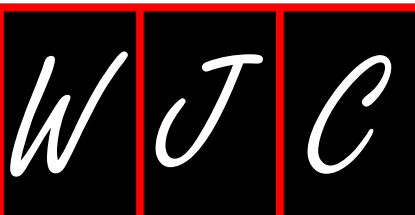


# World Journal of *Cardiology*

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## Percutaneous closure of patent foramen ovale: "Closed" door after the last randomized trials?

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### Abstract

Patent foramen ovale (PFO) percutaneous closure has previously been an accepted intervention for the prevention of recurrent cryptogenic stroke on the basis of observational studies. However, randomized trials have been lacking until now. Three recently published randomized trials (CLOSURE I, PC and RESPECT) do not demonstrate the superiority of this intervention versus optimal medical therapy, therefore making this practice questionable. Nonetheless, these trials have had certain pitfalls, mainly a lower than initially estimated number of patients recruited, therefore lacking sufficient statistical power. On the other hand, different closure devices were used in the three trials. In two of them (PC and RESPECT), the Amplatzer PFO Occluder was used and the STARflex device was used in the other one (CLOSURE I). Taken altogether, a meta-analysis of these three trials does not demonstrate a statistically significant benefit of percutaneous PFO closure (1.9% vs 2.9%;  $P = 0.11$ ). However, if we analyze only the PC and RESPECT trials together, in which the Amplatzer PFO Occluder was used, a statistically significant benefit of percutaneous PFO closure is observed (1.4% vs 3.0%,  $P = 0.04$ ). In conclusion, our interpretation of these trials is that the use of a dedicated, specifically designed Amplatzer PFO device could possibly reduce

the risk of stroke in patients with PFO and cryptogenic stroke. This consideration equally applies to patients who have no contraindications for anticoagulant or antithrombotic therapy.

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**Key words:** Patent; Foramen; Ovale; Closure; Percutaneous; Device; Cryptogenic; Stroke; Risk

**Core tip:** Percutaneous patent foramen ovale (PFO) closure has been used for the prevention of recurrent cryptogenic stroke on the basis of observational studies; however, recent randomized trials do not support its use for this indication. A detailed analysis of these randomized trials could suggest that when the Amplatzer PFO Occluder is used, the risk of stroke is reduced.

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### COMMENTARY ON HOT TOPICS

Patent foramen ovale (PFO) is present in a very high proportion of healthy subjects but as its frequency is higher in patients that have suffered a cryptogenic stroke, PFO has been accepted as a potential cause of stroke, especially in younger patients and in the presence of atrial septal aneurysm<sup>[1-3]</sup>. As a result, percutaneous closure of PFO has been performed in some patients that have suffered a cryptogenic stroke and in whom a PFO has been demonstrated. The indications of this procedure have been widely debated. Guidelines have been conservative, accepting this strategy only for patients with recurrent

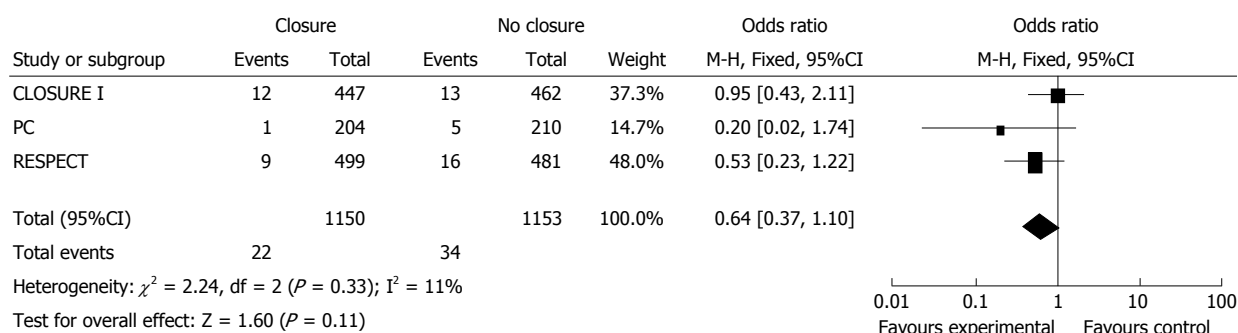


Figure 1 Meta-analysis of all three randomized trials.

stroke despite antithrombotic therapy<sup>[4]</sup>, but this procedure has also been performed in many patients after a first stroke, mainly in younger patients and in those with a concomitant atrial septal aneurysm.

Non-randomized studies suggested that the recurrence of stroke in patients with cryptogenic stroke was lower if a percutaneous closure of PFO was performed, compared with patients that remained on medical therapy alone<sup>[2,5,6]</sup>. However, the main limitation for a wider acceptance of percutaneous closure has been the absence of randomized trials<sup>[4]</sup>.

Last year, the final results of the CLOSURE I trial were published. In this study, 909 patients between 18 and 60 years of age with a cryptogenic stroke (72%) or transient ischemic attack (TIA) (28%) and a PFO were randomized to percutaneous closure using the STARflex (NMT Medical Inc.) device in addition to medical treatment (aspirin 81 or 325 mg daily for two years and clopidogrel for the first six months) or to medical treatment alone (aspirin 325 mg daily and/or warfarin for a target INR 2.0-3.0) and followed-up for two years<sup>[7]</sup>. This study was negative, since the primary endpoint at 2 years (stroke or TIA, death from any cause during the first 30 d, or death from neurological causes between 31 d and 2 years) was not reduced with percutaneous closure (5.5% *vs* 6.8% in the medical therapy group;  $P = 0.37$ ). Moreover, the risk of stroke at 2 years was similar between both groups of patients (2.9% with percutaneous closure *vs* 3.1% with medical treatment;  $P = 0.79$ ). The CLOSURE I had some limitations, such as a much lower than initially intended number of patients recruited (909 instead of 1600)<sup>[8]</sup>, patients with either stroke or TIA were included, three of twelve (25%) strokes occurred within 30 d after the procedure, other possible causes of stroke became apparent in patients who had recurrences, patients with prothrombotic disorders were excluded, and randomization was not locally blind. Another possible explanation for the negative results is the relatively short follow-up period<sup>[9]</sup>.

Nonetheless, these results were very discouraging, especially for interventional cardiologists. On top of this, two other negative randomized trials regarding the same issue but using a device specifically designed for PFO closure (Amplatzer PFO Occluder, St Jude Medical) have been published in March of this year<sup>[10,11]</sup>. The RESPECT trial<sup>[10]</sup> randomized 980 patients to medical treatment or PFO closure using the Amplatzer PFO Occluder. The

primary endpoint was the occurrence of recurrent ischemic stroke or early death in patients 18-60 years of age. The intention-to-treat analysis was negative (HR = 0.49, 95%CI: 0.22-1.11,  $P = 0.08$ ), but due to a high dropout rate in the medical treatment group, the between-group difference was significant in the rate of recurrent stroke in the pre-specified per-protocol cohort (HR = 0.37, 95%CI: 0.14-0.96,  $P = 0.03$ ) and in the as-treated cohort (HR = 0.27, 95%CI: 0.10-0.75,  $P = 0.007$ ).

The PC trial randomized patients with a PFO and ischemic stroke, TIA or a peripheral thromboembolic event to undergo closure of the PFO with the Amplatzer PFO Occluder or to receive medical therapy. The primary endpoint was a composite of death, nonfatal stroke, TIA or peripheral embolism and was not reduced with percutaneous closure (HR = 0.63, 95%CI: 0.24-1.62,  $P = 0.34$ ). Non-fatal stroke occurred in 1 patient (0.5%) in the closure group and 5 patients (2.4%) in the medical therapy group (HR = 0.20, 95%CI: 0.02-1.72,  $P = 0.14$ ).

A simplistic interpretation of these three trials could lead us to conclude definitively that percutaneous closure of PFO is not effective in reducing the risk of stroke in patients with cryptogenic stroke. Since these trials have been flawed by marked difficulties in patient recruitment, it is evident that each of them individually will probably lack sufficient power to prove any possible differences. In this sense, if we perform a pooled analysis from the 3 trials, including 2303 patients overall, percutaneous closure of PFO does not reduce the incidence of stroke (1.9% *vs* 2.9%,  $P = 0.11$ ; Figure 1). However, if we include only the 2 trials in which an Amplatzer PFO Occluder device, specifically designed for PFO, was used, percutaneous closure was associated with a significant reduction in the incidence of stroke (1.4% *vs* 3.0%  $P = 0.04$ ; Figure 2).

Possible explanations for these differences may be the following: the STARflex closure system has been associated with a significantly higher thrombosis rate at 30 d than the Amplatzer PFO Occluder device in two different studies, 3.6% *vs* 0%,  $P < 0.01$  and 5.7% *vs* 0%,  $P < 0.05$ <sup>[12,13]</sup>, and the incidence of atrial fibrillation<sup>[14]</sup> has also been documented more frequently at 30 d with STARflex (4.5% *vs* 1.3%;  $P = 0.02$ ). Also, a lower rate of periprocedural complications in the PC and respect trials could partly explain the better results of percutaneous closure in the PC and RESPECT trials.

Our interpretation of these trials is that the use of a dedicated, specifically designed Amplatzer PFO device

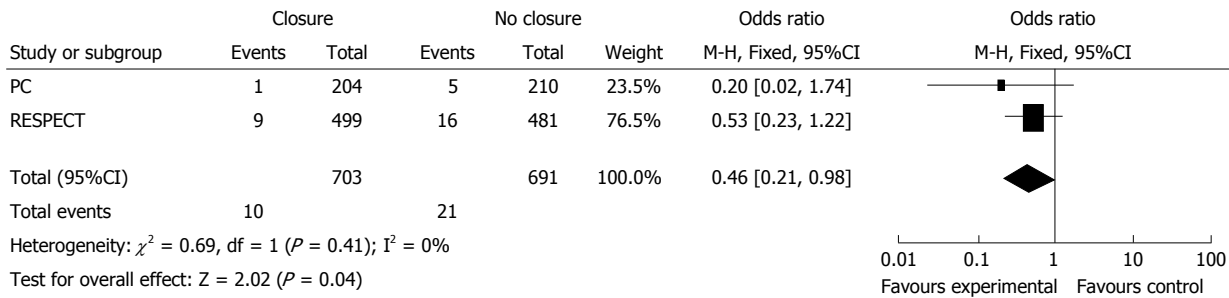


Figure 2 Meta-analysis of the two trials using an Amplatzer Patent Foramen Ovale Occluder.

could possibly reduce the risk of stroke in patients with PFO and cryptogenic stroke. Therefore, although present evidence does not support PFO closure for the prevention of recurrent cryptogenic stroke, a detailed analysis of recent randomized trials can make us consider that the door for PFO closure might not be entirely closed. This consideration equally applies to patients who have no contraindications for anticoagulant or antithrombotic therapy.

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## Physiology of natriuretic peptides: The volume overload hypothesis revisited

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### Abstract

The discovery of the natriuretic peptide system in the early 1980s aroused great interest among clinical cardiologists. The heart was not a mechanical pump alone, but also an endocrine organ that had powerful effects on blood circulation. Natriuretic peptides caused both natriuresis and diuresis, and they responded to a volume overload which caused either stretch or pressure on the heart. As a result, the findings led to the conclusion that the human body had a hormone with effects similar to those of a drug which treats high blood pressure. Later, it became evident that the volume contraction was fortified by extrarenal plasma shift. Here, a hypothesis is presented in which the role of natriuretic peptides is to regulate oxygen transport as the volume contraction leads to hemoconcentration with an increased oxygen-carrying capacity. Wall stress, either chemical or mechanical, changes the oxygen gradient of the myocardium and affects the diffusion of oxygen within a myocyte. In support of this hypothesis, hypoxia-response elements have been found in both the atrial natriuretic peptide and the brain natriuretic peptide genes.

