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EDITORIAL

# Environmental Pollution and Cardiovascular Diseases: Identify and Prevent!

Claudio Tinoco Mesquita

*Universidade Federal Fluminense, Niterói, RJ - Brazil*

*"Education is the most powerful weapon which you can use to change the world."*

*Nelson Mandela*

Exposure to environmental pollution is a key factor in the development and worsening of cardiovascular diseases. This alert was issued in a 2004 statement from the American Heart Association (AHA).[1] A large body of new scientific evidence has been accumulated since then, allowing for a better understanding of the aspects related to this modifiable risk factor for cardiovascular diseases.

Cardiovascular diseases (CVD) are the major cause of death worldwide, accounting for more than 17 million premature deaths in 2016. Out of these deaths, 3.3 million are attributable to air pollution, 2.1 million of which are due to ischemic heart disease (IHD) and 1.1 million due to stroke.[2] Air pollution accounts for 19% of all cardiovascular deaths, and those 3.3 million deaths linked to air pollution exceed the deaths caused by smoking (2.48 million), obesity (2.85 million) and elevated blood glucose levels (2.84 million). Hypertension is the only risk factor that compared to pollution contributes to a greater burden of cardiovascular mortality.[3]

Exposure to chronic pollution causes an increase in oxidative stress and a consequent inflammatory state, which accelerates atherosclerosis through vasoconstriction, increased heart rate, increased blood pressure, endothelial dysfunction, increased platelet aggregation, dyslipidemia and insulin resistance.[3] Figure 1 illustrates some of the mechanisms proposed for the pathophysiology of the effects of pollution on the cardiovascular system. However, it is not only chronic exposure to air pollutants that is dangerous, since short-term exposure to polluted air can be extremely harmful for cardiovascular health, with an increased risk of myocardial infarction and stroke.[4] One of the major studies was carried out in China and showed that a 10 $\mu g/m^3$ increase within a 2-day period in concentration of inhalable particles with aerodynamic diameters less than 10 microm (PM10) is associated with a 0.35% and 0.44% increase in total mortality and cardiovascular mortality, respectively.[5] Among the populations particularly susceptible to the effects of pollution are women, the elderly and lower-income individuals, obese individuals, diabetic individuals and those with traditional cardiovascular risk factors, such as hypertensive and dyslipidemic individuals.[6]

International cardiology societies have published reports recommending that cardiologists assume an active position in raising awareness of the risks for heart disease posed by pollution.[6,7] The active involvement of the cardiology community in public policy formulations aiming at the control of air pollution levels is essential. Individuals with heart disease who practice physical exercise for the sake of improving their cardiovascular health may not see its full benefit when exposed to traffic pollution, since it can prevent the beneficial cardiopulmonary effects of walking in people with ischaemic heart disease, and those free from chronic cardiopulmonary diseases.[8] Thus, it is essential that cardiologists begin to focus their attention on environmental pollution, identifying the more susceptible individuals and proposing changes in their lifestyle, which may mitigate the deleterious effects of this new risk factor. Hadley et al.,[3] proposed a series of actions with the purpose of developing a clinical approach to mitigate the effects of pollution on the cardiovascular system (Table 1).

## Keywords

Cardiovascular Diseases/mortality; Cardiovascular Diseases/prevention & control; Environmental Pollution; Air Pollution; Risk Factors; Oxidative Stress.

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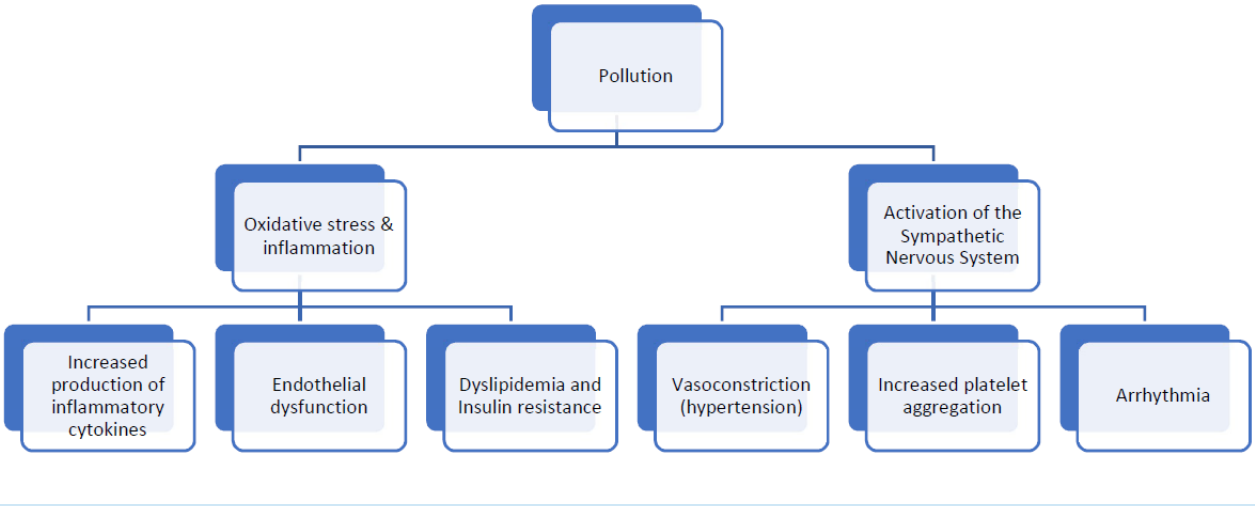


**Figure 1 - Mechanisms that link environmental pollution to cardiovascular diseases (adaptaded from Newby et al.[6] and Brook et al.[7])**

**Table 1 - Strategies for the assessment of individuals at risk of the effects of environmental pollution and ways to enhance their protection (adapted from Hadley et al.[3])**

| **Identification of individuals more susceptible to the cardiovascular effects of pollution** |
|---|
| Burning of solid fuels at home for heating or cooking |
| Live in residences with poor ventilation and with pollution sources, such as stoves or fireplaces |
| Live or work in urban industrial environment with intense pollution |
| Time spent routinely in heavy traffic areas |
| Outdoor physical activity in polluted environments or near highways or on busy urban roads |
| The obese, the elderly and individuals with traditional risk factors for cardiovascular disease |
| **Interventions & Recommendations to reduce the risk of environmental pollution** |
| Educate individuals at risk about the risk of pollution |
| Prioritize treatment of cardiovascular risk factors in individuals exposed to pollution |
| Collaborate with government efforts to reduce pollution emissions |
| Propose the use of more efficient heating, cooking and ventilation methods in patients' household |
| Educate patients to avoid exposure to environmental pollution: keeping the car's windows closed when in traffic or avoiding the practice of physical activity in high-exposure locations and times |
| Encourage the use of filters to reduce exposures, such as N95 respirator masks or central air conditioners with high efficiency filters |

In 2016, 95% of the world's population lived in areas where ambient PM2.5 levels exceeded 10 $\mu g/m^3$ (annual average), which is the maximum tolerated limit established by the World Health Organization. Global population-weighted PM2.5 concentrations are 18% higher compared to the 2010 levels, which means that the world's population is progressively more exposed to pollution.[9] This trend must be reverted so that we can have a healthier planet and healthier hearts. It is the responsibility of health-care professionals to disseminate ways to achieve the sustainable development goals of the United Nations Organization.[10] With regard to

environmental pollution, educating society, health-care professionals and patients is essential to mitigate the harmful effect of this new prevalent cardiovascular risk factor.

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ORIGINAL ARTICLE

# Mortality and Survival in Aortic Arch Surgeries with Preservation of Supra-aortic Vessels: Thirteen Years of Experience

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## Abstract

**Background:** The aortic arch diseases exhibit high morbidity and mortality rates. Some surgical strategies recommend partial preservation of the aortic arch and the supra-aortic vessels, but the immediate and medium-term mortality rates of patients undergoing this surgical strategy is uncertain.

**Objectives:** To compare overall mortality and mid- term survival curve of patients undergoing surgical strategy of partial preservation of the aortic arch and supra-aortic vessels (group A) compared to conventional strategies of the aortic arch approach (group B); to assess cardiovascular mortality over time.

**Methods:** Descriptive and retrospective study of the medical records of patients undergoing aortic arch repair surgery between February 2000 and July 2013. We analyzed 111 patients, 29 in group A and 82 in group B. The overall survival and survival from cardiovascular events were assessed by Kaplan-Meier test.

**Results:** In- hospital mortality from any cause was 31% in group A and 29.3% in group B. At 1 year, 2 year, and 5 year general survival was similar between the groups. In-hospital, 2 years and 5 years mortality from cardiovascular causes was 13.8%, 14.8%, e 22.7% in group A and 26.8%, 34.6% e 50.9% in group B. The difference between the groups in 5 years showed statistical significance (p = 0.0234). Survival from cardiovascular causes in 2 years and 5 years was 85.2% and 77,3% in group A and 65.4% and 49,1% in group B. Occurrence of urgent and emergency procedures were greater in group A, but without statistical significance.

**Conclusions:** There was no difference in all-cause mortality over time between the groups. Group A showed lower cardiovascular mortality at 5 years than group B. (Int J Cardiovasc Sci. 2018;31(5)466-482)

**Keywords:** Aorta, Thoracic / physiopathology; Aorta, Thoracic / surgery; Mortality; Aortic Aneurysm / surgery; Survivorship (Public Health); Comparative Study.

## Introduction

Despite considerable advances in diagnostic methods, surgical techniques (percutaneous or open surgical techniques) and postoperative care, thoracic aortic diseases, and especially aortic arch diseases are still major causes of cardiovascular mortality and challenge for physicians.[1]

The Global Burden of Disease Study 2010 showed that overall mortality rate for aortic aneurysm and aortic dissection increased from 2.49 per 100,000 population in 1990 to 2.78 per 100,000 population in 2010, with higher rates among men.[2,3]

The timing of surgical interventions in the management of thoracic aortic diseases considers the risk of rupture, possible postoperative complications and patients' life expectancy. Natural progression of thoracic aortic diseases is directly related to the aortic segment involved and the cause of the disease.[4]

Surgical management of the aortic arch is considered a complex approach, because of the high risk of brain

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injury caused by involvement of cerebral vessels. This is more evident in case of acute events, due to the need for performing the surgery in appropriate time using adequate techniques for each case.

Until the 1980's, increased mortality rates related to surgical repair of aortic arch had been mainly associated with visceral ischemia, due to diversion of blood flow to false lumen (when femoral artery perfusion was performed), neurological complications secondary to brain ischemic lesions, and hemorrhagic complications, i.e., often uncontrolled, perioperative bleeding.[5,6]

Symptomatic patients with aneurysm or dissection should be operated regardless of aneurysm size. In asymptomatic patients, aortic repair procedure is performed based on transverse diameter of the lumen, which is the main predictor of complications.[1]

Today, the most common techniques for protection of the central nervous system in aortic arch surgery are: profound hypothermia with complete circulatory arrest (18 - 20ºC),[7] profound hypothermia with retrograde cerebral perfusion (through superior vena cava)[8] and antegrade selective cerebral perfusion with moderate hypothermia (25 - 28ºC).[9] This can be performed bilaterally, or through one carotid artery, brachiocephalic trunk or subclavian artery. Antegrade selective cerebral perfusion is the most effective method for brain protection, and the technique of choice by many surgeons.[9]

Carreira et al.[5,6] described a new surgical strategy for aortic arch diseases with antegrade selective cerebral perfusion and preservation of part of patient's original vessels, which allows the aortic arch repair without interruption of cerebral blood flow, and a shorter period of unilateral antegrade cerebral perfusion. One of the main criticisms of this approach, however, is that preservation of part of patient's vascular tissue would increase the risk for recurrent aneurysmal disease or dissection.

In the present study, we compared mortality rate between patients who had undergone surgery with partial preservation of aortic arch and supra-aortic vessels (group A) and those who had undergone conventional surgical procedures of aortic arch (group B), and survival curve of these patients in a mean follow-up of 3.22 years (1,178.27 days).

The study was submitted to (Brazil online platform, May 2015) and approved by the Research Ethics Committee of *Casa de Saúde São José* (approval number 45613015300005664).

## Surgical strategies

### Surgical strategy of partial preservation of aortic arch and supra-aortic vessels (Group A)

Surgical strategy of partial preservation of aortic arch and supra-aortic vessels described by Carreira et al.[5,6] was the main focus of this study. The surgery involves median sternotomy to get access to the heart and great vessels, followed by dissection of aorta and supra-aortic arteries.

A curved clamp is placed on the brachiocephalic trunk and a 10 - 20 mm vascular graft anastomosis is made using a 5.0 polypropylene suture. An arterial cannula is inserted in the vascular graft next to the anastomosis. Venous cannulation depends on other associated procedures.

Nasopharyngeal temperature is decreased to 22 - 25ºC by extracorporeal circulation (ECC) and maintained during surgery of aortic valve and confection of proximal anastomosis with tubular graft. A vascular clamp is placed on ascending aorta before retroperfusion of the coronary sinus.

Then, a vascular clamp is positioned on the brachiocephalic trunk for a unilateral selective cerebral perfusion. Body perfusion is interrupted, and cerebral flow maintained at 300 - 500 mL/min through the right carotid artery for maintenance of right arterial pressure at 50 - 70 mmHg.

Blood is diverted to the brachiocephalic trunk using a roller pump or a centrifugal pump for ECC at 20ºC - 25ºC. Aorta is cut following the interruption of systemic perfusion, leaving enough aortic tissue to isolate both brachiocephalic trunk and left carotid artery.

Left subclavian artery is left close to the descending aorta. Isolation of brachiocephalic trunk and left carotid artery was achieved by closure of aortic "flap" with continuous 4.0 or 5.0 polypropylene suture.

Then, brachiocephalic trunk clamping is released, and bilateral antegrade selective cerebral perfusion is started and maintained at 500 - 1,000 mL/min and 20 - 25ºC. Distal portion of aorta is cut and prepared for placement of Dacron tubular prosthesis. Left subclavian artery is positioned next to distal anastomosis so that it can be ligated in case of significant lesion, and aortic endoprosthesis can be implanted by antegrade approach if necessary.

After completion of distal anastomosis with 4.0 polypropylene suture, an arterial cannula is inserted into aortic prosthesis and clamped for restauration of body perfusion by blood infusion at 25ºC. Rewarming (3ºC every 10 minutes) is performed during this period.

A vascular prosthesis is then anastomosed to the (valved or not) Dacron aortic graft by continuous suture technique using 5.0 polypropylene. The cannula placed into the brachiocephalic trunk is removed, and perfusion is maintained only through the cannula placed in the aortic prosthesis. Rewarming continue until nasopharyngeal temperature of 36ºC.

Distal and proximal aortic anastomoses can be performed with separate prostheses by anastomosis of proximal to distal aortic grafts.

**Conventional surgical strategies for aortic arch approach (Group B)**

In severe atherosclerotic disease and brachiocephalic trunk dissection, the surgical strategy of partial preservation of aortic arch and supra-aortic vessels cannot be performed, and many other procedures can be performed as alternative. Despite the differences between them, these techniques share common features.

Group B comprised different techniques, previously described by other authors, that included moderate hypothermia combined with antegrade cerebral flow, or profound hypothermia combined with brief circulatory arrest. Complete circulatory arrest for up to 15 minutes and temperature decrease to up to 25ºC is considered safe, with no risk of neurologic sequelae. Periods from 15 to 30 minutes, and periods of up to 40 minutes or up to 60 minutes of complete circulatory arrest seem to be associated with transient neurological dysfunction in nearly 10%, 15% or even 60% of patients, respectively.

In the first technique, described by a group from Mount Sinai Hospital, NY,10 the aortic convexity and cerebral vessels (not affected by dissection of atherosclerotic disease) are dissected en bloc and sutured to a 14 - 16 mm Dacron graft for posterior anastomosis to a second larger Dacron graft, placed between ascending and descending segment of thoracic aorta, resulting in the aortic arch reconstruction. Similarities with the technique described in Group A include prolonged periods of antegrade cerebral perfusion, and treatment of the aortic stump alone, which may include the insertion of an endoprosthesis in the descending aorta, as in type I aortic dissection.

Another technique for aortic arch disease involves the use of antegrade cerebral perfusion through catheterization of cerebral vessels, brachiocephalic trunk and left carotid artery or only profound hypothermia. In this case, cerebral vessels are also dissected en bloc (aortic convexity and brachiocephalic trunk, left carotid and left subclavian artery) and anastomosed to the interposed Dacron graft, substitute for the aortic arch.[11]

In a more recent technique, developed after the advent of branched Dacron grafts, the separated graft technique substitutes the en bloc repair technique for aortic arch reconstruction. A graft with four limbs is used, 3 of them in the arch of the graft and 1 used for reestablishment of ECC. Antegrade cerebral perfusion may also be used in this technique, as described by Kazui et al.[12] in 2000 with a catheter placed in the brachiocephalic trunk and left carotid artery.

## Objectives

### I. Primary objective

To evaluate medium-term (5 years) mortality and survival rates in patients undergoing the surgical technique of partial preservation of aortic arch and supra-aortic vessels in comparison with conventional strategies for aortic arch reconstruction.

### II. Secondary objective

To evaluate 30-day, 1 year, 2-year, 5-year cardiovascular mortality.

## Methods

### Study population

In this retrospective study, we evaluated medical records of patients hospitalized for surgical resection and/or surgical treatment of aortic arch aneurysm in hospitals in Rio de Janeiro. The initial sample was composed of 150 patients, and data of 111 patients operated from February 2000 to July 2013 were analyzed.

All patients underwent surgical repair of aortic arch and ascending aorta diseases performed by the same surgical staff. Of the 111 patients included, 29 underwent the strategy with partial preservation of aortic arch and supra-aortic vessels (Group A) and 82 underwent conventional surgical techniques for aortic arch reconstruction (Group B) (Figure 1).

The search for medical records was conducted by the medical records department of each institution. A standardized form (Appendix A) was used for collection of clinical and surgical data of patients.

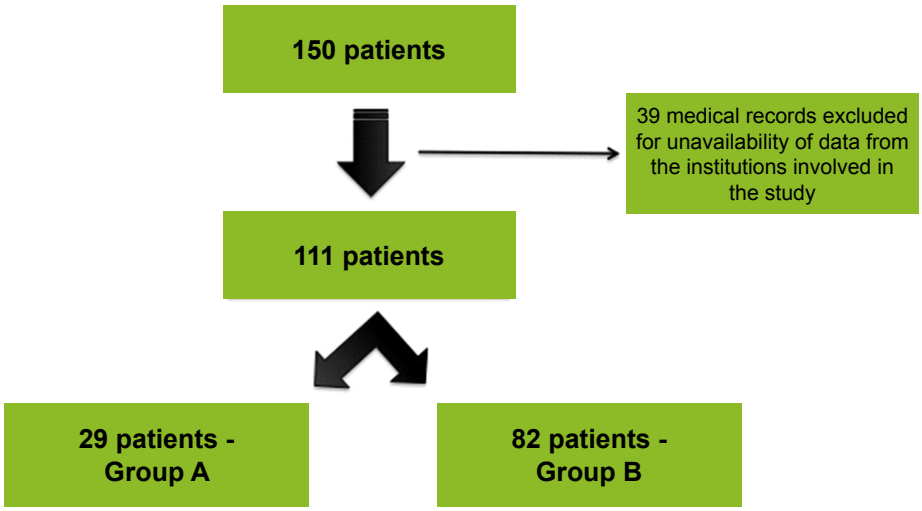



**Figure 1 - Flowchart of database construction.**

Thirty-nine patients were excluded from the initial sample (n = 350) due to missing data in the medical records and/or the medical records were not available.

As above mentioned, the strategy of partial preservation of aortic arch and supra-aortic vessels cannot be performed in severe atherosclerotic disease or brachiocephalic trunk dissection. In our study, patients with preserved brachiocephalic trunk who had not undergone this technique, this decision was left to the surgeons' discretion.

The study was conducted in the following private hospitals in Rio de Janeiro - Casa de Saúde São José (30 patients), Quinta`Dor Hospital (25 patients), Copa`Dor (21 patients) and Barra`Dor (20 patients), Pró-cardíaco Hospital (5 patients), Samaritano Hospital (5 patients), Status Cor Hospital (4 patients) and Santa Maria Madalena Hospital (1 patient).

For medium-term mortality and survival rates, data were collected from death certificates issued by the Rio de Janeiro State Secretary of Health from February 2000 to December 2014.

## Inclusion criteria

All patients who underwent aortic arch repair (elective or emergent, performed by the same surgical staff) for aneurysm or acute aortic dissection from February 2000 to July 2013 were included in the study.

## Exclusion criteria

Patients with missing data in the medical records, or whose medical records were not made available by the institutions.

## Data collection

Data were collected using a standardized form including sociodemographic and clinical data, as well as pre-, peri-, and post-operative data (Appendix A).

Preoperative data included: clinical and sociodemographic data – sex, age, systemic arterial hypertension (SAH), diabetes mellitus (DM), obesity, previous stroke (ischemic, hemorrhagic or unspecified), pre-operative serum creatinine, chronic renal failure, renal replacement therapy (hemodialysis or peritoneal dialysis), diagnosis of chronic obstructive pulmonary disease (obtained from the medical records), peripheral vascular disease, history of arrhythmia, history of acute myocardial infarction (AMI), unstable angina, heart failure and NYHA functional class, previous surgeries – myocardial revascularization surgery, heart valve replacement, partial aortic replacement, aortic dissection according to Stanford classification (type A or B), aortic arch aneurysm and/or aneurysm of ascending aorta.

The following perioperative data were evaluated: need for blood transfusion, combined procedure performed in aortic valve (valve repair or valve replacement),

endoprosthesis in descending aorta, time of ECC, aortic cross-clamping time, minimum temperature during hypothermia, nature of surgery: elective, urgent (24 - 72h of symptom onset) or emergent (within 24 hours of symptom onset), cardiorespiratory arrest during anesthetic induction, intraoperative complications, and death in the operating room.

Postoperative data evaluated were: clinical progress – low output syndrome (cardiogenic shock), cardiac tamponade, complications – ischemic, mechanical, respiratory, metabolic, neurological (ischemic or hemorrhagic event confirmed by imaging test according to medical records data), cardiologic, infectious and vascular complications, postoperative drainage volume within the first 24 hours, time of hospitalization, time of mechanical ventilation and hospitalization outcomes (death, discharge or transfer to other facilities).

### Mortality and survival

Thirty-day mortality was defined as the total number of deaths that occurred in 30 days after surgery divided by the total number of surgeries performed.

Hospital mortality was defined as the total number of in-hospital deaths after surgery divided by the total number of surgeries performed.

Cardiovascular deaths were defined by the codes – I00-I99, E10-E14, R57 and J81 according to the International Statistical Classification of Diseases, tenth revision (ICD- 10).

Survival was considered as time (in years) after surgery according to data registered by the death registration service (SES-RJ/SVS/CGVS/ADVITAIS).

Patient's anonymity was protected, and patients' consent for the use of their data for research purposes was sought using a proper form at admission.

Confidentiality of the data obtained from the SES-RJ/SVS/CGVS/ADVITAIS was assured and protected by password (Appendix C and D).

### Statistical analysis

The SPSS software version 21.0 for Windows was used in all analyses. Continuous variables were expressed as mean and standard deviation or median and interquartile range according to normality (or not) of data distribution, tested by the Kolmogorov-Smirnov test. Categorical variables were expressed as percentage. The unpaired Student's t-test and the Mann-Whitney test were used for analysis of parametric and non-parametric variables, respectively. The chi-square test and Fisher's exact test were used for comparison of parametric variables.

A conventional level of significance was adopted, $p < 0.05$. Overall survival and cardiovascular event-free survival were assessed by Kaplan-Meier curve and the log-rank test.

## Results

Data of 111 patients who had undergone surgical treatment of aortic arch dissection or aneurysm from 2000 to 2013 were evaluated.

Most patients were men (n = 73, 65.77%) with mean age of 63 ± 13 years in group A and 64 ± 15 years in group B. In the preoperative period, the most frequent risk factors were SAH (90%), DM (37.7%) and obesity (19.7%) in group B. In group A, the same risk factors were observed, with statistical significance for DM (41.7%, p = 0.036).

Median preoperative serum creatinine was 0.95 mg/dL (0.80 - 1.30 mg/dL) in group A and 1.10 mg/dL (0,90 - 1,30 mg/dL) in group B. The incidence of chronic renal failure was 7.7% in group A and 10.8% in group B; 3.9% of these patients were on hemodialysis or peritoneal dialysis. Patients with previous cardiac surgeries were found in group B (and not in group A); 3.9% (3 patients) underwent myocardial revascularization surgery, 6.5% (5 patients) valve replacement and 5.3% (4 patients) partial aortic replacement.

No patient had active endocarditis in the preoperative period. In group A, no patient had stable angina or heart failure and in group B, 2.7% of patients had unstable angina and 1.3% had heart failure in the preoperative period (Table 1).

Regarding surgical data, mean ECC time was 169 ± 42 minutes in group A and 156 ± 59 minutes in group B (p = 0.311); mean aortic cross-clamping time was 128 ± 44 minutes in group A and 116 ± 41 minutes in group B (p = 0.200).

Median minimum temperature achieved during hypothermia induced for aortic arch reconstruction was 26 ± 4ºC in group A and 27 ± 5ºC in group B (p = 0.169). Drainage volume within the first 24 hours of surgery was 468 mL and 375 mL in groups A and B, respectively (p = 0.469).

Blood transfusion was commonly required during the procedures (89.3% and 81.1% in groups A and B, respectively) (p = 0.321).

**Table 1 - Preoperative clinical characteristics of patients who underwent partial preservation of aortic arch and supra-aortic vessels (Group A) and patients who underwent conventional surgical techniques for aortic arch reconstruction (Group B)**

| Variable | Group A (n = 29) | | Group B (n = 82) | | p |
|---|---|---|---|---|---|
| | N | n(%), median (p25 - p75) or mean ± standard deviation | N | n(%), median (p25 - p75) or mean ± standard deviation | |
| Age | 29 | 63 ± 13 | 82 | 64 ± 15 | 0.889 |
| Sex | | | | | |
| Female | 10 | 34.5% | 28 | 34.1% | 0.974 |
| Male | 19 | 65.5% | 54 | 65.9% | 0.974 |
| HAS | 25 | 86.2% | 72 | 90.0% | 0.576 |
| Blood pressure at admission (mmHg) | | | | | |
| Systolic | 23 | 133 ± 32 | 67 | 126 ± 21 | 0.245 |
| Diastolic | 21 | 72 ± 20 | 67 | 70 ± 14 | 0.245 |
| Diabetes mellitus | 10 | 41.7% | 23 | 37.7% | 0.036 |
| Obesity | 4 | 14.3% | 15 | 19.7% | 0.523 |
| BMI (kg/m²) | 27 | 26.27 ± 3.38 | 77 | 26.85 ± 4.34 | 0.533 |
| Ischemic stroke | 3 | 10.7% | 3 | 4.8% | 0.301 |
| Highest creatinine level (mg/dL) | 22 | 0.95 (0.80 – 1.30) | 74 | 1.10 (0.9 – 1.30) | 0.934 |
| CRF | 2 | 7.7% | 8 | 10.8% | 0.648 |
| COPD | 1 | 3.7% | 8 | 11.0% | 0.260 |
| PAD | 1 | 3.6% | 3 | 4.1% | 0.911 |
| Arrhythmia | 2 | 7.4% | 8 | 11.9% | 0.519 |
| AMI | 3 | 10.3% | 8 | 10.7% | 0.962 |

*CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; PAD: Peripheral arterial disease; AMI: acute myocardial infarction.*

The frequencies of combined surgeries were 58.6% in group A and 72.7% in group B. In addition, in group A, 24.1% of patients underwent elective surgery, 58.6% urgent surgery and 17.2% emergent surgery, whereas in group B these frequencies were 45.7%, 44.4% and 9.9%, respectively.

Intraoperative complications – blood dyscrasia, hypotension secondary to the use of amine, etc. – occurred in 24.1% of patients in group A and no deaths were reported. In group B, intraoperative complications occurred in 22.5% of patients, with death in 1.3% (Table 2).

The most frequent postoperative complications were – blood transfusion (48.3%), drainage volume within the first 24 hours of surgery greater than 600 mL (41.4%), mechanical ventilation time longer than 24 hours (37.9%) and acute renal failure (32.1%). In group B, complications were – arrhythmia (34.2%), mechanical ventilation time longer than 24 hours (33.8%) and blood transfusion (32.5%) (Table 2).

One hemorrhagic event was reported in each group confirmed by clinical and imaging data obtained from the medical records.

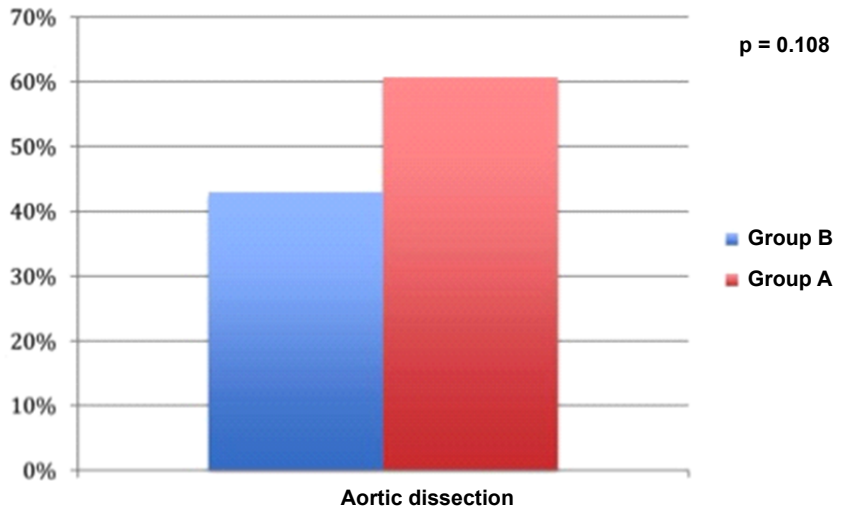
Reoperated patients were found only in 2 patients in group B (2.43%), during different hospital admissions.

Also, 60.7% and 43.0% of patients in groups A and B, respectively had aortic dissection (Graph 1).

**Table 2 - Surgical data of patients who underwent partial preservation of aortic arch and supra-aortic vessels (Group A) and patients who underwent conventional surgical techniques for aortic arch reconstruction (Group B)**

| Variable | Group A (n = 29) | | Group B (n = 82) | | p |
|---|---|---|---|---|---|
| | N | n(%), median (p25 - p75) or mean ± standard deviation | N | n(%), median (p25 - p75) or mean ± standard deviation | |
| Time of ECC (min) | 26 | 169 ± 42 | 79 | 156 ± 59 | 0.311 |
| Aortic cross-clamping time (min) | 26 | 128 ± 44 | 79 | 116 ± 41 | 0.200 |
| Hypothermia (ºC) | 26 | 26 ± 4 | 79 | 27 ± 5 | 0.169 |
| Drainage within the first 24 hours (mL) | 27 | 468 (250 – 850) | 72 | 375 (225 – 750) | 0.469 |
| Blood transfusion | 25 | 89.3% | 60 | 81.1% | 0.321 |
| Aortic valve repair | 9 | 34.6% | 20 | 27.0% | 0.463 |
| Descending aortic prosthesis | 9 | 36.0% | 16 | 21.9% | 0.163 |
| Coronary reimplantation | 4 | 17.4% | 20 | 27.8% | 0.318 |
| Combined surgery | 17 | 58.6% | 56 | 72.7% | 0.162 |
| Elective surgery | 7 | 24.1% | 37 | 45.7% | 0.042 |
| Urgent surgery | 17 | 58.6% | 36 | 44.4% | 0.190 |
| Emergent surgery | 5 | 17.2% | 8 | 9.9% | 0.292 |
| Intraoperative complications | 7 | 24.1% | 18 | 22.5% | 0.857 |

*ECC: extracorporeal circulation.*




**Graph 1 - Aortic dissection according to technique.**

Thirty-day mortality and in-hospital mortality was found in 24.1% (7 patients) and 31% (9 patients), respectively, in group A and in 26.8% (22 patients) and 29.3% (24 patients) in group B, with no statistically significant differences between the groups (Table 3).

Overall survival was 1,178.27 days (mean) and 843.00 days (median). In group A, mean survival was 1,182.83 days and in group B, 1,176.66 (OR = 268.114 days – 95% CI [-527.705-515.367]).

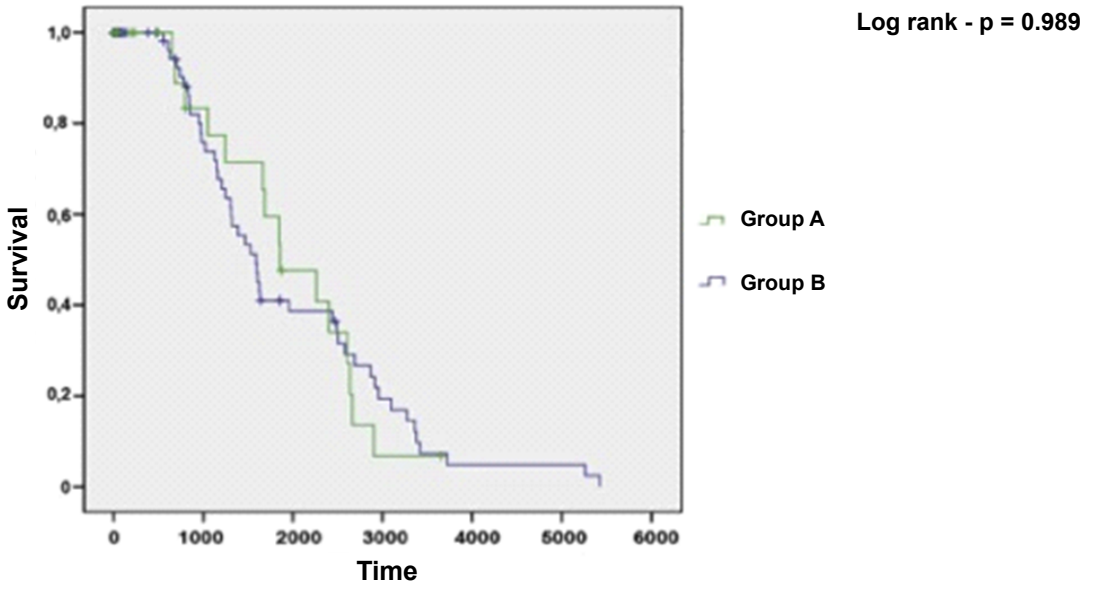
Regarding all-cause mortality, a two-year survival rate of 59.3% and 59% were observed in groups A and B, respectively, and a 5-year survival rate of 45.5% and 35.8% were observed in groups A and B, respectively, with no statistically significant difference between the groups (Graph 2).

