THROMBOCYTOPENIA SUPERIMPOSED WITH THE WANING OF CARDIAC SURGERY WITH CARDIOPULMONARY BYPASS. A REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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ABSTRACT

The occurrence of thrombocytopenia is almost systematic in cardiac surgery under cardiopulmonary bypass. Its usual causes are multiple and sometimes recognized but infrequent mechanisms are added causing the problem etiological diagnosis. We report 2 cases of thrombocytopenia superimposed with the waning of cardiovascular surgery with cardiopulmonary bypass. The first case report with rare drug immuno allergy and the second due to a septic shock and hemolysis by Intra-aortic balloon counter pulsation, then they describe the various common causes platelet changes induced by cardiopulmonary bypass. The appropriate care was difficult because of delayed diagnosis. Only one patient had a favorable outcome.

KEYWORDS: Platelets, thrombocytopenia, cardiopulmonary bypass, cardiac surgery.

ABREVIATIONS
ADP: Adenosine di phosphate
CPB: Cardiopulmonary bypass
IL: Interleukin
IABP: Intra-aortic balloon counter pulsation  
mcL: microliter  
HIT: Heparin-induced thrombocytopenia  
WBC: white blood cells  

INTRODUCTION  
The occurrence of thrombocytopenia in postoperative cardiac surgery under cardiopulmonary bypass (CPB) is almost systematic. On multifactorial origin, it runs the risk of bleeding or thrombotic complications secondary and the dilemma of its etiology and the challenge of appropriate care problems.  

The authors report 2 cases of thrombocytopenia in postoperative cardiac surgery with CPB, the first case report with rare drug immune allergy and the second due to a septic shock and hemolysis by Intra-aortic balloon counterpulsation (IABP).  

CASES REPORT  
FIRST CASE REPORT  
A patient of 48 years is scheduled for surgical correction of mitral stenosis and tricuspid regurgitation. The intervention involved the substitution of Coumadine by Heparin, the introduction of omeprazole and the judgment of the Digoxin. The platelet count in the immediate postoperative period of a mitral valve replacement and tricuspid valve plasty showed thrombocytopenia 55G per microliter (mcL) I corrected after several tracks, by stopping omeprazole associated with an inject able corticosteroid dose. A day+8 thrombocytopenia 33G / mcl requiring cessation of heparin and authorizing the resumption of omeprazole, the platelet collapsed 5G /mcl despite transfusion platelet pellets. The correction is obtained only after stopping omeprazole. The reintroduction of a single dose of the latter induces very severe reoccurrence of thrombocytopenia (12.G /mcl). The staging eliminated Central and septic thrombocytopenia origin. The patient was put on oral steroids for two weeks resulting in enhanced platelet to 117G /mcl.  

SECOND CASE REPORT  
A 51-year-old diabetic, whose preoperative Laboratory tests were normal, received a double mitral and aortic valve replacement with mechanical prostheses. Weaning from CPB needed assistance by IABP. The curative dose heparin was introduced to H+6 and day+2 the patient presented a pneumonia due to Pseudomonas aeruginosa with severe hypoxemia and
hemodynamic instability. Laboratory tests showed thrombocytopenia (63G /mcl), an
hemoglobin level to 10 g/dL, hyperleukocytosis (14 G /mcl), CRP = 169 mg / l, a fibrinogen
680 mg/dL , prothrombin time 56% and a rate of D.Dimères 80.5 micrograms / ml. The
diagnosis is one of thrombocytopenia by septic shock lung starting point associated with
hemolysis by IABP. Despite appropriate antibiotics and vasoactive amines, the evolution was
marked by the appearance of multiple organ failure leading to death of the patient to d+30.