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**Key words:** Natriuretic peptides; Hypoxia; Hemoglobin concentration; Volume overload

**Core tip:** A new concept is suggested for the understanding of the physiology of natriuretic peptides. Both chemical and physical challenges will ultimately increase the oxygen consumption of the heart which is the factor regulating the release of natriuretic peptides. Diuresis, natriuresis and plasma shift lead to hemoconcentration and the oxygen transport in human body will be enhanced.

Arjamaa O. Physiology of natriuretic peptides: The volume overload hypothesis revisited. *World J Cardiol* 2014; 6(1): 4-7 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i1/4.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i1.4>

### INTRODUCTION

In a recent state-of-the-art review, Mangiafico *et al*<sup>[1]</sup> discuss the possibility of inhibiting the natriuretic peptide system by neutral endopeptidases as an evolving strategy to treat hypertension and heart failure. The concept behind this review and the related drug trials, such as in the case of Solomon *et al*<sup>[2]</sup>, has been that both atrial natriuretic peptide [ANP (A-type)] and brain natriuretic peptide [BNP (B-type)] are secreted from the heart as a result of direct wall stress, caused either by stretch or pressure affecting cardiocytes, to protect the human body from a volume overload. NT-proBNP especially, the biologically inactive sequence of proBNP with a long half-time and circulating in blood, has been utilized either as an indicator of the metabolism of natriuretic peptides or as a guide of treatment in a wide array of heart diseases. The hypothesis was formulated about thirty years ago when a large and rapid intravascular volume increase resulted in high plasma levels of ANP in rats<sup>[3]</sup> and since then has prevailed without an alternative interpretation. At that time, it was also shown that an infusion of rat heart atrial extracts into a rat's circulation brought about massive diuresis and natriuresis<sup>[4]</sup>, reaffirming the hypothesis.

These findings were greeted with excitement in cardiology; now we had an endogenous hormone available that could combat all pressure-caused heart diseases, similar to those of the drugs previously developed to treat high blood pressure. The large numbers of articles published on natriuretic peptides, more than 28000 by the end of 2013, reflect the high expectations in clinical cardiology towards these peptides over a broad time frame, but perhaps also that the physiological role of the natriuretic peptide system in healthy humans has not been definitely clarified. As a result, the significance of the natriuretic peptide as a tool in cardiology has remained obscure.

## PHYSIOLOGY OF NATRIURETIC PEPTIDES

The conclusion that a direct mechanical load on myocytes is the key factor regulating the synthesis and release of the natriuretic peptide system, occurring across the whole animal kingdom, is rather confusing as it bypasses the function of nervous stretch receptors in the atria and disregards the effects of variable flow conditions in the atrial lumen occurring during physical activity. In addition, terrestrial mammals living in a dry and warm environment do not experience large intravascular volume overloads but, on the contrary, are constantly in danger of becoming dehydrated. In his review on volume and pressure regulation, Guyton, the single author of several textbooks of medical physiology and a specialist in blood pressure regulation, did not refer to the natriuretic peptide system as a pressure controller at all, a role which he gave solely to the kidneys<sup>[5]</sup>. What was not known in the early 1980s and became evident later, was that a natriuretic peptide has strong extrarenal vascular actions, contributing to contracting the plasma volume by transferring fluid and plasma protein from plasma to interstitial compartments<sup>[6]</sup>.

Apart from the pharmacological interest in developing a new class of drugs to treat high blood pressure, based on the volume overload hypothesis, Baertschi *et al*<sup>[7]</sup> showed that hypoxia was a direct and sufficient stimulus for ANP release from an isolated rodent heart. Later, hypoxia-sensitive elements were found from the promoter sequence of both the *ANP* and the *BNP* genes<sup>[8,9]</sup>. In line with these findings, there are many studies, performed with isolated myocytes, heart muscle strips and animals, which clearly provide evidence that there is a hypoxia sensitive component in the release mechanism of the natriuretic peptide system. When the blood flow in the coronaries of the pig heart was surgically blocked, the BNP mRNA increased significantly in the wall area that had become hypoxic<sup>[10]</sup> and the plasma levels of NT-proBNP were associated with the extent of myocardial damage and microvascular obstruction in patients, as assessed by contrast-enhanced cardiac magnetic resonance imaging<sup>[11]</sup>. Stockmann *et al*<sup>[12]</sup> studied the effects of oxygenation in the hypertrophied heart ventricular of the rat and showed that when normoxic conditions were restored, the ANP content decreased to control levels despite the persisting

hypertrophy. Salmon cardiac peptide, a hormone related to A-, B- and C-type natriuretic peptides<sup>[13]</sup> and localized in salmon heart ventricle<sup>[14]</sup>, has a hypoxia sensitive component in its release mechanism which is independent of contraction<sup>[15]</sup>.

It is interesting to note that in the clinical studies in which the oxygen delivery into contracting myocytes is impaired, the measurement of natriuretic peptides has shown its strength. A meta-analysis of 2784 patients from sixteen studies identified stress-induced myocardial ischemia as a significant condition linked with high plasma levels of BNP<sup>[16]</sup>. In a five year prospective longitudinal clinical study with 4775 primary care subjects, a single measurement of NT-proBNP significantly improved the prediction of incident cardiovascular events<sup>[17]</sup>. The combined endpoint in this study was restricted to the occurrence of myocardial infarction, coronary revascularization and cardiovascular mortality due to a sudden cardiac death or a fatal myocardial infarction. When comparing troponin assays with NT-proBNP assay in an acute coronary syndrome, Gravning *et al*<sup>[18]</sup> showed that the latter assay was superior to former ones to predict the long-term mortality in a prospective study of 458 patients. NT-proBNP predicted the extent of coronary artery disease and ischemia in the patients with stable angina pectoris, thus contributing to the diagnostic process<sup>[19]</sup>, and was linked to the severity of the aortic valve disease<sup>[20]</sup>. The recent ACTION Registry-GWTG study<sup>[21]</sup> reports the measurements of natriuretic peptides from a cohort of almost 30000 patients admitted to hospitals with an acute myocardial infarction. Among these patients without heart failure, natriuretic peptides were strongly and independently associated with the in-hospital mortality, even after adjustments for the severity of presentation. Also, in the patients with paroxysmal, persistent atrial fibrillation, most probably causing elevated oxygen consumption, plasma levels of natriuretic peptides were increased<sup>[22]</sup>. This accumulating experimental and clinical evidence for a direct role for oxygen has, however, been overshadowed by the wall stress hypothesis which alone has been used as a magnifying glass when looking at clinical results.

## CRITICAL DEBATE

What if the wall stress hypothesis has been misleading clinical cardiologists for nearly thirty years? The volume overload hypothesis originates from a rather small number of physiological experiments made in the 1980s. Additionally, as the following decade saw the rundown of physiology departments due to the strong emergence of molecular biology, the focus of natriuretic peptide research was rapidly moved towards clinical applications.

The role of the natriuretic peptide system is perhaps not to counterbalance pressure changes in circulation, but to regulate oxygen transport, both locally and systemically, by causing volume contraction (diuresis, natriuresis and *plasma shift*) leading to hemoconcentration and an increased oxygen-carrying capacity per unit volume of blood<sup>[23-25]</sup>. All the conditions that will increase the oxygen consumption or change the oxygen diffusion of

**Table 1 Established facts**

Already known fact 1	Volume overload (stretch or pressure) stimulates the synthesis and release of natriuretic peptides
Already known fact 2	Natriuretic peptides cause natriuresis, diuresis, vasodilatation and plasma shift

myocytes, such as stretch, pressure or metabolic challenges, will ultimately initiate the synthesis and enhance the release of natriuretic peptides from intracellular locations. Although these conclusions can be partly deduced from existing experimental and clinical results, more precise evidence can be obtained with the following sophisticated methods to support cardiologists in reanalyzing and reinterpreting their previous findings and to bring the natriuretic peptide associated drug development back onto a biologically correct basis.

To initiate a paradigm shift, the following methods should be introduced for the studies of the pathophysiology of natriuretic peptides. A method that is able to reveal perfusion defects in patients suffering from ischemia is positron emission tomography. Although the method has been available for several years, the properties of the tracers used have limited the interpretation of results. By means of newer tracers with a better defect contrast than the previous ones, it is or will be possible to quantify the perfusion of the myocardium during an exercise test or under a pharmacological challenge in patients with ischemia<sup>[26]</sup>.

Further evidence on the role of oxygenation can be obtained during congenital heart surgery with open chest cavity when an optical probe can be placed directly onto the free wall of the right ventricle, measuring the myoglobin saturation of myocytes<sup>[27]</sup>.

Experimentally, the Langendorff perfusion system is the method of choice if the effects of hypoxic conditions on the natriuretic peptide system are to be studied *in vitro*<sup>[28]</sup>. The isolated rodent heart can be perfused with different types of buffer solution, containing molecules with oxygen-carrying capacity, under appropriate left ventricular preload and afterload pressures. Imaging the fluorescence of NADH (the reduced form of nicotinamide adenine dinucleotide) from a local hypoxic ventricular area provides a measure of the mitochondrial redox state and the method has revealed that in the isolated biventricular working rabbit heart, different pacing rates produce hypoxic conditions<sup>[29]</sup>. In addition, the gene targeting technology of natriuretic peptides may provide us with new insights into their diverse functions and especially into the role of hypoxia in the physiology of natriuretic peptides<sup>[30]</sup>. Even the assessing the oxidative metabolism of a single myocyte with NADH fluorescence is possible<sup>[31]</sup>.

In all the methods mentioned above, natriuretic peptides can be measured either from the circulating plasma or from the perfusate and the concentration can be compared with the state of tissue oxygenation.

**Table 2 Novel insights**

New information 1	Natriuretic peptide system responds to oxygen tension (hypoxia-response elements in the promoter sequence of ANP and BNP genes). Volume overload causes wall stress and changes the consumption or diffusion of oxygen in heart
New information 2	The result of natriuresis, diuresis and plasma shift is volume contraction and increased oxygen-carrying capacity per unit volume of blood. Oxygen transport will be enhanced

ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide.

## NEW CONCEPT

According to the hypothesis outlined here, any chemical or mechanical challenge directed towards myocytes will eventually affect the diffusion or consumption of oxygen within a myocyte<sup>[32]</sup>, producing functional and regional heterogeneity of the oxygen supply-consumption ratio in the heart. During large and rapid changes in wall tension, as have occurred in volume overload experiments *in vivo* and pressure increase experiments with the Langendorff preparation *in vitro*, these manipulations have necessarily affected the oxygen metabolism of the heart. Interpreting the results from studies with single myocytes, isolated perfused hearts and with patients suffering from ischemia from a new angle will provide us with a new concept of the physiology of the natriuretic peptide system in healthy humans. To sum up, the role of the natriuretic peptide system is to increase oxygen transport in healthy humans to counteract hypoxic conditions and the stimulus to which the synthesis and release of natriuretic peptides responds is the oxygen gradient among cardiocytes (Tables 1 and 2).

It is worth noting that, in seal pups, able to experience a physiological eupnea-apnea cycle while sleeping, the plasma ANP was significantly higher when they were holding their breath than during the periods of eupnea<sup>[33]</sup>. Also, blood from seals showed an increase in hematocrit from 55.6% to 63.1% with a peak occurring within 1 min of the end of apnea<sup>[34]</sup>, reflecting an increased hemoglobin concentration.

