Cardiovascular Rehabilitation of Patients With Ischemic Heart Disease Undergoing Medical Treatment, Percutaneous Transluminal Coronary Angioplasty, and Coronary Artery Bypass Grafting

Tales de Carvalho, Ana Luiza Hallal Curi, Dalton Francisco Andrade, Julio da Motta Singer, Magnus Benetti, Alfredo José Mansur

Centro de Educação Física e Fisioterapia da Universidade do Estado de Santa Catarina, Instituto de Matemática e Estatística da Universidade de São Paulo - São Paulo, SP, Florianópolis, SC, Brazil

Objective: To evaluate the occurrence of death and myocardial infarction in subgroups of coronary artery disease patients with hemodynamically significant coronary stenoses undergoing treatment in a cardiovascular rehabilitation program and considered severely ill for: a) not having undergone intervention treatment; b) presenting signs of myocardial ischemia; c) presenting multivessel occlusive disease.

Methods: Retrospective cohort study of 381 patients presented previous coronary angiography showing hemodynamically significant coronary stenoses, for which, because of the anatomic bias, intervention treatment was indicated. The patients were categorized according to the presence or absence of intervention treatment; presence or absence of ischemia in the exercise test; and number of critical coronary stenoses. Statistical analysis was performed using the Kaplan-Meier and logistic regression methods.

Results: Survival probability was not different when patients undergoing medical treatment were compared to those undergoing previous intervention treatment (OR 0.813; 95% CI; 0.366-1.809); with and without evidence of ischemia in the exercise test (OR 0.785; 95% CI; 0.366-1.684); and with one-vessel coronary artery disease and with more-than-one-vessel coronary artery disease (OR 0.824, 95% CI; 0.377-1.798).

Conclusion: In this cohort study, no unfavorable outcome was observed in the subgroups comprised of medically treated patients, with evidence of myocardial ischemia and with multivessel coronary artery disease.

Key words: Cardiovascular diseases/rehabilitation, ischemic heart disease, angioplasty, transluminal percutaneous coronary, myocardial revascularization.

Ischemic heart disease is one of the major public health problems in Brazil[1,2]. Changes for a healthier lifestyle, including diet and regular physical activity, are important strategies of the therapeutic management[3-5].

Structured cardiac rehabilitation programs have been presented as a very interesting therapeutic modality in terms of cost-effectiveness; they are quite safe and, in the absence of contraindications, should be recommended as part of the treatment[6-11]. However, cardiac rehabilitation programs are not always available in proportion to the potential demand. Encouraged by this need, we started our experience with supervised cardiac rehabilitation programs in the city of Florianópolis, State of Santa Catarina, Brazil, in the early 1990's.

Many patients engaged in the program after intervention treatment - Coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. However, among the patients who sought the program, sometimes on their own initiative, with or without referral of their physician whose advices they frequently disagreed with, some had hemodynamically significant coronary stenoses as demonstrated by coronary angiography, and showed evidences of myocardial ischemia in the exercise test, and, in spite of it, they chose medical treatment alone. When coming from clinically stable patients, this request was cautiously complied with, and with time, it provided us with a clinical experience that should be evaluated.

The objective of this observational study was to evaluate the occurrence of hard endpoints (death and myocardial infarction) in subgroups of coronary artery disease patients with hemodynamically significant stable coronary stenoses undergoing treatment in a cardiovascular rehabilitation program and who were considered severely ill for: a) not having undergone intervention treatment; b) presenting signs of myocardial ischemia; c) presenting multivessel coronary artery disease.

Mailing Address: Tales de Carvalho •
Rua Rubens de Arruda Ramos, 2354/ 201 - 88015-702 – Florianópolis, SC – Brasil
E-mail: tales@cardiol.br
Manuscript received June 1st, 2004; revised manuscript received August 16, 2006; accepted October 20, 2006.

