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Could Accidental Ischemic Attacks Protect Against Subsequent Ischemic Reperfusion Injury?

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Abstract

Heart failure is the end result of various cardiac diseases that might be of ischemic or non-ischemic etiology. Implantation of ventricular assisting devices has been introduced as a bridge to heart transplantation, when heart failure reaches a critical degree of decompensation. The ischemic background of heart failure was suggested to have a protective effect in comparison to the non-ischemic background, based on the principles of ischemic conditioning. This manuscript tries to provide a short and concentrated answer to the question; whether or not the accidental ischemic attacks could provide a degree of protection during subsequent ischemic- reperfusion injury, based on basic and clinical knowledge.

Keywords

Cardiomyopathy, Heart failure, Ventricular assist device implantation, Ischemic preconditioning, Ischemic reperfusion injury

Introduction

Ischemic pre-conditioning (IPC) has been investigated in various animal species [1], where it has been found to protect against post-ischemic contractile dysfunction as well as ischemic- reperfusion injury (IRI) in the heart and the liver [2,3]. The significant protective effects of IPC have paid the attention to the question; whether some protection could be achieved through the accidental ischemic attacks.

The mechanisms underlying IPC are not totally clear. However, a considerable progress has been achieved towards the identification of many mediators involved in its mechanism of action. A role of paracrine mediators, released during the period of ischemia has been suggested. Various studies have also suggested a role of adenosine, acetylcholine, catecholamines, angiotensin II, bradykinin, endothelin, opioids, nitric oxide (NO) and reactive oxygen species (ROS) [2].

For instance, the breakdown of ATP in myocytes during periods of ischemia results in adenosine, which is involved in triggering pre-conditioning in most of the studied animal species and humans. Blockage of adenosine A_1 receptors in myocytes was found to block the protective effects of IPC, while re-stimulation of these receptors re-established the protective effects [2]. In addition to adenosine, protein kinase C, Ca^{2+}, opioid receptors, ROS and mitochondrial KATP could play important roles in mediating the protective effects achieved by IPC.

It has recently been established that the activation of KATP channels antagonizes the opening of mitochondrial permeability transition pore during reperfusion, thereby preventing uncoupling of the mitochondria. In addition, heme-oxygenase up regulation and NO have been identified to mediate IPC and remote IPC [2,4,5].

The half- lives of the above mentioned mediators and pathways could provide an answer to our addressed question. Accordingly, even if the accidental ischemic attacks were able to provide the protective effect of IPC, such protection would be expected to last for limited periods (2-3 hours) [6]. In other words, IPC should be applied shortly before the IRI to be able to exert its protective effects [7,8]. In addition, it is well established that the duration of the ischemia- reperfusion cycles plays an essential role in IPC, with cycles lasting less than 10 minutes are able to provide protection, while cycles of more than 10 minutes duration are not protective and may be harmful [7,8]. Accordingly, the accidental ischemic attacks don't seem to be able to provide the protective role of IPC, and the following is a clinical evidence of that.

Methodology

This is a retrospective randomized study, where 46 cardiomyopathy patients, subjected to left ventricular assist device (LVAD) implantation by our surgical team between 2011 and 2014, were randomized in 2 groups (23 patients each), based on the ischemic and the non-ischemic backgrounds of the advanced left ventricular systolic dysfunction, which was defined as left ventricular ejection fraction (LVEF) <40%, based on the echo-cardiographic findings. The classification into ischemic and non-ischemic cardiomyopathy patients was based on the referral data from the cardiology department, were careful history, examination and investigations were performed, including echocardiography and coronary angiography, when indicated. The ischemic background was claimed when the cardiomyopathy was associated with >75% stenosis in at least one major coronary artery, or when a history of myocardial infarction, and or infarct scar changes on the ECG, was identified. The non-ischemic cardiomyopathy (dilated CMP) was claimed as left ventricular dilatation and dysfunction in the absence of any of the above.

Calculation of the INTERMACS score

The INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) scale provides a classification of the

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Table 1: INTERMACS scale for classifying patients with advanced heart failure.

