in contact with the rib in front of the focal lesion, and a minute amount of methylene blue is injected (0.2 ml). Thereafter, the patient is transferred to the operating theater, and rib biopsy is performed under general anesthesia. The blue spot is readily perceived at dissection. This method is very straightforward, and we have found it useful for correctly localizing the portion of the rib to be resected.

Philippe Collard, M.D., and
Robert Ponlot, M.D.,
Cliniques Universitaires Saint-Luc,
Brussels, Belgium

REFERENCE


To the Editor:

The letter by Drs. Collard and Ponlot addresses one of the difficulties encountered by those doing rib biopsy, that is, accurate preoperative localization. Their method is a variation of an old technique, staining the rib abnormality location with methylene blue. Skin localization alone will not help unless the patient is in the operative position. Changing the patient from the supine to lateral position will invariably move the marked site and might create more confusion than aid. A technique that predictably marks the bone abnormality would certainly be helpful. Collard and Ponlot do not describe how they locate lesions prior to marking. If their method is reliable, preoperative bone labeling should provide confidence to the surgeon who at operation may see normal-appearing rib.

Robert W Ikard, M.D.,
Nashville, Tennessee

Diffusion Capacity in Heart Transplant Recipients

To the Editor:

We read with interest in the August 1992 issue of Chest the observation made by Groen et al of a fall in diffusion coefficient (Kco) capacity following cardiac transplantation and their hypothesis that cyclosporine had a causal relationship. The vascular effects of cyclosporine on the kidney are well documented, and it is possible that cyclosporine may affect the alveolar-microvascular structure of the lung. Indeed, a reduced transfer factor (DLco) has also been documented in other solid organ transplant populations, such as renal transplant recipients.

In the setting of an immunocompromised patient, however, variables affecting the alveolar-microvascular structure of the lung other than hemodynamic change and cyclosporine are important. Van Son et al have documented changes in diffusion capacity in renal transplant patients in the presence of cytomegalovirus (CMV) infection despite a normal chest radiograph. We, like Groen et al, have identified a cohort of heart transplant recipients who had a reduced Dco and Kco following cardiac transplantation. We found no correlation with whole-blood trough cyclosporine levels (either single measurements at lung function or cumulative dose) at a mean of 15 months following transplantation. We found, however, that patients with evidence of CMV infection had a lower DLco than patients free of CMV infection.

Cytomegalovirus infection of the lung may explain why the DLco/Kco was lowest at year 1 in the study by Groen et al, this being closer to the expected time frame for CMV infection. Do Groen et al have CMV data on their patients? If the impairment in Kco was entirely a result of cyclosporine, one might expect to see a steady decline in Kco with time, rather than the improvement observed at 2 years following transplantation. To say that measurements of Kco reflect changes in cyclosporine dose could only be substantiated by more frequent comparisons of pulmonary function tests and cyclosporine concentrations.

Their data support our belief that the lungs of a solid-organ transplant recipient experience a continuing occult injury. A detailed prospective trial is required to determine the combined influence of cyclosporine and occult viral infection on the lungs of heart transplant recipients.

James J. Egan, M.B., B.Ch., B.A.O,
Sanja Kalra, M.D., and
Ashley A. Woodcock, M.D.,
Wythenshawe Hospital,
Manchester, England

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To the Editor:

We thank Dr. Egan and his colleagues for their interest in our work. As our computer files did not include data about CMV infections, patient records were reviewed to evaluate the interesting hypothesis that the observed reduction in Kco is associated with CMV infection.

Of our cohort of 34 patients, 15 were CMV-seronegative allograft recipients, 5 of whom received the heart of a CMV-seropositive donor. In one seronegative recipient the serostatus of the donor was unknown. Nine recipient-donor combinations were matched for CMV status. Nineteen recipients were CMV-seropositive before the operation. All CMV-seronegative recipients were treated prophylactically with anti-CMV hyperimmunoglobulin (Cytotect, Biostest GmbH, Dreieich, Germany) for 10 weeks irrespective of the donor status. Cytomegalovirus infection was defined as any appearance of CMV-specific IgM antibodies, isolation of the virus from urine, throat washings, or blood; or detection of CMV antigen. Infection occurred in 12 patients (5 primary and 7 secondary infections). Cytomegalovirus disease was defined as infection coexistent with two of the following symptoms: otherwise unexplained fever (temperature >38°C) for at least 2 days; gastrointestinal, lung, retinal, or central nervous system involvement; leukocytopenia; thrombocytopenia; or elevated aminotransferase levels. Cytomegalovirus disease occurred in three patients (two primary infections) without evidence of pulmonary involvement.

