

# Cardiac Changes at Autopsy in Adult Liver Transplant Recipients Under Tacrolimus

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**T**ACROLIMUS (FK506) is being used as immunosuppressant in solid organ transplantation. However, its nephrotoxic and neurotoxic effects are well recognized. Recently reversible hypertrophic cardiomyopathy under tacrolimus has been described in five children.<sup>1</sup> In order to evaluate myocardial toxicity of the drug, we examined the cardiac findings at autopsy in adults and children following primary liver transplantation (OLTx) under tacrolimus and compared them with autopsy findings of patients who died of end-stage liver disease without OLTx and tacrolimus.

### MATERIALS AND METHODS

Patients who received OLTx between August 1989 and December 1992 (834 adults, age >18 years) were followed through April 1995. Sixty-seven (29%) of 228 patients who died during the follow-up period underwent autopsy (study group). Cardiac findings at autopsy were compared with 72 adults who died of end-stage liver disease without OLTx and Tacrolimus (control group). The parameters studied were weight of the heart, left (LV) and right (RV) ventricular wall thickness, circumferences of tricuspid (TV), pulmonary (PV), mitral (MV), and aortic (AV) valves, and macroscopic and microscopic appearances of the cardiac musculature. The presence of associated problems of hypertension, coronary artery disease, and infective endocarditis was taken into account. All hearts were subjected to formalin fixation for 12 to 24 hours followed by cutting according to "flow of blood method."<sup>2</sup>

### DEMOGRAPHICS

Mean age in the study group (51.3 ± 13 years) and the control group (52.5 ± 13.7 years) were comparable. There were more males in the study group (M = 44, F = 23) compared to the control group (M = 39, F = 33). The mean period of exposure to tacrolimus in the study group was 6.1 ± 8.6 months.

### RESULTS

Mean weight of the heart, wall thickness of both ventricles, and circumference of all valves are shown in Table 1. The mean weight of the heart in both the groups is comparable (458 ± 105 g study group and 470 ± 109.5 g control group). The average weight of the heart in both groups was increased as compared to normal population (275 ± 75 g). None of the patients in either group had had any congenital or acquired valvular abnormality.

Mean RV wall thickness in both the groups were comparable and normal (RV = 0.47 ± 0.2 cm study group, 0.5 ± 0.2 cm control group, 0.4 to 0.5 cm normal population). Mean LV wall thickness, however, was increased in both groups as compared to the normal population (LV = 1.65 ± 0.4 cm study group, 1.6 ± 0.3 cm control group, 0.8 to 1.5 cm normal population). Table 2 shows left ventricle wall thickness in both groups of patients. The circumferences of valves were comparable as shown in Table 1. Mean TV circumference 12 ± 1.3 cm in the study group as compared to 12 ± 1.2 cm in the control group, PV 8.1 ± 1.1 cm compared to 8.1 ± 1.1 cm in control group, the corresponding numbers for MV and AV being 10.5 ± 1.3 cm against 10 ± 1.2 cm, and 7.7 ± 1.2 cm against 7.4 ± 0.9

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**Table 1. Cardiac Changes at Autopsy in Adult Liver Transplant Recipients Under Tacrolimus**

|        | Study Group (A) N = 67 |                |      |                     |     |      |     | Control Group (B) N = 72 |                |     |                     |     |     |     |
|--------|------------------------|----------------|------|---------------------|-----|------|-----|--------------------------|----------------|-----|---------------------|-----|-----|-----|
|        | Weight (g)             | Wall thickness |      | Valve circumference |     |      |     | Weight (g)               | Wall thickness |     | Valve circumference |     |     |     |
|        |                        | RV             | LV   | TV                  | PV  | MV   | AV  |                          | RV             | LV  | TV                  | PV  | MV  | AV  |
| Mean   | 458                    | 0.47           | 1.65 | 12                  | 8.1 | 10.5 | 7.7 | 470.2                    | 0.5            | 1.6 | 12                  | 8   | 10  | 7.4 |
| SD     | 105                    | 0.2            | 0.4  | 1.3                 | 1.1 | 1.3  | 1.2 | 109.5                    | 0.2            | 0.3 | 1.2                 | 1.1 | 1.2 | 0.9 |
| Median | 440                    | 0.4            | 1.55 | 12                  | 8   | 10.5 | 7.6 | 460                      | 0.4            | 1.6 | 12                  | 8   | 10  | 7.5 |

RV = right ventricle; LV = left ventricle; TV = tricuspid valve; PV = pulmonary valve; MV = mitral valve; AV = aortic valve.