Profiles	Description
INTERMACS 1	*Hemodynamic instability in spite of increasing doses of catecholamines and/or mechanical circulatory support with critical hypo-perfusion of target organs (severe cardiogenic shock)*
INTERMACS 2	*Intravenous inotropic support with acceptable blood pressure, but rapid deterioration of kidney function, nutritional state, or signs of congestion*
INTERMACS 3	*Hemodynamic stability with low or intermediate, but necessary due to hypotesion, doses of inotropics, worsening of symptoms, or progressive kidney failure*
INTERMACS 4	*Temporary cessation of inotropic treatment is possible, but the patient presents frequent symptom recurrences and typically with fluid overload*
INTERMACS 5	*Complete cessation of physical activity, stable at rest, but frequently with moderate water retention and some level of kidney dysfunction*
INTERMACS 6	*Minor limitation on physical activity and absence of congestion while at rest. Easily fatigued by light activity*
INTERMACS 7	*Patient in NYHA functional class II or III with no current or recent unstable water balance*

NYHA: New York Heart Association

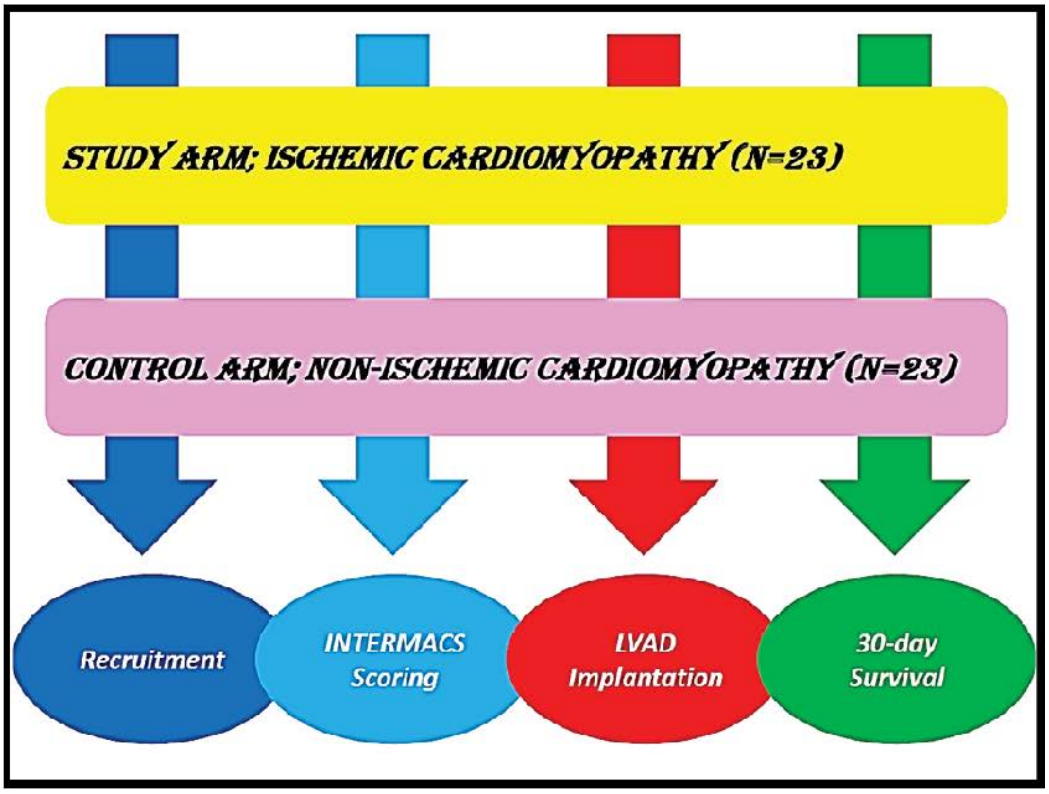

Figure 1: Diagrammatic representation of the study design.

Study design- Retrospective randomized clinical study

Study arm- LVAD patients with ischemic cardiomyopathy

Control arm- LVAD patients with dilated cardiomyopathy

Intervention- LVAD implantation

Study end points- INTERMACS score before LVAD implantation

Survival after LVAD implantation

patients of the advanced heart failure, according to their hemodynamic profile and the level of target organ damage (Table 1) [9]. The INTERMACS classification is an outcome of the ventricular assist device, multi-center registry, which aimed at unifying the criteria of the clinical state of the advanced heart failure patients [9,10]. The development of the INTERMACS classification system optimized the pre-operative risk prediction, and accordingly, the decision making regarding the therapeutic strategy. The INTERMACS scale has been confirmed as a reliable predictor of mortality [9,10] and postoperative complications following the implantation of ventricular assist devices [11]. Based on the history, clinical examination and investigations, the patients were assigned a pre-operative INTERMACS score, reference to the criteria listed in table 1.

