

# Evaluation of extracorporeal circulation effects on gallstone formation

*Avaliação dos efeitos da circulação extracorpórea na formação de cálculos biliares*

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## Abstract

**Objective:** The objective of the present study was to clarify the relationship between cardiopulmonary bypass with the use of a heart-lung machine and gallstones in a short-term follow-up.

**Method:** A total of 135 patients with ischaemic heart disease were included in this study. All were followed up by the Cardiology Department of Hospital São Paulo, Federal University of São Paulo. They were divided into three groups: Group 1 - 51 patients who were treated clinically; Group 2 - 43 patients who underwent coronary artery grafting bypass without cardiopulmonary bypass; and Group 3 - 41 patients who underwent coronary artery bypass grafting with cardiopulmonary bypass and the use of a heart-lung machine. There were no statistically significant differences between the groups in relation to gender, age, body mass index or

associated diseases ( $p < 0.05$ ). All the patients underwent ultrasound examinations 12 months after beginning their cardiological treatment (clinical treatment alone or surgical plus follow-up).

**Results:** The prevalence of gallstones in the groups was: Group 1 - 7.84%, Group 2 - 11.62%, and Group 3 - 19.51%. There was no statistically significant differences between the groups ( $p = 0.248$ ).

**Conclusion:** It was concluded that cardiopulmonary bypass does not appear to have a close relationship with gallstone formation one year after coronary artery bypass grafting. However, long-term follow-up is advisable.

**Descriptors:** Coronary disease. Extracorporeal circulation. Heart-lung machine. Gallstones. Cholelithiasis. Cross-sectional studies.

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### Resumo

**Objetivo:** Verificar a associação entre o uso da circulação extracorpórea e o desenvolvimento de colelitíase.

**Método:** Foram estudados 135 pacientes coronariopatas acompanhados na Disciplina de Cardiologia da Universidade Federal de São Paulo - Escola Paulista de Medicina, no período de janeiro de 2000 a setembro de 2002, distribuídos em três grupos: Grupo 1 - 51 pacientes tratados clinicamente; Grupo 2 - 43 pacientes revascularizados sem circulação extracorpórea e Grupo 3 - 41 pacientes revascularizados com circulação extracorpórea. Foram controladas as variáveis sexo, idade, índice de massa corpórea e doenças associadas entre os grupos e foi realizada ultra-sonografia total de abdome

em todos os pacientes, aos doze meses de tratamento (clínico ou cirúrgico), para verificar a existência de colelitíase.

**Resultados:** A prevalência de colelitíase encontrada nos grupos foi: Grupo 1 - 7,84 %; Grupo 2 - 11,62 % e Grupo 3 - 19,51 %. Não houve diferença estatisticamente significativa entre os grupos quanto à existência de colelitíase ( $p=0,248$ ).

**Conclusão:** Baseado neste estudo não se pode afirmar que o uso da circulação extracorpórea predisponha a maior prevalência de colelitíase.

**Descritores:** Coronariopatia. Circulação extracorpórea. Máquina coração-pulmão. Cálculos biliares. Colelitíase. Estudos transversais.

## INTRODUCTION

Cholelithiasis is an international public health problem at varying degrees around the world. In the era of ultrasonography its prevalence is around 10% in Western populations [1,2]; Coelho et al. [3] reported a prevalence of 9.3% in Brazil.

Several risk factors have been associated to the formation of gallstones; with female, age and obesity being commonly implicated in their genesis [1-6]. Associations have also been described with other diseases such as diabetes, hepatic cirrhosis, hyperlipoproteinemia, hemolytic diseases and inflammatory bowel disease [6-11]. The use of clofibrate and total parenteral nutrition, as well as certain abdominal operations, might be related to a greater frequency of this disease [6,12,13].

Until now, no association between coronary insufficiency and cholelithiasis [14] has been proven. However, a higher incidence of this disease has been seen in patients who underwent heart valve replacement surgeries [15,16].

In respect to other cardiac operative procedures, Azemoto et al. [17] described an association between cardiopulmonary bypass and the formation of gallstones. These authors suggested that not only hemolysis due to the use of cardiopulmonary bypass was significant to lithogenesis, but other factors such as motor alterations of the gall bladder and release of nucleation factors could also be involved. However, the sample of this study was heterogeneous and included patients with different heart diseases who were submitted to different types of operations, thereby creating a potential bias in the selection of patients.

The goal of the current study was to establish a correlation between cardiopulmonary bypasses and the formation of gallstones in a homogeneous population composed exclusively of patients with coronary

insufficiency, in the cross-sectional study utilizing ultrasonography as the diagnostic method.