Table 2.

| cm        | LV Wall Thickness  |                    |
|-----------|--------------------|--------------------|
|           | Group (A)<br>n (%) | Group (B)<br>n (%) |
| ≤1.3      | 11 (18)            | 13 (18)            |
| >1.3-<2.0 | 38 (63)            | 42 (61)            |
| ≥2.0      | 11 (18)            | 15 (20)            |

cm, respectively. These are normal when compared with the dimensions in normal population, TV = 10 to 12.5 cm, PV = 7 to 9 cm, MV = 8 to 10.5 cm and AV = 8 to 10 cm.

The incidence of myocardial infarction, coronary artery disease and, infective endocarditis was noted to be 12%, 45%, and 16% in the study group and 8%, 58%, and 4% in the control group, respectively.

## DISCUSSION

Liver failure and chronic liver disease are associated with peripheral vasodilatation and increased cardiac output hemodynamic changes which affect the myocardium causing hypertrophy. This has been well established and also confirmed in a series by Park et al.<sup>3</sup> They based their study on echocardiography findings in 73 liver failure patients before and after liver transplantation and confirmed that there is a tendency to myocardial hypertrophy, chamber enlargement, and increased cardiac output in patients with chronic liver disease. Echocardiography on these patients performed at 5 weeks to 15 months posttransplant showed reduction in LV end diastolic dimensions in all except one ( $P < .2$ ). There was also a reduction in stroke volume index from 53 mL/m<sup>2</sup> to 34 mL/m<sup>2</sup> and in mean cardiac index from 5.8 L/min/m<sup>2</sup> to 3.8 L/min/m<sup>2</sup> after OLTx ( $P < .001$ ).

In our study, an increase in weight of heart and LV thickness were comparable in both the groups. This could be due to a number of reasons. Liver failure, fluid status, repeat blood transfusions, and steroid therapy<sup>4</sup> contribute to a hyperdynamic state that can cause myocardial hypertrophy. It would have been helpful if we had pre- and posttransplant echocardiograms in the study and control population. This would have helped us compare these with autopsy dimensions.

Associated renal dysfunction, hypertension, and infusions of colloids (intravenous albumin and packed cell transfusion) would affect the hemodynamic status and could contribute to the development of cardiac hypertrophy. The improvement reported by Atkinson et al<sup>1</sup> in patients with cardiomyopathy after withdrawal of Tacrolimus may have been attributable in part to these factors. Microscopic examination of the myocardium confirmed the presence of

hypertrophy in our patients. Cardiotoxic side effects have not been reported in the experimental toxicologic evaluation of FK 506 in rats, dogs, and baboons.<sup>5</sup> Tacrolimus in high doses (0.4 mg/kg IV q d) has been known to cause myocardial necrosis in rabbits. This is reversible upon stopping the drug.<sup>6</sup> However, this experimental study did not show any evidence of hypertrophic cardiomyopathy induced by Tacrolimus.

## CONCLUSION

Liver failure is associated with cardiac changes that essentially include myocardial hypertrophy and increase in heart weight and dimensions, namely thickness of ventricles and circumferences of valves. The effect is related to hemodynamic changes accompanying liver failure. OLTx ameliorates the hyperdynamic state, thus improving the hemodynamic status which may cause regression of cardiac dimensions (repeat echocardiograms after 3 months). Cardiac hypertrophy, however, may persist after liver transplantation due to augmentation effect of steroids these patients routinely receive and failure of portosystemic shunts to close. It would be naive attribute these changes to a specific therapeutic agent.

This study confirms that cardiac findings at autopsy in primary OLTx recipients treated with Tacrolimus and patients with end-stage liver disease without OLTx and Tacrolimus are comparable for weight of the heart, wall thickness, valve circumference, and evidence of myocardial infarction. The rate of infective endocarditis was higher in the study group. The rate of coronary artery disease was higher in the control group. Left ventricle hypertrophy was found in 80% of the patients in both groups and is due to liver failure and hemodynamic changes associated with it rather than a direct effect of drug therapy.

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