Platelet hyperactivity and hypofunction of the fibrinolytic system in arterial hypertension

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Abstract

Several reasons have been pointed out to explain the relative failure of antihypertensive therapy in the prevention of the atherosclerotic complications of high blood pressure. The decrease of blood pressure has proved to reduce the hypertensive (mechanical) complications of hypertension but it did not prevent myocardial infarction, an atherosclerotic complication, as expected by the results of the epidemiological studies. In addition, it is not clear the real effect of antihypertensive therapy in the prevention of ischemic cerebrovascular accidents. Both situations are the result of thrombotic events and are strictly related to endothelial function, platelet aggregation, fibrinolytic system and coagulation.

In the last ten years it was demonstrated that increased platelet aggregation and decreased fibrinolytic activity are dysfunctions related to hypertension. They appear to be independent markers of hypertension and not a consequence of the increased blood pressure.

Blood pressure normalization with diuretics and beta-blockers, the main therapies used in the big trials, failed to normalize those dysfunctions, unaffecting the action of factors with a crucial role in atherogenesis and thrombogenesis.

The introduction of new antihypertensive therapies, which decrease platelet aggregation and increase fibrinolytic activity, permit us to question if with their utilization will it be possible to prevent the atherosclerotic complication of arterial hypertension.

Key words: arterial hypertension, platelet aggregation, fibrinolysis, cerebrovascular accident, myocardial infarction.

"The reduction of general mortality with anti-hypertensive treatment has been associated to a substantial increase in the proportion of deaths by coronary disease; it seems that those whose treatment avoided death by CVA, kidney or heart failure, survive to have a wider period of exposure to the risk of coronary disease" Smirk, 1972.[1]

Introduction

The wide random trials of therapeutic interventions have shown the benefits of treatment reducing cerebrovascular accidents. However, the smaller effect seen while preventing coronary accidents was well below the expectations created by epidemiology studies.[2]

But doubts are raised regarding the benefit uniformity of the therapy to reduce cerebrovascular accidents, i.e., if the latter revealed itself to be more effective preventing hemorrhage and less in cerebral infarction.[3,4]

Among us Soares Franco et als, studying patients admitted by acute CVA who underwent cranio-encephalic CAT scan, found a predominance of ischaemic over hemorrhagic accidents, both in the general population as in the hypertensive one.[5,6]

However, the population ageing may be influencing these findings. Due to the control of many other diseases, man gets old and comes a time where he is a confronted with the consequences of an aged vascular tree, namely with atherosclerosis and its complications. And this phenomenon can be contributing for the current excess of ischaemic accidents observed.

The anti-hypertensive therapy has contributed, undoubtedly to change the natural history of arterial hypertension: ischaemic cardiopathy is currently one of the main causes of congestive cardiac failure, a position occupied in the past by hypertensive cardiopathy. A recent study by Rui M. Santos et als.,[7] evaluating the clinical and echocardiographic aspects of 222 patients admitted in an Internal Medicine service with a congestive heart failure diagnosis has shown to be the ischaemic cardiopathy the most common cause of congestive heart failure (50%), immediately followed by hypertensive cardiopathy (31% of cases).

Mechanical and atherosclerotic complications in hypertension

Several reasons have been given to explain the relative failure of anti-hypertensive therapy preventing atherosclerotic complications in arterial hypertension,[8] but none explains the disturbing association

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of hypertension with thrombosis.

Zanchetti gives an important contribution to this matter while distinguishing vascular complications of blood hypertension, the relative weight of high blood pressure in the vascular disease pathogenic mechanisms and its events. It is on this basis that this author questions if what we measure in the big intervention trials with anti-hypertensive therapy is the prevention of vascular disease or, only those of events.[9]

Intracerebral hemorrhages due to the Charcot-Bouchard microaneurysm rupture are hypertension mechanical complications.[10] High blood pressure is not only the main determining factor of developing the basis vascular disease (microaneurysms),[12] as well as the main cause of the acute hemorrhagic accident (rupture of microaneurysm).[10-12]