Methods

Study design. Study population - Retrospective cohort observational study of 381 consecutive patients engaging in a rehabilitation program from January, 1992 to December, 2000 who had attended a supervised cardiac rehabilitation program for at least three months, comprising a minimum of 36 sessions in this period, which corresponds to a frequency of three times a week, and had a coronary angiography performed prior to engaging in the program, showing hemodynamically significant stenoses, for which, because of the anatomic bias, intervention treatment was indicated. According to what was established in the previous paragraph, medical charts from 390 patients were initially selected from the database of the Cardiology and Exercise Medicine Center of *Universidade do Estado de Santa Catarina* and from Cardiosport - Prevention and Rehabilitation Clinic, both operating in the city of Florianópolis, Brazil, under the same coordination, and using the same assistance method and human resources with similar technical and academic education. Of these, nine patients (2.6%) were excluded because their information could not be updated (we lost contact), which explains the total of 381 patients participating in the study. The Cardiology and Exercise Medicine Center's program assists patients both from the public and the private health systems, that is, private patients and those with a health plan. The Cardiosport Clinic assists only private patients and those with a private health plan.

Rehabilitation program protocol - Both programs are aimed at assisting individuals in phases 2 and 3 of the rehabilitation process, whether having or not participated in the first phase of the supervised cardiac rehabilitation in a hospital environment. The second phase, in which physical exercise sessions are supervised, started immediately after hospital discharge or a few days after a coronary event, and lasted up to three months. The third phase, also with supervised physical exercise sessions, but with a greater variety of activities, lasted up to nine months. After completing the third phase, the patients were advised to remain regularly active, in not necessarily supervised activities, but adequate to their availability and resources.

In phases 2 and 3, the patients exercised three to five times a week, in 40-minute sessions (mean) of aerobic activities such as outdoor walking or trotting, or activities in cycle ergometers and treadmills. Stretching and weight exercises, also called resistance exercises, with 12 to 16 repetitions in each series are part of the activity protocol. At admission to the cardiac rehabilitation program, all patients underwent exercise test assessment using their daily medication. Considering that in the period during which the patients were recruited for the study we were not yet routinely using the cardiopulmonary exercise test, also known as ergospirometry, we applied the conventional exercise test with the original Bruce protocol, except in more limited patients, for whom the Modified Bruce protocol was used[12]. Since test duration was considered, so asto facilitate performance comparisons when the Modified Bruce protocol was used, test time was counted from the stage corresponding to 1.7 miles per hour and incline of 10%, which corresponds to the first stage of the original Bruce protocol. Based on the maximum heart rates observed in the exercise test, the target zone was calculated at between 60 and 80% of the maximum heart rate for aerobic exercises. For exercise intensity control, the Borg rating of perceived exertion scale[13] was used in addition to the target heart rate and the patients were advised to exercise with mild to moderate intensity, corresponding to levels 11 to 13 of the scale, so that they would remain only mildly breathless. The aerobic component of the physical conditioning sessions was supplemented by warm-up, stretching and cool-down activities. At least two times a week exercises were performed with weights, in exercise series of 12 to 16 repetitions. The cardiac rehabilitation program also included learning sessions of techniques to improve stress control, lectures on healthy life habits, and social activities, such as gepping-together with games, ballroom dance and group tours.

Diagnostic criteria - a) Ischemic heart disease was diagnosed according to clinical manifestations, evidence of myocardial ischemia in the exercise test performed with the medication currently used, regional dyskinesia on the echocardiogram, and coronary lesions demonstrated in the coronary angiography. All patients selected for the study already presented a coronary angiography showing at least one hemodynamically significant stenosis resulting from an atherosclerotic plaque at admission in the study; b) the clinical condition was considered stable when the patient was able to remain in the physical conditioning sessions tolerating progressive loads or the same loads initially established. Patients with ischemic manifestations in response to stimuli of similar or increasingly greater intensity were also considered stable. When changes in the clinical picture leading to lower exercise tolerance occurred, patients would discontinue their activities and were referred to their physicians; d) diagnosis of myocardial infarction was based on clinical manifestations, electrocardiographic and laboratory findings, as well as on ventriculography obtained with echocardiography, hemodynamic study and nuclear medicine imaging, when available.

