

LIVER ISCHEMIA, CATECHOLAMINES AND PREOPERATIVE CONDITION INFLUENCING POSTOPERATIVE TACHYCARDIA IN LIVER SURGERY

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Summary

The aim of our study was to assess the influence of intraoperative hypoxic stress –unavoidably brought about by so called Pringle maneuver - on free and conjugated catecholamines during major hepatic resection. Judging from earlier results of fatigue-experiments in rats we also wanted to check the relationship between of poor general preoperative condition and conspicuously low triglyceride serum concentrations. The study included 26 patients with primary and secondary liver tumors. The mean age was 54 years (range 27-79). Twenty-one patients had segmental liver resections, 3 had hemihepatectomies and 2 hydatid cysts were treated by cystectomy. Blood samples were taken 2 days before and throughout surgery. Catecholamine plasma values were determined by high performance liquid chromatography. Statistical comparisons were made by t-test, ANOVA and chi square test. Free plasma catecholamines increased significantly during prolonged intraoperative ischemia (Pringle time 50-125 minutes). Patients with elevated intraoperative catecholamines had a significant correlation to postoperative episodes of tachycardia, and prolonged hospital stay. On the other hand, we could also see postoperative tachycardias in patients with short Pringle times (18-49 minutes) but with decreased preoperative serum triglycerides as an indicator of chronic stress and reduced general condition. Intraoperative hypoxic stress is associated with increased catecholamine values. Elevated catecholamines may well cause postoperative sinus-tachycardias (mean 20 hours) and are strongly related to postoperative liver failure and prolonged hospital stay.

Key Words: liver ischemia, free catecholamines, conjugated catecholamines, postoperative tachycardia

The influence of liver surgery on catecholamine behaviour is characterized by three facts: 1. Catecholamines act upon the liver by vasoconstriction, since periportal connective tissue and liver sinusoids are densely supplied with adrenergic innervation (1). 2. Also fat, protein and carbohydrate metabolism in the liver are strongly influenced by catecholamines (2). 3. The liver itself plays an important regulatory role within the degradation and conjugation system of catecholamines by hosting large amounts of enzymes like phenolsulfotransferase (PST) and arylsulfatases (2, 3).

We intended to assess the influence of intraoperative normothermic ischemia time (hypoxic stress) on free and conjugated catecholamines during major hepatic resection. Our aim was to prove the relationship of elevated catecholamines to long lasting tachycardias, one of the most unpleasant and uncontrollable events during and after liver surgery. In our clinical routine unexpected sinus-tachycardias during surgery required beta-blockers, but nevertheless returned after surgery and persisted for about 20 hours. An attempt was made to characterize tachycardia – prone patients by measuring their pre – and intraoperative pattern of serum catecholamines.

Determination of both free and conjugated catecholamine levels should enable us to make use of the vastly differing half life (some minutes for the free fractions and about 12 hours for the more inert conjugated ones) to check acute as well as more protracted alterations in order to relate them to possible development of tachycardias.

Judging from earlier results of fatigue-experiments in rats (4, 5), we also wanted to check the relationship between of poor general preoperative condition and conspicuously low triglyceride serum concentrations.

Materials and Methods

Our clinical study included 26 patients (17 females, 9 males), mean age 54 years (range 27-79). Diagnoses are listed in Table 1.

TABLE 1
Diagnoses of the study group

Diagnosis	Patients
Primary liver tumors	11
hepatocellular carcinoma	3
focal nodular hyperplasia	4
hepatocellular adenoma	2
hemangioma	2
Liver cyst	7
congenital	3
echinococcal	2
neoplastic	2
Liver metastases	7
colorectal	4
appendix carcinoid	1
pancreas	1
malignant melanoma	1
Neoplasm of the gallbladder	1

Twenty-one patients had segmental liver resections (one segment: 4, two or more segments: 17), 3 had hemihepatectomies (1 right, 2 left), 2 hydatid cysts were treated by cystectomy. To achieve a homogenous study collective negative cirrhosis and hepatitis markers (confirmed by postoperative histology) were taken as inclusion criteria. All operations were done by the same team with a standardized technique (6) of vascular clamping during the course of liver resection to reduce bleeding and subsequent complications. This maneuver, 1908 described by J.H. Pringle (7) causes hypoxia due to the temporary closure of hepatic artery and portal vein. Depending on the severity of our surgical procedure normothermic inflow occlusion has to be kept up from 18 to 125 minutes. The Pringle maneuver is usually well tolerated without any deleterious consequences for one hour and even more if the hepatic parenchyma is normal (8) For liver cell protection tocopherol, ascorbate and cortisol were administered intraoperatively (9). Our empirical observations in hundreds of hepatectomies had shown that Pringle manoeuvres of more than 50 minutes' duration cause a conspicuously increase of postoperative complications, as also emphasized by Barbieri et. al (10). We divided our patients into two groups with Pringle times above and below 50 minutes and so obtained two groups of almost equal size. A similar subdivision was carried out according to relevant postoperative tachycardia which was defined by a heart rate greater than 100 beats per minute (11) with a minimum duration of at least 3 hours, but which in many cases persisted for days. Mortality was defined as hospital death within 30 days. The whole study was approved by the local ethics committee according to the Helsinki charter.

