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Cardiovascular Reviews

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Table of Contents

1 **Cardiovascular and Diabetes Risk in Preschoolers**
Martha Nydia Ballesteros-Vásquez, Saraí García-Gámez, Elizabeth Artalejo-Ochoa, Bianca Vargas-Tequida, José Antonio Ponce-Martínez, Alma Elizabeth Robles-Sardin, María Isabel Grijalva-Haro

10 **A Case of Renal Hemorrhage After Mitral Valvuloplasty for Active Infective Endocarditis with Renal Infarction**
Atsushi Matsumoto, Shota Yasuda, Tomoki Cho, Yusuke Matsuki, Yoshiyuki Kobayashi, Kaori Mori, Keiji Uchida

17 **Importance of Cardiac Rehabilitation in Patients with Structural Heart Changes Secondary to Ankylosing Spondylitis: A Case Report**
Myllena Lemes Scardino Vieira, Tamires Mota Toni, Claudio Spinola Najas

24 **Dilated Cardiomyopathy in a Patient with Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)**
Julieta Lozita, Judith Mailén Vicentín, María Florencia Melgarejo Otarola, Jorge Andrés Paolasso, Roberto Miguel Ángel Colque, Pablo Ezequiel Sarmiento

30 **Comparison of the Effect of Clopidogrel and Ticagrelor on the Development of No-Reflow Phenomenon After Percutaneous Coronary Intervention in Patients with Acute Myocardial Infarction**
Emrah Yeşil, Hakan Uyar, Özcan Örsçelik, Buğra Özkan, Ahmet Çelik, İsmail Türkay Özcan, Mehmet Necdet Akkuş

40 **Clinical Effects of Insulin Glargine and Acarbose Tablets in the Treatment of Diabetes Mellitus in the Elderly and Analysis of Glycosylated Hemoglobin**
Hua Lu

46 **Analysis of the Clinical Effects of Clopidogrel in the Treatment of Unstable Angina and the Influence of Triacylglycerol and Total Cholesterol Levels**
Yuzhen Ning, Huailu Yang, Lian Shuang

52 **New Progress of Clinical Application of Nicorandil in the Treatment of Coronary Heart Disease**
Lingbo Wang, Chengguo Wang

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Cardiovascular and Diabetes Risk in Preschoolers

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Abstract: *Objective:* To perform an exploratory analysis of possible alterations in clinical markers of cardiovascular risk and type 2 diabetes in preschoolers living in urban and suburban areas of the municipality of Hermosillo, Sonora, Northwest Mexico. *Methods:* An observational and cross-sectional study was carried out on children from urban and suburban areas. Their weight, height, waist circumference, body fat percentage, and blood pressure were measured, and their lipid profile, glucose, and insulin concentrations were evaluated. *Results:* Eighty-two children with an average age of five were included in the study; 48 from the conurbation and 34 from the urban area. We found that malnutrition, overweight, and high body fat percentage (27 ± 0.52) coexist. In the suburban area, there was a higher percentage of children with pre-hypertension and alterations in lipids: elevated triglycerides (35%) and low HDL-c (25%) ($p < 0.01$). In the urban area, there was a higher percentage of children with altered glucose (12%), elevated insulin concentrations, and insulin resistance. *Conclusion:* The findings of this study show that cardiovascular risk factors and type 2 diabetes are prevalent in children aged three to six living in urban and conurbation areas of Hermosillo, Sonora.

Keywords: Preschool children; Malnutrition; Lipids; Glucose; Insulin; Risk factors; Cardiovascular disease; Obesity; Type 2 diabetes; Mexico

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1. Background

The obesity epidemic has reached the child population worldwide, thus necessitating the evaluation of risk factors for non-communicable diseases, such as type 2 diabetes and cardiovascular diseases, in school children. Thus far, investigations have shown that school children exhibit physical and metabolic changes associated with obesity, including alterations in blood lipid and markers of glucose metabolism [1]. Genetics, diet, and physical inactivity are implicated in its early onset [2].

Some studies suggest that excess weight gained before the age of five may persist into adulthood ("persistent obesity") [3,4]. Although obesity is uncommon in children or adolescents with cardiovascular disease, the risk factors that precipitate atherosclerosis can be observed in children as young as four [5].

Serum lipid and lipoprotein concentrations increase during early childhood at approximately two years of age and reach those observed in young adults [6-8]. Epidemiological studies have shown that if blood lipid concentrations are altered in childhood, there is a high risk of atherosclerotic lesions in adulthood [9]. Other research has established that blood lipids in children are correlated with obesity and insulin resistance [10].

Previous studies by our working group carried out in the Sonora population have confirmed overweight and obesity in children aged six to nine, as well as metabolic syndrome in urban (7%) and rural (5%) areas.

Diet and physical inactivity are the two main factors involved [11].

In Mexico, the problem does not seem to be confined to school children. According to the National Health and Nutrition Survey [12], 14.1% of children under five years of age are overweight and obese, and alterations in cardiovascular risk markers, such as lipid profile, can be observed, suggesting that cardiovascular diseases begin at an earlier age in this population.

The objective of this study was to perform an exploratory analysis of possible alterations in the clinical markers of cardiovascular risk and type 2 diabetes in preschoolers living in urban and conurbation areas of the municipality of Hermosillo, Sonora, northwestern Mexico.

2. Materials and methods

An observational and cross-sectional study was carried out on children from urban and suburban areas of Hermosillo, Sonora. This research is part of the Follow-up Studies of the School Breakfast Program in Sonora that is carried out every year at the Research Center for Food and Development A.C. Participating schools were randomly selected from a census of preschools belonging to the School Breakfast Program.

Inclusion criteria: children between three and six years of age, without respiratory disease, fever, or diarrhea; having taken all the measurements and informed consent signed by parents or legal representatives who agreed to participate (the objective of the study and the inherent benefits and risks of their children's participation were clearly detailed in accordance with what was stated and approved by the interinstitutional ethics committee of CIAD A.C.). Children who did not meet these criteria were excluded from the study.

2.1. Anthropometry, body fat, and blood pressure

Body weight and height were measured according to the procedure described by Jeliffe *et al*. [13]. The World Health Organization's Anthro software, version 3.2.2, was used to calculate the BMI z-score for age (z-BMI/E) [14]. Waist circumference was measured with a fiberglass tape measure (Lafayette Instrument, USA), considering the midpoint between the last rib and the iliac crest. Central obesity was considered to be a value more than or equal to the 90th percentile, according to sex and age, for the Mexican-American population [15]. Body fat was measured by electrical bioimpedance, with the IMP5™ equipment (Impedimed IMP5™ Impedimed Pty. Ltd., Australia). Body fat mass was calculated using the equation generated by Ramirez and his co-authors [16]. Blood pressure was measured with a mercury baumanometer (Desk Model Mercurial Sphygmomanometer, Model 100, USA), following the criteria of the National High Blood Pressure Education Program (NHBPEP) for children and adolescents [17].

2.2. Plasma lipid, glucose, and insulin

After fasting for 12 hours, 5 ml of blood was drawn from the median cubital vein. Plasma and red blood cells were separated by 2400 x g centrifugation. Total cholesterol and triglycerides were measured with commercial CHOD-PAP (Roche Diagnostics) and GPO-PAP (Roche Diagnostics) kits, respectively. High-density lipoprotein cholesterol (HDL-c) was determined in the supernatant after lipoprotein precipitation with Apo B (Roche Diagnostics); low-density lipoprotein (LDL-c) was calculated using the equation described by Friedewald and others [18]. Daniels and Greer's percentiles and cut-off points were used to classify lipid profile values [19]. Fasting glucose was measured by using the GOD-PAP glucose oxidase method (Roche Diagnostics), in which a value greater than 100 mg/dL was considered impaired fasting [20]. Insulin was determined by sandwich immunoassay (ELISA) with a commercial reagent kit (ALPO Insulin Diagnostics, NH, USA), using the reference values proposed by García-Cuartero and his group [21].

In order to reveal the characteristics of the population, the normality of the data was verified (19 quantitative variables using Kolmogorov-Smirnov, Shapiro-Wilks W, Anderson-Darling, D'Agostino tests), and descriptive statistics were performed, grouped by urban and conurbation areas. The data were

presented as mean ± standard deviation and as median and interquartile ranges, respectively. Student's t-test for independent samples was used to test the differences between groups, and the Mann Whitney U test was used for non-normal variables. In order to test the differences by body fat content (normal, moderate, and high), an analysis of variance (ANOVA) was used. In both analyses, the differences were considered significant with $p \leq 0.05$. The data were analyzed by using the statistical program NCSS 2007 (Number Cruncher Statistical System for Windows, Kaysville, Utah, USA).

3. Results

Eighty-two preschoolers aged three to six were evaluated from two different geographical areas of Hermosillo, Sonora; 34 from different neighborhoods in the urban area (13 girls and 21 boys), and 48 from the suburban area, including Poblado Miguel Alemán and the town of El Tazajal (25 girls and 23 boys).

Table 1 shows the data obtained on physical growth and metabolic profile, according to the study area. Preschoolers in the urban area had significantly higher concentrations of total cholesterol, glucose, insulin, and homeostatic model assessment for insulin resistance (HOMA-IR) ($p < 0.05$). In contrast, the mean age and waist circumference were higher in preschoolers from the conurbation area ($p < 0.05$).

Table 1. Physical characteristics, body composition, and biochemical-clinical variables of preschool children from urban and conurbation areas of Hermosillo, Sonora, Mexico

Parameter	Total (n=82)	UA (n=34)	CUA (n=48)	*p*
Age** (years)	5.07 (4.6–5.2)	4.9 (4.0–5.2)	5.1 (4.7–5.4)	0.05
Weight** (kg)	16.7 (15.6–18.6)	16.4 (15.7–18.6)	16.8 (15.2–18.9)	0.75
Height* (cm)	105.5 ± 5.0 (93.9–118.6)	105.5 ± 5.2 (97–118.6)	105.6 ± 5.0 (93.9–116.6)	0.93
Z–P/E*	–0.4 ± 0.9 (2.4–2.2)	–0.3 ± 0.8 (–2.4–1.8)	–0.5 ± 1 (–2.4–2.2)	0.28
Z–T/E*	–0.7 ± 1 (–3.0–2.1)	–0.5 ± 0.9 (2.6–2.1)	–0.9 ± 1.0 (3.0–1.0)	0.07
Z–IMC	–1.6 ± 0.8 (–1.7–2.6)	–0.0 ± 0.7 (–1.7–1.6)	0.0 ± 0.9 (–1.5–2.6)	0.81
Waist circumference**	50.15 (48.1–52.8)	49.1 (47.4–51.2)	51.1 (46.9–53.4)	0.03
Fat % (BIE)*	22.2 ± 5.9 (7.1–41.1)	21.6 ± 6.37 (7.1±34.8)	22.6 ± 5.5 (11.7–41.1)	0.45
PAS**	80 (70–87.5)	80 (72.5–90)	80 (70–84.3)	0.18
PAD**	50 (41.8–57.5)	51.2 (42.5–60)	50 (40–55)	0.75
TG (mg/dL)**	86.7 (44–189)	85.4 (44–189)	87.2 (49.2–187.4)	0.41
CT (mg/dL)*	114.3 ± 26.5 (64.4–196.1)	121.6 ± 26.6 (65.4–196.1)	109 ± 25.25 (64.4–169.2)	0.05
LDL–c (mg/dL)*	58.2 ± 25.2 (139–127.8)	62.1 ± 26 (18.6–127.8)	55.5 ± 24.5 (13.9–108.4)	0.24
HDL–c (mg/dL)**	37.8 (17.2–89.1)	40.93 (30.3–53.4)	35.76 (17.2–89.1)	< 0.01
Glucose (mg/dL)*	82.3 ± 14.0 (49–123)	87.9 ± 15.3 (67–123)	78.4 ± 11.2 (49–103)	< 0.01
Insulin, µIU/L (n=63)	2.45 (0.07–28.7)	3.5 (0.05–28.7)	1.87 (0.01–18.1)	< 0.01
HOMA-IR** (n=63)	0.49 (0.01–4.7)	0.75 (0.06–4.7)	0.36 (0.01–2.1)	< 0.01

*Mean ± standard deviation; **median (interquartile range [25–75]); UA: urban area; CUA: conurbation area; % fat (BIE): percentage fat by electrical bioimpedance; TC (mg/dL): total cholesterol; TG (mg/dL): triglycerides; HDL-c (mg/dL): high-density lipoprotein cholesterol; LDL-c (mg/dL): low-density lipoprotein cholesterol; SBP (mmHg): systolic blood pressure; DBP (mmHg): diastolic blood pressure [1]. The difference between groups was tested by using student's test for two independent samples, and Mann–Whitney U was used for non-normal data ($p < 0.05$).

3.1. Alterations in body composition and clinical indicators

In both study areas and age groups, stunted growth was observed (children aged three to five in the urban area = 5.8%; conurbation area = 5.2%; children older than five in the conurbation area = 17.2%). Only one

case of impairment was found in a child under five years of age in the urban area.

In addition, "risk of overweight," "overweight," and elevated waist circumference were observed (**Table 2**). In the conurbation area, there was a higher proportion of children under five years of age who were overweight and with elevated waist circumference (≥ 90 percentile; Fernandez and his group) [15] as well as elevated body fat percentage [22].

Table 2. Alterations in body composition and biochemical markers in preschoolers by study area

Classification	Reference value	3-5 years		≥ 5 years	
		UA (n=19)	CUA (n=17)	UA (n=29)	CUA (n=17)
Overweight$^{\Delta}$	BMI/E > 1DE	ND	10.5%	11.7%	7.1%
Elevated waist circumference*	> 90 percentile	11.7%	21%	5.8%	6.8%
Elevated body fat**	> 26% children > 34% girls	ND	ND	5.8%	6.8%
		UA (n=34)	CUA (n=48)		
High triglycerides$^{¥}$	> 85 mg/dL	30%	35%		
High total cholesterol$^{¥}$	> 200 mg/dL	3%	ND		
High LDL-c$^{¥}$	110–129 mg/dL	6%	ND		
Very low HDL-c$^{¥}$	38 mg/dL (≤5 percentile)	6%	25%		
Altered glucose$^{\delta}$	> 100 mg/dL	11.7%	2%		
High insulin$^{\delta}$	90 percentile/age	20%	2.6%		
HOMA-IR$^{\delta}$	90 percentile/age	16%	ND		
Pre-hypertension (diastolic)$^{\theta}$	90–94 percentile	41%	27%		
Pre-hypertension (systolic)$^{\theta}$	90–94 percentile	ND	6%		
High diastolic blood pressure$^{\theta}$	> 99 percentile	ND	4%		
High systolic blood pressure$^{\theta}$	> 99 percentile	ND	2%		

Abbreviations: CUA, conurbation area; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; UA, urban area.

In terms of clinical markers (**Table 2**), approximately 30% of the children had elevated triglycerides, above the 95th percentile (85 mg/dL) [19]. In contrast, their HDL-c levels were low (38-43 mg/dL), especially in the conurbation area, where there was a higher proportion of children with very low concentrations (≤ 5th percentile = 38 mg/dL).

More markedly, in the urban area, glucose and insulin alterations were found with cases of insulin resistance. Blood pressure measurements showed that in both areas, there were children with elevated normal diastolic blood pressure, a clinical condition called pre-hypertension [17]. Joint cases of diastolic and systolic hypertension were only observed in the conurbation area.

In both areas, there were cases of hypoglycemia (urban area = 8.8%; conurbation area = 27%) and pre-diabetes (urban area = 11.8%; conurbation area = 2%). Likewise, among the preschoolers studied (n=82), 9.5% had elevated insulin levels (≥ 90th percentile = 10.63 μIU/mL), indicating that this condition is more prevalent in the urban area (20% versus 2.6%) ($p < 0.01$). Insulin resistance was found in 6.3% of the total population studied [21].

An exploratory comparison analysis revealed some significant differences between sexes. Girls in the urban area had higher body fat percentage (24% ± 6.7 versus 20% ± 5.6) ($p \leq 0.05$) and triglyceride concentration (95.8 versus 71.9 mg/dL) ($p < 0.01$) than boys. In the conurbation area, girls had higher insulin and HOMA-IR values than boys ($p < 0.05$). An analysis of association between the variables showed

that there is a correlation between body fat percentage and waist circumference in both study groups (urban area, r = 0.71; $p < 0.01$; conurbation area, r = 0.64; $p < 0.01$).

The majority of children older than five years of age had normal body fat content (urban area = 64.7%; conurbation area = 72.4%) ($p < 0.01$); however, cases with moderate (urban area = 29.4%; conurbation area = 17.2%) and high (urban area = 5.8%; conurbation area = 10.3%) body fat content were also noted [22]. Using the body fat classification as a reference [22], possible changes in the biomarkers were evaluated, showing that children with moderate and high body fat percentages tend to have higher systolic and diastolic blood pressure, glucose, total cholesterol, LDL-c, as well as triglycerides.

4. Discussion

This study was carried out in the city of Hermosillo, Sonora, among preschool children living in urban and suburban areas. The global analysis of physical growth, considering P/E and T/E indicators, shows that approximately 10% of preschool children between three and five years of age and 6.8% of children older than five years of age have impaired growth. With regard to this, the WHO [23] points out that undernutrition during the first years of life can increase the risk of chronic non-communicable diseases in adulthood.

