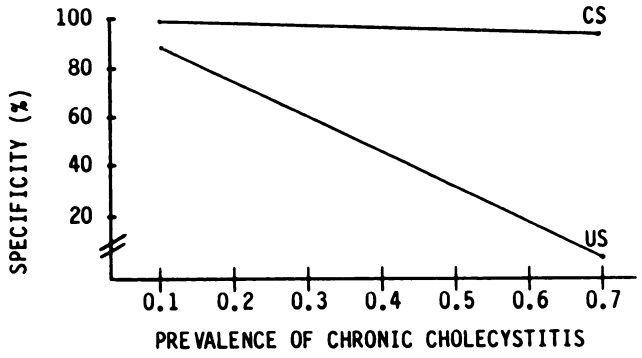

FIG. 1. Effect of chronic cholecystitis upon specificity of cholescintigraphy (CS) and real-time ultrasound (US). This graph assumes gallbladder visualization at 4 hr by CS in 90% of patients with chronic cholecystitis and US detection of all patients with chronic cholecystitis.

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

becomes negligible and the expression reduces to

$$C_B(t) = \lambda S(t - \lambda/f),$$

which describes a straight line of slope λS, intersecting the time axis at the point $t = \lambda f$. Since, by definition, the slope of the arterial concentration $C_A(t)$ compared with time (t) is S, the partition coefficient, λ, can be determined by comparing the slope of $C_A(t)$ with the slope $C_B(t)$ as obtained in an experiment with a constant value of f. Once λ is known, the value of f can be obtained from the intersection λ/f. The ramp injection of tracer permits the establishment of slope and intercept parameters by linear regression analysis. If the model is valid, then λ can be evaluated for each region of interest, eliminating the assumption of an average λ value.

The PET/autoradiography approach to measurement of cerebral blood flow requires a tracer that maintains its chemical integrity throughout the course of the study, and that data collection must not begin until the arterial concentration is defined as a constantly increasing function. Ginsberg et al. (*8*,*9*) used a modified ramp technique, but were limited to short-duration PET studies due to the in vivo instability of [C-11] 4-iodoantipyrene. We have used the ramp injection technique and the above model for CBF measurements with 10 ml (40–50 mCi) of $H_2{}^{15}O$ injected into baboons positioned in the PET VI. Three 30-sec scans are collected every 60 sec beginning 3 min after the onset of the ramp injection. The ramp approach is particularly suited to research with animals, since it permits physiological parameters to be altered during a series of experiments in which the animal serves as its own control.

We would prefer the bolus injection technique and a PET/autoradiographic model in which the assumptions are minimized. In this regard we have described (*10*) an algorithm to reconstruct PET count-rate curves from total counts. A source of error may be due to the radioactive decay. With the ramp injection, this error (*8*) is less than 0.02%, but with the bolus injection the error may be larger; Raichle et al. (*3*) claim less than 4% error for bolus injection as determined by simulation. We wrote about this error (*10*) and have described a more precise estimate of the correction needed when the counting time is larger than one minute. The algorithm (*10*) is being adapted for utilization in the simultaneous determination of CBF and λ following bolus injection of tracers. Without the aid of appropriate algorithms, we agree that it is preferable to minimize the duration of a PET determination of CBF to less than 1 min following the bolus injection of the tracer.

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Reply

We appreciate the detailed comments of Lambrecht and Rescigno, which relate not only to our adaptation of the Kety autoradiographic technique to positron emission tomography (PET) (*1*,*2*), but also to their own work in this field (*3*,*4*). They raise several issues worthy of comment.

Our approach and that of Lambrecht and colleagues are both based on the Kety tissue autoradiographic technique for measuring local cerebral blood flow. However, we use a bolus intravenous administration of radiotracer, rather than the ramp arterial input used by Lambrecht et al. (*3*). To our knowledge, Kety and his colleagues did not specify a ramp injection technique, they used a continuous intravenous infusion of radiotracer over one minute (*5–7*). This results in a sigmoid shaped arterial time-activity curve (*8*). Ginsberg (*9*) noted, in fact, that the exact form of the arterial concentration function is not critical, although a monotonically increasing function—not necessarily a ramp—is required to ensure a unique solution of the operational equation for flow. However, as we and others have shown (*1*,*10*,*11*), because the PET autoradiographic approach involves an integration of Kety's operational equation, one does *not* require that the arterial concentration be a monotonically increasing function with time. Furthermore, although Ginsberg et al. did use a modified ramp technique (*12*) to measure CBF in the rat with an external detection system, their one-minute radiotracer infusion time was not limited by the "in-vivo instability of C-11 4-iodoantipyrine" since they used oxygen-15 water as the flow tracer. In the study using C-11 iodoantipyrine (*13*), regional CBF was measured by indicator fractionation, not the Kety autoradiographic method, and a bolus radiotracer injection, not a modified ramp. Because the indicator fractionation method demands a very brief infusion period, a short study length (7 sec) was used (14).

We wish to clarify the statement of Lambrecht and Rescigno that a bolus input requires "guesswork associated with starting the PET data collection at precisely the time when the peak radioactivity reaches the brain." We stated that the PET data collection is started at the time of arrival of radioactivity in the brain. This is easily accomplished by observing the bank pair coincidence counting rate of the PETT VI system. Furthermore, this start time