Blood samples were taken 15 minutes after placing an antecubital vein catheter 2 days before operation and during surgery (skin incision, at the beginning of the Pringle maneuver, during normothermic ischemia, 10 minutes after reperfusion and at the end of operation). To determine catecholamines whole blood was sampled in a 5 ml heparinate-coated tube pretreated with 1.25 mg glutathione per ml blood. The tubes were carefully shaken and afterwards centrifuged at 3.500 r/min for 6 minutes. The resulting plasma was subdivided into 1000 μ l samples, transferred to 3 Eppendorf-vessels and stored immediately at -20° C. The catecholamine plasma levels were determined by high performance liquid chromatography (Beckman Gold, 5401 and BAS-LC 4B electrochemical detector) as described previously (12, 13). Conjugated dopamine in plasma was determined after hydrolysis with type 4 sulfatase (Sigma, Munich, Germany) according to the method of Johnson et al. (14). The detection limit for free NE was 50ng/l, for E 70 ng/l and for DA 15 ng/l, respectively. The variation coefficient for free NE was 4,1%, for E 3,8% and for DA 2.7% and was based on 52 consecutive measurements using an external standard. Normal CA levels for free CA were defined as follows: fNE (200-600 pg/ml), fE (200-500 pg/ml), fDA (60-200 pg/ml). Normal conjugated CA were: cNE (more than 2x fNE), cE (more than 2x fE) and cDA (3200-15000 pg/ml). Triglycerides were determined by GPO-PAP enzymatic colorimetric method (Böhringer Mannheim, Hitachi 747).

Statistical evaluations (unpaired student-t test, ANOVA and Chi Square test) were done with Excel and Prostat Software. A p value of <0.05 was considered significant. All data were presented as means \pm Standard Error of Mean (SEM).

Results

1. Patients classification according to the duration of intraoperative normothermic ischemia:

Increase in both free plasma norepinephrine (2468.2 ± 557.6 vs 1269.6 ± 228.2 pg/ml, $p=0.0375$, t-test) and free plasma dopamine (510 ± 162.1 vs 175.4 ± 30.7 pg/ml, $p=0.0273$, t-test) during prolonged Pringle manoeuvres (abscissa point 4) was significantly higher (50-125 minutes, 11 patients) than during shorter intraoperative normothermic ischemia (18-49 minutes, 15 patients,

Fig. 1). There was no significant difference in free epinephrine or in any of the conjugated catecholamines during ischemia

2. Patients classification according to the appearance of postoperative tachycardia:

The 10 patients with postoperative tachycardia showed a significant increase in free dopamine, norepinephrine and epinephrine values during normothermic ischemia compared to the 16 patients without postoperative tachycardia (fDA 385.1 ± 119 vs 153.6 ± 25.6 pg/ml, $p=0.0273$, fNE 2683.9 ± 570.9 vs 1209.7 ± 219.4 pg/ml, $p=0.0099$; fE 3935.3 ± 1341.3 vs 938.9 ± 164.1 pg/ml, $p=0.0098$; t-test, Fig. 2). Conjugated catecholamines did not differ significantly during ischemia at all.

Considering the distribution of tachycardic patients among the long and short Pringle groups, it turned out that 63% of the patients (7 out of 11) with long intraoperative hypoxic stress developed postoperative tachycardia ($p=0.0224$, Chi Square test).

In the short normothermic ischemia – group (18-49 minutes) only 20 % of the patients (3 out of 15), became tachycardic.

Obviously, development of tachycardia did not depend on the ischemia period and catecholamine increase alone. We thus attempted to find an additional parameter to describe the preoperative condition of the patients, because preoperatively neither free nor conjugated catecholamines differed significantly from each other.

