The "No-Reflow" Phenomenon in the Coronary Arteries

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In the last twenty years, the treatment of coronary heart disease with cardiac catheterization has greatly advanced. This therapeutic approach has had unexpected side effects, however, for which solutions must be found, particularly in the are of interventional cardiology. The "no-reflow" phenomenon, a side effect, is an uncommon and critical occurrence and, if not reversed, causes a high rate of morbidity and mortality. Its most intriguing clinical characteristic perhaps is its unpredictability.

Kloner and co-workers [1] first described the "no-reflow" phenomenon in 1974 in dogs with experimentally induced myocardial infarction. The coronary arteries of these dogs were occluded for 40 or 90 minutes, and after that, they were reperfused and studied by means of contrast medium injection. In the coronary arteries occluded for 40 minutes, there was uniform reperfusion of the ischemic myocardium; however, in those occluded for 90 minutes, there was no reperfusion after removal of the coronary occlusion. These investigators concluded that the absence of flow was an ischemic phenomenon, related to the duration of coronary occlusion, which resulted in muscle injury and death of myocardial cells [1].

Later, "no-reflow" was observed in patients who experienced short periods of ischemia and coronary reperfusion with thrombolytic agents [2] and, more recently, in different types of coronary interventions with catheter [3-5]. This phenomenon was also observed in other organs, such as the skin, kidneys and brain, where ischemia occurred [1].

The "no-reflow" phenomenon can be defined as an acute and severe reduction of coronary flow (TIMI 0 to 2)* after removal of an arterial occlusion, in the absence of spasm, thrombi, severe residual lesions, and arterial dissection. It is not to be confused with slow flow, which is a much less critical situation that is more frequently observed and usually reversible.

"No-reflow," when visualized by angiography, appears as a column of contrast medium with slow back and forth movements inside a vessel usually close to the site of the treated lesion without progression of the contrast medium to the distal portion of the coronary artery.

When coronary blood flow velocity is analyzed by Doppler flow-wire, retrograde systolic flow, reduction of anterograde systolic flow and fast deceleration of diastolic flow caused by the "no-reflow" phenomenon can be observed [6].

Pathophysiology - The mechanisms of "no-reflow" are not completely understood, and many explanations are merely speculations. Several hypotheses have been suggested, but not all have experimental confirmation. Initially, "no-reflow" was attributed to an obstruction of the microvasculature, resulting from neutrophil accumulation, endothelial edema and hemorrhage, and regional sustained contracture of myocytes [1].

With the description of the phenomenon in human beings, new hypotheses were formulated about the causes of "no-reflow". The most accepted of these are: "no-reflow" due to embolism, arterial thrombosis, microvasculature dysfunction, platelet action, endothelial injury mediated by leukocytes, and regional myocardial contracture.

The embolic hypothesis - Fragments of plaque and thrombi may detach from the plaque submitted to treatment and embolize to the distal portion of the circulation. Although attractive, this explanation has no angiographic basis, which weakens this theory.

Arterial thrombosis hypothesis - Some [7] speculate that "no-reflow" results when a thrombosis due to a red thrombus occurs. Anticoagulation therapy is an integral part of the therapeutic procedure when using a catheter. Therefore, a fresh red thrombus would be dissolved by the anticoagulants. Often, however, as in acute myocardial infarction, "no-reflow" occurs despite the use of thrombolytic agents. Arterial thrombosis as a cause of "no-reflow" is, therefore, unlikely.

Microvasculature dysfunction hypothesis - This hypothesis is attractive and frequently mentioned in the

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literature. The endothelium injured during a therapeutic procedure releases free radicals and vasoactive substances, such as endothelin-1 (ET-1), a peptide derived from endothelial cells and cardiomyocytes, and platelet thromboxane. During ischemia or after reperfusion, myocardial production and release of ET-1 are stimulated. An increase in the coronary constrictive response then occurs causing microspasm, which hinders coronary flow [8].

Confirming this hypothesis, it was reported [9] that in dogs that underwent transient coronary occlusion, "no-reflow" was attenuated by the administration of superoxide dismutase and catalase, which are powerful "removers" of free radicals.

