TOWARDS A BETTER COMPREHENSION OF ACUTE MESENTERIC ISCHEMIA AFTER CARDIAC SURGERY. AN ANALYSIS OF 33 PATIENTS.

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ABSTRACT

Background. Acute mesenteric ischemia (AMI) after cardiac surgery is a rare but serious complication associated to high mortality. The time of onset is the key point to correctly evaluate the clinical scenarios.

Methods. Data from adult patients who underwent laparotomy for AMI after elective or urgent cardiac surgery were reviewed (January 2005 - December 2019) to report their anatomoclinical features in relationship to time of onset. Early events (within 48 hours) were allocated to Group 1, whereas late onsets were allocated to Group 2.

Results. The incidence of risk factors for non occlusive mesenteric ischemia was higher in Group 1 (chronic renal failure 80% vs 38.8%, P <0.05, use of inotropes 60% vs 5.5%, P <0.01, early oligo-anuria requiring CRRT 80% vs 16.6%, P <0.01, prolonged ventilation 46.6% vs 5.5%, P <0.05), where a significative occurrence of postoperative de novo atrial fibrillation was noted in Group 2 (55% vs 5.5%, P <0.01). The number of patients who required bowel resection was proportionally higher in the Group 2

Conclusions. Two well distincted categories of AMI after cardiac surgery can be classified. The first consists of patients with well-known risk factors developing ischemia as a result of severe visceral hypoperfusion The second consists of patients with low comorbidity who experience late AMI as a consequence of“trigger events”, mainly de novo atrial fibrillation. This classification may be useful to better alert the medical staff to the possibility of bowel ischemia at any time after cardiac surgery, promoting early diagnosis and treatment.

Data Availability Statement

Complete Patients Files and derived Dataset are available at study site for consultation

Conflict of Interest Statement

None of the authors has conflict of interest to disclose

Ethical and Legal Adherence Statement

All Authors confirm that all research meets the ethical guidelines, including adherence to the legal requirements of the study country.

Funding Statement

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BackGround

Acute mesenteric ischemia (AMI) following cardiac surgery is a rare event (incidence 0.3-3%), probably underestimated, occurring from few hours (2-10 hours) to several days (10-60 days) after cardiac procedures, associated to high mortality rate (1-5). Most literature data reports as the main risk factors for AMI the conditions of peripheral malperfusion (low cardiac output, prolonged cardiopulmonary bypass times, use of vasoactive drugs and/or intra-aortic balloon pump), defining as "non occlusive" the majority of post-cardiac surgery intestinal ischemia (6-9). However, this interpretation does not completely reflect the dynamics of intestinal ischemia, which may be determinated by other pathophysiological mechanisms in a significative number of patients, who have a regular postoperative clinical course. Indeed, besides to patients who experience bowel ischemia few hours after surgery, as a consequence of intraoperative malperfusion, other patients with an initial uneventful postoperative course, will be affected by AMI later from cardiac procedure, probably as effect of different pathogenesis (10-12).

The time of onset is the key point to correctly evaluate the clinical scenario of abdominal ischemia and facilitate a better comprehension of this severe complication. In the present report we investigated the anatomoclinical features of cardiac patients undergoing laparotomy for AMI in relationship to the time of onset, to differentiate early from late events in terms of pathogenesis, clinical appearance, and outcome. The aim of this study was to suggest a better comprehension of this high lethal complication, optimizing prompt diagnosis and treatment.

Patients and Methods

Data from adult patients who underwent laparotomy for AMI after elective or urgent cardiac surgery were reviewed (January 2005 - December 2019). All patients singed an informed consent as regarding the condition and the proposed treatment.
The study was approved by the local Ethical Committee at the study Site.
Patients with diagnosis of AMI within 48 hours from cardiac surgery were allocated to Group 1 – early events (n.15), whereas patients with diagnosis of AMI later than 48 hours were allocated to Group 2 – late events (n.18). Patients in whom laparotomy did not confirm AMI were not included in this series as patients who experienced AMI more than 30 days after cardiac surgery.

