Infarct Combat Project

Originally published in Ars Cvrandi, a Brazilian Medical journal, V. 35 - N 7 - September 2002

English translation by ICP, 2013

Effects of the Cardiotonic + Coronary Dilator in Chronic Stable Coronary-Myocardial Disease, with and without Prior Myocardial Infarction, in the Long Run

Quintiliano H. de Mesquita*, Claudio A. S. Baptista**, Sostenes V. Kerbrie**, Sonia Maria Mari**, Maria Consuelo B. M. Grossi**, Jose Monteiro**

**Honorary Professor of the Faculty of Medicine from the Federal University of Paraíba; Founder and Chief of of the Cardiology-Angiology Institute of Matarazzo Hospital, 1945-1979; Founder and Executive Director of Instituto de Combate ao Enfarte do Miocardio, 1999-2000; Sao Paulo - SP, Brazil*
***Medical assistants from the Cardiology-Angiology Institute of Matarazzo Hospital*

Summary

Disclosure of the therapeutic conduct recommended by the Myogenic Theory: cardiotonic + coronary dilator in stable coronary-myocardial disease (or coronary-cardiomyopathy), with or w/out previous infarction in the long run, complementing the benefic and protective effects of collateral coronary circulation in front of severe coronary obstructions; having as objective the correction of the regional contractile deficiency state of ischemic myocardium and the preservation of myocardial inotropism, as prevention of unstable angina, myocardial infarction, cardiac insufficiency and severe arrhythmias that lead to sudden death.

Introduction

In this paper we aim to disseminate and to prove the precepts of the Myogenic Theory of myocardial infarction with new concepts of pathophysiology and therapeutics, developed by us in 1972. These concepts fit to the stages of symptomatic and myocardial stability or instability with pathophysiological criteria specific for each, but with unique therapeutic approach, based on the exclusive use of cardiotonic + coronary dilator, having as objective the correction and preservation of myocardial inotropism, against the degrading action of ischemia in the presence of atherosclerotic coronary disease (1-8).

From the clinical point of view, we must consider the segmental myocardial disease, with symptomatic and myocardial stability identified as stable angina, when symptomatic, and the silent ischemia that presents itself as asymptomatic, with and without previous myocardial infarction.

From the pathophysiological point of view both the orthodoxy based on the Thrombogenic Theory of myocardial infarction, as well the Myogenic Theory, that we advocate, accept consensually the mechanism attributed to stable angina, as ischemic process, always caused by stress and / or emotion and reflecting imbalance between the increased myocardial oxygen demand and the constant and insufficient coronary flow. However, in the Myogenic Theory, we have developed the conceptualization considering the effects of regional myocardial ischemia as primary process,

triggering whenever the secondary regional myocardial insufficiency, pioneered described by Tennant and Wiggers (1935) (9).

During the eighties the orthodoxy was awakened to this sense, when Braunwald and Kloner (1982) (10), recognizing such phenomenology secondary to myocardial ischemia, coined it under a new designation: "myocardial stunning" (Table 1).

Table 1

Stable Chronic Coronary-Myocardial Disease, With and Without Previous Myocardial Infarction

Pathophysiology of Effort Angina Pectoris

1. Regional Myocardial Ischemia, Primary.

2. Regional Myocardial Insufficiency, Secondary.
(Tennant and Wiggers, 1935; Mesquita et al, 1972; New designation: "Myocardial Stunning", Braunwald and Kloner, 1982).
(Records coincident with regional myocardial insufficiency, Secondary: circulatory stagnation. Depletion of energetic phosphate. Platelet aggregates. Possible coronary spasm "in situ" or distant. Increase of residual systolic and diastolic volumes. Increase of residual systolic and diastolic pressures in the left ventricle. Increase of pulmonary capillary pressure. Increase of the parietal tension and cardiac volume. Reduction in ejection fraction and left ventricular ejection time).

3. Immediate Cessation of Phenomenology and Symptomatic Aspects With the Interruption of the Provoking Cause.

In each episode of stable angina, the myocardial phenomenology develops important metabolic alterations and clear hemodynamic consequences which indicate myocardial suffering that, over time, becomes structurally compromised, regionally, reaching the ischemic cardiomyopathy process described by Burch and colleagues (1970) (11-13).