It is known that the synthesis of the endothelium-derived relaxing factor (EDRF), nitric oxide, a powerful dilator of the microvasculature, is severely affected in ischemic processes. Therefore, the synergic action of ET-1 and the decrease in the synthesis of nitric oxide would cause severe local constriction.

Experimentally, the pharmacological block of ET-1 promotes reduction in the infarcted area and enhances coronary flow [8].

Another important factor is that nitroglycerin does not promote dilatation of the microvasculature, acting mainly on the epicardial vessels [10-11], which strengthens the theory that the disturbance occurs only in the microvasculature. This sustained spasm would neutralize or even replace the local self-regulatory control [12].

"No-reflow" has a regional distribution and can be related to the duration of ischemia and, in cases of infarction, to the extent of necrosis [13].

Platelet action hypothesis - Rawitscher and co-workers [14] consider that platelets also actively participate in the "no-reflow" phenomenon. The traumatic instability of the atheroma induced by therapeutic maneuvers leads to an increase in platelet adhesiveness followed by a state of activation and increase in aggregation, resulting in the formation of white thrombi and vascular occlusion. This theory is supported by results of researchers, [14] who demonstrated the reversal of established "no-reflow" by using the inhibitor of the glycoprotein IIb/IIIa of the platelets.

Leukocyte-mediated endothelial injury hypothesis - In ischemic myocardial areas, there is an accumulation of neutrophils, which act as occlusive plugs and potential sources of free radicals, leading to constriction and mechanical obstruction of the microvasculature [15-17]. However, the presence of "no-reflow" has been experimentally demonstrated in isolated hearts perfused with solutions without neutrophils [1,18].

Perhaps the state of activation of neutrophils is of greater importance than their number [1]. Migration of white cells and intramural hemorrhage cause endothelial edema, leading to reduction of capillary diameter and difficulty in blood perfusion [18].

Regional myocardial contracture hypothesis - During reperfusion, vasoconstricting substances and calcium are released, resulting in a regional sustained myocardial contracture, hindering adequate perfusion and producing a vicious circle of ischemia – contracture – ischemia. Therefore, "no-reflow" would be a consequence of reperfusion following ischemia.

Currently, the hypothesis of microvascular injury mediated by free radicals is the most widely accepted [1]. However, as observed in the literature, the mechanism of "no-reflow" is multifactorial.

Whether the pathophysiology of this disorder is the same in human beings and experimental animals is another point yet to be elucidated.

Incidence

According to the literature, the incidence of "no-reflow" varies from 1% to 7.7% in coronary intervention, depending on the TIMI classification and on the patient population studied.

It occurs in 10% to 15% of the angioplasties performed in patients with degenerated saphenous bypasses and in patients with recent myocardial infarction, probably because in these situations the lesions are friable, rich in platelet thrombi and release vasoactive agents, such as serotonin. It is more frequent in patients with myocardial infarction, in cardiogenic shock, who have undergone primary angioplasty [4]. In a large review of 10,676 patients, [19] the global incidence of "no-reflow" was 0.6%, occurring more frequently with the rotational atherectomy "rotablator®" (7.7%), with the use of extraction atherectomy (4.5%), and with directional atherectomy (1.7%). It was less frequent with the excimer laser (0.3%) and after conventional angioplasty (0.3%). Another study [20] showed a higher incidence in patients who underwent stent placement and directional atherectomy (3%) when compared to patients undergoing conventional balloon angioplasty (1.7%).

In addition, "no-reflow" was detected in 19% of the patients with acute myocardial infarction, who underwent immediate angioplasty [21].

A retrospective analysis of a group of patients treated with rotational atherectomy showed that the management of large lesions with a long-lasting ablation time in an arterial segment with myocardial involvement increased the incidence of slow flow and "no-reflow" [22].

Clinical features

Usually, the first symptom of "no-reflow" is a precordialgia of insidious onset, with a continuous and increasing character and electrocardiographic abnormalities of the segment ST/T and arrhythmia. Mild hypotension can occur, as well as cardiogenic shock and myocardial infarction.

Treatment

No standard, single treatment has yet been found. Because many mechanisms are involved, it is unlikely that a single therapeutic approach will be appropriate for all cases.

