Myocardial Ischemia After Orthotopic Liver Transplantation

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A hypercoagulable state exists after orthotopic liver transplantation. This hematologic abnormality may predispose patients to coronary thrombosis and unstable angina. The incidence of postoperative myocardial ischemia in such patients is unknown.

Suitable electrocardiograms and clinical events of consecutive patients undergoing orthotopic liver transplantation (n = 45) and major intraabdominal surgery (n = 28) during a 3-month period at a major university teaching hospital and transplant center were examined retrospectively. Clinical myocardial ischemia or ischemic electrocardiographic changes, or both, occurred in 6 transplant patients compared with no patient in the nontransplant or comparison group. In 4 of the 6 patients with dramatic electrocardiographic changes and ischemic events, coronary arteriography failed to demonstrate significant obstructive disease. It is concluded that severe myocardial ischemia may occur in patients after orthotopic liver transplantation in the absence of significant coronary disease. A hypercoagulable state may predispose to coronary thrombosis in this setting, providing insight (and a future model for study) into the development of unstable angina.

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Of the many precipitants of unstable angina,[1-7] recent attention has focused on systemic thrombogenic risk factors including lipoprotein(a),[8] fibrinogen,[9,10] and factor VII.[9] Proteins C, S, and antithrombin III, and elements of the fibrinolytic system, however, have received less attention.[11-14] Their significance is documented in descriptions of patients with deficiencies in these proteins who develop venous and arterial thrombi.[15,16] A hypercoagulable state caused by decreased levels of proteins C, S, and antithrombin III exists early after orthotopic liver transplantation and contributes to hepatic artery thrombosis, a major postoperative complication.[17-21] After reperfusion of the transplanted liver, synthetic function of coagulant and anticoagulant proteins resumes at variable rates resulting in in vivo activation of clotting mechanisms.[20] This hypercoagulable state may predispose to vascular thrombosis. We have observed electrocardiographic and clinical evidence of extensive myocardial ischemia in patients after orthotopic liver transplantation, raising the possibility of spontaneous coronary thrombosis.

METHODS

Study patients: Standard 12-lead electrocardiograms were retrieved from 89 consecutive patients undergoing orthotopic liver transplantation over a 3-month period. In 50 patients, both a preoperative electrocardiogram within 5 months of transplant and an electrocardiogram recorded during postoperative days 2 to 14 were available. All recorded electrocardiograms were retrievable for analysis. Patients with ST-segment and T-wave deviation at baseline (n = 2), and with preexisting coronary disease (>70% diameter narrowing) were excluded. Thus, 45 patients were included for analysis. In patients with several preoperative electrocardiograms, only the tracing closest in time to transplantation was considered. When numerous electrocardiograms were obtained postoperatively, all were reviewed.

In a comparison group of 135 consecutive patients undergoing major intraabdominal surgery—elective or emergent—over the same time period, 36 patients had electrocardiograms recorded both within a 5-month period before surgery and at any point during postoperative days 2 to 14. Preoperatively, 7 patients manifested deviation of ST and T-wave segments as previously described and were excluded from analysis. An additional patient with polycythemia vera and a hypercoagulable state was also excluded. Patients with a history of coronary artery disease who nevertheless fulfilled these entry criteria were included. Major intraabdominal surgery consisted of cholecystectomies (n = 7), colectomies and hemicolectomies (n = 13), ureteroileostomies (n = 2), aortobifemoral bypasses and abdominal-aortic and tho-

racoabdominal aneurysm repairs (n = 3), splenorenal shunts (n = 1), and biliary reconstructions (n = 2).

Electrocardiographic criteria: Electrocardiograms from postoperative days 2 to 14 were compared with their respective preoperative tracings. Electrocardiograms were interpreted as positive for ischemia according to T-wave criteria defined as symmetric T-wave inversions measuring >0.2 mV $\times$ 0.08 second in ≥ 2 contiguous precordial or limb leads. Tracings were also read as positive if >1 mm (0.1 mV) of ST depression in ≥ 2 contiguous precordial or limb leads was noted. The TP segment was regarded as the isoelectric baseline.

Clinical assessment: Cardiac catheterization was performed in 4 of the 6 transplanted patients who demonstrated significant ST and T-wave changes. Timing of catheterization varied from 7 to 43 days after transplantation and from 0.5 to 37 days after initial electrocardiographic changes. Interpretation was performed by 3 independent angiographers unaware of each patient's clinical condition. Maximal percent stenosis varied by <20% between observers and was thus averaged.