In consequence of such mechanism foreseen in the Myogenic Theory, the association of cardiotonic + coronary dilator has come to represent a unique medication for stable coronary-myocardial disease, advocated in two different groups: without previous myocardial infarction and with previous myocardial infarction. Different clinical conditions in diverse stages, but fundamentally the same: patients with impaired regional contractility well characterized and exacerbated by effort or psycho-emotional stress.

In cases of an epicardial coronary artery, predominantly compromised, occurs the regional cardiomyopathy in confrontation with the other intact myocardial regions; and, as consequence, a pathological disharmony is observed which exacerbates the morphologic ventricular condition, leading to ventricular dyssynergia in ischemic area, characterizing a regional contractile deficiency.

Differently, in cases of two or three concomitant epicardial coronaries severely compromised, the ischemic cardiomyopathy process develops in two or three dependent regions; resulting in little or no confrontation between these, despite the contractile deficiency state in the myocardial regions involved , characterizing, the left ventricular silhouette with apparent pathological harmony.

Coronary atherosclerosis develops slowly but gradually to the arterial obstruction in varying times – months or years – and, usually, when reaches the subtotal obstruction degree for the total obstruction it develops, simultaneously, the spontaneous and automatic process of coronary collateral circulation, a system of self-defense and compensatory of myocardial revascularization, with overt anti-ischemic effects reported during percutaneous transluminal coronary angioplasty (14). The coronary collateral circulation is capable to prevent infarctions in front of complete obstruction of up to three epicardial coronaries ensuring good ventricular morphology. It has a fundamental role in the fate of coronary patients and represents the compensatory strengthening of the "Nature", complemented by the cardiotonic, in the preservation of myocardial contractility.

The aim of this paper is to demonstrate the necessity and validity of the association cardiotonic + coronary dilator in chronic stable coronary-myocardial disease, with and without prior myocardial infarction, uninterruptedly, highlighting the following effects:

- Neutralize the negative inotropic effects of ischemia;
- Preserve ventricular function, leveling over the ischemic segments - contractile defficient - with nonischemic segments, annulling the deleterious segmental confrontation;
- Preventing unstable angina, myocardial infarction, heart failure and sudden death - symptomatic and myocardial instability, ensuring permanent state of stability;
- Increase and to provide peaceful, comfortable and long survival, predominantly asymptomatic, in front of the common efforts and according to the achieved parameters.

Material and Methods

The symptomatic coronary-myocardial disease is easily and readily diagnosed by anamnesis well conducted and has been recorded in our casuistry in 83.8% of the cases, and that in 42.7% of cases the ECG appears normal at rest, lacking, therefore , effort electrocardiographic evidence - 30 rises in the two step electrocardiogram - we have revealed positivity in 90-93% of cases (15-17).

In asymptomatic patients (16.2%), apparently normal that underwent cardiac evaluation, have been discovered by abnormal resting ECG or, then, with normal ECG at rest and systematically submitted to effort ECG, since the ECG at rest only has value when pathological.

Such cases have been identified through the effort ECG being abnormal in 49% of cases examined at the hospital and in 28% in our Private Practice (15-17).

The effort ECG test - 30 rises in two step – test duplicated and improved by Master after 1961 (18-20), having as the key objective the diagnosis of relative coronary insufficiency. These tests are very simple, useful, necessary, reliable, safe and comfortable, without risk nor serious arrhythmias and,

usually, without awaken chest pain, although well characterizing the provoked ischemia. Such tests should not be compared with ergometric testing (21), because these are intended, quite specifically, to prognostic evaluation.

The cases described in this paper were divided into two groups:

- Group 1 - without previous myocardial infarction - consisted of 475 patients (247 Female and 228 Male), mean age 58 years (27-86 years) treated in our Clinic at Matarazzo Hospital, in the period 1972-79, and 684 patients (362 F and 322 M), mean age 55 years (25-86 years, and 9.2% under 50 years, 90.8% over 50 years, and 67.1% of those over 60 years); treated in our Private Clinic in the period 1972-89.
- Group 2 - with previous myocardial infarction - consisted of 562 patients (93F and 469 M), mean age 56 years (26-89 years) treated in our Clinic at Matarazzo Hospital, in the period 1972-79, and 114 patients (18 F and 96 M), mean age 59 years (42-90 years) treated in our Private Clinic in the period 1972-89.

The patients treated in the two different periods represented individuals with different cultural and socioeconomic levels.

Equal maintenance therapy was administered continuously in both groups (Table 2).