## METHOD

One hundred and thirty-five patients were included in this study. Eighty of them were men with age ranging from 35 to 84 years. All were being followed-up by the staff of the Cardiology sector of the Medicine Department of the Federal University of São Paulo.

In this study only patients with coronary insufficiency confirmed by clinical criteria, exercise testing or imaging examinations (cinecoronariography or scintigraphy) were included. All patients were submitted to clinical or surgical treatment exclusivity in the São Paulo Hospital. The objectives of this research were explained to all the patients and those who agreed to participate signed written consent forms. This study was approved by the Research Ethics Committee of São Paulo Hospital.

Exclusion criteria included: patients with cholelithiasis previously confirmed by imaging examinations, prior invasive radiological or endoscopic interventions of the biliopancreatic duct and patients with hemolytic disorders, hepatic cirrhosis or heart valve disease and patients suffering from morbid obesity. Patients using clofibrate or parenteral nutrition were also excluded, as well as those who underwent abdominal surgeries (supramesocolic) or heart surgeries in the period prior to the study.

The patients were divided in three groups: Group 1 – 51 patients who were treated clinically. Group 2 – 43 patients who underwent off-pump coronary artery bypass graft surgery and Group 3 – 41 patients who underwent on-pump coronary artery bypass graft surgery.

Twelve months after the start of clinical or surgical treatment, the patients were requested by telephone to

attend an interview where they underwent physical and radiological examinations. In relation to the physical evaluation, all were examined by the same physician and a standardized patient record was completed with specific data such as gender, age, race, body mass index, associated diseases, surgical time, cardiopulmonary bypass time, the existence of pain suggestive of bilious colic after coronary artery treatment (one month), postoperative complications, icterus, abdominal pain and abdominal scaring. These variables are illustrated in Table 1.

All patients of this study were rigorously submitted to ultrasound of the abdomen 12 months after the start of clinical or surgical treatment. These examinations were performed by the same physician from the Diagnostic Imaging Department of the Federal University of São Paulo who did not know which group the patient belonged to. In all examinations a Philips SD 800 apparatus with a 3.5-MHz transducer was used.

The examination was performed with the patient in the supine position, at deep inspiration and with relaxed musculature; the bladder was examined from three views: longitudinal, cross-sectional and diagonal.

The criteria for the diagnosis of cholelithiasis were: 1) One or more echogenic structures in the gall bladder with posterior acoustic shadow, 2) One or more echogenic structures in the gall bladder without posterior acoustic shadow, but which were seen in different views or due to mobilization that could clearly be differentiated from septa, Heister valves or polyps.

For statistical evaluation of categorical variables the chi-

squared and Fisher exact tests were utilized. To evaluate the relationship between categorical and numerical variables variance analysis (ANOVA) and the Student T-test were utilized. A p-value 0.05 was considered statistically significant.

## RESULTS

There were no statistically significant differences between groups in respect to gender, age, race, body mass index and associated diseases. In relation to the operated groups (Groups 2 and 3), there were no statistically significant differences in respect to the surgical time and the number of complications in the postoperative period.

The presence of abdominal pain suggestive of bilious colic in the postoperative period was observed in 8 out of 84 patients operated on but in none of the patients who underwent clinical treatment. In relation to this variable, statistically significant differences between the groups were not evidenced, as can be observed in Table 2.

According to the physical examination no alterations were evidenced in the evaluated patients.

In relation to the ultrasonographic evaluation, the gall bladder was inspected in all patients and 17 (11.59%) of the 135 individuals presented with cholelithiasis. The presence of the cholelithiasis by group is demonstrated in Table 3.

The groups who were submitted to surgery presented a higher prevalence of cholelithiasis with the highest prevalence seen in Group 3, but no statistically significant differences were observed between the groups (p=0.248).

Table 1. Characteristics of the patients

Characteristics	Group 1	Group 2	Group 3
Total patients (N)	51	43	41
Male (N)	30	26	25
Female (F)	21	17	16
Mean age (years)	62.6	62.57	58.5
Caucasians (N)	43	36	35
Other races (N)	8	7	6
Mean body mass index (kg/m <sup>2</sup> )	26.2	26.9	25.9
Systemic arterial hypertension (N)	41	36	30
Mellitus diabetes (N)	14	13	16
Hyperlipoproteinemia (N)	12	16	11
Mean surgical time (min)		227.85	268.97
Postoperative complications (N)		5	5

Table 2. Presence of gall-bladder colic

	Group 1 (n=51)	Group 2 (n=43)	Group 3 (n=41)
Number of patients with gall-bladder colic	0	4	4

Table 3. Prevalence of cholelithiasis

	Group 1 (n=51)	Group 2 (n=43)	Group 3 (n=41)
Number of patients with cholelithiasis	4	5	8
Percentage/ patients with cholelithiasis	7.84%	11.52%	19.51%

No associations between the existence of this disease and the surgical time ( $p=0.15$ ), cardiopulmonary bypass time ( $p=0.69$ ) or the number of postoperative complications ( $p=0.34$ ) were identified.