Data collected

The following items were retrospectively retrieved from the patients' medical records:

-demographic information and comorbidity;
-heart surgery procedure data;
-postoperative laboratory data (ICU admission, 24 and 48 postoperative hours);
-radiological findings (CT-scan, plain abdomen X-ray);
-abdominal surgery data;
-30-days mortality;
-hystopathological report.

Patient management

Following cardiac surgery, all patients were admitted to the cardiac intensive care unit (ICU) and weaned from mechanical ventilation. Blood samples were immediately collected and repeated every 24 hours, or more frequently, if clinically indicated. Since 2010 Procalcitonin (PCT) and Interleukin-6 (IL-6) levels were included in the laboratory protocol, using ELFA (*Enzyme Linked Fluorescent Assay*) and CLIA (*chemiluminescence-immunoassay*) test . Arterial blood gas and lactates values were monitored on clinical basis.

Diagnosis of AMI

AMI was mainly suspected in case of lactoacidosis (> 4mM/L), new onset of oliguria or anuria and abnormal trend of visceral enzymes, regardless of gastrointestinal symptoms. An increasing value of PCT and IL-6 was regarded as additional bioumoral marker of bowel ischemia and predictor of adverse outcome (13-17). These markers were evaluated at the ICU admission and in the following 48 hours. Diagnosis was confirmed by radiological findings (abnormally distended bowel loops, presence of free peritoneal fluid, reduction or absence of bowel wall enhancement, pneumatosis intestinalis, increased thickness of the mesenteric tissues, superior mesenteric artery thrombosis) and successive surgical exploration. Anatomical specimens following resection were studied for hystopathology.

Management of AMI

The algorithm of treatment initially consisted of intensive medical and

metabolic support including continuous renal replacement therapy (CRRT), but a prompt open intervention was considered mandatory, on the basis of CT-scan findings and clinical worsening.

Necrotic bowel was resected and proximal stoma or immediate reconstruction was performed by the judgment of the operator. In patients with borderline ischemia, bowels were not resected, to be evaluated in a "second look" operation, using an open abdomen technique. Endovascular treatment with selective infusion of vasoactive drugs was not performed in this experience. A superior mesenteric artery embolectomy was planned on the basis of CT-scan findings.

Endpoints

This paper aims: (1) to detail the anatomo-clinical differences related to the time of onset of AMI, (2) to compare the 30-days outcome between early and late ischemic events, (3) to present the institutional strategy in terms of diagnosis and treatment of AMI.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, after testing for normality with Kolmogorov-Smirnov test. Categorical variables are presented as numbers with percentage. Comparison of frequencies and outcomes between groups are tested by using Chi-square and Fisher exact test. For continuous variables, the differences between groups are compared using Student's t-test. A *P*-value <0.05 was considered statistically significant.

Results

Demographic and comorbidity (tab.I)

The incidence of chronic renal failure (CRF), was significantly higher in Group 1 (*P* <0.05). Diabetes, peripheral vascular disease (PVD), and depressed left ventricular ejection fraction (LVEF) were more frequently encountered in Group 1, with no statistical difference (*P* = ns). The association of coronary artery disease (CAD) and previous abdominal surgery was similar for both groups.

Operative data (tab.II)

More than 70% of patients in this series underwent isolated or associated valve procedure, with no distinction among groups. Aortic procedure were performed more often in Group 2 (P <0.05). Most of cardiac operations were performed on pump (75.7%), without significative difference between two groups. The extracorporeal circulation and aortic cross-clamping times were comparable. A longer cross-clamp time was observed in Group 2 (P = ns), may be related to the number of complex aortic procedures.