DISCUSSION
In cardiac surgery, the occurrence of more or less profound thrombocytopenia associated
with platelet dysfunction is almost systematic and is the primary hemostatic changes caused
by cardiopulmonary bypass.[1]

Indeed, the most massive bleeding after CPB is due to non-surgical causes, and platelets have
a major responsibility in microvascular bleeding.[2]

Several factors associated with CPB may affect platelet number and function as pH, initial
platelet count, hematocrit, pre and intraoperative medications, fibrinogen degradation
product, the amount and nature of the priming, type of oxygenator and release of
proinflammatory cytokines such as interleukin (IL1 AND IL6).[3]

The exposure of blood elements to several constraints such as hypothermia, hemodilution
(priming and cardioplegia) activation of tissue factor in contact with heparin and protamine,
mechanical trauma, contact with some biocompatible surfaces, prothrombin activation, leads
to platelet activation, and fibrinolysis and the creation of a certain degree of coagulopathy.

There by, in the first few minutes of the CPB occurs a sharp drop in platelets that worsens
throughout the circulatory support to achieve reduced by 50-60% compared to baseline rates.
Several mechanisms overlap in this phenomenon equally well depth of thrombocytopenia on
platelet function. However, this is transient thrombocytopenia and normalizes in 3-4 days.[4]
The 3 main mechanisms of these platelet changes are hemodilution, consumption and
activation of platelets.

The hemodilution by the priming volume with crystalloid or colloid contributes to filling
circuits CPB and improves blood rheology related to hypothermia. This is accentuated by the
hemodilution cardioplegia and is even the main cause of thrombocytopenia.[5]
Extreme hemodilution with a drop of less than 20% hematocrit, are accompanied by a true dispersion of platelets embedded in the blood stream. Thus, they lose their aggregating properties of particular vessels contact at high shear rates. Several studies have shown the existence of an inverse relationship between the degree of hemodilution and longer bleeding time.\cite{6,7}

While moderate hemodilution with 25-30% hematocrit improves blood rheological conditions in vessels at low shear rate without excessive stress on platelet function.

The second mechanism is the platelet consumption due to mechanical destruction by the CPB circuit (tank, filter, hoses ..... or by bio incompatibility which is dependent on phenomena related to the contact of blood with the artificial surface of any synthetic on the one hand and the specific characteristics of the circuit CPB other. [8] which joins consumption induced by thrombin, plasmin and inflammation (elastase , white blood cells, complement- platelet complex....)

The formation of intravascular micro-thrombi to contact surfaces circuits contributes to the worsening of thrombocytopenia in the CPB. Filters, CPB circuit and the nature of oxygenators are also responsible for capture and destruction of platelets.\cite{9}

The administration of protamine may also induce platelet consumption or activation.\cite{9} These consumption and / or platelet sequestration should now be able to benefit from effective prophylactic measures with the larger use of materials hemocompatibility, at least deleterious membrane oxygenators for blood elements, combined with a better control of the quality of anticoagulation of the patient and circuit.

The third mechanism is platelet activation due to different processes such as increased circulating agonists such as thrombin formed by the usual doses of heparin, adenosine di phosphate (ADP) released during the erythrocyte hemolysis caused by the CPB , at last the operating stress and non-pulsatile flow generated by the pump to increase the plasma concentration of adrenaline.

At these agonists, add, hypothermia, high shear forces at the circuit CEC and mixing with creating an interface air-blood (cardiotomy suction, bubble oxygenator and a phenomenon of amplification or self-recruitment of platelets and activation surrounding inflammation.\cite{8}
These 3 traditional mechanisms are recognized as responsible for usual platelet changes and are generally neither explored nor specifically treated. Indeed thrombocytopenia and platelet disorder spontaneously reversible after a few days.

At these common causes of platelet dysfunction may add other causes such as sepsis, hemolysis, drug allergy …

In our two patients the persistence of thrombocytopenia is the origin of its search mechanism. Thus in our first patient persistence of thrombocytopenia required to make etiologic including, among others, the search for a drug-induced thrombocytopenia other than heparin. Using an etiological approach according to the score of GEORGE and level of evidence.\[9\] Were able to conclude that it was a hypersensitivity to omeprazole, which is rare but previously described.\[10\]

The time to onset of these thrombopenia may be longer or shorter and the clinical expression spread over several weeks.\[1\]

Several molecules are known longstanding potential thrombopeniant more or less important. New observations thrombocytopenia drug are regularly reported in the literature and the list of offending molecules is far from over.\[2\]

**Thrombocytopenia by drug induced thrombocytopenia has four main consequences**

- The fear of bleeding caused or exacerbated by thrombocytopenia.
- The decision to transfuse platelets or not taking into account the potential harmful side effects.
- The initiation of complementary diagnostic exams.