LVAD implantation

Based on the INTERMACS score, the patients were indicated for LVAD implantation, either as a bridge to transplantation or as a destination therapy. The pre-, intra-, and post-operative management were performed for all patients of both groups according to our standard institutional protocols.

Study end points

In the present study, we concentrated on the INTEMACS score pre-operative and the 30-day survival post-operative as the main targets of comparison between the study groups (Figure 1).

Statistical analysis

The statistical analysis was performed using Microsoft Excel 2007 for the calculation of means and standard deviations. Comparison between both groups regarding the study parameters was done using the GraphPad Prism 5 Demo and non- paired T test to identify significant differences. Kaplan-Meier survival analysis and the log rank test were applied to confirm the comparison between groups regarding the cumulative survival. P values ≤ 0.05 were considered significant.

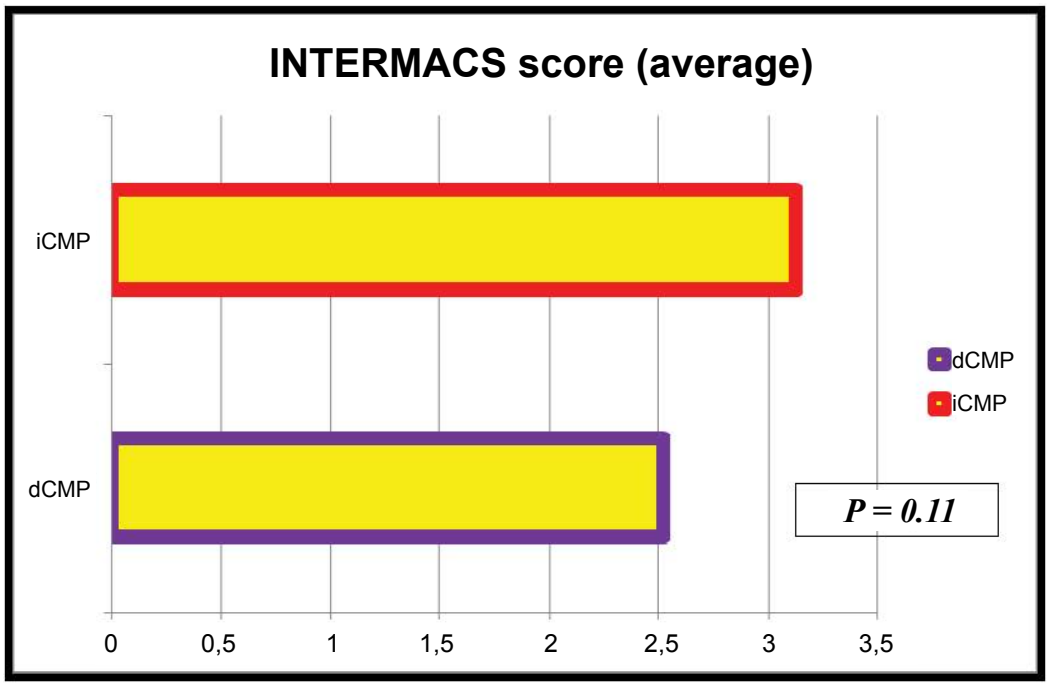

Figure 2: The average INTERMACS scores of both study groups. The difference was non-significant *(P>0.05)*

