ULTRASOUND IN THE EARLY DETECTION AND STUDY OF

POST-TRANSPLANTATION CARDIAC REJECTION

by

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Many of the ethical, legal, and technical problems associated with providing a new heart to a dying patient have been overcome and many cardiac homotransplantations have been performed successfully in man. The poor long term survival of these patients is related to the immunologic rejection process. This relationship may be direct with the rejection damaging the myocardium so extensively that the organ cannot function adequately. More often, however, the patient succumbs to overwhelming infection while on immunosuppressive medication which is given to prevent or modify the rejection process. The aim in long term management then is to keep a balance between the threats of infection and rejection by using the lowest dosage of immuno-suppressives which permit the patient to tolerate the foreign tissue. Ex-perimental and clinical data suggest that the acute rejection process is most easily aborted with the least residual damage when large dose immunosuppres-sives are given in the earliest phases of the rejection episode (1-4). The detection of the earlier stages of an acute rejection episode continues to be an important problem. The need to detect this rejection process at its in-ception before irreversible changes appear suggested to us the use of pulsed reflected ultrasound for evaluating the movements of the walls and their thickness in the transplanted hearts of our patients postoperatively.

These studies deal with twelve patients receiving cardiac transplantation at Stanford University Hospital from June 1968 until July 1969. The criteria for rejection by which the ultrasound data were judged included repeated clinical examinations, phonocardiography to document gallops and rubs, summation of QRS voltage in a standard set of electrocardiographic leads, epicardial ECG voltage, serial determinations of numerous serum enzymes and serial chest X-rays. In our experience a rapid drop in QRS voltage, development of an early diastolic

gallop, and changes detected by ultrasonic cardiac echograms (CEG) have been the earliest reliable signs of rejection.

The cardiac echograms were obtained at the bedside beginning with the second postoperative day or when the records were adequate for analysis. The echograms were made with the transducer placed in the third or fourth inter-costal space at the left sternal border and directed to record echoes from the anterior cardiac wall, interventricular septum, and left ventricular posterior wall just below the mitral valve. Transducer position was marked on the chest wall with indelible ink while the patients were in the hospital and sterile graphite was injected subcutaneously to mark transducer position prior to the patients leaving the hospital. Figure 1 shows the type of record used for analysis and is identical to that described previously for measurement of left ventricular posterior wall thickness and chamber size (5, 6). Overall cardiac diameter (AW-PW) from the anterior cardiac wall to the pericardial surface of the left ventricular posterior wall, posterior wall thickness (PWT) from the pericardial surface of the left ventricular posterior wall to its endocardial surface, left ventricular internal diameter (LVID) from the endocardial surface of the left ventricular posterior wall to the left side of the interventricular septum, and right ventricular diameter (RVD) from the right side of the inter-ventricular septum to the anterior cardiac wall or deepest chest wall echoes were determined from the echograms (see Fig. 1). In addition, the mean vel-ocity and total amplitude of the pericardial echo during systole was measured in the patients later in the series.

These various measurements were quite reproducible and varied only a few millimeters over a prolonged period of time when the patients were in a stable state. This was best shown in a patient who was followed for four months without any sign of rejection but who finally died of fulminant serum hepatitis.

In this patient the echographic parameters varied little throughout her course and there were no sudden changes. It is of note that the PWT measured at necropsy was the same as that measured from the echogram on the day of death.

.Figure 2 shows the type of changes that are seen in the echogram during acute rejection. The baseline record (left panel, Fig. 2) was taken on the second postoperative day with the patient clinically well, having normal vital signs, and not on positive inotropic agents. The fourth postoperative day there was a sudden drop in QRS voltage of the ECG and the PWT had increased by 4 mm. since the baseline record. Rightward axis shift of the ECG occured later the same day coincident with an increase in the RVD of 3 mm. By postoperative day nine the patient was in a state of clinical shock despite massive immunosuppressive and cardiac inotropic therapy. The increase in the PWT, RVD, AW-PW, and decreased left ventricular posterior wall motion can be seen in the right panel of Fig. 2. It is of interest that the administration of isoproterenol caused an increase in the amplitude and velocity of motion of the posterior wall echo. The echographic PWT on postoperative day eleven was the same as that measured at necropsy later that day. The right heart was dilated and the myocardium showed a severe inflammatory reaction with edema, arteritis, and platelet thrombi in the small vessels.