Table 2

Stable Chronic Coronary-Cardiomyopathy

Therapeutic of Maintenance

Cardiotonics used:	
Proscillaridin-A	0,75-1,50mg/day
Acetildigoxin	0,50mg/day
Lanatoside-C	0,50mg/day
Digitoxin	0,1mg/day
Digoxin	0,125-0,25mg/day
Betamethyldigoxin	0,10-0,20mg/day
Coronary dilators: Calcium antagonists:	
Verapamil	120-240mg/day
Prenylamine	120-180mg/day
Nifedipine	20-30mg/day
Fendiline	100-150mg/day
Diltiazem	90-180mg/day

Due to the interaction of Digoxin-Verapamil, with the increase in concentration of Digoxin in blood, a precaution has been taken to administer low dose of digoxin, when combined with Verapamil. The use of rapid-acting nitrates, sublingual, is free and according the symptomatic manifestations. The association of the cardiotonic with the coronary dilator calcium antagonist counteracts the initial negative inotropic effect of the latter and in this particular; curiously, potentiating the action of Verapamil over Digoxin represents, in practice, a technical advantage.

The methodology is intended for the fundamental purpose to give support to the myocardium, preserving the ventricular function and complementing the beneficial and protective coronary collateral circulation, in cases of severe coronary artery obstructions.

Results

The patients treated according our methodology presented themselves as stable coronary-myocardial disease carriers with and without prior myocardial infarction, but of course considered as different clinical conditions from the evolutionary point of view. Cases with previous myocardial infarction that seemed as having structurally processes more advanced, also benefited from the treatment type initiated, as can be demonstrated by the indexes really reduced of morbidity and mainly mortality (1.7% per year in 17 years).

These indices appeared to us as very significant when compared with the best ones recorded in the literature under different forms of clinical, invasive or surgical, and especially by the values of annual averages. Noteworthy, therefore, the low incidence of unstable angina, myocardial infarction and heart failure, which are now considered rare and accidental complications losing the meaning commonly accepted of successive and obligatory stages in the evolution of cases left to their fate (Table 3).

Table 3

Morbidity and Mortality Indices

	Period 1972 / 1979 Hospital Clinic				Period 1972 / 1989 Private Clinic			
Groups	**Cases**	**Morbidity %**		**Deaths**	**Cases**	**Morbidity %**		**Deaths**
		MI	**HF**	**%**		**MI**	**HF**	**%**
G1 - NPMI	**475**	**1,8**	**3,4**	**5,7**	**684**	**2,1**	**5,1**	**8**
Annual mean%		**0,2**	**0,4**	**0,8**		**0,1**	**0,3**	**0,4**
G2 - WPMI	**562**	**11,8**	**4,9**	**16,1**	**114**	**5,2**	**13,1**	**29,8**
Annual mean%		**1,6**	**0,7**	**2,3**		**0,3**	**0,7**	**1,7**

NPMI – W/out Previous Myocardial Infarction
WPMI – With Previous Myocardial Infarction
MI – Myocardial Infarction
HF – Heart Failure

Discussion

We should consider that the cases of coronary atherosclerosis when left to their fate have their evolution, gradual and progressive in the arterial tissue, developing the coronary myocardial disease with long period of myocardial stability, symptomatic or asymptomatic, until the evolutionary period with the installation of symptomatic and myocardial instability with alarming clinical pictures of unstable angina, often followed by myocardial infarction with or without Q wave. Usually showing up as successive and gradual stages, not mandatory, always followed by a return to symptomatic and myocardial stability; seeming as everything is starting again.

With the introduction of the therapeutic routine recommended by the Myogenic Theory, adjusted and directed to the stage of stability and instability with the use of the combination of the cardiotonic + coronary dilator, as exclusive medication, it is intended solely to give support to the recognized effects of coronary collateral circulation in advanced cases of coronary-cardiomyopathy, with the goal of preservation of cardiac function. It aims to ensure the inotropic state of the myocardium, structurally compromised by chronic ischemia imposed over the years by episodic diuturnal and dependent manifestations in the life of each patient with coronary-myocardial disease.

Consequently, we have recorded lower incidences of unstable angina, myocardial infarction, heart failure and sudden death in the long term which, by itself, seem to represent the effectiveness of the therapy used.