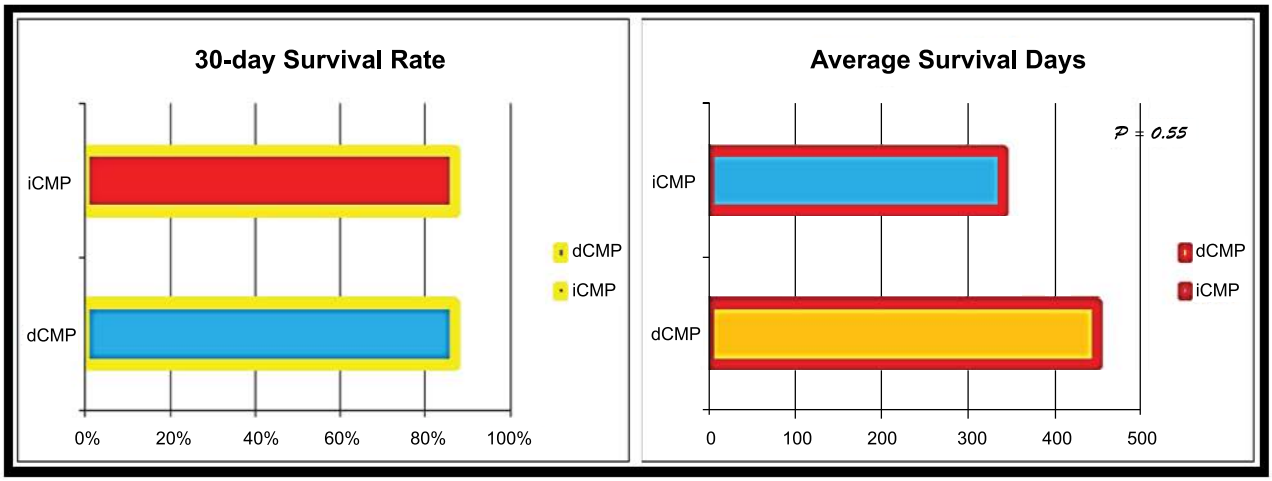

Figure 3: 30-day survival rates and the average survival days of both study groups. All rates showed non-significant differences (*P*>0.05).

Results

INTERMACS score

The average INTERMACS score of the dCMP group was 2.5 ± 1.3, compared to 3.1 ± 1.2 of the iCMP group. The difference between both groups was non-significant (P=0.11) (Figure 2).

Postoperative survival

The 30-day survival rates of both groups were similar (87%), where 3 patients died within the first 30 days postoperative in each group. However, the average survival of the dCMP patients was 449.39 days, compared to 399.86 days of the iCMP patients. The difference between both groups was not significant (P=0.55) (Figure 3).

Kaplan-Meier analysis

The Kaplan-Meier survival analysis and the log rank test confirmed the absence of a significant difference between both groups regarding the postoperative survival, which denies the ischemic background to be an independent predictor of patient survival (Chi-square=0. 314 and P=0.575) (Figure 4).

Discussion

Most of the previous clinical studies reported the benefit of the medical therapy for both iCMP and dCMP, however, with higher mortality and weaker response to treatment in the patients of the ischemic background, particularly in response to beta-blockers [12-14] and ACE inhibitors [15,16]. Accordingly, it was interesting to address this question on the level of the surgical therapy and postoperative survival, especially with the increasing evidence of the value of the ischemic preconditioning technique.

In a study of 3787 systolic heart failure patients, the ischemic background was a significant independent predictor of mortality during follow-up [17]. Supportively, Stevenson et al. [18] concluded the coronary heart disease as an independent mortality predictor and stated the ischemic background as an indication of the priority listing for heart transplantation [18]. Similar findings were reported by several studies, where the overall all statements were that; the ischemic heart failure has a worse prognosis than the non-ischemic heart failure [19,20]. Ng et al. [21] showed a greater symptomatic improvement during follow-up for the non-iCMP patients, who showed better ventricular remodeling than the patients of iCMP, however, the difference in mortality was not significant [21].