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## Is diabetic cardiomyopathy a specific entity?

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### Abstract

Diabetes mellitus (DM) is characterised by hyperglycemia, insulin resistance and metabolic dysregulation leading to diastolic and systolic dysfunction in diabetes. In this review, the pathogenetic and pathomorphological changes leading to diastolic and systolic dysfunction in diabetes are discussed. Changes in metabolic signalling pathways, mediators and effectors contribute to the pathogenesis of cardiac dysfunction in DM called diabetic cardiomyopathy (DC). Echocardiographic studies report on the association between DM and the presence of cardiac hypertrophy and myocardial stiffness that lead to diastolic dysfunction. More recently reported echocardiographic studies with more sensitive techniques, such as strain analysis, also observed systolic dysfunction as an early marker of DC. Depression of systolic and diastolic function is continuum and the line of separation is artificial. To conclude, according to current knowledge, DC is expected to be a common single phenotype that is caused by different pathogenetic and pathomorphological changes leading to diastolic and systolic dysfunction in diabetes.

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**Key words:** Diabetes mellitus; Diabetic cardiomyopathy; Pathogenesis; Diastolic dysfunction; Systolic dysfunction; Morphological changes; Apoptosis

**Core tip:** Changes in metabolic signalling pathways *via* several mediators contribute to the pathogenesis of cardiac dysfunction in diabetes called diabetic cardiomyopathy (DC). In this review, the pathogenetic and pathomorphological changes leading to diastolic and systolic dysfunction in diabetes are discussed. Echocardiographic studies report on the association between diabetes and the presence of cardiac hypertrophy and myocardial stiffness that lead to diastolic dysfunction. More recently reported echocardiographic studies with more sensitive techniques, such as strain analysis, also observed systolic dysfunction as an early marker of DC.

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### INTRODUCTION

Since 1972, when Rubler *et al*<sup>[1]</sup> described 4 diabetic patients with congestive heart failure and normal coronary arteries, our knowledge of the observed pathomorphological changes of the heart called diabetic cardiomyopathy (DC) has gradually increased<sup>[2,3]</sup>. However, the pathohistological changes in DC are not specific<sup>[1-3]</sup>. DC has been defined as ventricular dysfunction that occurs independently of hypertension and coronary artery disease (CAD)<sup>[2]</sup>. The prevalence of DC is estimated to 60% in well-controlled type 2 diabetic patients<sup>[4,5]</sup>. The most useful method for the detection of DC is echocardiography that usually describes cardiac hypertrophy and diastolic dysfunction<sup>[4,5]</sup>. DC is a poorly understood entity, however, some mediators leading to abnormalities in myocardial structure, ventricular dysfunction and heart failure have been reported so far<sup>[6]</sup>. Patients with diabetes mellitus (DM) are at high risk for developing heart failure<sup>[6]</sup>. The spectrum of heart failure syndrome in DC is also not precisely defined despite the usually used definition

of DC as a diastolic heart failure with normal ejection fraction. Anyhow, in different patients several different associated risk factors are observed, such as hypertension and adiposity or associated clinical entities, such as CAD, small vessel disease, autonomic dysfunction and arrhythmias. All of these entities have a significant influence on myocardial structure and function. In this review, the pathogenesis, as well as the prevalence and potential forms of DC and the question whether DC is either a unique specific cardiomyopathy starting with diastolic dysfunction that eventually leads to ventricular dysfunction and heart failure, are discussed.

## PREVALENCE

The prevalence of DM is increasing worldwide due to the increase in population, urbanisation, the prevalence of obesity and physical inactivity. The Framingham Heart study showed that DM increased the risk for heart failure 2.4-fold in diabetic men and fivefold in diabetic women compared with age- and sex-matched control subjects<sup>[6]</sup>. This risk was independent of hypertension, obesity and CAD. Diabetic patients also have an increased risk for heart failure after myocardial infarction, compared to non-diabetics<sup>[7,8]</sup>. However, not only patients with DM, but also patients with higher baseline glucose without diabetes have a higher incidence of heart failure<sup>[6]</sup>.

Mainly echocardiographic population-based studies report on the association between DM and the presence of cardiac hypertrophy and myocardial stiffness, independently of hypertension<sup>[4,5]</sup>. There are basically two pathophysiological processes leading to heart failure in diabetic patients, the first being CAD and the second DC. CAD is increased in patients with DM due to accelerated atherosclerosis associated with risk factors, such as visceral obesity, hypertension, dyslipidaemia, and prothrombotic factors<sup>[7,9]</sup>. Despite the increased burden of CAD in diabetic patients, the real prevalence of CAD in DM patients is unknown<sup>[7,9]</sup>. Population-based studies reported on the adverse effect of DM on life expectancy, mainly due to cardiovascular disease and also in patients with heart failure<sup>[10]</sup>.

## PATHOGENESIS

Various animal models of DC have proposed several mediators and effectors that are the consequence of altered metabolic signalling pathways and contribute to the pathogenesis of cardiac dysfunction in diabetes.

### ***Hyperglycemia, advanced glycation end products and insulin resistance***

DM is characterized by hyperglycemia, hyperinsulinemia, and insulin resistance<sup>[11]</sup>. The reduced glucose uptake in the diabetic heart as a result of insulin resistance facilitates a substrate shift towards increased fatty acids oxidation, resulting in reduced cardiac efficiency<sup>[12]</sup>. Epicardial adipose tissue (EAT) that covers 80% of the heart

surface and constitutes approximately 20% of the total heart weight have endocrine and paracrine properties that probably interfere with cardiac function. It is speculated that EAT facilitates the development of insulin resistance and cardiac dysfunction<sup>[13]</sup>. Glucotoxicity has been proposed in animal models as an important element of myocardial dysfunction. Glucose and collagen interact, and form Schiff bases. The fibrous network is reorganised with the so-called Amadori products. A further chemical modification of Amadori products leads to the formation of macromolecules that are labelled as advanced glycation end products (AGEs). AGEs are a stable form of cross-linked collagen that accumulate in vessel walls and in myocardial tissue and increase diastolic stiffness of the heart and contribute to endothelial dysfunction<sup>[14]</sup>. Higher diastolic left ventricular (LV) stiffness was related to both AGE deposition and interstitial fibrosis<sup>[15]</sup>. It was observed that serum levels of AGEs correlate with the prolongation of isovolumic relaxation time in patients with diabetes.

### ***Altered substrate metabolism***

Metabolic dysregulation in DM also involves fatty acid metabolism. Despite contradictory reports on the level of circulating free fatty acids (FFA), which are elevated in some studies and not in others<sup>[16,17]</sup>, there is a dys-regulated lipid signalling that leads to an increased FFA metabolism and accumulation of FFA<sup>[18,19]</sup>. In parallel, there is a decrease of insulin-mediated glucose uptake. FFA also induced the inhibition of glucose oxidation and resulted in abnormally high oxygen requirements during FFA metabolism. The net result of enhanced fatty acid oxidation and decreased glucose and pyruvate utilization led to the excess of glycolytic intermediates and increased the synthesis of ceramide leading to apoptosis. This process, called gluco-lipotoxicity induced mitochondrial uncoupling, decreased adenosine triphosphate synthesis and mitochondrial dysfunction<sup>[20,21]</sup>. Changes in substrate dependence lead to impaired systolic and diastolic function due to the perturbation of myocardial bioenergetics and contraction/relaxation coupling<sup>[21,22]</sup>.

### ***Increased oxidative stress***

Many studies report oxidative stress as a major common factor in the development of DC, however, the exact mechanisms involved in exacerbated reactive oxygen species (ROS) production are not well understood. Studies proposed insulin resistance and increased mitochondrial fatty acid flux that predisposes cardiac mitochondria to ROS overproduction<sup>[23]</sup>. In addition to the more important and larger fraction of total cellular ROS that are generated in mitochondria, enzymatic system in cytosol, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is also modulated by diabetes<sup>[24]</sup>. Increased oxidative stress causes cardiomyocyte cell damage, resulting in programmed cell death-apoptosis and fibrosis<sup>[25]</sup>.

### **Impaired calcium homeostasis and dysfunction of mitochondria and endoplasmic reticulum**

Oxidative stress exacerbates mitochondrial and endoplasmic reticulum (ER) dysfunction and produces subcellular remodelling and abnormalities of calcium handling<sup>[26]</sup>. There is calcium imbalance within the diabetic cardiomyocytes, which is characterized by calcium cytosolic overloading and reduced mitochondrial ATP production. The ER, through negative regulation of insulin's metabolic signalling, additionally impairs calcium homeostasis. There is a release of calcium from the ER into cytosol and reduced activity of the sarcoplasmic reticulum calcium pump<sup>[27]</sup>. The consequences of these changes are alterations in the calcium sensitivity of regulatory proteins involved in the regulation of the cardiac actomyosin system, leading to impaired left ventricular function<sup>[28]</sup>. As an initial dysfunction, researchers observed prolonged diastolic relaxation time, however later on cardiomyocyte apoptosis due to the formation of mitochondrial permeability transition pore has been observed<sup>[29]</sup>.

### **Activation of the renin-angiotensin-aldosterone and sympathetic system**

Hyperinsulinemia causes overactivation of the renin-angiotensin-aldosterone system<sup>[30]</sup>. This leads to cardiac insulin resistance and the activation of mitogen activated protein kinases, which promote fibroblast proliferation while inducing cardiomyocyte fibrosis and apoptosis<sup>[31]</sup>. The serum level of aldosterone is increased in the pre-diabetic and diabetic condition and triggers LV hypertrophy, fibrosis and cardiac remodelling<sup>[32]</sup>. Both angiotensin II and aldosterone cause increased production of ROS and the activation of NADPH oxidase, and they therefore increase cytosolic oxidative stress<sup>[33]</sup>. Aldosterone also aggravates cardiac fibrosis by triggering pro-inflammatory factors through activation of matrix metalloproteinases and the transforming growth factor  $\beta$  (TGF- $\beta$ )<sup>[34]</sup>. There are reports of overactivation of the sympathetic system in the pre-diabetic and diabetic condition that further contributes to metabolic abnormalities. Straznicky observed the association of blunted sympathetic responsiveness and insulin resistance, and disturbed sympathetic neurobiology is characterized by augmented resting sympathetic nervous activity and blunted sympathetic responsiveness to oral glucose ingestion<sup>[35]</sup>.

## **STRUCTURAL CHANGES**

Anatomic changes observed in DC are characterised by myocyte hypertrophy and myocardial fibrosis<sup>[2,3]</sup>. Beside pathohistomorphological findings, left ventricular hypertrophy, defined as an increase in the left ventricular mass by echocardiography or by magnetic resonance imaging has been reported in DC<sup>[2,3]</sup>.

### **Fibrosis, necrosis and apoptosis**

In DC, fibrosis is attributed to replacement fibrosis caused by myocyte necrosis and to increased interstitial fibrosis. Interstitial fibrosis in DC is driven mainly by

increased accumulation of collagen type III<sup>[3,36]</sup>. DC is characterised by accelerated myocyte cell death and accelerated apoptosis<sup>[3,36]</sup>. The processes of accelerated necrosis and apoptosis are driven by hyperglycemia, accelerated production of ROS, upregulation of the local renin angiotensin aldosterone system, and through modulation of the insulin-like growth factor-1 and the TGF- $\beta$  by angiotensin II. Apoptosis does not cause scar formation or accumulation of interstitial collagen, with nuclear fragmentation and cell shrinkage being replaced by the surrounding cells<sup>[37]</sup>. On the contrary, myocyte necrosis produces the widening of extracellular compartments among myocytes and increased deposition of collagen, resulting in replacement fibrosis and connective cell proliferation<sup>[38]</sup>. The presence of hypertension in patients with diabetes increases myocyte necrosis 1.4-fold compared to diabetes alone, but it has no influence on apoptosis<sup>[39]</sup>.