In the literature, we recorded therapeutic trials with the Digital or Strophanthin, with real benefits to myocardial ischemic regions, recognized as contractile deficient and without references to any adverse effects on the increase of oxygen demand by increasing contractility and disappearance of hemodynamic and myocardial alterations (22-29). We therefore believe that we can qualify the cardiotonic as the indispensable and principal agent and the coronary dilator, as the necessary adjunct to the symptomatic and myocardial stability, which we consider as the resulting permanent state for the cases treated in the long term.

Unstable angina, myocardial infarction, heart failure and sudden death, seem to us as accidental and rare complications losing importance, therefore, to the old concept of successive and obligatory stages in chronic coronary-myocardial disease when left to their fate.

According to the precepts of the Thrombogenic Theory there is no place for the cardiotonic, except when in the presence of heart failure and only concerned about myocardial reperfusion defects by the diversity of the coronary artery network's commitment giving rise to invasive procedures and surgical interventions for restoration and vascular recanalization, alongside thrombolytic agents, anticoagulants, antiplatelet agents, coronary dilators and adrenergic beta blockers.

In contrast, within the precepts of the Myogenic Theory, there is only room for the cardiotonic associated with coronary dilator, as agents who respect and help the nature in the process of self-defense of the coronary collateral circulation network, contributing to the preservation of cardiac function, capable to provide longer survival with a useful and productive life, without unnecessary suffering, and accessible to all patients.

We undervalue all resources used by the followers of the Thrombogenic Theory because they are unnecessary and, into our view, outweighed advantageously by our routine management, which have provided gratifying euphoria and complete satisfaction, by the more peaceful and comfortable evolution.

Finally we let a simple question: within the focus of Thrombogenic Theory, how one might interpret all effects reported in chronic stable coronary-cardiomyopathy with and without prior myocardial infarction, with such low rates of morbidity and mortality resulting from a treatment apparently so simple that have ensured the preservation of symptomatic and myocardial stability and prevention of usual complications; unstable angina, myocardial infarction, heart failure and sudden death - recorded in the natural history of chronic coronary-cardiomyopathy?

Conclusion:

The Therapeutic routine using this methodology has been credited with the achieved results and particularly the essential role of the cardiotonic through the following effects: neutralize the negative inotropic effect of myocardial ischemia; correct the regional contractile deficient state; to annul the myocardial intersegmental confrontation or pathological disharmony, observed in the case of a single coronary affected through the leveling of the tone in ischemic myocardial regions and non ischemic; preserve the cardiac function and ensure symptomatic and myocardial stability.

Also, in cases of 2 and 3 coronary affected and even completely blocked, but with apparent pathological harmony and without the registry of serious complications, probably because of the complementation by the coronary collateral circulation. In addition provides useful, normal, productive and asymptomatic life, within the parameters of each case.

References:

