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Influence of Scan and Pathologic Criteria on the Specificity of Cholescintigraphy: Concise Communication

Drs. Freitas et al. are to be commended for their insightful study on the influence of image and pathological criteria on the specificity of cholescintigraphy (*1*). Although briefly mentioned by the authors, I feel that another variable should be emphasized as having an equally significant impact on such specificity: the prevalence of chronic cholecystitis, however defined, in the population under study. Since, as stated in this and other articles, the large majority of false-positive cholescintigrams are associated with chronic cholecystitis, it follows that the specificity, false-positive rate, and predictive value of a positive test will be closely tied to the prevalence of chronic cholecystitis in the population under study (*2,3*). One could easily expect that this prevalence would be quite different in a population of patients referred from an emergency room as opposed to patients referred from a surgical clinic. Likewise the prevalence of chronic cholecystitis would be markedly different if a significant portion of the population under study consists of young traumatized males (Harborview Hospital, Seattle) as compared with middle-aged female native Americans (Alaska Native Medical Center Hospital, Anchorage).

This point was made recently in an editorial by Warren C. Phillips et al. in the *American Journal of Roentgenology* using one of our articles on the evaluation of acute right upper quadrant pain (*2,4*). This article reported accuracy, sensitivity, specificity, predictive values of a positive and of a negative test, and false-negative and false-positive rates for cholescintigraphy and sonography. The author of the editorial asked how many of these figures would be useful to a community hospital radiologist. The answer is "None!" because the prevalence of disease differs between the community hospital and our referred hospital.

As with most tests, the value of cholescintigraphy depends strongly on the prevalence of the disease under study (acute cholecystitis) in the population under study. But it depends equally on the prevalence of an accompanying morbid disease (chronic cholecystitis) that causes false-positive results (*5*). This latter prevalence can vary considerably between populations, independently of how it is defined.

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Reply

I thank Dr. Shuman for his interest in our article. As outlined in our introduction, this paper dealt primarily with only one of four factors that may have a profound influence on cholescintigraphic results. I agree with Dr. Shuman's desire for emphasis of the prevalence of chronic cholecystitis and its impact upon the specificity of cholescintigraphy. This is why the prevalence of chronic cholecystitis in the group reported in this prospective study is emphasized. In the clinical setting of acute right upper quadrant or epigastric pain, the prevalence of chronic cholecystitis varies from 20-33% in the literature (*1-6*). These prevalence rates were found in both community and university centers. In our prospective study, the gallbladder of 91.4% of our patients with chronic cholecystitis and with symptomatic right quadrant or epigastric pain were visualized by 4 hr.

Previously we had looked at our patients with asymptomatic chronic cholecystitis and found that 90% visualized their gallbladder by 1 hr, and 95% by 4 hr, whether in the asymptomatic or symptomatic state.

Using the cholescintigraphic specificity for chronic cholecystitis of 90%, and holding the prevalence of acute cholecystitis constant at 30%, the overall specificity of cholescintigraphy in a population changes little as the prevalence of chronic cholecystitis is increased from 10 to 70% (Fig. 1). Note also what happens to the specificity of real-time ultrasound as the prevalence of chronic cholecystitisis increased. Obviously, with increasing prevalence of chronic cholecystitis in a population, the specificity of real-time ultrasound declines markedly, whereas the effect upon cholescintigraphy is minimal.

Regarding the Editorial by W. C. Phillips et al., it is stated that the positive and negative predictive values will vary depending upon the prevalence of disease in that particular community or university center. Dr. Shuman omitted Phillips's next sentence, "However, if the disease prevalence were known, the predictive values could be determined." Thus, as in our article, the predictive values give meaningful information if the prevalences of the disease (both acute and chronic) are specified. Qualitative measurements of a test's performance must be viewed within the context of the study's