Perioperative risk factors (tab.III)

A prolonged use of inotropes was prevalent in the Group 1 compared to Group 2, where the use of vasopressors was minimal (n.9, 60% *vs* n.1, 5.5%, P <0.01). Regarding postoperative risk factors, early postoperative oligo-anuria (<24 hours) requiring CRRT and prolonged ventilation occurred more frequently in Group 1 than in Group 2 (80% *vs* 16.6%, P <0.01, 46.6% *vs* 5.5%, P <0.05, respectively). Postoperative *de novo* atrial fibrillation occurred in 14 patients of Group 2 (55%), with significative difference compared to group 1 (5.5%, P <0.01).

Clinical appearance (tab.IV)

First clinical signs of AMI occured 31.2±15.5 hours after surgery in Group 1 and 10.3±7.4 days after surgery in Group 2. Patients who experienced AMI presented with an increasing level of untreatable lactoacidosis, associated to a rapid deterioration of renal function. These signs were the main markers of visceral ischemia in the Group 1. Abdominal signs (distension, diffuse pain, melena) coupled with successive CT-scan findings featured the clinical onset of delayed AMI.

Bioumoral findings (tab.V-VI)

A similar elevation of visceral enzymes was distributed between the two groups. A significative difference in terms of prolonged lactoacidosis was observed within the first 48 hours, as Group 1 showed higher lactates compared to Group 2 (P <0.01). Besides lactoacidosis, a significant elevation of PCT and IL-6 was noted in Group 1 compared to Group 2, since the ICU admission (P <0.01).

Laparotomy findings and outcome (tab.VII)

Mean laparotomy delay (considered from the first clinical and bioumoral finding suggestive of mesenteric ischemia to the time of exploratory laparotomy) was significantly shorter for Group 1 than for Group 2, 7.6±6.9 hours and 14.8±1 hours, respectively. An open abdomen technique was used in 26 cases (78.8%).
Intraoperatively, diffuse bowel ischemia compatible with a hypoperfusion state (NOMI) was observed in 14 patients, 7 of Group 1 (46.7%) and 7 of Group 2 (38.4%). These patients underwent decompressive laparotomy without necessity of bowel resection. Segmental necrosis involving small and/or large bowel were noted in 19 patients, 8 of Group 1 (53.3%) and 11 of Group 2 (61.1%) These patients underwent primary or secondary bowel resection, most of them with terminal stoma. The number of patients who required bowel resection was proportionally higher in the Group 2 compared to Group 1 (P = ns).
Twenty of the 33 patients (60.6%) died within the first postoperative month, 8 in Group 1 and 12 in Group 2, corresponding to mortality rates of 53.3% and 66.6%, respectively (P = ns). The causes of death were multiorgan failure in 15 patients (75%) and recurrence of AMI in 5 patients (25%).

Hystological findings

Hystopathology study confirmed the presence of ischemic necrosis in all 19 patients undergoing bowel resection, with evidence of residual ischemia on the edge of resection in 9 cases (small bowel n.5, large bowel n.4), more frequent in Group 2 compared to Group 1 (33.3% *vs* 20%, P = ns).

Discussion

Among the abdominal complications occuring after cardiac operations, AMI has one of the highest rate of mortality, ranging from 70% to 100% (1, 4, 5, 18, 19, 20). The pathophysiological basis of AMI is the subclinical impairment of the intestinal mucosa that occurs during cardiac procedures, consisting in microcirculatory mesenteric dysfunction, increased GUT permeability, release of endotoxines and cytokines, variably related to the type of cardiac procedure and perfusion technique (21-24). This initial disorder of intestinal mucosa might be reversible or further compromised by the intervention of intraoperative or

postoperative factors, responsible of hypoperfusion, atheroembolism, and hepatic congestion (5, 25-28). Basing on the time of onset, in this series we identified two well distincted categories of AMI, comparing patients who experienced bowel ischemia few hours after cardiac surgery (n.15, 45.4% - Group 1) to patients in which AMI presented later (n.18, 54.6% - Group 2). Group 1 consisted of patients with more comorbidity (CRF, diabetes, PVD, depressed LVEF) and perioperative risk factors for NOMI (use of inotropes, IABP, prolonged aortic cross-clamp time, early oligo-anuria requiring CRRT, prolonged ventilation) in which the early onset of bowel ischemia was the result of a severe visceral hypoperfusion occurring throughout the cardiac procedure and precipitating during the first postoperative hours. Group 2 consisted of patients with less comorbidity and without perioperative visceral hypoperfusion, having an uneventful clinical course. In these patients, the intervention of postoperative "trigger events", mainly *de novo* atrial fibrillation and bleeding, present in more than 70% of our cases, resulted crucial to compromise the intestinal mucosa, probably through microembolic and functional mechanisms (25-28).