Preoperative triglyceride values (4, 5) seemed to provide the best hints in this case:

Patients in the short Pringle group who nevertheless developed postoperative tachycardia had a distinctly and significantly lower serum triglyceride level preoperatively (60 ± 6.8 vs 181.9 ± 18.7 mg/dl, $p=0.0074$, t-test, Fig. 3). No such differences were evident in the long Pringle group (134.7 ± 20.7 vs 134 ± 26 mg/dl).

Assessment of hospital stay: Tachycardic patients averaged 25.1 ± 8 days in hospital, while non tachycardic patients averaged 12.6 ± 0.7 days ($p=0.0486$). One patient died from an acute myocardial infarction on the 6th postoperative day (mortality 3.8 %). The morbidity rate was 15.3 % (4 patients).

Discussion

The aim of our study was to provide solid evidence to support our empirical observation that postoperative complications may be related to the duration of intraoperative normothermic ischemia. Tachycardia with postoperative onset is an unpleasant complication of major liver surgery. Since ischemic stress is well known to provoke catecholamine secretion and catecholamine secretion, and it is also well known to trigger tachycardia, we tried to link up both events by measuring free as well as conjugated plasma catecholamines pre- and intraoperatively. To cover the two different aspects of the problem, namely the influence of ischemia on the one hand and the incidence of tachycardia on the other, we had to divide our patients at first into two groups according to different Pringle times and secondly into two further groups depending on development of tachycardia. The overlap should then indicate the closeness of the relation between the two events, as well as the possible existence of other important factors besides ischemic time that may possibly trigger postoperative tachycardia. Considering the problem from the first point of view, the influence of Pringle times, it turned out that patients with high Pringle times had significantly increased levels of free dopamine and free norepinephrine but not epinephrine during ischemia compared with those with lower Pringle times. The more inert (15) conjugated catecholamines did not seem to play any important role. Splitting of the group of patients along the line of tachycardia development we noted significantly increased values of dopamine, norepinephrine as well as epinephrine in later tachycardic patients during ischemic events. As far as the overlap of postoperative tachycardia with the long and the short Pringle group is concerned,