General management - Initially, the angiogram should be very cautiously analyzed to eliminate the dissections, thromboses, spasms, and important residual injuries as causes of "no-reflow". These situations require specific treatment and are detailed below. 1) Usually, the intracoronary injection of nitroglycerin at a dose of 200 to 1000µg reverses the spasm of pericardial vessels. The action is fast and the results are usually good; 2) the coronary thrombus can be mechanically treated by inflation of the balloon catheter or by means of thrombolytic agents, such as streptokinase; 3) usually, the coronary dissection can be diagnosed in one of the several projections filmed, sometimes requiring intravascular ultrasound and, eventually, angioscopy. Once confirmed, the coronary dissection can be treated with the perfusion balloon catheter, using low pressures and a long period of inflation (15 to 30 minutes) to fix the intima. The placement of a stent constitutes a more definitive treatment.

Once the above possibilities are excluded, the specific treatment can begin.

The patient should be sedated to relieve the pain and anxiety associated with the release of catecholamines. Maintenance of good ventilation is important.

Blood pressure should be monitored and, if necessary, maintained preferably with volemic expanders and, in more severe cases, with vasoactive amines. The activated coagulation time should be above 300 seconds [20] to avoid thrombotic phenomena.

The increase in the pressure of coronary perfusion can be maintained with the injection of oxygenated blood withdrawn through the guide catheter and injected under pressure into this same catheter or into the central lumen of the balloon catheter after the withdrawal of the guide line. Physiological saline can also be injected in this way to improve distal flow through mechanical clearance of thrombi and cellular fragments present in the microvasculature.

Streptokinase and other thrombolytic agents have already been used experimentally [23] and in clinical circunstances with no beneficial action. Their use is even considered risky.

Another management option is the intraaortic balloon for counterpulsation to increase the diastolic pressure of coronary perfusion, which can promote the clearance of cellular debris and thrombi and also the washing of vasoactive substances and calcium released during ischemia. However, evidence exists that the intraaortic balloon has a better performance in states of slow flow induced by hypotension.

The cardiopulmonary bypass, which is a measure of temporary cardiocirculatory support, can be used in extreme cases.

Pharmacological treatment - Several drugs have been used for treatment of the "no-reflow" phenomenon in an attempt to reverse microvasculature vasoconstriction. Mononitrate or nitroglycerin is used for intracoronary infusion, in a bolus of 200 to 1000µg. Usually the result is not good because the resisting vessels respond to nitrates with weak dilatation. The response to nitrates is more intense in the epicardial vessels.

Perhaps calcium antagonists, in particular verapamil and diltiazen, are the most frequently used drugs. These drugs reverse the condition in 67% of cases [19]. Verapamil, 100 to 200µg by slow intracoronary infusion with cautious attention to the cardiac rhythm, seems to be more effective. Diltiazen at a dose of 2 to 10mg is also administered by intracoronary via. These drugs, unlike the nitrates, have a more intense effect on the microvasculature.

Several reports have shown that this group of drugs limits the infarct size and prevents a stunned myocardium [20].

These drugs are administered through the central lumen of the balloon catheter to obtain an effective concentration of the drug inside the considered artery. An electrode of a cardiac pacemaker should be available to stimulate the right ventricle, because some patients can develop pharmacological atrioventricular blocks of different grades.

It is important to consider that these drugs can worsen the hypotension that is a consequence of this perfusion disorder. Therefore, auxiliary measures, such as volemic reposition, use of positively inotropic agents and, eventually, counterpulsation, are important.

Papaverine (6,7-dimethoxy-1-veratrylisoquinoline), an opium-derived alkaloid and a powerful spasmolytic, has an unknown molecular mechanism of action. It is known to have an arteriolar dilating action in systemic, cerebral, and coronary circulation.

It is speculated that the papaverine dilating action is related to its ability to inhibit phosphodiesterase. Its use is recommended in the literature [24,25] and we have already had the opportunity to use it successfully more than once. It is administered by intracoronary infusion at the dose of 10 to 20mg, which can be repeated 2 or 3 times. Its effect is immediate, with an accentuated enhancement of the coronary flow and pain relief.