RESULTS

Transplanted patients tended to be younger than patients in the comparison group (50 ± 12 vs 57 ± 18 years; p = 0.07). There was no difference in gender. Similar numbers of postoperative electrocardiograms were retrieved in the study and comparison groups (2.1 ± 1.4 2.2 ± 1.1, respectively, p = 0.45). Of the 45 patients u dergoing liver transplantation, 6 (nos. 1 to 6) had si nificant ischemic electrocardiographic changes (Figu 1, Table I). Of these 6 patients, 3 (nos. 3, 5, and 6) h pulmonary edema, with regional wall motion abnorm ities in patients 3 and 6 (Figure 2) documented at t time of electrocardiographic changes. Repeat evalu tions days later showed normal wall motion. Patient demonstrated ischemic electrocardiographic chang with a marked regional wall motion abnormality echocardiography. Persantine thallium-201 imaging vealed a corresponding reversible perfusion defect. L ventriculography performed 3 weeks later was norm Patient 1 had severe chest discomfort with ischemic ele trocardiographic changes. Patient 4 had an uncomp cated clinical course. Her follow-up ejection fraction w normal. Patients 1, 2, 3, and 6 underwent coronary teriography. No patient exhibited >50% narrowing of a major vessel. Findings suggestive of thrombus w found in the left anterior descending artery of patient An increased myocardial oxygen demand, as reflected double product, was not responsible for the observed chemia since no patient was hypertensive and only 1 tient was tachycardic at the onset of clinical deterio

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DISCUSSIC

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FIGURE 1. Twelve-lead electrocardiograms recorded before *(top)* and after *(bottom)* liver transplantation, demonstrating dramatic T-wave inversions typically seen at times of myocardial ischemia (patient 2, Table I).
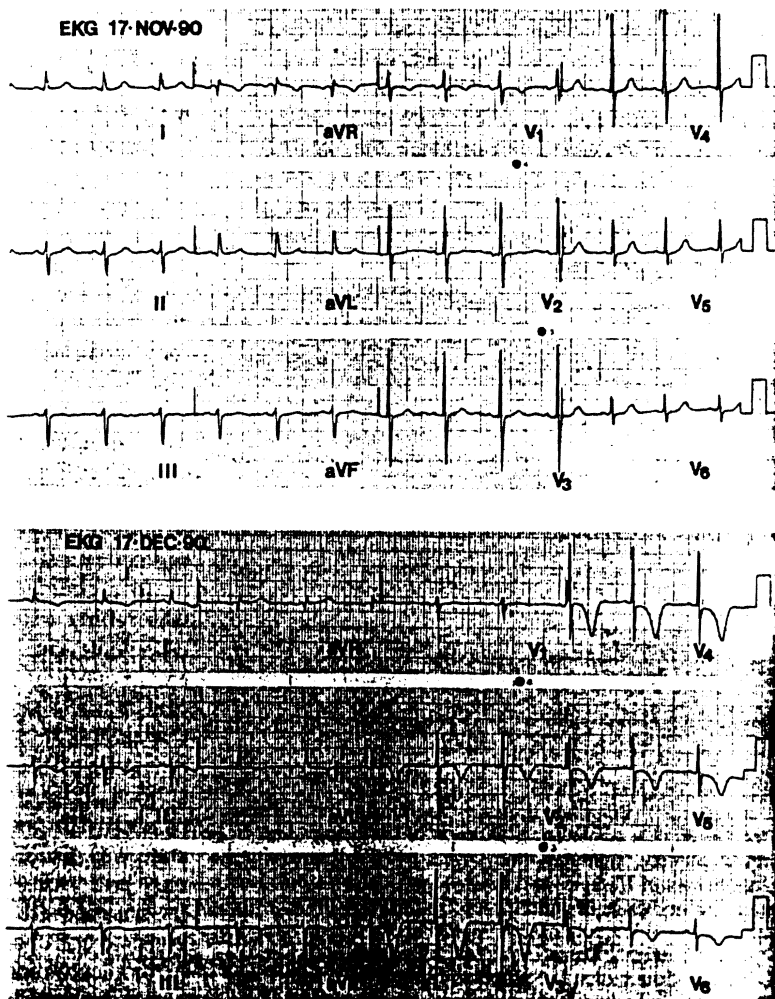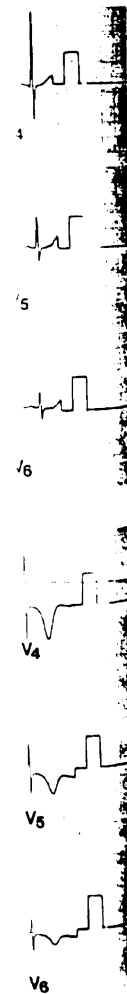
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Of the 28 patients undergoing major intraabdominal surgery, 1 patient had precordial ST changes unaccompanied by clinical symptoms in the specified postoperative period. An echocardiogram recorded at the time of these changes showed normal ventricular function. In patients excluded from the comparison group because of baseline ST abnormalities, no clinical cardiac events were noted.