The excessive mortality remains the major problem of bowel ischemia after cardiac surgery, regardless the time of onset. Although the surgical results may be improved by the use of open abdomen technique (29, 30), the early identification of AMI remains the most reliable mean to decrease mortality. Literature data show that patients who undergo laparotomy with a delay up to 13 hours show a mortality rate lower than 50%, confirming the need to reduce the time to laparotomy as much as possible (31, 32). Although no biochemical or haematological test can be considered discriminatory for AMI, we regarded an increasing level of blood lactates and bioumoral markers (PCT, IL-6) as highly predictive for visceral ischemia, particularly when associated to a rapid deterioration of the renal function. Alongside a transient increase in blood lactates, uncomplicated cardiac surgery generally induces a postoperative increase in serum IL-6 and PCT levels, that reaches a peak within 24 hours postoperatively and return to normal levels within the first week. The expression of IL-6 reflects the inflammatory response after surgery, while PCT has been shown as a marker of bowel ischemia scarcely influenced by other conditions during the first postoperative hours (13-16). In our analysis, the high levels of IL-6 and PCT reported in Group 1 during the first 48 hours after surgery were suggestive for a severe post-pump syndrome, with significant release of cytokines and ischemic impairment of intestinal mucosa, appearing much less evident in Group 2.

The increase of bioumoral markers coupled with lactoacidosis, rapid deterioration of renal function and CT-scan findings was a reliable indication to early surgery in our experience (<8 hours from the start of symptoms), mainly in unconscious patients of Group 1, who underwent laparotomy with an acceptable

mortality rate of 53.3%. A longer surgical delay (15 hours) with increased mortality (66.6%) was observed in Group 2, probably due to the insidious clinical presentation and misleading diagnosis. Indeed, all patients of this group showed atypical abdominal signs during a regular postoperative clinical course, with less degradation of renal function and with no clear evidence of acute bowel disease from the start of symptoms.

Diagnosis and prompt treatment of mesenteric ischemia after cardiac surgery requires a high degree of awareness. Although a real single marker of AMI is not currently available, in unconscious patients a heightened clinical suspicion and consequently shorter time to laparotomy may be achieved through the routine monitoring of traditional bioumoral indicators (PCT and IL-6) and a more extensive use of new markers, such as intestinal fatty acid binding protein (IFABP), alfa-glutathione-S-transferase (alfa GST), and D-lacatate, eventually combined in scoring system (13, 14, 15, 33, 34). On the other hand, any unusual abdominal symptoms should be viewed with suspicion in conscious patients having a regular postoperative course, especially in the case of *de novo* of atrial fibrillation and postoperative bleeding. However, regardless the time of onset any element suggestive for AMI, clinical or instrumental, need to be consider useful in alerting medical staff to the possibility of this complication leading to reduced mortality through appropriate treatment.

Limitations of the study

This actual series has several limitations. Although data retrieval was optimal by carefully analysis of the electronic databases, our report is a retrospective observational study and not a randomized controlled study. Therefore, the comparison between the 2 groups may be biased with potential confounding factors. Since the diagnosis of AMI is infrequent, the numbers of patients are limited and the small size of the series underpowered the statistical comparisons. Moreover, a unique therapeutic approach was considered for all patients.

Conclusions

1. AMI after cardiac surgery is a rare event associated to high mortality, secondary to a subclinical impairment of the intestinal mucosa that occurs during cardiac procedures.