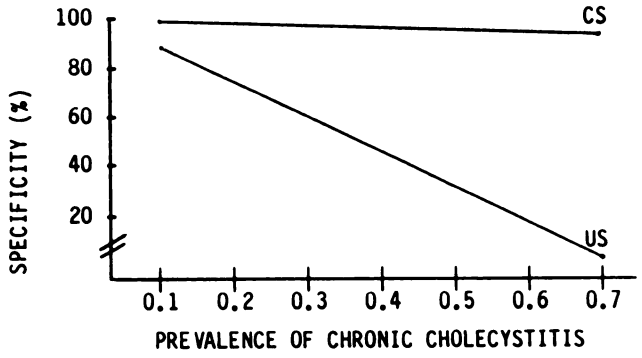

FIG. 1. Effect of chronic cholecystitis upon specificity of cholescintigraphy (CS) and real-time ultrasound (US). This graph assumes gallbladder visualization at 4 hr by CS in 90% of patients with chronic cholecystitis and US detection of all patients with chronic cholecystitis.

design and the patient population. Thus, using the same population as outlined in Fig. 1, the predictive value for a positive cholescintigram decreased from 97 to 81% as the prevalence of chronic cholecystitis increased. Similarly, the predictive value of real-time ultrasound decreased from 75 to 30% as the prevalence of chronic cholecystitis increased. Thus, at all prevalence levels for chronic cholecystitis in the clinical setting of suspected acute cholecystitis, cholescintigraphy is the best modality available to the clinician to discriminate acute from chronic disease. It is not perfect, and the results should be interpreted with knowledge of its limitations, as discussed.

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Re: Brain Blood-Flow Measurement with Bolus Intravenous $H_2{}^{15}O$

Recently Raichle and colleagues described an implementation of the PET/autoradiographic technique for the measurement of regional cerebral blood flow with intravenously administered oxygen-15-labeled water (*1*). They successfully modified the operational equation of the one compartment arising from the Kety-Schmidt method (*2*) to compensate for the fact that current PET instruments cannot measure the instantaneous tissue count rate. PET images typically require the summing of decay events for the order of 5-180 seconds. Raichle et al. (*1,3*) critically outlined several potential sources of error in the adaptation of tissue autoradiography to PET. Although their model has limitations, which they noted, it does offer a convenient and validated method for determining regional cerebral blood flow with a diffusible tracer.

We agree with the authors that an appreciation of the validity of assumptions in the kinetic models and their accuracy will lead to more precise quantification of regional cerebral blood flow with positron emission tomography. We are therefore taking exception to the generality of the assertion that the duration of a PET study to determine CBF must be constrained such that the length of data collection *must not exceed* 1 min for accurate, quantitative results. We suggest that their caveat is specific to the model and the method of approximation of the instantaneous tissue concentration following bolus injection of tracer. The duration of a PET/autoradiographic determination of CBF is particularly important with the data-collection and data-transfer capabilities of current PET technology, either if the tracer does not maintain its chemical integrity once injected (due to metabolism or dissociation, as is the case with iodoantipyrene) (*4*), or if it is seriously diffusion-limited (*5*) as a function of flow rate (e.g., antipyrene).

Kety is credited (L. Sokoloff, personal communication) with recognizing that the ramp injection technique overcomes time limitations for tissue autoradiography, if the radiotracer maintains its chemical integrity during the CBF determination. The concept of ramp injection requires that the arterial concentration of the radiotracer be described as a constantly increasing function. Ramp injection in some instances is preferable to either bolus injection or constant infusion because: (a) tissue saturation does not occur, (b) regional CBF is specified by the onset of the tissue concentration from the arterial ramp; (c) the time constraints of the analysis interval (i.e., PET data-collection period) do not alter the results, and (d) the effects of short half-life and long counting time are minimized. The advantage of the bolus injection technique is that it results in a lower radiation dose, and a simple monitor of arterial concentration is adequate. The ramp technique does eliminate the guesswork associated with starting the PET data collection at precisely the time when the peak radioactivity reaches the brain.

We recently described (*6,7*) a device for the ramp injection of radiotracers, for use in the PET determination of CBF in animal models. Our motivation is the development of kinetic models and understanding of the processes associated with blood flow and metabolism. The operational equation for application, of the Kety-Schmidt method to ramp injection and measurement of tracer concentration in brain $C_B(t)$ was expressed (*7*) as:

$$C_B(t) = \lambda S(t - \lambda/f) + [C_B(t_0) - \lambda S(t_0 - \lambda/f)] \exp[-(t - t_0)f/\lambda],$$

where S is the slope of the ramp, f is the CBF, $C_B(t_0)$ the concentration of tracer at the initial time, t_0, and λ is the partition coefficient. After a short transient (~3 min) the exponential term