Survival curve was also analyzed by the causes of death registered in death certificates and classified into cardiovascular and non-cardiovascular death.

Group A showed a thirty-day cardiovascular mortality of 10.3%, an in-hospital cardiovascular mortality of 13.8%, and a 2-year and 5-year mortality for cardiovascular diseases of 14.8% and 22.7%, respectively. In group B,

**Table 3 - Overall mortality by techniques for aortic arch reconstruction (partial preservation of aortic arch and supra-aortic vessels, Group A or conventional surgeries, Group B)**

| Outcome | Group A | | Group B | | p |
|---|---|---|---|---|---|
| | N | n(%) | N | n(%) | |
| 30-day mortality | 7 | 24.1% | 22 | 26.8% | 0.777 |
| In-hospital mortality | 9 | 31.0% | 24 | 29.3% | 0.858 |
| 1 year- mortality | 10 | 34.5% | 28 | 34.1% | 0.974 |
| 2-year mortality | 11 | 40.7% | 32 | 41.0% | 0.979 |
| 5-year mortality | 12 | 54.4% | 34 | 64.2% | 0.437 |




**Graph 2 - Overall survival curve in patients who underwent partial preservation of aortic arch and supra-aortic vessels (Group A, n = 29) and patients who underwent conventional surgical techniques for aortic arch reconstruction (Group B, n = 82).**

these percentages were 25.6%, 26.8%, 34.6% and 50.9%, respectively. Five-year mortality was significantly different between the groups (Table 4).

Overall cardiovascular mortality was 20.7% in group A and 32.9% in group B, with no statistic difference between the groups (Graph 3).

## Discussion

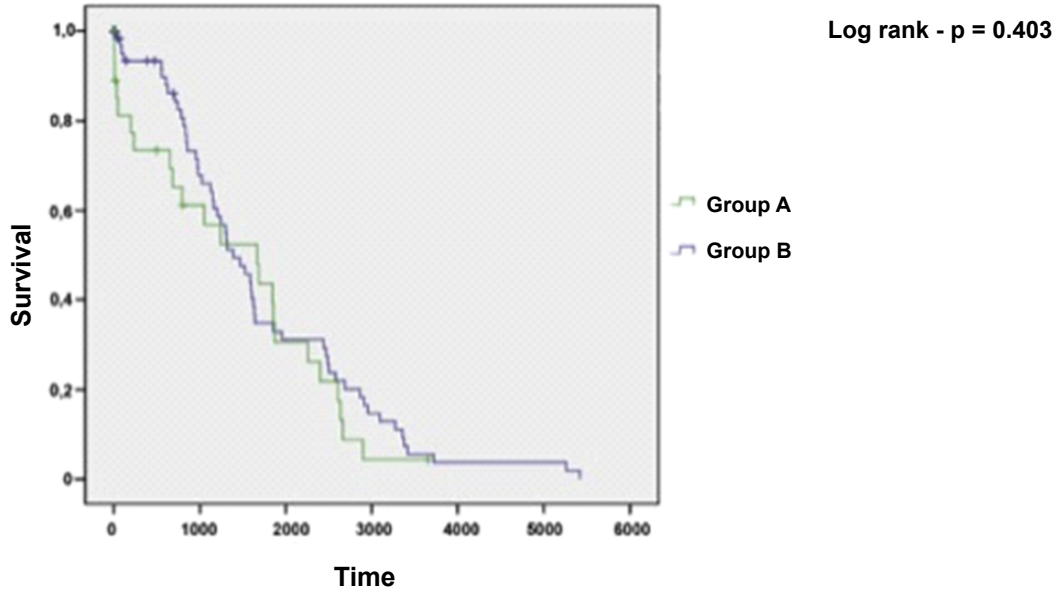
Antegrade cerebral perfusion is recognized as the best method to protect the brain against ischemic injuries, regardless of the surgical technique or strategy adopted for the aortic arch approach. Also, moderate hypothermia (approximately 25ºC) is not associated with neurologic sequalae.

Total aortic arch replacement, as in group A, was performed under selective cerebral perfusion and moderate hypothermia since, as reported by Kazui et al.,[9] selective cerebral perfusion is a reliable technique for brain protection and facilitates time-consuming total arch replacement.

In group B, many conventional techniques for aortic arch reconstruction were performed, with a wide theoretical base and practical applicability. Brain

**Table 4 - Cardiovascular mortality by techniques for aortic arch reconstruction (partial preservation of aortic arch and supra-aortic vessels, Group A or conventional surgeries, Group B)**

| Outcome | Group A | | Group B | | p |
|---|---|---|---|---|---|
| | N | n(%) | N | n(%) | |
| 30-day mortality | 3 | 10.3% | 21 | 25.6% | 0.086 |
| In-hospital mortality | 4 | 13.8% | 22 | 26.8% | 0.154 |
| 2-year mortality | 4 | 14.8% | 27 | 34.6% | 0.052 |
| 5-year mortality | 5 | 22.7% | 27 | 50.9% | 0.024 |
| Global mortality | 6 | 20.7% | 27 | 32.9% | 0.215 |




**Graph 3 - Cardiovascular survival curve in patients who underwent partial preservation of aortic arch and supra-aortic vessels (Group A, n = 29) and patients who underwent conventional surgical techniques for aortic arch reconstruction (Group B, n = 82).**

protection was also established by selective cerebral perfusion. In the study by Tang et al.,[13] a review of the contemporary practice in total arch replacement by using the trifurcated graft technique was performed. The authors concluded that unilateral and bilateral antegrade cerebral perfusion and profound hypothermia can be performed without adding significant complexity to the procedure while conferring maximal cerebral protection.

Surgical strategy for aortic arch reconstruction described in group A includes axillary artery cannulation. Although femoral arterial cannulation is considered a routine procedure, Benedetto et al.[14] reported that there is a growing perception that this technique, by reversing the flow in the thoracoabdominal aorta, may increase the risk of retrograde brain embolization, dissection and organ malperfusion in type A aortic dissection. Axillary artery cannulation shows better surgery outcomes by allowing antegrade outflow. In this meta-analysis, acute aortic dissection was demonstrated to be superior to femoral artery cannulation in reducing in-hospital mortality and the incidence of permanent neurological deficit in patients operated for type A acute aortic dissection.

Characteristics of the study population are similar to those of other groups[15] studied for operative outcomes of surgical approaches of aortic arch diseases, including the high prevalence of the most common risk factors. In group A, there were patients with history of neurologic events (ischemic or hemorrhagic), representing 10.7% and 7.4% of total study population, respectively.

In both groups, there were patients who were submitted to surgical procedure despite suffering a stroke in the preoperative period, which until a few years ago, would be considered contraindication to surgery. However, this fact started to change by the study by Most et al.[16] The authors retrospectively studied 53 patients with recent neurological deficit (which were considered a contraindication for surgery due to poor prognosis) who received surgical repair for acute aortic dissection type A between 2005 and 2012. They showed that more than half of them recovered from surgery without neurological sequelae and concluded that patients with acute type A aortic dissection and neurological deficit before surgery should not be excluded from emergency surgery.

In group A, 24.1% of patients underwent elective surgery, 58.6% urgent and 17.2% emergent surgery. Aortic dissection was the predominant procedure among these patients, similar to the study by Martín et al.[15] However, in this study, 93% of patients underwent emergent surgery and 7% urgent surgery, and positive outcomes were observed even in patients in coma.[16] Early diagnosis and therapy for acute aortic dissection is crucial for postoperative outcome. While less significant improvements were associated with surgical interventions performed more than 9 hours of symptom onset, patients who underwent surgery less than 5 hours of symptom onset showed more favorable outcomes.

It is of note that postoperative drainage volume within the first 24 hours was associated with possible postoperative bleeding. Mean drainage volume was 468 mL and 375 mL in groups A and B, respectively (no statistical significance). In Miana et al.,[17] mean 24-hour bleeding volume was 610 ± 500 mL in a group of 411 patients undergoing surgery for acquired heart diseases. In the subgroup of patients who underwent aortic surgery, mean bleeding volume was 765 ± 770 mL among those at higher risk of bleeding and 604 ± 479 mL among those at lower bleeding risk.

Although surgical strategy performed in group A proposes a more careful approach of hemostasis, a greater bleeding volume was observed in these patients. This may be explained by the longer ECC time and higher rates of emergent surgeries, which are independent risk factors for bleeding.[17] Also, in this group, most patients underwent surgical repair of acute aortic dissection.

Among postoperative neurological complications, hemorrhagic stroke occurred in 1 patient (3.4%) in group A and 1 patient (1.3%) in group B. In a group of 98 patients undergoing surgery for type A aortic dissection, the incidence of permanent stroke was 9%.[15] In a recent meta-analysis, 7.3% of patients undergoing antegrade cerebral perfusion and moderate hypothermia had permanent neurological dysfunction.[18] In the study by Kazui et al.[9] the incidence of temporary and permanent neurological dysfunction was 4.2% and 2.4%, respectively.

Hagl et al.[19] examined 717 patients who survived aortic arch and ascending aorta operations through median sternotomy for risk factors for stroke. When all patients with total cerebral protection time between 40 and 80 minutes were examined, the method of cerebral protection did not influence the occurrence of stroke; however, antegrade cerebral perfusion resulted in a significant reduction in the incidence of temporary neurological dysfunction ($p = 0.05$; OR 0.3).

Postoperative AMI was present in 10.3% of patients in group A and in 1.3% of patients in group B ($p = 0.025$).

However, this result should be interpreted with caution, as these frequencies corresponded to 3 patients in group A and only 1 patient in group B in absolute number due to the small sample size, and maybe these frequencies would not be repeated in larger populations.

Diagnosis of AMI was established very subjectively, only by medical records data, without considering electrocardiographic or clinical (cardiac enzymes) criteria. It is also worth pointing out that the lack of difference in the frequency of cardiogenic shock between the groups and the use of BIA reinforce the hypothesis that the frequency of AMI in the postoperative period was not relevant or, if present, not clinically significant.

Early mortality in patients with type A aortic dissection varies between 15 and 35% in the literature, with an estimated 5-year survival between 65% and 75%.[20] In our study, 30-day mortality (24.1% in group A and 26.8% in group B) and in-hospital mortality (31.0% in group A and 29.3% in group B) were similar between the groups, with no statistically significant difference. Overall 30-day mortality in a group of 518 patients undergoing type A aortic dissection repair was 20.2%.[21]

Martín et al.[15] reported an in-hospital mortality rate of 15% in patients undergoing aortic dissection surgery. In another study comparing partial aortic arch repair with total aortic arch repair, in-hospital mortality rate was 6.7% and 6.9%, respectively.[22]

In the study by Dossche et al.,[23] including 163 patients, 55% of them with degenerative aneurysm and 28% with acute type A dissection, in-hospital mortality or perioperative neurological complications did not significantly affect the duration of selective antegrade cerebral perfusion. In univariate analysis, some factors had a significant influence on overall mortality – acute type A dissection ($p = 0.003$), central neurological damage less than 24 h before the surgery ($p < 0.001$), preoperative hemodynamic instability ($p = 0.034$), and thoracotomy for any cause ($p = 0.036$).

Patel and Deeb[24] also reported that morbidity increases with the necessity of (total or partial) aortic arch resection, with an increased risk from 5% to 7%. Early mortality in type A aortic dissection is greater than 20%. In addition, repair of thoracoabdominal aortic aneurysm is still recognized as a high-risk procedure, with mortality and paraplegia rates higher than 20%, according Acher & Wynn.[25]

Kazui et al.[9] evaluated 330 patients who underwent aortic arch surgery using selective cerebral perfusion. Surgeries were performed with hypothermia, ECC, selective cerebral perfusion and systemic circulatory arrest. Total aortic arch replacement with a branched graft was performed in 288 patients (94%). In-hospital mortality rate was 11.2%.

Short- and long-term survival in patients with acute type A aortic dissection varies from 52 - 94% (1 year) and 45 - 88% (5 years). Ten-year survival rate of patients with acute dissection after initial hospitalization was reported to be between 30% and 60% in many studies. In the study by Shiono et al.,[22] a 55% and a 30% survival rate within 10 years and 20 years, respectively were reported.

In our study, survival rates were 65.5% and 65,9% within 1 year, 59.3% and 59.0% within 2 years, and 45.5% and 35.8% within 5 years in groups A and B, respectively. These results are in accordance with the review by Braverman,[20] in which a 5-year survival rate of 45 - 88% was described.

Our results do not corroborate the hypothesis that a partial aortic arch repair with preservation of part of affected tissue could worsen mortality and morbidity by increasing the risk for recurrent dissection or aneurysm expansion of remaining tissue. Five-year mortality rate was similar between the groups (45.5% vs. 35.8%). In the meta-analysis by Li et al.,[18] comparing partial and total aortic arch repair, 5-year survival rate was also similar between the groups (77.4% vs. 80.8%). In addition, the authors point out that, although the literature does not support superiority of total aortic replacement over partial replacement, a more extensive resection may be necessary in case of extensive lesions, or those located in the aorta. The choice for this method should be individually considered according to clinical and anatomic conditions, as well as pathologic features of the dissection.

Considering only deaths for cardiovascular causes, group A was superior than group B, with a 5-year cardiovascular mortality of 22.7% and 50.9%, respectively. These rates demonstrate both safety and efficacy of surgical strategy used in group A for aortic aneurysm and dissection (whenever possible).

## Conclusions

This study showed that cardiovascular mortality was significantly different between the groups after a 5-year follow-up. The group in which a partial preservation of aortic arch and supra-aortic vessels was performed

showed a lower 5-year cardiovascular mortality than the group in which conventional strategies for aortic arch repair were used. No statistically significant differences were found in other time intervals.

Thirty-day and 5-year overall mortality after surgery were not statistically different between the groups.

## Limitations

Due to its retrospective and descriptive nature, this study has some inherent limitations, such as – data collected from medical records, which involves incomplete data or data of difficult interpretation, lack of test results at hospital admission or in postoperative follow-up, in addition to unavailability of medical records from some institutions.

Although the study was conducted in different hospitals, all procedures analyzed in the study were performed by the same surgical staff and, for this reason, both performance and learning curve of the techniques are linear.

The study groups are very heterogeneous, which make some comparisons and analysis impossible. Also, sample size is considered small for the establishment of definitions.

Finally, it is worth mentioning that the study was not designed to evaluate the best surgical strategy for aortic arch repair. This retrospective analysis of patients that had undergone aortic arch repair may add information about 30-day mortality and in-hospital mortality. In this 5-year multicentric analysis, no difference was observed regarding 30-day mortality, in-hospital mortality or survival rates between the two techniques

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## Author contributions

Conception and design of the research: Oliveira PF, Sá MPL, Almeida Junior GLG, Carreira VJ. Acquisition of data: Oliveira PF, Almeida Junior GLG, Carreira VJ, Rangel BSS, Silva SP. Analysis and interpretation of the data: Oliveira PF, Sá MPL, Almeida Junior GLG, Silva FB. Statistical analysis: Oliveira PF, Almeida Junior GLG, Silva FB. Obtaining financing: Oliveira PF. Writing of the manuscript: Oliveira PF, Sá MPL, Almeida Junior GLG, Silva FB. Critical revision of the manuscript for intellectual content: Oliveira PF, Sá MPL, Almeida Junior GLG, Silva FB, Carreira VJ. Supervision / as the major investigador: Oliveira PF, Sá MPL, Almeida Junior GLG. Providing the database: Carreira VJ.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

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### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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# Appendix

## Appendix A - Standardized data collection form

**DATA COLLECTION FORM**

FILE _____

**1. Demographic data**

Hospital: _____

Medical record (number): _____ Date of admission: _____/_____/_____

Name of patient: _____

Date of birth: _____/_____/_____ Age (years) _____

Sex: ( ) female ( ) male ( ) NI

Skin color: ( ) white ( ) pardo ( ) yellow ( ) black ( ) other _____ ( ) NI

**2. Clinical data**

**a. Risk factors (at admission)**

Family history CAD: ( ) yes ( ) no ( ) NI

Sudden death: ( ) yes ( ) no ( ) NI

Diabetes mellitus: ( ) yes ( ) no ( ) NI Glycemia: _____

Use of medication: ( ) yes ( ) no ( ) NI Time of disease _____(years) ( ) NI

SAH ( ) yes ( ) no ( ) NI Sys: _____ Day: _____

Use of medication: ( ) yes ( ) no ( ) NI Time of disease _____(years) ( ) NI

Dyslipidemia: ( ) yes ( ) no ( ) NI Total Chol _____ LDL _____ HDL _____ TG _____

Use of medication: ( ) yes ( ) no ( ) NI

Obesity: ( ) yes ( ) no ( ) NI BMI _____ weight _____ (kg) Height _____ (cm) ( ) NI

Smoking: ( ) current smoker ( ) ex-smoker ( ) never smoker ( ) NI

Current – time of smoking _____ (years)( ) NI Cigarettes per day _____ ( ) NI

Ex-smoker – time since quitting _____ (years) ( ) NI

Time of smoking _____ (years) ( ) NI Cigarettes per day _____ ( ) NI

Sedentary lifestyle: ( ) yes ( ) no ( ) NI

Marfan syndrome: ( ) yes ( ) no ( ) NI

Rheumatic fever: ( ) yes ( ) no ( ) NI

Collagenosis: ( ) yes ( ) no ( ) NI

**b. Comorbidities (past events)**

Ischemic stroke: ( ) yes ( ) no ( ) NI Recent: ( ) yes ( ) no ( ) NI

Hemorrhagic stroke: ( ) yes ( ) no ( ) NI Recent: ( ) yes ( ) no ( ) NI

Unspecified stroke: ( ) yes ( ) no ( ) NI Recent: ( ) yes ( ) no ( ) NI

Motor incapacity caused by musculoskeletal or neurological dysfunction: ( ) yes ( ) no ( ) NI

Higher creatinine before the procedure: _____ Date: _____/_____/_____

Chronic kidney failure: ( ) yes ( ) no ( ) NI

Hemodialysis or peritoneal dialysis: ( ) yes ( ) no ( ) NI

COPD: ( ) yes ( ) no ( ) NI

Peripheral vascular disease: ( ) yes ( ) no ( ) NI

Previous arrhythmia: ( ) yes ( ) no ( ) NI
Specified: ( ) yes ( ) no ( ) NI
ECG in the records: ( ) yes ( ) no ( ) Which one _____
PM: ( ) yes ( ) no ( ) temporary ( ) permanent
Previous AMI: ( ) yes ( ) no ( ) NI
How long ago _____ ( ) NI (days/weeks/years/NI)
Unstable angina: ( ) yes ( ) no ( ) NI
Heart failure: ( ) yes ( ) no ( ) NI NYHA HF: ( ) I ( ) II ( ) III ( ) IV ( ) NI
Mod/Severe valve failure: 1. Mitral: ( ) yes ( ) no ( ) NI
2. Aortic: ( ) yes ( ) no ( ) NI
3. Tricuspid : ( ) yes ( ) no ( ) NI
Mod/Severe valve stenosis: 1. Mitral: ( ) yes ( ) no ( ) NI
2. Aortic: ( ) yes ( ) no ( ) NI
3. Tricuspid : ( ) yes ( ) no ( ) NI
Extracardiac vascular disease
Claudication: ( ) yes ( ) no ( ) NI
Carotid artery occlusion or stenosis > 50%: ( ) yes ( ) no ( ) NI
Amputation for vascular disease: ( ) yes ( ) no ( ) NI
Abdominal aortic, iliac or carotid arterial intervention: ( ) yes ( ) no ( ) NI
Active endocarditis: ( ) yes ( ) no ( ) NI
Previous surgeries
Myocardial revascularization: ( ) yes ( ) no ( ) NI
Valve replacement: ( ) yes ( ) no ( ) NI
Partial aortic arch replacement: ( ) yes ( ) no ( ) NI
Structural repair/tumor resection: ( ) yes ( ) no ( ) NI
Aortic dissection (Stanford classification)
Type A: ( ) yes ( ) no ( ) NI
Type B: ( ) yes ( ) no ( ) NI
Aortic arch aneurysm: ( ) yes ( ) no ( ) NI
Ascending aortic aneurysm: ( ) yes ( ) no ( ) NI

**3. Echocardiographic data**

Echocardiography test: ( ) yes ( ) no ( ) NI Date: _____/_____/_____
Ejection fraction _____ ( ) NI LVd: _____ ( ) NI
SIV: _____ ( ) NI VDs: _____ ( ) NI
PP: _____ ( ) NI LVH: _____ ( ) NI
LA: _____ ( ) NI PASP: _____ ( ) NI
Functional subjective assessment
LV systolic function: ( ) normal ( ) mild disf. ( ) Mod disf. ( ) Severe disf. ( ) NI
LV diastolic function: ( ) normal ( ) mild disf. ( ) Mod disf. ( ) Severe disf. ( ) NI
RV: ( ) normal ( ) mild disf. ( ) Mod disf. ( ) Severe disf. ( ) NI
Pericardial effusion: ( ) yes ( ) no ( ) NI

| | | | | |
|---|---|---|---|---|
| Mod/Severe valve insufficiency | 1. Mitral: | ( ) yes | ( ) no | ( ) NI |
| | 2. Aortic: | ( ) yes | ( ) no | ( ) NI |
| | 3. Tricuspid: | ( ) yes | ( ) no | ( ) NI |
| Severe/Mod valve stenosis | 1. Mitral: | ( ) yes | ( ) no | ( ) NI |
| | 2. Aortic: | ( ) yes | ( ) no | ( ) NI |
| | 3. Tricuspid: | ( ) yes | ( ) no | ( ) NI |

**4. Surgery data**

Blood transfusion: ( ) yes ( ) no ( ) NI
Aortic valvuloplasty: ( ) yes ( ) no ( ) NI
Descending aortic endoprosthesis: ( ) yes ( ) no ( ) NI
Coronary reimplantation: ( ) yes ( ) no ( ) NI
Prosthesis
Biologic: ( ) yes ( ) no ( ) NI Number _____
Mechanical: ( ) yes ( ) no ( ) NI Number _____
Combined surgery: ( ) yes ( ) no ( ) NI
Which one? _____
ECC time _____ (minutes)
Clamping time _____ (minutes)
Hypothermia _____ (°C)
Elective surgery: ( ) yes ( ) no ( ) NI
Urgent surgery: ( ) yes ( ) no ( ) NI
Emergency surgery: ( ) yes ( ) no ( ) NI
Resuscitation (pre anesthetic CRA): ( ) yes ( ) no ( ) NI
Intraoperative complication: ( ) yes ( ) no ( ) NI
Which one? _____
Death in the operating room: ( ) yes ( ) no ( ) NI
Reoperation: ( ) yes ( ) no ( ) NI

**5. Postoperative data**

| | | | | |
|---|---|---|---|---|
| Course: | Low cardiac output syndrome (cardiogenic shock): | ( ) yes | ( ) no | ( ) NI |
| | Bleeding: | ( ) yes | ( ) no | ( ) NI |
| | Cardiac tamponade: | ( ) yes | ( ) no | ( ) NI |
| | Intra-aortic balloon: | ( ) yes | ( ) no | ( ) NI |
| | Another ventilatory assistance device: | ( ) yes | ( ) no | ( ) NI |
| Ischemia | Infarction: | ( ) yes | ( ) no | ( ) NI |
| | Angina: | ( ) yes | ( ) no | ( ) NI |
| | CRA: | ( ) yes | ( ) no | ( ) NI |
| Mechanical | Acute MI: | ( ) yes | ( ) no | ( ) NI |
| | IVC: | ( ) yes | ( ) no | ( ) NI |
| | Free-wall rupture: | ( ) yes | ( ) no | ( ) NI |
| Respiratory: | Mechanical ventilation >24 h: | ( ) yes | ( ) no | ( ) NI |

Pneumonia: ( ) yes ( ) no ( ) NI
SARS: ( ) yes ( ) no ( ) NI
Uni/bilateral pleural effusion: ( ) yes ( ) no ( ) NI
Metabolic: Post-operative acute renal failure (ARF): ( ) yes ( ) no ( ) NI
Dialysis: ( ) yes ( ) no ( ) NI
If ARF o dialysis: Highest serum Cr _____ Highest glycemia _____
Insulin: ( ) yes ( ) no ( ) NI
Hyperkalemia: ( ) yes ( ) no ( ) NI
Neurologic: stroke ( ) Embolic ischemic ( ) Thrombotic ischemic ( ) Unspecified ischemic
( )Hemorrhagic ( ) Unspecified ( ) No ( ) NI
Confirmation of stroke: CT: ( ) yes ( ) no ( ) NI
MRI: ( ) yes ( ) no ( ) NI
Without tests: ( ) yes ( ) no ( ) NI
Coma: ( ) yes ( ) no ( ) NI
Convulsive episode: ( ) yes ( ) no ( ) NI
Psychiatric disorder (delirium): ( ) yes ( ) no ( ) NI
Paraplegia: ( ) yes ( ) no ( ) NI
Cardiologic HF: ( ) yes ( ) no ( ) NI
PTE: ( ) yes ( ) no ( ) NI
Arrhythmia: ( ) yes ( ) no ( ) NI
Which one? _____
Infection Superficial: ( ) yes ( ) no ( ) NI
Soft tissues: ( ) yes ( ) no ( ) NI
Mediastinum: ( ) yes ( ) no ( ) NI
Sepsis: ( ) yes ( ) no ( ) NI
Septic shock: ( ) yes ( ) no ( ) NI
Amines: ( ) yes ( ) no ( ) NI
Other sites: _____ ( ) NI
Peripheral vascular DVT: ( ) yes ( ) no ( ) NI
Other complications: MSOF ( ) yes ( ) no ( ) NI
Bleeding ( ) Yes, without transfusion ( ) Yes, with transfusion ( ) no ( ) NI
( ) Yes, without reoperation ( ) Yes, with reoperation ( ) no ( ) NI
Drain output (first 24 hours) _____ (mL) ( ) NI

**6. In-hospital course**

Time of hospitalization _____ ( ) NI Number of days
Time of ICU _____ ( ) NI Number of days
Time of MV _____ ( ) NI Number of days
Hospital course ( ) Death ( ) Discharge ( ) Transfer ( ) NI
Date _____/_____/_____
Cause of death _____
IDC _____ ( ) NI
Place of death ( ) Ward/room Surgical ( ) Operating room ( ) ICU
( ) Semi-intensive care unit ( ) NI ( ) Survivor

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ORIGINAL ARTICLE

# SAMe-TT$_2$R$_2$ Score: A Useful Tool in Oral Anticoagulation Decision-Making for Venous Thromboembolism Patients?

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## Abstract

**Background:** The SAMe-TT$_2$R$_2$ score was introduced to identify atrial fibrillation patients with a high risk of not achieving a good time in therapeutic range (TTR) during vitamin K antagonists (VKA) therapy.

**Objective:** The aim of this study was to evaluate this score in venous thromboembolism (VTE) patients.

**Patients and methods:** A retrospective cohort study of patients receiving care at the outpatient anticoagulation clinic of a tertiary care teaching hospital. Patients were classified as having low (score 0-1) or high risk (score ≥ 2) of not achieving a good TTR. The area under the ROC curve was calculated to assess the ability of the score to predict a TTR ≥ 65%. Adverse event-free survival curves according to the SAMe-TT$_2$R$_2$ score were calculated by the Kaplan-Meier method and compared by the log-rank test. A p-value < 0.05 was considered statistically significant.

**Results:** We investigated 111 patients during a median follow-up of 2.3 (0.7-6.4) years. Mean age was 54.1 ± 15.7 years and 71 (64.0%) were women. Low- and high-risk groups had similar mean TTR (51.9 vs. 49.6%; p = 0.593). The two groups did not differ significantly in the percentage of patients achieving a TTR ≥ 65% (35.6 vs. 25.8%; p = 0.370). The c-statistic was 0.595 (p = 0.113) for TTR ≥ 65%. Adverse event-free survival during anticoagulation was also similar in both groups (p = 0.136).

**Conclusions:** The SAMe-TT$_2$R$_2$ score does not seem to be a useful tool in oral anticoagulation decision-making for patients with VTE and should not be used in this setting. (Int J Cardiovasc Sci. 2018;31(5)483-491)

**Keywords:** Venous thrombosis; Venous thromboembolism; Pulmonary embolism; Anticoagulants; Decision support techniques.

## Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are clinical manifestations of the same pathological process, collectively termed venous thromboembolism (VTE), which is the third most common cardiovascular condition after myocardial infarction and stroke, with an estimated incidence rate of 0.7-2.0 per 1,000 person-years.[1] Another important feature of the disease is the high mortality rate associated with PE. In Brazil, PE accounted for 0.05% of total hospital admissions (46,421 of 89,499,700) from 2008 to 2015, with a mortality rate of 21.4%.[2] In a Canadian study including 67,354 definite and 35,123 probable cases of VTE, the 30-day and 1-year case-fatality rates after definite or probable VTE were 10.6 and 23.0%, respectively.[1]

One-quarter to one-third of acute episodes of VTE are recurrences,[3] and VTE has been recognized as a chronic disease associated with short- and long-term morbidity and mortality.[4] Therefore, the management of VTE requires recurrence prevention, often through prolonged anticoagulant treatment, which has been traditionally performed using vitamin K antagonists (VKA), but now can be performed with the use of novel anticoagulants (NOAC). The efficacy and safety of VKA treatment are

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determined mainly by the time in therapeutic range (TTR), i.e., the percentage of days that prothrombin time/international normalized ratio (PT/INR) remains in the interval 2.0-3.0. Thus, the ability to identify patients treated with VKA who will present poor anticoagulation control may be useful in establishing the indication for NOAC rather than VKA.[5]

The SAMe-TT$_2$R$_2$ score uses clinical risk factors to identify patients with atrial fibrillation (AF) at high risk of not achieving a good TTR (≥ 65%) during VKA therapy, who are, consequently, suitable candidates for the use of NOAC. It takes into account sex (S, 1 point), age (A, 1 point), medical history (Me, 1 point), treatment - especially interacting drugs, such as amiodarone - (T, 1 point), tobacco use in the previous 2 years (T, 2 points) and race (R, 2 points). The maximum score is 8, and patients scoring 0-1 are most likely to benefit from warfarin because they are also most likely to have a TTR ≥ 70%, indicating good anticoagulation control. Patients with scores ≥ 2 are at risk of suboptimal anticoagulation control. In the original study that developed the score, the score showed good discrimination performance in both the internal (c-statistic of 0.72 for TTR ≥ 64%; 95%CI: 0.64-0.79) and external (c-statistic of 0.7 for TTR ≥ 67%; 95%CI: 0.57-0.82) validation cohorts.[6] In a previous study conducted at our anticoagulation outpatient clinic, including only patients with AF, the low-risk group (score 0-1) had a better median TTR than the high-risk group (score ≥ 2): 69.2 vs. 56.3% p = 0.002. Similarly, the percentage of patients with a TTR ≥ 65% was higher in the low-risk group (58.7 vs. 36.8%; p = 0.001).[7]

Use of the SAMe-TT$_2$R$_2$ score in patients with VTE to predict a good TTR during anticoagulant therapy was only recently assessed, with conflicting results. Two studies showed that patients classified as at high risk (score ≥ 2) had a lower TTR than those at low risk,[8,9] whereas one study found no association between the SAMe-TT$_2$R$_2$ score and TTR.[5] Moreover, the results regarding the association of the score with bleeding or thrombotic events were also contradictory. These studies differ in terms of their selection criteria, cutoff points, and study design, which may be a possible explanation for the conflicting results but precludes the widespread applicability of the SAMe-TT$_2$R$_2$ score in patients with VTE. The present study was therefore designed to evaluate the SAMe-TT$_2$R$_2$ score in patients with VTE and determine its usefulness in predicting TTR and adverse events.

## Material and methods

This was a retrospective cohort study of patients on oral anticoagulant therapy with VKA at the outpatient anticoagulation clinic of a tertiary care teaching hospital in southern Brazil. All patients receiving care at the clinic from January to March 2014 were screened for inclusion in the study (screening period). Patients anticoagulated for lower-limb DVT and/or PE were included. Patients with upper-limb, abdominal or cerebral DVT and those using VKA for other indications (e.g., AF) were excluded. The study was approved by the Research Ethics Committee of the institution. Informed consent was waived due to the retrospective nature of data collection.

The patients' medical records were retrospectively reviewed for outpatient visits, emergency visits, and hospitalizations since the first PT/INR measurement after the start of VKA treatment until the end of treatment or the end of the study. Patients who were lost to follow-up, who died or whose anticoagulant therapy was discontinued were included in the analysis, and, in these cases, TTR was calculated until the last PT/INR measurement available.

For the SAMe-TT$_2$R$_2$ score (0-8 points), the following variables were assessed: female sex (1 point), age < 60 years (1 point), presence of > 2 comorbidities (1 point), use of amiodarone to control heart rhythm (1 point), tobacco use within the past 2 years (2 points), and non-white race (2 points). The following conditions were considered comorbidities: previous stroke, diabetes, peripheral artery disease, coronary artery disease, liver disease, pulmonary disease, renal disease, hypertension and heart failure. Based on the SAMe-TT$_2$R$_2$ score, patients were divided into two groups: low risk (score 0-1) or high risk (score ≥ 2) of not achieving a good TTR during VKA therapy.