In addition, stunted growth was detected, and children at risk of overweight (conurbation area = 10.5%; urban area = no cases) and overweight (conurbation area = 15.7%; urban area = 5.8%) were observed. In their analysis of the issues of overweight and obesity in preschool children worldwide, De Onis and her colleagues reported a prevalence of overweight risk of 14.4% globally and 13.6% for developing countries [24]. The overweight risk figure observed in this study is 1.5% higher than those reported worldwide. Our findings also highlight that the area around the city of Hermosillo is the most affected by overweight issues, and it is noteworthy that no cases of obesity were found in the study areas (> 3 SD). The national report for this age group revealed that the combined prevalence of overweight plus obesity in urban areas and rural areas was 14.1% and 8.7%, respectively. Our overweight results are very similar to this report; however, a direct comparison is not feasible because the reference used employs combined prevalence.

A high proportion of children in both age groups and study areas had waist circumference values above the 90th percentile. In children older than five years of age, a concordance was found between the proportion of children with elevated waist circumference and that of children with elevated body fat percentage [22]. Considering the limitations that may exist due to the lack of percentile references for our population, it can be assumed that a portion of these children's body fats accumulates around the viscera. Excess fat accumulated before puberty is associated with increased blood lipid concentrations, and thus increased risk of chronic degenerative diseases [25].

The results obtained from the growth indicators point to a preschool population, in which undernutrition and overweight coexist, especially in the urban area; the double burden of malnutrition is evident. It has been shown that malnutrition in childhood is a marker of premature chronic diseases in adulthood, such as diabetes and cardiovascular disease [26]. It is important to consider that at this stage of life, overweight can be a factor favoring atherosclerosis that will manifest itself as cardiovascular disease in adulthood.

In accordance with the pediatric recommendations for lipid profiling suggested by Daniel and Greer [19], this study shows that the preschool population evaluated had elevated plasma triglycerides (95th percentile = 85 mg/dL) and low HDL-c concentrations (5th percentile = 38 mg/dL). Both indicators are considered independent cardiovascular risk factors, as well as being part of the metabolic syndrome. Blood lipids are influenced by genetics, diet, and physical activity.

This study did not evaluate any of these variables and hence cannot explain the influence of any of these factors on the alterations found. Epidemiological studies have shown that if blood lipid concentrations are altered during childhood, atherosclerotic lesions will eventually occur in adulthood [9].

HDL particles have antioxidative properties (PON1 enzyme) that prevent the oxidation of LDL particles, and thus atherosclerosis [27]. In this study, 25% of the children in the suburban area and 5.8% in the urban area had values below the 5th percentile of HDL-c, a condition referred to as hypoalphalipoproteinemia. It is also important to highlight that most of the children were below the 10th percentile (43 mg/dL) (conurbation area = 54%; urban area = 50%), suggesting that this population may have very low antioxidant protection against LDL-c and also less capacity to catabolize stored cholesterol, which could lead to the onset of fatty streak formation at a young age.

The clinical pattern of elevated triglycerides and low HDL-c (86.7 mg/dL and 37.8 mg/dL) agrees with that reported by Reaven and his co-authors for the Mexican-American school population (84.6 mg/dL and 47 mg/dL) [28]. Additionally, with previous studies carried out in the same region but among school children aged six to twelve, in whom the same pattern of alterations was observed, Ramirez found a similar lipid pattern, characterized by metabolic syndrome, in rural (5%) and urban (7.4%) areas [11].

The findings of this study are significant as they show that the alterations in blood lipids that had been previously reported in school children and adults in the same region can be observed in preschool age. The alterations at this age also suggest that there may be a genetic factor involved [29].

Another important risk factor for cardiovascular disease is arterial hypertension, which is associated with other factors such as overweight, obesity, physical inactivity, and high lipid concentrations [2]. In this study, only those in the conurbation area were found to have diastolic (4%) and systolic (2%) hypertension; however, according to the National High Blood Pressure Education Program Working Group 17 (NHBPEP 17), a large proportion of preschoolers have diastolic prehypertension. A previous study by our group reported 12% prevalence of hypertension in school children in this same area. The proportions reported in this study are smaller but are significant since the issue is detected at an even earlier age.

Fasting glucose and insulin concentrations, as well as the HOMA-IR values were significantly higher in the urban area ($p < 0.01$). Children with impaired glucose had a mean value of 116 mg/dL, where the highest value recorded was 123 mg/dL in the urban area, which received medical attention for a possible diagnosis of diabetes. The elevation of insulin observed in the children (urban area = 20%; conurbation area = 2.6%) suggests possible metabolic compensation in the attempt to normalize glucose concentration [30].

According to the diagnostic criteria of Garcia and his group [21], children, in the urban area, have insulin resistance with HOMA-IR values above the 90th percentile. Both, insulin and insulin resistance coincide with the findings of altered glucose, indicating possible impairments in glucose metabolism that could trigger type 2 diabetes at an earlier age [20]. Acanthosis nigricans, which is associated with hyperinsulinemia, was also looked for in this study, especially in the neck region, but no cases were found. The data for two additional variables, birth weight and type of birth (cesarean section or delivery) (conurbation area n = 37; urban area n = 29), were also recorded when possible. Of the total number of records obtained for each case, the average birth weight was as follows: conurbation area = 3417 ± 568 g; urban area = 3259 ± 579 g (p = 0.2). In the conurbation area, 21% of the children were macrosomic (birth weight greater than 4 kg), and 78% were delivered without complications. In contrast, in the urban area, 3.6% were macrosomic, and 58% were delivered without complications.

The results obtained from this investigation show the double burden of malnutrition, in which undernutrition and overweight issues coexist with high percentages of body fat. Cardiovascular risk factors and type 2 diabetes have also been verified to coexist in this age group. The conurbation area had a higher percentage of children with lipid abnormalities, high triglycerides (35%), low HDL-c (25%), and prehypertension, while the urban area had a higher percentage of children with altered glucose (12%) and elevated insulin concentrations along with insulin resistance.

The dietary study carried out by Ayala-Mendivil [31] on school children from the same region showed that their diet is high in fat (> 30%), of which 37.6% comes from saturated fats and 5.4% from trans fats; likewise, 39% of the total carbohydrates consumed comes from simple sugars. These results suggest that preschoolers may have a similar dietary pattern that, in part, would respond to the clinical indicators observed in this study.

It is possible that other variables that have not been evaluated in this study, such as physical activity and heredity, play an important role in the occurrence of these clinical alterations, which, in addition, are risk factors of the metabolic syndrome [32]. In the case of children in the urban area, their birth weight seems to reflect that there may be a metabolic decompensation since pregnancy. In addition to the small sample size, we did not have adequate information to be able to prove this because we did not collect data on the mother's diet, weight gain during pregnancy, nor on the diagnosis of gestational diabetes, which are all aspects that remain as an unresolved task.

5. Conclusion

The findings of this study show that cardiovascular risk factors and type 2 diabetes are prevalent in children aged three to six living in urban and suburban areas of Hermosillo, in northwestern Mexico.

One of the limitations of this study lies in the fact that it has a small sample size, which prevented us from extrapolating the results to the rest of the preschool population. However, it is possible to demonstrate that there are indeed alterations in the clinical indicators of cardiovascular disease and diabetes in the preschool population, with significant differences between the groups evaluated. The birth weight registry gathered appears to point to a plausible explanation for the alterations at such a young age; however, further information is required to confirm it.

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Disclosure statement

The authors declare no conflict of interest.

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A Case of Renal Hemorrhage After Mitral Valvuloplasty for Active Infective Endocarditis with Renal Infarction

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Abstract: A 55-year-old woman with atopic dermatitis was admitted to the hospital with a diagnosis of septic shock. She had multiple cerebral and left renal infarctions. Transesophageal echocardiography revealed a 10 mm mobile verrucous lesion at the mitral valve. Emergency mitral valvuloplasty was performed, and the verrucous lesion was successfully removed. The patient was hemodynamically stable and was admitted to the postoperative intensive care unit (ICU) under ventilatory support. On postoperative day 3, anemia progressed, and on postoperative day 4, the patient went into shock. Emergency embolization was performed for hemostasis, and the patient's circulation improved. This is the first report of a case of renal hemorrhage after surgery for infective endocarditis. This case is valuable for the treatment of this disease in which various complications occur.

Keywords: Infective endocarditis; Embolism; Renal hemorrhage; *Staphylococcus aureus*

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1. Introduction

Patients with infective endocarditis (IE) complicated with embolic events caused by verrucous lesions may have a complicated clinical course in view of the various complications that may arise depending on the site of the embolus. We report a case of left renal hemorrhage after mitral valvuloplasty for a patient with *Staphylococcus aureus* mitral valve endocarditis and systemic embolism.

2. Case

A 55-year-old woman who had been under the care of a local doctor for atopic dermatitis was admitted to the hospital with fever and impaired consciousness two days later for septic shock. Blood culture was positive for *Staphylococcus aureus*, and computed tomography (CT) showed multiple cerebral and renal infarctions. Transesophageal echocardiography revealed a 10-mm mobile verrucous lesion at the mitral valve (**Figure 1**), and a diagnosis of active IE was made. Four days after admission, the patient was transferred to our center for treatment.

The patient had known allergies to metal (details unknown) and cefaclor. On admission, her blood pressure was 110/74 mmHg, heart rate was 77 beats/min, temperature was 37.6°C, respiratory rate was 19 breaths/min, oxygen saturation (SpO_2) was 99% under room air, Glasgow coma scale (GCS) was E3V4M6, and Japan coma scale (JCS) was II–10. She was able to provide her name; otherwise, she was not orientated

to place and time.

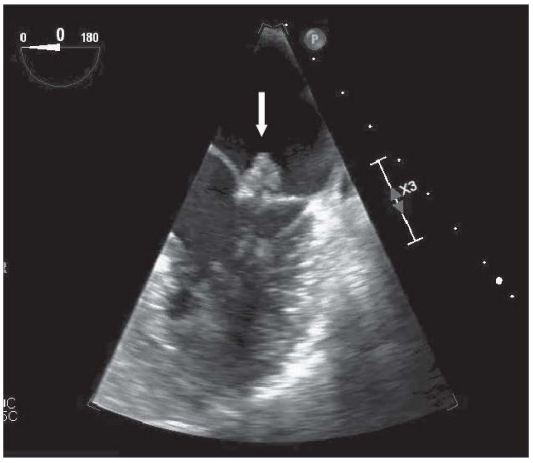

Figure 1. Transesophageal echocardiogram (TEE) showing vegetation (10 × 10 mm in size) attached to the mitral valve (arrow)

Her blood investigations were as follows: white blood cell (WBC) count 14,900/μL, red blood cell (RBC) count 3.89 million/μL, hemoglobin (Hb) 12.3 g/dL, hematocrit (Ht) 36.0%, platelet (Plt) 121,000/μL, activated partial thromboplastin time (aPTT) 28.0 s, international normalized ratio (INR) 0.98, fibrin degradation product (FDP) 8.1 μg/mL, D-dimer 2.9 μg/mL, albumin (Alb) 2.4 g/dL, creatine kinase (CK) 56 U/L, aspartate transaminase (AST) 94 U/L, alanine transaminase (ALT) 163 U/L, lactate dehydrogenase (LDH) 527 U/L, alkaline phosphatase (ALP) 495 U/L, gamma-glutamyl transpeptidase (γ-GTP) 119 U/L, blood urea nitrogen (BUN) 33 mg/dL, creatinine (Cre) 0.88 mg/dL, sodium (Na) 159 mEq/L, potassium (K) 4.3 mEq/L, chloride (Cl) 123 mEq/L, calcium (Ca) 8.5 mg/dL, total bilirubin (T-Bil) 0.8 mg/dL, C-reactive protein (CRP) 10.881 mg/dL, and brain natriuretic peptide (BNP) 116.5 pg/mL.

During her previous admission, her blood investigations were as follows: BUN 23 mg/dL, Na 148 mEq/L, CRP 10.881 mg/dL, and BNP 11.5 pg/mL. Her consciousness disorder was already observed at this point.

On chest radiography, cardiothoracic ratio was 43%, and electrocardiogram showed sinus rhythm, with a heart rate of 89 beats/min. A 10-mm mass adherent to the mitral valve was observed on transthoracic echocardiography. A contrast-enhanced CT scan of the left kidney showed an area of contrast loss, suggesting left renal infarction (**Figure 2**). Magnetic resonance imaging (MRI) of the brain showed scattered high-intensity areas in the cerebral cortex on diffusion-weighted imaging (**Figure 3**).

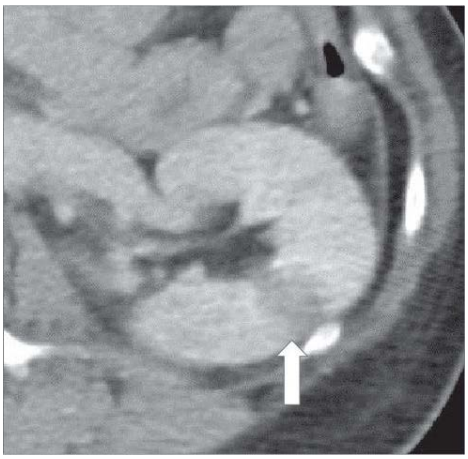

Figure 2. Contrast-enhanced computed tomography of the abdomen showing reduced enhancement of the left kidney (arrow), consistent with infarction

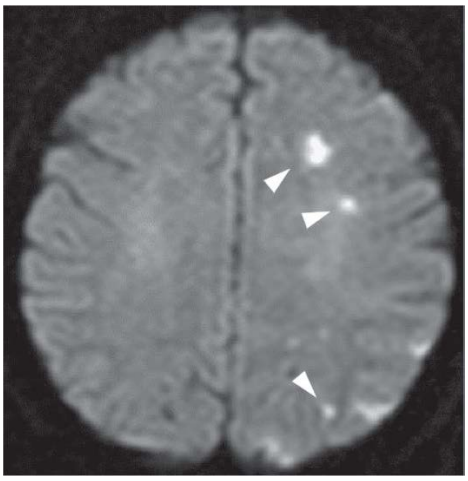

Figure 3. Diffusion-weighted brain magnetic resonance imaging detected multiple acute cerebral infarctions (arrowhead)

Based on the above findings, we concluded that the patient had already developed systemic embolism and had high risk of further embolism due to the large verrucous lesion. Therefore, we decided to perform an emergency surgery. The median sternotomy approach was used, and cardiopulmonary bypass was established by removing venous blood from the superior and inferior vena cava and returning oxygenated blood into the ascending aorta. A longitudinal right lateral left atrial incision was made to gain access to the mitral valve. A verrucous lesion was observed from C1 to P1. The verrucous lesion and valve leaflets were resected from C1 to P1 (**Figure 4**). The valve ring from C1 to A1/P1 was sutured closed, and the apex defect was closed. Since no obvious mitral regurgitation was observed by regurgitation test, the procedure was terminated without any prosthetic valve ring because of the infection and the suspicion of metal allergy. The aortic cross-clamping time was 90 min, and the operative time was 3 h and 40 min.

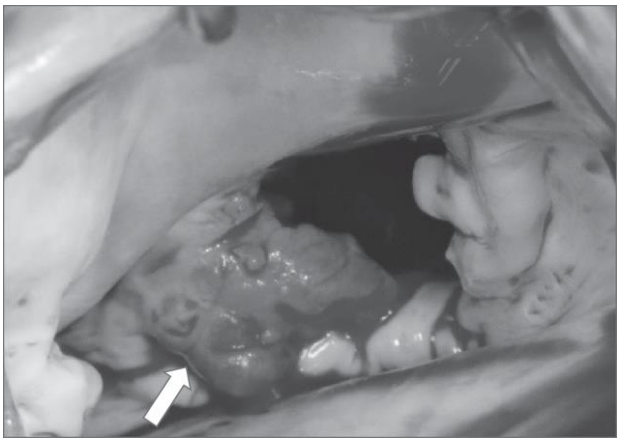

Figure 4. Intraoperative finding showing the vegetation from the anterior commissure to the posterior leaflet of the mitral valve (arrow)

Immediately after surgery, the patient was hemodynamically stable, and she remained on ventilator support due to poor arousal. On postoperative day 2, her Hb and platelet levels decreased and her LDH increased, but the patient was unresponsive to blood transfusion. On postoperative day 4, the patient went into shock, requiring an increase in dose of vasopressors. The left side of her abdomen was noted to be swollen; a contrast-enhanced CT scan revealed massive hematoma in the left retroperitoneum with extravascular leakage of contrast medium (**Figure 5**). An arterial hemorrhage in the left kidney was suspected, and we decided to perform an emergency angiography. Since neither prosthetic valve nor prosthetic valve ring was used, no anticoagulation therapy was initiated.

Figure 5. Contrast-enhanced computed tomography of the abdomen showing massive left renal hematoma with contrast extravasation

Femoral artery puncture was performed for angiography. When the left renal artery was selected for angiography, extravascular leakage of contrast medium was observed from the peripheral end of the superior branch of the left renal artery (**Figure 6A**). The superior branch of the left renal artery was selected for embolization with 20% n-butyl-2-cyanoacrylate (NBCA) to eliminate the contrast leak. The inferior branch of the left renal artery was preserved (**Figure 6B**). The use of NBCA for emergency hemostasis was approved by the Ethics Committee of the hospital.