Another case illustrates the changes in left ventricular posterior wall motion more clearly. The patient was recovering normally through the second postoperative day but showed a decreased QRS voltage and ectopic atrial beats on the morning of the third postoperative day. This was followed within twenty-four hours by the appearance of an early diastolic gallop, right axis shift of the ECG, and elevated jugular venous pressure. After three days of increased steroid dosage and actinomycin-D the heart size began to decrease on X-ray, the ECG returned toward the baseline measurements and the patient

improved clinically. The acute changes and their reversal with therapy established the diagnosis of rejection firmly in this patient. The sequence of echograms in Figure 3 shows the decreased left ventricular posterior wall velocity and amplitude, and increased heart size seen with rejection, and the reversal of these changes after therapy.

The same type of changes as seen in another patient are shown by representative echograms in Figure 4. The donor heart had pre-existing right bundle branch block and unfortunately a uniform ECG lead was not used in this set of records. With rejection the PWT, RVD, and AW-PW increase, and the posterior wall motion decreases. With successful therapy these changes are reversed. This patient's postoperative course is summarized in Figure 5. Note the sharp changes in the RVD and AW-PW at the time there is an abrupt drop in the QRS voltage. In this case an increase in the PWT could not be appreciated until the next day.

The course of another patient is summarized in Figure 6. Here the PWT increased at the time the QRS voltage dropped, there was an increase in AW-PW and RVD at the time of a right axis shift. Therapy caused a temporary reversal, but the PWT, AW-PW, and voltage again changed after steroid dosage was reduced. The patient was re-treated later with final shift of all parameters toward baseline levels. But note that the axis stayed stable after the initial therapy as did the RVD. At the time of this presentation this patient is fourteen months post-transplantation and doing well.

Our findings are summarized in Table 1. We have attempted to correlate the objective findings, using various methods, with the sequence of pathologic processes which occur during acute rejection. The rejection reaction seems to progress through stages of cellular infiltration, with endothelial injury

and edema formation, followed by stasis and thrombosis in the capillaries and

venules, with acute arteritis, and finally severe myocellular necrosis with

hemorrhagic foci. We believe that we are able to detect the process at its

onset and by using proper therapy, hopefully we avoid the more destructive

advanced stages. This enables us to maintain our patients on decreasing dosage

of immunosuppressives in order to diminish the chances of severe and life

threatening infections. This project using ultrasonic techniques has had

several results. The changes seen in the echograms are among the earliest

detectable by the present means and thus the CEG continues to be used in

following such patients at Stanford. Also, we have convinced ourselves that

rapidly occurring and fine changes in cardiac measurements can be reliably ob-

served with the CEG. And finally, this study has helped to confirm the pre-

vious theoretical explanations of such findings as decreased QRS voltage and

right axis shift seen during rejection by providing an in vivo correlation

of these events with changes in cardiac anatomy .

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TABLE 1

Stage of Rejection	Cardiac Echogram	Electrocardiogram	Clinical Exam	Pathology
Early	Increased posterior wall thickness,	Decreased QRS voltage, atrial arrhythmias	Early S3:gallop	Cellular infiltration, endothelial injury,
	Decreased posterior wall motion			edema
	Increased right ventricular diameter, overall heart size, & decreased left ventricular diameter	Right axis shift, St-T wave changes	Right ventricular heave, increased venous pressure, and heart size	Capillary and venule stasis-thrombosis, acute arteritis
	Very poor posterior wall motion	Ventricular ectopic beats intraventricular conduction defects	Low cardiac output, shock	Focal hemorrhage, cellular necrosis.
Late				

LEGENDS:

Figure 1: Echogram taken on the fourth postoperative day, ACW = anterior chest wall;

AW=PW = overall heart diameter; RVD = right ventricular diameter;

IVS = interventricular septum; LVD = left ventricular diameter; PWT =

posterior wall thickness; L = lung; EKG = electrocardiogram (See Text)

Figure 2: Baseline echogram on postoperative day two. Echogram on postoperative

day nine during acute rejection (See Text)

Figure 3: Echograms of the pericardial echo only with a superimposed scale of

tissue distance. Baseline study on postoperative day two, during

rejection on postoperative day four, and after reversal of rejection

on postoperative day seven.

