

Why Myogenic Theory not Thrombogenic Theory

(English translation)

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Introduction

Our initiation in cardiology (1941) was based according the principles of the thrombogenic theory (TT) from Herrick (1, 2).

The introduction of anticoagulants – cumarinics and heparin – in 1944, in prevention and in treatment of the acute myocardial infarction (MI) represented the consolidation of Herrick's Theory and was the great hope for therapeutic. These were administered with great enthusiasm and consecrated in anticipation, recording crescent bibliography that only reflected success and glorification of the new therapeutic. We adopted the use of anticoagulants moved by enthusiasm and conviction. However, observing its use with the necessary critical evaluation, in the treatment of unstable angina, in crescendo, (UA) having as the main objective the immediate prevention of MI, frequently culminated in its occurrence or in sudden death (SD). The UA, since that time, was considered as the intermediate stage of stable angina (SA) and of MI, with ease clinical identification and resistant to the current therapeutic in use, constituting itself as an alarming syndrome for the cardiologist and, specifically, to the old patient with angina arriving afflicted with the new clinical characterization of spontaneous angina, at rest, lasting and insensible to sublingual nitrates and nitrites by inhalation, demanding analgesics and even narcotics.

In 1954 we came to the conviction that anticoagulants in UA didn't prevented MI and SD, when we abandoned its use in acute or chronic coronary-myocardiopathy. In 1962 we have published a paper about this matter (3), where we presented the opinion from Schluchmann (4) about the failure of anticoagulants in UA and the formal counter-indication from Master (5) in this same clinical condition. In the 60's decade, the cardiology was enriched by the important assistance supplied by angiography and ventriculography, distinguishing the slow and degrading action of atherosclerotic coronariopathy and consequent ischemic myocardiopathy in the dependent myocardial segments (6-10). The cardiology arrived to the recognition of the ischemic myocardiopathy identity (11-15), as clinical condition, through the paper from Raftery and col (11) and, specially, from Burch and col (12-14) when also gained more importance the experimental and pioneer work from Tennant and Wiggers (16), about the negative inotropic effect of ischemic myocardiopathy, showing the regional myocardial insufficiency (RMI) (16-19), recognized in vivo by echocardiography (17, 18), during the crisis of angina. In these conditions the ischemic myocardium lose its contractility and the non-ischemic shows a vicariant augmentation of its contractility, characterizing, in this way, the inter-segments confrontation with serious implications in symptomatic and myocardial instability stage, capable to trigger episodes of UA or even MI.

In 1969, was recorded the universal recognition of the absolute failure of anticoagulants in prevention and treatment of acute myocardial infarction, resulting in the abandon of this medication and a critical moment in cardiology that profoundly shocked the TT concept.

In 1970, Hellstrom (20-21) demonstrated, experimentally, the coronary thrombosis (CT) as consequence of MI, produced by ligation of coronary artery without endothelial lesion.

In 1972, starting from a simple hypothesis for the possible interpretation of the pathophysiological mechanism of MI, and having as its basis on the chronic coronary-myocardiopathy, we have admitted the installment of regional myocardial insufficiency, primary, followed by secondary coronary thrombosis, but not obligatory (22-24). In this manner we have delineated the principles of the myogenic theory (MT).

The concept of myogenic theory seemed to us to justify the failure of anticoagulants in UA as prevention of MI, mainly because in prevention of venous thrombosis processes the anticoagulants were well succeed.

Roberts and col. (25, 26) published a bibliographic review about histological studies that since 1956 presented the acute MI as primary process and the coronary thrombosis as secondary (27-54), but not obligatory; conflicting aspects with the TT that helped us in divulging the MT. Roberts and col. referred in the same paper the incidence of CT in only 10% of cases of subendocardial MI and in 60% of the cases of transmural MI. Special attention must be deserved to the studies from Spain and Bradess (30,31) about necropsies made during 25 years, showing total coronary obstruction of atherosclerotic nature in about 75% and recent coronary thrombosis in just 25% of cases in acute MI. They also recorded the crescent incidence of CT with the crescent duration of survival after MI: 16% with CT with survival time inferior to 1 hour; 36% with CT with survival between 1h and 24 h; and 53% with CT with survival time superior to 24 hours.