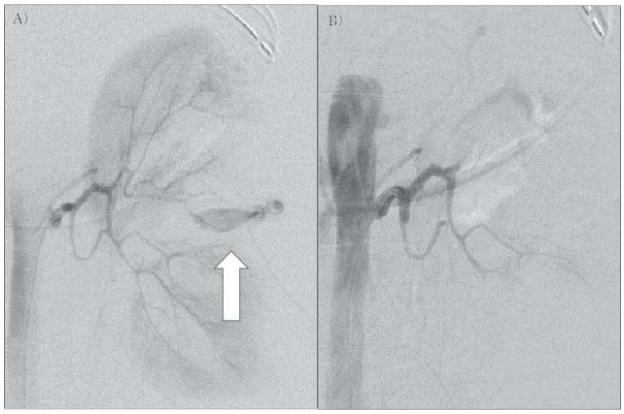

Figure 6. Angiography showing (A) active extravasation from the superior branch of the left renal artery (arrow) and (B) no contrast extravasation from the inferior branch of the left renal artery

Postoperatively, the patient was weaned off the ventilator with improvement in hemodynamic status and level of consciousness. The patient was discharged from the ICU the day after embolization. Two weeks after embolization, CT scan showed that the hematoma was shrinking (**Figure 7**). The patient's renal function did not deteriorate. Antibiotic therapy for IE was continued. Ceftriaxone and clindamycin were administered for a total of 8 weeks after surgery, and the antibiotics were changed to amoxicillin-clavulanic acid following the negative conversion of CRP. On postoperative day 82, the patient was transferred for rehabilitation after establishing that the patient was free of inflammation. The patient was discharged home without any loss of activity of daily living (ADL) and placed under close observation under our department's outpatient clinic. Seven months after surgery, echocardiography revealed moderate mitral stenosis, with a mitral annular area of 1.4 cm^2 and a mean pressure gradient of 4.8 mmHg, without any mitral regurgitation. Postoperative dental examination revealed no abnormalities in the oral cavity that could be the source of infection.

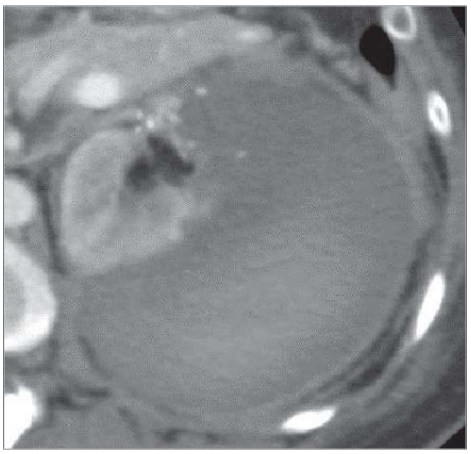

Figure 7. Contrast-enhanced computed tomography of the abdomen showing hematoma with no contrast extravasation

3. Discussion

IE has a wide range of symptoms of which the most common is fever, occurring in 90% of cases [1]. Embolisms occur in about 30% of all cases of IE [2] and may be the first manifestation of IE. Another vascular complication is bacterial aneurysm, commonly cerebral aneurysm, which is widely known to occur in 1%–5% of cases. Cerebral aneurysms are often asymptomatic, even when they expand, but when they rupture, they are fatal [3,4]. Although the frequency is unknown, there have been reports of aneurysms in the mesenteric artery, coronary artery, ulnar artery, gluteal artery, femoral artery, popliteal artery, splenic artery, and renal artery, such as the one described in our case report. Bacterial aneurysms are believed to be caused by bacterial arteritis originating from microemboli, and the inflammation causes the outer membrane to weaken and enlarge [5]. When bleeding occurs as a result of ruptured peripheral aneurysms, catheter embolization is the standard treatment, and the same is true for renal hemorrhage.

There are only a few reports of IE causing renal hemorrhage and thus requiring emergency hemostasis, including one case in Japan [6] and two cases overseas [7,8]. Such cases are considered to be rare. In our case, although the preoperative CT scan showed no obvious aneurysm formation around the kidney, the sudden renal hemorrhage occurring 6 days later suggests that the aneurysm may have formed and expanded rapidly during the perioperative period, leading to rupture. This case should be taken as a lesson for future clinical and surgical treatment of IE.

In another report, a retroperitoneal hematoma was observed around the abdominal aorta in the absence of arterial diameter enlargement or aneurysm [9]. It is possible that the patient had a direct rupture without aneurysm formation. Emergency angiography confirmed extravascular leakage of contrast medium but did not show any clear mass, which may have been obscured by the fact that it had already ruptured. *Staphylococcus aureus* is known as a highly virulent bacterium that often has an acute course. Hence, it is possible that the outer membrane of the bacterial aneurysm may have weakened due to inflammation and ruptured before an aneurysm could form. In a previous report, an autopsy of a patient with intracranial hemorrhage due to IE caused by *Staphylococcus aureus* showed that the arterial wall was destroyed by bacteria without forming any aneurysm [10]. This seems to support the aforementioned hypothesis. Another study has reported that *Staphylococcus aureus* is a risk factor for intracranial hemorrhage in *Staphylococcus aureus* IE (hazard ratio: 2.35) [11], suggesting that the risk of bleeding in other organs increases in *Staphylococcus aureus* IE. None of the three previously reported cases of IE with renal hemorrhage was caused by *Staphylococcus aureus*; this is the first report of a case of renal hemorrhage associated with IE caused by *Staphylococcus aureus*, which may have led to the sudden development of the disease. In addition, the patient underwent surgery using an artificial heart and lung during the acute phase of the disease, and factors such as extracorporeal circulation and systemic heparinization may have had an influence on the

outcome.

Staphylococcus aureus is a common cause of IE, with skin penetration being the most common means leading to IE, accounting for about 40% of cases [12]. In particular, cases of IE due to bacteremia caused by *Staphylococcus aureus* in atopic dermatitis, such as the present case, have been reported [14-16]. The number of patients with atopic dermatitis is estimated to be 450,000 nationwide as of 2014 [17], and since *Staphylococcus aureus* is a common pathogen, many of these patients may develop severe IE. The former is an underlying disease that cardiovascular surgeons should be aware of. In addition, there have been reports of recurrent IE due to the lack of appropriate dermatology treatment in patients with IE complicated by atopic dermatitis [15]; hence, it is important to treat and follow-up patients with atopic dermatitis alongside dermatologists.

In recent years, the importance of preventing mitral stenosis following mitral valvuloplasty has been underlined. In the present case, apex replacement with autologous or bovine pericardium and reconstruction with artificial tendon cords were necessary to ensure adequate mitral valve orifice. However, considering that the patient is 55 years old and had acute stroke, we allowed a certain degree of mitral stenosis and opted for suture closure. This surgical technique is controversial and thus requires close follow-up.

4. Conclusion

We report a case of renal hemorrhage 2 days after surgery for active IE, which was successfully treated with emergency embolization. IE has a wide range of symptoms and complications, and IE caused by *Staphylococcus aureus* may cause sudden bleeding. Therefore, IE must be carefully managed, even during the perioperative period.

Disclosure statement

The authors declare no conflict of interest.

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Importance of Cardiac Rehabilitation in Patients with Structural Heart Changes Secondary to Ankylosing Spondylitis: A Case Report

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Abstract: Patients with ankylosing spondylitis (AS) may present with cardiac manifestations, mainly valvular disease and dilation of the aortic root. Rehabilitation programs to improve cardiovascular capacity are important for maintaining the quality of life of these patients, which often deteriorates with disease impairments and dysfunctions when not corrected. We report a case of a 67-year-old man, diagnosed with ankylosing spondylitis 20 years ago with structural cardiac changes. The patient underwent a rehabilitation program that involves stretching, aerobic and resistance exercises, and health education. In order to analyze the patient's effort during activities of daily living and instrumental activities, we used Borg Rating of Perceived Exertion Scale. With constant rehabilitation, the patient maintained functional capacity in activities of daily living and instrumental activities over the years even with structural heart changes.

Keywords: Heart disease; Heart valves; Ankylosing spondylitis; Connective tissue

Online publication: May 22, 2023

1. Introduction

Ankylosing spondylitis (AS) is considered a chronic disease that directly affects the connective tissue, axial skeleton, spine, and sacroiliac joints, resulting in their fusion. Patients with AS commonly present with cardiac manifestations, such as aortic root dilatation, valve disease, conduction and rhythm abnormalities, decreased coronary flow reserve, myocardial infarction, and diastolic dysfunction [1,2].

The main clinical manifestations of AS include back pain and progressive stiffness of the spine, as well as inflammation of the hip joint, shoulders, peripheral joints, fingers, and toes [3]. In addition to physical changes, studies have shown that the onset of comorbidities in AS intensifies the progression of the disease, contributing to the onset of functional disability and increased mortality [4].

Among the comorbidities caused by AS, cardiac manifestations, such as aortic disease and aortic regurgitation [5], have been studied. Based on the National Health Insurance Research Database of Taiwan, a cohort study conducted between 2000 and 2005 demonstrated a relationship between AS and cardiac manifestations and the prevalence. A significant number of cardiac complications has been identified in male patients over 40 years old and diagnosed with AS [2].

Other studies have revealed a prevalence of cardiac complications of 0.1%–0.5% in patients with AS, predominantly in the Caucasian population, in young HLA-B27 positive males (female-to-male ratio 1:9), and in those with spinal and sacroiliac join involvement [6,7].

The implementation of rehabilitation programs with physical activity improves the cardiovascular capacity and quality of life of patients with cardiac manifestations secondary to AS [8]. Regular physical exercise allows physiological restructuring of the cardiovascular and musculoskeletal systems, reducing oxidative stress and inflammation, correcting baroreflex dysfunction, increasing vagal tone, decreasing sympathetic activity, reversing hypertrophic arteriolar remodeling in exercised tissues, and reducing peripheral vascular resistance (reducing BP and controlling similar blood pressure levels) [8-10]. Thus, it is necessary to evaluate the clinical changes in these patients after rehabilitation.

In this study, we evaluated the benefits of rehabilitation in a patient with structural heart changes complicated by AS who showed maintenance of functional capacity after cardiac rehabilitation.

2. Case

A 67-year-old male, former smoker, with non-insulin-dependent diabetes mellitus, systemic arterial hypertension, AS, and heart failure with reduced ejection fraction, followed-up at the cardiac rehabilitation center of a physiotherapy clinic in the West of São Paulo. The patient signed an informed consent form, agreeing to participate in the study. This study was approved by the Research Ethics Committee of Universidade do Oeste Paulista (CAAE: 51309321.4.0000.5515), in accordance with CNS Resolution 466/2012.

In 2001, the patient compliant of severe pain in the cervical and lumbar region, and he was diagnosed with AS. In 2013, he had an episode of rheumatic fever, with consequent involvement of the cardiovascular system. The echocardiogram at the time revealed mild mitral valve insufficiency and stenosis due to calcification in the mitral valve. Since then, the patient had been undergoing cardiovascular rehabilitation. In 2016, his cardiovascular condition worsened, with episodes of shortness of breath. He underwent 24-hour Holter monitoring, which identified a variation in heart rate from 49 to 176 beats per minute and four episodes of non-sustained ventricular tachycardia. In 2017, his echocardiogram showed left ventricular contractile dysfunction (ejection fraction of 46.6%), mitral dysfunction with stenosis and insufficiency, significant left atrial enlargement, and mild dilatation of the ascending aorta. Due to the clinical picture and structural cardiac changes, a pacemaker was implanted in the same year. Then, the patient was placed under the cardiac rehabilitation protocol; however, in 2018, he presented with atrial fibrillation, as shown on electrocardiogram.

Another echocardiogram was performed in 2020, showing irregular rhythm, significant left ventricular contractile dysfunction (ejection fraction of 24.4%), mitral dysfunction with moderate stenosis and insufficiency, mild aortic insufficiency, mild/moderate tricuspid insufficiency, and significant left atrial enlargement.

Under the cardiac rehabilitation program, the patient was classified as high risk according to the American College of Sports Medicine (ACSM) in view of cardiovascular disease (rheumatic valvulopathy and heart failure with reduced ejection fraction) and metabolic disease (diabetes mellitus). The Cardiovascular Risk Stratification chart (**Table 1**) was used to stratify the patient's risk, and heart rate reserve (HRR) was used to calculate the intensity of effort, in the range of 40%–70%, as recommended by the ACSM. The heart rate reserve ranged from 103 to 119 beats per minute.

The patient was classified as high risk under cardiac rehabilitation and as class 3 by the New York Heart Association (NYHA) classification of heart failure based on his symptoms in the last evaluation. The rehabilitation program involved stretching exercises, aerobic exercises, resistance exercises, and health education. The program began with self-stretching exercises of the main muscle groups (neck, trunk, and upper and lower limbs), maintaining over 30 seconds in standing or sitting position. Aerobic exercises were performed on a treadmill, beginning with a 5-minute warm-up, and then 20 minutes of moderate intensity physical conditioning, calculated by means of HRR and Borg Rating of Perceived Exertion Scale. At the

end of the aerobic activity, 5 minutes was spent to cool down. Resistance exercises were performed at the clinic's gym, and for each exercise, the ideal load was calculated based on the patient's maximum repetition (1RM) according to his body percentage. In order to analyze the subjective effort of the patient during aerobic exercises and activities of daily living, we used Borg Rating of Perceived Exertion Scale (**Table 2**).

Table 1. American College of Sports Medicine risk stratification chart

Risk	Criteria
Low	Men under 45 years of age and women under 55 years of age who are asymptomatic and do not meet more than one major risk (positive factors: family history, smoking, hypertension, hypercholesterolemia, increased fasting glucose, obesity, and sedentary lifestyle; negative factors: high serum HDL cholesterol).
Moderate	Men aged 45 or older, women aged 55 or older, or those who meet the threshold for two or more major risk factors described above.
High	Individuals with one or more signs and symptoms (pain; discomfort in the chest, neck, jaw, or arms; shortness of breath at rest or on exertion; dizziness or syncope; orthopnea or paroxysmal nocturnal dyspnea; swelling of the ankles; palpitations or tachycardia; intermittent claudication; known heart murmur; excessive fatigue; and shortness of breath in daily activities) or cardiovascular disease (heart disease, cerebrovascular disease, and peripheral vascular disease), lung disease (chronic obstructive pulmonary disease, asthma, interstitial lung disease, and cystic fibrosis), or known metabolic disease (diabetes mellitus, thyroid disorders, and kidney or liver disease).

Table 2. Borg Rating of Perceived Exertion

6 7 8	Very easy
9 10	Easy
11 12	Relatively easy
13 14	Relatively tiring
15 16	Tiring
17 18	Very tiring
19 20	Exhaustive

3. Discussion

Patients with AS are more susceptible to developing aortic insufficiency, conduction abnormalities, aortitis, pericarditis, and even mitral insufficiency, as observed by the classic study by Kawasuji *et al*. [11]. Of these changes, aortic disease and aortic regurgitation are the most common cardiovascular diseases associated with AS [12].

Since that study, several reports describing these associations have been published. Thomas *et al*. [13] observed that among the AS patients studied, 27% of them had mild aortic root dilatation and one of them

aortic insufficiency. Roldan *et al*. [14] reported that the prevalence of valve disease was 82% in patients with AS.

This information corroborates the findings in our study, in which the patient developed aortic and mitral insufficiency, in addition to aortic dilatation. Although he presented with rheumatic fever, as a triggering factor, these structural cardiac alterations may have been accentuated by AS. However, it is impossible to determine the exact mechanism of the cause-and-effect relationship between rheumatic fever/AS and heart disease [15].

Even with the worsening structural cardiac parameters in the 2017 to 2020 echocardiograms, a progression that is part of the natural history of rheumatic fever/heart failure, the patient maintained his quality of life and functional independence through cardiac rehabilitation as demonstrated by the NYHA scale and functional capacity assessment [15,16].

SPSS 22.0 was used for statistical analysis. Data normality was assessed by Kolmogorov-Smirnov test. For comparison of parametric data, independent *t*-test was used, while for non-parametric data, Mann-Whitney test was used. The data were described in mean ± standard deviation. The significance level considered was 5%.

In the case study, the patient's vital signs at rest and during exercise were observed. **Tables 1–7** detail the averages of the vital signs at each of the times.

In the tables, Time 1 and Time 2 refer to 2018 and 2021, respectively. They are arranged according to the collection time, as the number of sessions varied with each time, and for this reason, each table will have the number of sessions (n).

Table 1. Vital signs during rest

	Time 1 (n = 29)	**Time 2 (n = 22)**	***P***
SBP	105.52 ± 10.21	103.64 ± 13.99	0.5810
DBP	69.62 ± 5.66	70.00 ± 8.16	0.8455
HR	70.90 ± 11.52	66.77 ± 11.16	0.2054
$SatO_2$	96.45 ± 2.49	97.18 ± 0.59	0.1826
Borg	8.03 ± 2.03	7.21 ± 1.90	0.1607

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; $SatO_2$, peripheral oxygen saturation; SBP, systolic blood pressure.