1. Mesquita, QHde: Angina de esforço e síndrome de enfarte miocárdico iminente: aspectos sintomáticos dependentes de insuficiência miocárdica regional. Nota prévia. Anais do 28º Congresso Brasileiro de Cardiologia, 1972:35
2. Mesquita, QHde, Reis, JP, Kerbrie, SV, Mari, SM, Baptista, CA, e col.: Emprego do cardiotônico no tratamento da angina pectoris e síndrome de enfarte miocárdico iminente, RBCTA, 1973;2:1
3. Mesquita, QHde: Kerbrie, SV, Mari, SM, Baptista, CA, Monteiro, J e Ribeiro, DDL: Administração contínua de cardiotônico na profilaxia do enfarte do miocárdio, RBCTA, 1976;5:309
4. Mesquita, QHde, Kerbrie, SV, Mari, SM, Baptista, CA, Monteiro, J e Maciel, MC: Preservação funcional do miocárdio isquêmico (Recateterização de 29 casos), Medicina de Hoje, 1978;Março:154
5. Mesquita, QHde: Livro, Teoria Miogênica do Enfarte Miocárdico – Novos conceitos de Fisiopatologia e Terapêutica., Edição do autor, 1979. (Myogenic Theory of Myocardial Infarction – Book, Download free of Charge - Summary in English at http://www.infarctcombat.org/MyogenicTheory.html)
6. Mesquita, QHde, Baptista, CAS, Grossi, MCBM e Mari, SM: O cardiotônico na coronariopatia crônica e prevenção do enfarte miocárdico, Rev Bras Med, 1982;39:359
7. Mesquita, QHde: Como escapar da ponte de safena e do enfarte do miocárdio só com remédio, Ícone editora, 1991
8. Mesquita, QHde, Cláudio Baptista: Porque Teoria Miogênica e não Teoria Trombogênica, Arq Bras de Cardiol, 1994,62(4)
9. Tennant, R e Wiggers, CJ: Effect of coronary occlusion on myocardial contraction, Am J Physiol, 1935;112:351
10. Braunwald, E e Kloner, RA: The stunned myocardium: Prolonged post-ischemic ventricular dysfunction, Circulation, 1982;66:1146
11. Burch, GE, Giles, TD e Colcolough, HL: Ischemic cardiomyopathy, Am Heart J, 1970;79:291
12. Burch, GE, Tsiu, CY e Harb, JM: Ischemic cardiomyopathy, Am Heart J, 1972;83:340
13. Burch, GE: Ischemic cardiomyopathy, Am Heart J, 1973;86
14. Khaja, F, Sabbah, HN, Brymer, JF e Stein, PD: Influence of coronary collaterals on left ventricular function in patients undergoing coronary angioplasty, Am Heart J, 1988;116:1174
15. Mesquita, QHde: Eletrocardiograma de esforço na angina do peito, Arq Bras Cardiol, 1954;7:137
16. Mesquita, QHde: 30 subidas no duplo degrau – teste padronizado para diagnóstico da isquemia miocárdica, Arq Bras Cardiol,1974;27 (supl):72
17. Mesquita, QHde: ECG de esforço (30 subidas no duplo degrau) para diagnóstico de insuficiência coronária relativa, Rev Bras Med (Cardiologia), 1985;4:139
18. Master, AM, Nuzia, S, Brown, RC e Parker, RC: The electrocardiogram and the "two step" exercise. A test of cardiac function and coronary insufficiency, Am J Med Sci, 1944;207:435
19. Master, AM e Rosenfeld, I: The "two step" exercise test brought up to date, New York J Med, 1961;61:1850
20. Master, AM: Tests for the diagnosis of latent (silent) coronary heart disease, In Coronary Heart Disease, p. 191, Russek, HI e Zohman, BL; J B Lippincott Co, 1971, Philadelphia, USA
21. YasbekJr, P, Papaleo Netto, M, Del Nero Jr, E, Moffa, P, Ortiz, J, Barbato, A, Braga, MV, Alfieri, RG, Moraes, AV e Pillegi, FJC: Contribuição ao estudo comparativo entre o "teste de Master" e o ergométrico em portadores de insuficiência coronária crônica, Arq Bras Cardiol, 1983;40/4:251
22. Kotter, V, Schuren, KP e Shroeder, R: Effect of Digoxin on coronary blood flow and myocardial oxygen consumption in patients with chronic coronary artery disease, Am J Cardiol, 1978;42:563
23. O' Rourke, RA, Henning, H, Theroux, P, Crawford, MH e Ross Jr, J: Favorable effects of orally administered Digoxin on the left heart size and ventricular wall motion in patients with previous myocardial infarction, Am J Cardiol, 1976;37:708
24. Amsterdan, EA, DeMaria, AN, Miller, RR, Awan, N, e Mason, DT: Enhancement of left ventricular function in chronic ischemic heart disease by digitalis differential contractile effects on normal and dyssynergic myocardium, Circulation, 1976;54 (suppl II):832
25. Ferlinz, J, DelVicario, M e Aronow, WS: Effect of rapid digitalization on total and regional myocardial performance in patients with coronary artery disease, Am Heart J, 1978;96:337
26. Vogel, R, Frischknecht, J e Steele, P: Short and long-term effects of digitalis on resting and posthandgrip hemodynamics in patients with coronary artery disease, Am J Cardiol, 1977;40:171

27. Vogel, R, Kirch, D, LeFree, M, Frisshknecht, J e Steele, P: Effects of digitalis on resting and isometric exercise myocardial perfusion in patients with coronary artery disease and left ventricular dysfunction, Circulation, 1977;56:335
28. DeMots, H, Rahimtoola, SH, Kremkau, EL, Bennett, W, e Mahler, D: Effects of Ouabain on myocardial oxygen supply and demand in patients with chronic coronary artery disease. A hemodynamic, volumetric, and metabolic study in patients without heart failure, J Clin Invest, 1976;58:312
29. Kleiman, JH, Ingels, NB, Daughters II, G, Stinson, EB, Alderman, EL, e Goldman, RH: Left ventricular dynamics during long-term digoxin treatment in patients with stable coronary artery disease, Am J Cardiol, 1978;41:937