Transvenous endomyocardial biopsy—application of a method for diagnosing heart disease

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Introduction

Although biopsy of the kidney, liver, and many other organs is routine in clinical medicine, biopsy of the heart is infrequently performed. In consequence, little is known of the serial histological changes which occur in non-fatal myocardial disease. Published techniques for obtaining myocardial biopsies have included percutaneous needle biopsy of the left ventricle, catheter needle biopsy of the interventricular septum, and open thoracotomy. The associated morbidity and mortality with these methods have precluded their widespread acceptance (Shirey et al., 1972).

Transvenous biopsy of the endomyocardium of the right or left ventricle using a catheter forceps was first described 13 years ago by Sakakibara and Konno in Japan (1962). Despite the availability of the Konno-Sakakibara bioptome in this country, there have been few reports of its use outside Japan. In 1972, a modified Konno-Sakakibara bioptome was first used at Stanford to obtain biopsies from the dog heart after orthotopic cardiac transplantation. For the first time it was possible to correlate the day-by-day changes in graft histology with indirect parameters of graft function such as the electrocardiogram. It was soon demonstrated that histological examination of the biopsy specimens permitted an accurate assessment of the recipient dog's immune response to the donor heart. Serial biopsies of the transplanted heart could thus be used to monitor acute cardiac allograft rejection, and a technique was developed for the performance of repeated cardiac biopsy in the dog via the external jugular vein (Caves et al., 1973a). Subsequently, development of a technique for percutaneous introduction of the biopsy forceps into the internal jugular vein in man provided the means by which serial endomyocardial biopsies could be obtained from the human heart (Caves et al., 1973b).

This paper describes the technique and instrument developed at Stanford which have been used for the performance of over 500 cardiac biopsy procedures.

The instrument and biopsy technique

The cardiac biopsy instrument is illustrated in Fig. 1. Opening and closing the instrument handle at one end of the flexible catheter controls the position of the jaws at the other end. The jaws are constructed from steel and consist of one fixed and one mobile part, each of which ends in a hollow cup 1-5 mm in diameter. The edges of the cup are sufficiently sharp to provide removal of the specimen by cutting action rather than avulsion. The length of the catheter is 50 cm.

The biopsy forceps are introduced percutaneously (Fig. 2) under local anaesthetic. A 16 Medicut cannula is inserted directly into the right internal jugular vein. A flexible guidewire is inserted through the cannula and a 9F Desilets-Hoffman false catheter and sheath are passed over the guidewire into the vein. After removal of the guidewire and false catheter, the biopsy forceps are introduced through the sheath and the rubber plug is inserted into the luerlok connection on the sheath to prevent leakage of blood. The forceps are advanced to the apex of the right ventricle under fluoroscopic control (Fig. 3). The open jaws of the instrument are easily pressed against the endomyocardium from this approach, since the catheter has only a gentle curve in it where...
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FIG. 1. (a) The Caves-Schulz-Stanford cardiac biopsy forceps; (b) close-up view of the jaws.

it passes through the tricuspid valve. The jaws are closed and the instrument is withdrawn steadily. A slight jerk occurs as a biopsy specimen is removed from the endomyocardium. After removal of the biopsy specimen from the jaws of the instrument, the forceps may be reintroduced to obtain further specimens as necessary. Finally, the patient is positioned upright and the sheath is removed from the vein while pressure is applied over the puncture site. Bleeding is, thus, immediately controlled and the vein remains patent for subsequent use. The biopsy procedure may be completed within 5 min, using only a few seconds of fluoroscopy time.

The electrocardiogram is monitored throughout the procedure and a routine chest X-ray film is obtained afterwards.

Results and discussion

Diagnosis of acute rejection in heart transplant recipients

The principal use of this new cardiac biopsy technique has been in the diagnosis and management of early acute rejection episodes in heart transplant recipients. The transplanted heart has proved to be uniquely valuable in assessing the clinical use of cardiac biopsy because impressive and readily observed changes in the endomyocardial histology evolve so rapidly during acute graft rejection episodes (Fig. 4). However, before the histological changes seen on biopsies of the transplanted heart could be accepted as reliable evidence of the host immune response to the graft, it was important to answer several questions.
that there was excellent correlation between the histological changes seen in these specimens and so, more recently, only one biopsy specimen has been routinely obtained during each procedure. Further confirmation that the samples obtained are representative has come from biopsies performed not long before the death of three recipients. The histological changes seen in these biopsies have been the same as those seen throughout the myocardium at autopsy.