Figure 4: Echograms prior to rejection, during rejection, and after reversal of

rejection (See Text).

Figure 5: Postoperative course of the patient shown in Figure 4 (See Text)

pred = methylprednisilone.

Figure 6: Postoperative course showing partially treated or recurrent rejection.
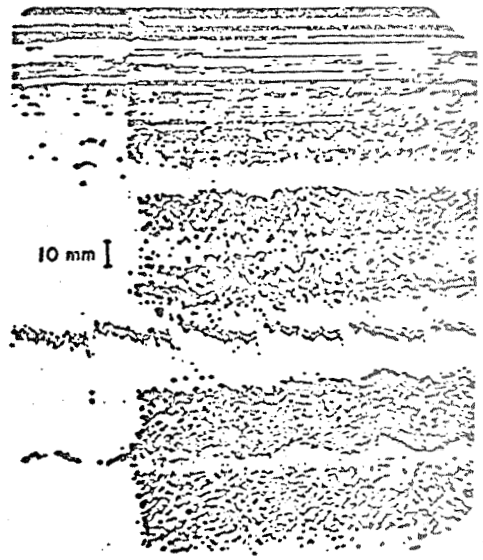
(See Text)

Figure 1

ACW
10 mm
RVD
IVS
AW·PW
EKG
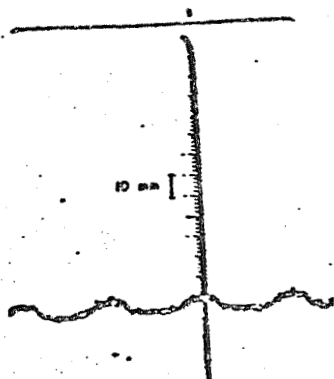LVD
PWT
P
L

S.G.

P.O.D. 4

Figure 2

10 mm

10 mm

D.A.
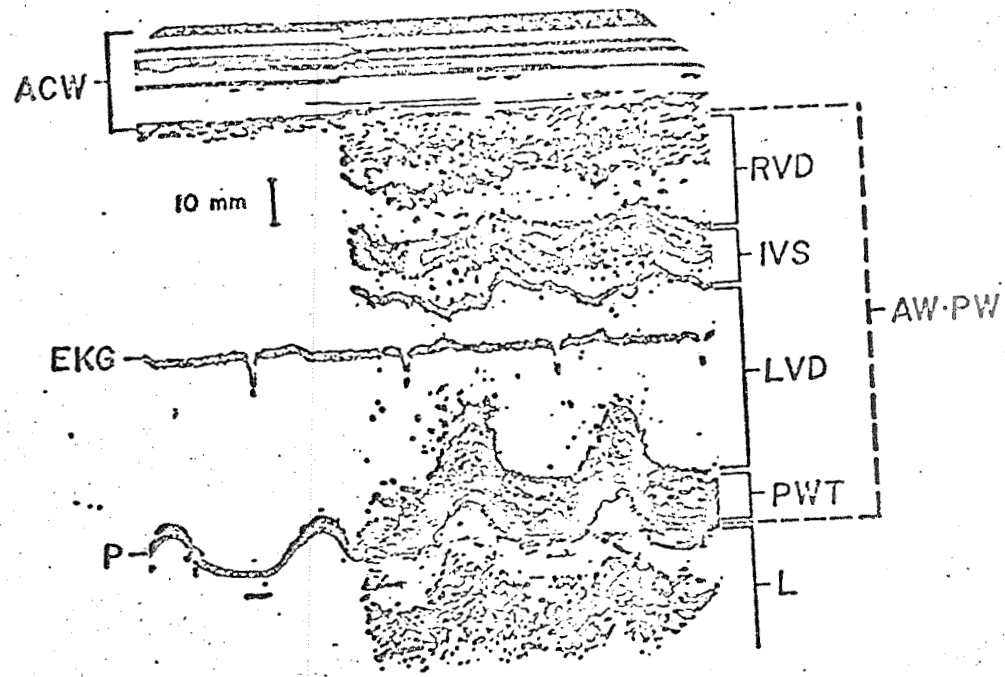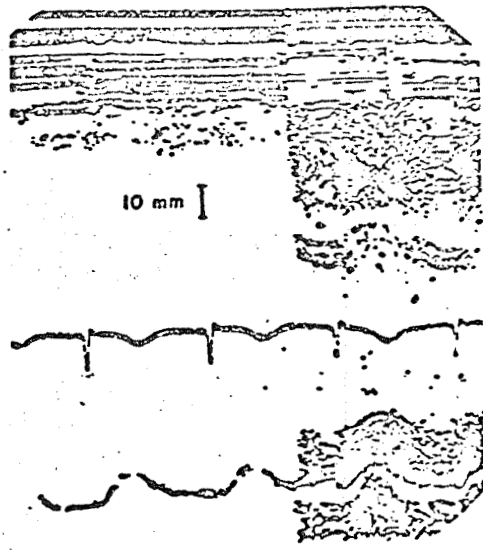
P.O.D. 2