Coronary artery disease was defined as prior myocardial infarction, angina pectoris, percutaneous coronary intervention or coronary artery bypass surgery.[10] Patients with left ventricular ejection fraction (LVEF) < 40% or with recently decompensated heart failure requiring hospitalization, regardless of LVEF, were classified as having heart failure.[11] LVEF was obtained preferably from the transthoracic echocardiogram and calculated by the Simpson's method in the presence of segmental changes or by the Teichholz method in the absence of segmental changes (if more than one test was available, the lowest value was used for the analysis).

Liver disease was defined as the presence of chronic liver disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2x the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3x the upper limit of normal).[12] Peripheral artery disease was defined as the presence of any of the following: claudication, carotid occlusion or > 50% stenosis, and previous or planned intervention on the abdominal aorta, limb arteries, or carotids.[13] Pulmonary disease was defined as long-term use of bronchodilators or steroids for lung disease.[13] Renal disease was defined as kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, or glomerular filtration rate < 60 mL/min/1.73m$^2$ for ≥ 3 months.[14]

Thromboembolism during anticoagulation was defined as acute lower-limb DVT, PE, or thromboembolism at other sites, demonstrated by objective diagnostic techniques, such as compression ultrasonography, lung ventilation-perfusion scintigraphy, and computed tomography angiography. Only patients with clinical signs or symptoms of VTE underwent specific evaluation. Major bleeding was defined as fatal bleeding, and/or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or bleeding causing a drop in hemoglobin level ≥ 2 g/dL or leading to transfusion of ≥ 2 units of whole blood or red cells.[15]

All decisions regarding the management of anticoagulation were based on the protocol published by Kim et al.[16] The Rosendaal linear interpolation method was used to calculate TTR.[17]

### Statistical analysis

Data were analyzed using SPSS, version 21.0 (IBM, Armonk, NY, USA). Qualitative variables were expressed as absolute and relative frequencies, while quantitative variables were expressed as mean ± standard deviation for normally distributed data and as median (25-75$^{th}$ percentile) for non-normally distributed data. The Shapiro-Wilk test was used to assess data distribution. Quantitative variables were compared between groups using non-paired Student t test for normally distributed data, and Mann-Whitney U test for non-normally distributed data. The chi-square test was used for categorical variables. Fisher exact test was used in cases of low frequency. Pearson's (if normally distributed) or Spearman's (if non-normally distributed) correlation test was used for TTR and the SAMe-TT$_2$R$_2$ score. The area under the receiver operating characteristic (ROC) curve was calculated to assess the ability of the SAMe-TT$_2$R$_2$ score to predict a TTR ≥ 65%. Adverse event-free survival curves according to the SAMe-TT$_2$R$_2$ score were calculated by the Kaplan-Meier method and compared by the log-rank test. A p-value < 0.05 was considered statistically significant.

## Results

During the screening period, of 681 consecutive patients who received care at the outpatient anticoagulation clinic, 111 (16.3%) were included in the analysis after applying the inclusion and exclusion criteria (Figure 1). The demographic characteristics of the sample are shown in Table 1. Mean patient age was 54.1 ± 15.7 years, and 71 (64.0%) were women. Twenty-five (22.5%) patients had cancer (16 current and 9 previous). Patients with current cancer were initially treated with heparin and then switched to VKA after being in the therapeutic range. Median follow-up was 2.3 (0.7-6.4) years. During this period, 34 (30.6%) patients discontinued anticoagulation following appropriate treatment, 5 (4.5%) due to adverse events (bleeding) and 1 (0.9%) due to switch to NOAC. Nineteen (17.1%) patients were lost to follow-up.

The VKA of choice was warfarin, used in 109 (98.2%) patients. Only 2 (1.8%) patients used phenprocoumon. Anticoagulation monitoring consisted of 5,657 PT/INR measurements. Of these, 2,379 (42.1%) were within the PT/INR interval of 2.0-3.0, over a total treatment time of 438.8 patient-years. The median time between PT/INR measurements was 25.7 (14.7-35.1) days. Mean TTR was 50.6 ± 21.9%. Patients were below this range for a median time of 31.3% (16.8-47.9) and above this range for a median time of 12.9% (6.2-20.9). Duration of VKA treatment was < 6 months in 7 (8.1%) cases, 6-12 months in 21 (24.4%) cases, and > 12 months in 58 (67.5%) cases, not including patients who died during the anticoagulant treatment or were lost to follow-up. Forty-four (39.6%) patients were still on VKA treatment at the end of follow-up.

The median SAMe-TT$_2$R$_2$ score was 2 (1-2), and 66 (59.5%) patients had a score ≥ 2. The most prevalent score component was female sex (64.0%), followed by age < 60 years (61.3%), medical history of > 2 comorbidities (14.4%), non-white race (10.8%), and tobacco use within the past 2 years (8.1%). No patient was using amiodarone.

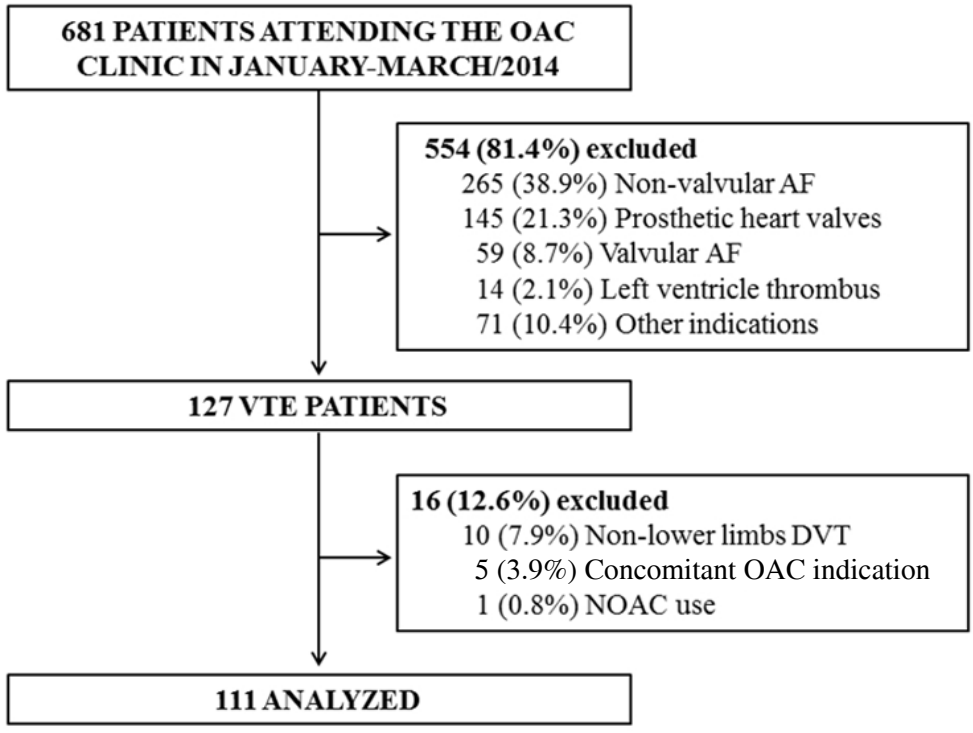


**Figure 1 - Study diagram.**
*OAC: oral anticoagulation; AF: atrial fibrillation; VTE: venous thromboembolism; DVT: deep vein thrombosis; NOAC: novel oral anticoagulants.*

Low- and high-risk SAMe-TT$_2$R$_2$ groups had similar mean TTR: 51.9 ± 20.1% vs. 49.6 ± 23.1% (p = 0.593) (Figure 2). The results for the two groups remained similar even after excluding patients on anticoagulation for up to 3 months (n = 6, 5.4%): 51.8 ± 19.7% vs. 49.1 ± 22.6% (p = 0.593). The two groups did not differ significantly in the percentage of patients achieving a TTR ≥ 65% (35.6 vs. 25.8%; p = 0.370). The correlation between TTR and SAMe-TT$_2$R$_2$ score was poor (r = - 0.093; p = 0.330). The c-statistic was 0.595 (95%CI: 0.482 - 0.708; p = 0.113) for TTR ≥ 65%.

Adverse events during anticoagulation are shown in Table 2. There were no cases of stroke, transient ischemic attack or myocardial infarction during follow-up. None of the deaths during follow-up was related to bleeding. Of six deaths, five were cancer-related and one was related to respiratory tract infection. Adverse event-free survival was similar in both low- and high-risk SAMe-TT$_2$R$_2$ groups (p = 0.136) (Figure 3).

## Discussion

In the present study, low- and high-risk SAMe-TT$_2$R$_2$ groups had similar mean TTR, and the prevalence of patients with a high TTR did not differ significantly between groups. In addition, the SAMe-TT$_2$R$_2$ score had poor accuracy in predicting both good TTR and adverse events during anticoagulation. Therefore, based on these findings, the score does not seem to be a useful tool in oral anticoagulation decision-making for patients with VTE.

The SAMe-TT$_2$R$_2$ score has been developed and validated for use in patients with AF,[6] with good results in predicting which patients will have poor anticoagulation control with VKA therapy. Several studies have confirmed the predictive ability of the score in patients with AF[7,18-29] and described its association with adverse events (death, bleeding, and stroke).[7,18-21,25,26] Its use in patients with VTE, however, has only been recently assessed in three studies, with conflicting results. In a multicenter European study including 1,308 patients,[9] high-risk patients (score ≥ 2) had a lower TTR than low-risk patients, both during the first 3 months of treatment (53 vs. 61%; p = 0.0001) and during the entire treatment period (56 vs. 61%; p = 0.017). Despite the promising results, c-statistic was only 0.52 (p = 0.35) for TTR < 65% and there was no association with bleeding or thrombotic events. Conversely, in a

**Table 1 - Demographic characteristics of the sample**

| Variable | n = 111 |
|---|---|
| Sex, female | 71 (64.0) |
| Age (years) | 54.1 ± 15.7 |
| More than 2 comorbidities | 16 (14.4) |
| Hypertension | 49 (44.1) |
| Diabetes | 20 (18.0) |
| Previous stroke | 10 (9.0) |
| Renal disease | 10 (9.0) |
| Heart failure | 9 (8.1) |
| Coronary artery disease | 7 (6.3) |
| Pulmonary disease | 6 (5.4) |
| Peripheral artery disease | 2 (1.8) |
| Liver disease | 1 (0.9) |
| Thrombophilia | 31 (27.9) |
| Any cancer (current/previous) | 25 (22.5) |
| Race, non-white | 12 (10.8) |
| Tobacco use (within the past 2 years) | 9 (8.1) |
| Previous VTE | 37 (33.3) |
| Isolated DVT | 29 (26.1) |
| Isolated PE | 5 (4.5) |
| DVT + PE | 3 (2.7) |
| VTE on treatment | |
| Isolated DVT | 78 (70.3) |
| Isolated PE | 23 (20.7) |
| DVT + PE | 10 (9.0) |
| Initial heparin use (LMWH/UFH)* | 82 (73.9) |

*VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; (*) 14 (12.6%) patients without initial treatment data. Data are presented as number (%), mean ± standard deviation, or median (25-75$^{th}$ percentile).*

Spanish study including 135 patients,[5] no differences were found in TTR between low- and high-risk patients (64.7 vs. 66.0%; p = 0.73), similar to our results. The score also had poor accuracy in the ROC curve analysis (c-statistic of 0.517 for TTR ≥ 65%). A study conducted in the United States involving 1,943 patients, excluding individuals with current/previous cancer, showed that, compared to a low SAMe-TT$_2$R$_2$ score (0-1), a high score (> 2) was associated with both lower TTR (50 vs. 57%) and a higher proportion of patients with a TTR < 60% (63.4 vs. 52.3%; p < 0.0001). The SAMe-TT$_2$R$_2$ score had a modest predictive ability for poor anticoagulation control (TTR < 60%) (c-statistic of 0.61), and its predictive performance did not change significantly at higher TTR cutoffs (0.65 for TTR < 65 and 70%). High-risk patients also had higher VTE recurrence rates and bleeding (7.9 vs. 4.5/100 patient-years; p = 0.002).[8] Taken together, these results demonstrate a modest agreement between the SAMe-TT$_2$R$_2$ score and TTR, and only studies with large samples (n > 1,000 patients) were able to detect this association. This indicates that the score has limited clinical usefulness in patients with VTE. Moreover, its ability to predict TTR in this particular population was poor (c-statistic of 0.5 to 0.6). Our results are consistent with these findings, and a larger sample would probably allow greater statistical power to show this association, although without clinical applicability.

The most likely explanation for the difference observed between studies assessing the ability of the SAMe-TT$_2$R$_2$ score to predict TTR in patients with AF and VTE is that patients with VTE are usually younger, make less frequent use of amiodarone, and have a lower prevalence of comorbidities, all of which are components of the score. In the study that developed the SAMe-TT$_2$R$_2$ score, which included only patients with AF, 14.4% of patients in the internal validation cohort were < 60 years of age.[6] However, this age group accounted for 34.1 and 54.6% of patients with VTE included in the studies conducted by Palareti et al.[9] and Kataruka et al.,[8] respectively. In the present study, the proportion of patients aged < 60 years (61.3%) was almost 4 times that of the original SAMe-TT$_2$R$_2$ study.[6] Amiodarone was used by 0-1.1% of patients in VTE studies assessing the SAMe-TT$_2$R$_2$ score,[5,8,9] while 12.7% of patients were receiving this drug in the original SAMe-TT$_2$R$_2$ study.[6] Regarding comorbidities, previous stroke and heart failure were found in 12.8 and 19.3% of patients in the original SAMe-TT$_2$R$_2$ study[6] against only 5.0-5.2% and 2.8-3.7% in VTE studies.[5,9] In addition, patients with VTE are more likely to have other comorbidities that are not included in the score, such as cancer. As pointed out by Rose et al.[30] in a case-control study, compared to matched controls, cancer patients receiving warfarin spend less time in the target PT/INR range, have more variable PT/INR values and more thrombotic events. Contributing factors may include drug interactions, fluctuations in dietary vitamin

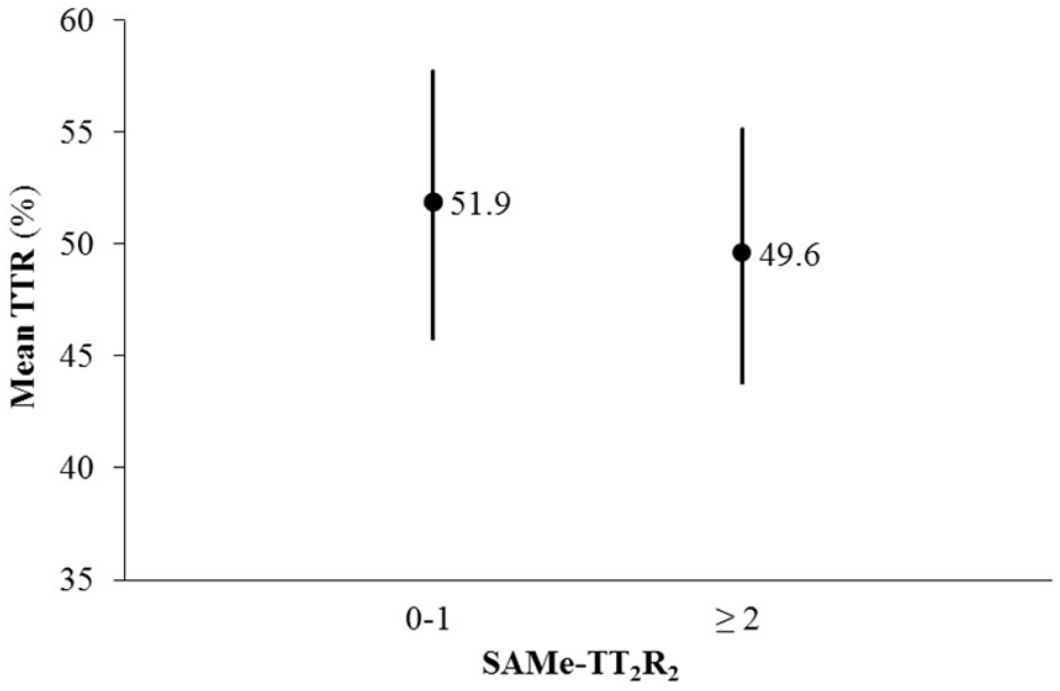


**Figure 2 - Mean time in therapeutic range (TTR) according to SAMe-TT$_2$R$_2$ score (p = 0.593 - non-paired Student t test). Bars represent 95% confidence intervals.**

**Table 2 - Adverse events during anticoagulation according to the SAMe-TT$_2$R$_2$ score**

| Type of event | n | Incidence rate (/100 patient-years) | Patients with event (n = 111) | SAMe-TT$_2$R$_2$ score | | p (0-1 vs. ≥ 2) |
|---|---|---|---|---|---|---|
| | | | | 0-1 | ≥ 2 | |
| DVT | 11 | 2.5 | 11 (9.9) | 6 (13.3) | 5 (7.6) | 0.348† |
| PE | 2 | 0.5 | 2 (1.8) | 1 (2.2) | 1 (1.5) | 1.0† |
| Major bleeding | 11 | 2.5 | 11 (9.9) | 7 (15.6) | 4 (6.1) | 0.117† |
| Death | 6 | 1.4 | 6 (5.4) | 2 (4.4) | 4 (6.1) | 1.0† |
| Any event | 30 | 6.8 | 26 (23.4)* | 14 (31.1) | 12 (18.2) | 0.177‡ |

*DVT: deep vein thrombosis; PE: pulmonary embolism; (*) 4 (3.6%) patients had 2 events during follow-up. Data are presented as number (%). †Fisher exact test; ‡Chi-square test.*

K intake, treatment interruptions, hepatic dysfunction, mucositis, diarrhea, and the hypercoagulable state induced by cancer itself.

An important methodological aspect of the assessment of the SAMe-TT$_2$R$_2$ score is the use of ROC curve analysis, which provides the best statistical method to assess the diagnostic accuracy of a test that has a continuous spectrum of test results.[31] The AUC, also known as c-statistic or c-index,[31] is an effective and combined measure of sensitivity and specificity that describes the inherent validity of diagnostic tests. The AUC can be interpreted as the probability that a randomly selected diseased individual will be rated or ranked as more likely to be diseased (in our study, with a TTR ≥ 65%) than a randomly selected non-diseased individual.[32] In previous studies assessing the SAMe-TT$_2$R$_2$ score in

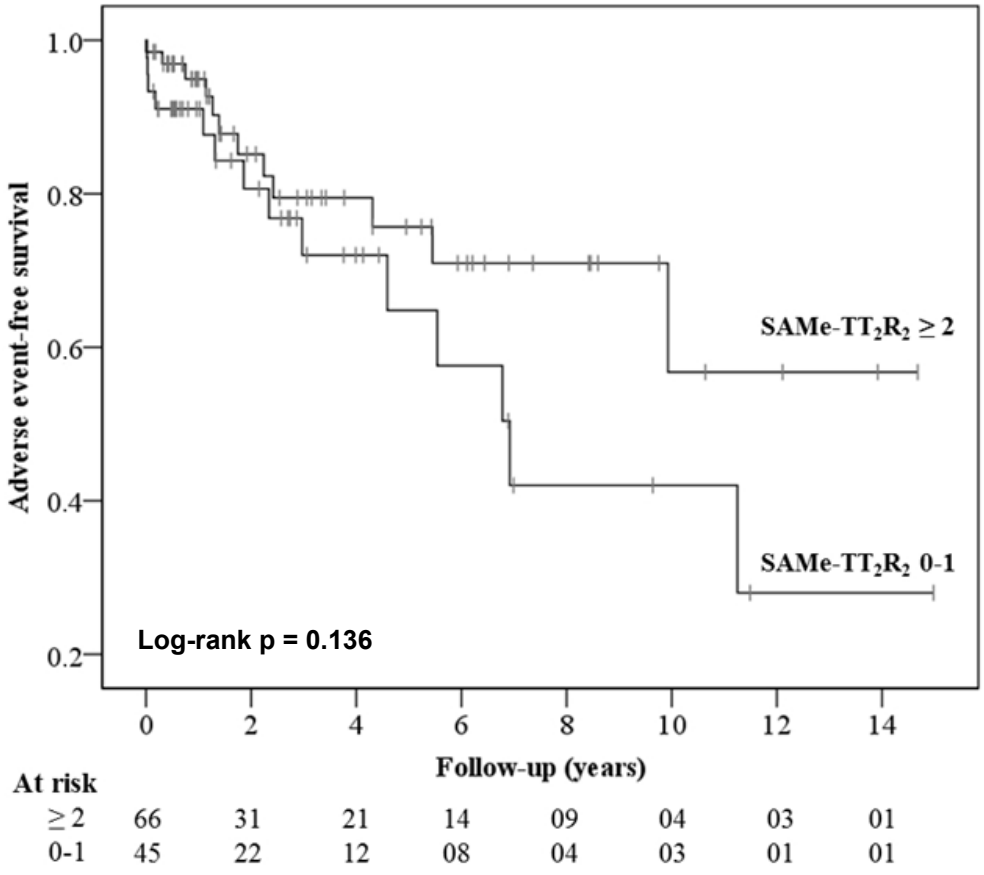


**Figure 3 - Adverse event-free survival according to TTR and SAMe-TT$_2$R$_2$ score.**

patients with VTE, the AUC indicated that the score has a unsatisfactory predictive value (< 0.7), as observed in the present analysis (AUC = 0.595). The values described by Demelo-Rodríguez et al.[5] (AUC = 0.517) and Palareti et al.[9] (AUC = 0.52) were considered poor (0.5 < AUC < 0.6), while the value described by Kataruka et al.[8] (AUC = 0.65) was considered only fair (0.6 ≤ AUC < 0.7).

This study has some limitations. The retrospective design has inherent limitations that may have influenced the quality and consistency of the data collected. Nevertheless, we believe that there was no significant loss of data required for the study, since, at our institution, patients receive systematic care by means of protocols and structured outpatient visits. Thus, most data required for the analysis were systematically collected during outpatient visits. Moreover, the comorbidities were carefully defined to reduce the possibility of misclassification. Another limitation is that the review of medical records allows the identification of only in-hospital adverse events or events reported by patients during outpatient visits, and some events may have been underestimated. Finally, although the fact that the study was performed at a single center ensured a more organized and consistent follow-up care of patients in this cohort, this might have decreased its external validity.

## Conclusion

Based on the present findings, the SAMe-TT$_2$R$_2$ score does not seem to be a useful tool for determining which patients with VTE are more likely to achieve a good TTR and to have adverse events during anticoagulation with VKA. Population differences between patients with AF and VTE may explain the differences in score performance and highlight the importance of studying scores in specific populations before their clinical application. We believe that our data, derived from a cohort of patients with VTE from a South American

reference center, add to the existing body of knowledge suggesting that the SAMe-TT$_2$R$_2$ score should not be used in patients with VTE in its present form. To predict response to VKA therapy in patients with VTE, we believe that a new score or a modification of the SAMe-TT$_2$R$_2$ score will be necessary.

## Author contributions

Conception and design of the research: Pivatto Júnior F, Salla RF, Cé LC, Biolo A, Scheffel RS. Acquisition of data: Pivatto Júnior F, Salla RF, Cé LC, Führ B. Analysis and interpretation of the data: Pivatto Júnior F, Salla RF, Cé LC, Biolo A, Silva ALFA, Scheffel RS. Statistical analysis: Pivatto Júnior F. Writing of the manuscript: Pivatto Júnior F, Salla RF, Cé LC, Blaya MB, Scheffel RS. Critical revision of the manuscript for intellectual content: Pivatto Júnior F, Salla RF, Cé LC, Biolo A, Silva ALFA, Führ B, Amon LC, Blaya MB, Scheffel RS. Supervision / as the major investigador: Pivatto Júnior F.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital de Clínicas de Porto Alegre (HCPA) under the protocol number 16-0489. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Free and informed consent was dispensed because of the retrospective nature of data collection.

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International Journal of Cardiovascular Sciences. 2018;31(5)492-498

ORIGINAL ARTICLE

# Cardiovascular Risk Estimation by the ASCVD Risk Estimator Application in a University Hospital

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## Abstract

**Background:** Cardiovascular diseases (CVDs) are responsible for many deaths in Brazil and in the world, especially in the economically active population. Risk factors for these diseases include comorbidities such as high blood pressure (HBP), diabetes mellitus (DM) and dyslipidemia. Innovation of portable technology combined with the high prevalence of CVDs motivated the development of the ASCVD Risk Estimator by the American Heart Association / American College of Cardiology.

**Objectives:** Estimate the cardiovascular risk of patients hospitalized in the internal medicine wards of Gaffrée e Guinle University Hospital (HUGG) using the ASCVD Risk Estimator, and describe the main risk factors in this population.

**Methods:** A prospective, cross-sectional study was conducted, the following data were collected from the medical records: sex, age, ethnicity, presence of HBP, DM, systolic arterial pressure, smoking habits, total cholesterol and HDL levels. Statistical analysis was performed by the chi-square test, with calculation of p-value, relative risk and confidence interval in the correlations.

**Results:** A total of 339 medical records were reviewed, and 72 (21.2%) fulfilled the inclusion and exclusion criteria. Twenty-three (32%) patients were classified as at high cardiovascular risk by the application. The main risk factors in the high risk group were age greater than or equal to 60 years (n = 21; 91.30%), dyslipidemia (n = 15; 65,2%), high blood pressure (n = 15; 65.2%), male sex (n = 13; n = 56.5%) and smoking (n = 11; 47.8%).

**Conclusion:** Approximately one third of the study population had a high cardiovascular risk; HBP and dyslipidemia were the most prevalent modifiable risk factor in the high risk group. We may say that there is no single protocol or score available able to estimate the cardiovascular risk of all individuals in the same way, and therefore, the physician must individually evaluate the patients and be updated on the best methods of disease prevention to improve current approaches. (Int J Cardiovasc Sci. 2018;31(5)492-498)

**Keywords:** Cardiovascular diseases, Technology, Risk Factors.

## Introduction

Cardiovascular diseases (CVDs) account for more than 308,000 deaths a year from acute myocardial infarction (AMI) and stroke.[1] Because of the high frequency of these conditions, Brazil is among the ten countries with the greatest number of deaths caused by CVDs.[1,2] Half of these deaths in Brazil involve adults aged 30-69 years, i.e., in the productive period of life.[3]

The most common non-communicable diseases, such as high blood pressure (HBP), type 2 diabetes mellitus (DM) and dyslipidemia have many risk factors in common and, for this reason, the World Health Organization (WHO) proposes an integrated preventive and control approach based on reduction of blood pressure (BP), smoking habits, alcohol consumption, sedentary lifestyle, unhealthy diet, obesity and hypercholesterolemia.[2,3]

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Several risk scores and algorithms have been developed to estimate the severity of CVD, such as the Framingham score. This instrument estimates the 10-year risk of AMI or death for coronary disease in individuals with no history of clinical atherosclerosis and identifies those at high and low risk.[4,5]

With the development of portable technology and new mobile phone apps, combined with the increase in information access, the ASCVD Risk Estimator was created. This instrument follows the American Heart Association and American College of Cardiology (AHA/ACC) guideline (2013) on the assessment of cardiovascular risk and the 2013 ACC/AHA Cardiovascular Risk Guideline on the treatment of dyslipidemia to reduce the cardiovascular risk in adults.[6,7]

Considering the relevance of the prevention of CVD risk factors and high rates of mortality, this study aimed to evaluate cardiovascular risk in patients hospitalized in the internal medicine wards of Gaffrée e Guinle University Hospital (HUGG) using the ASCVD Risk Estimator, classify them into high, moderate and high risk, as well as identify associated (modifiable and non-modifiable) risk factors.

## Methods

This was an observational, prospective, cross-sectional study conducted at the HUGG from March 2015 to January 2016.

Eligible patients were aged between 40 and 79 of both sexes, hospitalized in the internal medicine wards of the HUGG, with their hospital admission report attached to the medical record, and laboratory blood test results including lipid profile before admission or from 2 to 5 days of hospitalization.

Patients admitted for cardiovascular conditions such as AMI, ischemic or hemorrhagic stroke, and thromboembolism and its complications, patients with total cholesterol lower than 130 mg/dL and HDL lower than 20 mg/dL (due to the score calculation restrictions), and patients with LDL higher than 190 mg/dL and previously diagnosed atherosclerotic disease (due to the high / confirmed risk of atherosclerotic disease) were excluded.

All inclusion and exclusion criteria followed the ASCVD Risk Estimator recommendations for estimation of the 10-year risk.

Patients' medical records were examined during the 11-month period of the study. The variables necessary for risk estimation were collected – age, sex, race/ethnicity, chronic diseases (DM and HBP) being treated, systolic BP (SBP) at admission, smoking habits, total and HDL cholesterol levels, cause of admission, weight and height, regularly used medications for DM and HBP, and family history (FamH) of CVD. Data collection was started after ethical approval was obtained in *Plataforma Brasil*, the national integrated database of study projects involving human beings.

Weekly visits were made to the internal medicine wards for review of the medical records. Data were weekly recorded and updated in Excel spreadsheets, separated by ward. The number of individuals who were not included in the study was added to the total number of admissions and the reason for exclusion registered for further analysis.

For risk classification, each patient's data were entered in the fields of the ASCVD Risk Estimator (Figure 1). Patients were considered at high risk if they had an estimated 10-year risk ≥ 20%, at moderate risk if they had an estimated 10-year risk > 10% and < 20%, and at low risk if they had an estimated 10-year risk ≤ 10%, following the AHA/ACC criteria. Patients were considered hypertensive and diabetic if they were under medication for these conditions, and dyslipidemic if they showed LDL levels > 160 mg/dL and/or HDL< 40 mg/dL.

During this analysis, we also identified the main factor that may be related to high risk, including sex, age, comorbidities (HBP, DM, dyslipidemia), smoking, FamH of CVD. Patient's 10-year risk with optimal risk factors was also calculated; these factors included total cholesterol values of 170 mg/dL, HDL of 50 mg/dL and SBP of 110 mmHg in non-hypertensive patients, non-diabetic patients and non-smokers.

Results are expressed as absolute values and percentages. Statistical analysis was performed by chi-square test using the GraphPad Instat 3 software; p-value, relative risk and confidence interval were analyzed.

The study received no external funding.

## Results

A total of 339 medical records were reviewed in the period from March 2015 to January 2016; 267 (78.8%) were excluded considering the inclusion and exclusion criteria (Graph 1).

Seventy-two patients were included, 35 men and 37 women. Thirty-five patients were aged between 40 and 59 years and 37 between 60 and 79 years.

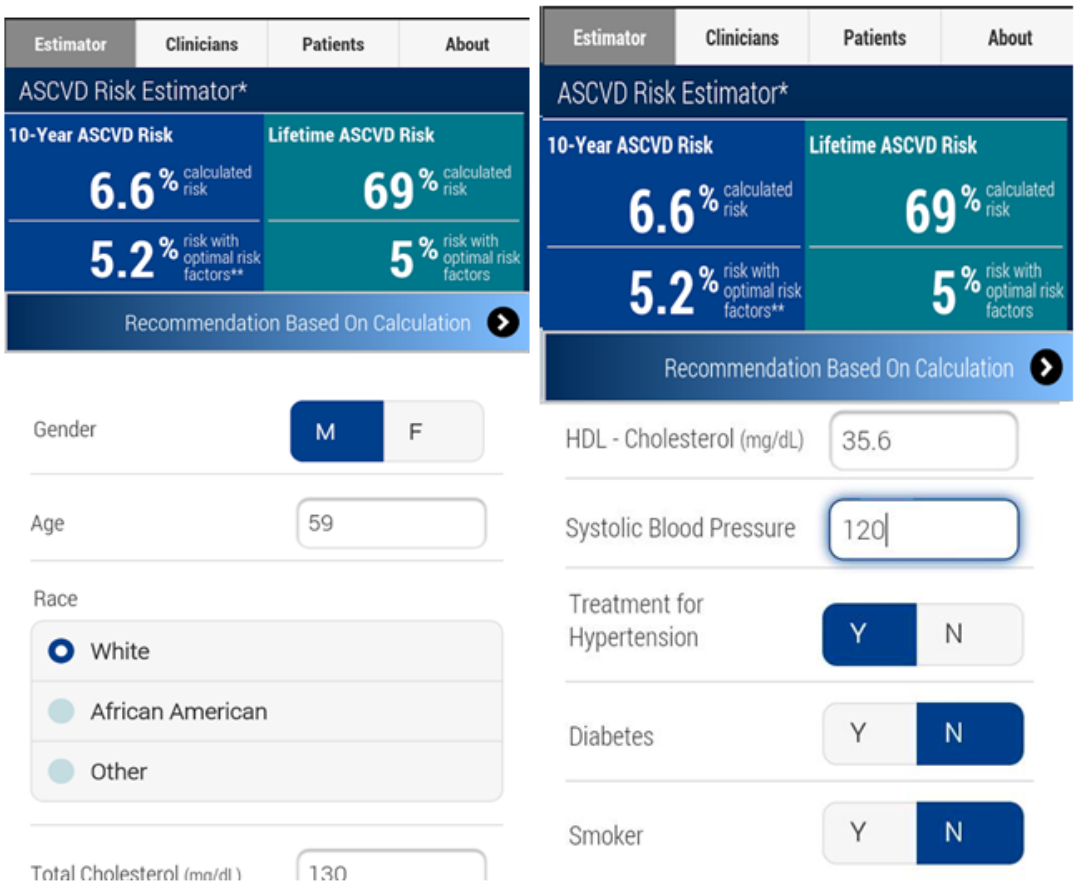



**Figure 1: App layout with an example of 10-year and lifetime cardiovascular risk estimates.**

With respected to related risk factors, there were 41 dyslipidemic, 39 hypertensive, 27 non-smoking and 21 diabetic patients. Data from the hospital admission report revealed that 26 patients had a FamH of CVD, including AMI, ischemic or hemorrhagic stroke, thromboembolism or sudden death; 19 did not have a family history of CVD; 28 did not know or this information was missing in the report (Table 1).