The need for therapeutic substitutions, sometimes impossible, which could have significant consequences in the pursuit of medical care.

In our case four molecules were implicated in the onset of thrombocytopenia, these molecules are Digoxin, Omeprazole, Heparin and Furosemide. Resting on omeprazole accountability criteria, only meets all the criteria with a level of evidence I, digoxin is classified as Level II, for against heparin was excluded because it does not meet any criteria accountability. However concomitant heparin and omeprazole may have an effect on the fall in the platelet count within 50G / l.
Furosemide was used throughout the observation without judgment, therefore it was impossible to classify according to the criteria of accountability but is believed to be involved in thrombocytopenia occurred preoperatively, and is responsible for non-standardization of platelets at the end of the observation.

In the case of drug-induced thrombocytopenia, discontinuation of causative medication is necessary and often sufficient in situations where the prognosis is not threatened. In the context of poly-medication this interruption should interest all suspected drugs when unable to connect thrombocytopenia a specific molecule. The judgment must be final once also established accountability. It is imperative to report the "accident" pharmacovigilance.

Threatening bleeding in severe functional or life-threatening, may be used to corticosteroids and intravenous immunoglobulin, plasma exchange or platelet transfusion.\(^3\)

Generally this type of etiology poses a problem of cardiovascular surgery for the diagnosis on the one hand, it is based on the elimination of other causes and therefore heavy and expensive staging and other share in the management which requires sometimes stopping the administration of the molecule concerned and molecules belonging to the same family which are difficult or impossible to replace and taking high-dose corticosteroids may increase the risk of infection in a field already weakened by such surgery.

In our second patient, the use of IABP and heparin may also be implicated in platelet consumption.

Decreased platelet > 50% was reported in 26% to 58% of patients treated with IABP.\(^{12, 13}\) Rigal\(^{14}\) found a frequency of 4.5% of heparin-induced thrombocytopenia (HIT) in patients treated with an IABP. There is no criterion for distinguishing HIT.

Thrombocytopenia occurring frequently in patient with IABP. The usual course of the platelet count after setting up a IABP is a gradual decline of about 50% with a maximum of decline between the third and fourth day of laying.

In our patient the presence of DIC cannot rule out the diagnosis of heparin-induced thrombocytopenia (HIT) as they may be involved in 15-20% of cases.
In a number of cases, the platelet count rises spontaneously even under IABP, lower platelet persists until the IABP remains in place.

In the case presented, we observed an unusual pattern of thrombocytopenia, with a sharp decline from 63 to 18 G/l, while the removal of the IABP was performed, was suggestive of another cause of thrombocytopenia.

The non-resolution of thrombocytopenia after cessation of heparin has averted the diagnosis of HIT and the search for anti-PF4 antibodies by ELISA was not performed because there are often non-pathogenic antibodies anti-PF4 in a context of post-CPB, A50 15% of patients may have a positive ELISA so that there is no HIT.

Two different functional tests that could assist the diagnosis in our case it is the platelet aggregation test and especially the release test-serotonin.

If no obvious cause drug reaction or origin (hemophagocytic syndrome reaction) diagnosis of thrombocytopenia septic origin was retained.

Indeed on day 1 of hospitalization in intensive care our patient to an infection with Gram-negative germ is complicated by septic shock associated with DIC. Sepsis is the first risk factor for thrombocytopenia in intensive care and is associated with DIC in 15-50% of cases. The thrombocytopenia is more frequent in a Gram negative germ infection than Gram positive germ.[15]

These two observations remind us as "trivial" causes of thrombocytopenia with the waning of the CPB can add more rare causes, requiring careful analysis and etiologic investigation capable of guiding the therapeutic management for spontaneous resolution or correction by transfusion may prove to be insufficient.

**CONCLUSION**

Thrombocytopenia is almost systematic in cardiac surgery under cardiopulmonary bypass. Their etiologies are highly variable and it is important to try to determine responsible mechanism to develop the best therapeutic management.
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