At rest, no significant statistical differences in vital signs were observed in the two "times" analyzed. **Tables 2–7** show a significant reduction in heart rate and subjective perceived exertion in Time 2 at the 5th, 10th, 15th, 20th, 25th, and 30th minutes of exercise.

Table 2. Vital signs at the 5th minute of exercise

	Time 1 (n = 29)	**Time 2 (n = 22)**	***P***
SBP	107.24 ± 12.51	105.91 ± 14.03	0.7222
DBP	69.31 ± 5.51	70.91 ± 8.68	0.2552
HR	85.83 ± 16.16	69.82 ± 12.16	0.0003*
$SatO_2$	96.14 ± 2.42	96.45 ± 1.60	0.5970
Borg	11.66 ± 1.14	9.41 ± 2.46	0.0001*

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; $SatO_2$, peripheral oxygen saturation; SBP, systolic blood pressure.
*$P < 0.005$.

Table 3. Vital signs at the 10th minute of exercise

	Time 1 (n = 29)	Time 2 (n = 22)	*P*
SBP	110.34 ± 12.67	111.43 ± 14.59	0.7806
DBP	69.62 ± 6.81	72.38 ± 8.89	0.2195
HR	94.21 ± 12.70	69.48 ± 12.09	0.0000*
$SatO_2$	95.66 ± 4.14	95.90 ± 2.47	0.8068
Borg	12.10 ± 0.72	10.43 ± 2.16	0.0003*

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; $SatO_2$, peripheral oxygen saturation; SBP, systolic blood pressure.
*$P < 0.005$.

Table 4. vital signs at the 15th minute of exercise

	Time 1 (n = 29)	Time 2 (n = 22)	*P*
SBP	111.00 ± 12.64	114.50 ± 14.32	0.3714
DBP	70.31 ± 6.81	72.00 ± 8.34	0.4400
HR	95.17 ± 14.81	71.70 ± 11.36	0.0000*
$SatO_2$	9634 ± 2.33	97.05 ± 1.43	0.2354
Borg	12.17 ± 0.76	10.85 ± 2.21	0.0044*

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; $SatO_2$, peripheral oxygen saturation; SBP, systolic blood pressure.
*$P < 0.005$.

Table 5. vital signs at the 20th minute of exercise

	Time 1 (n = 29)	Time 2 (n = 22)	*P*
SBP	112.14 ± 13.43	111.54 ± 12.14	0.8909
DBP	71.07 ± 6.29	69.23 ± 8.62	0.4438
HR	96.86 ± 13.07	74.85 ± 14.74	0.0000*
$SatO_2$	96.61 ± 2.44	96.46 ± 1.13	0.8392
Borg	12.36 ± 0.83	11.38 ± 1.98	0.0312*

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; $SatO_2$, peripheral oxygen saturation; SBP, systolic blood pressure.
*$P < 0.005$.

Table 6. Vital signs at the 25th minute of exercise

	Time 1 (n = 29)	Time 2 (n = 22)	*P*
SBP	112.48 ± 8.29	110.00 ± 8.16	0.5826
DBP	72.40 ± 5.97	70.00 ± 11.55	0.5190
HR	97.00 ± 13.04	75.25 ± 21.50	0.0085*
$SatO_2$	96.84 ± 1.97	96.50 ± 0.58	0.7382
Borg	12.48 ± 0.51	10.00 ± 1.83	0.0000*

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; $SatO_2$, peripheral oxygen saturation; SBP, systolic blood pressure.
*$P < 0.005$.

There was also a significant reduction in diastolic blood pressure in Time 2 at the 30th minute of exercise (**Table 7**).

Table 7. Vital signs at the 30th minute of exercise

	Time 1 (n = 29)	Time 2 (n = 22)	*P*
SBP	109.65 ± 7.69	100.00 ± 0.00	0.0951
DBP	72.17 ± 6.71	60.00 ± 0.00	0.0193
HR	98.00 ± 11.78	72.00 ± 16.97	0.0076*
$SatO_2$	96.91 ± 1.35	96.00 ± 1.41	0.3679
Borg	11.78 ± 1.65	9.00 ± 1.41	0.0308*

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; $SatO_2$, peripheral oxygen saturation; SBP, systolic blood pressure.
*$P < 0.005$.

As described in literature and reported in this case, AS can cause cardiac manifestations that are potentially detrimental to the quality of life of patients due to several factors. Cardiac rehabilitation has shown to be effective in delaying the progression of symptoms, even with structural changes in the heart, which in this case resulted in a significant decrease in the patient's left ventricular ejection fraction. The maintenance of functional capacity for activities of daily living through the subjective perception of effort and during exertion in cardiovascular rehabilitation was observed, as the patient only had physiological changes in their vital data throughout the sessions.

Disclosure statement

The authors declare that there is no potential conflict of interest that could interfere with the impartiality of this scientific work.

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Dilated Cardiomyopathy in a Patient with Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

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Abstract: Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare pathology that belongs to a group of diseases characterized by necrotizing vasculitis of small and medium-sized systemic blood vessels. Symptomatic cardiovascular involvement occurs in 27%–47% of cases of EGPA and is one of the most severe manifestations. The diagnosis is usually confirmed by eosinophilic infiltration observed in tissue biopsy, but with the recent inclusion of cardiac magnetic resonance imaging (MRI), the former can be replaced. Early diagnosis is important because timely treatment is often associated with improvement.

Keywords: Dilated cardiomyopathy; Churg-Strauss syndrome; Heart failure

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1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, belongs to a group of diseases characterized by necrotizing vasculitis of small and medium-sized blood vessels [1]. Its prevalence and annual incidence are 7.3–17.8 and 0.9–2.4 per million population, respectively [2]. The organs most commonly affected in EGPA are the lungs and skin. Symptomatic cardiovascular involvement occurs in 27%–47% of cases [3] and is one of the most severe manifestations, accounting for approximately 50% of deaths from this disease [4]. Pericarditis, arterial hypertension, valvular heart disease, eosinophilic myocarditis, arrhythmias, and/or congestive heart failure are some of its manifestations [2]. We present a case of EGPA with cardiovascular involvement in a patient who showed good response to timely pharmacological treatment.

2. Case

A 49-year-old man with history of ischemic stroke five years ago, asthma, chronic sinusitis, and EGPA diagnosed by right sural nerve biopsy performed in view of lower limb polyneuropathy associated with systemic eosinophilia complaint of epigastralgia for 4 months associated with progressive functional class III dyspnea and edema in the lower limbs for which he was hospitalized in another institution with presumptive diagnosis of decompensated heart failure secondary to dilated cardiomyopathy with severely impaired systolic function (ejection fraction of 31%). He was referred to our institution for further

investigations and treatment.

Physical examination showed lower limb edema, jugular vein distention, hepatojugular reflux, and crepitus in both lung fields up to the middle one-third of the lungs.

Laboratory investigations on admission showed eosinophilia and elevated levels of high-sensitivity troponin T (22.5 ng/L), N-terminal prohormone of brain natriuretic peptide (Nt-proBNP; 6,546 pg/mL), and D-dimer (1,260 ng/mL). His rheumatology profile showed marked elevation of immunoglobulin E (IgE; 1,556 IU/mL, normal value of IgE < 100 IU/mL). Viral and Chagas serologies were negative.

Electrocardiogram showed frequent ventricular extrasystoles alternating with sinus rhythm and fusion beats, complete right bundle branch block and left anterior hemiblock. Doppler echocardiogram showed biventricular dilatation with impaired left ventricular systolic function (ejection fraction 25%) and moderately dilated left atrium. No angiographically significant coronary lesions were observed on coronary angiography; thus, coronary involvement as a cause of ventricular dysfunction was ruled out.

Cardiovascular magnetic resonance imaging (MRI) with gadolinium was performed given the history. The results were consistent with non-ischemic/necrotic dilated cardiomyopathy, with severe dilatation and functional impairment of the left ventricular cavity (ejection fraction 16%); apical subendocardial fibrosis and small foci of late intramyocardial enhancement in the basal region were also observed (**Figures 1** and **2**).

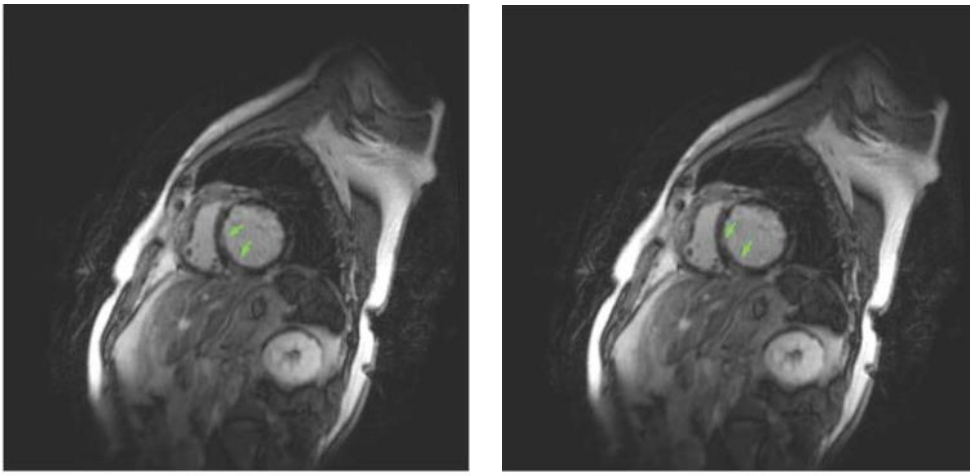

Figure 1. Short-axis phase-sensitive inversion recovery (late enhancement) sequences showing focal intramyocardial fibrosis in basal septal and anteroseptal regions (arrows)

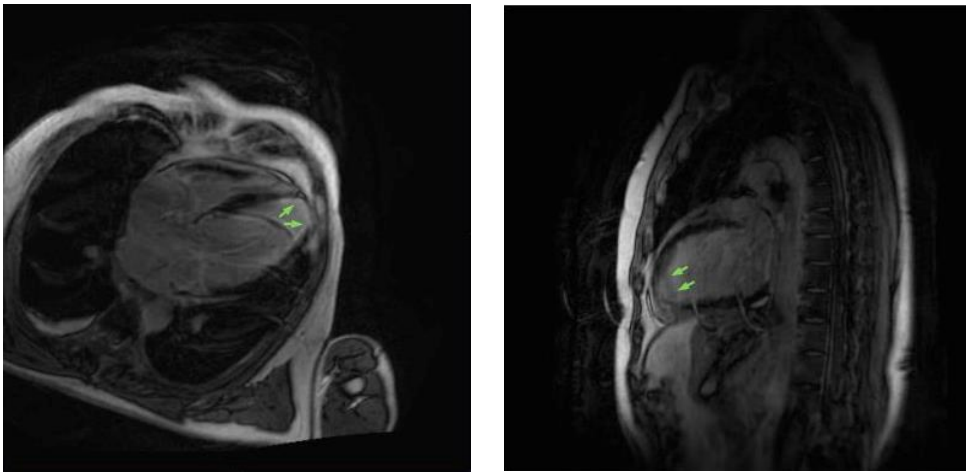

Figure 2. Long-axis phase-sensitive inversion recovery (late enhancement) sequences showing subendocardial fibrosis in the apical region (arrows)

We then decided to evaluate for respiratory involvement by means of chest and paranasal sinus computed tomography. The former reported diffuse ground-glass opacities, with central distribution, in both lung parenchyma, and granulomas in both lungs; in addition, moderate right pleural effusion associated with subtotal atelectasis of the right lower lobe and multiple mediastinal lymph nodes were observed. Signs of chronic sinusitis were observed on paranasal sinus CT.

Given the findings, a diagnosis of EGPA with cardiovascular involvement was made. Treatment was initiated with corticosteroids (methylprednisolone 500 mg intravenous pulses for 3 days and subsequent maintenance with meprednisone 40 mg per day), immunosuppressants (azathioprine 50 mg every 12 hours orally), and heart failure medications (spironolactone 25 mg per day, bisoprolol 5 mg twice a day, and sacubitril/valsartan 50 mg every 12 hours).

Subsequent follow-up after 9 months of treatment showed marked clinical improvement (functional class I) and improved ventricular function (ejection fraction 40%) on echocardiogram.

3. Discussion

EGPA, formerly known as Churg-Strauss syndrome, is a specific variant of a group of systemic diseases characterized by necrotizing vasculitis of medium- and small-sized vessels associated with antineutrophil cytoplasmic antibodies (ANCA). The other subtypes include granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis [1,2].

The diagnosis of EGPA is based on the presence of asthma, peripheral eosinophilia, and systemic vasculitis, along with an anatomopathological study showing necrotizing vasculitis, inflammatory infiltrate consisting of eosinophils, and extravascular granulomas [6].

The diagnostic criteria are shown in **Table 1**.

Table 1. American College of Rheumatology (ACR) diagnostic criteria for eosinophilic granulomatosis with polyangiitis

American College of Rheumatology (ACR) diagnostic criteria	
(i)	Previous history of asthma
(ii)	Peripheral eosinophilia > 10%
(iii)	History of allergy
(iv)	Mono- or polyneuropathy
(v)	Migratory pulmonary infiltrates
(vi)	Paranasal sinus abnormalities
(vii)	Typical anatomopathological findings, such as eosinophilic vasculitis and fibrinoid necrosis

Note: With 4 or more criteria, eosinophilic granulomatosis with polyangiitis is diagnosed with a sensitivity of 85% and a specificity of 99.7%.

EGPA is a rare condition; its incidence is 0.9–2.4 cases per million people, while its prevalence is 7.3–17.8 cases per million [2]. It tends to affect men more than women, with a mean age of presentation at 45.5, and it is more common in people of European descent [7].

Patients who are positive for ANCA (about 40%) usually have a vasculitic phenotype and often present with myalgia, migratory polyarthralgia, weight loss, mononeuritis multiplex, and renal involvement, such as necrotizing or crescentic glomerulonephritis. In contrast, patients without ANCA usually have an eosinophilic phenotype, with a higher incidence of myocarditis [8]. EGPA is one of the most common systemic vasculitides affecting the heart. The reported frequency of cardiac involvement is 62%, with symptomatic cases ranging from 27% to 47% [3]. This manifestation is of great clinical importance, as it

represents the main cause of morbidity and mortality (50%) in these patients despite the overall favorable prognosis of the disease [4]. The lesion is caused both by mediators released by activated eosinophils and by vasculitic lesions in the myocardium and coronary arteries [9].

The cardiac manifestations include pericarditis, arterial hypertension, valvular heart disease, eosinophilic myocarditis, arrhythmias, congestive heart failure, coronary artery disease, cardiomyopathies, and eosinophilic pericardial effusion [2]. Among them, myocarditis is the most common in EGPA, and patients may present with mild symptoms, such as precordial pain and palpitations, or even life-threatening conditions, such as cardiogenic shock, in severe cases [11].

The risk of myocarditis increases in patients between 20 and 30 years of age, and cardiac manifestations occur later in women than in men [3]. Cardiac involvement in EGPA may also mimic acute coronary syndrome. Electrocardiography may reveal nonspecific ST-T changes or, rarely, ST elevation due to coronary vasospasm or intracoronary thrombi. Coronary angiography, on the other hand, may show stenotic lesions, coronary ectasia, or vasospasm.

Significant coronary involvement is seen in 36.4% of patients [10]. Coronary vasospasm has been considered the main cause of chest pain in patients with EGPA without significant coronary artery disease. Coronary ectasia has been previously described in many systemic inflammatory vasculitides and is associated with ectasia in other arterial beds, such as the renal and cerebral vasculature [10]. At the laboratory level, eosinophil count is markedly higher in patients with myocarditis, as is the white blood cell count due to eosinophilia. In addition, erythrocyte sedimentation rate and C-reactive protein are often elevated, indicating an active inflammatory response. Patients with EGPA and myocarditis are usually negative for ANCA [3].

The use of Doppler echocardiography is very useful for the initial evaluation of these patients [10]. Echocardiographic findings consist of left ventricular systolic dysfunction (83.9%), significant diastolic dysfunction (3.2%), segmental wall motion disorders (9.7%), ventricular hypertrophy and valvular insufficiency (12.9%), pulmonary hypertension (6.5%), pericardial effusion (37.1%), and intracardiac thrombi (22.6%).

Cardiac MRI with gadolinium is indicated in cases of EGPA with electrocardiographic or echocardiographic abnormalities, since it correlates with eosinophilic infiltration in endomyocardial biopsy [12] and with evidence of fibrosis and necrosis in advanced cases [13]. MRI may be useful for stratification of patients with EGPA and individualization of treatment [14]. However, in many cases, further studies are needed to differentiate the active phases of fibrosis. The exact sensitivity and specificity of MRI in EGPA with cardiac involvement is still unknown; however, there are studies that have reported a sensitivity of 88% and specificity of 72% [15].

The treatment of EGPA with cardiac involvement depends on the stage of the disease; the suggested regimens are shown in **Table 2** [5].