2. In patients with severe comorbidity and low cardiac output syndrome, AMI occurs early after surgery, as effect of the perioperative visceral hypoperfusion secondary to the use of inotropes and IABP.

3. In patients having an uneventful clinical course, AMI occurs more late after surgery due to the intervention of postoperative "trigger events", mainly *de novo* atrial fibrillation and bleeding, which probably act through microembolic and functional mechanisms.

4. Misleading clinical symptoms and late diagnosis are the main problem concerning high mortality of AMI.

5. Increasing levels of blood lactates and bioumoral markers are highly predictive for visceral ischemia and represent a reliable indication to early surgery, especially in unconscious patients presenting a rapid deterioration of the renal function.

6. Any unusual abdominal symptoms should be viewed with suspicion in conscious patients having a regular postoperative course, mainly in the case of *de novo* of atrial fibrillation, because AMI presents with an insidious clinical presentation.

7. Regardless the time of onset, any element suggestive for early or late AMI, clinical or instrumental, need to be consider useful in alerting medical staff to the possibility of this complication leading to reduced mortality through appropriate treatment.

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Tab.I – Demographics and comorbidity

	Group 1 (AMI <48 hours) *n (%)*	**Group 2 (delayed AMI)** *n (%)*
Patients	15	18
Males	13	10
Females	2	8
M/F ratio	6.5	1.25
Age (min-max)	74.1 ± 5.9	74.2 ± 7.7
Comorbidity		
CAD	8 (53.3)	10 (55.5)
Hypertension	11 (73.3)	11 (61.1)
Diabetes	6 (40)	2 (11.1)
CRF (Cr>1.8 mg/dl)	12 (80)*	7 (38.8)
COPD	3 (20)	4 (22.2)
PVD	7 (46.6)	5 (27.7)
LVEF <40%	3 (20)	2 (11.1)
Chronic AF	2 (13.3)	3 (16.6)
Previous abdominal surgery	8 (53.3)	10 (55.5)
***P <0.05**		

CAD, coronary artery disease; CRF, chronic renal failure; Cr, creatinine; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; LVEF, left ventricular ejection fraction; AF, atrial fibrillation.

Tab.II – Operative data

	Group 1 (AMI <48 hours) *n (%)*	**Group 2 (delayed AMI)** *n (%)*
Type of procedure		
Ascending aorta/arch repair ± valve procedure, *n (%)*	1 (6.6)*****	8 (44.4)
Isolated valve replacement/repair, *n (%)*	6 (40)	3 (16.6)
CABG ± valve procedure, *n (%)*	7 (46.6)	5 (27.7)
ISD repair, *n (%)*	1 (6.6)	/
Elective mediastinal revision (no infection), *n (%)*	/	2 (11.1)
Type of perfusion (data on 25 pts.)		
Off pump procedures, *n (%)*	3 (20)	5 (27.7)
Emergency procedures, *n (%)*	2 (13.3)	1 (5.5)
Redo procedures, *n (%)*	/	2 (11.1%)
CPBP:*****		
-*Total time, min*	95.4 ± 43.7	100.8 ± 48.1
-*Aortic clamp time, min*	58.1 ± 23.8	77.5 ± 33.7
-*T°C (mean)*	34.3 ± 2.3	33.7 ± 3
P <0.05		

CPBP, cardiopulmonary bypass; T°C, rectal temperature; IABP, intra-aortic ballon pump; CRRT, continuous renal replacement therapy; AF, atrial fibrillation.