### **Cardiomyocyte hypertrophy**

In DC, Huyn and Rosenkrans observed the increase of several markers of cardiomyocyte hypertrophy, including increased cardiomyocyte width and myofiber disarray<sup>[40,41]</sup>. The loss of cardiomyocytes due to apoptosis and necrosis lead to compensatory hypertrophy of the remaining viable cardiomyocyte. Researchers observed an upregulation of hypertrophic gene expression of  $\beta$ -myosin heavy chain, ANP, and BNP. The causes of the diabetes-induced hypertrophic response are probably hyperglycemia and oxidative stress<sup>[40,41]</sup>.

## **CHANGES IN CARDIAC FUNCTION**

### **Diastolic dysfunction**

A number of echocardiographic studies have characterised functional changes early in the course of DC. Diastolic abnormalities have been reported in 23% to 75% of patients with DM<sup>[42-45]</sup>. A high variability in the prevalence of diastolic dysfunction raises a question on the implemented methodology. Most of the patients included in these studies were asymptomatic without overt heart disease and their report based on mitral inflow pattern where they observed an increased E/A ratio (where E is mitral peak early-diastolic filling velocity; A is mitral late diastolic filling velocity), prolonged deceleration time, increased isovolumic relaxation time, or described combined indices derived from mitral inflow pattern and pulmonary venous flow<sup>[46-48]</sup>. Later on, some investigators analysed Doppler tissue imaging diastolic velocities and mitral inflow pattern and reported on their indices, such as E/e' that is non-invasive correlate of left ventricular filling pressure (e' is the early diastolic mitral annular velocity)<sup>[45,49]</sup>. Ernande reported a 47% prevalence of diastolic dysfunction, with 33% grade I or pattern of impaired relaxation and 14% grade II or pseudonormal pattern<sup>[50]</sup> in patients with DM with normal ejection fraction and controlled blood pressure. Anyhow, most of these studies have been completed before the reliable complex diagnostic algorithm of diastolic function was accepted, and therefore did not allow us a conclusion based on

single parameters<sup>[51]</sup>.

### Systolic dysfunction

Although many studies have shown that diabetic patients have abnormal diastolic function but preserved systolic function, this may well be due to techniques used for the evaluation of systolic and diastolic dysfunction. Usually applied techniques are probably more sensitive for diastolic dysfunction than for systolic dysfunction. When thinking of systolic function, we usually think of ejection fraction that depends a lot on radial contractile function, but the longitudinal contractile function of ventricle is primary depressed. Moreover, with the application of more sensitive techniques for the analysis of systolic function, such as strain deformation imaging, researchers observed that the systolic function is impaired despite normal left ventricular ejection fraction. Ernande reported that preclinical radial and longitudinal systolic strain is depressed in 28% of patients with DM with normal diastolic function<sup>[50]</sup>. This study indicates that systolic strain alteration may exist despite normal diastolic function, or otherwise indicating that diastolic dysfunction should not be considered the first marker of a preclinical form of DC.

### Continuum of diastolic and systolic dysfunction

Deterioration of systolic and diastolic function is continuum. There is no separation of diastolic and systolic function in DM, nor in other metabolic cardiomyopathies. Diastolic dysfunction was associated with increased cardiac triglyceride content in the ob/ob mice model of DM<sup>[52]</sup>. The role of calcium homeostasis studied in the db/db mice model of DM showed increased diastolic sarcoplasmic reticulum Ca<sup>2+</sup> leak, reduced synchrony of Ca<sup>2+</sup> release, lower peak systolic and diastolic Ca<sup>2+</sup> have, therefore, an influence on both systolic and diastolic function<sup>[53]</sup>. Abnormality in systolic and diastolic function is also associated with myocardial structural changes. Obviously, there are numerous factors that might have an unfavourable effect on systolic and diastolic function in subjects with DM.

## PHENOTYPE OF DC

There is still a debate on how DC should be defined. DC is not an isolated diastolic entity. Due to metabolic abnormalities, we observed systolic and diastolic dysfunctions that are initially subclinical and gradually progress to a full-blown syndrome of congestive heart failure. To conclude, according to current knowledge, DC is expected to be a common single phenotype that is caused by different pathogenetic and pathomorphological changes leading to diastolic and systolic dysfunction in diabetes.

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## Primary reperfusion in acute right ventricular infarction: An observational study

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classified as without right ventricular failure (RVF) (class A,  $n = 425$ , 64%), with RVF (class B,  $n = 158$ , 24%) or with cardiogenic shock (CS) (class C,  $n = 96$ , 12%). Of the 679 patients, 148 (21.7%) were considered to be eligible for thrombolytic therapy (TT) and 351 (51.6%) for primary percutaneous coronary intervention (PPCI). TIMI 3-flow by TT was achieved for A, B and C RVI class in 65%, 64% and 0%, respectively and with PPCI in 93%, 91% and 87%, respectively.

**RESULTS:** For class A without RT, the mortality rate was 7.9%, with TT was reduced to 4.4% ( $P < 0.01$ ) and with PPCI to 3.2% ( $P < 0.01$ ). Considering TT vs PPCI, PPCI was superior ( $P < 0.05$ ). For class B without RT the mortality was 27%, decreased to 13% with TT ( $P < 0.01$ ) and to 8.3% with PPCI ( $P < 0.01$ ). In a TT and PPCI comparison, PPCI was superior ( $P < 0.01$ ). For class C without RT the in-hospital mortality was 80%, with TT was 100% and with PPCI, the rate decreased to 44% ( $P < 0.01$ ). At 8 years, the mortality rate without RT for class A was 32%, for class B was 48% and for class C was 85%. When PPCI was successful, the long-term mortality was lower than previously reported for the 3 RVI classes (A: 21%, B: 38%, C: 70%;  $P < 0.001$ ).

**CONCLUSION:** PPCI is superior to TT and reduces short/long-term mortality for all RVI categories. RVI CS patients should be encouraged to undergo PPCI at a specialized center.

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**Key words:** Right ventricular infarction; Reperfusion therapy; Ventricular failure; Cardiogenic shock; Morbidity; Mortality

**Core tip:** It is, up to our knowledge the largest series of

### Abstract

**AIM:** To investigate the impact of primary reperfusion therapy (RT) on early and late mortality in acute right ventricular infarction (RVI).

**METHODS:** RVI patients ( $n = 679$ ) were prospectively

acute right ventricular infarction (RVI) patients where all the clinical RVI spectrum is considered. RVI is analyzed in relation to primary reperfusion procedures, over a study period with a more widespread use of primary percutaneous coronary intervention (PPCI) together with the advent of stents and antiplatelet agents to provide a better insight into reperfusion trends and results in acute RVI. According to our findings, in all RVI hemodynamic scenario PPCI is superior to thrombolytic therapy (TT) and reduces short and long-term mortality for all 3 RVI categories. Patients in cardiogenic shock should be encouraged to undergo PPCI rather than TT at a specialized center.

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## INTRODUCTION

Right ventricular infarction (RVI) is relatively common in patients with acute inferior-posterior left ventricular myocardial infarction (IPLVMI). RVI can depress right ventricular (RV) function, resulting in right ventricular failure (RVF) or cardiogenic shock (CS)<sup>[1-5]</sup>. There are scarce and somewhat conflicting clinical data concerning the effects of interventions designed to achieve reperfusion of the RV myocardium in acute ischemia. Several investigators have suggested that RV function improves only after successful thrombolytic therapy (TT), whereas others have reported recovery in the absence of early or even any reperfusion of the right coronary artery (RCA)<sup>[6]</sup>. In a study involving limited number of patients, rapid hemodynamic improvement and excellent clinical outcomes have been reported after successful primary percutaneous coronary intervention (PPCI) of the RCA and its major RV branches<sup>[1]</sup>. At the most extreme end of the hemodynamic spectrum for RVI, when CS is analyzed in relation to reperfusion, the results can be disappointing, partly due to the time frame of the study (1993-1998), or the results can be better than the outcomes in patients with left ventricular (LV) pump failure in a study from 1984 to 2004<sup>[7]</sup>. The present study aimed (1) to evaluate the trends and impact of TT and PPCI over time and on early and late mortality in RVI patients with or without RVF; and (2) with CS over a study period with a more widespread use of PPCI together with the advent of stents and potent antiplatelet agents to provide a better insight into reperfusion results in acute RVI.

## MATERIALS AND METHODS

### Ethics

This work has been carried out in accordance with the

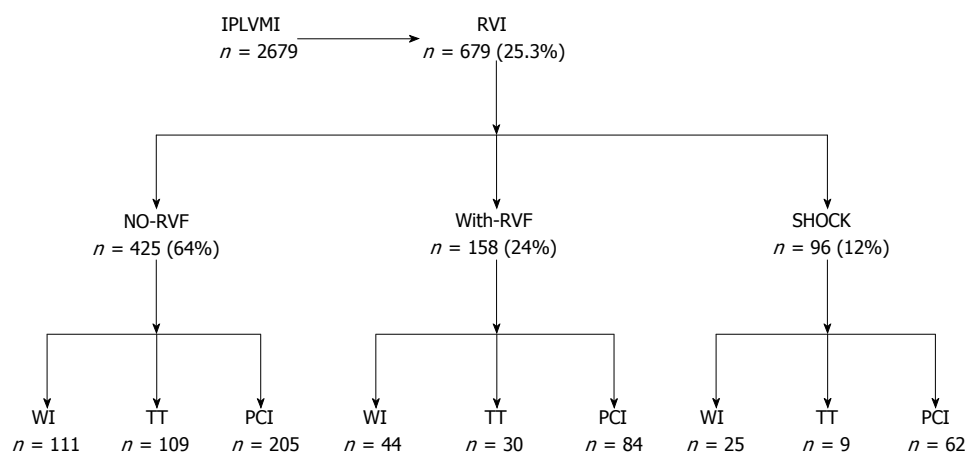
Declaration of Helsinki (2000) of the World Medical Association. The protocol was approved by the ethics committee of the institution. All patients provided informed written consent.

### Patients

We prospectively screened 2679 consecutive patients admitted with a first acute (defined as the time from symptom onset to admission of  $\leq 48$  h) IPLVMI (defined as chest pain with  $> 1$  mm in leads II, III and aVF) from January 1996 to March 2009, and identified 679 (25.3%) patients with infarction extending to the walls of the right ventricle (84% were studied in the last 10 years). Isolated acute RVI, history of valve heart disease, and previous heart or renal failure were exclusion criteria for this study.