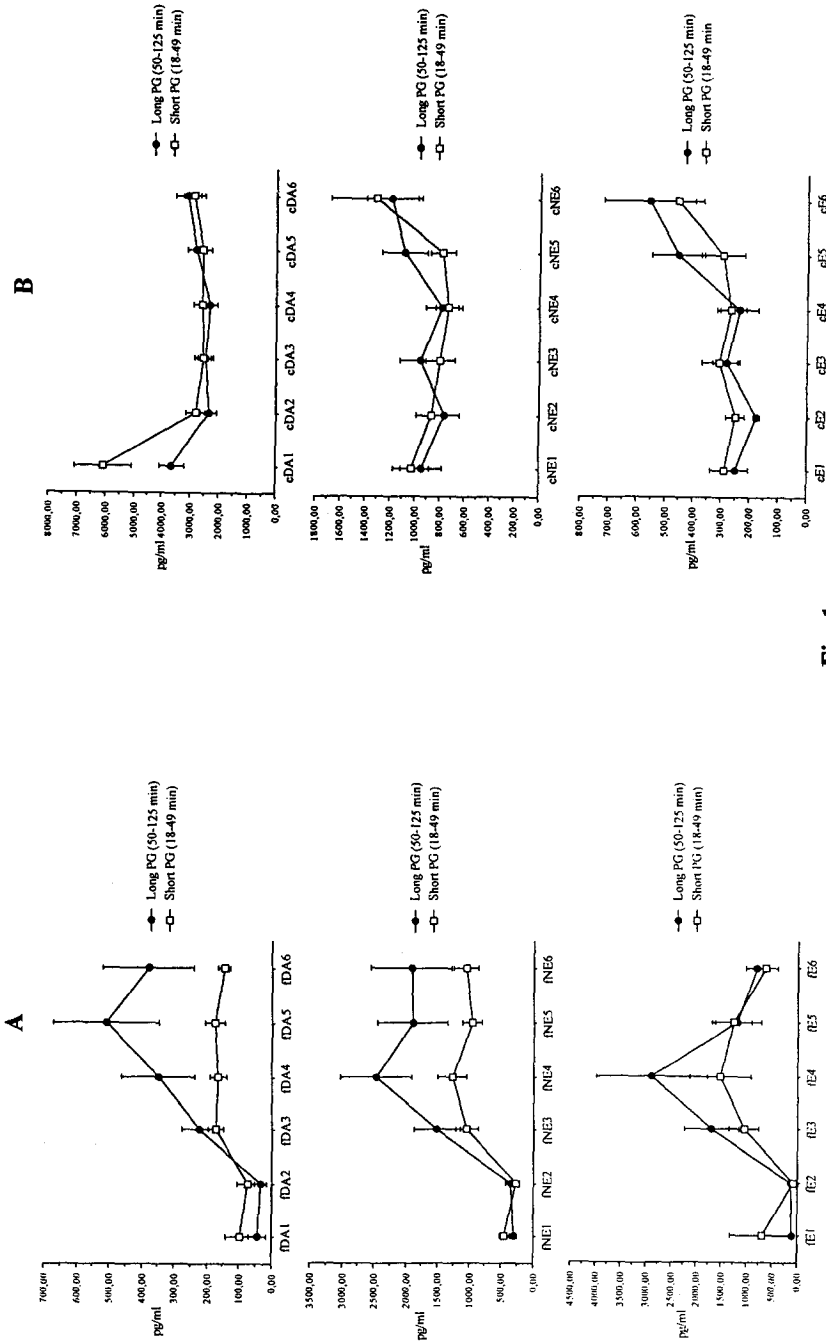


Fig. 1

A Significant increase in free dopamine (fDA) and free norepinephrine (fNE) during long liver ischemia B No significant differences in conjugated plasma catecholamines. (long PG : long Pringle group, n=11; short PG: short Pringle group, n=15) Abscissa: 1: 2 days preoperative, 2: skin incision, 3: pringle maneuver, 4: liver ischemia, 5: reperfusion, 6: end of operation. Ordinate: pg/ml