Tab.III – Perioperative risk factors

	Group 1 (AMI <48 hours) *n (%)*	**Group 2 (delayed AMI)** *n (%)*
Perioperative risk factors		
CPBP > 120 min, *n (%)*	3 (20)	5 (27.7)
Aortic clamp > 60 min, *n (%)*	6 (40)	6 (33.3)
Cardiocirculatory arrest, *n (%)*	1 (6.6)	2 (11.1)
Use of inotropes >24h, *n (%)*	9 (60)*	1 (5.5)
IABP, *n (%)*	3 (20)*	/
Early oligo-anuria requiring CRRT, *n (%)*	12 (80)*	3 (16.6)
Acute *de novo* AF, *n (%)*	1 (6.6)	10 (55.5)*
Postoperative bleeding requiring surgical revision, *n (%)*	/	4 (22.2)
Prolonged ventilation (> 24h after surgery), *n (%)*	7 (46.6)^	1 (5.5)

P <0.01
^P <0.05

CPBP, cardiopulmonary bypass; IABP, intra-aortic ballon pump; CRRT, continuous renal replacement therapy; AF, atrial fibrillation.

Tab.IV – Clinical appearance

	Group 1 (AMI <48 hours) *n (%)*	**Group 2 (delayed AMI)** *n (%)*
Onset	31.2 ± 15.6 hours	10.7 ± 7.4 days
Clinical features		
-Abdominal symptoms (%)	8 (53.3)	12 (66.6)
-Lactates >4mM/L (%)	12 (80)	10 (55.5)
-Positive Rx/CT scan (%)	10 (66.6)	14 (77.7)
-Oligo-anuria + CRRT (%)	12 (80)*****	7 (38.8)
P <0.05		

CRRT, continuous renal replacement therapy.

Tab.V – Postoperative visceral enzymes (CRRT in 12 patients of group 1 and 3 patients of Group 2)

	Group 1 (AMI <48 hours)	**Group 2 (delayed AMI)**
LDH:	*U/L*	*U/L*
-ICU admission	1012.8 ± 1329	746.5 ± 322
-24 hours	2973 ± 4298	836 ± 449
-48 hours	5776 ± 6036.3*	1393.4 ± 1875.7
CK:	*U/L*	*U/L*
-ICU admission	356.8 ± 244.1	398 ± 339.3
-24 hours	2883.9 ± 2825.9	2195 ± 3625.5
-48 hours	8146 ± 53	3152.3 ± 5265
***P <0.05**		

LDH, lactate dehydrogenase; CK, creatine kinase.

Tab.VI – Postoperative bioumoral markers (CRRT in 12 patients of group 1 and 3 patients of Group 2)

	Group 1 (AMI <48 hours)	**Group 2 (delayed AMI)**
Lactates:	*mM/L*	*mM/L*
-ICU admission	4.9 ± 4.4	2.8 ± 1.2
-24 hours	5.6 ± 2.5*****	2.4 ± 1.4
-48 hours	5.4 ± 3.6*****	1.8 ± 0.6
IL6 (data on 22 pts):	*pg/ml*	*pg/ml*
-ICU admission	1152.63 ± 522.10*****	335.93 ± 447.90
-24 hours	1026.80 ± 533.30^	538.53 ± 588.01
-48 hours	683.42 ± 609.08	779.30 ± 848.06
PCT (data on 22 pts):	*ng/ml*	*ng/ml*
-ICU admission	16 ± 14.6*****	4.8 ± 5.8
-24 hours	20.1 ± 16.5*****	5.4 ± 8.4
-48 hours	29 ± 26.6*****	4.3 ± 7
****P <0.01***		
^P <0.05		

IL6, interleukin-6; PCT, procalcitonin.

Tab.VI – Laparotomy findings and outcome

	Group 1 (AMI <48 hours) *n (%)*	**Group 2 (delayed AMI)** *n (%)*
Small/large bowel resection:*	8 (53.3)	11 (61.1)
-resection+anastomosis	2	3
-resection+stoma	5	8
Laparotomy without primary resection:	7 (46.7)	7 (38.9)
-adhesiolysis/decompressive laparotomy	6	6
-exploration (massive bowel ischemia)	/	1
-superior mesenteric artery embolectomy	1	/
30-days mortality	8 (53.3)	12 (66.6)

** small bowel resection n.8, right emicolectomy n.6, left emicolectomy n.5.*