Estimation of the 10-year risk score using the ASCVD Risk Estimator showed that 32% of patients were at high risk (n = 23), 26% at moderate risk (n = 19) and 42% at low risk (n = 30) (Graph 2).

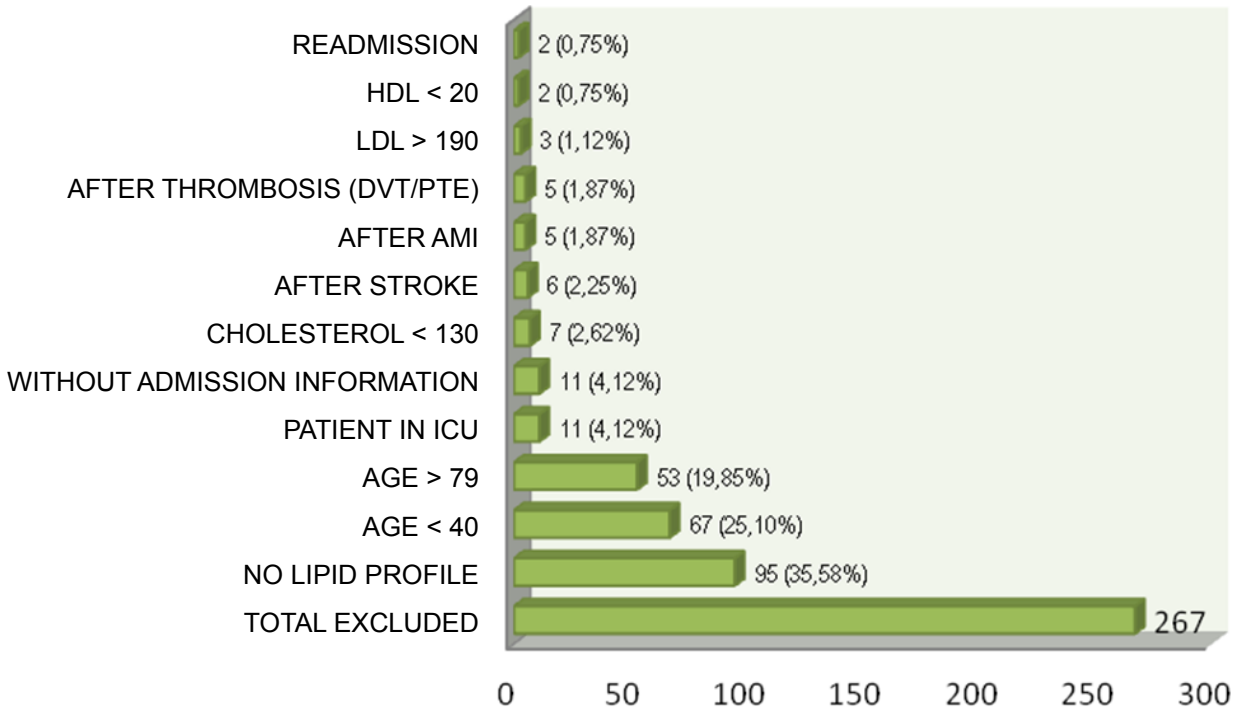
Table 2 describes percentages, relative risk (odds ratio – OR) and confidence interval obtained in the between-group comparisons (chi-square test).

Considering the optimal risk factors defined by the ASCVD Risk Estimator, 52% (n = 12) of patients at high risk and 84% (n = 16) of patients at moderate risk had a risk lower than 10% with optimal risk factors.

## Discussion

The ASCVD Risk Estimator, developed by the AHA/ACC in 2013 grounded in the Framingham study,[8,9] evaluates the variables sex, age, ethnicity, total cholesterol and HDL levels, SBP, HBP and DM and smoking habits for the estimation of the 10-year cardiovascular risk.[8] Although the risk score proposed by the 2013 AHA/ACC Guideline[7] considered several groups and large populations, only AMI (fatal and non-fatal) and stroke were considered CVDs.[7]

Approximately 90% of patients with CVDs have at least one related risk factor.[10] In addition to the risk factors described in the Framingham study, other risk factors include obesity, alcohol consumption, stress, depression, low intake of vegetables and fruits, and irregular or no physical acitivity.[10] Also, some studies have correlated inflammatory markers, e.g. C-reactive protein and homocysteine with the incidence of cardiovascular events and cardiovascular risk prediction.[11]




**Graph 1 - Distribution of patients by exclusion criteria, n(%). HDL: high-density lipoprotein; LDL: low-density lipoprotein; DVT: deep vein thrombosis; PTE: pulmonary thromboembolism; AMI: acute myocardial infarction; ICU: intensive care unit.**

**Table 1 - Characteristics of the study population**

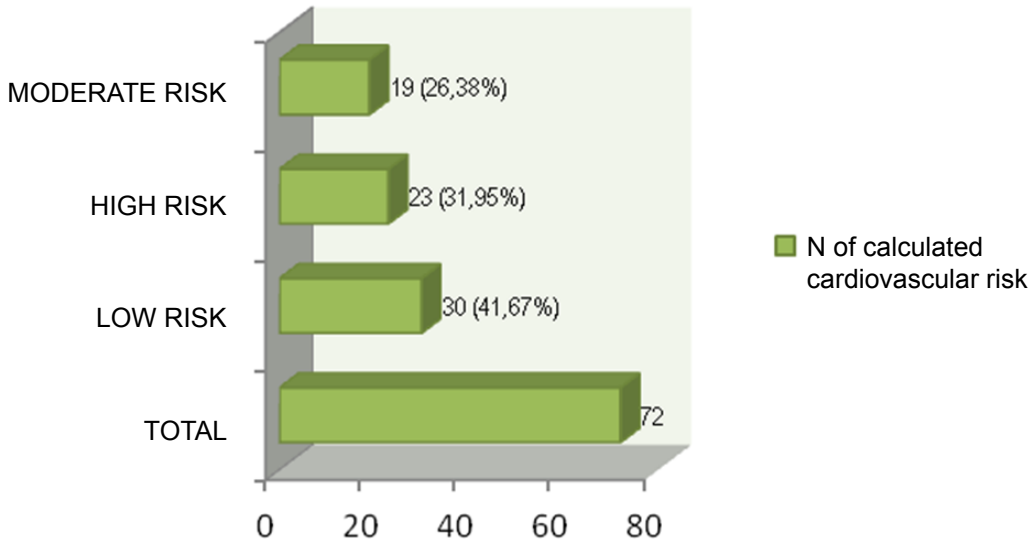
| Variables (%) | Total of patients (n = 72) | Men (n = 35) | Women (n = 37) | p value |
|---|---|---|---|---|
| Non-modifiable risk factors | | | | |
| Age ≥ 60 years | 51% | 51% | 51% | 1.00 |
| Age < 60 years | 49% | 49% | 49% | 1.00 |
| Family history + | 36% | 29% | 43% | 0.039 |
| DM | 29% | 23% | 35% | 0.061 |
| Modifiable risk factors | | | | |
| HBP | 54% | 37% | 70% | 0.00003 |
| DLP | 56% | 69% | 43% | 0.00021 |
| Smoking | 38% | 46% | 30% | 0.0197 |

*DM: diabetes mellitus; HBP: high blood pressure; DLP: dyslipidemia.*

Family history has been considered and independent risk factor, especially if observed in first degree relatives aged younger than 55 years for men and 65 years for women.[12] This factor, alone, increases cardiovascular risk by 40-60%.[13] In our study, however, we found no significant difference between the groups in the risk related to this variable.

Our findings were different from the statistics of the prevalence of risk factors in the Brazilian population described in a previous publication (VIGITEL)[14]. This may be explained by the lower number of participants and their characteristics – we included only hospitalized patients, who might be at considerable risk already.

In a study conducted in a family health center in Alagoas, the Framingham score was used to stratify 127 patients according to their cardiovascular risk; 11% of these patients were considered at high risk. Regarding the risk factors, 6.3% were smokers, 48.8% hypertensive, 19.7% diabetic and 43.1% dyslipidemic.[15] Another study carried out in a cardiology outpatient center of a university hospital in Porto Alegre showed that 36.5% of the patients had a moderate or high cardiovascular risk, and 83.8% of them were hypertensive, 30.7% diabetic and 26.4% dyslipidemic; 12% were smokers, and 86.8% of them had a FamH of CVD.[16] In addition, in a descriptive study performed at the cardiology




**Graph 2 - Distribution of patients by cardiovascular risk estimated by the 2013 AHA/ACC (American Heart Association (AHA) and American College of Cardiology) ASCVD (Atherosclerotic Cardiovascular Disease) Risk Estimator; n (%).**

**Table 2 - Comparisons between the groups with high, moderate and low cardiovascular risk**

| Variables (%) | High risk (n = 23) | Moderate risk (n = 19) | Low risk (n = 30) | CI | OR | p value |
|---|---|---|---|---|---|---|
| | | | Non-modifiable risk factors | | | |
| Male sex | 57% | 63% | 33% | 1.274 | 0.9203 – 1.762 | 0.1777 |
| Age ≥ 60 years | 91% | 63% | 17% | 7.628 | 3.999 – 14.549 | < 0.0001 |
| Age < 60 years | 9% | 37% | 83% | 0.1311 | 0.0687 – 0.2501 | < 0.0001 |
| DM | 39% | 37% | 17% | 1.423 | 1.035 – 1.957 | 0.0466 |
| Family history + | 35% | 37% | 37% | 0.9435 | 0.6736 – 1.322 | 0.7994 |
| | | | Modifiable risk factors | | | |
| HBP | 65% | 68% | 37% | 1.420 | 1.009 – 1.999 | 0.0479 |
| DLP | 65% | 47% | 53% | 1.519 | 1.079 – 2.140 | 0.0143 |
| Smoking | 48% | 37% | 30% | 1.485 | 1.083 – 2.037 | 0.0169 |

*CI: confidence interval; OR: odds ratio; DM: diabetes mellitus; HBP: high blood pressure; DLP: dyslipidemia.*

outpatient department of Goiânia Emergency Hospital, 103 medical records of hypertensive patients were reviewed, and a frequency of 11% of dyslipidemic patients, 9% of diabetic, 8% of smokers, and 20% of patients with a FamH of CVD were reported. This illustrates the important association of the risk factors for the development of CVDs.[17]

Our study population were aged 43 years or more, with a maximum age of 79 years and median of 60 years. Among patients with a high cardiovascular risk, age ranged from 57 to 79 years (median 68 years). We found significantly relevant correlations of a high cardiovascular risk with age > 60 years and < 60 years, DM, HBP, dyslipidemia and smoking. Age

between 60 and 79 years was classified as a risk index, whereas age < 60 years as a protective index for CVDs for the development of CVD. The other factors (male and FamH of CVD) showed no statistically relevant correlations or confidence interval that indicate them as risk index for CVDs.

Our sample showed similar sex and age distribution between men and women, and a high prevalence of HBP in women and dyslipidemia in men. In the high risk group, age ≥ 60 years was the most prevalent risk factor, which is in accordance with the higher incidence of cardiovascular events at this age range in the Brazilian population.

The present study had some limitations in the collection of other data that would enable a better comparison of risk factors that were not analyzed in the ASCVD Risk Estimator, but were included in other risk score estimators, such as obesity and FamH of CVD.

A critical point of the ASCVD Risk Estimator is the ethnic definition for the 10-year risk calculation. This instrument considers two possible ethnicities for a reliable calculation – white and Afro-American. In case the answer "others" is chosen, a warning pops-up on the app screen saying that the estimated risks may be underestimated in American-Indian populations, and over- or underestimated in Asian- and Hispanic- and Americans.[8] Considering miscegenation in Brazil, and the difficulty in stratifying the population in white and non-white only, estimation of cardiovascular risk by the ASCVD Risk Estimator may be over- or underestimated. Although this does not nullify the usefulness of the instrument in the Brazilian population, caution is needed in interpreting these results and in individualized assessment of patients, since the Framingham score has not been validated in Brazil.

In addition to the 10-year risk and lifetime risk, the ASCVD risk estimator app also estimates these risks in patients with optimal risk factors, that is, patients with optimal values and conditions of the variables analyzed. This additional tool is of great value for the analysis of modifiable risk factors and their impact on final risk score. The present study showed that 52.2% of patients with a 10-year risk ≥ 20% had a risk < 10% with optimal risk factors, i.e., those classified as high cardiovascular risk by the 10-year risk estimation would have a low risk if they had well-controlled comorbidities including HBP, DM, dyslipidemia, reinforcing the importance of prevention and control of modifiable risk factors.

Investments on programs of control of chronic diseases, promotion of physical activity and balanced diet, and anti-smoking campaigns highlighting the risks for developing CVDs associated with smoking could contribute to reduce the number of individuals classified as high cardiovascular risk and prevent cardiovascular events.

## Conclusions

We concluded that patients with high cardiovascular risk represented approximately one third of the study population; age greater than or equal to 60 years was the main non-modifiable risk factor, and HBP and dyslipidemia were the most prevalent modifiable risk factor in the high risk group.

Also, this study evaluated the risk in patients with optimal risk factors and found that more than half of these patients would be classified as low risk, reinforcing the importance of the control of modifiable risk factors for the prevention of CVDs.

We still don't have a single protocol or score able to estimate the cardiovascular risk of all individuals in the same way, or that encompasses all risk factors involved in the pathophysiology of CVDs. Therefore, the physician must perform and individualized evaluation of patients and be updated on the best methods of disease prevention to improve current approaches.

## Author contributions

Conception and design of the research: Azevedo TA, Nucera APCS, Moreira MLV. Acquisition of data: Azevedo TA. Analysis and interpretation of the data: Azevedo TA, Nucera APCS, Moreira MLV. Statistical analysis: Azevedo TA, Nucera APCS, Moreira MLV. Writing of the manuscript: Azevedo TA, Nucera APCS, Moreira MLV. Critical revision of the manuscript for intellectual content: Azevedo TA, Nucera APCS.

### Potential Conflict of Interest

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This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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ORIGINAL ARTICLE

# Influence of Pulmonary Rehabilitation on Clinical Characteristics in Patients with Chronic Heart Failure and Chronic Obstructive Pulmonary Disease

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## Abstract

**Background:** The improvement of treatment strategies in patients with chronic obstructive pulmonary disease (COPD) and especially with comorbid pathology should provide rational conversion of standard schemes of therapy and rehabilitation in accordance with their clinical, pathogenic, functional and economic feasibility.

**Objective:** To assess the influence of pulmonary rehabilitation on clinical characteristics in patients with chronic heart failure (CHF) and concomitant COPD.

**Methods:** The study included 102 patients with CHF and concomitant COPD (males, 62%; mean age, 68.2 ± 4.5 years). All patients were divided into two groups: control group (CG) (n = 54), received only standard therapy of CHF and COPD; and intervention group (IG) (n = 48) were additionally taught the full yogic breathing as a program of pulmonary rehabilitation. Calculation of points by clinical evaluation scale (CES), assessment of CHF functional class (FC) (NYHA) and 6-minute walk test (6MWT - with the evaluation of dyspnea by the Borg scale) were performed in all patients on admission to the department and at discharge. Significant association was defined by p value < 0.05.

**Results:** At baseline, there were no significant differences in clinical characteristics of the patients and studied parameters between the groups. At discharge both groups showed significant reduction of dyspnea by the Borg scale (in CG: from 7.2 ± 0.8 points to 5.2 ± 0.3; in IG: from 7.4 ± 0.6 points to 3.2 ± 0.4), the number of points by CES (in CG: from 10.8 ± 0.3 points to 7.2 ± 0.4; in IG: from 10.7 ± 0.6 points to 5.9 ± 0.6). Increase in exercise tolerance (by the distance of 6MWT) was observed in both groups (in CG: from 215 ± 24 m to 275 ± 22 m; in IG: from 219 ± 21 m to 308 ± 24 m). The changes were more significant in IG compared to CG. We observed the prominent decrease in CHF FC and length of hospital stay in IG.

**Conclusions:** Application of full yogic breathing as the program of pulmonary rehabilitation in addition to standard therapy of the patients with CHF and COPD is associated with a significant decrease in CHF FC, an increase in exercise tolerance and a reduced length of hospital stay. (Int J Cardiovasc Sci. 2018;31(5)499-504)

**Keywords:** Cardiac Insufficiency / physiopathology; Pulmonary Disease, Chronic Obstructive / rehabilitation; Exercise Therapy; Oxygen Consumption.

## Introduction

Scientists have extensively been discussing the necessity of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease (COPD), the main objectives of which are to reduce symptoms and improve the quality of life.[1] It was found that the rehabilitation measures have a positive impact on important aspects of the patient's life. The results of several studies show that pulmonary rehabilitation could increase physical activity, oxygen consumption and patients' endurance, reduce the frequency and duration of hospitalization, and greatly improve the efficiency of therapy.[2-4] It follows that the improvement of treatment strategies in patients with

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COPD should provide rational conversion of standard schemes of therapy and rehabilitation in accordance with their clinical, pathogenic, functional and economic feasibility. Pulmonary rehabilitation is currently viewed as a key strategy in the management of respiratory system diseases.[5] The selection process for the rehabilitation of patients take into account their functional status, severity of dyspnea, motivation level, and smoking status, although the creation of individualized programs for the integrated treatment of patients with COPD remains an unsolved problem of scientific and practical medicine. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations,6 the minimum length of an effective rehabilitation is 6-12 weeks (at least 12 sessions, 2 times per week, for at least 30 minutes). A complete rehabilitation program should include physical exercise, smoking cessation, nutritional therapy, patient education and psycho-emotional support.[7] However, until now we have no effective program to maintain a therapeutic effect for a long time especially for the patient with comorbid pathology COPD and chronic heart failure (CHF). A perspective area of pulmonary rehabilitation is a full yogic breathing exercise.[8] Therefore, the aim of the present study was to assess the effectiveness of pulmonary rehabilitation in addition to the standard medical care of patients with COPD and CHF.

## Methods

### Sample

This was a prospective, single-center, non-blinded trial conducted in the Donetsk National Medical University, based on Department of Urgent Cardiology and Rehabilitation of Institute of Emergency and Reconstructive Surgery, enrolling 102 participants between September 2013 and November 2015. Patients were included if they met the GOLD criteria for a diagnosis of COPD:[6] a post-bronchodilator ratio [forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC)] < 0.70 and a < 15% or 200-mL increase in FEV1 following inhalation of a β2 agonist; age ≥ 18 years; stable ischemic heart disease in history and decompensation of CHF with symptoms leading to hospitalization. Chronic heart failure was diagnosed with the presence of history of CHF and at least one symptom (dyspnea, orthopnea, or edema) and one sign (moist rales, peripheral edema, ascites, or pulmonary vascular congestion on chest radiography). Patients with a gastroesophageal reflux disease, diaphragmatic hernia, cancer, pregnancy, cardiac surgery within 90 days of enrollment, comorbid conditions with an expected survival of less than 6 months, acute myocardial infarction at time of hospitalization, retinal detachment, increased intracranial and intraocular pressure were excluded.

All participants read and signed the informed consent form before the participation in the study. Both informed consent form and the prospective analysis of the data for research purposes were approved by the Ethics Committee (report number 108/7).

### Full yogic breathing

Patients were assigned to either standard CHF and COPD therapy alone (control group, CG) or standard CHF and COPD therapy plus full yogic breathing (intervention group, IG). Patients of IG were additionally taught the full yogic breathing - deep slow breathing, consisting of three consecutive phases: abdominal, thoracic and clavicular. Inhale was made wavelikely, with consistent use of abdominal muscles and diaphragm, intercostal muscles rather than the muscles of the shoulder girdle. Exhale was done in the same sequence. At the beginning, participants of IG practiced full breathing in the supine or sitting position 4 times per day, 8-10 breaths at a time; then during exercise they increased the number of rounds up to 10 per day and performed it also while sitting, standing or walking when they encountered unbearable shortness of breath.

All patients kept diaries while they performed breathing exercises during the observation period. Then investigators estimated their compliance to this method of treatment according to their diaries.

### Assessment of physical fitness components: clinical evaluation scale, 6-minute walk test, pre- and post-bronchodilator spirometry data, $SpO_2$

Calculations of points by clinical evaluation scale (CES), assessment of CHF FC and 6-minute walk test (6MWT - with the evaluation of dyspnea by the Borg scale) were performed in all patients on the admission to the department and at discharge. Pre- and post-bronchodilator spirometry assessments were performed with a portable spirometer (BTL-08 Spiro Pro; BTL, United Kingdom), in accordance with the American Thoracic Society criteria.[9] Values of FEV1 were expressed in liters, as percentages of the FVC, and as percentages of the reference values. The peripheral capillary oxygen saturation ($SpO_2$) was assessed

with an oximeter (M70; Biolight, China) while the patients were breathing room air.

### Statistical analysis

Processing of the results was performed on a personal computer using statistical analysis package "Statistica 6.0". The D'Agostinho & Pearson, Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test the normality of data distribution. The paired and unpaired Student t test was used for comparisons of continuous, normally distributed variables between groups. The Mann-Whitney test was used for analysis of continuous variables without normal distribution, and the chi-square statistics for categorical variables (clinical features). Results are shown as mean and standard error for continuous, normally distributed variables, and as median and interquartile range ($25^{th}$-$75^{th}$ percentile) or percentage (as appropriate) for the others. Significant association was defined by p value < 0.05.

## Results

The pre-specified duration of the enrollment period was two years and during that time we interviewed 168 patients. Forty-two did not meet inclusion criteria, 24 declined to participate. A total of 102 patients were enrolled, 54 to CG and 48 to IG.

At baseline, there were no significant ($p > 0.05$) differences between the groups in the patients' clinical characteristics (Table 1). At admission patients received in both groups standard therapy in comparable doses.

By the end of the observation period, a significant reduction in office heart rate (HR), respiratory rate (RR) at rest, severity of dyspnea by the Borg scale, the number of points by CES, and increased 6MWT distance were observed in both groups. Moreover, all these changes were more considerable in the IG as compared with the CG (Table 2).

Oxygen saturation increased in both groups (in CG: from 93 (84; 95)% to 94 (83; 97)%, $p = 0.01$; in IG: from 93 (84; 95)% to 98 (95; 98)%, $p < 0.001$), more pronounced in IG ($p = 0.03$).

A reduction of CHF FC (NYHA) was observed in 82% of the IG patients and only in 61% of the CG patients ($\chi^2 = 4.55$, $p = 0.03$).

Average duration of hospitalization was shorter in the IG (16.7 ± 3.1 days versus 19.9 ± 3.8 days in CG, $p < 0.05$).

**Table 1 - Clinical characteristics of the groups of patients**

| Parameter | CG (n = 54) | IG (n = 48) | p values |
|---|---|---|---|
| Age, years | 67.2 ± 6.1 | 69.3 ± 5.6 | p = 0.67 |
| Gender (male: female) | 32 : 22 | 26 : 22 | $\chi^2 = 0.1$, p = 0.75 |
| BMI (kg/m²) | 26.6 ± 0.9 | 24.8 ± 0.5 | p = 0.07 |
| Smoker (actual) | n = 31 (57%) | n = 31 (64%) | $\chi^2 = 0.04$, p = 0.83 |
| Duration of smoking, years | 32.5 ± 5.8 | 27.7 ± 3.5 | p = 0.5 |
| FC II (NYHA) | n = 9 (17%) | n = 10 (22%) | $\chi^2 = 0.04$, p = 0.84 |
| FC III (NYHA) | n = 35 (65%) | n = 30 (62%) | $\chi^2 = 0.01$, p = 0.96 |
| FC IV (NYHA) | n = 10 (18%) | n = 8 (16%) | $\chi^2 = 0.01$, p = 0.96 |
| FEV1/FVC | 0.62 [0.55 - 0.66] | 0.60 [0.57 - 0.62] | p = 0.34 |
| Diabetes mellitus, type 2 | n = 12 (22%) | n = 9 (19%) | $\chi^2 = 0.01$, p = 0.91 |
| Arterial hypertension | n = 45 (83%) | n = 35 (73%) | $\chi^2 = 1.07$, p = 0.3 |
| Hypercholesterolemia | n = 28 (52%) | n = 27 (56%) | $\chi^2 = 0.06$, p = 0.8 |
| History of myocardial infarction | n = 35 (65%) | n = 35 (73%) | $\chi^2 = 0.05$, p = 0.82 |

*CG: control group; IG: intervention group; BMI: body mass index; FC: functional class; NYHA: New York Heart Association; FEV1: forced expiratory volume for 1 second; FVC: forced vital capacity.*

**Table 2 - Dynamics of clinical parameters in both groups**

| Parameter | Patients | | | |
|---|---|---|---|---|
| | CG (n = 54) | | IG (n = 48) | |
| | At baseline | At discharge | At baseline | At discharge |
| RR at rest, per min | 24.3 ± 2.2 | 20.2 ± 1.6* | 24.2 ± 2.1 | 18.1 ± 1.7* |
| Office HR, beats/min | 71.8 ± 3.9 | 66.7 ± 2.5* | 72.1 ± 3.8 | 62.4 ± 2.4* |
| 6MWT, m | 215.2 ± 24.8 | 275.7 ± 22.1* | 219.1 ± 25.1 | 308.3 ± 24.1* |
| Number of points by CES | 10.8 ± 0.3 | 7.2 ± 0.4* | 10.7 ± 0.6 | 5.9 ± 0.6* |
| Severity of dyspnea by the Borg scale, points | 7.2 ± 0.8 | 5.2 ± 0.3* | 7.4 ± 0.6 | 3.2 ± 0.4* |
| $SpO_2$, % | 93 (84; 95) | 94 (83; 97)* | 93 (84; 95) | 98 (95; 98)* |

*CG: control group; IG: intervention group; BMI: body mass index; FC: functional class; NYHA: New York Heart Association; FEV1: forced expiratory volume for 1 second; FVC: forced vital capacity.*

Thus, our findings showed that the application of pulmonary rehabilitation in addition to standard therapy in patients with CHF and COPD is associated with a significant increase of exercise tolerance and decrease in length of hospital stay.

## Discussion

One important extrapulmonary manifestation of COPD is skeletal and respiratory muscle dysfunction.[10] With the increasing severity of the disease, COPD patients lose exercise endurance and often complain of fatigue and dyspnea. These symptoms curtail patients' ability to exercise and compromise cardiac fitness, which further limits their exercise tolerance, creating a vicious downward spiral that can eventually lead to generalized debility and immobility.[11] Encouragingly, early interventions with exercise programs may restore some of the lost health status related to muscle dysfunction and increase patients' exercise tolerance and stamina.[12-14] On this basis, a perspective direction of physical rehabilitation among patients with COPD and CHF is training of respiratory muscles. By increasing the strength and endurance of the respiratory muscles, as well as improving the efficiency of gas exchange, application of the full yogic breathing leads to an improvement of spirometry indices and arterial oxygen saturation. In our research we obtained data of increased arterial oxygen saturation after practicing the full yogic breathing.

The positive impact of the yogic breathing exercises in the rehabilitation among patients with CHF and COPD has been described by many researchers. Thus, Soni et al.[15] have noted a positive effect of yoga training on diffusion capacity in COPD patients. The results of another study[16] have shown that 1 month of yoga practice, including breathing exercises, led to a significant reduction of dyspnea according to the visual analogue scales. A prospective, randomized, controlled study[17] involving 24 patients with COPD, who performed pranayama in addition to standard therapy, has also shown the improvement of lung function parameters and quality of life. Similar results have been described by Bernardi et al.,[18] who have noted an increase in exercise tolerance and a decrease in dyspnea severity after one month of performing the full yogic breathing by patients with CHF. In addition, Gomes-Neto et al.[19] have shown that yoga practice, including breathing exercises, led to an increase in exercise tolerance in patients with CHF.

Mechanisms of influence of the full yogic breathing on the status of patients with CHF and COPD are not entirely clear. It is known that CHF is characterized by impaired autonomic regulation - decreased parasympathetic tone and, consequently, increased sympathetic activity.[20] There is evidence of autonomic balance optimization and increasing sensitivity of arterial baroreflex on the background of yoga.[21] By acting on lung tissue baroreceptors, as well as stretch receptors located in the smooth muscle layer of the large airways, slow deep yogic

breathing activates the parasympathetic nervous system. The influence of yogic breathing on the respiratory and vasomotor centers of the medulla oblongata cannot be ruled out. This phenomenon may be based on some general respiratory and cardiac neuronal network.

In addition to active participation in the development of the respiratory muscles and autonomic balance optimization, deep yogic breathing reduces body weight, the effects on lipid peroxidation, normalizes blood pressure and HR, which is very important in the context of frequent comorbidity of respiratory and cardiovascular disease.

The study by Guleria et al. "Yoga is as effective as standard pulmonary rehabilitation in improving dyspnea, inflammatory markers, and quality of life in patients with COPD" has evoked a wide response, comparing the efficacy of yoga with standard pulmonary rehabilitation in patients with COPD.[22] Scientists have found an equivalent reduction in C-reactive protein and interleukin-6 levels after performing pranayama as well as at the end of a standard pulmonary rehabilitation. These results allowed concluding that yoga is a cost-effective form of rehabilitation that is just as effective as standard rehabilitation.

## Conclusions

Application of full yogic breathing in addition to standard therapy of patients with CHF and COPD is associated with a significant decrease in CHF FC and dyspnea severity, and an increase in exercise tolerance and arterial oxygen saturation.

## Author contributions

Conception and design of the research: Smyrnova GS. Acquisition of data: Taradin GG. Analysis and interpretation of the data: Taradin GG. Statistical analysis: Vatutin MT. Writing of the manuscript: Smyrnova GS. Critical revision of the manuscript for intellectual content: Vatutin MT. Supervision / as the major investigador: Babkina TM.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the DNMU under the protocol number 108/7. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

# Protective Effects of Accumulated Aerobic Exercise in Infarcted Old Rats

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## Abstract

**Background:** Aerobic exercise exerts cardioprotective effects on myocardial infarction. However, there is lack of information about the possible protective effects of continuous or accumulated aerobic exercise performed prior to myocardial infarction in aging.

**Objective:** To evaluate the preventive effects of continuous or accumulated aerobic exercise on physical capacity, pulmonary congestion and ventricular weight in rats submitted to myocardial infarction.

**Methods:** Old male Wistar rats were divided into four groups: sham control, sedentary infarcted, continuous aerobic exercise submitted to myocardial infarction, and accumulated aerobic exercise submitted to myocardial infarction. Body weight and maximum speed were evaluated at the beginning and at the end of the protocol. Trained groups performed continuous (1 h a day) or accumulated (30 minutes in the morning and 30 minutes in the afternoon) exercise. All groups, except the sham control, were submitted to myocardial infarction surgery at the end of the protocol. Heart, skeletal muscles, as well as wet and dry lung were weighed. The significance level in statistical analysis was established at $p < 0.05$.

**Results:** Both continuous and accumulated exercise caused an increase in physical capacity in rats, as well as prevented its further impairment after myocardial infarction, and in the accumulated exercise group this prevention was greater. The continuous exercise group demonstrated an increase in lung water content, while the accumulated exercise group presented a reduction in body weight and an increase in left ventricle relative weight.

**Conclusion:** In conclusion, the data of the present study indicate that accumulated aerobic exercise present a better protective effect than continuous aerobic training in the context of myocardial infarction and aging. (Int J Cardiovasc Sci. 2018;31(5)505-512)

**Keywords:** Myocardial Infarction/prevention & control; Exercise; Physical Endurance; Aging; Rats.

## Introduction

Myocardial infarction (MI) is one of the leading causes of death worldwide. Its pathophysiology consists of myocardial cell death due to prolonged ischemia resulting from the occlusion of coronary artery ramification. After MI, a process of ventricular remodeling is initiated, in which cardiac changes - such as ventricular dilatation - accompanied by increased sympathetic activity occur as compensatory mechanisms that, at the beginning, regulate survival but, over time, worsen the prognosis of the infarcted patient.[1,2] In aging, due to changes such as stiffening of the arteries, which in turn results in increased afterload on the left ventricle, systolic blood pressure and changes in the left ventricular wall, the elderly are more susceptible to develop cardiovascular diseases, such as MI.[3,4]

In this sense, physical training has been used as an important strategy in the management of cardiovascular diseases, due to its several benefits, such as reduction of adiposity and increased heart rate variability, thus contributing to prevent cardiac events.[5] However, if a

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cardiac event does occur, the vascular, neurohumoral and cardiopulmonary adaptations from exercise are effective in attenuating cardiometabolic complications and minimizing the deleterious effects of ischemia.[6] Experimentally, it has been shown that moderate intensity aerobic training prior to MI attenuates cardiac dysfunction and deterioration promoted by ischemia and preserves the contractile properties of cardiomyocytes,[7] as well as attenuates the loss of physical capacity and autonomic cardiac dysfunction.[8]

One of the recommended ways to perform physical activity is accumulated aerobic training, which consists of performing the exercise in bouts over the course of a day,[9,10] and represents an interesting approach for individuals who have little time in their daily lives, as well as for the elderly.[11] This type of training can increase adherence to physical activity and, consequently, the number of people who follow the recommendations for physical exercise.[12]

However, there is lack of knowledge concerning the possible protective effects of continuous or accumulated exercise performed prior to MI in aged rats. Thus, the aim of the present study was to evaluate the preventive effects of continuous and accumulated aerobic exercise on physical capacity, pulmonary congestion and ventricular weight in rats submitted to MI.