In our first publications (22-24) and in monographs about the MT (58, 59), we have mentioned many papers on histopathological studies, indicating the CT as consequence of acute MI and great variation of CT in necropsies findings (25-54). Erhard and col. registered the CT incorporating fibrinogen marked by the radioactive isotope 125, administered within 10-15 hours after the beginning of clinical manifestations of acute MI, fact that suggests the CT as consequence of primary myocardial necrosis, seeming to be reinforced by the observation of one case that, receiving the radioactive isotope 125 around 47 hours after the starting of MI, showed the exclusion of the radioactive agent in the formed thrombus. In another paper (48) using the radioactive isotope 131, these authors came to the same results. Important findings were registered about the incidence of intracoronary thrombus (55-57), that were evidenced in the acute period of UA (52-85%), within few hours after the symptoms and until 2 weeks, meanwhile its incidence in chronic period have been ever low (0-12%), seeming in this manner that in UA the regional myocardial insufficiency episodes and prolonged myocardial ischemia can generate a hyper aggregation of platelets and formation of intracoronary thrombus, that disappear or are reduced, within 30-90 days after the last occurrence of UA.

In consequence of the new pathophysiological mechanism of acute MI, as essentially myogenic, the introduction of the cardiotoxic was the natural demand and would serve to the confirmation of MT (22-24). Since the critical stage of this new pathophysiological mechanism of acute MI is the regional myocardial insufficiency, with its hemodynamic, metabolic, and ischemic effects, preceding the primary myocardial necrosis, the cardiotoxic should be administered the earliest possible, with the intention to correct the regional myocardial insufficiency in course, yet without definite necrotic process. We have elected the intravenous strophanthin (K or G) as the reliable cardiotoxic from our preference, based in our experience in all cases of acute MI complicated by heart failure (HF) treated until then (3). In these conditions the cardiotoxic is considered as myocardial protective (60-63), because would save the failing myocardial fibers, ischemic but viable, from the necrosis that certainly occur in processes leaved to his fate. Taking in account that the use of cardiotoxics in such clinical conditions conflicting with the TT, we have to give emphasis to the rarity of MI in patients with chronic heart failure, submitted to the continuous use of cardiotoxic.

In addition, integrated in the conjuncture of natural evolution of the chronic coronary-myocardiopathy, atherosclerotic, step by step we took clinical conscience of the circumstances and triggering factors, analogous in cardiac asthma and acute pulmonary edema, in one side, and in UA and acute MI, on the other side, both dependent of identical myogenic mechanism of progressive functional deterioration, until the triggering of global failure from the left ventricle, when

compromised around 30% of the area in the two first conditions, while in the last conditions the myocardial failure is regional and worsened, functionally, by the confrontation with the others myocardial segments that are intact.

Also conflicting with the TT is the recording of cases of acute MI in front of angiographically normal satellite coronaries, interpreted as syndrome X or in cases of carriers of pervious coronary artery bypass grafting (64-98), conveniently interpreted as consequence of spontaneous fibrinolysis. Such cases were referenced by Bulkley and col. as paradoxical MI (91). On contrary, when cases with coronary arteries completely obstructed do not have corresponding MI, are also conflicting with TT. Ambrose and col. (102) started to accept the MI without Q wave as an evolutionary period between the UA and MI with Q wave. This postulation seems to conform more to MT than with TT. They have recorded total coronary obstructive processes in 26% of the cases without Q wave and in 90% of the cases of MI with Q wave. In this particular, coronary angiograms performed earlier in the acute MI has showed indexes of total obstruction in 75% of cases with Q wave and 46% in cases of MI without Q wave (99-103). DeWood and col. (99) in MI without Q wave recorded total coronary occlusion in 32% of the cases and in a study more detailed observed with detached importance the incidence of total obstruction, significantly and progressively enlarged in relation to the time interval for the execution of the angiographic examination: 26% inside 24 hours; 37% from 24-72 hours; and of 42% from 72 hours till 7 days. However, they have noted subtotal occlusion (>90%) in the MI without Q wave, in particular signification the incidence gradually diminished: 34% inside 24 hours; 26 inside 24 to 72 hours; and in 18% from 72 hours until 7 days.