PWT 12 mm
RVD 25 mm
AW·PW 99 mm
P.W. VELOCITY 80 mm/sec

P.O.D. 9

PWT 22 mm
RVD 34 mm
AW·PW 113 mm
P.W. VELOCITY 31 mm/sec

Figure 3

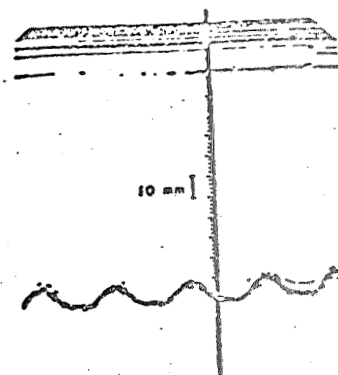
		D.G.
P.O.D. 2	P.O.D. 4	P.O.D. 7
P.W. VELOCITY 72 mm/sec	P.W. VELOCITY 31 mm/sec	P.W. VELOCITY 80 mm/sec
AW·PW 113 mm	AW·PW 116 mm	AW·PW 105 mm
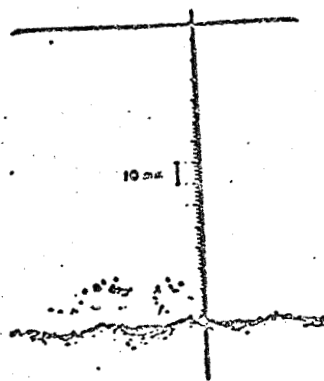
Figure 4
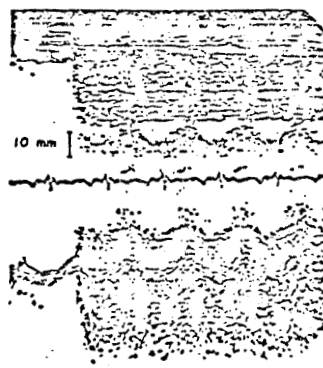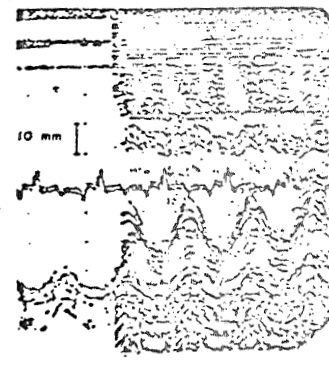
		G.L.
P.O.D. 4	P.O.D. 11	P.O.D. 17
PWT 11 mm	PWT 13 mm	PWT 10 mm
RVD 20	RVD 32	RVD 24
AW·PW 82	AW·PW 90	AW·PW 80
P.W. VELOCITY 50 mm/sec	P.W. VELOCITY 40 mm/sec	P.W. VELOCITY 55 mm/sec

Figure 6