1% of acute MI cases had a history of current and former smoking. A point of special notice was that among the tobacco smokers, a significant proportion (81.8%) smoked “beedis” (a local form of cigarette that has tobacco in a rolled leaf). The risk of tobacco smoking is greater if smoked in the form of a “beedi” than a cigarette. Rissam *et al.*<sup>[11]</sup> reported that tobacco use in India is mainly in the form of “beedis” rather than cigarettes. If we consider just the male cases, two-thirds were current smokers, and more than half (55%) smoked “beedis” exclusively.

The proportion of known hypertensives in our study (33.3%) was similar to that in the CREATE registry study (37.7%)<sup>[24]</sup>, and in the INTERHEART study (29.6%)<sup>[8]</sup>. The proportion of known diabetics was 18.1% in the present study, which matched the findings in the INTERHEART study (20.2%), but was lower than that in the CREATE study (30.4%). An important finding was that less than half (42.4%) of the known hypertensives were taking regular antihypertensive treatment.

Obesity is also known to be one of the conventional risk factors for CHD<sup>[23]</sup>. If classified as per the conventional cut-off of BMI ( $30 \text{ kg/m}^2$  or more), only 19 (6.9%) of the cases could be termed obese. In the CREATE study too (that utilized the older cut-offs), a similar proportion of obesity cases was found (6.2%)<sup>[24]</sup>. However, India has recently published new guidelines regarding the classification of BMI, and if we go by the new cut-off for obesity ( $25 \text{ kg/m}^2$ ), 91 (33%) of the patients could be termed as obese.

The large-scale INTERHEART study indicated that the presence of psychosocial stressors is associated with increased risk of acute MI, but it also acknowledges that measuring stress objectively is a problem<sup>[10]</sup>. In our study, we used the DASS questionnaire to assess depression, anxiety and stress among the cases. It was seen that 19.9%, 26.4% and 13.8%, respectively, had scores indicating the presence of these conditions.

The results of the hematological investigations carried out among the cases were also noted. The mean total cholesterol level was lower in our study ( $159.3 \pm 48.5 \text{ mg/dL}$ ) than that found among MI cases in Tirupati, India<sup>[25]</sup>, in the Kolkata, India study<sup>[26]</sup>, and also in the Iran study<sup>[7]</sup>. The same was noticed for the mean LDL level also. However, the levels of the protective HDL were also found to be lower in our study ( $36.5 \pm 7.7$ ) than in the earlier studies<sup>[7,25,26]</sup>. The levels of serum triglycerides were roughly in the same range as the previous studies. The mean level of glycosylated hemoglobin was found to be very high ( $10.1 \pm 1.7 \text{ mg/dL}$ ), but this can be explained by the fact that the test was carried out in only 68 of the total subjects, indicating that it was probably done only for cases with a high index of suspicion for diabetes.

The waist circumference was classified as per the new consensus national guidelines for India<sup>[14]</sup>. Based on this, it was found that 157 (56.9%) of the cases had an increased waist circumference. It has been stated that based

on current evidence, waist circumference is preferred over waist-hip ratio as a measure of abdominal obesity<sup>[14]</sup>.

Based on an analysis of the conventional risk factors, it was found that all the risk factors were present to some extent among the subjects presenting to the hospital. The two risk factors found to be present most frequently among the cases were inadequate physical activity and abnormal lipid profile. A significant proportion of the cases were also had the known risk factor of tobacco smoking.

We also analyzed the distribution of these known conventional risk factors for CHD among the cases. There was not a single case among the 276 studied, who did not have one or more of the risk factors considered. Nearly 90% ( $n = 248$ ) had three or more risk factors present, indicating the importance of multiple risk factors in the etiology of CHD. More than one-quarter of cases ( $n = 76$ ) had as six or more of the studied risk factors present.

A comprehensive analysis of the presence of conventional risk factors of CHD was carried out among the newly diagnosed cases visiting a tertiary hospital in Delhi. While the risk factors remain generally the same globally, it is important to study the regional epidemiology of the occurrence of cardiovascular disease events.

A limitation of the present study was that the patient recruitment was done through a CCU setting only. The risk profile of the patients who did not come to a health facility may differ from those who did. More community-based studies can be planned to study the risk factor distribution among CHD patients in general. Another limitation of the current study design was that the course of management of the patients in-facility and the subsequent outcomes in terms of coronary angiographies performed, interventional procedures performed, *etc.*, were not recorded. The outcome of the CHD events may differ by the risk factor profile, and further studies can be planned to investigate the prognostic factors for CHD events.

Our finding that there was not even a single case without one or more of the risk factors studied, shows the importance of targeting these risk factors for reducing the burden of CHD in the population. The majority of the CHD patients had multiple (three or more) risk factors present at the time of the event, which means that the focus should also be on reducing the clustering of risk factors in an individual at-risk person, as a step towards the ultimate impact at the community level in terms of reducing the CHD burden of disease.