The diagnostic criteria for IPLVMI with extension to the walls of the right ventricle, RVF and CS have been published previously<sup>[4]</sup>. Briefly, in addition to standard electrocardiographic (EKG) leads, a right-sided precordial EKG (leads V<sub>3R</sub>-V<sub>7R</sub>) was recorded in all patients immediately after admission. An ST-segment elevation in lead V<sub>3R</sub> or V<sub>4R</sub> of greater than 0.1 mV was used to diagnose RVI. The diagnosis of RVI was also based on clinical features that have been described and have been associated with this variety of infarction, and on echocardiographic findings<sup>[2]</sup>. The diagnosis of RVF was based on clinical features, including persistent systemic hypotension [systemic systolic pressure (SSP)  $\leq 100$  mmHg, right-sided S<sub>3</sub> and S<sub>4</sub>] without features of shock, echocardiographic evidence of ischemic RVF (RV wall motion abnormalities (WMA) associated with gross RV dilatation), findings that suggest globally depressed RV function and invasive hemodynamic monitoring identifying RVI by a combination of findings that suggest RV dysfunction [low cardiac output (CO) and a disproportionate elevation of the mean right atrial pressure (mRAP) compared to the mean pulmonary wedge pressure (mPWP)]<sup>[2,8,9]</sup>. The diagnosis for shock was made if all of the following criteria were satisfied: SSP persistently  $\leq 90$  mmHg or vasopressors required to maintain SSP  $> 90$  mmHg; very low CO [cardiac index (CI)  $< 2.1$  L.min/m<sup>2</sup>]; evidence of end-organ hypoperfusion. We did not include in this category patients with hypotension related to hypovolemia, transient hypotension due to vasodilatation and bradycardia associated with spontaneous reperfusion (Bezold-Jarisch reflex), or hypotension due to atrioventricular block (AVB), cardiac arrhythmias or mechanical complications (ventricular septal or myocardial wall rupture or cardiac tamponade) at admission.

We risk-stratified RVI patients into 3 subsets based on clinical features, echocardiographic findings upon admission and hemodynamic findings as follows: class A (without RVF), comprised of patients without evidence of systemic hypotension (SSP  $\geq 100$  mmHg) or RVF (by clinical features, echocardiographic and/or hemodynamic findings); class B (with RVF), those with persistent systemic hypotension (SSP  $< 100$  mmHg) or RVF, but without other clinical features of shock; class C, those with



**Figure 1 Study outline.** Patients with inferior-posterior left ventricular myocardial infarction (IPLVMI) ( $n = 2679$ ), with right ventricular infarction (RVI): 679 (25.3%). We risk-stratified RVI patients into 3 subsets: class A (without RVF), class B (with RVF) and class C (with cardiogenic shock). WI: Without intervention; TT: Thrombolytic therapy; PCI: Primary coronary intervention; RVF: Right ventricular failure.

CS (Figure 1).

### Evaluation of atrial and ventricular function

Echocardiograms were analyzed according to previous methods<sup>[4]</sup>. LV systolic dysfunction was defined as an ejection fraction below 50%. The RV was divided into eight segments; of these segments 3 corresponded to the basal segments, 3 to the middle segments of the anterior, lateral and inferior walls (IW), and 2 to the apical anterior and inferior segments. The wall movement index (WMI) of both ventricles was obtained by assigning a value to the movement of each wall segments and dividing the sum by the number of segments corresponding to the ventricle in question. A score of 0 was classified to normal movement, 1 as = hypokinesis (diminished thickening), 2 as = akinesis (absence of thickening) and 3 as = dyskinesis (paradoxical systolic movement). The overall score for RV and LV wall motion (LVWM) was calculated as the average score for the segments, and the ratio of the diastolic diameters of the two ventricles diastolic ratio of the two ventricles (RVD/LVD) was also calculated. The echocardiographic evidence of ischemic RV was based on a combination of the following features: right ventricular wall motion abnormalities (RVWMA) and RV dilatation with/without tricuspid regurgitation (TR). Right atrial (RA) ischemia was defined according to the following criteria: akinesis of the RA free wall (FW) despite left atrial contraction, thrombosis at the site of akinesis, presence of spontaneous contrast in the RA, and inversion of the interatrial septal convexity<sup>[4]</sup>.

### Evaluation of coronary anatomy and perfusion

The location of the culprit lesion was assessed using Bowers criteria<sup>[1]</sup>. The initial and post-reperfusion flow grades in the coronary artery and in the RV branches were scored from 0 to 3 [thrombolysis in myocardial infarction (TIMI) flow classification]. Successful reperfusion was defined as < 50% residual stenosis and restoration of TIMI grade 3 in the main RCA and its major RV branches (> 1 mm). Coronary collateral blood flow was

evaluated according to Rentrop *et al.*<sup>[10]</sup>. Multivessel disease was defined as a lesion  $\geq 50\%$  in  $\geq 2$  major coronary arteries. We analyzed all of the patients who had a coronary angiogram at admission and a second angiogram after reperfusion. For those who received TT, the second coronary angiogram was performed 90-180 min after the thrombolytic infusion. Information on the coronary arteries was evaluated independent of and blinded to the other study data.

### Treatment protocol

Patients were treated with unfractionated heparin (bolus: 60 IU/kg, maximum 5000 IU; 10 IU/kg per hour, maximum 1000/h) and aspirin (300 mg) in the emergency room and transferred to the coronary care unit or to the catheterization laboratory to undergo coronary angiography, based on the individual's. Patients who were eligible for reperfusion were consecutively assigned to TT or PPCI. TT was administered intravenously to all of the eligible RVI patients. The inclusion criteria for classes A and B were defined before admission as follows: symptoms of ST elevation myocardial infarction (STEMI) lasting less than 12 h or > 12 h in patients with ongoing ischemia, age  $\leq 75$  years and absence of other accepted contraindications. TT was performed with either streptokinase (32%) or recombinant tissue plasminogen activator (68%), preceded by heparin. Post-TT consisted of an intravenous heparin dose that was adjusted to maintain TPTa between 60-75 s for 72 h and aspirin. For PPCI, the same inclusion criteria for STEMI symptoms and duration and age were applied; stents were deployed according to standard techniques followed by standard antiplatelet therapy. Stents and glycoprotein II b/IIIa platelet inhibitors became a standard therapy in eligible patients in 1995 and 1996, respectively. Clopidogrel was used in stented patients with a loading dose of 300 mg or 600 mg and later, a daily dose of 75 mg for  $\geq 6$  mo in patients treated with bare metal stents and for 6 to 12 mo in patients treated with drug-eluting stents. RVI patients in shock were considered to be candidates for PPCI if age

**Table 1 Clinical characteristics of the 679 patients separated according to right ventricular infarction class**

Variables	Class A <i>n</i> = 425 (64%)	Class B <i>n</i> = 158 (24%)	Class C <i>n</i> = 96 (12%)
Age (yr)	59.7 ± 9.4	61 ± 10	62.4 ± 8.4
Age 64-74 yr	41.9%	38.7%	37.5%
Men	82%	81%	83%
Pre-IA	38%	40%	41%
Peak CK IU/L	1854	1994	2109
median (25 <sup>th</sup> -75 <sup>th</sup> percentiles)	(1654-2490)	(1214-2634)	(1532-2812)
Peak MB fraction IU/L	188	201	192
median (25 <sup>th</sup> -75 <sup>th</sup> percentiles)	(111-350)	(126-312)	(104-333)
Diabetes	26.9%	27.8%	30.6%
Hypertension	40.7%	44.3%	44.4%
Hypercholesterolemia	23%	19%	21%
Smoking	58%	60%	55%
BMI (kg/m <sup>2</sup> )	28.2 ± 4.4	26.7 ± 5.2	27.2 ± 3.9

No statistically significant differences between right ventricular infarction classes were found. Pre-IA: Infarction angina; CK: Creatine kinase; BMI: Body mass index; MB: Myocardial B.

< 75 years and shock developed within ≤ 48 h of the STEMI.

Conservative therapy for A and B class was provided to patients who delayed seeking medical attention, for class C > 75 years of age or those who developed shock > 48 h after the onset of myocardial infarction. Patients underwent PPCI or coronary artery bypass graft surgery (CABGS) only if ischemia recurred despite medical therapy during hospitalization or occurred during a pre-discharge stress test.

### Morbidity and mortality analysis

The following adverse cardiac events were recorded: hypotension (> 1 h), hypotension necessitating volume infusion (200-400 mL/h), pharmacological hemodynamic support (inotropic agents/vasopressors), or intra-aortic balloon pump (IABP); high grade AVB (> 1 h, need for a transient pacemaker); ventricular arrhythmias requiring treatment; recurrent ischemia (defined as recurrent chest pain with or without new EKG changes or recurrent myonecrosis as indicated by serum biomarkers (increase in creatine kinase level and MB fraction higher than the nadir); death. Urgent target vessel revascularization was defined as the need to repeat PPCI or urgent CABGS for recurrent ischemia or hemodynamic compromise during the hospital stay.

The primary end point was in-hospital cardiac death at 30 d. Follow-up information after hospital discharge was obtained from the hospital records database, which is updated at each patient visit and upon patient death.

### Statistical analysis

We analyzed: (1) the clinical, echocardiographic, angiographic and hemodynamic characteristics of our patients at baseline separately for those in classes A, B, and C; (2) among the 3 RVI classes; (3) within each class, all patients sent for reperfusion were compared to those who were

not referred for reperfusion; and (4) within each class, TT vs PPCI was compared.

The continuous data are expressed as the mean ± SD unless otherwise specified. A Student's *t* test, 1-way-ANOVA (Bonferroni's-test for multiple comparisons),  $\chi^2$ , or Fisher exact test was used as appropriate.

Univariate analysis based on the logistic regression model was used to examine the relationship between the selected demographic, medical history, clinical examination, and hemodynamic data to determine the likelihood of overall mortality. After the univariate analysis, any variable that had a univariate test value of  $P < 0.25$  was considered to be a candidate for the multivariate analyses. The results are expressed as odds ratios and 95%CI. The Kaplan-Meier method was used to estimate the overall survival distribution (log-rank test). The analyses were performed using the STATA-9 software.

## RESULTS

### Clinical data

From all of the RVI patients, echocardiography, invasive hemodynamic evaluation and coronary angiograms were performed in 94.5%, 89% and 73%, respectively. The diagnosis of RVI was made by EKG, echocardiographic, hemodynamic or coronary angiographic criteria in 100% and by 3 criteria (echocardiographic, hemodynamic and angiographic) in 85% of the patients. The RVI subgroups had no differences in their baseline clinical characteristics (Table 1).

### Echocardiography

At baseline, there was evidence of IPLVMI dysfunction in all of the RVI patients (WMI  $1.8 \pm 0.4$ ). The echocardiographic data at baseline by clinical class was documented as follows. In all of the classes A patients without RV-dilatation, WMA were only found in the IW (LV + RV) = 84% and the FW = 16%. In class B and C patients with RV-dilatation, WMA was not only confined to the IW; TR, and abnormal ventricular septal movement were observed in 78% and 70%, respectively, with abnormal RA wall movement in 18% and 25%, respectively. Abnormal values for the right ventricular motion index were found in all of the patients, with a significant increase in the WMA score classes between A, B and C classes ( $P < 0.01$ , respectively). An RVD/LVD of = 1 was most frequently observed in class B, and an RVD/LVD > 1 was observed in C patients (Table 2).

### Hemodynamics

The hemodynamic data according to the RVI class ( $n = 604$ , 89%) was documented as follows. In class A patients ( $n = 350$ ), all of the hemodynamic parameters were within normal limits. In class B patients ( $n = 158$ ), an elevated mRAP ( $12.9 \pm 3.6$  mmHg) and decreased CI ( $2.4 \pm 0.21$  L.min/m<sup>2</sup>) and mean systemic arterial pressure [mSAP ( $78.7 \pm 12.3$  mmHg)] were found, with an increased RAP/PWP > 0.8 compared to class A patients.