In relation to the effect of thrombolytics administered in UA (104-107), the results have indicated improvement in arterial coronary events and inefficacy regarding the clinical events. Consequently, the authors do not recommend its use in UA. As can be seen, the failure of anticoagulants in UA and now the unsuccessfulness of thrombolytics also in UA, clearly conflicts with TT and reinforce the MT, mainly in front of the results achieved with the cardiotonic. Referring to the use of cardiotonic in the acute myocardial infarction and contradicting old concepts about its harmful effects to the acute MI processes without heart failure (108-110), recent experimental studies (111-114) and clinically studies well prepared and conclusive (115-123), cancel such prejudices, confirmed in excess by our group (24, 58, 59, 149) attributing to the cardiotonic a protective myocardial effect (60-63).

The serial enzymatic reactions (124-135) justify the cardiotonic protective myocardial effect (60-63) helping us to give the interpretation of the clinical picture of acute MI, as yet infarcting (22-24, 124), in the moment of admission to hospital and administration of the new therapeutic; also contributing for the division of our cases in infarcting clinical picture – halted (ICP-H = in 67% of cases with enzymatic peaks inferior to 3 times the normal; 708 patients with 7 deaths: 0.9% and infarcting clinical picture – infarcted (ICP-I) = in 33% of cases with enzymatic peaks superior to 3 times the normal (N); inside an average of 5xN; 401 patients with 129 deaths: 32,1%. In 20% of the cases of infarcting clinical picture – halted, the enzymatic peaks were normal or little enlarged (<2xN), being interpreted as cases of MI –avoided.

Follows the practical aspects recorded by us since 1972, according the postulations of the myogenic theory, considering the 3 stages of coronary-myocardiopathy, conflicting of course with the thrombogenic theory postulations:

I – Stable Angina – Evolution from 1972-1989 (136-146)

The cardiotonic use may neutralize the negative inotropic effect from myocardial ischemia; to preserve the ventricular function, over leveling the ischemic and non ischemic segments, annulling the deleterious intersegments confrontation; prevent UA, MI and HF, favoring long survival; and, to complement the effect of collateral coronary circulation in case of severe arterial obstructions.

a) Patients without previous MI: 1159 pts.

- MI: 2.1%;

- Mortality: 8% (mean age at death: 72 years)

b) Patients with previous MI: 676 pts.

- MI: 5.2%;
- Mortality: 29.2% (mean age at death: 70 years)

II – Unstable Angina –199 patients (22, 23, 147, 148)

The cardiotonic has been insuperable in the immediate correction of regional myocardial insufficiency and interruption of episodic and spontaneous crises of angina, conditioning the prompt re-establishing of symptomatic and myocardial stability.

- Evolution to acute MI: 0,5%, non-fatal
- Mortality: 0%

III – Acute MI with Q wave – 1109 patients

- Mortality: 12.2% (136 pts.) – treated at the ICU of Matarazzo Hospital (63, 111-123, 149, 150)

The cardiotonic has been admitted as myocardial protective, benefic and responsible for great transformations in the evolution of acute myocardial infarction; correction of regional myocardial insufficiency, reducing the zone of secondary myocardial ischemia and interruption of the infarcting clinical picture, avoiding or attenuating the evolution to MI and may prevent the secondary coronary thrombosis.

Our case study was divided according the beginning of crisis/hospitalization interval:

- < 6 hours: 586 pts. in total, with 53 (9.7%) deaths
- > 6 hours: 523 pts. in total, with 83 (15.8%) deaths

There were also established 4 subgroups:

1. > 6 hours with > 70 years: 97 pts., 31 (31.95%) deaths
2. > 6 hours with < 70 years: 426 pts. 52 (12.20%) deaths
3. < 6 hours with > 70 years: 56 pts. 12 (21.42%) deaths
4. < 6 hours with < 70 years: 530 pts. 41 (7.73%) deaths

In relation to mortality we have recorded a clear prevalence of cases with beginning of crisis/hospitalization interval > 6 hours, from those designated as infarcting clinical picture – infarcted (enzymatic peaks > 3 x N), those with age > 70 years and those of female sex.

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