## Material and methods

Experiments were performed in old male Wistar rats (24 months; ~475g), from the Animal House of the São Judas Tadeu University, São Paulo, Brazil. Rats were fed standard laboratory chow and water ad libitum. Rats were housed in collective polycarbonate cages, in a temperature-controlled room (22°C) under a 12h dark–light cycle (lights on 07:00 - 19:00 hours). The experimental protocol was approved by the Institutional Animal Care and Use Committee of the São Judas Tadeu University and the study was conducted in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publication number 96-23, revised 1996).

The experimental design can be observed in Figure 1. At the beginning of the protocol, rats were assigned by simple random distribution to four groups, in which the sample size was defined by convenience: sham control (C, n = 6); sedentary infarcted (S, n = 5); continuous aerobic exercise submitted to MI (CE, n = 6), and accumulated aerobic exercise submitted to MI (AE, n = 7). All experiments are described below in detail; however, in summary, groups were adapted to the treadmill and submitted to a maximal treadmill exercise test (MTET) to determine aerobic capacity and exercise training intensity. Trained animals - CE and AE - were submitted to aerobic exercise protocols for 1 month,[13] whereas sedentary groups - C and S - were placed on the stationary treadmill at least three times a week to provide a similar environment. Twenty-four hours after the last session of exercise, or in a relative period for the sedentary groups, animals were underwent to MI (i.e., S, CE, and AE) or sham (i.e., C) surgeries. 1 day after MI, the animals were again submitted to the MTET. Four days after MI,[8] the animals were killed by decapitation in order to remove the organs.

### Maximal exercise test and aerobic exercise training

Approximately one month before MI or sham surgeries, sedentary and trained rats were adapted to the treadmill (10 minutes per day; 0.3 km/h) for four days. All animals were submitted to a MTET to determine aerobic capacity and exercise training intensity at the beginning of the protocol, after aerobic ET protocol and post myocardial infarction. These evaluations were conducted by a blinded observer. MTET was based on a ramp protocol, which consisted of treadmill exercise with 0.3 km/h increments every 3 minutes, and finished when the animals were not able to run. Our group previously demonstrated that MTET could detect differences in aerobic performance; since that, the maximal running speed achieved in the test has presented a good correlation with the maximum oxygen consumption.[14]

After the adaptation period, the sedentary groups (i.e., C and S) underwent exercise only during the maximum running test. However, the animals were placed on the stationary treadmill at least three times a week to provide a similar environment. Aerobic training was performed on a motor treadmill (Inbramed TK-01, Brazil) at low intensity (30% of maximum running speed on MTET). Nevertheless, CE group performed the training on a continuous form for 1 h a day, while the AE group performed cumulatively (30 minutes during the morning – 8:00-9:00 a.m. and 30 minutes during the afternoon – 16:00-17:00 p.m.). Both trainings were conducted 5 days a week for 4 weeks.

### Myocardial infarction

Twenty-four hours after the last session of exercise, or in a relative period for the sedentary groups,

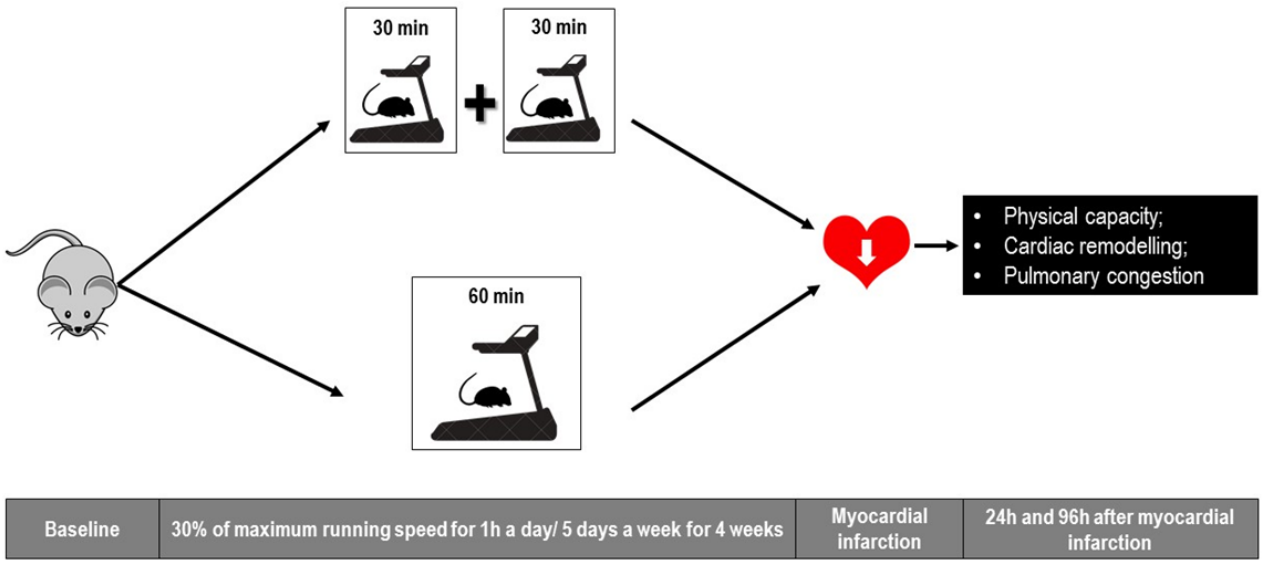


**Figure 1 - Experimental design of the current study.**

anaesthetized rats (80 mg/kg ketamine and 12 mg/kg xylazine, i.p.) underwent surgical occlusion of the left coronary artery, which resulted in MI as described previously.[8] Briefly, after intubation, animals were positive-pressure ventilated with room air at 2.5 mL, 65 strokes/min with a pressure-cycled rodent ventilator (Harvard Apparatus, Model 683, Holliston, MA, USA). For induction of MI, a 2-cm left lateral thoracotomy was performed in the third intercostal space, and the left anterior descending coronary artery was occluded with a nylon (6.0) suture at approximately 1 mm from its origin below the tip of the left atrium. The C animals underwent the same procedures except that myocardial ischemia was not induced (Sham surgery). The chest was closed with a silk suture.

## Lung water content

The lungs were removed and weighed (wet weight) and then placed in an oven for 24 hours at 80ºC. Posteriorly, the lungs were weighed again (dry weight). The water content (%$H_2O$) of each lung was defined by the equation: % $H_2O$ = (wet weight - dry weight) / wet weight x 100.[15]

## Organ and muscles relative weight

The left ventricle (LV), right ventricle (RV), soleus and gastrocnemius were removed and weighed. The calculation of the organs relative weight of each rat was performed dividing the weight of each organ (in grams) by the body weight of each animal, and multiplying the result by 100. The result was then expressed in grams/100 grams of live weight (g/100 g l.w.).[16]

## Statistical analyses

Statistical analyses were performed with GraphPad Prism software (Version 7.0 for Windows; GraphPad Software, Inc., San Diego, CA). Data are reported as mean ± SEM. After confirming that all continuous variables were normally distributed using the Kolmogorov-Smirnov test, statistical differences between the groups were obtained by two-way ANOVA followed by the Bonferroni posttest. Statistical differences between the data measured over time were assessed using repeated-measures ANOVA. All tests were two-sided and the significance level was established at $p < 0.05$.

# Results

At the beginning of the protocol, MTET indicated that physical capacity was similar in all groups (C = 0.9 ± 0.0 km/h; S = 0.8 ± 0.11 km/h; CE = 0.9 ± 0.09 km/h; AE = 0.9 ± 0.04 km/h). However, after the experimental protocol, CE and AE groups demonstrated higher MTET in comparison with the initial assessment (CE: +55%; AE: +33%), C group (CE: +100%; AE: +71%) and S group

(CE: +100%; AE: +71%). No further differences were observed among exercised groups. At post MI moment, CE group, but not AE, showed reduced physical capacity in comparison with the final assessment (after the last session of ET) (-35%). Nevertheless, MTET values of both trained groups were still higher (100%) in relation with the S group (100%) (Figure 2).

Regarding the morphological parameters, body weight was similar among all groups in the beginning of the protocol (~475g). However, after MI, AE group demonstrated significant reduction on body weight in relation to the initial assessment (Figure 3).

On the other hand, organ analysis demonstrated increased LV relative weight in AE. There were no further significant differences between the groups in relation to RV, soleus and gastrocnemius relative weight (Table 1).

Figure 4 shows the results of lung water content, an index of pulmonary congestion, in all groups. Data demonstrated a slight, but significant, increase in pulmonary congestion in CE in relation to all the other groups.

## Discussion

The main findings of the present study are that aerobic training, regardless of the arrangement of the program - continuously or fractioned -, causes significant increase on physical capacity of elderly rats, as well as acts protecting against further impairments caused by MI injuries. However, an interesting phenomenon was observed after MI, since CE showed decreased exercise capacity in comparison with the time before MI, as well an elevated index of pulmonary congestion. On the other hand, both parameters were still stable in the AE group, which might indicate a superior protective effect of this kind of intervention in relation to the continuous ET program.

Regarding the physical capacity before MI, the data of the present study are in line with most evidence in the literature from animal[17,18] and human studies,[12,19,20] since both trained groups showed increased aerobic capacity after ET (CE: +55%; AE: +33%). However, data have demonstrated inconsistent results regarding the magnitude of the increase after the protocols, so that is possible to observe evidence indicating more favorable results towards continuous protocols,[17,19] whereas others showed highest levels of physical capacity after accumulated aerobic training.[20] In the current study, accumulated and continuous aerobic training propitiated similar improvement on physical capacity. The inconsistencies among these findings could be a

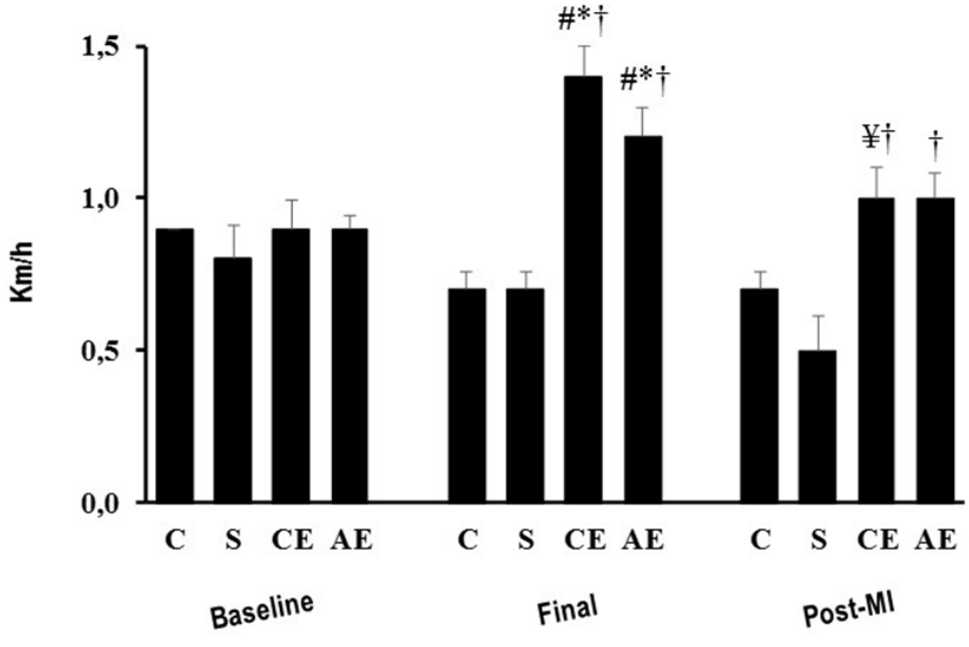


**Figure 2 - Maximal treadmill exercise test in control (C), infarcted sedentary (S), continuous exercise (CE) and accumulated exercise (AE) groups. Values expressed as mean ± SEM. #p < 0.05 vs. Baseline; ¥p < 0.05 vs. Final; *p < 0.05 vs. C; †p < 0.05 vs. S.**

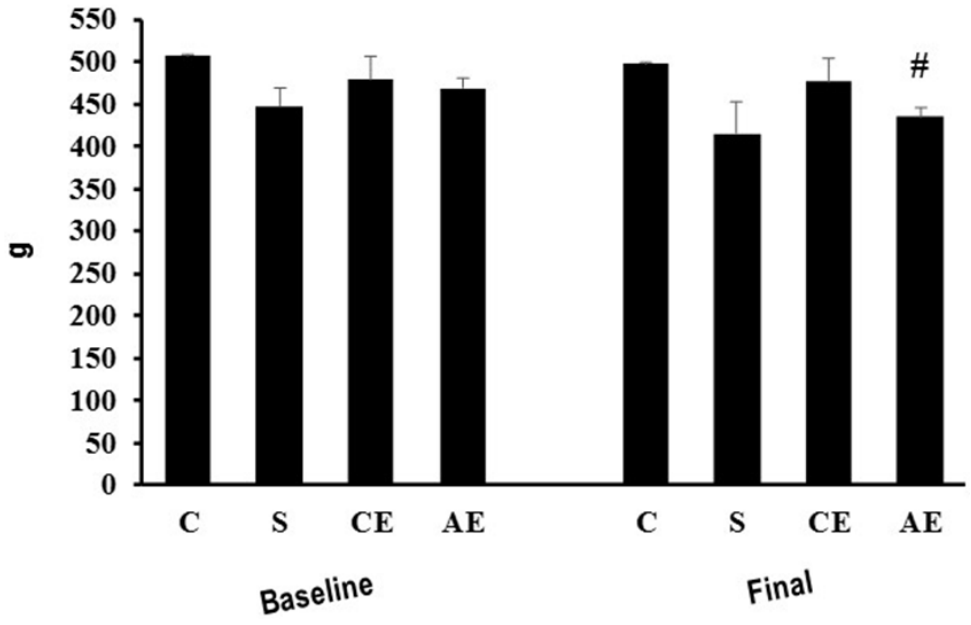


**Figure 3 - Body weight in control (C), infarcted sedentary (S), continuous exercise (CE) and accumulated exercise (AE) groups. Values expressed as mean ± SEM. #p < 0.05 vs. Baseline.**

**Table 1 - Organ and muscles relative weight in control (C), infarcted sedentary (S), continuous exercise (CE) and accumulated exercise (AE) groups**

| | C | S | CE | AE |
|---|---|---|---|---|
| LV (g/100 g l.w.) | 0.206 ± 0.002 | 0.253 ± 0.009 | 0.257 ± 0.010 | 0.276 ± 0.017* |
| RV (g/100 g l.w.) | 0.064 ± 0.012 | 0.056 ± 0.001 | 0.056 ± 0.001 | 0.061 ± 0.006 |
| Soleus (g/100 g l.w.) | 0.028 ± 0.003 | 0.035 ± 0.003 | 0.032 ± 0.002 | 0.035 ± 0.001 |
| Gastrocnemius (g/100 g l.w.) | 0.338 ± 0.03 | 0.362 ± 0.059 | 0.371 ± 0.029 | 0.388 ± 0.039 |

*Values expressed as mean ± SEM. LV: left ventricle; RV: right ventricle. *p < 0.05 vs. C.*

function of the differences in the design of exercise program and sample types. Indeed, when Martinez et al.[17] underwent Wistar rats to a moderate-intensity aerobic exercise protocol similar with the ET that was used in the current study, the researchers observed a similar magnitude of improvements among the groups.

Interestingly, after MI, both groups demonstrated a two-fold increase on physical capacity in relation to the S group. However, this evaluation was significantly decreased in CE when it was compared with the time before MI, whereas no significant alterations were observed in CE. Furthermore, CE demonstrated a higher index of pulmonary congestion - lung water content - in comparison with all other experimental groups. These data suggest that elderly rats trained through continuous aerobic training might present decreased capacity to cope with MI injury in relation to elderly rats trained through aerobic fractioned exercise.

Decreased physical capacity in S is widely described in the literature. Indeed, after MI, cardiorespiratory fitness is commonly decreased due to a central mechanism - characterized by decreased cardiac output, which is the product of cardiomyocyte death and, consequently, impaired cardiac function and unwanted cardiac remodeling - and a peripheral mechanism - caused by marked alterations on skeletal muscle architecture (i.e.,

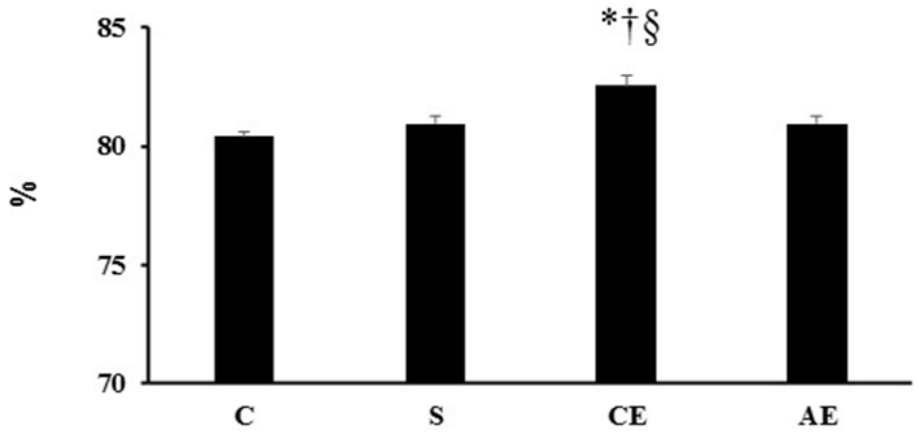


**Figure 4 - Lung water content in control (C), infarcted sedentary (S), continuous exercise (CE) and accumulated exercise (AE) groups. Values expressed as mean ± SEM. *p < 0.05 vs. C; †p < 0.05 vs. S; §p < 0.05 vs. AE.**

atrophy) and function (e.g., impaired metabolism), which may collaborate with the development of the myopathy observed during heart failure.[18,21,22,23] Regarding the preserved capacity demonstrated by both trained groups, our data are in line with evidence that have demonstrated that adult rats underwent to exercise training programs previous to MI showed increased cardiorespiratory fitness in comparison with sedentary groups.[8]

However, as aforementioned, the CE group demonstrated a phenomenon that was not described before in the literature, indicating that older rats submitted to surgical induction of MI might show decreased aerobic capacity associated with pulmonary congestion. These controversial results are probably a product of the animal used in the current study. In fact, most studies have studied adult animals and, for the first time, the protective effect of exercise training was investigated in older animals.

The plausibility behind this theory is based on the decreased capacity of the old organic system to cope with stressful agents (e.g., physical, chemical), as postulated by Fransceschi et al.[24] in the inflammaging metatheory. This possibility has been confirmed by several experiments, including the recent data from El Assar et al.[25] that indicated that frail older adults present a low expression of genes involved in the cellular response to stress (i.e., oxidative stress and cellular hypoxia). [25] In congruence, a phenomenon denominated as myocardial injury - which is characterized by a transient myocardial injury in the right ventricle (RV) - might be observed in response to aerobic exercise due to the greater hemodynamic load and wall stress.[26-28] In fact, animal and human studies have demonstrated impaired RV function, decreased cardiac handling, and increased cardiac biomarkers (i.e., creatine kinase and N-terminal pro-brain natriuretic peptide), during and immediately after the end of the aerobic exercise.[26-28]

Therefore, it is possible to infer that very-old adult rats present an impaired capacity to cope with the stressful environment developed in response to continuous aerobic exercise, leading to significant pulmonary congestion; thus, fractioned aerobic exercise seems to be a more beneficial recommendation for older adults, especially those with increased risk to develop cardiovascular diseases and frailty, since after an ischemic event they can present a better prognosis.

Although some limitations of the present study should be considered (e.g., the absence of echocardiographic evaluations to evaluate left ventricle dimensions and function) our observations suggest that the improvements observed after accumulated aerobic training may have occurred due to beneficial cardiac remodeling induced by the exercise training, as shown by the increased LV relative weight observed in AE. These data are supported by several evidences, which indicate a beneficial cardiac remodeling after exercise training due to increased LV cavity and dilation, inducing significant functional changes in cardiac contractility and, consequently, improving cardiac output.[29,30] Additionally, MI area was not evaluated and this is a limitation of the present study.

## Conclusions

In conclusion, data of the present study are that aerobic training, regardless the arrangement of the program - continuously or fractioned -, causes significant increase on physical capacity of elderly rats, as well as acts protecting against further impairments caused by MI injuries. However, accumulated aerobic exercise seems to be a better approach once CE showed decreased exercise capacity in comparison with the time before MI, as well an elevated index of pulmonary congestion, whereas both parameters were stable in the AE group.

## Author contributions

Conception and design of the research: Rodrigues B. Acquisition of data: Feriani DJ. Analysis and interpretation of the data: Feriani DJ, Coelho-Júnior HJ. Statistical analysis: Feriani DJ, Coelho-Júnior HJ. Obtaining financing: Rodrigues B. Writing of the manuscript: Feriani DJ, Coelho-Júnior HJ, Rodrigues B. Critical revision of the manuscript for intellectual content: Irigoyen MC, Rodrigues B.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the Universidade São Judas Tadeu under the protocol number 008/2013.

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ORIGINAL ARTICLE

# Acute Myocardial Infarction and Primary Percutaneous Coronary Intervention at Night Time

Roberto Ramos Barbosa, Felipe Bortot Cesar, Denis Moulin dos Reis Bayerl, Renato Giestas Serpa, Vinicius Fraga Mauro, Walkimar Ururay Gloria Veloso, Roberto de Almeida Cesar, Pedro Abilio Ribeiro Reseck

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## Abstract

**Background:** Primary percutaneous coronary intervention is the preferred treatment in ST-elevation myocardial infarction. At night period, the delay until performing primary percutaneous coronary intervention may be determinant to prognosis worsening.

**Objective:** To analyze the results of primary percutaneous coronary intervention performed at day and night periods.

**Methods:** Cohort study that included patients admitted with ST-elevation myocardial infarction who underwent primary percutaneous coronary intervention from December 2013 until December 2016 in a ST-elevation myocardial infarction reference hospital of a metropolitan region in Brazil, followed from admission to hospital discharge or death, compared according to time of primary percutaneous coronary intervention (night or day). Statistical analysis comprehended the Chi-square test, the Fisher test, the Student's t-test and the analysis of variance, with significance level of 5%.

**Results:** 446 patients were submitted to primary percutaneous coronary intervention, 159 (35.6%) at night time and 287 (64.4%) at day time. No differences were found between the two groups concerning clinical baseline characteristics. Door-to-balloon time (101 ± 81 minutes vs. 99 ± 78 minutes; p = 0,59) and onset-to-ballon time (294 ± 158 minutes vs. 278 ± 174 minutes; p = 0,32) did not differ between the groups. The incidence of combined major adverse cardiac events (15.1% vs. 14.3%; p = 0,58) and in-hospital mortality (9.4% vs. 8.0%; p = 0,61) were similar between the groups, as well as length of hospital stay (6.0 ± 4 days vs. 4.9 ± 4 days; p = 0,91).

**Conclusion:** Primary percutaneous coronary intervention at night time showed similar results as the procedure performed at day time, without significant increase of in-hospital adverse events, length of stay or mortality. (Int J Cardiovasc Sci. 2018;31(5)513-519)

**Keywords:** Myocardial Infarction; Percutaneous Coronary Intervention; Cohort Studies; Night Care.

## Introduction

In the treatment of ST-segment elevation myocardial infarction (STEMI), mechanical coronary reperfusion through primary percutaneous coronary intervention (PPCI) has an important position and its efficacy has been demonstrated and proven in large studies.[1-3] In addition to attaining target vessel patency in more than 90% of cases, it is able to increase survival and reduce the rates of reinfarction and cerebrovascular accident (CVA) related to chemical thrombolysis.[3-6] PPCI is a class I indication for treatment of the STEMI within the first 12 hours of evolution, when available in a timely manner and performed in qualified centers.[7-9]

Access to PPCI is not always easy to achieve, and its unavailability can lead to severe delays and the ineffective treatment of STEMI, with significantly more severe clinical outcomes. The nocturnal period is particularly complex in this context, and previous studies suggest

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that hospital admission at night culminates in higher mortality rates, when compared to the daytime period.

However, several factors seem to be related to impediments to this access experienced at night, and Brazilian cities have structural problems; plus the fact that emergency care systems usually depend on the on-call Interventional Cardiology professionals, which may prolong the delay until the definitive treatment of STEMI is implemented.[10]

Data evaluating the treatment of STEMI in the nighttime period in Brazil are scarce. To date, there have been no outcome-related analyses in Hemodynamic Services with on-duty Interventional Cardiologists. Therefore, the aim of this study was to evaluate the results of PPCI performed during the daytime and nighttime periods in a cardiology referral center, which has a regular, on-duty interventional cardiologist, together with a specialized nursing team.

## Methods

A prospective observational, single-center cohort study was developed, which included patients with a diagnosis of STEMI of any wall submitted to PPCI within the first 12 hours of the clinical presentation in a tertiary cardiology institution in the municipality of Vitória, state of Espírito Santo, Brazil, between December 2013 and December 2016.

The inclusion criteria were the clinical and electrocardiographic diagnoses of IAMCSST, and the indication for treatment by PCI by the attending physician, corroborated by the interventional cardiologist. Exclusion criteria were IAMCSST with more than 12 hours of evolution, diagnosis of nonconfirmed or doubtful IAMCSST, patients not submitted to PCII immediately after coronary angiography,

The inclusion criteria were the clinical and electrocardiographic diagnoses of STEMI, and the indication of PPCI treatment by the attending physician, corroborated by the interventional cardiologist. The exclusion criteria were STEMI with more than 12 hours of evolution, nonconfirmed or uncertain diagnosis of STEMI, patients not submitted to PPCI immediately after the coronary angiography, patients younger than 18 years of age or refusal to sign the Free and Informed Consent Form (FICF) or to participate in the study through prospective data collection. All patients were interviewed at hospital admission and followed until hospital discharge. The study was approved by the local Research Ethics Committee, according to the Declaration of Helsinki.

The patients included in the study were compared according to the period of admission at the Hemodynamics service, regardless of the day of the week, specifically at night time, from 7:00 p.m. to 6:59 a.m.; and daytime, from 7 am to 6:59 p.m. The clinical variables evaluated were age, gender, arterial hypertension, diabetes mellitus, dyslipidemia, smoking status, chronic renal failure, prior PCI, previous myocardial revascularization surgery, disease severity at admission described by the Killip-Kimball classification, use of glycoprotein IIb / IIIa inhibitors during PPCI and treatment delay time (door-to-balloon time and pain-to-balloon time).

The primary endpoint of the study consisted in combined Major Adverse Cardiac Events (MACE) - death from any cause in the in-hospital phase, new nonfatal AMI or CVA during hospitalization. The secondary outcomes included all-cause death, CVA and new AMI alone, successful PPCI and hospital length of stay in days. At the analysis of hospitalization time, only those patients who were discharged to their homes were considered, excluding those who died during the hospitalization period.

All STEMI cases treated at the referral institution had spontaneous demand or were transferred after initial treatment and recognition of the clinical picture at another institution. The emergency nature of the PPCI procedure was followed in all patients, and they were taken to the interventional laboratory as soon as possible after communicating with the emergency unit team. The service had a regular on-duty interventional cardiologist, including at non-commercial hours, operating 24 hours a day.

According to the institution's STEMI care protocol, patients received a loading dose of 200 to 300 mg of acetylsalicylic acid and 300 to 600 mg of clopidogrel or 180 mg of ticagrelor. All patients received full heparinization with unfractionated heparin in the interventional laboratory (70 to 100 U/kg). the patients were taken to undergo the procedure as soon as the interventional laboratory was available after conduct confirmation by the interventional cardiologist. After the PPCI procedure, dual antiplatelet therapy was maintained systematically in all patients.

The total time of myocardial ischemia in STEMI until the PPCI was performed (pain-to-balloon time) was

routinely recorded in the service by the emergency room and interventional laboratory medical staff, as well as the door-to-balloon time (delay from admission at the referral service emergency unit until the implementation of PPCI).

## Statistical analysis

The data obtained were stored in a Microsoft Office Excel spreadsheet for subsequent descriptive and comparative analysis according to the time of the treatment at the Hemodynamics Service.

In the descriptive analysis of the data, the categorical variables were expressed as absolute and percentage frequencies, and the continuous variables as mean and standard deviation. The data were considered as having a normal distribution through the Shapiro-Wilk's test. For comparisons, the statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 20.0, for Windows, and comprised Pearson's chi-square test, Fisher's exact test, the unpaired Student's t-test, and one-way ANOVA, with p values <0.05 being considered statistically significant.

## Results

During the assessed period, 522 patients were identified and referred for cardiac catheterization as a matter of urgency, of which 446 (85.4%) were diagnosed with STEMI and submitted to PPCI during the first 12 hours since symptom onset, comprising the assessed sample. Of these, the procedure was performed in the nighttime period in 159 (35.6%), and 287 (64.4%) in the daytime period.

When comparing the Nighttime and Daytime Groups, no differences were observed regarding the basal clinical characteristics (Table 1). When analyzing the severity of the STEMI clinical presentation through the Killip-Kimball classification, we observed a predominance of class I in both groups, with no statistically significant difference for the classification when comparing the Nighttime and Daytime Groups, as shown in Table 2.

The means of the door-to-balloon and pain-to-balloon times did not differ statistically between the Nighttime and Daytime Groups. Table 3 shows the time delays until the performance of PPCI.

There was no difference regarding the mean number of stents per patient, number of drug-eluting stents, mean stent diameter and length in the two groups. The administration of acetylsalicylic acid and clopidogrel or ticagrelor was similar between the Nighttime and Daytime Groups. During the PPCI procedures, there was a higher rate of use of glycoprotein IIb / IIIa inhibitors at nighttime, with similar procedure success rates in both periods. The characteristics related to the PPCI procedures are described in table 4.

The PPCI procedure success rate did not show a significant difference when the time schedules were compared (91.1% in the Nighttime Group vs. 93.3% in the Daytime Group, p = 0.38). The mean time of

**Table 1 - Basal clinical characteristics, according to the time of admission at the Hemodynamics service**

| Characteristic | Nighttime group | Daytime group | p value |
|---|---|---|---|
| Male gender, n (%) | 123 (77.3) | 207 (72.1) | 0.09 |
| Age, years ± SD | 58.9 ± 11.8 | 60.2 ± 12.4 | 0.08 |
| Arterial hypertension, n (%) | 153 (96.2) | 240 (83.6) | 0.06 |
| Diabetes mellitus, n (%) | 40 (25.1) | 74 (25.8) | 0.68 |
| Dyslipidemia, n (%) | 60 (37.7) | 90 (31.3) | 0.24 |
| Smoking, n (%) | 61 (38.3) | 95 (33.1) | 0.12 |
| Chronic renal failure, n (%) | 13 (8.1) | 31 (10.8) | 0.33 |
| Previous PCI, n (%) | 10 (6.2) | 20 (6.9) | 0.4 |
| Previous CABG, n (%) | 4 (2.5) | 6 (2.1) | 0.89 |

*Statistical tests used: Pearson's chi-square test, Fisher's exact test and unpaired Student's t-test. SD: standard deviation; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.*

**Table 2 - Severity of the acute myocardial infarction clinical presentation through the Killip-Kimball classification**

| Killip-Kimball class | Nighttime group n (%) | Daytime group n (%) | p value |
|---|---|---|---|
| I | 121 (76.1) | 239 (83.2) | 0.06 |
| II | 12 (7.5) | 21 (7.3) | |
| III | 6 (3.8) | 3 (1.0) | |
| IV | 18 (11.3) | 24 (8.3) | |

*Statistical tests used: one-way Analysis of Variance (ANOVA).*

**Table 3 - Mean times delays until the performance of the primary percutaneous coronary intervention**

| Time delays | Nighttime group | Daytime group | p value |
|---|---|---|---|
| Door-to-balloon time, minutes ± SD | 101 ± 81 | 99 ± 78 | 0.59 |
| Pain-to-balloon time, minutes ± SD | 294 ± 158 | 278 ± 174 | 0.32 |

*Statistical tests used: unpaired Student's t-test. SD: standard deviation.*

hospitalization among patients who were discharged to their homes was 6.0 ± 4.3 days in the Nighttime Group and 4.9 ± 4.0 days in the Daytime one (p = 0.91).

Regarding the in-hospital evolution after the PPCI, similar mortality rates were observed in both groups. No cases of CVA were diagnosed in the total sample. In-hospital outcomes and their comparison between the Nighttime and Daytime Groups are shown in table 5.

## Discussion

The non-business hours represent a challenge to medical assistance in the presence of STEMI, a diagnosis that requires rapid decisions and availability of several links in an urgency and emergency network. In this study, we demonstrated that it is possible to attain satisfactory results in the Brazilian scenario, with times of delay and incidence of similar adverse events among the PPCIs performed in the nighttime and daytime periods.

National and international guidelines have strong recommendations for the implementation of effective STEMI treatment systems, with necessary adaptations and regionalizations.[8,11,12] This includes the integration of several links in the chain of care, especially the pre-hospital level and the availability of a referral service with Interventional Cardiology and PPCI training, aiming at increasing survival of patients with STEMI.[13-15] Nonetheless, the nighttime period usually has an on-call Interventional Cardiology team, and the increase in the time of delay can greatly affect the prognosis.