Of the 8 patients with pain suggestive of gall-bladder colic in the postoperative period, two presented cholelithiasis in the ultrasonography examination. Both belonged to Group 2; this diagnosis was confirmed by surgery.

## DISCUSSION

The coronary insufficiency is a highly lethal disease due to the lack of importance placed in it in the Western world and coronary artery bypass grafting is one of the most commonly performed surgical procedures. At the São Paulo Hospital, a reference center for the treatment of heart disease, in the period between 1981 and 1994, approximately 8751 patients were submitted to coronary artery bypass grafting [18].

On-pump coronary artery bypass grafting circumvents angina, however, it is associated to substantial morbidity [19]. One of the principal factors of morbidity related to cardiopulmonary bypass is systemic inflammatory response syndrome [20,21]. Cardiopulmonary bypass triggers the release of a complex sequence of non-localized inflammatory response mechanisms; the contact of plasmatic proteins and red blood cells with the surfaces of the heart-lung machine activates a series of plasmatic proteolytic systems, including coagulation, fibrinolysis, complement cascade, kallikrein-kinin systems as well as those of cell elements, such as leucocytes, platelets and endothelial cells [22].

Many complications have been described as a consequence of the utilization of cardiopulmonary bypass, among which the most frequently observed are neurological, hemorrhagic, renal, pulmonary and cardiovascular complications [23,24]. Until now, only Azemoto et al. [17] has described cholelithiasis as a cardiopulmonary complication. But, his series of patients was heterogeneous with individuals submitted to different cardiac surgical procedures such as valve replacement, commissurotomies, revascularizations and surgeries to repair congenital heart diseases. These patients were compared with a sample of 52 healthy patients. All the patients of this study were submitted to the abdominal ultrasound examinations in the 3rd, 6th, 12th and 24th months of follow-up. It was observed after one year that 30.4% of the operated patients presented with gallstones against 0% on the healthy control group. These authors found a statistically significant difference between the groups and suggested that this finding may be associated with the use of cardiopulmonary bypasses [17].

In contrast with the sample of Azemoto et al. [17], the patients of the present study were homogenous; bringing together only patients with coronary insufficiency that is clearly not related to the development of gallstones [14]. The patients were rigorously selected, according to the exclusion criteria of factors recognized as a risk for cholelithiasis such as, for example, obesity, hemolytic diseases, heart valve diseases, hepatic cirrhosis, the use of clofibrate, parenteral nutrition and operations of the upper abdomen. Other risk factors such as gender, age, race, body mass index, diabetes mellitus and hyperlipoproteinemia were adequately controlled; no differences relating to these variables were evidenced between the groups studied. The groups were similar in respect to all studied variables and so the only difference was the form of treatment. This homogeneity of the sample was, in our point of view, important to avoid a possible bias in the selection of patients.

By adopting a single examiner, experienced in the diagnostic method and blinded in relation to the groups, as well as using the same apparatus and transducer in all examinations, selection biases were minimized.

The general prevalence of cholelithiasis in Group 1 was similar to that found in the general population in Brazil [3]. This finding suggests that maybe coronary insufficiency is not associated to cholelithiasis and, so, this disease is not a risk factor. This finding confirms the finding of Bates et al. [25], who did not find a greater prevalence of this disease in the coronary artery disease patients when compared to the general population.

In the present study, the prevalence of cholelithiasis was greater in Group 3 (on-pump coronary artery bypass grafting) than in other groups, however, this difference was not statistically significant ( $p=0.248$ ) contrary to the findings of Azemoto et al. [17]. This finding suggests that it is possible that coronary artery bypass grafting is not as important to the formation of gallstones as suggested by these authors.

In the current study, no association between duration of cardiopulmonary bypass and cholelithiasis was observed. If exposure to the risk factor, in the case of cardiopulmonary bypass, were really important to the lithogenesis, a greater prevalence of cholelithiasis in patients with longer times of cardiopulmonary bypass would be expected.

## CONCLUSION

The correlation between cardiopulmonary bypass and cholelithiasis may be possible, but it is not as significant as Azemolto et al. [17] described. Hence, new well designed controlled studies with homogenous groups and with a greater sample size must be performed to definitively respond this question.

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