**Table 2** Echocardiographic data at baseline according to right ventricular infarction class

Variable	Class A ( <i>n</i> = 396)	Class B ( <i>n</i> = 152)	Class C ( <i>n</i> = 94)	Total ( <i>n</i> = 642)
RV-dilatation	0%	100% <sup>b</sup>	100%	38.3%
VWMA	100%	100%	100%	100%
WMA only for IW	84%	0%	0%	51.7%
WMA for IW + OW	16%	100% <sup>b</sup>	100%	48%
TR	17%	100% <sup>b</sup>	100%	48%
AVSM	25%	78% <sup>b</sup>	70%	43.9%
RVMi	1.9% ± 0.3%	2.5% ± 0.2% <sup>b</sup>	3.4% ± 0.5% <sup>d</sup>	2.4% ± 4%
RVD/LVD > 1	0%	25% <sup>b</sup>	83% <sup>d</sup>	18%
RVD/LVD = 1	0%	65% <sup>b</sup>	17% <sup>d</sup>	18%
ARAWM	0%	18% <sup>b</sup>	25%	8%
RA-DPS <i>n</i> (%)	0 (0)	19 (70)	10 (43) <sup>d</sup>	29 (58)
LVEF < 0.5	11%	22%	34% <sup>d</sup>	16%

Echocardiographic data at baseline according to right ventricular infarction class (*n* = 642/679, 94.5%); transthoracic (TT): 375 (58%), transesophageal (TE): 267 (42%). <sup>b</sup>*P* < 0.01 *vs* classes A; <sup>d</sup>*P* < 0.01 *vs* classes B. RV: Right ventricle; VWMA: Ventricular wall motion abnormalities; IW: Inferior wall for LV + RV; OW: Other walls; TR: Tricuspid regurgitation; AVSM: Abnormal ventricular septal motion; RVMi: Right ventricular motion index (mean ± SD); RVD/LVD: Diastolic ratio of the two ventricles; ARAWM: Abnormal right atrial wall movements; RA-DPS: Right atrium dobutamine positive stress; LVEF: Left ventricular ejection fraction.

**Table 3** Hemodynamic data at baseline according to the right ventricular infarction class

Variable	Class A ( <i>n</i> = 350)	Class B ( <i>n</i> = 158)	Class C ( <i>n</i> = 96)
mRAP (mmHg)	4.6 ± 2.1	12.9 ± 3.6 <sup>b</sup>	21.4 ± 5.15 <sup>d</sup>
REVD (mmHg)	3.4 ± 1.7	11.2 ± 4 <sup>b</sup>	16 ± 5.4 <sup>d</sup>
sPAP (mmHg)	16.2 ± 4.4	16.4 ± 3.9	36.8 ± 9.3 <sup>d</sup>
dPAP (mmHg)	9.7 ± 3.7	13.4 ± 2.2	22.2 ± 3.9 <sup>d</sup>
mPWP (mmHg)	8.6 ± 3.1	12.1 ± 1.8	19.9 ± 6.2 <sup>d</sup>
CI (L.min/m <sup>2</sup> )	3.4 ± 0.71	2.4 ± 0.21 <sup>b</sup>	1.67 ± 0.5 <sup>d</sup>
mSAP (mmHg)	108.8 ± 7	78.7 ± 12.3 <sup>b</sup>	62.7 ± 9.5 <sup>d</sup>
RAP/PWP ≥ 0.8	2%	96% <sup>b</sup>	92%

Hemodynamic data at baseline according to the right ventricular infarction class (*n* = 604, 89%). <sup>b</sup>*P* < 0.01 *vs* classes A; <sup>d</sup>*P* < 0.01 *vs* classes B. m: Mean; s: Systolic; d: Diastolic; RAP: Right atrial pressure; REVD: Right ventricular end diastolic pressure; PAP: Pulmonary artery pressure; PWP: Pulmonary wedge pressure; CI: Cardiac index; SAP: Systemic arterial pressure.

For class C patients (*n* = 96), an elevated mRAP (21.4 ± 5.15 mmHg), systolic pulmonary artery pressure [sPAP (36.8 ± 9.3 mmHg)], diastolic PAP (22.2 ± 3.9 mmHg) and mPWP (19.9 ± 9.2 mmHg) and decreased CI (1.67 ± 0.5 L.min/m<sup>2</sup>) and mSAP (62.7 ± 9.5 mmHg) were found compared to class B patients (Table 3).

### Angiography

The RCA was the infarct-related artery in 95% of the RVI patients. There was severe compromise of RV perfusion, as indicated by the TIMI grade flow (0.7 ± 1).

The culprit RCA lesion was most commonly found proximal in class B and C patient and had a mid location in class A patients. The 3 RVI subgroups had no differences in prevalence of 1 and 2 vessels disease (VD), but 3-VD was more frequently observed in classes B and C.

**Table 4** Coronary angiographic data at baseline according to the right ventricular infarction class *n* (%)

Variable	Class A ( <i>n</i> = 425)	Class B ( <i>n</i> = 158)	Class C ( <i>n</i> = 96)	Total
Angiography	291 (68)	123 (77)	85 (88)	499 (73)
PCI	213	93	76	382 (76.5)
TT	78	30	9	117 (23.4)
RCA culprit vessel	266 (91)	123 (100)	85 (100)	474 (95)
RCA CL-location				
Proximal	42 (16)	85 (69) <sup>b</sup>	78 (92) <sup>d</sup>	205 (43)
Mid	144 (54)	26 (21) <sup>b</sup>	6 (7) <sup>d</sup>	176 (37)
Distal	80 (30)	12 (9) <sup>b</sup>	1 (1) <sup>d</sup>	93 (19)
1-VD	144 (54)	39 (32) <sup>b</sup>	11 (14)	194 (40.9)
2-VD	96 (36)	31 (25)	32 (37)	159 (33.5)
3-VD	26 (9)	53 (43) <sup>b</sup>	42 (49)	121 (25.5)
RCA + LAD-D	29 (11)	44 (36) <sup>b</sup>	45 (53) <sup>d</sup>	118 (24.8)
100% RCA-O	119 (45)	68 (55)	53 (62)	240 (48)
Without CCC	47 (40)	36 (53)	47 (89) <sup>d</sup>	130 (54)
With CCC	72 (60)	32 (47)	6 (11) <sup>d</sup>	110 (45)
Grade 1	9	10	0	19
Grade 2	36	12	0	48
Grade 3	27	10	6	43
RCA-RVB-RAB flow				
TIMI grade flow	0.8 ± 1.4	0.7 ± 1	0.6 ± 0.7	0.7 ± 1
TIMI 3 flow in all RVB	194 (72)	0 (0) <sup>b</sup>	0 (0)	194 (40)
Impaired flow in 1 RVB	56 (21)	11 (8.9) <sup>b</sup>	0 (0)	67 (14)
Impaired flow in ≥ 2				
RVB	16 (6)	41 (33) <sup>b</sup>	6 (7) <sup>d</sup>	63 (13)
No flow in all RVB	0 (0)	71 (57) <sup>b</sup>	79 (92) <sup>d</sup>	150 (31)
RAB with no flow	0 (0)	19 (15) <sup>b</sup>	29 (34) <sup>d</sup>	48 (10)

Coronary angiographic data at baseline according to the right ventricular infarction class (*n* = 499/679, 73%). <sup>b</sup>*P* < 0.01 *vs* classes A; <sup>d</sup>*P* < 0.01 *vs* classes B; TIMI: Thrombolysis in myocardial infarction. V: Vessel; D: Disease; O: Obstruction; RCA: Right coronary artery; CL: Culprit lesion; CCC: Coronary collateral circulation; RVB: Right ventricular branch; RAB: Right atrial branch; PCI: Primary coronary intervention; LAD-D: Left anterior descending diseases; TT: Transthoracic.

The combination of RCA and significant left anterior descending (LAD > 50% stenosis) disease was most commonly found in C patients (53%), and it was significantly different from A (11%) and B (36%) patients (*P* < 0.01).

Complete RCA obstruction was found in 240 patients (48%), and 45% of these patients had coronary collaterals. Significant differences in collateral blood flows were found among A, B, and C patients (60%, 47% and 11%, respectively, *P* < 0.01). None of the class A patients demonstrated an absence of flow to all of the RV or RA branches. For class B and C patients, no flow to all of the RV or RA branches was observed in 57% and 15%, and 92% and 34%, respectively (Table 4).

### Reperfusion

Of the 679 RVI patients, 148 (21.7%) were eligible for TT and 351 (51.6%) for PPCI. TIMI 3-flow by TT was achieved for 65%, 64%, and 0% for RVI classes A, B, and C. TIMI 3-flow was achieved with PPCI in 93%, 91%, and 87%, respectively. The mean residual coronary artery lesion at 90-180 min for the group RVI patients treated with TT or PPCI was 68% ± 10% and 10% ± 8%, respectively (*P* < 0.000).

Reversible RVWMA at 24-48 h with successful re-

**Table 5** Procedural variables and results of primary reperfusion at entry according to right ventricular infarction class (*n* = 679)

Variable	Class A ( <i>n</i> = 425)	Class B ( <i>n</i> = 158)	Class C ( <i>n</i> = 96)	Total
Symptoms to admission time (min-max) h	4.6 (2-23)	5.5 (3.4-19)	27 (19-48) <sup>d</sup>	
Medical treatment	111 (26)	44 (27)	25 (26)	180 (26.5)
TT	109 (25)	30 (19) <sup>b</sup>	9 (9) <sup>d</sup>	148 (21.7)
Primary PCI	205 (48)	84 (53)	62 (64)	351 (51.6)
Stent use	182 (88)	80 (95)	62 (100)	324 (92)
II b/ III a GI use	49%	47%	52%	
Inotropes/ vasopressors	0%	100% <sup>b</sup>	100%	
Temporary pacemaker	1.20%	10.7% <sup>b</sup>	29% <sup>d</sup>	
IABP support	0	0	73.9% <sup>d</sup>	
MVA	0	0	100% <sup>d</sup>	
Median time from MI to reperfusion treatment (min-max) h	1.9 (1.3-4)	2.1 (1.4-3.8)	14 (8-22) <sup>d</sup>	
Door-to-needle time (min)	42 ± 18	48 ± 16	-	
Door-to-balloon time (min)	93 ± 24	89 ± 37	198 ± 102 <sup>d</sup>	
TIMI 3 flow after PCI	93%	91%	87%	
TIMI 3 flow after TT	65%	64%	0% <sup>d</sup>	
RCA-Extensive clot burden	17%	22%	75% <sup>d</sup>	
At 24-48 h reversal of RVWMA with SR	84%	78%	69% <sup>d</sup>	

<sup>b</sup>*P* < 0.01 *vs* classes A; <sup>d</sup>*P* < 0.01 *vs* classes B. TT: Transthoracic; PCI: Primary coronary intervention; IABP: Intra-aortic balloon pump; MVA: Mechanical ventilatory assistance; RCA: Right coronary artery; SR: Success reperfusion; RVWMA: Right ventricular wall motion abnormalities; GI: Glucoprotein inhibitors; MI: Myocardial infarction; TIMI: Thrombolysis in myocardial infarction.