Keeping the Interventional Cardiology team on duty at the referral centers is an attractive strategy to reduce the delay until the coronary reperfusion is performed and to extend the possibility of effective treatment to patients with STEMI. The applicability of PPCI within the recommended time, that is, within 90 minutes of admission to the emergency unit is, in itself, a challenge in the context of the urgency and emergency network,[16,17] and the nighttime period discloses even greater difficulties. To ensure a well-functioning and qualified

**Table 4 - Characteristics of the primary percutaneous coronary intervention procedures, according to the time of admission at the Hemodynamics service**

| Characteristic | Nighttime group | Daytime group | p value |
|---|---|---|---|
| Acetylsalicylic acid, n (%) | 154 (96.8) | 281 (97.9) | 0.19 |
| Clopidogrel / ticagrelor, n (%) | 150 (94.3) | 276 (96.1) | 0.32 |
| Glycoprotein IIb/IIIa inhibitors, n (%) | 43 (27.0) | 54 (18.8) | 0.04 |
| Treated vessels (territory) | | | |
| Anterior descending artery, n (%) | 76 (47.8) | 130 (45.3) | 0.61 |
| Right coronary artery, n (%) | 52 (32.7) | 103 (35.9) | 0.49 |
| Circumflex artery, n (%) | 28 (17.6) | 61 (21.3) | 0.35 |
| Left main coronary artery, n (%) | 5 (3.1) | 6 (2.1) | 0.19 |
| Access route | | | |
| Femoral, n (%) | 144 (90.6) | 245 (85.3) | 0.11 |
| Radial, n (%) | 15 (9.4) | 42 (14.6) | 0.11 |
| Pré-dilation | 132 (83.0) | 256 (89.2) | 0.06 |
| Post-dilation | 38 (23.9) | 82 (28.6) | 0.28 |
| Number of stents, total (mean stents per patient ± SD) | 215 (1.3 ± 0.4) | 349 (1.2 ± 0.6) | 0.9 |
| Drug-eluting stents, n (%) | 7 (3.2) | 19 (5.4) | 0.33 |
| Stent nominal diameter | 2.98 ± 0.41 | 3.09 ± 0.49 | 0.93 |
| Stent nominal length | 23.4 ± 7.3 | 20.5 ± 8.1 | 0.91 |
| Procedural success, n (%) | 151 (94.9) | 278 (96.8) | 0.31 |

*Statistical tests used: Pearson's chi-square test, Fisher's exact test, unpaired Student's t-test and one-way Analysis of Variance. SD: standard deviation.*

**Table 5 - Comparison of in-hospital outcomes between the Nighttime and Daytime Groups after the primary percutaneous coronary intervention**

| Outcome | Nighttime group n (%) | Daytime group n (%) | p value |
|---|---|---|---|
| Combined MACE* | 24 (15.1) | 41 (14.3) | 0.58 |
| Death | 15 (9.4) | 23 (8.0) | 0.61 |
| New non-fatal AMI† | 9 (5.6) | 19 (6.6) | 0.15 |

*Statistical tests used: Pearson's chi-square test. * Death from all-cause in the in-hospital phase, new non-fatal AMI or CVA during hospitalization. MACE: major adverse cardiovascular events; AMI: acute myocardial infarction.*

system is of utmost importance for health strategy policies, since about 50% of STEMI cases occur outside regular business hours.[18]

Studies consistently suggest that PPCI may have different results, according not only to the total time of myocardial ischemia,[17,19,20] but also the time when it is performed.[21-26] Nighttime or weekends may show a PPCI procedure failure rate up to 81% higher,[21] a door-to-balloon time up to 21.3 minutes longer,[24] time from the electrocardiogram to arrival in the Hemodynamics unit 20.7 minutes longer[24] and mortality in 30 days up to 121% higher,[21] when compared to the business hours. In our study, the only statistically significant difference between the Nighttime and Daytime Groups was the rate of glycoprotein IIb/IIIa inhibitor use. The main hypothesis for this finding is the greater anxiety by the operator to optimize the anterograde coronary flow and to resolve the finding of intracoronary thrombi at nighttime.

A Brazilian study showed that the delay associated with nocturnal PPCI was 18 minutes (102 ± 98 minutes vs. 84 ± 66 minutes, $p < 0.01$). The in-hospital mortality rate was 10.2% vs. 7.6%, and the one-year mortality rate was 12.6% vs. 9.5% (PPCI at nighttime vs. daytime), both showing no statistical significance.[25] The differences in results between the Nighttime and Daytime Groups in comparison to the data in our study can be explained by the presence of a regular on-duty interventionist cardiologist in our service, not one on-call regimen.

We demonstrated that the strategy of having an on-duty Interventional Cardiology team at nighttime can shorten the delay in STEMI treatment at these times. Although this point is only one of the necessary care links, there is an increase in the possibility of performing PPCI in a timely manner, being able to reach the recommended goals even at non-business hours and to avoid an increase in mortality. In a study by Nguyen et al.,[27] the use of the 24-hour on-duty presence of the interventionist cardiologist led to a reduction of 57% in the door-to-balloon time, with a mean absolute reduction of 71 minutes, and a 54% reduction in hospital length of stay.

The mean door-to-balloon time over 90 minutes observed in the present study was probably due to avoidable in-hospital delays and to the immaturity of the care system at the time, which still relied on the wait for non-medical staff who were on-call due to contractual issues. Also, the result reflects the practical difficulty of reaching the time goals recommended for STEMI treatment in our country. However, the nighttime schedule did not interfere in the total delay, demonstrating the feasibility of attaining adequate reperfusion times, aiming to improve the quality of care, with no harm to the patient as a result of the time of day when the event occurs.

## Limitations

Although the present study is relevant, some limitations should be mentioned. The single-center characteristic limits the extrapolation of results to other populations. Clinical follow-up restricted to the in-hospital period, despite having the power to demonstrate differences between the two groups, underestimates the real impact of the time when the PPCI was performed on the results, by not evaluating outcomes in the medium or long term. Potentially relevant data, such as kidney dysfunction and hemorrhagic complications during the in-hospital evolution were not collected and evaluated in this study. The times used to divide the groups do not always accurately represent the business and non-business hours, which were the object of our study due to the potential difference regarding the speed and quality of medical care. As the study included only patients actually submitted to PPCI in a timely manner, some patients that were not transferred or were not diagnosed with STEMI were not analyzed, restricting the results to outcomes after the PPCI, and not all patients with STEMI.

## Conclusion

The results of the primary percutaneous coronary interventions performed in the nighttime and daytime

periods were comparable, showing similar mortality rates and incidence of major adverse cardiovascular events between the two groups. With logistic optimization and the prioritizing of immediate care in STEMI cases, it is possible to overcome the accessibility, availability and information barriers, which are extremely common in Brazilian metropolitan regions, especially at nighttime.

## Author contributions

Conception and design of the research: Barbosa RR, Cesar FB, Bayerl DMR, Serpa RG, Veloso WUG, Cesar RA, Reseck PAR. Acquisition of data: Barbosa RR, Cesar FB, Mauro VF. Analysis and interpretation of the data: Barbosa RR. Statistical analysis: Barbosa RR. Writing of the manuscript: Barbosa RR. Critical revision of the manuscript for intellectual content: Barbosa RR, Bayerl DMR, Reseck PAR. Supervision / as the major investigador: Barbosa RR.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória under the protocol number 492.764. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

# Knock on the Right Door. How we are Treating the Patient with Acute Myocardial Infarction

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## Abstract

**Background:** To reduce mortality of acute myocardial infarction, medical care must be provided within the first hours of the event.

**Objective:** To identify the "front door" to medical care of acute coronary patients and the time elapsed between patients' admission and performance of myocardial reperfusion in the public health system of the city of Joinville, Brazil.

**Methods:** The study was a retrospective analysis of the medical records of 112 consecutive patients diagnosed with acute myocardial infarction by coronary angiography. We identified the place of the first medical contact and calculated the time between admission to this place and admission to the referral hospital, as well as the time until coronary angiography, with or without percutaneous transluminal angioplasty. A descriptive analysis of data was made using mean and standard deviation, and a $p < 0.05$ was set as statistically significant.

**Results:** Only 16 (14.3%) patients were admitted through the cardiology referral unit. Door-to-angiography time was shorter than 90 minutes in 50 (44.2%) patients and longer than 270 minutes in 39 (34.5%) patients. No statistically significant difference was observed in door-to-angiography time between patients transported directly to the referral hospital and those transferred from other health units ($p < 0.240$). Considering the time between pain onset and angiography, only 3 (2.9%) patients may have benefited from myocardial reperfusion performed within less than 240 minutes.

**Conclusion:** Management of patients with acute myocardial infarction is not in conformity with current guidelines for the treatment of this condition. The structure of the healthcare system should be urgently modified so that users in need of emergency services receive adequate care in accordance with local conditions. (Int J Cardiovasc Sci. 2018;31(5)520-526)

**Keywords:** Guidelines Adherence; Failure to Rescue, Health Care; Unified Health, System; Myocardial Infarction; Emergency Medical Services.

## Introduction

Acute myocardial infarction (AMI) is one of the major causes of death in Brazil.[1,2] Heart failure and sudden death, the most severe complications of AMI, are the most serious manifestations of atherosclerotic disease. The majority of deaths occur in the first 24 hours of disease onset, and nearly half of them in the first hour.[1-3] Similar to the in-hospital mortality, 30-day mortality decreased from 8.6% to 3.6% in some North American states between 1988 and 2000.[3] In Brazil, 30-day mortality is 15.4%[2] according to the Brazilian Unified Health System (SUS) Computing Department (DATASUS).

When AMI patients seek medical care, therapeutic interventions should be promptly performed to result in beneficial outcomes. Fibrinolytic therapy and coronary angioplasty have no or low efficiency when performed after four hours of AMI with ST-segment elevation.[1-19]

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For this reason, patients' diagnosis, transportation and treatment should be fast.

In 2011, the Ministry of Health implemented an integrated system for AMI management (the *Linha de Cuidado do Infarto Agudo do Miocárdio*) through healthcare units of the SUS, and a clinical protocol on acute coronary syndrome (ACS) (the *Protocolo Clínico sobre Síndrome Coronariana Aguda*).[2] These were created to propose an integrated action for ACS treatment, grounded on its high prevalence and important role in morbidity and mortality.

In the city of Joinville, SUS provides emergency care units, general hospitals and a referral hospital. Coronary angiography and angioplasty are available in the referral hospital only, and none offers cardiac care services available 24 hours a day. Joinville Secretary of Health promoted the publication of a booklet entitled "*Bata na porta certa*" ("Knock on the right door") to guide healthcare providers and users in directing themselves to the correct units for health assistance.[20] For example, the booklet suggests the best emergency care units for chest pain in the city. Our study aimed to identify where AMI patients sought medical care at first place (the "front door") and the time elapsed from initial care received by the patients (first medical contact) and myocardial reperfusion.

## Methods

This was a retrospective analysis of medical records, including 112 patients with ST-segment elevation myocardial infarction (STEMI) who had undergone coronary angiography in the period between 09/28/2013 and 05/28/2014. Data were collected at the Catheterization Laboratory, at Santa Catarina State referral hospital, at Joinville Hospital and at three emergency care units of the city.

We registered: the place where patients received initial care, the time (min) between pain onset and the moment the patient was seen at the unit; the time (min) between admission to the first unit and admission to the referral hospital; the time (min) between admission to the referral hospital and coronary angiography test; and whether coronary thrombolysis was performed. Due to missing data, the door-to-balloon time was not recorded. When the "front door" to medical care was not found in patients' records, we attempted to contact patients by telephone. In addition, we also collected data on the occurrence of heart failure, myocardial revascularization and death.

The study was approved by the ethics committee of Joinville Regional University (UNIVILLE), by Joinville Secretary of Health, and by hospitals and catheterization laboratory involved in the study.

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows version 17 (SPSS Inc. Chicago, Illinois). Continuous variables with normal distribution were expressed as mean ± standard deviation, and frequency analysis was used for categorical variables. Data normality was verified by the Kolmogorov-Smirnov test. Between-group comparisons were performed by the Student's t test for independent, continuous variables and by the chi-square test for nominal variables. The level of significance was set at 5% (95% confidence interval, 95%CI).

## Results

We studied 87 men and 24 women, mean age of 58.3 (23-82) years. The "front door" to the emergency care was the emergency care unit for 44 patients, the referral hospital for 16 patients, the city hospital for 4, the emergency medical service transport system for 5, and primary health centers for 2 patients; in 29 patients this information was not available. The other patients were transfered from other cities. Event duration (time elapsed between pain onset and coronary angiography) was probably shorter than 12 hours in 71 patients (65.7%) and longer than 12 hours in 39. This was in fact an estimate, calculated as the sum of minutes during the period between the first medical assistance and coronary angiography test, since duration of pain was not recorded in the medical records. In addition, in emergency care units, most of the medical records could not be accessed, since they were usually registered behalf of patients and filled in other institution. The medical records of patients referred from other cities were also not available, and we rarely obtained useful information by phone contact in these cases. Percutaneous transluminal angioplasty (PTA) was performed in 92 (82.1%) patients and the door-to-angiography time (DAT) was shorter than 90 minutes in 50 (44.2%) patients (Table 1). No statistically significant difference was seen in DAT, sex or age between patients admitted to the referral hospital and the others. DAT was not available in 14 patients. No patients received thrombolytic drugs.

**Table 1 - Comparison of door-to-angiography time (DAT) between patients seen at the referral hospital patients seen in other healthcare units**

| | Referral hospital * | Others** | Total |
|---|---|---|---|
| Initial care | 16 | 96 | 112 |
| DAT < 90 min | 7 (43.7%)* | 43 (44.3%)** | 50 (44.2%) |
| DAT > 270 min | 4 (25%)* | 45 (46.3%)** | 49 (43.3%) |
| DAT > 720 min | 3 (18.7%)* | 36 (37%)** | 39 (34.8%) |
| Maximum DAT | 15.695 | 48.439 | 48.439 |
| Minimum DAT | 19 | 10 | 10 |
| Mean DAT | 1,433 | 2,132 | 2,033 (+/-5,542) |
| Angioplasty | 14 (87.5%) | 78 (80.41%) | 92 (82.1%) |

**Pearson $X^2 = 2.124$; P = 0.145 /Fisher`s Exact Test 0.169; ** Pearson $X^2 = 0.436$/Fisher´s Exact Test 0.511.*

## Discussion

In 2001, Gibson posed a question he was often asked: "what do we need to do to improve mortality by another 1% in the setting of acute myocardial infarction?" and then answered that this could not be achieved exclusively with new drugs and devices but also by reducing the time to treatment.[4] Our results suggest that we are far from achieving these objectives. When mentioning the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT 2) report,[5] Gibson emphasized the importance of performing electrocardiography for the diagnosis and a time to treatment < 2 hours.

In the ASSENT-2 trial, the investigators assessed electrocardiographic changes and 1-year mortality in 13,100 patients undergoing primary thrombolysis. In-hospital mortality and late mortality were proportional to pain duration and inversely proportional to ST-T resolution (lower and upper limits of 3.8 and 13%) in one year.[5]

In our study, analysis of the medical records revealed that results of cardiac enzyme tests for diagnosis and treatment decisions are still lacking in many of them.

Acute coronary syndrome, notably AMI, is the major cause of cardiac deaths in Brazil.[1,2] A considerable percentage of deaths occur quickly and unexpectedly before patients get medical care.[1-3] Until 1980, there were insufficient medical resources to achieve significant reductions in in-hospital and late mortality. In 1979, Rentrop published the first results of intracoronary injection of streptokinase. Coronary angiography performed during and after STEMI showed spontaneous recanalization in nearly 40% of patients, increased to 70% with thrombolytic therapy. These findings were confirmed by Ganz in 1982. The potential of reperfusion therapy with thrombolytic drugs and angioplasty in reducing mortality has already been shown;[1-17] nevertheless, a significant reduction in mortality depends on how early reperfusion therapy is performed.[5-19,21] In Stemi, the therapy should be started within the first four hours of the event.[5,12,15,17-19] A mean reperfusion time < 180min has been reported in attempt to provide adequate assistance to patients before (by administration of thrombolytic drugs) and during hospitalization (primary angioplasty). Systematic reviews by Keeley et al.,[13] updated by Asseburg et al.,[14] including short term and six-month outcomes, showed that compared with thrombolytic agents, reduction in mortality and in non-fatal outcomes with primary angioplasty was only significant when time delay was shorter than 45 minutes and 90 minutes, respectively.[15,16] The use of thrombolytic therapy was even more efficient in reducing mortality according to six randomized studies by Morrison et al.[15] In-hospital thrombolysis and prehospital thrombolysis decreased the mean duration of pain until reperfusion by 162 and 104 minutes, respectively. Thrombolytic therapy followed by short-term angioplasty is efficient in reducing short-term and long-term events, regardless of the presence of multi-vessel or one-vessel injury.[16]

Many factors can influence the rescue of patients with STEMI – the patient, who should seek medical assistance as soon (and if) he perceives the symptoms; healthcare professionals who should diagnose the condition and provide the patient with adequate treatment as early as possible, and performance of reperfusion therapy. In Joinville, the SUS offers three emergency care units and three public hospitals (including one referral center for coronary angiography and angioplasty). The efficacy of this system was unknown, although there were reports of difficult accessibility of paramedics to the referral hospital and delayed arrival of patients to the catheterization laboratory. With the permission of the catheterization laboratory, we identified the patients with ACS seen at the unit, their "front door" to medical care, and the time from the first assistance to reperfusion with angioplasty. Patients' transportation depends on the experience of the

staff in dealing with ACS patients and symptoms, as well as possibility of transport to well-equipped facilities.[6,7,10,20-23] It is estimated that approximately 20% of patients arrive at the clinics within two hours of pain onset.[2]

In fact, public health systems can provide guidance for their users through several actions.[3,10,20] Healthcare providers are expected to be able to identify the disease, especially by recognizing suggestive symptoms and electrocardiographic changes.[1-4,21-23] Electrocardiography (ECG) is an old, cheap test, essential in diagnosing and guiding therapeutic approaches. In 2002, a European task force emphasized the importance for both patients and healthcare providers to identify high-risk chest pain.[24] When symptoms occurred at home, patients wait a mean of 60 minutes before seeking help, and up to 25% of them wait for four hours or more.[7,24] In emergency services, the unawareness of the low sensitivity (approximately 50%) of the ECG test in confirming AMI may affect the diagnosis. The authors reinforced the need for serial ECG at short intervals (minutes) to diagnose the disease, in accordance with Brazilian guidelines recommendations,[1] rather than performing ECG tests every three hours, as usually occurs.

Unfortunately, some paramedics do not receive adequate training in ECG and rely on cardiac enzyme tests. In STEMI, cardiac enzymes are useful for confirming the event and indicating the prognosis but are not essentially required for the diagnosis.[1-3,21] Delay in the results leads to a delayed and inefficient reperfusion therapy.

Boersma et al.,[12] in a review of 22 studies published between 1983 and 1993 including 50,246 patients undergoing coronary thrombolysis showed that the greatest benefit on 30-day mortality is achieved by the therapy performed within the first two hours. In case of STEMI, thrombolytic drugs are recommended when waiting time to angioplasty is longer than 90 minutes.[7-9,11,13-17]

The ACCEPT/SBC (Clinical Outcomes at 30 days in the Brazilian Registry of Acute Coronary Syndromes),[22] a multicenter study of 47 Brazilian hospitals carried out in 2010 and 2011 showed a use of thrombolytic drugs lower than 15%. In addition, reperfusion therapy was not performed in 22.3% of patients with STEMI; mortality in this group was higher than that in the group that received reperfusion therapy (8.1% vs. 2.0%). In the reperfusion group, mean door-to-angiography was 125 (± 90) minutes.

The Global Registry of Acute Coronary Events (GRACE), in a six-month follow-up, also showed greater mortality in patients that did not receive reperfusion therapy.[26] In our sample, no patient used thrombolytic drugs (which are not available in the emergency care units but are available in the hospitals). Transluminal angioplasty was performed in 86.1% of patients. Our results indicated that almost all STEMI patients were negatively affected by delayed or absent reperfusion. Approximately 40% of STEMI patients survive the event irrespectively of the medical therapy, and among these patients with less severe infarction, those with late presentation STEMI cause biases in analyzing the benefits of myocardial reperfusion.[10-13] Several reports[3,6,13,15,21-23] have demonstrated that extensive myocardial infarction depends on the best quality medical care to prevent complications and in-hospital and late mortality.

Due to incomplete or missing data in the medical records, we could not identify the complications of STEMI. In the study group, two in-hospital deaths were registered, suggesting the presence of less severe conditions in this group. One limitation of the study is the lack of documentation of pain duration before medical assistance in all medical reports. If we assume a 2-hour period for that,[1,4,5,24] few patients would have been undergone angioplasty within a four-hour period. Some patients had a very short DAT (10-20 minutes) because the front door, in these cases, was the catheterization laboratory. Only three patients went directly to the referral hospital and hence may have had a pain-door-angiography time shorter than 4 hours.

Wang et al.,[27] analyzed the data from 101 hospitals in the "Get With the Guidelines" program of the American Heart Association, started in 2000 and reinforced by the D2B Alliance campaign focused on reducing door-to-balloon time. Data of 43,678 AMI patients were compared between 2005 and 2007. After exclusion of patients with non-STEMI, patients transferred in from other hospitals, patients without angioplasty or with late angioplasty, 5,881 patients undergoing primary angioplasty were assessed. Although door-to-balloon time decreased from 101 to 87 minutes, there was no significant reductions (from 5.1% to 4.7%) in in-hospital mortality. Since 2005 data had already revealed satisfactory in-hospital mortality parameters, the authors highlighted the importance of prehospital measures.

Between 2002 and 2008 in Denmark, Terkelsen et al.,[10] included 13,439 consecutive patients with STEMI referred for reperfusion therapy. The Danish National Health Service provides ambulances equipped with electrocardiographic system and defibrillator. Users

of the health service can call the emergency medical service, and those deemed in need of an ambulance are transported to the catheterization laboratory. The study was designed to evaluate the effect of several variables on late mortality. Patients were allocated into two groups, one transported directly to the percutaneous coronary intervention center and the other group transported to local hospitals first and then transferred to the treatment center. The time from pain onset to initiation of reperfusion therapy was calculated and categorized in patient delay, transportation delay, door-to-balloon time, system delay and total delay in both groups, in addition to hospital delay and prehospital system delay (time between transportation and arrival at the percutaneous coronary intervention center in one of the groups. After exclusion of patients that did not receive reperfusion, patients with a treatment delay longer than 12 hours, and patients with missing data, a total of 6,209 patients were followed-up. Door to balloon time was 39 (24-70) minutes in the group directly transported to treatment center and 29 (21-72) minutes in the other group. The study showed that in the group transferred from other hospitals, treatment delay was significantly longer (240 minutes vs. 170 minutes) than in the group directly transported for treatment. Mean follow-up period was 3.4 (1.8-5.2) years, with mortality of 15.4% in patients with system delays < 60 minutes, 23.3% in those with delays of 61-120 minutes, 28.1% in those with delays of 121-180 minutes, and 30.8% in those with delays of 180-360 minutes. Multivariate analysis showed that both prehospital delay and door-to-balloon time were associated with mortality, and efforts should be made to reduce them. Barreto et al.,[28] also demonstrated that transportation delay from other centers to the catheterization laboratory was a predictor of adverse events.

Bagai et al.,[22,23] compared patients evaluated in the emergency department and those transported directly to the catheterization laboratory. The authors reported that a median time of 30 minutes was spent in the emergency department, with potential decrease. The authors confirmed the beneficial effects of ambulance services and direct transportation of patients to the catheterization laboratory on the door-to-balloon time. However, the authors highlighted that the service is used infrequently and no differences in in-hospital mortality was observed between the groups.

Jollis et al.,[21] published the first results of the STEMI Systems Accelerator project, a large national effort to adequate regional STEMI care to national guidelines in the USA. The program was developed in 2012 and included emergency medical services and hospitals, regional and central coordinators, training of leaders, physicians and paramedics, ambulance and emergency staff, development of protocols, establishment of common criteria for STEMI diagnosis and treatment, and data storage in a national registry and timely feedback. Analysis of the program during the first two years revealed that the call for medical emergency by the citizens causes a decrease in the pain-to-first medical contact time and in door-to-balloon time, incrementing the percentage of patients who receives primary percutaneous coronary intervention within 90 minutes of paramedic arrival. Shorter delays in emergency services resulted in a reduction in in-hospital mortality.

In our study, prehospital delay was estimated using partial data, and seemed to be greater than 240 minutes in almost all patients. Also, the DAT was elevated, suggesting many possibilities for improvement.

In view of the studies cited in this study, we can say that difficulties in the treatment of STEMI are present (and similar) in many countries, and the strongest difference is in the efforts for their improvement.

In Brazil, some interventions have been published.[29-32] Escosteguy et al.,[29] published the results of a multidisciplinary program for implementation of clinical guidelines on AMI in a public emergency unit in Rio de Janeiro. Caluza et al.,[30] described the implementation steps and the first results of an AMI treatment system in Sao Paulo. The program standardized the processes of clinical diagnosis of STEMI, immediate ECG using tele-ECG, therapy decision (PTA or thrombolysis) and availability of care in the referral hospital. Andrade et al.,[31] described an integrated system for cardiovascular emergency services in Marilia, Brazil, with direct transportation of patients to the catheterization laboratory. The authors reported high symptom-to-balloon time in patients transferred from other units (5.0 ± 2.2 hours) and in those directly admitted to the hospital (3.3 ± 2.2 hours). Marcolino et al.,[32] reported the results of an integrated system for AMI approach (*Linha de Cuidado do Infarto Agudo do Miocárdio*) implemented in the city of Belo Horizonte, Brazil, between 2010 and 2011, which included training and motivation programs of the emergency service staff, interaction between the units and accessibility to the catheterization laboratory.

## Study limitations

Limitations of the study include its retrospective nature, the limited number of patients, the inclusion of patients undergoing catheterization only, the impossibility of determining the time interval from pain onset, patient admission and procedure, and the lack of data at the time of angioplasty.

## Conclusions

We identified a flawed healthcare system for STEMI management, in which the first medical contact rarely occurs in the referral hospital, physicians have difficulties in diagnosing the disease and do not use validated therapeutic approaches, and much data are missing from the medical records (which are filed in inadequate locations). Difficulties are encountered in the transfer of patients to the referral hospital and the emergency medical services are infrequently called, causing a delay in mechanical reperfusion. The importance of the catheterization laboratory is highlighted, with more than half of patients treated within a DAT consistent with current guidelines, reinforcing the need for a direct transportation of patients to this facility. We recommend the implementation of an integrated system for AMI management compatible with local conditions and patients' needs, characterized by centralized coordination, continuing education of the medical staff, presence of paramedics trained in ECG and use of thrombolysis therapy. We believe that the situation here described is not exclusive of the city of Joinville, justifying and encouraging the development of further studies and improvements in the system. We suggest a prospective, continuing study to evaluate the development and adherence of the system to current guidelines.

## Author contributions

Conception and design of the research: Hoepfner C. Acquisition of data: Roma E, Lana JV, Santin AL, Borga AL, Yamamoto AC, Techentin JV. Analysis and interpretation of the data: Hoepfner C, Roma E, Lana JV, Santin AL. Writing of the manuscript: Hoepfner C, Lana JV, Santin AL, Borga AL, Yamamoto AC, Techentin JV. Critical revision of the manuscript for intellectual content: Hoepfner C, Roma E, Lana JV, Santin AL.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Fundação Educacional da Região de Joinville - UNIVILLE under the protocol number 33651114.6.0000.5366. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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ORIGINAL ARTICLE

# Incidence and Characteristics Angiographic of Patients with Acute Myocardial

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## Abstract

**Background:** Acute myocardial infarction (AMI) is defined as the death of cardiomyocytes due to prolonged ischemia, caused by thrombosis and / or vasospasm on an atherosclerotic plaque.

**Objective:** To determine the incidence of patients with myocardial infarction undergoing primary angioplasty; characterize the anthropometric variables and identify the risk factors in this population.

**Methods:** This was a cross-sectional, observational, retrospective study in which we collected secondary data from medical records of a hospital in a city in the state of São Paulo, where the largest number of interventions is via Public Health System, patients with a diagnosis of Myocardial Infarction, undergoing primary coronary angioplasty, from January 2011 to December 2013.

**Results:** The total sample consisted of 437 subjects, 282 male and 155 female. In this study, there was predominance of myocardial infarction in the anterior descending artery ADA (45.51%), followed by right coronary artery RCA (38.46%), in carrying out the rescue angioplasty and stent implantation in 96.62% of cases. There was a predominance of high blood pressure as risk factors for 73.71%, followed by smoking with 41.66% of the sample.

**Conclusion:** According to the present study data, it appears a higher prevalence of infarction occurred in the ADA, with individuals performing the rescue angioplasty procedure and the placement of the stent, and a growing incidence of drug stent placement. We observed a high incidence of risk factors, prevailing hypertension. (Int J Cardiovasc Sci. 2018;31(5)527-531)

**Keywords:** Myocardial Infarction; Risk Factors; Angioplasty; Drug-Eluting Stents; Hypertension; Tobaco Use Disorder.

## Introduction

Cardiovascular diseases (CVD) are among the leading causes of death in Brazil and acute myocardial infarction comes second on this list as being the leading cause of death in most developed countries. Estimates suggest that this will also occur in the coming decades in developing countries.[1]

Acute myocardial infarction (AMI) is defined as the death of cardiomyocytes due to prolonged ischemia, caused by thrombosis and/or vasospasm on an atherosclerotic plaque.[2] Most events are caused by sudden rupture and thrombus formation on plaques inflamed, lipid-rich and thin fibrous layers. The myocardium undergoes progressive aggression due to areas of ischemia, injury and necrosis, caused consecutively by electrolytic disturbances, reversible morphological changes and definitive damages. Clinical presentation may range from non-ST segment elevation AMI to ST-segment elevation myocardial infarction. Rapid diagnosis, immediate clearance of the coronary artery, maintenance of blood flow in the myocardium,

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prophylaxis of distal embolization and prevention of complications (mechanical disorders, arrhythmias and heart failure) are necessary.[2] In the face of the advances of the last decades in medical procedures, such as the use of the stent in angioplasty procedures, the mortality rate in cases of AMI in the world fell from 50% in the 1950s to the current 6-10% in the 1980s.[3]

Percutaneous transluminal coronary angioplasty (PTCA) or salvage coronary angioplasty is used for the immediate treatment of AMI. Percutaneous revascularization is performed without previous use of thrombolytic agents, and may or may not implant the stent.[4,5] Stents generated more predictable and long-term results in the short and long term in percutaneous intervention scenarios that when operated with balloon angioplasty.[6]

The present study aimed to verify the incidence of patients diagnosed with AMI undergoing primary angioplasty, to characterize the anthropometric and angiographic variables and to identify the risk factors for CVD in this population.

## Methods

This is a cross-sectional, observational, retrospective study in which secondary data were collected from medical records of patients diagnosed with AMI undergoing PTCA in a hospital in a city in the interior of the state of São Paulo. The majority of the interventions was carried out by the Unified Public Health System (SUS), from 2011 January to 2013 December.

From the medical records were collected the variables as: anthropometric data, risk factors for ischemic heart disease: arterial hypertension (HA), diabetes mellitus (DM), dyslipidemia, smoking, sedentary lifestyle, heredity and obesity; angiographic data: location of the coronary lesion; ACTP, stent implantation and implanted type. The hemodynamic and cineangiocardiographic study was performed through left cardiac catheterization, puncture of the right radial artery and puncture of the right femoral artery, under local anesthesia (lidocaine 2%). The cineangiocardiographic films and reports were interpreted by hemodynamicist cardiologists experienced in the area.

Inclusion criteria were: patients submitted to PTCA during the first 24 hours of the diagnosis of AMI. Medical records improperly filled up were excluded.

This study was approved by the research ethics committee, CAAE nº 35527714.0.0000.5495 in accordance with the Directives and Norms Regulating Researches involving Human Beings. The results will be presented in the form of absolute and relative numbers in percentages.

## Results

The total sample comprised 437 individuals, 282 males and 155 females, whose anthropometric characteristics can be observed in table 1.

According to the Obesity Guidelines 2010,[7] the sample is included in the classification of pre-obese, defined by

**Table 1 - Anthropometric features of patients diagnosed with acute myocardial infarction (n = 437) that underwent primary coronary angioplasty at a hospital in a city in the interior of the state of São Paulo between the years 2011 to 2013**

| Year | n | Age (years) m / sd | Weight (kg) m / sd | Height (cm) m / sd | BMI m / sd |
|---|---|---|---|---|---|
| Male | | | | | |
| 2011 | 103 | 59.50 ± 10.69 | 80.28 ± 14.63 | 1.71 ± 0.07 | 27.40 ± 4.01 |
| 2012 | 104 | 60.03 ± 11.04 | 78.77 ± 16.62 | 1.71 ± 0.07 | 26.77 ± 4.96 |
| 2013 | 75 | 60.09 ± 10.86 | 82.16 ± 14.74 | 1.72 ± 0.05 | 27.75 ± 4.33 |
| Female | | | | | |
| 2011 | 53 | 59.83 ± 14.32 | 69.8 ± 13.9 | 1.60 ± 0.06 | 27.3 ± 4.46 |
| 2012 | 47 | 64.36 ± 11.85 | 70 ± 14.3 | 1.59 ± 0.08 | 27.4 ± 4.94 |
| 2013 | 55 | 64.89 ± 10.48 | 68.60 ± 12.53 | 1.60 ± 0.06 | 26.61 ± 4.36 |

*M: mean; sd: standard deviation.*

the BMI calculation. The high BMI ratio is a correlated risk factor for chronic diseases and a high mortality rate.

Analyzing risk factors for CVD of the sample, we observed that HTN is the predominant factor in both sexes, followed by smoking for men and dyslipidemia for women, as shown in table 2.

When considering the coronary arteries in the AMI, the anterior descending artery (ADA) is the most prominent, and its revascularization a survival factor.[8] The descriptions of the affected arteries are shown in table 3.

The stent implantation has a marked predominance when compared to the use of the balloon, it has being mainly used in 96.62% of the angioplasties performed in 2011, 91.26% in 2012 and 92.3% in 2013.

There was a rise in the use of the pharmacological stent, increasing from 3.88% in 2011, to 4.52% in 2012 and to 10.90% in 2013, becoming more and more a priority in hospitals that perform PTCA.