Inclusion and exclusion criteria – All patients with stable clinical condition were included in the study, provided that they: a) participated in a cardiac rehabilitation program for at least three months, in a total of 36 supervised sessions (deemed compliant to rehabilitation); b) presented coronary artery stenoses qualitatively estimated as greater than 70% as observed in coronary angiography. Coronary patients not meeting these criteria or those whose information could not be updated were excluded from the study.

Study sample - A total of 381 patients with ischemic heart disease who met the inclusion criteria, who did not meet the exclusion criteria, and who started participating in rehabilitation programs from 1992 to 2000 were included. Mean age at admission in the cardiac rehabilitation program was 56 years; 307 (80.6%) individuals were males and 74 (19.4%) were females.

Clinical characteristics of the patients - Treatment prior to admission in the rehabilitation program*: in this cohort study, the 381 patients studied were initially divided into two groups, according to having or not undergone intervention treatment, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting prior to admission in the cardiac rehabilitation program. Also, subgroups were formed according to the presence of myocardial ischemia at admission in the cardiac rehabilitation program and number of critical coronary artery stenoses.

A total of 263 (69.0%) individuals undergoing intervention treatment were followed; 210 (79.8%) were males and 53 (20.2%) were females; 118 (31.0 %) individuals were on medical treatment alone, of which 97 (82.2%) were males and 21 (17.8%) were females.

At admission in the program, the mean age of patients in the intervention group was 55.8 years, standard deviation 10.0, and that of the medical treatment alone group was 56.5 years, standard deviation 9.6.

Other clinical aspects regarding the study subjects are shown in Table 1 (attachment 1).

Follow-up period - The mean follow-up period of the subjects in the intervention group was 975.9 days, standard deviation 795.0, and of the subjects in the medical treatment alone group was 1074 days, standard deviation 828.52.

Variables studied - The following variables were studied: a) gender; b) age; c) body mass index; d) high blood pressure; f) diabetes mellitus; g) previous myocardial infarction; h) LV ejection fraction; i) exercise tolerance; j) metabolic profile (TC, HDL-C, TC/HDL-C ratio, LDL-C, plasma triglyceride levels; k) smoking; and l) use of cardiovascular medication.

Variables were also analyzed in relation to the previous treatment, whether medical or intervention treatment (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting).

Endpoints - Myocardial infarction and death were considered endpoints. The cause of death was verified in the death certificate, hospital medical chart and/or interview with spouses or close relatives. When death followed myocardial infarction after a few hours, both infarction and death were considered parts of the same event.

Statistical analysis - A descriptive analysis was preliminarily performed, using means and standard deviations for the quantitative variables and proportions for the qualitative variables. To evaluate the association between the qualitative variables of interest, the Pearson's chi-square test was used.

The likelihood of endpoints in the medical group was compared with that of the intervention group using logistic regression; control variables were gender and age and each of the other variables individually considered: LV ejection fraction; exercise tolerance; TC, HDL-C, TC/HDL-C ratio, LDL-C; plasma triglyceride levels; smoking, high blood pressure, diabetes mellitus, previous myocardial infarction, body mass index and use of cardiovascular medications.

Values of $p<0.05$ were considered significant.

Ethical aspects - the project was approved by the Institutional Ethics Committee.

Results

Clinical characteristics of the patients - in relation to the different variables shown in Table 1, statistically significant differences were observed between the groups with or without previous intervention treatment alone as regards the number of coronary stenoses, myocardial ischemia and use of beta-blockers. Single-vessel disease was more prevalent in the medical treatment alone group ($p = 0.019$), and three-vessel disease and/or main left coronary artery disease was more prevalent in the intervention group ($p = 0.001$). Myocardial ischemia was more prevalent in the medical treatment alone group ($p = 0.002$). Beta-blockers were more frequently used in the medical treatment alone group ($p = 0.025$). In relation to the other variables studied no significant difference was observed.