**Table 6** Hospital outcomes based on reperfusion for each RVI class *n* (%)

Variable	Class A				Class B				Class C			
	NR ( <i>n</i> = 111)	TT ( <i>n</i> = 109)	PCI ( <i>n</i> = 205)	Total ( <i>n</i> = 425)	NR ( <i>n</i> = 44)	TT ( <i>n</i> = 30)	PCI ( <i>n</i> = 84)	Total ( <i>n</i> = 158)	NR ( <i>n</i> = 25)	TT ( <i>n</i> = 9)	PCI ( <i>n</i> = 62)	Total ( <i>n</i> = 96)
AVB+	16 (14)	7 (6) <sup>b</sup>	11 (5)	34 (8)	14 (31)	9 (30)	6 (7) <sup>d</sup>	29 (18) <sup>b</sup>	22 (88)	8 (88)	13 (20)	43 (45) <sup>f</sup>
SVT/VF+	18 (16)	6 (5) <sup>b</sup>	9 (4)	33 (8)	18 (40)	9 (30)	4 (4.7) <sup>d</sup>	31 (19.6) <sup>b</sup>	14 (56)	5 (55)	9 (14) <sup>d</sup>	28 (29) <sup>f</sup>
AF/PAT	4 (3)	3 (2.7)	0 (0)	7 (1.6)	5 (11)	6 (20)	4 (4.7) <sup>d</sup>	15 (9.4) <sup>b</sup>	4 (16)	2 (22)	5 (8)	11 (11)
R-MI+	6 (5)	8 (7.3)	2 (0.9)	16 (4)	4 (9)	3 (10)	1 (1)	8 (5)	2 (8)	2 (22)	3 (4.8)	7 (7.2)
UTVR+	6 (5)	4 (3.6)	2 (0.9)	12 (3)	3 (6)	1 (3)	1 (1)	5 (3)	2 (8)	1 (11)	3 (4.8)	6 (6)
MR/T+	0 (0)	2 (1.8)	0 (0)	2 (0.4)	4 (9)	2 (6)	0 (0)	6 (3.7)	4 (16)	2 (22)	2 (3)	8 (8.3)
ARF	4 (3)	3 (2.7)	2 (0.9)	9 (2)	4 (9)	2 (6)	4 (4.7)	10 (6)	5 (20)	3 (33)	10 (16)	18 (19)
SSH+	18 (16)	2 (1) <sup>b</sup>	0 (0)	20 (5)	-	-	-	-	-	-	-	-
E-CS+	8 (7)	6 (5)	0 (0)	14 (3.2)	10 (22)	4 (13) <sup>b</sup>	8 (9)	22 (14) <sup>b</sup>	-	-	-	-
Death	9 (7.9)	5 (4.4) <sup>a</sup>	5 (3.2) <sup>f</sup>	19 (4.4)	12 (27)	4 (13) <sup>b</sup>	7 (8.3) <sup>d</sup>	23 (14.5) <sup>b</sup>	20 (80)	9 (100)	27 (44) <sup>d</sup>	56 (58) <sup>f</sup>

<sup>a</sup>*P* < 0.05, <sup>b</sup>*P* < 0.01 *vs* NR; <sup>d</sup>*P* < 0.01 *vs* primary coronary intervention (PCI); <sup>f</sup>*P* < 0.01 *vs* classe B; <sup>b</sup>*P* < 0.01 *vs* classe C. NR: Not send to reperfusion; TT: Transthoracic; AVB: Atrio-ventricular block requiring pacing; SVT: Sustained ventricular tachycardia; VF: Ventricular fibrillation; AF: Atrial fibrillation; PAT: Paroxysmal atrial tachycardia; R-MI: Reinfarction of the myocardium; UTVR: Urgent target vessel revascularization; MR/T: Myocardial rupture/tamponade; ARF: Acute renal failure; SSH: Sustained systemic hypotension (lasting < 12-24 h reversed with volume infusion and inotropic support); E-CS: Evolution to cardiogenic shock; +: Considered to be major cardiac complications.

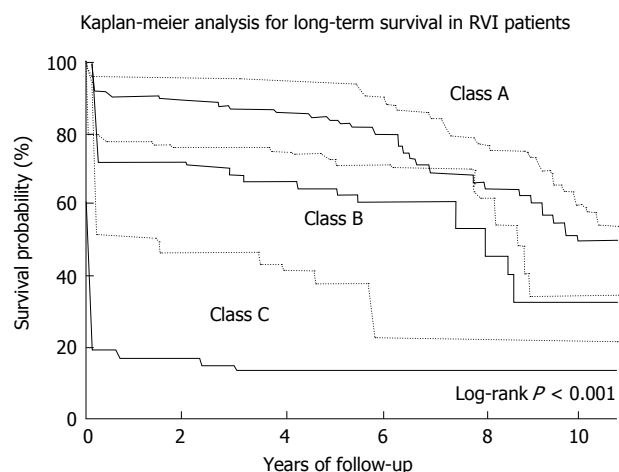
perfusion was observed for classes A, B, and C patients in 84%, 78%, and 69%, respectively. Reversible RVF (defined as the normalization of the SSP without volume infusion or inotropic agents and/or improvement or normalization of RVWMA and RV dilatation by echocardiography) was documented for class B in 83% and for CS in 43% (Table 5).

### Outcome

Class A: Half of the patients had uneventful clinical courses, although 3.2% developed CS, and 4.4% died. Hemodynamic data recorded at 48-72 h in 134 patients with or without successful reperfusion did not show any significant changes compared to baseline hemodynamics measurements. For those patients who received conservative treatment the mortality rate was 7.9%. With TT or

PPCI, decreased rates of bradyarrhythmias, AVB, ventricular arrhythmias and in-hospital mortality were observed. After PPCI, no patient progressed to CS, and significantly fewer patients died compared to those treated with TT (*P* < 0.01 and *P* < 0.05, respectively) (Table 6).

Class B: PPCI was associated with a decrease in AVB and ventricular arrhythmias. When reperfusion was successful, the mRAP and right ventricular end diastolic pressure (RVEDP) decreased (although not always to normal), and the CI and mSAP increased. The progression to CS was less frequently observed in patients who underwent TT and PPCI compared to patients who did not receive reperfusion. Without reperfusion therapy (RT) the mortality rate was 27%; with TT the rate was reduced to 13% (*P* < 0.01) and with PPCI to 8.3% (*P* < 0.01), with significant differences between the two strategies (*P*



**Figure 2** Kalan-Meier analysis for long-term survival in right ventricular infarction patients. Significant differences between the 3 right ventricular infarction (RVI) classes without intervention (solid lines) and with successful primary percutaneous coronary intervention (dashed lines) at 8 years.

< 0.01) (Table 6).

Class C: When PPCI was successful, decreased ventricular arrhythmias, mRAP, RVEDP, mPWP and sPAP were found to be associated with an increased CI and mSAP. Without RT, the in-hospital mortality rate was 80%. With TT, the rate was 100%, and with PPCI, the rate was reduced to 44% ( $P < 0.01$ ) (Table 6).

### Mortality analysis

To establish the likelihood of mortality, clinical, echocardiographic and hemodynamic variables were tested. When submitted to stepwise logistic regression analysis, age 64-74 years (OR = 5.1; 95%CI: 1.9-14.1,  $P < 0.01$ ), age  $\geq 75$  years (OR = 24.2; 95%CI: 7.1-66.5,  $P < 0.001$ ), SSP < 100 mmHg (OR = 7.7; 95%CI: 2.4-19.1,  $P < 0.001$ ) and classes B and C (OR = 38.6; 95%CI: 11.5-97.4,  $P < 0.01$ ) were independent, significant predictors of mortality in the multivariate model.

A progressive increase in long-term mortality was noted for all of the RVI patients. At 8 years, without primary reperfusion, the mortality rate was 32% in class A patients, 48% in class B patients and 85% in class C patients (solid lines). When PPCI was successful, the mortality rate at 8 years was lower than previously observed for each RVI classes (21% for A, 38% for B, and 70% for C,  $P < 0.001$ , dashed lines) (Figure 2).

## DISCUSSION

Our findings indicate that there are significant differences in early outcomes and late mortality among the 3 RVI classes. Thus, our discussion for RVI primary reperfusion treatment will focus on the results of reperfusion procedures in each RVI classes.

### Class A

This class is the only RVI category in which the following question can be raised: Which is best for treating RVI:

TT, PPCI or neither?<sup>[6]</sup>. The query was based on the supposition that (1) many RCA occlusions do not result in significant necrosis or RV dysfunction; (2) some thrombolytic studies have suggested little or no benefit in the absence of RVF; and (3) there are no controlled trials in any category of RVI with TT or PPCI<sup>[1-3,11-21]</sup>.

Nevertheless, more than 40% of class A RVI patients presented at least one major in-hospital complication. Clinical and life threatening risks of an initially hemodynamically silent RVI can not be dismissed when considering timely RT. Although both reperfusion procedures decreased in-hospital mortality in A class RVI patients, our findings suggest that all patients with a hemodynamically silent RVI should undergo PPCI (when available).

### Class B

Successful reperfusion of the RCA was associated with near normalization of the mRAP and RVEDP, improvement in the CO and mSAP and reversal of RVWMA/RVF in 78% and 83%. For this category of RVI patients our results demonstrate superior outcomes using PPCI over TT, based on following observations: (1) TIMI 3 RCA flow was obtained with TT in 64% and with PPCI in 91% of the patients; (2) more major complications such as AVB and ventricular arrhythmias, were observed using TT; and (3) mortality was lower in the PPCI treated patients compared to the TT-treated patients (13% *vs* 9%,  $P < 0.01$ ).

### Class C

The higher mortality in CS patients resulted from the substantial myocardial damage reflected by the more severe abnormalities in the RV hemodynamic measurements compared to those for class B patients. These findings are also consistent with the subset of patients who were likely to have suffered concomitant severe RA and RV ischemic dysfunction and, as expected, presented with major cardiac complications<sup>[2,3,14,15,22,23]</sup>.

However, with PPCI we demonstrated a significant reduction in mortality (44%) due to (1) restored perfusion of the RCA and its major branches (TIMI 3 flow: 87%) and reversal of RVWMA (69%); (2) reduced mRAP, RVEDP and mPWP and increased CO and mSAP; and (3) a significant decrease in ventricular arrhythmias.

The mortality with PPCI in our study was lower than that in the SHOCK Registry<sup>[14]</sup> (53%), but was higher compared to the study by Brodie *et al.*<sup>[15]</sup> in 30 patients (23%). When we compared Brodie's<sup>[15]</sup> results with ours, there are close similarities in age, door-to-balloon time, IABP support, stent use and TIMI grade 3-flow after PPCI. However, two important differences were noted. Although twice as many of our patients were sent for PPCI and could make our population more representative of RVI shock patients, the time from the first symptom to reperfusion was twice as long as Brodie's<sup>[15]</sup> study.

### Prognosis

In our study, we found that the long-term mortality rate continued to increase after the first year and was different

for the 3 RVI classes<sup>[4,11,24-27]</sup>. The differences in long-term survival after RVI in the 3 classes in our study could be due to coronary artery disease progression to complete RCA obstruction, significant LAD disease and/or poorly developed collateral coronary circulation, conditions that are most frequently observed in class B and C RVI patients. Perhaps the most important factors affecting outcome were the success or failure of the RT<sup>[1,3,12,16-18]</sup>.

### A study limitation

The major limitation; this analysis used nonrandomized, prospective surveillance and retrospective analysis; thus identified and unidentified confounders may have influenced the trends in reperfusion over time and clinical outcomes. Therefore, it is only an observational study. Nevertheless, this study reports results of RT over time in a large number of patients in 3 RVI categories and the information should be useful in current clinical practice.

In conclusion, PPCI seems to be superior to TT and reduces short and long-term mortality for all 3 RVI categories. Patients in CS should be encouraged to undergo PPCI rather than TT, as a primary reperfusion procedure; consequently, these patients should be transferred to a primary coronary intervention center to decrease the high morbidity and mortality of RVI class C patients.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Right ventricular infarction (RVI) is relatively common in patients with acute inferior-posterior left ventricular myocardial infarction. RVI can depress right ventricular (RV) function, resulting in right ventricular failure (RVF) or cardiogenic shock (CS). There are scarce and somewhat conflicting clinical data concerning the effects of interventions designed to achieve reperfusion of the RV myocardium in acute ischemia.