(b) Would the histological changes seen in the biopsies be specific and reliable in the diagnosis and management of acute graft rejection?

It was found that on each occasion the biopsy histology appeared to be normal, the patients were clinically well without evidence of rejection. Conversely, histological evidence of advancing rejection was invariably followed by confirmatory clinical signs which prompted initiation of increased immunosuppressive treatment. Importantly, rejection episodes were histologically evident in patients 2–4 days before rejection could be established clinically on the basis of significant changes in the electrocardiogram or physical examination. Routine serial biopsy in the early post-transplant period may, thus, give the first indication of an acute rejection episode and permit the earlier initiation of increased immunosuppressive treatment before serious damage is caused to the graft by the host immune response.

Serial endomyocardial biopsies also permitted an accurate assessment of the response to immunosuppressive treatment (Fig. 4.) When regression of the histological changes of rejection occurred, it correlated well with the normalization of clinical parameters.
FIG. 4. (a) Biopsy obtained from a heart transplant recipient 16 days post-transplantation. Acute rejection is present with oedema and an infiltrate of mononuclear cells. (b) Biopsy from the same patient on post-transplant day 33 following a course of increased immunosuppression. The myocardium now appears normal with complete reversal of the previously seen histological changes.

(c) Would multiple cardiac biopsies be simple and safe—and acceptable to the cardiac transplant recipient?

Our experience to date has confirmed that these criteria have been satisfied and frequent biopsy of the donor heart is now a routine aspect of clinical management during the first 2 months after transplantation. With the described technique, one to four biopsy specimens can be obtained in 3–5 min, using 20–60 sec fluoroscopy time. The patient feels only the injection of the local anaesthetic and is left with a tiny incision which quickly heals to an imperceptible scar without suturing. No serious complications have occurred. Three patients have been found to have a small right pneumothorax on postoperative chest films, and two patients developed supraventricular arrhythmias during the biopsy which required cardioversion to sinus rhythm. The risk of this procedure is similar to that of right heart catheterization by a central vein, and, thus, would appear to be
substantially less than that associated with left ventricular needle biopsy by percutaneous puncture (haemorrhage, cardiac tamponade, ventricular fibrillation, myocardial infarction) (Shirey et al., 1972). The technical difficulties encountered in transvenous biopsy via peripheral veins are avoided. The rapidity and safety with which transvenous cardiac biopsy can be performed have led to its ready acceptance by the transplant recipients.

**Histological studies in long-term cardiac transplant survivors**

Transvenous cardiac biopsy has provided an important new method for the assessment of long-term cardiac transplant survivors. A total of thirty-four biopsy procedures have now been performed in eleven long-term survivors following cardiac transplantation. These biopsies have demonstrated for the first time that the healthy cardiac transplant recipient can have normal cardiac histology up to 3 years following transplantation. Since some of these patients also have normal cardiac function as demonstrated by cardiac catheterization and left ventricular cineangiography, and normal coronary arteriograms, their prospects for continued long-term survival would appear to be excellent.

**Studies in patients with primary cardiomyopathies**

More recently, transvenous cardiac biopsy has been extended to the study of patients with primary cardiomyopathies. Biopsies obtained from patients have been examined by light and electron microscopy and histochemical techniques. These biopsies have already provided new information about these poorly understood diseases and serial biopsies in these patients may be of particular value in the determination of long-term prognosis. Hopefully, biochemical analyses will be performed on the biopsy specimens enabling a haemodynamic, morphological and biochemical correlation of the cardiomyopathies to be performed.

**Conclusion**

Our initial experience with serial percutaneous transvenous endomyocardial biopsy has established this new technique as a valuable aid to the study of myocardial disease. It has been of particular value in the management of patients following heart transplantation in whom it has greatly improved the early management of acute rejection episodes. On the basis of our favourable experience with cardiac transplant recipients, we have extended this technique to the study of patients with primary myocardial disorders. The technique is safe, efficient and has rapid patient acceptance. Furthermore, it can be performed with less morbidity than biopsy of other solid organs.

**References**