Table 2. Recommended treatment regimens according to the stage of disease

Stage	Recommended treatment regimen
No indicators of poor prognosis	Regimen 1: Oral prednisone 1 mg/kg per day for 3 weeks, and then reduce to 0.5 mg/kg and until cessation. Regimen 2: Intravenous methylprednisolone (15 mg/kg), followed by oral prednisone as in Regimen 1.
With poor prognostic indicators	3 pulses of intravenous methylprednisolone (15 mg/kg) + 12 pulses of cyclophosphamide (600 mg/m^2) every 2 weeks for 1 month, and then every 4 weeks, or 1 short cycle of cyclophosphamide (oral 2 mg/kg) for 3 months, or 6 pulses of cyclophosphamide (600 mg/m^2) every 2 weeks for 1 month, and then every 4 weeks + azathioprine 2 mg/kg for 1 year or more.

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Stage	Recommended treatment regimen
Relapses	Oral azathioprine 2 mg/kg per day for at least 6 months, or cyclophosphamide pulses (600 mg/m^2) every 2 weeks for 1 month, and then every 4 weeks.
Maintenance for remission	Methotrexate (10–25 mg per week). Cyclosporine A (1.5–2.5 mg/kg per day). Azathioprine (2 mg/kg per day).
Refractory disease	Plasmapheresis. Intravenous immunoglobulin (0.4 g/kg per day for 5 days). Interferon-alpha (3 million IU, 3 times per week subcutaneously). Tumor necrosis factor inhibitors: infliximab, etanercept, adalimumab, or rituximab (325 mg/m^2 for 4 consecutive weeks).

Our patient was considered to have poor prognosis due to cardiac involvement, as assessed by MRI, with confirmed EGPA by sural biopsy. However, a favorable outcome was observed with the combined treatment as demonstrated by the increase in ventricular function from 25% to 40% in the last follow-up. The use of cardiac MRI made it possible to rule out any other cardiac conditions that could lead to confounding diagnosis and thus delay treatment.

With early detection and timely treatment, EGPA has a favorable prognosis with a 5-year survival of 90%. The relapse rate is estimated at approximately 20%–30% and is often lower with fever, joint pain, and constitutional symptoms [5].

4. Conclusion

Cardiac involvement in EGPA can manifest in a highly variable manner but it remains subclinical in most cases. This warrants an in-depth cardiac evaluation of all patients with a confirmed diagnosis of EGPA regardless of symptom status to detect cardiac involvement in its early phase and thus begin optimal treatment.

We present a case of decompensated heart failure secondary to non-ischemic/necrotic dilated cardiomyopathy in a patient diagnosed with EGPA. The therapeutic response showed improvement in symptoms and ventricular function on echocardiographic follow-up.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

All authors contributed to the conceptualization, data collection, and preparation of the manuscript, taking public responsibility for its content and approving its final version.

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Comparison of the Effect of Clopidogrel and Ticagrelor on the Development of No-Reflow Phenomenon After Percutaneous Coronary Intervention in Patients with Acute Myocardial Infarction

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Abstract: *Background:* No-reflow phenomenon (NRP) is one of the most important factors affecting myocardial reperfusion. *Objective:* In this study, we investigated the effect of ticagrelor and clopidogrel on the development of NRP in patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI). *Methods:* Our single-center, retrospective study included 200 patients with AMI who underwent PCI. The patients were divided into two groups according to the antiplatelet regimen given before PCI: clopidogrel- and ticagrelor-loaded groups. NRP was defined based on TIMI flow classification or post-procedural ST segment resolution. The difference in the parameters between patients with no-reflow and patients with normal flow as well as the effect of ticagrelor and clopidogrel on NRP were evaluated. *Results:* There was no difference in baseline characteristics between patients with no-reflow and patients with normal flow. The number of patients with ST-elevation myocardial infarction was higher in the ticagrelor-loaded group compared with the clopidogrel-loaded group (P = 0.013). Age, aspartate aminotransferase (AST), C-reactive protein (CRP), peak creatine kinase MB (CK-MB), diabetes mellitus (DM) rate, length of stent, number of stents, and number of patients with low ejection fraction were significantly higher in the no-reflow group compared with the normal flow group. The rate of NRP development was significantly lower in ticagrelor-loaded patients (19% P = 0.001), independent of other independent variables, including age, DM, AST, CRP level, number of stents implanted, and type of myocardial infarction (odds ratio = 0.228, 95% confidence interval = 0.102–0.512, P < 0.001). *Conclusion:* Ticagrelor is superior to clopidogrel in preventing the development of NRP.

Keywords: Ticagrelor; Clopidogrel; No-reflow

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1. Introduction

Atherosclerosis is a chronic inflammatory fibroproliferative vascular disease characterized by endothelial dysfunction that affects the intima of large and medium-sized arteries and may also affect the media and adventitia.

Ischemic heart disease as a result of atherosclerosis is the most common cause of death in our country and in the world [1]. The increase in invasive interventions in acute coronary syndrome (ACS), which constitute the most important part of ischemic heart diseases, has introduced new problems. Angiographically, the abrupt interruption of coronary flow without factors such as dissection, thrombus, spasm, or high-grade residual stenosis (Thrombolysis in Myocardial Infarction [TIMI] 0–1) is considered "no-reflow," while lesser impairment in flow (TIMI 2) is generally defined as "slow flow" [2]. In addition, in some cases where normal flow is observed on angiography, "no-reflow" can be observed at the microvascular level [3]. Therefore, the most important point in acute myocardial infarction (AMI) reperfusion therapy is to ensure microvascular perfusion [3]. The best method to prevent no-reflow is to open the artery responsible for the infarct as soon as possible, reduce oxygen demand with effective anti-ischemic therapy, and prevent distal embolization of the thrombus with appropriate antiplatelet therapy [4]. An adenosine diphosphate (ADP) receptor inhibitor is routinely added to acetylsalicylic acid as secondary antiplatelet therapy in the treatment of patients implanted with intracoronary stents to prevent ischemic events [5]. Clinical benefits of adding clopidogrel to acetylsalicylic acid for the prevention of cardiovascular events after percutaneous coronary intervention (PCI) have been demonstrated in scientific studies [6,7]. Ticagrelor is a novel ADP receptor antagonist called cyclopentyltriazolopyrimidine [8]. Compared to clopidogrel, ticagrelor shows a higher degree of platelet inhibition, reaches maximum inhibition of platelet aggregation more rapidly, and inhibits platelet aggregation more consistently [8-10]. In this study, we aimed to evaluate myocardial reperfusion in light of the electrocardiography (ECG) and angiography data of patients with AMI who underwent PCI after ticagrelor or clopidogrel preload as well as to investigate the relationship between ticagrelor and clopidogrel on the development of no-reflow phenomenon.

2. Materials and methods

Local ethics committee approval was obtained for our single-center, retrospective study. The records of patients with AMI admitted to our hospital between September 2014 and November 2015 were reviewed. We included 200 patients who were over 18 years of age, who were not given thrombolytic therapy at admission, who were given one of the ADP receptor antagonists (clopidogrel or ticagrelor) before coronary angiography, and who underwent PCI in subsequent coronary angiography by scanning coronary angiography video image records, patient files, and electrocardiography hospital records. These patients were included in date order. There were 100 clopidogrel-loaded patients and 100 ticagrelor-loaded patients. Patients younger than 18 years of age, patients in pregnancy and lactation, patients who received thrombolytic therapy, patients who did not receive clopidogrel or ticagrelor in the preload, and patients who did not undergo PCI after coronary angiography were excluded.

All patients admitted with AMI received a loading dose of 300 mg acetylsalicylic acid and 180 mg ticagrelor or 300–600 mg clopidogrel, and all patients underwent coronary stenting. No glycoprotein IIb-IIIa antagonist was given to the patients before the procedure. Unfractionated heparin or low molecular weight heparin was administered at a dose titrated according to weight.

Coronary angiography was performed with Philips Integris Allura angiography device using the standard Judkins method through the femoral artery and iopromide (Ultravist 370) as opaque material. Coronary angiography images were recorded and analyzed on compact disks in DICOM format. No-reflow phenomenon was defined as abrupt cessation of coronary flow in the absence of factors such as dissection, mechanical obstruction, or significant residual stenosis, post-procedural TIMI flow < 3 or TIMI flow 3, myocardial staining (blush) index 0 or 1, or ST resolution < 70% within four hours after the procedure [11]. The patients were divided into two groups, 61 patients with no-reflow and 139 patients with normal flow.

Physical examination findings and detailed medical history were obtained from patient archive files. Risk factors for coronary artery disease (CAD) were recorded. ST resolution was analyzed on a 12-lead

ECG obtained within four hours after the procedure. Complete blood count (CBC), creatinine, lipid profile, peak creatine kinase MB (CK-MB), and troponin levels were recorded via the hospital data processing system. Troponin-T values above 0.1 ng/mL were considered positive. We performed hemogram evaluation with Beckman Coulter LH 780 device; lipid panel, liver function tests, and renal function tests with Roche Cobas C501 device; and troponin evaluation with Roche Elecsys 2010 device.

In this study, in which the effect of clopidogrel and ticagrelor on the development of no-reflow in patients with AMI was examined, there were two groups, patients loaded with clopidogrel or ticagrelor. According to the power analysis, with 80% power and 5% Type I error, a minimum of 96 people in each group and 192 people in total were required.

SPSS for windows, version 16.0 (SPSS Inc, Chicago, Illinois, USA) was used as the statistical program. Quantitative data were defined as mean ± standard deviation (SD). Median and 25/75th percentile values were defined for non-normally distributed data. Mean values between groups were compared with parametric independent-sample *t*-test or non-parametric Mann Whitney U test (if appropriate) according to the distribution of data. Categorical data were compared with chi-square test. Qualitative data were expressed as percentages. Binary logistic regression analysis was used to determine independent predictors for the development of no-reflow. *P*-values below 0.05 were considered significant.

3. Results

A total of 200 patients, 50 women (25%) and 150 men (75%), with a mean age of 59.91 ± 12.16, were included in the study. Of the patients in the study group, 101 (50.5%) had hypertension, 48 (24%) had previous myocardial infarction, 40 (20%) had DM, 132 (66%) smoked, and 46 (23%) had hyperlipidemia. There was no statistically significant difference between ticagrelor-loaded patients and clopidogrel-loaded patients in terms of age, gender, DM, hypertension, previous myocardial infarction, hyperlipidemia, smoking history, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, triglycerides, white blood cell (WBC), mean platelet volume (MPV), platelet (PLT), hemoglobin (HBG), C-reactive protein (CRP), peak troponin, and CK-MB values (**Table 1**).

Table 1. Baseline characteristics and clinical features of the patients in the no-reflow and normal flow groups

Parameters	No-reflow (n = 61)	Normal flow (n = 139)	*P*
Age (years)	63.07 ± 13.13	58.53 ± 11.64	0.016
Female (%)	31.1	22.3	0.215
Diabetes mellitus (%)	32.8	14.4	0.004
Hypertension (%)	45.9	52.5	0.240
Smoking (%)	60.7	68. 3	0.332
Hyperlipidemia (%)	31.1	19.4	0.099
Creatinine (mg/dL)	0.905 ± 0.370	0.829 ± 0.227	0.076
ALT (U/L)	21 (13–34)	21 (16–28)	0.682
AST (U/L)	30 (19.5–83.5)	29 (20–50)	0. 005
LDL (mg/dL)	104.93 ± 35.605	106.16 ± 38.548	0.833
HDL (mg/dL)	36.606 ± 11.299	35.654 ± 10.305	0.560
Total cholesterol (mg/dL)	189.62 ± 40.005	190.55 ± 42.484	0. 885
Triglyceride (mg/dL)	158.11 ± 66.644	156.32 ± 83.760	0.883

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Parameters	No-reflow (n = 61)	Normal flow (n = 139)	*P*
WBC (× 10^3/μL)	12.051 ± 3.707	11.203 ± 3.661	0.135
MPV (fL)	9.785 ± 0.992	9.601 ± 1.206	0.297
PLT (× 10^3/μL)	252.05 ± 95.302	262. 81 ± 153.187	0.613
HBG (g/dL)	13.716 ± 1.975	14.202 ± 1.802	0.090
CRP (mg/L)	7.3 (2.8–22.4)	3.2 (1.55–7.1)	< 0.001
cTn-T peak (ng/mL)	9.7 (2.3–31.1)	5.8 (1.54–23)	0. 191
CK-MB peak (ng/mL)	69.6(33.4-139)	41(3.8 -107.6)	0.031
Stent diameter (mm)	2.885±0.448	2.892±0.372	0.911
Stent length (mm)	19.311±6.469	17.518±5.617	0. 049
Number of atents	1.360±0.484	1.187±0.391	0.008
EF (%)	42.918±8.177	45.690±7.602	0.021
Clopidogrel-loaded patients (n,%)	42(42%)	58(58%)	0. 001
Ticagrelor-loaded patients (n,%)	19(19%)	81(81%)	0.001
STEMI (n,%)	49(80.3%)	73(52.5%)	<0.001
NSTEMI (n,%)	12(19.7%)	66(47.5%)	<0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase MB; CRP, C-reactive protein; EF, ejection fraction; HBG, hemoglobin; HDL, high-density lipoprotein; cTn, cardiac troponin; LDL, low-density lipoprotein; MPV, mean platelet volume; NSTEMI, non-ST-elevation myocardial infarction; PLT, platelet; STEMI, ST-elevation myocardial infarction; WBC, white blood cell.

Of the 200 patients, 61 (30.5%) had no-reflow phenomenon and 139 (69.5%) had normal flow. Post-PCI ECGs of 139 patients with normal flow showed > 70% ST resolution. In terms of type of myocardial infarction, 49 (80.3%) of 61 patients with no-reflow had ST-elevation myocardial infarction (STEMI) and 12 (19.7%) had non-ST-elevation myocardial infarction (NSTEMI), while 73 (52.5%) of 139 patients with normal flow had STEMI and 66 (47.5%) had NSTEMI; the rate of STEMI was significantly higher in patients with no-reflow ($P < 0.001$), as shown in **Table 1**.

Of the 200 patients included in the study, 122 had STEMI, and the number of patients with STEMI was higher in ticagrelor-loaded patients (70, 57.37%; $P = 0.013$), as shown in **Figure 1**.

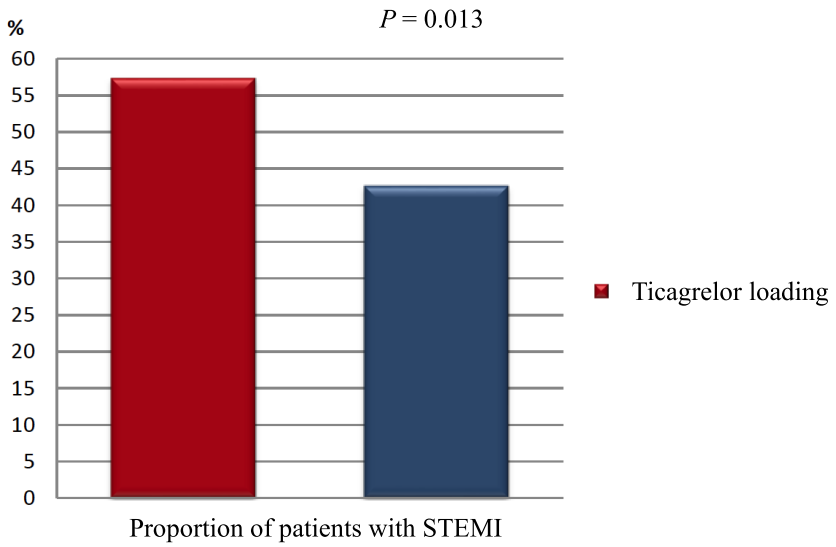

Figure 1. Proportion of patients with STEMI according to drugs loaded

There was no significant difference between the no-reflow (61 patients) and normal flow (139 patients) groups in terms of gender, hypertension, smoking, and hyperlipidemia ($P > 0.05$), as shown in **Table 1**. The mean age of the no-reflow group was significantly higher than that of the normal flow group (63.07 ± 13.13 and 58.53 ± 11.64, respectively; $P = 0.016$). In the study, 20 (32.8%) of 61 patients with no-reflow and 20 (14.4%) of 139 patients with normal flow had history of DM, and the rate of diabetes was higher in the group with no-reflow ($P = 0.004$), as shown in **Table 1**.

There was no statistically significant difference in creatinine, ALT, LDL, HDL, total cholesterol, triglyceride, WBC, MPV, PLT, HBG, and peak troponin levels between the no-reflow and normal flow groups ($P > 0.05$), as shown in **Table 1**. The median and 25/75th percentile values of AST were 30 (19.5–83.5) U/L in the no-reflow group and 29 (20–50) U/L in the normal flow group, and the AST level measured at admission was higher in the no-reflow group ($P = 0.005$). The median and 25/75th percentile values of CRP were 7.3 (2.8–22.4) mg/L in the no-reflow group and 3.2 (1.55–7.1) mg/L in the normal flow group, and the CRP level measured at admission was significantly higher in the no-reflow group ($P < 0.001$). The median and 25/75th percentile values of peak CK-MB were 69.6 (33.4–139) ng/mL in the no-reflow group and 41 (3.8–107.6) ng/mL in the normal flow group, and the peak CK-MB level was significantly higher in the no-reflow group ($P < 0.001$), as shown in **Table 1**.