Endpoints - twenty cases of acute myocardial infarction (AMI) and 17 deaths occurred, of which 14 were related to ischemic heart disease. The three deaths from non-cardiac causes were not considered study endpoints. The overall incidence of these major coronary events was of 34 cases, with incidences of 9.6% in the intervention group and 7.7% in the medical treatment alone group (RR=1.25; 95%IC=0.60-2.58). For one individual out of the 33 who were affected by a major coronary event, two major endpoints were verified, because non-fatal AMI and cardiac death occurred with a one-year interval between the two events.

When the likelihood of endpoints, AMI or cardiac death, was compared using logistic regression controlled for gender and age, and considering each variable individually (BMI, smoking, LVEF, exercise tolerance; TC, HDL-C, TC/HDL-C, LDL-C, Tg, HBP, DM, previous AMI, and use of cardiovascular medications), no statistically significant difference was observed between the groups initially formed according to an occasional previous intervention treatment and to the presence of ischemia and number of stenotic coronary arteries: a) individuals undergoing medical treatment alone versus individuals undergoing intervention treatment (OR 0.813; 95%CI; 0.366-1.809); b) patients without evidence of myocardial ischemia versus patients with ischemia (OR 0.785; 95%IC; 0.366-1.684); c) patients with one critically diseased coronary artery versus patients with two or more critically diseased coronary arteries (OR 0.824, 95%CI; 0.377-1.798). The survival curve estimated with the Kaplan-Meier method for the medical treatment alone and percutaneous transluminal coronary angioplasty and/or coronary artery bypass grafting groups did not show significant differences (Figure 1).

Discussion

We should point out that no significant difference was observed in relation to the incidence of AMI and cardiac death between the groups compared according to the previous treatment: medical treatment alone versus intervention treatment (OR 0.813; 95%CI; 0.366-1.809). This can be understood in light of the results of medical treatment alone shown in several studies[14-18].

The lack of relation between major coronary events and the number of stenotic arteries demonstrated in the comparison of the group comprised of patients with single-vessel stenosis versus the group comprised of patients with multivessel stenosis (OR 0.824, 95%CI; 0.377-1.798) corroborates the results found in other studies that show lack of a positive correlation between the occurrence of these events and the higher degree of stenosis and number of coronary arteries affected[19-21]. Fissure with atherosclerotic plaque rupture and thrombosis, responsible for the great majority

Treatment	Intervention	Medical	P value
Body mass index (BMI)			
Mean (kg/m2)	27.2 + 3.9	26.8 + 3.3	
BMI< 25kg/m2 (%)	31.3	29.3	0.7 NS
BMI≥25kg/m2 (%)	49.2	56.9	0.16 NS
BMI<30kg/m2 (%)	19.5	13.8	0.17 NS
Smoking			
Never smoked (%)	25.9	30.7	
Former smokers (%)	68	8.9	
Still smoking (%)	59.6	9.6	
Myocardial ischemia			
Individuals with ischemia (%)	34.2	48.3	0.002
High blood pressure			
Hypertensive (%)	54.7	61.2	0.24 NS
Diabetes mellitus			
Diabetics (%)	20.6	23.7	0.49 NS
Myocardial infarction (MI)			
Previous MI (%)	63.9	55.9	0.091 NS
Exercise tolerance			
Mean ET duration*	7′17″	7′52″	
LVEF*			
LVEF < 40% (%)	9.5	4.7	0.24 NS
LVEF ≥ 40% (%)	15.1	10.9	0.43 NS
LVEF < 55% (%)	75.4	84.4	0.15 NS
Coronary stenosis			
Single-vessel disease (%)	31.74	44.34	0.019 NS
Two-vessel disease (%)	32.14	36.52	0.4 NS
Three-vessel disease (%)	36.11	19.13	0.001
Metabolic data			
TC (mg/100ml)	213.05 + 58.65	216.49 + 60.92	0.66 NS
HDL-C (mg/100ml)	40.05 + 9.55	43.57 + 24.28	0.36 NS
LDL-C (mg/100ml)	138.5 + 52.12	140.53 + 62.53	0.47 NS
Triglycerides (mg/100ml)	160.14 + 81.42	181.38 + 115.93	0.49 NS
Uric acid (mg/100ml)	5.43 + 1.61	5.63 + 1.64	0.33 NS
Use of medications			
Aspirin (%)	80.2	83.9	0.29 NS
Beta-blocker (%)	44.8	53.7	0.025
Nitrate (%)	61.5	61	0.92 NS
Statin (%)	36.4	34.5	0.71 NS
ACEI*** (%)	29.3	27.8	0.76 NS
CCA**** (%)	38.5	33.3	0.33 NS