In a different manner, a high blood pressure is only one among the many factors that contribute for atherosclerosis of big extracranial cerebral arteries or the coronary epicardial arteries. Also the acute occlusive accident, coronary or cerebral, is related with high blood pressure only remotely. The acute myocardial infarction, the occlusion of a cerebral artery in the place of an atherosclerotic plaque, or an artero-arterial embolism are accidents very closely related to the formation of thrombus in an atherosclerotic plaque with endothelial disruption. The increase on blood pressure may be one among the different contributing factors but in no way it has a dominant role in the formation of the occlusive thrombi, as it has in the cerebral microaneurysms rupture.[9-12]

The hypertensive disease evolution seems to have two types of complications: mechanical and hypertensive, and the intracerebral hemorrhage is a paradigmatic example, where a dominant etiopathogenic factor is high blood pressure, and the atherosclerotic complications as a myocardial infarction or a thrombotic vascular cerebral accident, events closely linked to thrombogenesis and they seem to evolve in parallel but independently of controlling hypertension.

If on the etiopathogenesis of the hypertensive vascular disease is accepted as true these mechanisms, we can understand the partial benefit reached with anti-hypertensive therapy: the reduction of hypertension values will prevent mechanical complications, i.e., those more directly linked to a high blood pressure; but will not reduce in the same way the atherosclerotic complications, dependent on the thrombotic phenomena, and as such, of the platelet activations, of blood clothing and the fibrinolytic system dysfunction.

Importance of platelet aggregation in the atherosclerosis pathogenesis

The platelet aggregation and thrombosis have a primordial importance in the pathogenesis of acute ischemic accidents but also in the development and progression of arterial stenosis.[13,14] Necropsy studies in patients who died after and episode of unstable angina, have documented the existence of stratified thrombus in atherosclerotic plaques, even in previously asymptomatic individuals. These observations suggest that recurring mural thrombosis episodes, many of which without a clinical expression, may give an important contribution to the silent progression of the atherosclerotic disease.[14]

But the platelet intervention in the development of the atherosclerotic disease is not limited to the formation of the platelet thrombus: they take part in the endothelial fibro-proliferative over-reaction and on the smooth muscle cells of the arterial wall in response to different vascular aggressions.[15]

Platelets segregate a wide variety of substances interfering with the endotelial cells function , smooth muscles and macrophages, as well as TGF b (Transforming Growth Factor b), PDGF (Platelet-Derived Growth Factor), IGF-1 (Insulin-Derived Growth Factor) and the PD-ECGF (Platelet Derived Endothelial Cell Growth Factor) among others. TGF b has a chemotactic effect over the macrophage and the smooth muscle cells, inhibits the endothelial proliferation (regeneration), stimulates the proliferation of the smooth muscle cells of the vascular wall, induces the genetic expression of regulator growth factor as PDGF, also the synthesis and endothelial secretion of the connective tissue matrix. This and other factors have mitogenic effects, inducing the proliferation of vascular smooth muscle cells in atherosclerotic lesions. PDGF, TGF b and IGF-1 are also responsible for the migration of smooth muscle cells of the arterial tunica media to the intima (myointimal proliferation).[15]

How to explain the association between hypertension and thrombotic accidents?

There is growing evidence, clinical and experimental, that platelets do take part not only in the development of the basic atherosclerotic disease,[13-15] as well as in the pathogenesis of the acute thrombotic accident in

hypertensive patients.[13,16,17] The demonstration that there is platelet hyperactivity [17-26] and depression of the fibrinolytic activity [24-27] in hypertensive patients, can be the key to explain the association between high blood pressure and an increased risk of thrombotic accidents.

Platelet hyperactivity and hypofibrinolysis in hypertension

Platelet and fibrinolytic dysfunctions seem to be independent markers of high blood pressure but correlated to it.