The mean decrease (±SEM) in Kco after 1 year appeared to be 14 (5.5) percent predicted in the group with CMV infection. This figure was 11 (3) percent predicted in the group without such an infection. Both mean decreases were significantly (p<0.05) greater than zero, and did not significantly differ from each other. Using multiple regression analysis to evaluate the relation between Kco...
at 1 year vs preoperative Kco, cyclosporine level in the first postoperative year, and presence of CMV infection, we also found no significant relation with CMV infection (Table 1).

The relation between cyclosporine level in the first year and Kco in the first year was highly significant, whereas no significant relation with the occurrence of CMV infections was found. In view of the large SEM related to the effect of CMV infection, however, a relation with the decrease of Kco cannot be ruled out from our data.

In CMV disease without obvious pulmonary involvement, two of three patients had a more pronounced decrease in Kco in the first postoperative year (28 and 44 percent predicted). These recipients showed reversibility in the second and third years after the operation. If CMV disease were the only cause, reversibility would not be expected. Not only was there some reversibility in Kco, but other side effects of cyclosporine, such as kidney function changes, seemed to be partly reversible within the first postoperative year. Indeed, our data do not rule out CMV disease as an additional cause of Kco decrease. We do agree that further investigations in larger cohorts of patients are necessary.

**REFERENCES**


To the Editor:

The exclusion of patients with atrial fibrillation from anticoagulant trials will vary depending on whether they are in a clinical trial or in routine clinical practice. The selective nature of the AFASAK, BAATAF, SPAF, CAFA, and SPINAF antiocoagulant trials was specifically designed to evaluate patients with nonrheumatic atrial fibrillation. Atrial fibrillation coexisting with conditions such as rheumatic mitral stenosis, hyperthyroidism, and severe myocardial disease is well established as an increased risk for thromboembolism and is an absolute indication for anticoagulant therapy. In addition, patients with atrial fibrillation receiving anticoagulant therapy for other indications, such as previous thromboembolism, transient ischemic attacks, stroke, and unstable angina, were also eliminated from the study population. Patients with known heart or central nervous system disease were eliminated to avoid confusion with primary and secondary end points.

The large number of patients who needed to be screened to obtain a strictly defined population is not unique to these prospective, randomized trials. For example, the Studies of Left Ventricular Dysfunction (SOLVD) trial screened 39,924 patients and excluded 37,355 (94 percent). Similarly, the Lipid Research Clinics Coronary Primary Prevention Trial screened approximately 480,000 patients and excluded 99 percent before enrolling 3,810 patients.

In the SPINAF trial, 7,982 patients were screened in order to randomize 525 patients with chronic atrial fibrillation to receive warfarin or placebo. Of the patients excluded, 1,732 (22 percent) had intermittent atrial fibrillation (not an exclusionary criterion for routine anticoagulant treatment), and 901 (11.3 percent) had another definitive indication for anticoagulation or antiplatelet treatment, such as a prosthetic heart valve (6.2 percent), mitral stenosis (3.7 percent), active thromboembolic disease (2.4 percent), coronary artery surgery (0.2 percent), intracardiac thrombus (0.05 percent), and myocardial infarction within 1 month (0.05 percent). In addition, 477 (6 percent) had received prior anticoagulation therapy (not a clinical exclusion), 468 (5.9 percent) were using aspirin or a

The absolute risk reduction that they reveal. Physicians need to be aware of the following data: 30,762 patients were screened for enrollment in these five trials, and 27,102 (about 88 percent) were deemed unsuitable for study because of a wide variety of medical, psychosocial, and administrative reasons. When all was said and done, only 55 primary outcome events (ischemic strokes) were prevented in these studies at a small increased risk of hemorrhage. One can distill these data into a clinically useful statistic—a doctor may have to screen nearly 560 patients with atrial fibrillation (in order to find 67 who can be treated with warfarin appropriately) to prevent one ischemic stroke. My conclusion after studying these trials is that they demonstrate a significant benefit for oral anticoagulation in a handpicked minority of patients. Physicians should be as scrupulous as the investigators who performed these studies when they consider whether their patients will prove to be candidates for antithrombotic therapy in atrial fibrillation.

Donald Venes, M.D.
Department of Medical Education
Spartanburg Regional Medical Center
Spartanburg, South Carolina