### Research frontiers

Several investigators have suggested that RV function improves only after successful thrombolytic therapy (TT), whereas others have reported recovery in the absence of early or even any reperfusion of the right coronary artery (RCA). In a study involving limited number of patients, rapid hemodynamic improvement and excellent clinical outcomes have been reported after successful primary percutaneous coronary intervention (PPCI) of the RCA and its major RV branches. Authors demonstrate that PPCI seems to be superior to TT and reduces short and long-term mortality for all 3 RVI categories. Patients in CS should be encouraged to undergo PPCI rather than TT, as a primary reperfusion procedure.

### Innovations and breakthroughs

The findings indicate that there are significant differences in early outcomes and late mortality among the 3 RVI classes. Two important differences were noted. Although twice as many of our patients were sent for PPCI and could make the authors population more representative of RVI shock patients.

### Applications

They found that the most important factors affecting outcome were the success or failure of the reperfusion. PPCI seems to be superior to TT and reduces short and long-term mortality for all 3 RVI categories. Patients in CS should be encouraged to undergo PPCI rather than TT, as a primary reperfusion procedure; consequently, these patients should be transferred to a primary coronary intervention (PCI) center to decrease the high morbidity and mortality. The authors

consider that their findings must be taking into consideration to be included in treatment guidelines for the RVI.

### Terminology

The diagnosis of RVF was based on clinical features, including persistent systemic hypotension (systemic systolic pressure  $\leq 100$  mmHg, right-sided S<sub>3</sub> and S<sub>4</sub>) without features of shock, echocardiographic evidence of ischemic RVF (RV wall motion abnormalities associated with gross RV dilatation), findings that suggest globally depressed RV function and invasive hemodynamic monitoring identifying RVI by a combination of findings that suggest RV dysfunction (low cardiac output and a disproportionate elevation of the mean right atrial pressure compared to the mean pulmonary wedge pressure).

### Peer review

This study investigated the impact of reperfusion therapy by means of primary PCI on clinical outcomes in acute RV infarction comparing with TT. The authors concluded that primary PCI is superior to TT and reduces the short-and-long-term mortality. The results are interesting and provide important impact on clinical practice.

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## Occurrence of longitudinal stent compression before stent deployment: Two case studies

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### Abstract

Several recent reports have described the occurrence of longitudinal stent deformation (LSD, defined as the distortion or shortening of a stent along the longitudinal axis), following its successful deployment. However, few reports have described LSD prior to any stent deployment. This previously unrecognized complication is the result of modifications to stent design. It has been noted that the new-generation stent platforms have a reduced number of connectors, which in turn causes a reduction in longitudinal stent strength. To corroborate previous findings by our lab and others (Vijayvergiya *et al*, 2013), we describe here two cases of LSD prior to stent deployment that occurred due to crushing of the proximal stent edge by the guide catheter while attempting to withdraw the crimped stent. In addition, we discuss the associated risk factors, such as the length of the stent, and specific management strategies, including technical guidelines and use of fluoroscopic guidance for maneuvering the stent during the procedure.

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**Key words:** Longitudinal stent deformation; Longitudinal stent compression; Stent structure; Percutaneous

coronary intervention; Complication

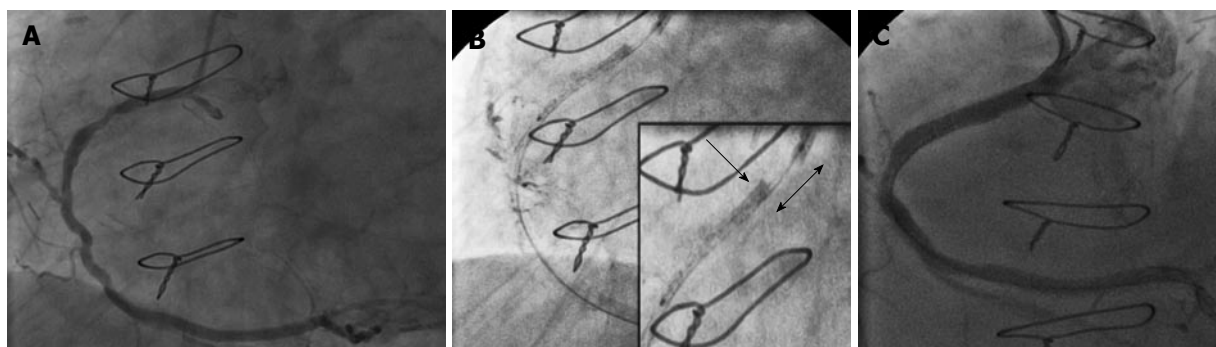
**Core tip:** We describe here two cases of longitudinal stent deformation before deployment. This report corroborates the findings previously made by us and others (Vijayvergiya *et al*, 2013) and emphasizes the risk of physical distortion of the stent prior to deployment. We also discuss specific risk factors of and management strategies for this unusual complication.

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### TO THE EDITOR

The case study published by Vijayvergiya *et al*<sup>[1]</sup> on longitudinal stent deformation (LSD) has been of great interest to us. The authors describe two cases of proximal LSD involving Promus Element stents that occurred before stent deployment. In both cases, the stent deformations were due to crushing of the proximal stent edge by the guide catheter that occurred while attempts were made to withdraw the crimped stent. Our group was the first to report a similar case involving a non-deployed 3.5 mm × 38 mm Taxus Element stent<sup>[2]</sup>. Since then, we have encountered two additional cases of LSD involving non-deployed stents.

The first case was a 69-year-old woman, who was required to undergo elective percutaneous coronary intervention (PCI) of the proximal and distal right coronary artery (RCA). Access was obtained *via* the right radial artery using a 6.5 Fr sheathless JR4 guide catheter (Asahi Intecc Co, Japan). Extensive guidewire-induced dissection of the RCA led to complications in the procedure. A 3.5 mm × 38 mm Multi-Link 8 stent (Abbott Vascular,



**Figure 1** Longitudinal stent deformation of a non-deployed stent in a 81-year-old woman. A: Coronary angiogram showing a long, severe and calcified stenosis involving the proximal and the mid-section of the right coronary artery; B: Severe longitudinal compression of a non-deployed 3.5 mm  $\times$  28 mm Multi-Link stent by the guide catheter, resulting in an 8-10 mm shortening in stent length and an accorded aspect of the proximal stent edge; C: Placement of a 3 mm  $\times$  26 mm Integrity stent for residual lesion coverage. The final angiographic result is shown.

United States) and a 3 mm  $\times$  38 mm Promus Element stent (Boston Scientific, United States) were placed in the proximal and mid-section of the RCA, respectively. Angiographic control showed the presence of residual dissection in the distal RCA. An attempt was made to place a 2.75 mm  $\times$  38 mm Promus Element stent in the distal RCA, but it failed to pass the mid-RCA. While withdrawing the crimped stent, deep engagement of the sheathless catheter occurred, and the proximal edge of the stent became blocked at the distal tip of the catheter. Further attempts to capture the crimped stent resulted in significant compression of the proximal stent edge. Hence, the operator decided to deploy the stent in the proximal RCA on a previously implanted stent. After performing serial high-pressure post-dilatation with a 3.75 mm non-compliant balloon and with the help of a guide catheter extension, a 3 mm  $\times$  28 mm Xience Prime stent (Abbott Vascular) was successfully deployed in the distal RCA. Notably, the patient recovered well and remained asymptomatic throughout the 20-mo clinical follow-up.

The second case was an 81-year-old woman, who was required to undergo elective PCI of the proximal and mid-RCA (Figure 1A). Access was obtained *via* the right femoral artery using a 6 Fr JR4 guide catheter. After performing serial predilatations with a 3 mm balloon, an attempt was made to place a 3.5 mm  $\times$  28 mm Multi-Link stent (Abbott Vascular) but it failed to pass the mid-lesion. While withdrawing the crimped stent, the guide catheter was pulled in and the proximal RCA was engaged. Concomitantly, the proximal edge of the stent was blocked at the distal tip of the guide catheter. After several attempts were made to pull the crimped stent into the guide catheter, it became angiographically evident that the guide catheter had crushed the proximal edge of the stent while the supporting balloon had partially entered the guiding catheter. As a result, the stent was shortened in length by approximately 8-10 mm before being deployed and had an accorded aspect at the proximal stent edge (Figure 1B). It was decided to deploy the stent in the proximal RCA and to cover the mid-section with a second stent. Post-dilatation was performed at high-pressure with a 3.5 mm non-compliant balloon and a 3 mm

$\times$  26 mm Integrity stent (Medtronic, United States) was placed on the residual mid-lesion. The final angiographic result was deemed acceptable (Figure 1C). The patient recovered well and remained asymptomatic throughout the 15-mo clinical follow-up.

Mamas *et al.*<sup>[3]</sup> defined LSD as the distortion or shortening of a stent along the longitudinal axis following its successful deployment. We have reviewed the collective findings from the two cases reported by Vijayvergiya *et al.*<sup>[1]</sup> and the three cases from our center, where LSD occurred prior to stent deployment. In all cases, the crushing of the proximal stent edge by the guide catheter during withdrawal of the balloon-stent system caused the LSD. A second important observation is that stent deformation led to an inability to recapture the crimped stent into the guide catheter and severely limited balloon-stent maneuverability. This difficulty arose in certain complex cases, mainly involving the Element Platform (4 out of 5 cases) and the Multi-Link Platform (1 case). Since all five cases utilized a long stent (38 mm long in 4 cases, and 28 mm long in 1 case), stent length could be an important risk factor in causing this unusual complication. Fluoroscopic images showed a clear separation between the proximal balloon marker and the proximal stent edge in all cases, making the diagnosis quick and conclusive. This case series confirms previous findings and highlights the risk of occurrence of LSD prior to stent deployment. The mechanism of the mishap reported here seems consistent with previous reports and involves a reduction in longitudinal stent strength frequently noted with newer stent-platforms.

Based on these reports, we recommend that in cases where withdrawal of a non-deployed new-generation stent into the guide catheter is difficult, the stent should be maneuvered carefully under fluoroscopic guidance. It is imperative to keep the guide catheter and the crimped stent in parallel axes. If resistance persists, advancement and careful rotation of the crimped stent could be attempted before its removal. When proximal stent deformation is visible or if a gap appears between the proximal balloon marker and the proximal stent edge, we strongly advocate avoiding forceful removal of the crimped stent, as it could worsen the stent deformation. In such cases,

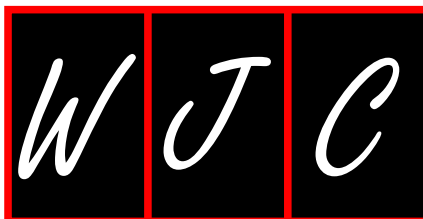
the operator has the option to either inflate the stent in another non-consequential location, or to pull back the stent and the guide catheter together. However, the latter strategy risks either loss of the coronary guidewire, which could be inconvenient in specific settings, such as dissections, or the previously reported difficulty in guidewire crossing through lesions. When choosing to deploy the deformed stent, efforts should be made to post-dilate the stent to avoid under-expansion and malapposition, which can lead to stent restenosis and thrombosis. We also recommend avoiding, as much as possible, deep intubation of the guide catheter during stent withdrawal, although sometimes this is unavoidable.

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

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- 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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programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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- 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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