## COMMENTS

### Background

Currently, cardiovascular diseases are the leading cause of mortality in the developing world, including India. Since the early 1960s, many countries have been able to reduce the rate of coronary heart disease (CHD) and subsequently the death rates due to them by implementing preventive and control measures along with better treatment. In contrast, India still has the highest mortality rates due to CHD amongst all ethnic groups studied so far. Considering also the fact that India has a population in excess of one billion, it becomes pertinent to study the distribution of risk factors for cardiac disease among the Indian ethnic population.

### Research frontiers

The important focus in the current study was to identify the distribution of conventionally regarded risk factors for CHD among newly diagnosed patients of CHD in an Indian population. The observation of the distribution of such risk factors and the study of clustering of more than one risk factor in an individual patient, would help to show the importance of targeting these risk factors for reducing the burden of CHD in the general population.

### Innovations and breakthroughs

A comprehensive analysis of risk factors has been carried out among newly diagnosed patients of CHD. This involved taking detailed personal and family histories, a general physical examination, anthropometric measurements and laboratory investigations. A profile of each individual subject was created so that we could study the clustering of risk factors in each patient.

### Applications

The finding that there was not even a single case without one or more of the risk factors studied, shows the importance of targeting these risk factors for reducing the burden of CHD in the population. The authors have also brought out the clustering effect of risk factors, as a majority of the diagnosed patients had three or more risk factors present. This knowledge can be applied to focus public health attention on identifying "high-risk" individuals in the community who have clustering of risk factors and to aggressively target them with measures to prevent manifest cardiac disease. The other application for a public health approach to cardiac diseases is to renew the attention on reducing the conventional risk factors for CHD among the general population, to achieve a long-term reduction in the burden of disease due to CHD in a large populous country like India.

### Terminology

CHD is a narrowing of the small blood vessels that supply blood and oxygen to the heart. CHD is usually caused by a condition called atherosclerosis. Atherosclerosis is a condition in which fatty material collects along the walls of arteries. This fatty material thickens, hardens (forms calcium deposits), and may eventually block the arteries.

### Peer review

In this paper the authors report the results of a study performed to assess the major risk factors present in an Indian sample of 276 consecutive subjects newly diagnosed with coronary artery disease admitted to the Coronary Care Unit of Guru Tegh Bahadur Hospital in Delhi. The study is well performed and the results are interesting.

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## Events Calendar 2011

January 25

Moving towards a national strategy  
for Chronic Obstructive Pulmonary  
Disease  
London, United Kingdom

February 24-26

Abdominal Obesity 2011 -  
2nd International Congress on  
Abdominal Obesity  
Buenos Aires, Argentina

February 25-27

CardioRhythm 2011  
Hong Kong, China

March 19-26

Cardiology Update: Caribbean  
Cruise  
San Diego, CA, United States

March 25

Cardiology for General Practice

London, United Kingdom

April 1-2

11th Annual Spring Meeting on  
Cardiovascular Nursing  
Brussels, Belgium

April 14-16

EuroPrevent 2011  
Genova, Switzerland

April 30-May 4

ATC 2011 - 2011 American  
Transplant Congress  
Philadelphia, United States

May 11-14

3th Radiochemotherapy and  
Brachitherapy Congress & 6th  
Medical Physycs Meeting  
Córdoba, Argentina

May 15-18

ICNC10 - Nuclear Cardiology and

Cardiac CT

Amsteden, The Netherlands

May 19-20

Adult Cardiovascular Pathology  
London, United Kingdom

May 20-22

XXIX NATIONAL CARDIOLOGY  
CONGRESS  
Córdoba, Argentina

May 20-22

4th Meeting Uremic Toxins and  
Cardiovascular Disease  
Groningen, The Netherlands

May 21-24

Heart Failure Congress 2011  
Gothenburg, Sweden

June 2-5

CODHy 2011 - The 1st Asia Pacific  
Congress on Controversies to

Consensus in Diabetes,  
Obesity and  
Hypertension  
Shanghai, China

June 26-29

EHRA EUROPACE 2011  
Madrid, Spain

June 29-July 1

Hands-on Cardiac  
Morphology - Summer Edition  
London,  
United Kingdom

August 27-31

ESC 2011 - European Society of  
Cardiology Congress 2011  
Paris, France

October 23-26

9th International Congress on  
Coronary Artery Disease  
Venecia, Italy



## INSTRUCTIONS TO AUTHORS

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#### Columns

The columns in the issues of *WJC* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in cardiology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of cardiology; and (13) Guidelines: To introduce consensus and guidelines reached by international and national academic authorities worldwide on the research in cardiology.

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- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID: 2516377 DOI: 10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI: 10.1097/01.ju.0000067940.76090.73]

*No author given*

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI: 10.1136/bmj.325.7357.184]

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- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI: 10.1046/j.1526-4610.42.s2.7.x]

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- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI: 10.1097/00003086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS A Careaction* 2002; 1-6 [PMID: 12154804]

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*Personal author(s)*

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorffheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

**Patent** (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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