The normalization of arterial pressure in hypertensive patients, on its own, it is not followed by a significant modification of platelet activity scores (plasmatic levels of beta-thromboglobulin, platelet factor 4 and B2 thromboxane in a stable metabolite of A2 thromboxane) or the increase on the platelet aggregation threshold in stimulating tests (platelet aggregation induced by adrenaline, collagen and ADP). In studies in essential hypertensive patients, prazosin,[28] labetalol,[29] and quinapril,[30] an ACE inhibitor without a sulphydryl group, in spite of getting arterial blood pressure back to normal they did not reduce the serum level of beta-thromboglobulin or the platelet aggregation induced by adrenaline, collagen and ADP.[28] These results suggest, apparently an absence of cause-effect relation between an haemodynamic change of *high blood pressure* and platelet dysfunction. However there is a close association between one and the other: more severe is the hypertensive disease higher tends to be the serum level of beta-thromboglobulin and platelet factor 4, regardless of the patient's age.[31]

In hypertensive patients, the presence of left ventricular hypertrophy, which expresses a more severe form of hypertension, is associated to an increased risk of cardiovascular accidents, namely coronary. In these patients, larger the left ventricular mass, higher the platelet reactivity.[32] A group of hypertensive patients without left ventricular hypertrophy, the platelet aggregation in response to ADP concentrations of 0.5 microM, did not differ of the observed in a control normotensive population.[32] Some works point to a consistent reduction on the platelet activation threshold in hypertensive patients whose mean blood pressure is higher than 120 mmHg.[17] Below this value there are contradictory results.[17,19]

It seems clear that the platelet dysfunction is related to blood hypertension as an independent marker and not as a consequence of this one. A positive correlation between a severe arterial hypertension and the degree of platelet hyperactivity on one hand, and the absence of change of the platelet dysfunction as the normalization of the blood pressure, on the other, are favorable arguments to this thesis.

In hypertensive patients, the levels of fibrinogen are above normal[27] and, in parallel with the platelet hyperactivity, there is a reduction of the fibrinolytic activity, documented by a low activity of the tissue plasminogen activator (t-PA) – the enzyme responsible for converting plasminogen in plasmin – and an increase on the plasminogen activator inhibitor (PAI).[24,33]

Similar to what is seen with the platelet hyperreactivity, also the fibrinolysis depression seem as independent marker of a high blood pressure. The normalization of blood pressure, on its own, is not followed by a fibrinolytic dysfunction.[26]

Anti-hypertensive therapy effects

The treatment in monotherapy with diuretics, beta-blockers, calcium antagonists, ACE inhibitors and others, in optimal therapy dosages, it leads to a similar reduction in blood pressure in mild to moderate hypertensive patients,[34] but it does not affect the same way platelet and/or fibrinolytic dysfunctions: some as methyldopa, diuretics or beta-blockers, may have a neutral or even a deleterious effect; others, as calcium antagonists, adrenergic alpha-1 blockers (daxozubine), serotonin inhibitors (ketanserin) and some ACE inhibitors have a positive effect.[18,19,25,26]

Such changes in the platelet and fibrinolytic activities appear to be independent of the hypotensive effect and linked to direct and indirect effects by these drugs over platelets and activity of factors determining fibrinolysis.

Conclusions

The changes on the platelet and fibrinolysis activity, the systems linked to thrombogenesis, seem to be together with high blood pressure, markers of hypertensive disease. Therefore, it could be explained, through such dysfunctions, the association of high blood pressure to thrombotic events.

In the big trials of therapy intervention of high blood pressure mainly diuretics and beta-blockers, anti-hypertension drugs were used, and those, as seen, do not have a beneficial influence over hypertensive

disease other markers. This way, a modification of a *high blood pressure* marker, without a normalization of others, would justify the partial benefit reached with the treatment, i.e., a reduction observed in hypertensive complications and the absence of the expected reduction on atherosclerotic complications. The increased risk of thromboembolic complications would be, therefore linked to thrombogenic markers – platelet hyperactivity and hypofibrinolysis – apparently not neutralized directly only by reducing a high blood pressure.

The absence of studies in a wide scale with the new classes of anti-hypertensive drugs with normalization effects on the platelet activity and fibrinolytic dysfunction, as calcium antagonists, some ACE inhibitors, blockers of S2-receptors of serotonin and daxozubin, does not enable us to access data on the impact of these new therapies on the cardiovascular mortality and morbidity, being difficult to rely on the hypotheses advanced previously. ■

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