*Exercise test, **left ventricular ejection fraction, ***angiotensin converting enzyme inhibitor, **** calcium channel blockers, NS: non-significant.

Table 1 - Clinical characteristics of the patients

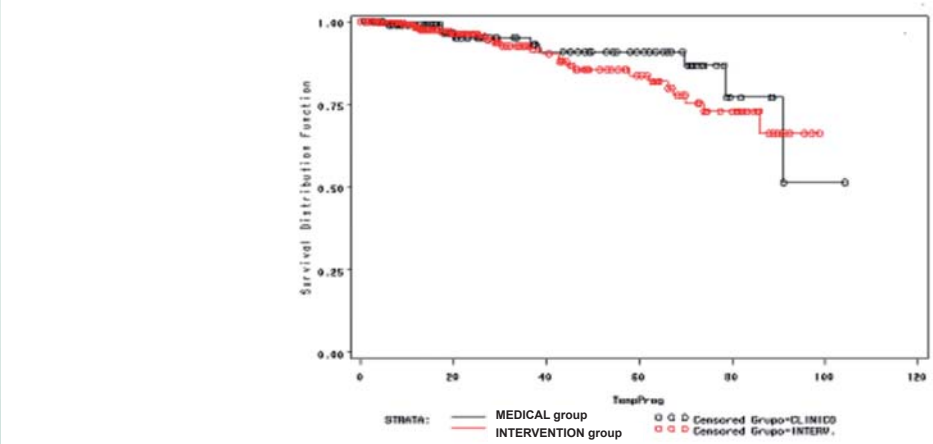

Fig. 1 - *Probability of survival of ischemic heart disease patients undergoing a supervised cardiac rehabilitation program, who were medically treated or had previously undergone intervention treatment (coronary artery bypass grafting or percutaneous transluminal angioplasty).*

of coronary events, is admitted to occur more frequently in mild to moderate stenoses[22,23]. The occurrence of a greater number or coronary stenoses has been verified in patients with stable angina than in patients with unstable angina or myocardial infarction, thus demonstrating the human body's natural adaptation mechanism that could be optimized by a full medical treatment including rehabilitation resources, especially physical exercises[24,25]. In addition to the patients' choice not to undergo intervention treatment, with or without their physician's support, since patients frequently refused the intervention treatment proposed, the results of the studies mentioned[19-25] allowed us to keep these patients with hemodynamically significant chronic coronary stenoses subject to intervention treatment from the anatomic point of view in the rehabilitation program.

It is also worth pointing out that among other benefits from the full medical treatment, the normalization of the plasma lipoprotein profile contributes to stabilize atherosclerotic plaques, whether small or large, thus considerably reducing the likelihood of acute coronary events[26,27]. Therefore, several mechanisms are to be considered for modifying the prognosis of patients with ischemic heart diseases, including those resulting from the practice of physical exercises[3,7,8], and other non-pharmacologic measures[4-8]. Even the hypothesis of regression of the coronary atherosclerotic process should be considered as a pathophysiological mechanism, thus reinforcing the possibility of a treatment that also includes cardiac rehabilitation[5,7,26,27].