Although this effect of papaverine is not limited to the coronary bed, the above referred dosages determine maximum reduction of the coronary vasculature resistance, with minimal alterations in blood pressure and cardiac frequency [24,25].

Unlike papaverine, calcium blockers do not produce maximum dilatation of the coronary bed resistance.

Recently, two cases [14] of successful treatment with the inhibitor of the glycoprotein IIb/IIIa of the platelets (abciximab) were reported. The drug was administered in the form of an endovenous bolus, at a dose of 0.25mg/kg, followed by slow venous infusion during 12 hours at the velocity of 10mg/min.

Some authors (26) report success in the reversion of "no-reflow" phenomenon with intracoronary infusion of adenosine at a dose of 10 to 20µg.

Prophylaxis

Because the pathophysiology of "no-reflow" is not completely understood, its prophylaxis is difficult.

When the rotablator® with big olives is used, rotation velocities less than 5,000 rpm and greater than 180,000 rpm [27] should be avoided. It seems that the pulverization of the plaque beyond these limits often causes the formation of microemboli and arterial dissections, which are clinically significant in many occasions. It is advisable that the ablation period be short and intermittent, providing intervals of recuperation from ischemia in the myocardial territory related to the treated artery.

In the management of complex lesions, one can use saline solutions with verapamil (10µg/mL), nitroglycerin (4µg/mL), and heparin (20U/mL) for intracoronary perfusion, under pressure, in the lateral sheath of the rotablator®. It is important to use a pacemaker electrode, especially when the right coronary and the circumflex artery are the vessels considered, because atrioventricular blocks frequently occur.

When dealing with saphenous bypasses with thrombosed lesions, it seems useful to infuse streptokinase by systemic via, 24 hours prior to the intervention, to induce lysis of the thrombotic component of the plate, thus reducing the chance of microembolizations.

Another option is urokinase. It can be injected into the saphenous bypass via infusion catheter, prior to the mechanical approach of the lesion, with the advantage of being administered in a short period of time and having a more selective effect than streptokinase.

As alternative managements, there is the possibility of initial treatment with AngioJet Hydrodynamic Thrombectomy (Possis Medical – 2095 Northwest Boulevard, Minneapolis, MN, USA) or the Cordis Hydrolyzer (Cordis Corporation – Miami Lakes, FL, USA). These devices emit saline solution through specific catheters located in the lumen of the venous graft, originating the Venturi effect inside the vessel leading to fragmentation and dissolution of the thrombi. There are reports about experiments in which ultrasound waves emitted through the extremity of a catheter were used to fragment intravascular thrombi.

TEC – transluminal extraction catheter (InterVentional Technologies, Inc. – San Diego, CA, USA) is a device that enables the fragmentation and extraction of intracoronary thrombi. These new technologies use different methods to reduce the thrombotic mass and to "prepare" the vessel for a definitive treatment such as stent placement.

Pilot clinical trials, such as VeGas (Possis) and TECBest (IVT), will clearly define the role of each of these new therapeutic modalities in the management of degenerated saphenous bypasses.

Prognosis

The "no-reflow" phenomenon is associated with a mortality rate of up to 15%, an incidence 10 times greater than that in an ordinary interventional procedure [19]. Myocardial infarction occurs in about 30% of patients [19]. Considering that the phenomenon worsens with time, the earlier the diagnosis and the onset of the therapy, the better and faster the reversion [15].

Patients who undergo primary angioplasty and develop absence of flow and cardiogenic shock have a very bad prognosis [4]. Reversion is only obtained in 30% of cases [4].

When the phenomenon is secondary to the use of the rotablator®, flow restoration can be achieved in about 63% of cases [19]. On the other hand, "no-reflow" associated with the use of the extraction atherectomy catheter is usually irreversible [19].

In cases where the possibility of occurrence of the phenomenon can be predicted, such as in the manipulation of saphenous bypasses and in acute myocardial infarction, the few known prophylactic measures should be taken. In some cases, they can prevent the development of the process [27]. Therefore, we believe that the diagnosis should be made speedily and the treatment should be aggressive from the beginning to prevent the occurence of a vicious circle of slow flow - hypotension - "no-reflow" - hypotension.

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