The number of coronary stents used during coronary intervention was 1.36 ± 0.48 and 1.18 ± 0.39 in the no-reflow and normal flow groups, respectively, and the number of stents used was significantly higher in the no-reflow group ($P = 0.008$). The length of the stents used was also significantly longer in the no-reflow group ($P = 0.049$). There was no statistical difference in stent diameter between the no-reflow and normal flow groups ($P > 0.05$). On transthoracic echocardiography performed before PCI, left ventricular ejection fraction was significantly lower in patients with no-reflow compared to those with normal flow ($P = 0.021$), as shown in **Table 1**.

The rates of no-reflow development in patients loaded with ticagrelor or clopidogrel before PCI were 19% and 42%, respectively, with statistically significant difference between the groups ($P = 0.001$), as shown in **Figure 2**.

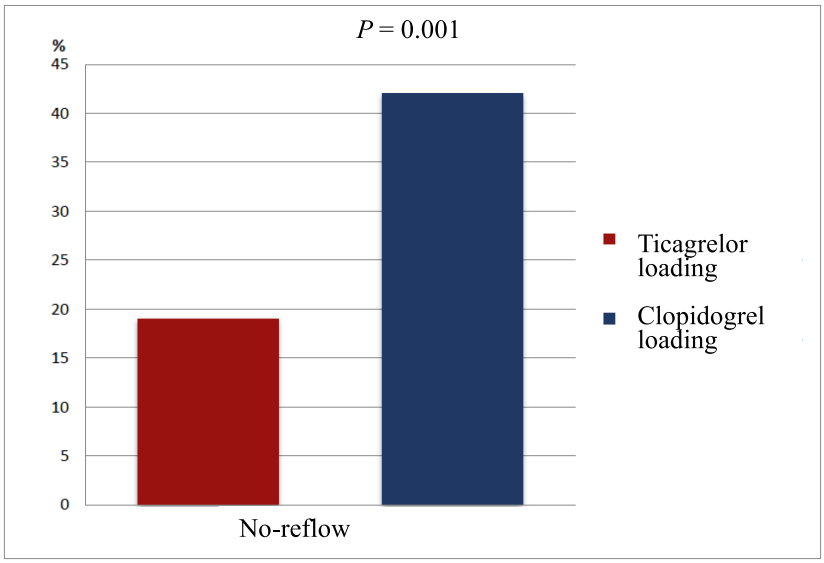

Figure 2. Rates of no-reflow development in patients loaded with ticagrelor or clopidogrel

Independent predictors of no-reflow were analyzed by regression and summarized in **Table 2**.

Table 2. Binary logistic regression of independent variables determining no-reflow development

Variable	*P*	β	95% CI
Age	0.028	1.037	1.004–1.071
DM	0.026	2.869	1.133–7.260
AST	0.054	1.005	1.000–1.011
CRP	0.044	1.014	1.000–1.027
Number of stents	0.027	2.685	1.121–6.429
STEMI	< 0.001	6.454	2.642–15.766
Loading ticagrelor	< 0.001	0.228	0.102–0.512

Abbreviations: AST, aspartate aminotransferase; CI, confidence index; CRP, C-reactive protein; DM, diabetes mellitus; STEMI, ST-elevation myocardial infarction.

Advanced age, presence of DM, increased number of stents, and type of MI (STEMI) increased no-reflow by 1.037-fold, 2.8-fold, 2.6-fold, and 6.4-fold, respectively, while ticagrelor loading reduced no-reflow by 78% relative risk reduction compared with clopidogrel loading.

4. Discussion

In our study, NRP was observed less frequently in ticagrelor-loaded patients, and ticagrelor was superior to clopidogrel in preventing no-reflow. The predictors of NRP were advanced age, history of DM, elevated AST, elevated peak CK-MB, elevated CRP, type of MI, low ejection fraction, stent length, and number of stents used.

The incidence of NRP is as high as 2% in elective PCIs and 11%–40% in primary interventional revascularization of AMI [12]. The pathophysiology of no-reflow is complex, and there are several contributing factors. The reasons for the high rate of no-reflow in AMI include endothelial injury, inflammation, neutrophil plugging, vasospasm, thrombus agglutination, and greater distal microembolization. NRP can be demonstrated by methods other than coronary angiography. Myocardial contrast echocardiography is one of the most sensitive methods for the assessment of no-reflow [13]. No-reflow can also be detected by scintigraphy, nuclear magnetic imaging, positron emission tomography, intracoronary pressure measurement, and coronary artery flow velocity [14,15]. ST-segment regression on ECG is widely used to diagnose no-reflow because it reflects successful myocardial perfusion rather than epicardial coronary flow restoration and the results of this method are highly parallel with myocardial contrast echocardiography [13,16]. The development of no-reflow after AMI is associated with increased mortality, left ventricular systolic dysfunction, left ventricular remodeling, malignant arrhythmias, and cardiac rupture [17]. No-reflow contributes to all of these parameters, and progressive left ventricular enlargement has been observed in patients with persistent no-reflow. Therefore, the main goal of AMI treatment is to ensure perfusion at the microvascular level and the complete opening of the artery responsible for the infarction [18]. No-reflow is influenced by many factors such as age, gender, infarction location, reperfusion time, severity of inflammation, and medication used before and during the procedure.

In order to determine the efficacy and safety of one-year treatment with ticagrelor + aspirin or clopidogrel + aspirin, the phase III Platelet Inhibition and Patient Outcomes (PLATO) trial enrolled patients with either STEMI (38%) intended for primary PCI or NSTEMI-unstable angina pectoris (UAP) (62%) intended for interventional or medical approach. Patients were randomized to either the 180 mg ticagrelor loading dose followed by 90 mg twice daily or the 300–600 mg clopidogrel loading dose followed by 75 mg daily treatment for the prevention of cardiovascular events. The primary endpoint (a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) occurred at 12 months in 11.7%

of patients receiving clopidogrel and 9.8% of patients receiving ticagrelor (relative risk reduction of 16%; $P < 0.001$). In one analysis, the difference in treatment effect was evident within the first 30 days of treatment and persisted up to 12 months after excluding patients with any primary event during the first 30 days. In patients with stents, ticagrelor was associated with a 25% relative risk reduction in absolute/probable stent thrombosis compared to clopidogrel. All-cause mortality was found to be 22% lower with ticagrelor compared to clopidogrel ($P < 0.001$) [19].

The precipitating event in STEMI is atherosclerotic plaque rupture resulting in intraluminal thrombus formation. Distal embolization of thrombus, possibly associated with or independent of PCI, is associated with a higher no-reflow rate in patients with STEMI. Although there were more STEMI patients in the ticagrelor group, significantly fewer NRP were observed in the ticagrelor group (**Figure 1**).

In our study, we demonstrated that ticagrelor, which has a higher degree of platelet inhibition compared to clopidogrel, reaches maximum inhibition of platelet aggression faster, inhibits platelet aggregation more consistently [8-10], significantly increases regional myocardial blood flow, protects endothelial cell integrity, prevents leukocyte activation, and increases plasma concentration of adenosine [20]; it is superior to clopidogrel in preventing no-reflow. In the PLATO trial, the primary outcome (as mentioned above) occurred at 12 months in 9.8% of patients receiving ticagrelor compared to 11.7% receiving clopidogrel. Perhaps, the main factor contributing to the superiority of ticagrelor over clopidogrel in this study was the prevention of no-reflow.

Large-scale prospective studies in older patients with AMI have shown that older patients have higher in-hospital and long-term mortality rates as well as lower success rates of primary PCI compared with younger patients [21]. The difference is mainly due to delayed time to hospital admission and increased co-morbidities in the elderly. Perhaps, complex coronary anatomy, such as diffuse coronary atherosclerosis and severe vascular calcification, which are more common in the elderly, predisposes to distal microembolization and impaired microcirculation. These pathological changes are associated with advanced age and cause distal embolization during PCI, leading to the development of no-reflow. There are many studies in literature supporting the increase in NRP in elderly patients. In a large-scale study by Oduncu *et al*. in which 1,617 patients were screened, it was found that the development of no-reflow increased above the age of 65 [22]. In our study, the mean age of the group with no-reflow was significantly higher than the that of the group with normal flow ($P = 0.016$), and we observed that advanced age is a risk factor for no-reflow; this finding is consistent with available literature data.

Hyperglycemia and history of DM are associated with increased mortality after MI. Diabetic patients have a higher risk of developing no-reflow regardless of their glycated hemoglobin (HbA1c) levels [23]. It has been observed that the accumulation of leukocytes in the coronary capillary bed after PCI is much higher in diabetic than in non-diabetic animal hearts [24]. Leukocyte plugs in the capillary bed are one of the factors involved in the development of NRP. Hyperglycemia also increases thrombus formation, leading to microthrombus formation in the capillary bed and NRP. Consistent with our current knowledge, a history of DM increased the risk of no-reflow in our study ($P = 0.004$).

Elevated CRP, a marker of inflammation and an acute phase reactant, is recognized as a risk factor for cardiovascular diseases. Many large-scale epidemiologic studies have shown that CRP, when measured with high sensitivity (hs-CRP), is a strong and independent risk factor for MI, stroke, and sudden cardiac death even in healthy individuals. Studies have shown that hs-CRP is associated with increased cardiovascular events in healthy individuals, patients with stable and unstable coronary arteries, and in acute MI [25,26]. Inflammation is also attributed for the development of no-reflow, for which multiple mechanisms are responsible. Jesel *et al*. evaluated no-reflow in patients with AMI using magnetic resonance imaging. Through univariate analysis, a significant correlation was found between microvascular occlusion score and admission CRP [27]. In our study, CRP levels at admission were found to be significantly higher

in patients with angiographic no-reflow.

In our study, AST and peak CK-MB levels were evaluated for infarct size and left ventricular ejection fraction after PCI for the amount of myocardium saved in the group with no-reflow. Peak CK-MB level was found to be higher in the no-reflow group. Our study showed that the amount of myocardium at risk saved by PCI was lesser in the group with no-reflow compared to that in the group with normal flow. Left ventricular ejection fraction was lower in the no-reflow group. Our study, in which the area of myocardium at risk correlated with no-reflow, supports previous studies, showing a close correlation between infarct area and anatomic no-reflow area [28].

In our study, we also observed that the number of stents used during PCI and the length of stent increased the development of no-reflow. The reason may be that the plaque content exposed by coronary stent implantation may cause slowing of flow and development of no-reflow by platelet aggregation and distal embolization.

5. Study limitations

This study was based on a single-center, retrospective design. Although TIMI flow grading is still the most common method used to assess reperfusion, myocardial contrast echocardiography, which provides more meaningful results, was not used, and the role of adenosine in the superiority of ticagrelor over clopidogrel in preventing the development of no-reflow could not be determined, as plasma adenosine concentration could not be measured.

Disclosure statement

The authors declare no conflict of interest.

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Clinical Effects of Insulin Glargine and Acarbose Tablets in the Treatment of Diabetes Mellitus in the Elderly and Analysis of Glycosylated Hemoglobin

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Abstract: *Objective:* To analyze the clinical effects of insulin glargine and acarbose tablets in the treatment of diabetes mellitus in the elderly and the analysis of glycosylated hemoglobin. *Methods:* Patients (80 cases) from Taizhou City Hospital of Traditional Chinese and Western Medicine (January 2021–December 2022) were randomly divided into two groups (40 cases/group). Patients in the control group were treated with acarbose tablets, whereas those in the observation group were treated with insulin glargine and acarbose tablets. The clinical effects were compared. *Results:* The difference in blood glucose level and quality of life score between the two groups before treatment was insignificant ($P > 0.05$). The total effective rate (97.5%) of the observation group was significantly higher than that of the control group (85.0%); the blood sugar indices of the observation group were significantly lower than those of the control group; and the observation group scored higher in the quality-of-life scale than the control group ($P < 0.05$). *Conclusion:* Diabetes in elderly is characterized by repeated attacks. The elderly often suffers from chronic diseases, such as cardiovascular disease and respiratory system disease, making it is challenging to achieve the desired effect in treatment. Therefore, it is necessary to explore new treatment methods for the management of diabetes in the elderly. Insulin glargine is a new type of insulin analog, which can last for 24 hours, effectively controlling patients' blood sugar level. According to research, insulin glargine can effectively regulate the blood sugar level of diabetic patients for an extended period of time, significantly lower the fasting blood sugar, and reduce the complications caused by hypoglycemia. Acarbose tablet, on the other hand, is an alpha-glucosidase inhibitor, which prevents the breakdown of starch into sugar, thereby reducing postprandial blood sugar levels. For diabetic patients, especially those whose staple food is starch, acarbose is a suitable drug.

Keywords: Insulin glargine; Acarbose tablets; Elderly diabetes mellitus; Clinical effect; Glycosylated hemoglobin

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1. Introduction

As society ages, the prevalence of diabetes is on the rise. At the same time, most elderly patients have concomitant coronary heart disease, hypertension, and other diseases. Without early intervention or treatment, long-term complications involving multiple organs including the nerves and kidneys may occur [1]. In addition, due to the prolonged disease duration and low treatment compliance, drug selection in elderly diabetic patients often leads to relatively insufficient levels of insulin secretion or decreased insulin sensitivity [2]. For the elderly, controlling blood sugar, preventing complications, and restoring normal

insulin secretion are crucial in the course of treatment. However, treatment with a single drug may not achieve satisfactory outcomes, while long-term insulin injections may easily lead to abnormal blood sugar and even threaten their lives [3,4]. According to experts, the combined use of insulin glargine and acarbose can significantly improve the therapeutic effect of diabetes in the elderly. Therefore, 80 elderly diabetic patients (admission time from January 2021 to December 2022) were selected and randomly divided into two groups: an observation group and a control group. Patients in the control group were managed with acarbose tablets, whereas those in the observation group were managed with insulin glargine and acarbose tablets.

2. Materials and methods

2.1. General information

The study subjects were 80 elderly patients with diabetes admitted from January 2021 to December 2022. The patients were divided into two equal groups according to the treatment used. Patients in the control group were treated with acarbose tablets, whereas those in the observation group were treated with insulin glargine and acarbose tablets. The gender ratio (male/female) of the control group and the observation group were 29/11 and 30/10, respectively, and their mean age was 69.54 ± 4.18 (61–78 years old). The difference between the two groups was insignificant ($P > 0.05$).

2.2. Treatment methods

All patients received diet guidance and exercise guidance. On this basis, acarbose tablets were prescribed TDS with meals at 50 mg/day. Given that the patients did not develop any adverse reaction, the dose of drug was increased, not exceeding 300 mg/day, and their blood glucose levels were controlled at 7–8 mmol/L 2-hour postprandial. Patients in the observation group were treated with insulin glargine on the basis of acarbose tablets. The daily dose was determined based on fasting blood glucose (FBG), with a target value of 5.6 mmol/L; 2 U of insulin glargine was required for every excess of 1 mmol/L, the dosage was adjusted once every 3 days, and the 2-hour postprandial blood glucose was maintained at the standard value. All patients continued treatment for 3 months.

2.3. Outcome indicators

(i) Curative effect: markedly effective, FBG < 7 mmol/L; effective, 7 mmol/L ≤ FBG ≤ 8 mmol/L; ineffective, does not meet the above criteria. Total effective rate = markedly effective + effective.

(ii) Blood glucose indices: FBG, 2-hour postprandial glucose (2-hour PG), and glycosylated hemoglobin (HbA1c).

(iii) Quality of life: a scale consisting of eight items, each with 100 points; the higher the score, the higher the quality of life.

2.4. Statistical analysis

Data were processed using SPSS 22.0. Measurement data were represented by mean ± standard deviation, and t-test was used. Enumeration data were expressed in percentage (%), and χ^2 test was used. $P < 0.05$ indicates statistically significant difference.

3. Results

3.1. Curative effect

As shown in **Table 1**, the total effective rate of the observation group (97.5%) was significantly higher than that (85.0%) of the control group ($P < 0.05$).

Table 1. Comparison of curative effects

Group	Number of cases	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	40	29 (72.5)	10 (25.0)	1 (2.5)	39 (97.5)
Control group	40	20 (50.0)	14 (35.0)	6 (15.0)	34 (85.0)
χ^2		1.03 0	0.514	3.295	3.295
P		0.016	0.473	0.0 01	0.0 01

Data are presented in n (%).

3.2. Blood sugar indices

As shown in **Table 2**, there was little difference in the blood glucose indices of the two groups before treatment ($P > 0.05$). However, after treatment, the blood glucose indices of the observation group were lower compared those of the control group ($P < 0.05$).

Table 2. Comparison of blood glucose indices

Group	Number of cases	FBG (mmol/L)		2-hour PG (mmol/L)		HbAlc (%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	40	8.12 ± 2.24	5.12 ± 1.03	11.60 ± 1.42	8.03 ± 0.34	9.13 ± 3.46	5.12 ± 0.43
Control group	40	8.91 ± 3.42	5.35 ± 1.47	11.45 ± 1.07	9.35 ± 0.27	8.47 ± 2.35	6.28 ± 0.57
t		1.195	7.813	0.962	34.665	1.799	18.524
P		0.233	0.000	0.337	0.000	0.073	0.000

Data are presented in mean ± standard deviation. Abbreviations: 2-hour PG, 2-hour postprandial glucose; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin.