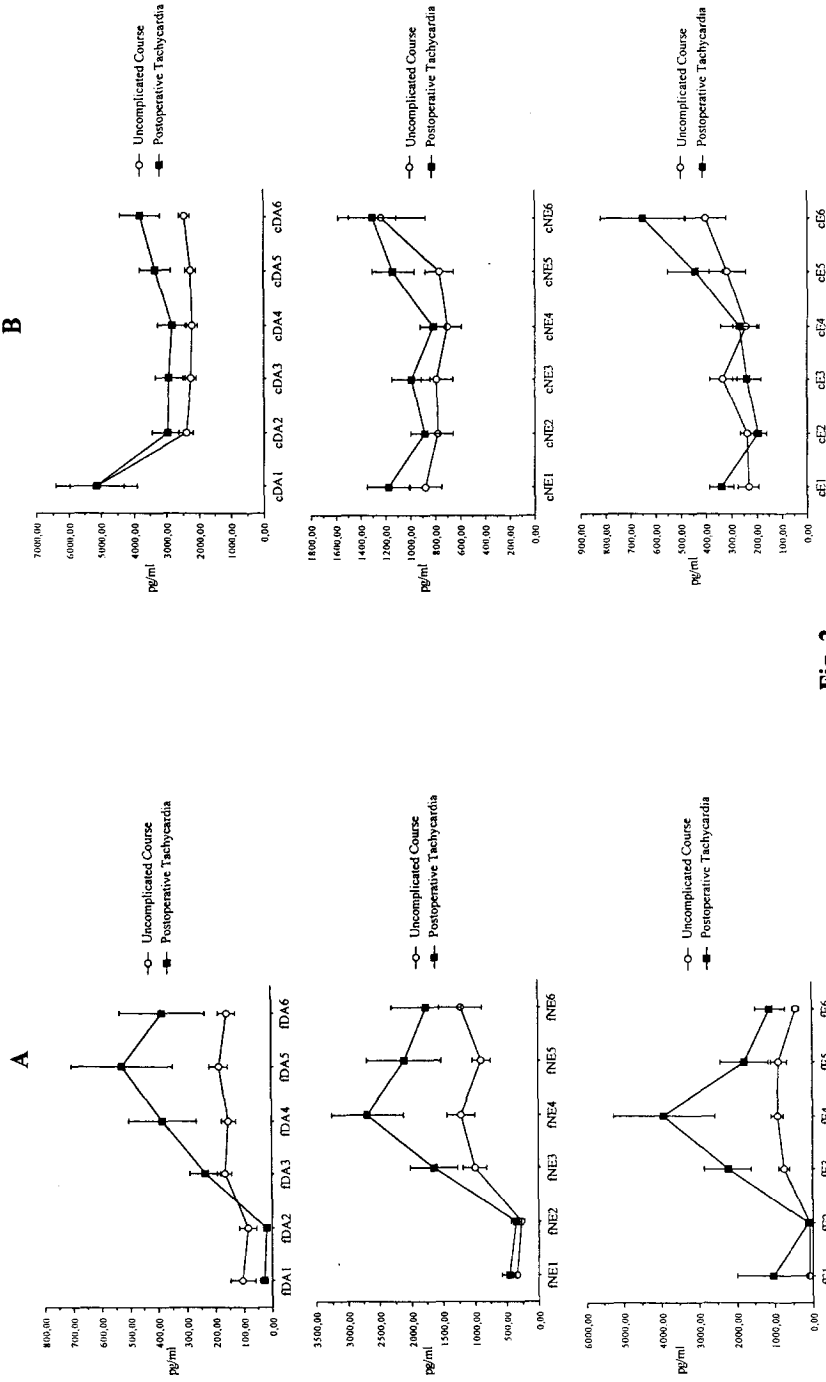


Fig. 2

A Significant intraoperative increase in free plasma catecholamines (fDA, fNE, fE) in patients (n=10) with postoperative tachycardia. **B** No significant differences in conjugated plasma catecholamines. Abscissa: 1: 2 days preoperative, 2: skin incision, 3: Pringle maneuver, 4: liver ischemia, 5: reperfusion, 6: end of operation. Ordinate: pg/ml

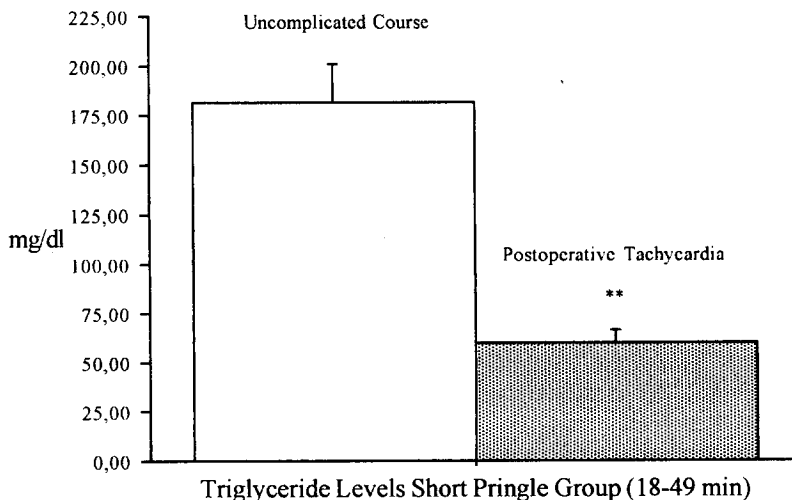


Fig.3

Significant low preoperative triglyceride levels in patients with short Pringle time and postoperative tachycardia. ** $p < 0.01$ Abscissa: Groups without and with tachycardia. Ordinate: mg/dl

there was a striking incidence in the long Pringle group. Nevertheless, there were patients in the long Pringle group who did not develop tachycardia, just as there were patients in the short Pringle group who did. Obviously there must be other factors than ischemia-induced catecholamine increase involved in the triggering system for postoperative tachycardia. A measurable parameter characterizing the general preoperative condition of the patient could well be either free or conjugated catecholamine levels. But in our case there was never any difference between the free or conjugated catecholamine concentrations of those who developed postoperative tachycardia or those who did not, except a nearly significant difference between preoperative conjugated dopamine levels.

Our own experiments with chronic application of epinephrine in rats as well as the scarce literature references (4,5) prompted us to check preoperative triglyceride serum values. Our reasoning was that fatigue or poor general condition as well as prolonged exposure to increased catecholamine levels seem to manifest themselves in surprisingly low triglyceride concentrations which should be especially conspicuous in patients who according to their weight, age and degree of physical fitness could rather be expected to have high triglyceride levels. And indeed it turned out that in the short Pringle group, where only a minority was developed postoperative tachycardia, exactly this minority had surprisingly low triglyceride serum levels. They were found to have triglyceride levels that differed with high significance from the triglyceride levels of those patients in the short Pringle group who did not develop tachycardia later on. In the long Pringle group no such differences were seen. This led us to believe that long term ischemia is a much more powerful trigger for postoperative tachycardia than a short ischemic period. However, tachycardia even after short Pringle times could well develop if the patient is in poor condition prior to surgery.

In conclusion, we think that our investigation demonstrates a connection between intraoperative ischemia, increase of catecholamines triggered by this ischemia and postoperative tachycardias evolving therefrom. Also the preoperative condition of the patient has to be taken into consideration, whereby even with short Pringle time, poor preoperative condition obviously may produce an equally potent trigger for postoperative tachycardia as long Pringle times alone.

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