Important to be considered is the high cost of the pharmacological stent, since in the sample there is a predominance of patients using SUS, being 73.17% in 2011, 82.25% in 2012 and 89.87% in 2013. Regarding the use of private health, is 27.76% in 2011, 17.87% in 2012 and 10.11% in 2013.

**Table 2 - Risk factors for cardiovascular diseases in patients diagnosed with acute myocardial infarction (n = 437) who underwent primary coronary angioplasty at a hospital**

| Risk factor | 2011 | | | | 2012 | | | | 2013 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male n% | | Female n% | | Male n% | | Female n% | | Male n% | | Female n% | |
| Hypertension | 73 | 70.87% | 42 | 79.24% | 69 | 66.34% | 35 | 76.59% | 53 | 70.66% | 47 | 85.45% |
| Smoking | 44 | 42.71% | 21 | 39.62% | 50 | 48.07% | 16 | 34.04% | 22 | 29.33% | 22 | 40.0% |
| Dyslipidemias | 31 | 30.09% | 19 | 35.84% | 32 | 30.76% | 21 | 44.68% | 24 | 32% | 28 | 50.90% |
| Heredity | 35 | 33.98% | 20 | 37.73% | 27 | 25.96% | 11 | 23.40% | 16 | 21.33% | 17 | 30.90% |
| Obesity | 25 | 24.27% | 12 | 22.64% | 13 | 12.50% | 10 | 21.27% | 18 | 24% | 11 | 20% |
| DM | 16 | 15.53% | 7 | 13.20% | 9 | 8.65% | 6 | 12.76% | 10 | 13.33% | 16 | 29.09% |
| Sedentariness | 18 | 17.47% | 10 | 18.86% | 6 | 5.76% | 0 | 0% | 1 | 1.33% | 0 | 0% |

*DM: diabetes mellitus.*

**Table 3 - Arteries affected by acute myocardial infarction in diagnosed patients (n = 437), submitted to primary coronary angioplasty, in a hospital in a city in the interior of the state of São Paulo, between the years 2011 to 2013**

| Artery | 2011 | | | | 2012 | | | | 2013 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male n% | | Female n% | | Male n% | | Female n% | | Male n% | | Female n% | |
| ADA | 46 | 44.66% | 25 | 47.16% | 40 | 41.60% | 19 | 40.42% | 33 | 44% | 20 | 36.36% |
| RCA | 39 | 37.86% | 21 | 39.62% | 39 | 37.50% | 19 | 40.42% | 27 | 36% | 24 | 43.63% |
| CA | 13 | 12.62% | 5 | 5.43% | 16 | 15.38% | 7 | 14.89% | 10 | 13.30% | 10 | 13.33% |
| DA | 5 | 4.85% | 0 | 0% | 7 | 6.73% | 1 | 2.12% | 0 | 0% | 1 | 18.18% |
| MA | 0 | 0% | 2 | 3.77% | 2 | 1.92% | 1 | 2.12% | 5 | 6.66% | 0 | 0% |

*ADA: anterior descending artery; RCA: right coronary artery; CA: circumflex artery; DA: diagonal artery; MA: marginal artery.*

## Discussion

The latest advances in the treatment of AMI in centers of invasive cardiology allow angioplasty to be performed in the first hours as an immediate resource method for coronary reperfusion.[9] The early myocardial revascularization operation is indicated when there is consensus on the risks and benefits of the procedure, such as the time to revascularization after AMI. The success of the procedure is related to the preoperative risk factors such as: sex, age, Q-wave infarction and presence of cardiogenic shock. In a study by Jante et al,[10] it was verified that these risk factors determine a poor prognosis for revascularized patients exposed to them.

Evaluating percutaneous coronary intervention, there is a limitation to its efficacy and safety since there is the possibility of uncontrolled acute occlusion of the vessel under treatment and coronary restenosis. The rate of occurrence of these can be reduced by using the pharmacological stent. In 1977, in a study by Gonçalves et al,[4] restenosis rates using the balloon catheter alone ranged from 30 to 50%, up to the sixth month after the procedure.

The stent was the first percutaneous device that promoted significant reductions in rates of coronary restenosis. According to Serruys et al,[11] there was a reduction of 30 to 35%, demonstrated in controlled multicenter studies. Powel[12] analyzed the coronary angiography of patients undergoing surgery, and found that only 6% of these patients would be candidates for pharmacological stent use. However, evaluating patients with chronic coronary occlusion, 46% would be candidates for myocardial revascularization.

The use of coronary stents in AMI is a recent therapeutic option, which aims at immediate and also long term results.[10] To become an ideal option, results should be obtained with greater efficiency and spending less money, what is difficult because, as all implementation processes, demands significant additional costs, so the evaluation of the economic impact in the private sector as well as in the public sector is extremely important.[13]

According to the study by Rassi Jr. et al,[13] the calculation for replacement of the conventional stent by the pharmacological one would involve additional costs of about R$ 24 million, increasing in the SUS budget of 12.8%. Data from 2003 were used for this calculation when 30,666 coronary angioplasty procedures with conventional stent were performed by SUS.

Analyzing the cost-effectiveness of the initial hospitalization for implantation of the pharmacological stent with the use of Rapamycin, Quadro et al[14] demonstrated an increase of only US$ 309 in clinical cost in nine months, avoiding US$ 1,650 cost for a new revascularization. Clinical success was observed because of the decreasing rate in emergency myocardial revascularization surgery or death by the procedure.

The incorporation of new technologies in Brazil depends on comparative studies, aiming the reimbursement or financing of the pharmacological stent, in both the private and public sectors. The adoption of this technology in both systems is still low due to its high cost.[15]

Following the history of the evolution of the treatment and the resources spent for infarcted patients it is possible to observe, from the data of the present study, that it is necessary to raise awareness of risk factors, especially HTN, in an attempt to prevent future cardiovascular events. The lack of data in the spreadsheets can be considered a bias, such as the death index, since the lesion of greater prevalence in the individuals analyzed in this study was in the ADA. In terms of an immediate resource in the AMI treatment, the implantation of the pharmacological stent shows an effective evolution.

## Conclusions

According to the results of the present study, a higher prevalence of infarction occurred in the ADA artery, with the rescue angioplasty procedure being performed, placing the stent, and an increasing incidence of the pharmacological stent placement. High blood pressure and smoking still appear as risk factors present in the sample, reinforcing the need for emphasis on medication adherence, changes in lifestyle, weight control and post-infarction follow-up in this sample.

## Author contributions

Conception and design of the research: Kallás Bachur CK. Acquisition of data: Bachur JA. Analysis and interpretation of the data: Machado JP. Statistical analysis: Veiga EV. Writing of the manuscript: Candido SS. Critical revision of the manuscript for intellectual content: : Barbosa R, Carraro JG, Gonçalves DF, Tonello MGM.

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No potential conflict of interest relevant to this article was reported.

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**Study Association**

This study is not associated with any thesis or dissertation work.

**Ethics approval and consent to participate**

This study was approved by the Ethics Committee of the Universidade de Franca (CEPE/UNIFRAN) under the protocol number 35527714.0.00005495. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

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REVIEW ARTICLE

# Neutrophil-Lymphocyte Ratio in Cardiovascular Disease Risk Assessment

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## Abstract

The development of cardiovascular diseases with atherosclerotic origin is associated with a severe inflammatory process. Neutrophils and lymphocytes are cells sensitive to this type of disorder and their ratio, known as the NLR (neutrophil/lymphocyte ratio), has shown to be useful in clinical practice. The aim of this study was to assess the role of NLR in cardiovascular disease risk assessment. We carried out a literature review in the PubMed databases searching for articles published between 2001 to 2017 and found that NLR is in fact a useful marker for cardiovascular disease. Using NLR in patients at cardiovascular risk would be useful to delineate the prognosis of patients with this disease pattern.

## Introduction

Among the diseases that affect humans, those related to the cardiovascular system warrant great prominence.[1,2] Currently, these diseases account for more than 17 million deaths worldwide each year, and the estimate for 2030 is that this figure will reach 23.6 million, with acute myocardial infarction being the most common cause of these deaths.[3,4]

Very often, this cardiac event is associated with the appearance of atheroma plaques lodged in the intima layers of the coronary arteries, triggering inflammatory processes. This risk factor may be diagnosed by the concentration/amount of inflammatory markers found in the peripheral blood, such as neutrophils and lymphocytes.[4,5]

## Keywords

Cardiovascular Diseases / physiopathology; Biomarkers; Neutrophils; Leukocyte Count; Atherosclerosis / physiopathology; Inflammation.

Considering the potential of these different cell types, i.e., neutrophils and lymphocytes, in the genesis and evolution of atheroma plaques, the neutrophil/lymphocyte ratio (NLR) has a high diagnostic potential for cardiovascular diseases. Neutrophil and lymphocyte analyses are simple, relatively inexpensive, and widely available.[6] Therefore, this review aimed to discuss the importance of NLR and its inclusion in the list of useful tools for the diagnosis/prognosis of atheroma-related heart disease.

## Atherogenesis and the Neutrophil/Lymphocyte Ratio

As shown in figure 1, endothelial dysfunctions related to atherosclerotic plaques are usually associated with states of neutrophilia, together with lymphopenia processes. The antagonism between inducing and protective factors of inflammatory processes favors the onset of injuries in the vascular endothelium, as well as the onset of atherosclerosis.

The body is exposed to systemic stress in the immunological lack of control due to the inflammatory process related to cardiovascular diseases, increasing the levels of cortisol and catecholamines, so that the lymphocytes are affected by this imbalance, weakening its role in modulating the inflammatory response.[7-9]

Infarcted patients have elevated cortisol levels. This increase induces the reduction of lymphocytes by apoptosis, and CD4+ and CD8 cells become more sensitive to tumor necrosis factor-alpha (TNF-α).[10] This is one of the most likely mechanisms to explain lymphopenia developed during cardiovascular disease evolution. However, the pathophysiological mechanism of this decrease has not yet been fully elucidated.[9]

On the other hand, mechanisms related to neutrophilia in cardiovascular diseases are more clarified,

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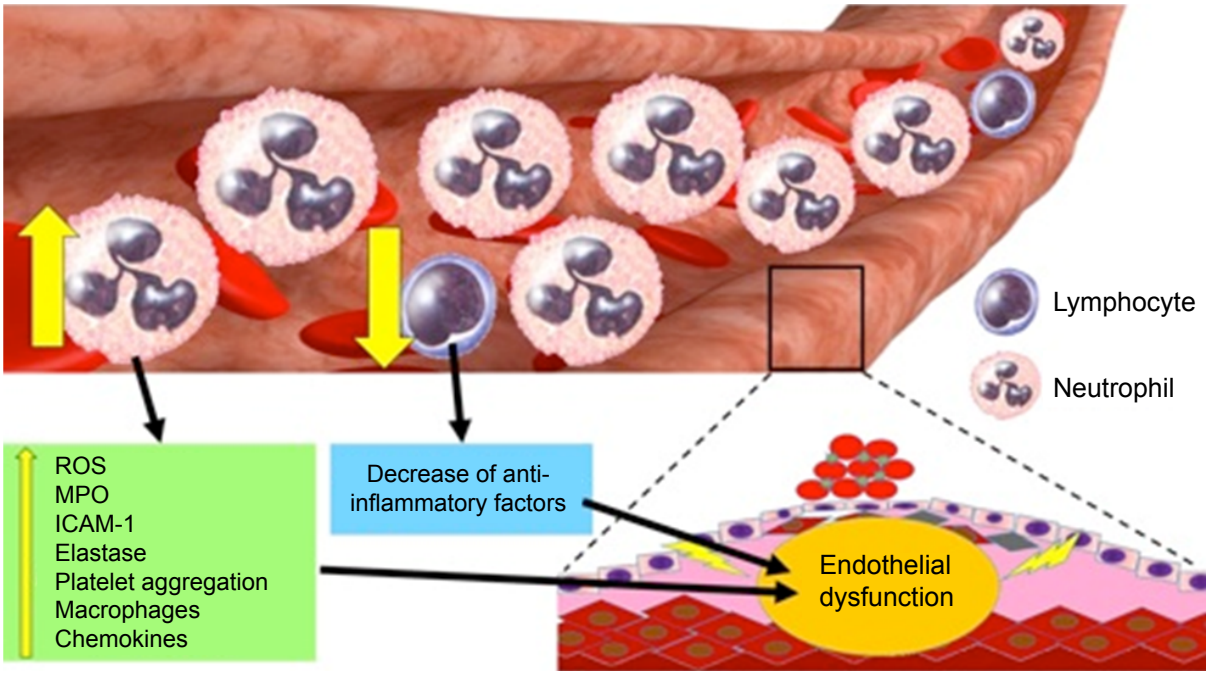


**Figure 1 - Pathological mechanisms triggered by neutrophils and lymphocytes during the evolution of cardiovascular diseases. As the neutrophil / lymphocyte ratio increases, there is an association with the pathophysiological mechanism of endothelial dysfunction. Pro-inflammatory factors are derived from increased numbers of neutrophils (green frame), while the attenuation of anti-inflammatory factors is the result of decreased lymphocytes.**
*ROS: reactive oxygen species; MPO: myeloperoxidase; ICAM-1: intercellular adhesion molecule-1. Source: Santos e Izidoro.*

especially in atherosclerosis. Neutrophils are related, since the initial phase, to a more advanced stage of atherosclerosis, participating in the inflammatory process as a hyperlipidemia mediator, until the development of atherothrombosis, infiltrating the atherosclerotic arteries.[11]

In such pathophysiological circumstances, it seems that the increase in neutrophils is associated with the maturation stage of these cells, exhibiting nuclear segmentation.[10,12-15] Therefore, it is more likely that the predominant neutrophilia originates from the segmented cell type, since atherosclerosis is a chronic inflammatory condition,[16,17] as well as the process of thrombosis.[18,19]

The neutrophils activate the macrophages, acquiring the lipid mediation function. Subsequently, macrophages express atherogenic factors, such as interleukin-6 (IL-6), CD40 and CD80, in addition to being susceptible to foam cell formation.[7,8,20-25] The neutrophil cells, themselves, also express atherogenic factors, such as chemokines and cytokines.[11]

When myocardial tissue damage occurs, leading to inflammation, neutrophils are highlighted, releasing arachidonic acid metabolites, chemokines, reactive oxygen species (ROS), intercellular adhesion molecules-1 (ICAM-1), platelet factors and several enzymes, such as myeloperoxidase (MPO) and elastase, facilitating the rupture of the atherosclerotic plaque by weakening the fibrotic layer, and the matrix ends up being degraded.[3,11,26]

MPO, an enzyme abundantly expressed in primary neutrophil granulocytes, is one of the most impacting components of endothelial dysfunction, as it limits nitric oxide and, through its catalytic activity, promotes the formation of oxidized low-density lipoprotein (LDL). Thus, subsequently, macrophages phagocyte the oxidized LDL, forming the foam cells.[11]

## Pathological mechanisms originating from neutrophils and lymphocytes during cardiovascular diseases

Epidemiological evidence has shown the predictive role of NLR in atherosclerotic manifestations.[27-30] The states of lymphopenia disclosed by the whole blood count are associated with atherosclerosis progression, and the decrease in lymphocytes may be caused by apoptotic

processes triggered during atherosclerotic lesions.[27] On the other hand, the quantitative increase in neutrophils is also related to the atherogenic process, acting through lipid mediation, necrosis and inflammation, secreting chemokines and cytokines. This cell type regulates ICAM-1 and expresses MPO, a protein that contributes to the formation of free radicals, promoting greater LDL oxidation, exacerbating the pathological process.[11] Based on the interpretation of the NLR results, it is possible to predict the presence of atherosclerotic processes before the coronary angiography is performed.[28,31]

Additionally, this tool is useful to help attain a diagnosis of acute myocardial infarction more quickly and can be used in emergency situations in medical care units.[32]

The NLR is commonly increased in patients with coronary disease when compared to healthy patients. Neutrophil values and NLR are also correlated with the number of noncalcified atherosclerotic plaques, as shown by coronary assessment through angiotomography and invasive angiography.[30] Patients with total coronary occlusion also have a higher NLR value, being significantly more pronounced than in patients with normal coronary arteries ($p < 0.001$).[33]

In a study of 194 volunteers with coronary artery disease submitted to coronary angiography,[19] those with severe atherosclerosis had higher neutrophil and lower lymphocyte percentages when compared to patients with mild atherosclerosis and normal individuals, and the NLR was higher than 2.5 in these conditions.

Recently, computed tomography coronary angiography studies have shown that increased NLR is associated with the presence, severity, and extent of atherosclerotic plaques in coronary arteries. A higher white cell and neutrophil counts and a lower absolute lymphocyte count were observed in the patients. A value of NLR higher than 2.25 increased the likelihood of developing coronary atherosclerosis (OR = 2.30) and critical luminal stenosis (OR = 2.60).[17]

The detection of obstructive coronary disease and coronary calcium score was significantly higher in type 2 diabetic patients with NLR higher than 2.05, when compared to patients with type 2 diabetes and NLR lower than or equal to 2.05.[34] In a retrospective study, it was observed that of 2,121 patients diagnosed with peripheral obstructive arterial disease and with NLR higher than 3.95, 680 of them had a higher percentile of acute myocardial infarction (48.5%) increase, previous myocardial infarction (7%) and cerebrovascular accident (10%), when compared to patients with NLR < 3.95. Thus, the NLR higher than 3.95 was associated with an OR of 2.5 for acute myocardial infarction and showed higher levels of C-reactive protein (mean 5.6 mg/L) and high plasma fibrinogen levels (mean 412 mg/dL).[35]

## Neutrophil-lymphocyte ratio in cardiovascular diseases

In a meta-analysis involving ten cohorts, a higher relative risk (RR) of all-cause mortality was observed, due to the elevation of the NLR levels when compared with low levels (RR = 2.33), as well as of cardiovascular events in patients submitted to angiography or cardiac vascularization (RR = 1.89).[3] In an observational cohort containing 2,833 patients hospitalized with acute coronary syndromes, it was detected that NLR elevations are associated with higher chances of in-hospital mortality (OR = 2.04).[26]

In decompensated heart failure, of 1,212 individuals, patients with a higher tertile of NLR, showing a mean of 9.6, had an increase in the mortality rate during an average follow-up of 26 months. Nevertheless, the highest tertile of NLR was associated with older age, systemic arterial hypertension, diabetes mellitus, history of coronary artery disease and arterial fibrillation. In the blood sample analyses, the highest NLR tertile was associated with the increase in B-type natriuretic peptide, urea, serum creatinine and hemoglobin levels. Consequently, the chest x-ray examination showed that the highest tertile of the NLR was associated with a higher incidence of cardiomegaly, pleural effusion and interstitial edema.[36]

When analyzing a cohort of 3,005 patients for 3 years, it was evident that NLR values higher than 3 are associated with high chances of fatal coronary artery disease (OR = 2.45), as well as with the rate of major cardiovascular events (Hazard Ratio - HR = 1.55).[29]

Considering the NLR and the presence of troponin in peripheral blood in the analysis of 244 patients with chest pain treated at the emergency department, a high correlation was found between high NLR and high plasma troponin levels when acute myocardial infarction was confirmed. In those cases in which troponin was positive, the mean NLR was 5.49. On the other hand, negative troponin results showed a mean a NLR of 2.40.[32]

A meta-analysis of 21 studies, including more than 34,000 patients, showed that neutrophilia causes NLR imbalance, favoring the development of cardiovascular

disorders compatible with acute myocardial infarction, unstable angina, acute coronary syndrome, heart failure development or aggravation, cerebrovascular accident, and even increased mortality.[30]

### Perspectives: association of the neutrophil-lymphocyte ratio with several diseases and need for laboratory reference

Heart disease pathophysiological processes are associated with the hemodynamic and inflammatory imbalance of other diseases, such as kidney and intestinal diseases.[37,38] For instance, concerning kidney diseases, the mean NLR value of 4.59 in patients submitted to hemodialysis with a diagnosis of atherosclerotic plaques was associated with greater common carotid artery intima-media thickness and higher cardiovascular mortality than patients undergoing hemodialysis but without atherosclerotic plaques, who had a mean NLR of 2.38.[39]

The association between inflammatory bowel diseases such as Crohn's disease and ulcerative colitis and heart disease is probably due to the processes of atherosclerosis and thrombotic events, which lead to an increase in NLR.[40] The imbalance of the lipid profile caused by inflammatory bowel diseases reflects in the decrease of HDL levels and function, in addition to inducing an increase in the levels of LDL, C-reactive protein, pro-inflammatory cytokines, endotoxins, homocysteine and coagulation factors. Therefore, such organic conditions favor endothelial dysfunction, with the onset of the atheroma plaque and other cardiovascular diseases, and an increase in NLR is expected.[41]

Moreover, NLR may be used as a marker of clinical follow-up in cancer cases, which involve significant changes in inflammatory responses concomitantly with the immune system. NLR as a ratio ≥ 5 being considered elevated was significantly correlated with larger tumor size in patients with advanced esophageal squamous cell carcinoma than patients with NLR < 5.[42] The NLR cutoff value ≥ 5 also reflected a lower response to Kawasaki disease therapy than patients with NLR < 5, which is associated with coronary abnormalities.[43] Furthermore, two meta-analyzes have also shown that the NLR increase is significantly associated with larger tumor size and lower overall survival in patients with cervical cancer.[44,45] The NLR was also considered a new prognostic marker in patients with liver cancer.[46]

Due to the importance represented by recent studies regarding NLR in the prognosis for cardiovascular diseases[39,43,47-49] and its association with other inflammatory diseases,[42,44,45,50] establishing a laboratory reference specific for the NLR is promising. Differences in demographic classifications, such as classifications by age group and gender, should be considered.

## Conclusion

The genesis of atherosclerotic processes, as well as other diseases associated with inflammatory processes, directly influence the neutrophil/lymphocyte ratio; thus, the NLR emerges as an auxiliary tool mainly in the prognosis of atherosclerosis-related cardiac disorders. The use of this ratio can help the physician to stratify patients into different categories of risk for cardiovascular disease development. It can be easily incorporated into the laboratory routine and it practically does not involve additional costs. However, it is necessary to standardize NLR cutoff points for this type of disorder, as well as in other disease processes.

## Author contributions

Conception and design of the research and writing of the manuscript: Santos HO, Izidoro LFM; Acquisition of data and analysis and interpretation of the data: Santos HO; Critical revision of the manuscript for intellectual content: Izidoro LFM.

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REVIEW ARTICLE

# Cardiovascular Complications of HIV

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## Abstract

With the advent of the antiretroviral therapy (ART), people infected with HIV are experiencing a significant increase in life expectancy. However, as this population ages, the morbidity and mortality due to events not related to HIV infection and/or treatment become increasingly clear. Cardiovascular diseases are among the major causes of death, and, thus, understanding the factors that trigger this situation is necessary. This review article will assess how the intrinsic and extrinsic factors related to HIV, ART and the associated risk factors can aid the epidemiological transition of mortality in this population. Moreover, we will present the studies on the epidemiology and pathogenesis of each clinical condition related to HIV-infected individuals, in addition to introducing the major markers of cardiovascular disease in this population. Finally, we will point the main issues to be addressed by health professionals for an adequate prognosis.

## Introduction

Since the first case reported, HIV infection has become a worldwide public health problem. Over 36 million people are estimated to be infected with HIV, and approximately 1.1 million deaths were attributed to that infection in 2015. In addition, by the end of 2015, more than 2.1 million new cases were identified.[1]

Pharmacological strategies have been created aimed at reducing HIV replication in infected individuals. The pharmacological intervention was monotherapy with zidovudine (AZT), which inhibits the action of reverse transcriptase.[2] Later, in the mid-1990s, antiretroviral therapy (ART) was introduced, significantly changing the course of HIV infection, with consequent increase in the life expectancy and quality of life of infected individuals.

Although essential to treat HIV infection, ART is associated with several side effects. The most studied impairments are those related to the metabolism of glucose and lipids, and the lipodystrophy syndrome.[3,4]

This set of changes has affected the mortality of those individuals. Previous studies have confirmed that their causes of death are associated with diseases not related to HIV, but to ART.[5] The major causes are neoplasms and cardiovascular diseases.

This review was aimed at summarizing the studies on cardiovascular diseases and their risk factors in HIV-infected people.

## Keywords

Cardiovascular Diseases; HIV; Acquired Immunodeficiency Syndrome; Acute Retroviral Syndrome/therapy; Inflammation Mediators.

## Cardiovascular diseases in HIV-infected people

Traditional cardiovascular risk factors are known to be directly related to mortality in the general population.[6] In HIV-infected people, some risk factors, such as smoking habit and use of illicit drugs, can be more frequent than in the non-infected population.[7,8] In addition, the infection per se can pose a higher risk of cardiovascular disease because of the adverse effects of the continuous use of ART.[9,10]

One of the major characteristics of the relationship between HIV and cardiovascular disease is the higher carotid intima-media thickness. This condition of subclinical atherosclerosis is directly associated with modifiable risk factors, except for the male sex.[11] One possible explanation for that characteristic is associated with ART effects on the lipid metabolism, with increased LDL-c, triglycerides and total cholesterol.[12]

Regarding the modifiable risk factors and mortality in HIV-infected people, the smoking habit, arterial

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hypertension and diabetes were independently associated with a higher risk for death during ART.[13] Such findings show the immediate need to create resources to raise that population's awareness about those risk factors.

Of the cardiovascular diseases that affect HIV-infected people undergoing ART, ischemic and non-ischemic myocardial diseases stand out.[14,15]

## Ischemic cardiovascular diseases

Regarding the ischemic diseases that affect HIV-infected people, acute myocardial infarction stands out. In addition, the incidence of sudden cardiac death of HIV-infected patients is significantly higher as compared to that of the general population with similar risk factors.[16]

In the D:A:D study, acute myocardial infarction accounted for more than 50% of the causes of death due to cardiovascular diseases, followed by stroke.[13] In addition, as age advantages, the mortality rate due to those causes increases from 0.27 per 1,000 among young people to 16.99 per 1,000 in people aged over 70 years.[17] Corroborating those data, the mortality due to acute myocardial infarction of HIV-infected people was shown to be as much as three times higher than that of people of their same age.[18,19] According to a recently published study, HIV-infected people are at a higher risk for cardiovascular diseases as compared to the general population of the United States. In addition, seropositive males develop a higher risk of cardiovascular diseases throughout life, while women are at lower risk as compared to the general population of the United States.[20]

Of the risk factors associated with acute myocardial infarction in HIV-infected people, the following are worth noting: age, male sex, smoking habit, hypertension, diabetes mellitus, dyslipidemia, moderate to high Framingham score, and use of protease inhibitors for at least 18 months.[19,21]

## Disorders of the heart's electrical conduction system

People with HIV infection have a change in the heart's electrical conduction system. The major findings have shown a prevalence of prolonged QT interval on the electrocardiogram ranging from 28% to 65%.[22,23] In addition, regardless of the autonomic dysfunction or ART, there is a greater risk for ventricular arrhythmias and mortality due to prolonged QT interval in HIV-infected patients on combined ART.[24]

Moreover, autonomic cardiac dysfunction has been shown in that population. Individuals infected with HIV undergoing ART have increased sympathetic activity and a consequent increase in heart rate variability, shown by the heart rate values at rest.[25,26] Those data indicate an autonomic system imbalance, in which the sympathetic activity overlaps the parasympathetic activity.

## Pulmonary hypertension

Pulmonary hypertension related to HIV has a conflicting epidemiology. In developing countries, its prevalence ranges from 0.6% to 13%, while in developed countries, it is 0.5%.[27,28] Pulmonary hypertension related to HIV can occur in any stage of the infection and associates with neither CD4+ cell levels nor viral load.[29] The most frequent symptom of pulmonary hypertension is dyspnea, but other symptoms, such as lower limb edema, syncope, fatigue, dry cough and chest pain, can be reported.[30] For individuals classified as NYHA functional class III-IV, the prognosis tends to be unfavorable, with a survival time of three years.[31]

Although there is no cure, the condition can be treated. The options include support treatment, such as oxygen therapy, diuretics and oral anticoagulants, and specific medications for pulmonary hypertension, such as prostaglandins, endothelin receptor antagonists and calcium channel blockers.[30] Special care should be taken regarding the interaction between ART and the medications for pulmonary hypertension, mainly calcium channel blockers.

## Cardiomyopathy

With the advent of ART, cardiomyopathy became frequent in HIV-infected people. The prevalence of systolic and diastolic dysfunction is approximately 8.3% and 43.3%, respectively.[32] In addition, myocarditis and dilated cardiomyopathy are observed in that population. Cardiomyopathy is associated with the increase in mortality caused by heart failure,[33] and is usually associated with socioeconomic status, long use of ART, low lymphocyte count (mainly CD4+ cell), high viral load and low serum level of selenium.[34]

The assessment of HIV-infected individuals with cardiomyopathy should follow the recommendations for the general population. However, factors that can require specific therapies, such as opportunistic diseases, cardiotoxic drugs and coronary artery disease, should be investigated.[35]

## Pericardial disease

Pericardial disease is the most common heart disease among HIV-infected individuals. One of the major risk factors for its development is opportunistic infection, mainly tuberculosis.[36] Pericardial disease can be caused by opportunistic diseases, being used as a marker of progression of HIV infection, because it associates with a shorter survival.[37]

## Markers of cardiovascular diseases in HIV-infected individuals

Some markers that are directly related to cardiovascular mortality in HIV-infected people can be measured and, therefore, used in clinical practice. Regarding inflammation, interleukin (IL)-6 and C-reactive protein stand out.[38] In HIV-infected people, those markers are increased by 50% to 152% as compared to those of non-infected individuals.[39,40] In addition, they are associated with all-cause mortality, including that due to cardiovascular diseases.[41,42]

Of the thrombolytic factors, fibrinogen and D dimer stand out. Those markers are increased by 8% to 94% in HIV-infected people as compared to those in the non-infected population. In addition, they correlate directly with viral load (amount of HIV RNA copies) and all mortality causes.[40,43,44]

The endothelial function is measured by use of the vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM). Those molecules relate directly to the viral load and consequent cardiovascular death, because they affect more than 40% of the arterial lumen of HIV-infected patients.[43,45,46]

Finally, it is worth noting that the HDL-c concentrations, which are reduced by 13% to 21% in HIV-infected people as compared to non-infected people, are inversely related to the viral load and directly related to cardiovascular mortality.[39,47]

## Dyslipidemia

In HIV-infected people, undergoing or not ART, the change in the lipid profile can promote the atherosclerotic process and increase the risk for cardiovascular diseases.[11] Thus, in clinical practice, it is important to understand how the factors inherent in infection and in treatment can trigger changes in the lipid profile.

The HIV infection per se causes changes in the lipid profile. The HIV viremia increases the serum concentrations of triglycerides and LDL-c.[48] Studies on the mechanisms of how HIV causes dyslipidemia are scarce. However, factors, such as an exacerbated inflammatory profile, reduced lipid clearance and increased hepatic vLDL-c synthesis, can be an explanation.[49,50]

Another triggering factor of dyslipidemia in HIV-infected people is the use of ART. The drug increases the concentrations of triglycerides, LDL-c and total cholesterol. Although initially associated with the use of protease inhibitors, some studies have shown that nucleoside analog and non-nucleoside analog reverse transcriptase inhibitors can trigger that condition.[51-53] The mechanisms of how the ART causes dyslipidemia have not been totally clarified, but the binding site seems to have high affinity with the catalytic site of the HIV protease, thus, binding and inhibiting the homologous protein involved in the lipid metabolism, inducing an increase in the blood concentrations of that substance.[54]

## Metabolic syndrome

Metabolic syndrome (MS) is characterized by the presence of hyperglycemia or diabetes mellitus, altered blood pressure or systemic arterial hypertension, abdominal obesity and dyslipidemia.[55,56] Metabolic syndrome has been reported to relate to morbidity and mortality worldwide, mainly because of complications involving the cardiovascular system.[57,58] Epidemiological studies have shown that the incidence of MS in HIV-infected people ranges from 18% to 50%.[59-61]

Some factors are known to be fundamental for the diagnosis of MS in HIV-infected people. Conditions related to the infection, ART, adipose tissue distribution and dyslipidemia seem to stand out.[62-64]

One of the major side effects of ART is the lipodystrophy syndrome, characterized by lipoatrophy (reduced adipose tissue) of the upper and lower limbs and face, with lipohypertrophy (increased adipose tissue) in the central and cervical regions. As a consequence, the waist circumference increases, but for HIV-infected patients this criterion seems not to be fundamental for the diagnosis of MS.[65] Finally, the adipose tissue accumulation in the central region of the body can lead to other disorders, such as insulin resistance and cardiovascular diseases.

## Glucose metabolism disorder

Diabetes mellitus is a systemic disease caused by an insulin and/or glucose metabolism disorder. Although the

risk factors for its development in HIV-infected people are similar to those in the general population, epidemiological studies have reported a prevalence of type 2 diabetes mellitus in HIV-infected people ranging from 3% to 14%.[66-70] In addition, 35% to 63% have insulin resistance.[71-74]

Diabetes mellitus can relate to the development of other diseases in HIV-infected people, such as neurocognitive changes, kidney failure and albuminuria.[75] In addition, it associates with an increased risk for cardiovascular diseases and consequent mortality.[76]

The mechanisms leading to type 2 diabetes mellitus in HIV-infected people remain to be explained. However, type 2 diabetes mellitus is known to be directly related to the accumulation of adipose tissue, an increase in proinflammatory cytokines (mainly TNF-alpha), and, thus, insulin resistance.[77,78] Therefore, physical exercise and/or dietary reeducation programs become important to prevent and treat that condition.

## Future perspectives

Based on that information, programs of cardiovascular disease prevention are required. A recent study has suggested the use of cardiovascular disease stratification and prevention programs.[79] Thus, multidisciplinary care should be encouraged to significantly reduce the side effects of ART, and, consequently, ART-related mortality.[80]

## Conclusion

The risk factors for cardiovascular diseases of HIV-infected people are similar to those of the general population. However, because of HIV infection and its treatment, those individuals are at higher risk for cardiovascular morbidity and mortality. In addition, the mechanisms by which HIV and ART lead to cardiovascular diseases are yet to be explained. Finally, prevention should be the first step to reduce the incidence of that type of disease in that population.