3.3. Quality of life

As shown in **Table 3**, there was no significant difference in quality-of-life scores between the two groups before treatment ($P > 0.05$); however, after treatment, the quality-of-life scores of the observation group were lower than those of the control group ($P < 0.05$).

Table 3. Comparison of quality-of-life scores

Group	Number of cases	Mobility		Body pain		Emotion		Mental health	
		Before	After	Before	After	Before	After	Before	After
Observation group	40	65.87 ± 8.22	95.35 ± 13.48	66.12 ± 8.46	97.34 ± 1.28	66.33 ± 2.40	96.82 ± 1.24	71.42 ± 2.56	95.42 ± 3.20
Control group	40	65.74 ± 6.28	84.44 ± 10.47	66.33 ± 8.58	80.64 ± 2.20	66.42 ± 2.41	80.54 ± 2.30	71.77 ± 2.65	79.58 ± 2.60
t		0.078	4.043	0.110	41.497	0.167	39.405	0.601	24.298
P		0.937	0.000	0.913	0.000	0.868	0.000	0.550	0.000
Group	**Number of cases**	**Vitality**		**Role limitation**		**Social skills**		**General health**	
		Before	**After**	**Before**	**After**	**Before**	**After**	**Before**	**After**
Observation group	40	66.22 ± 9.15	96.44 ± 13.67	67.44 ± 1.92	95.15 ± 10.88	63.28 ± 6.87	95.87 ± 2.23	70.64 ± 1.82	96.44 ± 13.67

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Group	Number of cases	Vitality		Role limitation		Social skills		General health	
		Before	After	Before	After	Before	After	Before	After
Control group	40	66.57 ± 9.22	85.45 ± 11.84	67.50 ± 1.43	82.14 ± 8.64	63.66 ± 6.99	79.85 ± 2.24	70.25 ± 1.65	85.45 ± 11.84
t		0.170	3.843	0.159	5.923	0.245	32.055	1.004	3.843
P		0.865	0.000	0.875	0.000	0.807	0.000	0.319	0.000

Data are presented in mean ± standard deviation. Before and After refer to before and after treatment, respectively.

4. Discussion

With the development of society and the improvement of people's living standards, the number of diabetic patients is increasing. Diabetes and its complications have become one of the significant challenges that the medical field needs to face [5,6]. Especially since the 19th century, it is important to accurately assess and determine the blood glucose level of patients. In elderly diabetic patients, blood sugar rises over a longer period of time, increasing the risk of cardiovascular and cerebrovascular diseases and thus negatively affecting their life and quality of life. Therefore, it is imperative to improve the prevention and treatment of diabetes. The occurrence of diabetes in elderly is related to genetic and environmental factors, and its symptoms include weight loss, thirst, hunger, *etc*. The disease favors people over the age of 60 and is often associated with hypertension and cardiovascular disease. For treatment, oral drugs and insulin can generally be used. However, the course of treatment for elderly patients is often complicated and lengthy, and this group of patients cannot completely rely on the basic treatment used for diabetes. These treatments may cause side effects on the brain, which would worsen the condition.

Acarbose is a commonly used drug and widely used as an oral treatment. Acarbose is a glucosidase inhibitor, which can effectively inhibit the activity of glucosidase, strengthen the function of carbohydrate degrading enzymes, promote the absorption of glucose, and help stabilize blood sugar levels. Especially for those who prefer starchy food, the use of acarbose has a significant and rapid effect. However, it should be noted that the drug has a short half-life and its long-term use will damage the function of islet cells, resulting in the weakening of its effect in lowering blood sugar levels [7,8]. Insulin glargine has a longer duration of action but rapidly metabolizes in as short as 10 minutes, lasting for a few hours. After subcutaneous injection, the drug is quickly absorbed through fat, muscle, and liver tissues, effectively reducing blood sugar levels. Elderly diabetic patients can use the aforementioned two drugs together to improve cell function, make up for the deficiency of single acarbose treatment, and achieve blood sugar control goals at a faster rate [9,10]. The hexameric structure of insulin breaks down into yellow dimers that inhibit the release of primary glycogen. Like the substances released by islet cells, insulin functions the same and can enhance the secretion of insulin [11,12]. Compared with insulin-resistant preparations, its peak value is lower, thereby reducing the occurrence of adverse reactions, improving insulin resistance, and effectively controlling blood sugar levels in patients. Insulin glargine belongs to the group of medications called long-acting insulins, which when injected, redistribute tiny medicine particles and release small amounts of insulin, maintaining the drug at a relatively constant concentration within a mild expected range. The effect of the drug varies depending on the rate of absorption. It regulates blood sugar levels by absorbing glucose from small amounts of tissues such as bone and fat to control blood sugar levels.

HbA1c is a marker that reflects average blood sugar levels. The UK Prospective Diabetes Study (UKPDS) has found that controlling HbA1c levels in different types of diabetes could reduce related heart attacks by 14%, risk of diabetes complications by 21%, related deaths by 21%, and microvascular complications by 37% [13,14]. Therefore, the key is to control HBA1c to 6.5% to combat the long-term complications of diabetes. The results of the present study showed that after treatment, all blood sugar

indexes of the observation group significantly reduced ($P < 0.05$). In addition, the most common complication of diabetes in the elderly is hypoglycemia. After the onset of hypoglycemia, symptoms such as confusion, headache, and dizziness will appear, and some patients may be in a critical state. Hypoglycemia can damage their brain tissue, cause stroke, and even threaten the life of patients [15]. According to research, the combined treatment can stabilize patients' blood sugar indices, with the biological effect lasting for more than one day. This prevents large fluctuations in blood sugar, thus maintaining the stability of blood glucose levels. Compared with the sole application of a drug, the combined treatment has less hypoglycemic effect and can improve patients' treatment compliance. In addition, it does not impose an additional burden on the gastrointestinal function of patients and is relatively safe and reliable.

In conclusion, for elderly patients with diabetes, the intervention of adding insulin glargine to conventional acarbose in the treatment of diabetes can ensure the long-term maintenance of blood glucose levels and optimize HbA1c. This method provides a scientific, reasonable, and effective reference for future clinical treatment of diabetic patients. Therefore, the application and popularization of this method are of great significance.

Disclosure statement

The author declares no conflict of interest.

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Analysis of the Clinical Effects of Clopidogrel in the Treatment of Unstable Angina and the Influence of Triacylglycerol and Total Cholesterol Levels

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Abstract: *Objective:* To explore the clinical value of clopidogrel as the main treatment for patients with unstable angina. *Methods:* From January 2020 to December 2022, we assigned 50 cases to the control group (basic treatment) and 50 cases to the observation group (basic treatment with clopidogrel). The clinical data of both groups of patients were analyzed. *Results:* The total effective rate of the observation group was significantly higher than that of the control group after treatment ($P < 0.05$). Before treatment, there were no significant differences in the duration of angina pectoris and frequency of attacks between the two groups ($P > 0.05$); after treatment, the duration of angina pectoris and frequency of attacks in the observation group were significantly lower than those in the control group ($P < 0.05$). Before treatment, there were no significant differences in hemorheological indices, triacylglycerol (TG), total cholesterol (TC), and platelet aggregation rate between the two groups ($P > 0.05$); however, after treatment, they were significantly lower in the observation group than in the control group ($P < 0.05$). Before treatment, there was no significant difference in the scores of SF-36 between the two groups ($P > 0.05$); after treatment, the SF-36 score of the observation group was significantly higher than that of the control group ($P < 0.05$). *Conclusion:* Clopidogrel can promote the rehabilitation of patients with unstable angina during treatment. Compared with conventional basic treatment, it can reinforce the final therapeutic effect. In addition, our study showed that the duration of angina pectoris and the frequency of attacks were shortened after clopidogrel therapy and the treatment had an effect on improving patients' hemorheological indices, TG, TC, and platelet aggregation rate. Clopidogrel therapy plays an important role in ensuring the quality of life of patients after recovery.

Keywords: Unstable angina; Clopidogrel; Triacylglycerol; Total cholesterol

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1. Introduction

Unstable angina is a type of acute coronary syndrome common in cardiovascular medicine. According to the severity of symptoms, its clinical manifestation may vary between stable angina and acute myocardial infarction [1,2]. Due to its rapid progression and high incidence, it may transition to acute myocardial infarction, and in severe cases, induce sudden death. Even if the patient survives, their quality of life would be affected [3-6]. It should be noted that unstable angina is reversible and can stabilize and become stable angina. Some literatures have pointed out that in unstable angina, clopidogrel is usually used for treatment. This drug can inhibit platelet aggregation, prevent thrombosis, and minimize the risk of ischemic events, such as ischemic stroke, myocardial infarction, or cardiac death [7,8]. In view of this, we aimed to determine

the clinical value of clopidogrel therapy as the main treatment for patients with unstable angina.

2. Materials and methods

2.1. General information

From January 2020 to December 2022, we assigned 50 cases to the control group (basic treatment) and 50 cases to the observation group (basic treatment with clopidogrel). The male to female ratio of the control group and the observation group were 25 to 25 and 28 to 22, respectively. The mean age of the patients in the control group was 63.41 ± 3.10 (46–84 years old), while the mean age of those in the observation group was 63.38 ± 3.22 (46–80 years old). There were no significant differences in baseline data between the two groups ($P > 0.05$).

Inclusion criteria: (i) patients who had not received surgical treatment before participating in the study; (ii) patients who understood the significance of the study, cooperated throughout the treatment process, and signed the "Informed Consent"; (iii) patients without active pathological bleeding in the recent period; (iv) patients without major organ dysfunction; (v) patients without abnormal platelet function or coagulation function; (vi) patients without acute myocardial infarction.

Exclusion criteria: (i) patients with communication disorders; (ii) patients with a history of severe allergy to clopidogrel; (iii) patients with malignant tumors, systemic infection, or bleeding tendencies; (iv) patients who left the study midway.

2.2. Treatment methods

Patients in the control group received basic treatment, which included oxygen therapy, sedation, myocardial oxygen consumption reduction therapy, *etc*. At the same time, the patients were given enteric-coated aspirin at a dose of 100 mg once a day, Xiaoxintong (with isosorbide dinitrate as the main ingredient) at a dose of 10 mg three times a day, nitroglycerin via a micropump at 10-30 μg per minute, oral calcium channel blocker, simvastatin, angiotensin-converting enzyme inhibitor or β-receptor blocker, and 5000 U of low-molecular-weight heparin calcium (Q12H) via subcutaneous injection. The patients were treated as such for 28 days.

Patients in the observation group received basic treatment with clopidogrel. The basic treatment was the same as that of the control group, followed by an additional dose of 75 mg clopidogrel, QD, for 28 days.

2.3. Observation indicators

(i) Treatment effect: markedly effective, disappearance of symptoms of angina pectoris and normalized levels of TG and TC after treatment; effective, significant improvement in symptoms of angina pectoris and levels of TG and TC after treatment; ineffective, none of the above standards were met. Total effective rate = 100% – total ineffective rate.
(ii) Duration of angina pectoris and frequency of attacks.
(iii) Hemorheological indices (plasma viscosity and whole blood viscosity), TG, TC, and platelet aggregation rate.
(iv) Quality of life: evaluation of quality of life using the SF-36 assessment scale; the higher the score, the better the quality of life.

2.4. Statistical analysis

SPSS 21.0 was used for statistical processing. Count data were expressed in percentage (%), the χ^2 test was used. Measurement data were expressed in mean ± standard deviation, and t-test was used. $P < 0.05$ indicates statistically significant difference.

3. Results

3.1. Treatment effect

After treatment, the total effective rate of the observation group was significantly higher than that of the control group ($P < 0.05$). See **Table 1** for details.

Table 1. Comparison of treatment effect

Group	Number of cases	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	50	37 (74.0)	11 (22.0)	2 (4.0)	48 (96.0)
Control group	50	24 (48.0)	20 (40.0)	6 (12.0)	44 (88.0)
x^2		14.208	7.574	4.348	4.348
P		0.000	0.006	0.037	0.037

Data are presented in n (%).

3.2. Duration of angina pectoris and frequency of attacks

Before treatment, there were no significant differences in the duration of angina pectoris and frequency of attacks between the two groups ($P > 0.05$). However, after treatment, the duration of angina pectoris and frequency of attacks in the observation group were significantly lower than those in the control group ($P < 0.05$). See **Table 2** for details.

Table 2. Comparison of duration of angina pectoris and frequency of attacks

Group	Number of cases	Duration of angina pectoris (min/time)		Frequency of angina attacks (times/week)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	50	8.87 ± 3.10	4.47 ± 1.88	4.93 ± 1.70	2.19 ± 1.13
Control group	50	8.99 ± 2.91	5.45 ± 2.08	4.81 ± 1.86	2.98 ± 1.78
t		0.200	2.472	0.337	2.650
P		0.842	0.015	0.737	0.009

Data are presented in mean ± standard deviation.

3.3. Hemorheology indices, triacylglycerol, total cholesterol, and platelet aggregation rate

Before treatment, there were no significant differences in hemorheological indices, TG, TC, and platelet aggregation rate between the two groups ($P > 0.05$). However, after treatment, the hemorheological indices, TG, TC, and platelet aggregation rate of the observation group were significantly lower than those of the control group ($P < 0.05$). See **Table 3** for details.

Table 3. Comparison of hemorheology indices, triacylglycerol (TG), total cholesterol (TC), and platelet aggregation rate

Group	Number of cases	Whole blood viscosity (mPa/s)		Plasma viscosity (mPa/s)		TG (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	50	9.34 ± 2.45	6.26 ± 1.87	2.99 ± 0.67	1.54 ± 0.55	12.43 ± 1.09	4.36 ± 0.33
Control group	50	9.51 ± 2.58	7.47 ± 1.98	2.86 ± 0.80	2.06 ± 0.60	12.59 ± 1.12	7.78 ± 0.25

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Group	Number of cases	Whole blood viscosity (mPa/s)		Plasma viscosity (mPa/s)		TG (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
t		0.338	3.142	0.881	4.518	0.724	58.413
P		0.736	0.002	0.381	0.000	0.471	0.000

Group	Number of cases	TC (mmol/L)		Erythrocyte aggregation index		Platelet aggregation rate (%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group		5.83 ± 1.28	2.29 ± 0.30	1.97 ± 0.33	1.49 ± 0.28	39.46 ± 10.65	26.85 ± 9.33
Control group		5.77 ± 1.35	3.82 ± 1.34	1.94 ± 0.38	1.62 ± 0.30	38.83 ± 10.94	33.57 ± 9.99
t		0.228	7.879	0.422	2.240	0.338	3.476
P		0.820	0.000	0.674	0.027	0.736	0.001

Data are presented in mean ± standard deviation. Abbreviations: TC, total cholesterol; TG, triacylglycerol.

3.4. SF-36 score

Before treatment, there was no significant difference in the scores of SF-36 between the two groups ($P > 0.05$). However, after treatment, the observation group had significantly higher scores than the control group ($P < 0.05$). See **Table 4** for details.

Table 4. Comparison of SF-36 scores

Group	Number of cases	Mental health		Body pain		Social function		Physiological function	
		Before	After	Before	After	Before	After	Before	After
Observation group	50	81.03 ± 5.03	90.22 ± 8.08	82.24 ± 4.29	93.22 ± 8.08	82.24 ± 8.53	93.53 ± 8.85	82.28 ± 8.05	92.50 ± 10.35
Control group	50	80.02 ± 5.02	80.28 ± 8.05	82.25 ± 4.28	82.23 ± 8.03	82.20 ± 8.52	85.20 ± 8.20	82.25 ± 8.04	85.83 ± 9.08
t		1.005	6.162	0.012	6.822	0.024	4.882	0.019	3.426
P		0.317	0.000	0.991	0.000	0.981	0.000	0.985	0.001

Group	Number of cases	Emotional function		Vitality		Physiological function		General health	
		Before	After	Before	After	Before	After	Before	After
Observation group	50	88.00 ± 8.53	95.03 ± 9.43	78.53 ± 8.05	92.89 ± 5.08	75.87 ± 7.80	97.37 ± 8.85	78.54 ± 5.00	90.85 ± 8.00
Control group	50	88.09 ± 8.52	87.48 ± 9.48	78.54 ± 7.07	85.87 ± 5.08	75.87 ± 7.88	88.73 ± 5.08	78.57 ± 5.03	77.85 ± 8.58
t		0.053	3.987	0.007	6.909	0.000	6.014	0.030	7.836
P		0.958	0.000	0.995	0.000	1.000	0.000	0.976	0.000

Data are presented in mean ± standard deviation (points). Before and After refer to before and after treatment, respectively.

4. Discussion

Unstable angina is a clinical angina syndrome between stable angina and acute myocardial infarction. In unstable angina, atherosclerosis occurs simultaneously with plaque rupture, while local platelets continue to aggregate and adhere, eventually forming a thrombus [9,10]. In addition, vasospasm also occurs, narrowing

or even occluding the vascular cavity, resulting in reduced coronary blood flow, myocardial hypoxia and ischemia, and a continuous increase in acidic metabolites. Intracoronary thrombus is a white thrombus that is rich in platelets and relatively weak in response to fibrinolytic drugs. The coagulation cascade is activated by thrombin and platelets, and the partially occlusive thrombus progresses into a complete occlusive thrombus, which leads to vascular obstruction, induces acute myocardial infarction, and increases the risk of sudden death in severe cases. Therefore, in the treatment of patients with such diseases, the principles of stabilizing the disease, inhibiting the development of the disease, and reducing or preventing the possibility of developing myocardial infarction or death should be adhered to. In recent years, the preferred treatment for patients with unstable angina is active antithrombotic and anti-ischemic therapy [11,12].