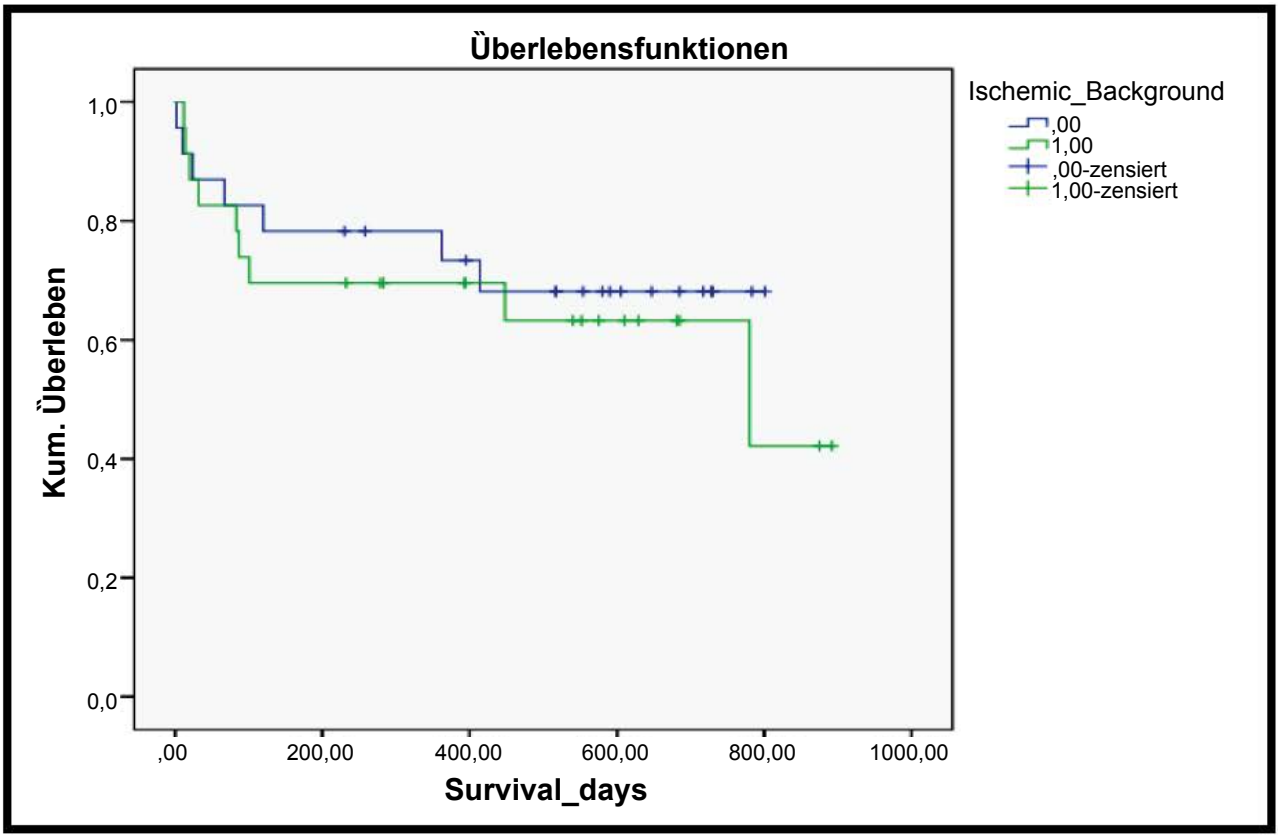

Figure 4: Kaplan-Meier analysis of postoperative survival based on the presence or absence of the ischemic background.

Such worse prognosis associated with iCMP was referred to the older age of the patients, the presence of many other co-morbidities, and the potential association with a higher level of neuro-hormonal and immunological activation [21-23], where, in both dCMP and iCMP, there is a risk of sudden death due to heart failure, with an additional risk arising from the coronary disease, which might result in necrotic and or scarring tissue that might have the potential to impede the ischemic preconditioning [18,19].

On the other side, data from the Framingham community study, claimed the ischemic heart failure to be associated with better clinical outcomes than those of the non-ischemic heart failure [24]. In addition, the current guidelines do not distinguish between the heart failure etiologies [25,26], because whatever the basic etiology was, the subsequent pathophysiology of heart failure would be similar [27].

In the middle between both claims, Lourenco et al. [28] reported greater in-hospital mortality of iCMP, based on a univariate analysis. However, the multivariate analysis revealed that the etiology is not an independent mortality predictor [28]. Accordingly, they stated no significant difference between iCMP and non-iCMP regarding the long-term prognosis. The results that go with those of the recent registries of acute heart failure, such as *ADHERE* [23], *OPTIMIZE-HF* [24] and *The Euro Heart Failure Survey* [29], where the increased mortality risk associated with iCMP may be practically observed in patients with preserved systolic functions, however, in patients with advanced systolic heart failure, the ischemic background has no specific impact on the prognosis [30].

While all the previous studies focused on the prognosis and survival of heart failure in response to medical therapy, in the present study, we provided a statement regarding the survival following LVAD implantation. As LVAD implantation involves exposing the heart to an ischemic reperfusion injury (due to cardiopulmonary bypassing), the principles of ischemic preconditioning raised the attention towards the notion that the previous ischemic attacks might have provided some degree of protection that could be reflected on the postoperative survival.

In the present study, the INTERMACS scoring reflected the prognosis of heart failure based on the ischemic and non-ischemic etiologies. However, the survival after LVAD implantation reflected whether or not the accidental ischemic attacks could provide a degree of protection against the subsequent ischemic reperfusion injuries. Our results clearly showed similarity between the ischemic and the non-ischemic cardiomyopathy patients in the INTERMACS scoring pre-operative and in the survival postoperative.

As the present study is a retrospective short comment, whose study groups are of a relatively small size, with many clinical parameters (such as ventilation time, ICU stay, requirement of ECMO and total in hospital stay) were not included, a prospective randomized study is required for further confirmation of our results.

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