## Author contributions

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### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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BRIEF COMMUNICATION

# The Influence of Comorbid Conditions on Graft Stenosis in Patients with Coronary Artery Bypass Graft Operation

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## Abstract

The primary goal of coronary artery bypass grafting is to achieve complete revascularization with grafts that will remain patent throughout the patient's lifetime. This study investigated the association between bypass graft patency and comorbidity burden determined by Charlson comorbidity index (CCI) among patients with previous bypass operation who underwent a control angiography. One-hundred and two patients who had undergone CABG in the past were included to the study. Critical stenosis was defined as 50% or greater coronary luminal obstruction of any coronary vessel or its lateral branch. Patients were divided into 2 groups group 1; critical graft stenosis; (54 pts; 41M, mean age 66.5 ± 7.8 years), group 2; graft patent (48 pts; 31M, mean age; 65.9 ± 8.2 years). Charlson comorbidity index (CCI) and modified CCI scores were used for detecting comorbidities. The comparison of continuous variables between the control and critical CAD groups was performed by the independent sample test. A p value less than 0.05 was considered statistically significant. The two groups were statistically similar with respect to demographic properties, time since bypass operation, cardiovascular risk factors, systolic blood pressure, heart rate, medications used, complete blood counts parameters, and lipid profiles. CCI was significantly higher in Group 1 compared to Group 2 (7.14 ± 2.02 vs 4.72 ± 1.58; $p < 0.001$). Modified CCI scores were also higher in Group 1 than in Group 2 (6.14 ± 2.02 vs 3.73 ± 1.60; $p < 0.001$). Graft occlusion was more common among patients with a high comorbidity burden. CCI scoring system may be helpful for determining patients at increased risk at both the preoperative and postoperative periods.

## Keywords

Coronary Artery Disease; Myocardial Revascularization; Coronary Stenosis; Comorbidity; Vascular Patency.

## Introduction

Coronary artery bypass grafting (CABG) operation remains an important procedure despite advances in percutaneous transluminal coronary angioplasty.[1] The ultimate goal of CABG is to ensure the long-term symptom-free patency of bypass grafts.[2] It is known that graft patency is dependent on several factors such as operative factors, graft selection, vessel diameter, postoperative medication use, and patient compliance.[3] Charlson comorbidity index (CCI) is a global index obtained from a cohort of general medical patients that is widely used to detect comorbidities among various populations.[4] This study investigated the association between bypass graft patency and comorbidity burden determined by CCI in patients with previous bypass operation who underwent a control angiography procedure for any reason.

## Methodology

One hundred and two patients with a history of CABG after presenting with acute coronary syndrome or who underwent coronary angiography for any reason were included in the study (72 M, 30 F; mean age 66.2 ± 7.9 years). Coronary angiography was performed in all patients due to stable angina pectoris (SAP), unstable angina pectoris (UAP), non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI). A monoplane angiography system (Artis Zee, Siemens Erlangen, Germany) was used for all coronary angiography procedures. Critical stenoses were

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defined as 50% or greater coronary luminal obstruction affecting any coronary vessel or its lateral branch. The stenosis percentage was defined through the consensuses of two separate operators. Charlson co-morbidity index (CCI) and modified CCI score (calculated by subtracting 1 point from the original CCI score) were used to detect comorbid conditions. The patients were categorized into two groups based on severity of bypass graft stenoses. Group 1 consisted of 54 patients with critical graft stenoses (41 men, 13 women; mean age 66.5 ± 7.8 years), and group 2 of 48 patients (31 men, 17 women; mean age 65.9 ± 8.2 years). Detailed patient history was taken from each patient, and data on demographic characteristics, medications, systolic and diastolic blood pressure and heart rate were recorded. Fasting blood glucose levels, lipid profile, renal and hepatic function tests were obtained from venous blood samples taken at the time of admission. All patients underwent transthoracic echocardiography to quantify ejection fraction and left ventricular diameters. The local ethics committee approved the study.

### Statistical analysis

All statistical analyses were carried out using SPSS for Windows 13.0. The Kolmogorov-Smirnov test was used to test the normality of quantitative data distribution. The Chi-square test and Fisher's Exact Chi-Square test were used to compare categorical variables between the groups. The comparison of continuous variables between the control and critical coronary artery disease (CAD) groups was performed by the independent sample test when the parametric test assumptions were met and by Mann-Whitney U test when the parametric test assumptions were not met. The association between time since the bypass operation and scores were analyzed by Pearson's/ Spearman correlation analysis. The statistical significance was set at $p < 0.05$ and the confidence interval at 95%.

## Results

The two groups were statistically similar with respect to demographic properties, time since bypass operation, cardiovascular risk factors, systolic blood pressure, heart rate, medications used, complete blood counts parameters, and lipid profiles (Table 1). CCI score were significantly higher in Group 1 compared to Group 2 (7.14 ± 2.02 vs 4.72 ± 1.58; $p < 0.001$). Modified CCI score was also higher in Group 1 than in Group 2 (6.14 ± 2.02 vs 3.73 ± 1.60; $p < 0.001$). There was no correlation between time since bypass operation and CCI score.

## Discussion

CABG is a globally recognized procedure that not only cures angina pectoris, but also improves cardiac functions and life expectancy. Saphenous grafts were initially used for the procedure, which were later followed by internal thoracic and radial arteries.[5] Saphenous veins are the most commonly used conduits, 50% of which remain patent without flow-limiting stenoses by 10 years. Early graft restenosis is a process characterized by the activation of various molecular pathways and cellular components, and the simultaneous activation of hemostatic systems with endothelial dysfunction and oxidative stress ultimately results in the appearance of a systemic inflammatory response.[6] During the intermediate and long terms, on the other hand, intimal hyperplasia and superimposed atherosclerosis are the main responsible mechanisms for graft occlusion.[7]

In a large-scale study from the Cleveland Clinic, the main factors causing reoperation were a young age at operation and graft type; other factors include incomplete revascularization, higher NYHA functional class, ventricular dysfunction, and single- or two-vessel disease at the initial operation.[8] In a study by Goldman et al.,[9] the main factors determining long-term graft patency included graft type (internal mammary artery - IMA - better than venous grafts), left anterior descending artery – LAD - being the bypassed vessel, and bypassed vessel being larger than 2 mm. Desai et al.[10] showed that radial artery grafts had an important effect on long-term graft patency, which was more pronounced among women. They also demonstrated that the diameter of the bypassed vessel and bypass grafting proximal stenoses were determinants of bypass patency.

In our study, the mean time since bypass operation was 7.6 ± 4.3 years. Patients who had occluded bypass grafts more commonly had saphenous grafts. There were no differences between patients with and without graft occlusion with respect to graft type, time since bypass, risk factors, and medications. However, CCI and modified CCI scores were significantly higher in the graft occlusion group. Despite similar demographic characteristics and risk factor profiles, the significant difference between the CCI scores may have contributed to the restenosis process.

**Table 1 - Demographic, laboratory, echocardiographic parameters and Charlson comorbidity indices of the groups. (Data with normal distribution were expressed as mean ± SD, and data with abnormal distribution were expressed as min-max; median)**

| | Occluded graft (n = 54) | Patent graft (n = 48) | p |
|---|---|---|---|
| Age (years) | 43 - 89; 66.5 | 47 - 83; 66 | 0.72 |
| Gender (M, n) | 44 | 31 | 0.06 |
| Systolic blood pressure (mm Hg) | 90 - 190; 127 | 90 - 180; 130 | 0.87 |
| Diastolic blood pressure (mm Hg) | 78.5 ± 12.2 | 78.0 ± 11.0 | 0.85 |
| Heart rate (beat/min) | 58 - 114; 82 | 53 - 106; 78 | 0.18 |
| SAH (n) | 39 | 32 | 0.65 |
| DM (n) | 25 | 19 | 0.55 |
| Family history of CAD (n) | 13 | 12 | 0.86 |
| Hyperlipidemia (n) | 31 | 30 | 0.51 |
| Smoking (n) | 11 | 9 | 0.67 |
| Duration (years) | 1 - 23; 8 | 2 - 22; 7.5 | 0.97 |
| Total cholesterol (mg/dL) | 105 - 289; 185 | 129 - 351; 210 | 0.11 |
| Triglyceride (mg/dL) | 56 - 641; 140 | 62 - 507; 184 | 0.22 |
| HDL (mg/dL) | 45.9 ± 11.7 | 44.6 ± 12.8 | 0.65 |
| LDL (mg/dL) | 114.1 ± 40.1 | 123.1 ± 42.9 | 0.32 |
| CCI | 7.1 ± 2.0 | 4.7 ± 1.6 | < 0.001 |
| Modified CCI | 6.1 ± 2.0 | 3.7 ± 1.6 | < 0.001 |
| Occluded IMA (n) | 4 | - | |
| Occluded saphenous graft (n) | 50 | - | |
| Occluded radial graft | 0 | - | |
| EF (%) | 45.0 ± 8.2 | 46.9 ± 9.9 | 0.36 |
| Beta blocker (n) | 29 | 18 | 0.41 |
| ACEI (n) | 46 | 39 | 0.42 |
| Statin (n) | 25 | 20 | 0.13 |
| Nitrate (n) | 6 | 2 | 0.33 |
| Diuretic (n) | 12 | 9 | 0.95 |
| OAD (n) | 20 | 18 | 0.23 |
| Insulin (n) | 7 | 5 | 0.43 |

*Abbrevations: M: male, SAH: sstemic arterial hypertension, DM: diabetes mellitus, CAD: coronary artery disease, HDL: high density lipoprotein, LDL: low density lipoprotein, CCI: Charlson comorbidty index, IMA: internal mammary artery, EF: ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; OAD: oral antidiabetic drugs.*

## Conclusion

Graft occlusion is more common among patients with a high comorbidity burden. Our opinion is that considering comorbid conditions along with conventional atherosclerotic risk factors at the preoperative and postoperative periods would have a favorable impact on graft patency among patients undergoing bypass surgery. The CCI scoring system may be helpful to identify patients at increased risk at both the preoperative and postoperative periods.

## Author contributions

Conception and design of the research: Karabag T. Acquisition of data: Karabag T, Sahin B, Coskun E, Somuncu UM, Cakir MO. Analysis and interpretation of the data: Karabag T, Somuncu UM. Writing of the manuscript: Karabag T, Kalayci B, Coskun E, Cakir MO. Critical revision of the manuscript for intellectual content: Kalayci B, Coskun E. Supervision / as the major investigador: Karabag T.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any thesis or dissertation work.

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CASE REPORT

# Persistent Primitive Hypoglossal Artery Associated with Brain Stem Ischemia in an Elderly Patient

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## Introduction

The primitive hypoglossal artery (PHA) crosses the hypoglossal canal, being one of the four vessels that acts as anastomosis between the primitive dorsal aorta and longitudinal neural arteries. The PHA typically retracts 40 days after pregnancy but may persist in some situations.[1]

Direct anastomoses between the basilar and carotid arteries are rare.[1-3] These vessels retreat during the fortieth day of fetal development, when the emergence of the posterior communicating arteries occurs.[1] Among these primitive communicating vessels are the trigeminal, the primitive hypoglossal, the proatlantal and the ophthalmic vessels.[1,2,4] The persistence of the primitive hypoglossal artery has an incidence of 0.01% to 0.03%, being the second most frequent among the four vessels.[4-6]

Persistent PHA (PPHA) occurs when it emerges at the level of C1 to C3 and enters the posterior fossa, crossing the hypoglossal canal, and ending at the basilar artery.[4] The posterior communicating artery is hypoplastic or absent. The diagnosis may be attained through angiotomography and angiography assessments.[1]

## Case report

An 80-year-old man, a patient with systemic arterial hypertension and diabetes mellitus, had malaise with lipothymia for two days, and therefore sought medical assistance. After he showed no improvement, he returned to the emergency unit a few days later, with persistent symptoms of dysarthria and apathy, as well as right hemiparesis. During his clinical evolution, he showed worsening of the condition and homolateral dysmetria.

Initially, the patient was diagnosed with left-sided cerebrovascular accident (CVA) in the brainstem, with diffusion restriction disclosed by a skull MRI (Figure 1A). Subsequently, the carotid and vertebral Doppler showed the following findings: calcified plaques in both carotid bulbs with approximately 50% of bilateral obstruction and preserved flow in both vertebral arteries.

In the angiotomography of the carotid and vertebral arteries, PHA persistence was shown combined with the basilar artery (Figures 1B and 1C), as well as atherosclerotic arterial disease with slight carotid bulb lumen reduction on the right and moderate on the left.

In most cases, PPHA occurs only as an incidental finding at an examination indicated for other reasons. It is important, however, to be aware that when a carotid endarterectomy is intended for some other reason, there are some risks in the presence of such condition. Among these are the high carotid exposure and the challenges of maintaining cerebral perfusion.[1]

In our case, the patient developed brainstem CVA, with subsequent hemorrhagic transformation. At the angiotomography, the patient showed the presence of mixed plaque, affecting the distal end of the left common carotid, bulb and ostium of the internal carotid artery, generating moderate luminal reduction of the internal carotid on this side. He also showed signs of contralateral carotid bulb atherosclerotic disease. This fact is described in the literature,[6] according to which patients with persistent hypoglossal artery have high risks of atherosclerotic disease and cerebrovascular accidents, as well as subarachnoid hemorrhage and aneurysms.

## Keywords

Cerebrovascular Disease, persistent primitive hypoglossal artery; primitive arteries, carotid-basilar anastomoses, Arteriosclerosis.

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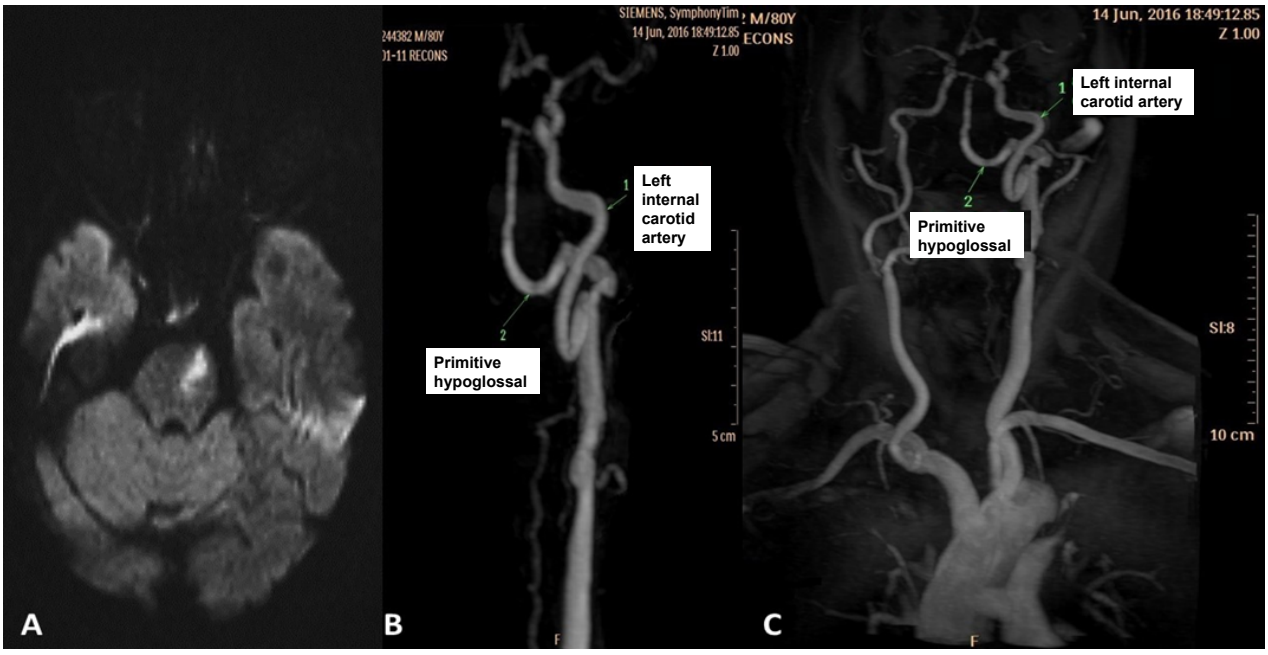


**Figure 1 - (A) Magnetic resonance showing diffusion restriction in the brain stem on the left. (B) Angiotomography with MIP reconstruction and bone subtraction, demonstrating the emergence of the hypoglossal artery and the left internal carotid artery. (C) Comparative image between the two carotid arteries and the emergence of the primitive hypoglossal on the left.**

PPHA is often identified in imaging tests; however, in the presence of atherosclerotic disease, it may be of clinical importance due to the increased chance of developing cerebral infarction.[6,7] Associated with this condition, the passage of emboli from the internal carotid artery to the vertebrobasilar system becomes possible.[8]

Our patient did not receive dual antiplatelet therapy due to the hemorrhagic transformation of the CVA and was submitted to an expectant conduct, as recommended by the literature.[9] The drainage of bulky hematomas is essential for the maintenance of life, but more discrete hemorrhagic events can be followed without major interventions,[9] as in this case.

## Conclusion

The above case report showed the clinical importance of the persistence of primitive arteries, more specifically the primitive hypoglossal artery, in a context of cerebrovascular accident and its consequences.

## Author contributions

Conception and design of the research: Souto RM, Santos AASMD, Nacif MS. Acquisition of data: Souto RM, Nacif MS. Analysis and interpretation of data: Souto RM, Nacif MS. Writing of the manuscript: Souto RM, Nacif MS. Critical revision of the manuscript for intellectual content: Souto RM, Santos AASMD, Nacif MS.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

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CASE REPORT

# Monomorphic Ventricular Tachycardia as the First Manifestation in a Patient with Anomalous Coronary Artery

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## Introduction

Coronary artery anomalies comprise a heterogeneous group of rare congenital heart defects, being classified according to their origin, course and distal bed, with an incidence ranging between 0.3% and 1.5% in the overall population. Dodge-Khatami et al.[1] subdivided them into seven categories, according to their clinical complexity: coronary arteries originating from the pulmonary artery, coronary arteries with anomalous aortic origin, congenital atresia of the left main coronary artery, coronary arteriovenous fistulas, coronary arteries forming myocardial bridges, coronary artery aneurysms and coronary stenosis. The Texas Children's Hospital classification uses angiotomography with virtual angioscopy and divides the classification into three topics: origin of the anomalous coronary artery, coronary artery course and ostium morphology. From the viewpoint of anatomical risk, the anomalous left coronary artery with an interarterial course, presence of intramurality and a slit-like ostium are the main predictive factors of severity.[1-3]

A specific type is the anomalous origin of the left coronary artery from the right coronary sinus with an interarterial course, which is associated with hard outcomes in approximately 60% of the cases.[2] Clinically, patients may present with nonspecific symptoms, ranging from palpitations, chest pain, post-exertion syncope or remain asymptomatic throughout life, with sudden death being the first and only manifestation of this condition.[4]

Most cases have been reported in young male individuals, but there is no scientific evidence yet whether the incidence is actually higher in males, or if this gender is more often diagnosed by performing more intense physical activities, therefore triggering symptoms.

The most common of these conditions is the anomalous origin of the left coronary artery from the pulmonary artery. However, we present herein a case with an anomalous origin of the left coronary artery from the right coronary sinus, with a proximal course between the aortic and the pulmonary arteries in a 31-year-old man.

## Case report

A previously healthy 31-year-old male patient, a mason, was admitted to the Emergency Unit in October 2012, complaining of palpitations and cold sweats, with hypotension (BP = 90 x 50 mmHg), which developed into syncope at the hospital unit. He was submitted to the first electrocardiogram (Image 1A), which disclosed sustained monomorphic ventricular tachycardia (SMVT). He underwent electrical cardioversion and was transferred to intensive care unit (ICU) for clinical stabilization.

Therapy with amiodarone was started in the ICU, with some episodes of slow ventricular tachycardia (VT) and periods of accelerated idioventricular rhythm (Image 1B), albeit asymptomatic. He reverted to sinus

## Keywords

Arrhythmias, Cardiac; Tachycardia, Ventricular; Coronary Vessel Anomalies; Death. Sudden, Cardiac.

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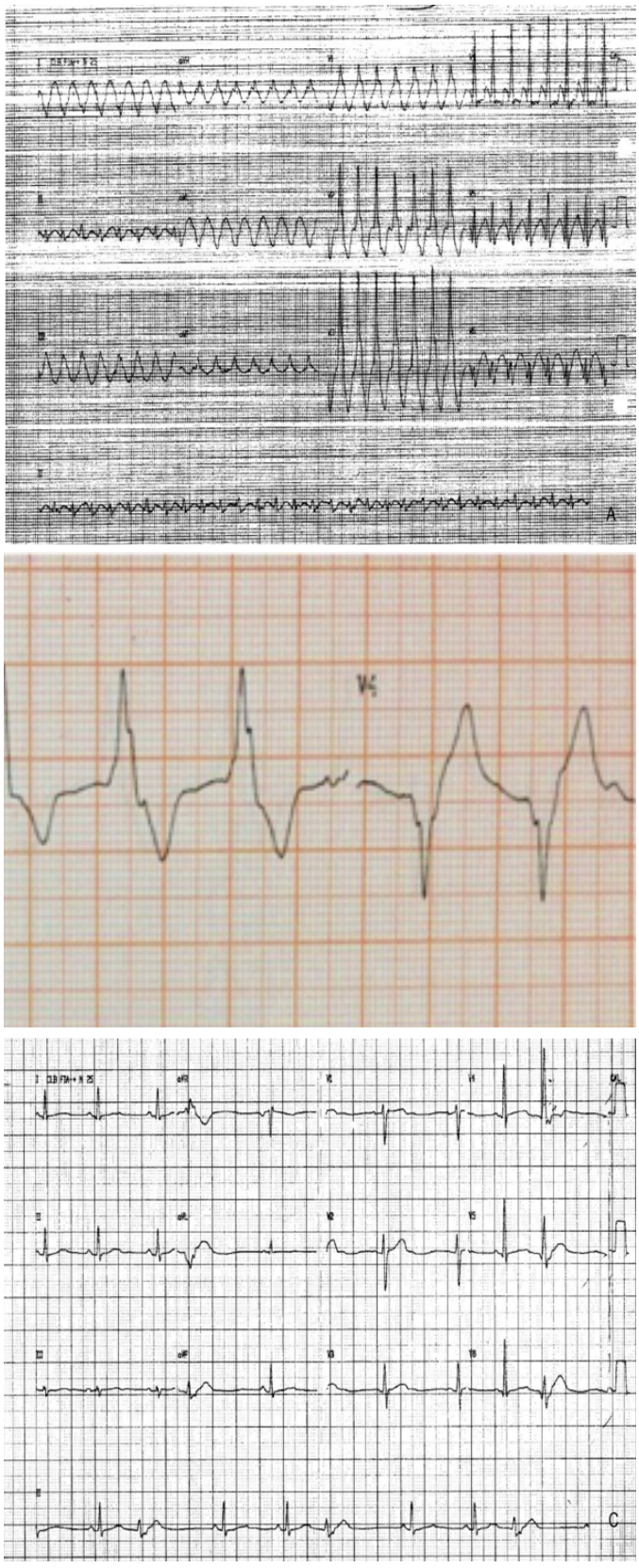

**Figure 1 - A - Sustained monomorphic ventricular tachycardia. B - Accelerated idioventricular rhythm. C - Sinus rhythm with isolated ventricular extrasystoles.**

rhythm (Image 1C) after 24 hours and the etiological investigation was initiated with a transthoracic echocardiogram, which disclosed only mild and diffuse left ventricular impairment. The exercise testing and magnetic resonance imaging of the heart showed no alterations, and serologic tests for Chagas' disease and cardiac markers were negative.

Acute myocarditis was suspected, which would have lead to the VT and a tachycardiomyopathy caused by the time he remained on sustained VT.

The patient received amiodarone, carvedilol, captopril and spironolactone, remaining asymptomatic and being followed at the outpatient clinic in the following months, without complications.

Ventricular function was normal at the transthoracic echocardiography and exercise testing at 3 and 6 months after the event, without arrhythmias or myocardial ischemia. As there was no symptom recurrence, even after the patient returned to his work routine, amiodarone was withdrawn.

However, without the antiarrhythmic drug, a new event was triggered in December 2014, which led the patient to once again seek the emergency care unit with palpitations and cold sweats. The VT was reverted again with electrical cardioversion, and the patient returned to the cardiology outpatient clinic for assessment. An angiotomography was then requested, which disclosed the anomalous origin of one of the coronary arteries (Figure 2). The diagnosis was confirmed after a coronary angiography, which concluded that the left coronary artery originated from the right coronary artery, coursing between the pulmonary artery and the aorta (interarterial course). With the anatomical definition of the condition, the surgical correction was chosen, using an internal mammary artery graft to the anterior descending and circumflex arteries, with the left main coronary artery ligation being successfully performed. The patient has been followed for 2 years, with no new episodes of VT and no medication.

## Discussion

Ventricular arrhythmias comprehend a spectrum that range from ventricular extrasystoles, VT, to ventricular fibrillation. Ventricular fibrillation is the one most frequently associated with acute coronary syndrome. On the other hand, the SMVT has as its electrophysiological mechanism of re-entry related to scarring due to structural heart disease (e.g., previous infarction and Chagas' disease). In the younger population - children, adolescents, and young adults - with sustained episodes of VT, the condition is usually due to diseases that manifest early in life, including genetically-determined arrhythmias, acute myocarditis, and congenital heart disease – among the latter, coronary artery anomalies.[5]

Congenital anomalies of the coronary arteries may result in benign or malignant clinical consequences depending on their course and origin.[2] They are usually classified into four groups: according to the coronary origin and course (absent left main coronary artery, anomalous location of the coronary ostium inside or outside the appropriate Valsalva sinus, anomalous location of the coronary ostium in the inappropriate Valsalva sinus and single coronary artery); intrinsic to the coronary anatomy (stenosis or atresia of coronary ostia, coronary aneurysm, coronary hypoplasia and myocardial bridge); anomalies of terminal coronary circulation (fistulas into cardiac chambers, inferior vena cava or pulmonary arteries and veins); and anomalous anastomotic vessels.[2]

The anomaly described in this case is that of the left coronary artery originating from the right coronary sinus, a rare congenital abnormality, with a prevalence of 0.15% in the overall population.[6] This anomalous coronary artery is most commonly related to sudden death (59% of cases), usually preceded by physical activity (in 81% of these cases). The cases in which the coronary artery courses between the aorta and pulmonary (interarterial) arteries, as described in the reported patient, are the ones most often associated with severe outcomes.[6] One of the potential mechanisms that explains this fact is the coronary artery compression by the aorta and the pulmonary trunk during exercise, leading to myocardial ischemia.[2,7,8] When only the origin is anomalous, but the coronary artery does not follow this course, there is no risk of sudden death.[4] In general, the pre-pulmonary, subpulmonary or retroaortic courses are considered benign.[3,4]

In general, most patients remain asymptomatic or exhibit symptoms only after strenuous physical exercise, which may have a fatal outcome in these cases. Clinical presentation ranges from palpitations, dyspnea, chest pain and syncope to sudden death,[4,6,7] being the second leading cause of sudden death in young individuals.[2,6] Basso et al.[8] reported that only ten (36%) of the 27 cases with sudden death (23 anomalous left coronary arteries and four right coronary artery anomalies from the

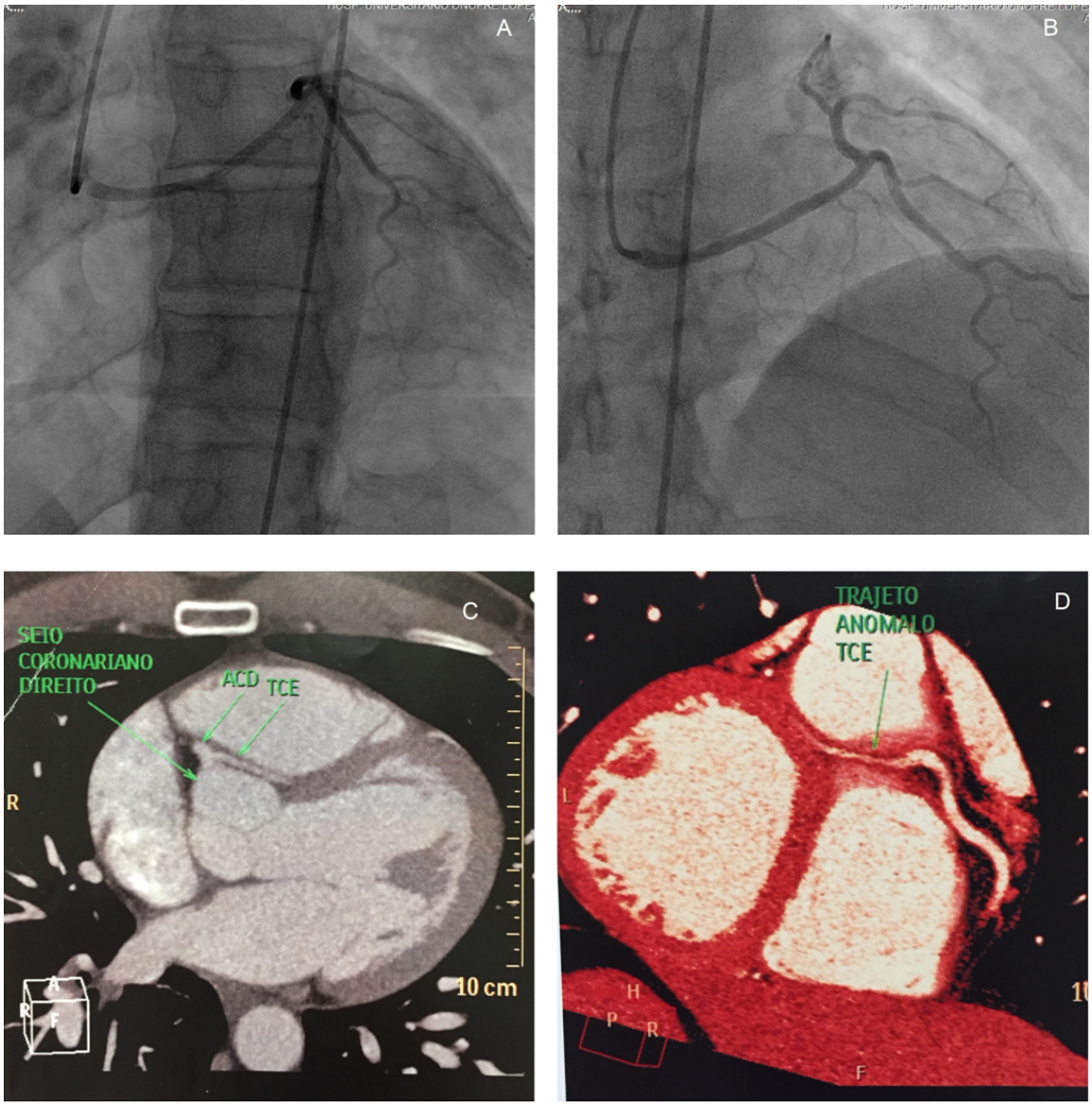


**Figure 2 - A, B, C - Images showing the left coronary artery anomalous origin, from the right coronary artery. D - Coronary angiotomography showing the left coronary artery interarterial course.**

opposite Valsalva sinus) had symptoms before the event, including syncope, chest pain and palpitations. All cases had an acute-angled outflow and a slit-like ostium.[8]

Due to the varied and nonspecific symptomatology, clinical suspicion and detailed investigation are necessary. Thus, a 12-lead electrocardiogram, exercise testing and an echocardiogram are suggested for the initial approach of symptomatic patients, which in some cases may suggest the diagnosis or disclose another cause for the symptoms.

Subsequently, a coronary angiotomography and a coronary angiography should be performed for diagnostic confirmation.[7] In cases of symptomatic patients, surgical revascularization is the therapeutic indication, especially when the left coronary artery originates from the opposite coronary sinus and courses between the aorta and the pulmonary artery, due to the risk of coronary compression by the larger-caliber vessels.[4,9] There is no consensus regarding the treatment of the anomalous anatomy with no evidence of ischemia or with an intramural course

or ostium anomaly.[9] The management tends to be more conservative, with the use of beta-blockers and changes in lifestyle, aiming to avoid strenuous physical exercises.

Therefore, the anomalous origin of the coronary artery is a group of rare congenital cardiac malformations with variable presentation. Due to the possibility of a lethal prognosis, it is necessary to identify the target population to establish screening methods to attain an early diagnosis of the anatomical alteration. Because it is more frequently associated with sudden death, a protocol should be established for young individuals practicing highly competitive sports or those subject to strenuous physical activities, aiming to prevent such an outcome. The diagnosis should always be recalled in cases of ventricular tachyarrhythmias[10] with no other apparent cause, being a challenge for clinical practice, since this is a silent condition, but with definitive surgical treatment.

## Author contributions

Conception and design of the research: Sousa JCV, Miranda RM, Silva PMN, Madruga GM, Figueiredo NMS, Farias DC. Acquisition of data: Miranda RM, Silva PMN, Madruga GM, Figueiredo NMS, Farias DC. Analysis and interpretation of the data: Sousa JCV, Miranda RM, Silva PMN, Madruga GM, Figueiredo NMS, Farias DC. Writing of the manuscript: Miranda RM, Silva PMN, Madruga GM, Figueiredo NMS, Farias DC. Critical revision of the manuscript for intellectual content: Sousa JCV. Supervision / as the major investigador: Sousa JCV.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Sources of Funding

There were no external funding sources for this study.

### Study Association

This study is not associated with any thesis or dissertation work.

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# NEWS

## Calendar

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Maceió (AL)
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Salvador (BA)
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