In the past, treatment of patients with unstable angina was based on conventional treatment predicated on the expansion of peripheral blood vessels, so that the preload and afterload of the heart can be significantly reduced, the myocardial contractility and rhythm can be improved, and the myocardial oxygen consumption can be reduced as much as possible to ensure sufficient blood supply to the myocardium, thereby relieving myocardial ischemia and angina pectoris [13,14]. However, if the patient suffers from coronary atherosclerotic plaque rupture or secondary thrombus, this conventional treatment will be ineffective. As a thienopyridine compound, clopidogrel belongs to a new generation of diphosphate acyl glycoside receptor antagonists. The drug itself does not have antiplatelet activity but mainly forms active antiplatelet substances through the oxidation of cytochrome P450 by the liver enzyme system. The product can selectively and irreversibly bind to adenosine diphosphate (ADP) receptors on the platelet surface to inhibit platelet aggregation and prevent thrombus formation. In addition, the drug can also effectively block the cascade amplification reaction following platelet activation. The inhibitory effect of the drug reaches a stable state after about one week of continuous administration, and the maximum inhibitory effect can be up to three months or even longer. The bleeding time and platelet aggregation return to the baseline five days after the drug is discontinued. The results of the present study showed that the total effective rate of the observation group was significantly higher than that of the control group after treatment; in addition, the duration of angina pectoris and frequency of angina attacks were significantly lower in the observation group than in the control group; the hemorheology indices, TG, TC, and platelet aggregation rate of the observation group were also significantly lower than those of the control group; the SF-36 scores were also observed to be significantly higher in the observation group, compared with control group ($P < 0.05$). The results confirm that the comprehensive intervention with clopidogrel, compared with the conventional treatment plan, can significantly improve the curative effect and various indicators, relieve the degree of angina pectoris, and facilitate the early recovery of patients [15].

In short, clopidogrel should be used in patients with unstable angina to stabilize their condition and reduce the degree of angina. On the basis of ensuring a significant therapeutic effect, clopidogrel can improve the symptoms of unstable angina and the quality of life of patients. However, it should be noted that the antiplatelet mechanism of this drug is very complex. Therefore, further explorations are needed to investigate its long-term therapeutic benefit and ideal period of use in clinical settings.

Disclosure statement

The authors declare no conflict of interest.

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New Progress of Clinical Application of Nicorandil in the Treatment of Coronary Heart Disease

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Abstract: Nicorandil (NIC) is a calcium channel blocker, which has been widely used in the treatment of coronary heart disease (CHD). Although NIC has shown good efficacy and safety clinically, there are still some unresolved issues with its therapeutic mechanism and pathway of action. Studies in recent years have shown that the clinical application of NIC in the treatment of CHD has made new progress, such as being widely used in stable angina pectoris (AP), myocardial infarction, and percutaneous coronary intervention (PCI). In this article, we discuss the new progress of NIC in the treatment of CHD.

Keywords: Nicorandil; Coronary heart disease; Clinical application

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1. Introduction

Coronary heart disease (CHD) is a type of heart disease that results from ischemia and oxygen deprivation of the heart muscle due to narrowing or blockage of the coronary arteries. Nicorandil (NIC) can improve the symptoms and prognosis of CHD by inhibiting the entry of calcium ions into cardiomyocytes, reducing myocardial oxygen consumption and inhibiting myocardial contraction. NIC, which can protect the myocardium and thus inhibit the progression of CHD and reduce its complications, is now a widely used drug for CHD. Therefore, the specific use of NIC in the treatment of CHD is comprehensively analyzed in this paper.

2. Mechanism of action of nicorandil on coronary heart disease

CHD is a cardiovascular disease characterized by narrowing, blockage, and/or hardening of the walls of coronary arteries. Its pathogenesis comprises a complex process of multiple factors, including (i) endothelial cell dysfunction (endothelial cells make up a layer of cells in the blood vessel wall, secreting a series of biologically active substances that are important for maintaining vascular endothelial function and vascular tone; endothelial cell dysfunction is an early event in the pathogenesis of CHD, which can lead to vessel wall damage and inflammatory response, thereby promoting plaque formation); (ii) dyslipidemia (hyperlipidemia is an important risk factor for CHD; it can lead to vascular endothelial cell damage and inflammatory response, promoting plaque formation and development); (iii) inflammatory response (the formation and development of CHD plaques are closely related to inflammatory response; there are a large number of inflammatory cells and inflammatory mediators in plaques, such as monocytes, T lymphocytes, and inflammatory cytokines, which are involved in the formation, stability, and rupture of plaques); (iv)

oxidative stress (oxidative stress refers to the imbalance between oxygen free radicals and other oxidants inside and outside cells and antioxidant substances in cells, leading to a series of harmful reactions; in CHD, the generation of oxidative stress is closely related to intraplaque inflammatory response, dyslipidemia, and endothelial cell dysfunction).

NIC, as a calcium channel blocker with a high application rate, can block the influx of calcium ions, reduce the metabolic level of myocardial cells, and play a role in reducing myocardial ischemia and myocardial injury. NIC also has the effect of widening coronary arteries and peripheral blood vessels, reduces blood pressure and cardiac load, improves cardiac function, and reduces cardiac oxygen consumption. In addition, NIC can also inhibit the automaticity and conduction of the heart, slow down the heart rate, and reduce the oxygen demand of cardiomyocytes, thereby alleviating the onset of myocardial ischemia and angina pectoris. The drug also plays a role in the treatment of CHD through some other mechanisms of action. For example, the antioxidant and anti-inflammatory effects of NIC can inhibit the generation of oxygen free radicals and inflammatory responses, thereby alleviating myocardial ischemia and injury. As another example, NIC can inhibit platelet aggregation and thrombus formation, thus preventing the occurrence of serious consequences such as myocardial infarction caused by thrombus formation. Hu *et al.* [1] demonstrated that the intravenous pre-injection of NIC has a protective effect on the brain and can improve the neurological function and cerebral blood flow of rats after cardiopulmonary resuscitation. Shi *et al.* [2] proposed that the drug can resist the specific apoptosis process of hypoxic/reoxygenated cardiomyocytes, thereby reversing the manifestations of myocardial hypoxia.

3. Clinical application of nicorandil in stable angina pectoris

The narrowing or blockage of the coronary arteries in patients with angina predisposes them to myocardial ischemia. At this time, cardiomyocytes require more oxygen and nutrients to maintain normal function. When the myocardial oxygen supply and demand are out of balance, angina pectoris occurs. NIC can increase blood flow, improve myocardial oxygen supply, and reduce cardiac contractility and heart rate, thus reducing myocardial oxygen demand. At the same time, it can also reduce the preload and afterload of the heart, further reducing the burden on the myocardium. In a study by Gao [3], conventional therapy (control group) and NIC therapy (observation group) were used for AP patients. The results showed that the total effective rate of the observation group was 100%. The number of angina attacks, the duration of angina, and the cardiac function indexes of the observation group were better compared with the control group. It is evident that NIC can suppress the symptoms of angina pectoris and restore the relevant indexes of heart function, with a definite curative effect.

4. Clinical application of nicorandil in myocardial infarction

Myocardial infarction is often accompanied by arrhythmias. NIC can reduce the excitability of cardiomyocytes, thereby reducing the occurrence of arrhythmias. After myocardial infarction, patients are also prone to re-infarction. This drug can reduce coronary artery spasm and platelet aggregation, thereby preventing the occurrence of re-infarction. It is evident that NIC can improve the prognosis of myocardial infarction through multiple mechanisms, but it should be noted that NIC is not the only drug for the treatment of myocardial infarction. Appropriate treatment options should be selected depending on the case. Ji [4] proposed that the combined therapy of rosuvastatin and NIC should be used for acute non-ST-segment elevation myocardial infarction. The results showed that the clinical efficacy of the combination was better compared with rosuvastatin monotherapy. The levels of high-sensitivity C-reactive protein and nitric oxide also significantly improved in these patients, confirming that the combination of NIC and rosuvastatin can improve the curative effect and protect vascular endothelial function. In the research by Li *et al.* [5], nitroglycerin and NIC intracoronary injection were given before acute myocardial infarction surgery, and

the results showed that the myocardial blood perfusion and cardiac function indicators were better after NIC treatment; moreover, postoperative hypotension and anxiety were lower, without an increase in readmission or mortality rates. NIC clearly plays a role in regulating myocardial blood perfusion in patients with myocardial infarction, optimizes coronary microcirculation, does not affect blood pressure, and improves the prognosis. Zhan *et al.* [6] initiated conventional treatment (control group) and NIC treatment (observation group) for patients with acute myocardial infarction in cardiac arrest. The results showed that the left ventricular ejection fraction, vascular recanalization rate, and the one-year survival rate was higher in the observation group than in the control group; in addition, there were less complications observed in the observation group. This study confirms that NIC, other than having high safety benefits, can improve the prognosis of patients with acute myocardial infarction in cardiac arrest, improve their short-term survival rate, protect their myocardium, and optimize their heart function.

5. Clinical application of nicorandil in unstable angina pectoris

Unstable angina pectoris (UAP), a heart condition that is usually manifested by chest pain or discomfort and caused by insufficient blood supply or the lack of blood to the heart muscle, is more dangerous than stable angina because it may be a precursor to myocardial infarction. In addition, delayed treatment may aggravate the condition and cause irreversible consequences. NIC can quickly relieve the symptoms of UAP and reduce the severity of the disease. Tian *et al.* [7] treated UAP patients with conventional drugs and NIC. The results showed that the total effective rate after NIC treatment was as high as 96.08%, the improvement rate of ECG was as high as 94.12%, and the adverse event rate was only 11.76%. The frequency of angina attacks was less, and the duration was shorter. It can be seen that the drug has a good therapeutic effect on UAP patients as well as high safety and benefits. Yu [8] treated UAP patients with NIC, along with symptomatic treatment such as nitrates, plaque-stabilizing drugs, and anti-platelets. The results showed that after the combined treatment, the clinical efficacy and the symptom score of angina pectoris significantly improved. It is evident that the drug has a relatively strong effect on platelet activation and can comprehensively improve the therapeutic effect on UAP.

6. Clinical application of nicorandil in heart failure

Heart failure (HF) is caused by myocardial ischemia and hypoxia due to coronary artery disease, often resulting in decreased cardiac function and increased risk of death. Myocardial ischemia and hypoxia can lead to myocardial cell death and fibrosis, resulting in decreased myocardial contractility, impaired diastolic function, and ultimately heart failure. HF can lead to pulmonary edema and pulmonary hypertension, causing dyspnea, pneumonia, and other diseases. Myocardial electrophysiological abnormalities and cardiac structural changes, which can easily lead to arrhythmia and sudden death, may be evident in severe cases. The curative effect of NIC in the treatment of this disease is remarkable, and the manifestations of HF can be corrected as soon as possible. Li *et al.* [9] used recombinant human brain natriuretic peptide on the basis of conventional treatment to treat patients with HF (control group) and added NIC for treatment of patients in the study group. The results showed that the total effective rate of the study group was 96%. After 4 weeks of treatment, their heart function was better than that of the control group, the level of nitric oxide increased, and the content of endothelin decreased. However, the incidence of adverse reactions between the groups were similar (12% in the study group versus 10% in the control group). It is evident that NIC combined with recombinant human brain natriuretic peptide on the basis of conventional treatment can improve the curative effect of HF and protect heart function.

6. Clinical application of nicorandil in percutaneous coronary intervention

Percutaneous coronary intervention (PCI) is a commonly used cardiac interventional therapy, often in the

treatment of CHD. This procedure is effective for the dilatation of coronary artery stenosis, restoration of myocardial blood supply, and prevention of myocardial infarction and other serious consequences. In recent years, with the continuous advancements in equipment and technology, the success rate and safety of PCI have greatly improved. Compared with open surgery, PCI does not require the opening of the chest cavity, has less postoperative pain, faster recovery, and high reliability, and reduces the risk of postoperative complications. In PCI, NIC functions as follows: (i) relieve intraoperative myocardial ischemia (the operation of the equipment in PCI may compress the myocardium, resulting in intraoperative myocardial ischemia; NIC can improve myocardial ischemia and thus alleviate intraoperative myocardial ischemia); (ii) prevent postoperative myocardial ischemia (complications such as vasospasm and thrombosis caused by intravascular mechanical devices or drugs may lead to postoperative myocardial ischemia; NIC can block the massive influx of calcium ions, relieve coronary artery spasm, and prevent postoperative myocardial ischemia). In a study, Liu [10] divided patients undergoing PCI into two groups by lottery; the reference group received conventional treatment, whereas the test group received NIC. The results showed that the test group had higher partial pressure of oxygen and pH value and lower partial pressure of carbon dioxide after treatment, and the majority of patients had TIMI flow 3; the incidence of adverse reactions was similar to that of the reference group. The study suggests that NIC can correct slow blood flow during PCI, improve the blood flow and blood gas index of patients, and increase the coronary artery flow velocity, with good safety and benefits. Gong *et al*. [11] analyzed the preventive effect of NIC on contrast-induced nephropathy after PCI. The results showed that the incidence of contrast-induced nephropathy after NIC treatment was only 2%, which was lower than that of conventional treatment (14%), and the levels of urea and β2-microglobulin at different time points after PCI were lower with NIC treatment. It is evident that NIC is more preventive of contrast-induced nephropathy and can improve various physiological indicators.

7. Nicorandil safety analysis

NIC is a drug widely used in the treatment of CHD. Although NIC has relatively accurate therapeutic effect, it can result in some adverse reactions: (i) facial flushing and headache, which are the most common adverse reactions of NIC due to blood vessel dilation, but they usually disappear within hours of taking the drug, and most patients can tolerate them; (ii) gastrointestinal reactions, including nausea, vomiting, diarrhea, and other symptoms, which may lead to indigestion and loss of appetite; (iii) hypotension and bradycardia, which usually occur after starting NIC, as the drug can cause vasodilation and a drop in heart rate, resulting in hypotension and bradycardia, but they disappear or reduce after adjustment of indications and dosage; (iv) increased blood pressure, especially when NIC is used at high doses; (v) respiratory reactions, such as bronchospasm and asthma, but they are less common; (vi) central nervous system reactions, such as dizziness, headache, insomnia, *etc*.; (vii) allergic reactions, such as urticaria, rash, facial edema, angioedema, *etc*. In addition to the adverse reactions mentioned above, long-term use of NIC may also lead to edema and liver injury. When using this drug, its use should be strictly according to doctor's advice, and patients' vital signs and drug reactions should be monitored regularly. In case of discomfort, medical attention should be sought immediately.

In conclusion, the application prospect of NIC in the treatment of CHD is very broad. In future research, we should continue to explore the combination of NIC with other drugs and propose a variety of drug combinations based on the patient's underlying disease, degree of CHD, age, and treatment needs. At present, the administration routes of NIC are mainly oral and coronary injection. Although it is suitable for the treatment of most CHD patients, the dosage form is limited. Future research can consider enriching its dosage forms, such as patches, suppositories, *etc*., to adapt to the needs of different patients and treatment options. With the advancement of medical technology, individualized treatment with NIC must be emphasized. Through methods such as molecular diagnosis and biomarkers, it is possible to predict the

patient's response to NIC and formulate a corresponding individualized treatment plan.

Disclosure statement

The authors declare no conflict of interest.

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[1] Yao Y., Xia B. Application of Phase Frequency Feature Group Delay Algorithm in Database Differential Access. Computer Simulation, 2014, 31(12): 238-241.

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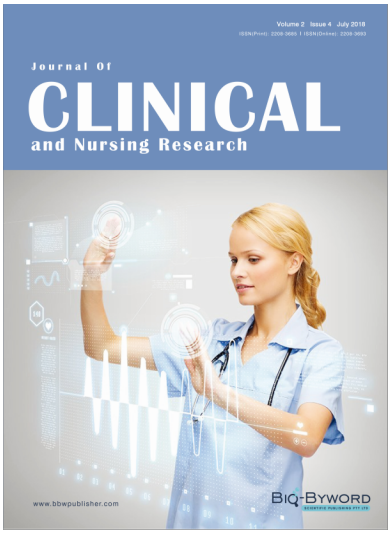

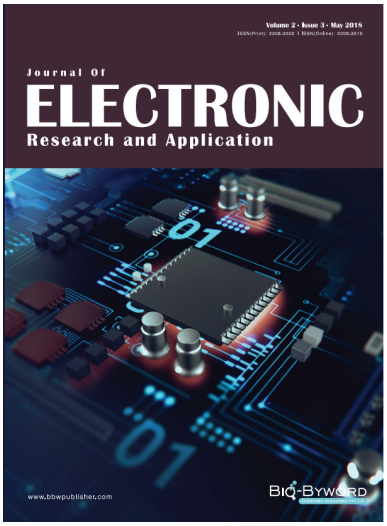

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