The higher prevalence of myocardial ischemia in the group comprised of patients undergoing medical treatment alone, when compared to the group comprised of patients undergoing intervention treatment (48.3% versus 34.2%, 95%CI, p=0.002), did not result in poorer outcomes. Since ischemia was not positively correlated with the endpoints (OR 0.785; 95% CI; 0.366-1.684), it was not considered a predictive factor for major coronary events in this study, and this could be interpreted by the hypothesis of ischemic preconditioning, according to which previous ischemic episodes would prepare the myocardium to prevent or become more resistant to subsequent episodes, including a major acute coronary event, such as myocardial infarction. One of the possible consequences of elective intervention revascularization would be the suppression of ischemia with subsequent loss of the protective mechanisms, such as the ischemic preconditioning and collateral circulation followed by restenosis, which would affect a now unprotected myocardium[28-30].

Therefore, the lack of correlation between the number of critical coronary lesions and myocardial ischemia and major coronary events – AMI and death – verified in this study, and already observed in other studies[19-21,28-31], and the low incidence of complications in cardiac rehabilitation programs[11] are some of the aspects that provide the proposal of a medical treatment encompassing the physical conditioning process with an acceptable safety margin.

Our study has limitations inherent to a retrospective cohort. Among these limitations, we can mention the fact that there was no control group comprised of patients not undergoing treatment in a cardiovascular rehabilitation program, and that the groups were not randomly divided. However, even without a randomized selection the characteristics of the groups were not very different, considering the majority of the variables studied. Nor was the cost-effectiveness ratio between the two types of treatment – the medical alone and the intervention plus medical treatment – assessed, which would have been relevant in the comparison of the different treatment groups. This can be considered another study limitation. Nevertheless, it would only have been possible in a controlled study with patients randomly assigned for the different treatments[8-10,18]. On the other hand, we should point out that the study was conducted with data obtained from a medical practice that was new when the study was initiated, thus enabling a discussion that reflects the real world, unlike within protocol conditions which are developed with very homogenous patient groups because of strict selection criteria.

Conclusion

Considering cardiovascular death and acute myocardial infarction as endpoints, no unfavorable outcome was observed in the subgroups comprised of medically treated patients with evidence of myocardial ischemia and multivessel coronary artery disease undergoing treatment in a supervised cardiovascular rehabilitation program in this cohort of coronary artery disease patients.