DISCUSSION

The same hypercoagulable state contributing to hepatic artery thrombosis after orthotopic liver transplantation may cause myocardial ischemia and unstable an-

FIGURE 2. Left ventricular angiogram at end-diastole (A) and at end-systole (B) in the 30° right anterior oblique projection. The basal portions (arrows) of the left ventricle contract vigorously, while an extensive regional wall motion abnormality involving the anterolateral, apical, and inferoapical segments is noted (patient 3, Table I).

TABLE I Clinical Characteristics in Six Patients After Transplant

Patient	Age (yr) & Sex	Diagnosis	Preop. Studies Ventricular Function	Preop. Studies Exercise Thallium	ECG Change MTWA	K	PT/PTT	Hg/Pl	Cardiac Catheterization Ventricular Function	Cardiac Catheterization Angiography	Follow-Up Studies Ventricular Function	Follow-Up Studies Exercise Thallium
1	46 M	Cryptogenic cirrhosis	–	Normal	V_{1-4},L	4.7	13/20	9/299	–	50% LAD	–	Normal
2	65 M	Laennec's cirrhosis	Normal	–	V_{1-6},I,L	4.1	12/23	12/176	Normal	20% LAD & LC, 40% right	–	–
3	58 M	Laennec's cirrhosis	–	–	V_{2-6},I,L	3.6	13/20	11/37	A akinesia, S hypokinesia	40% LAD & LC, 40% right	Normal	–
4	52 F	Cryptogenic cirrhosis	Normal	–	V_{4-6}	3.9	12/22	9.6/165	–	–	Normal	–
5	62 F	Primary biliary cirrhosis	Normal	–	V_{4-6}	3.8	14/27	10.3/59	–	–	Normal	–
6	52 F	Metastatic gastrinoma	Normal	–	V_{3-6}	3.1	13/24	10/27	–	Normal	Normal	–

A = anterior; ECG = electrocardiographic; Hg = hemoglobin; K = potassium (mEq/dl); LAD = left anterior descending artery; LC = left circumflex artery; MTWA = marked T-wave abnormality; Pl = platelet count (x 1,000); Preop. = preoperative; PT = prothrombin time (s); PTT = partial thromboplastin time (s).

gina. In our series of consecutive liver transplant recipients, 6 of 45 patients (13%) had ST or T-wave changes consistent with myocardial ischemia. The absence of significant underlying atherosclerotic disease and the transient nature of regional left ventricular dysfunction support a role for coronary thrombus or vasoconstriction, or both, in the observed myocardial ischemia. The finding of possible thrombus in only 1 of 4 patients undergoing angiography may be secondary to the delay in performing catheterization and spontaneous lysis.[22,23]

The propensity for arterial thrombosis after orthotopic liver transplantation appears highest during the first postoperative week when the discrepancy between coagulant and anticoagulant proteins is greatest. Proteins C and S remain depressed for ≥5 days, and antithrombin III for ≥10 days after transplantation.[20,21] Evidence for activation of coagulation pathways leading toward thrombus deposition in unstable angina is provided by the increased levels of circulating and urinary markers of fibrin, fibrinopeptide A, and other fibrin-related antigens found in patients during episodes of chest pain.[6,24,25] Coronary vasomotion also may have contributed to the development of unstable angina in our patients. Although the clinical features in the present study do not support spasm as the predominant pathophysiologic trigger, coronary spasm need not be dismissed from the present study because it may simply be the initiating event prompting a critical narrowing whereby hemostatic and fibrinolytic mechanisms become the principal determinants of whether coronary occlusion occurs.

The findings of this study are clearly limited by their retrospective and observational nature. Patients in the comparison group had been routinely screened and treated for coronary artery disease. The development of silent ischemia was not specifically addressed. Holter monitoring may better address the prevalence of silent ischemia after operation. Nevertheless, a hypercoagulable state after orthotopic liver transplantation allows insight into a deficient fibrinolytic system and its potential for coronary thrombosis and resulting myocardial ischemia. Deficient levels of proteins C, S, and antithrombin III likely contribute to intracoronary thrombus formation after liver transplantation. Prospective studies of anticoagulant proteins and the development of myocardial ischemia appear warranted.

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