Potential Conflict of Interest

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

References

1. Lotufo PA. Premature mortality from heart diseases in Brazil: a comparison with other countries Arq Bras Cardiol. 1998; 70: 321-5.
2. Lessa I. Medical care and death due to coronary artery disease in Brazil, 1980-1999. Arq Bras Cardiol. 2003; 81: 329-35.
3. Steffen-Batey L, Nichaman MZ, Goff DC, Frankowski RF, Hanis CL, Ramsey DJ, et al. Change in level of physical activity and risk of all-cause mortality of reinfarction. Circulation. 2000; 102: 2004-9.
4. De Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complication after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation. 1999; 99: 779-85.
5. Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA. 1998; 280: 2001-7.
6. Niebauer J, Hambrecht R, Velich T, Hauer K, Marburger C, Kalberer B, et al. Attenuated progression of coronary artery disease after 6 years of multifactorial risk intervention: role of physical exercise. Circulation. 1997; 96: 2534-41.
7. Hambrecht R, Wolff A, Gielen S, Linke A, Hofer J, Erbs S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med. 2000; 342: 454-60.
8. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2001;1: CD001800. Review.
9. Oldridge N, Perkins A, Marchionni N, Fumagalli S, Fattirolli F, Guyatt G. Number needed to treat in cardiac rehabilitation. J Cardiopulm Rehabil. 2002; 22: 22-30.
10. Carvalho T, Cortez AA, Ferraz A, Nóbrega ACL, Brunetto AF, Herdy AH, et al. Diretriz. Reabilitação Cardiopulmonar e Metabólica: Aspectos Práticos e Responsabilidades. Arq Bras Cardiol. 2006; 83 (suppl. 5): 448-52.
11. Vongvanich P, Paul-Labrador MJ, Merz CN. Safety of medically supervised exercise in a cardiac rehabilitation center. Am J Cardiol. 1996; 77: 1383-5.
12. II Diretrizes da Sociedade Brasileira de Cardiologia sobre Teste Ergométrico. Arq Bras Cardiol. 2002; 78 (suppl. II): 1-17.
13. Borg G, Hassmen P, Lagerstrom M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. Eur J Appl Physiol Occup Physiol. 1987; 56: 679-85.
14. Hueb WA, Bellotti G, De Oliveira AS, Arie S, De Albuquerque CP, Jatene AD et al. The medicine-angioplasty surgery study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. J Am Coll Cardiol. 1995; 26: 331-9.
15. Peduzzi P, Kamine A, Detre K. Twenty-two-year follow-up of VA cooperative study of coronary artery by pass surgery for stable angina. Am J Cardiol. 1998; 81: 1393-9.
16. Bucher CH, Hengstler P, Schindler C, Guyatt HG. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. BMJ. 2001; 321:73-7.
17. RITA-2 trial participants. Coronary angioplasty versus medical therapy for angina: the second randomized intervention treatment of angina (RITA-2) trial. Lancet. 1997; 350: 461-8.
18. Hambrecht R, Walther C, Mobius-Winkler S, Gielen S, Linke A, Conradi K, et al. Percutaneous coronary angioplasty compared with exercise training in patients with atable coronary artery disease: a randomized trial. Circulation. 2004; 23;109:1371-8.
19. Giroud D, Li JM, Urban P, Meier B, Rutishaner W, Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. Am J Cardiol. 1992; 69: 729-32.
20. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, et al. Can coronary angiography predict the site of a subsequent myocardial infartion in patients with mild-to-moderate coronary artery disease? Circulation. 1988; 78: 1157-66.
21. Ambrose JA, Taunenbaum MA, Alexopoulos D, Hijemdhal-Monsen CE, Leavy J, Weiss M, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol. 1988; 12: 56-62.
22. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation. 1995; 92: 657-71.
23. Arbustini E, Dal Bello B, Morbini , Burke AP, Bocciarelli M, Specchia G, et al. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. Heart. 1999; 82: 269-72.
24. Bogaty P, Brecker SJ, White SE, Stevenson RN, El-Tamini H, Balcon R, et al. Comparison of coronary angiographic findings in acute and chronic first presentation of ischemic heart disease. Circulation. 1993; 87: 1938-46.
25. Cianflone D, Ciccirillo F, Buffon A, Trani C, Scabill EV, Finicchiaro ML, et al. Comparison of coronary angiographic narrowing in stable angina pectoris, unstable angina pectoris, and in acute myocardial infarction. Am J Cardiol. 1995; 76: 215-9.
26. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, et al. Regression of coronary artery disease as a result of lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990; 323:1289-98.
27. Brown G, Zaho XQ, Sacco DE, Albers JJ. Lipid lowering plaque regression. New insights into prevention of plaque disruption and clinical events in coronary disease. Circulation. 1993; 87:1781-9.
28. Antelmi I, Kalil R, Lopes NH, Forlenza LM, Barduco MS, Piva de Albuquerque C, et al. Evaluation of ischemic preconditioning on collateral circulation, ventricular function and clinical outcome in acute myocardial infarction. Arq Bras Cardiol. 1996; 66: 11-4.
29. Hirai T, Fujita M, Yoshida N, Yamanishi K, Inoko M, Mina K. Importance of ischemic preconditioning and collateral circulation for left ventricular functional recovery in patients with successful intracoronary thrombolysis for acute myocardial infarctation. Am Heart J. 1993; 126: 827-31.
30. Pasceri V, Lanza GA, Patti G, Pedrotti P, Crea F, Masceri A. Preconditioning by transient myocardial ischemia confers protection against ischemia-induced ventricular arrhytmias in variant angina. Circulation. 1996; 94: 1850-6.
31. Naqvi TZ, Hachamovitch R, Berman D, Buchbinder N, Kiat H, Shah PK. Doe-s the presence and site of myocardial ischemia on perfusion scintigraphy predict the occurrence and site of future myocardial infarction in patients with stable coronary artery disease? Am J Cardiol. 1997; 79: 124-4.