Measurement of Metabolic Extraction of Tracers in the Lung Using a Multiple Indicator Dilution Technique

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Selective pulmonary uptake of many natural and synthetic substances has been demonstrated by physiologists and pharmacologists using isolated perfused lung preparations or invasive techniques. It is difficult, however, to relate these laboratory studies to disease processes and to the study of problems encountered in a clinical environment. Our goal was to develop a noninvasive method for studying the pulmonary uptake of tracer substances using available radiotracers, gamma cameras, and computers that would give information similar, if not identical, to that from the invasive laboratory methods, and that could be applied in a clinical setting. The multiple-indicator dilution technique, modified for external counting, is well suited for such studies of pulmonary uptake of tracer substances. In this study, Tc-99m micro sulfur colloid (Tc-99m micro SC) was used as an intravascular reference tracer, N-isopropyl-p-[^{123}I]iodoamphetamine (I-123 IMP) as a cellular test tracer amine, and In-111 DTPA as an extracellular tracer. Calculated first-pass lung uptakes of I-123 IMP and In-111 DTPA were 0.92 ± 0.04 and 0.17 ± 0.04, respectively, relative to the reference tracer. Using this approach, the first-pass pulmonary extraction of a variety of radiolabeled test tracers can be measured in a clinical environment in a variety of physiologic settings.

It has only recently been appreciated that the lung is an important metabolic organ, with active functions in addition to those associated with gas exchange. In the past two decades, numerous investigators have demonstrated that the lungs produce, inactivate, and modulate a variety of hormones, drugs, and amines. The metabolic activities of the lungs have been the subject of a recent symposium (*1*) and several reviews (*2-5*). Because these studies have used in vitro or invasive techniques almost exclusively, their clinical application has been limited. However, by using suitable radiotracers and quantitative imaging techniques, many ethical and technical problems can be overcome, making it possible to study metabolic lung functions in patients (*6*).

The potential for using emission imaging to study pulmonary metabolic processes has been recognized by other investigators; Fowler et al. (*7*) and Gallagher et al. (*8*) published lung images and data on the uptake and washout of C-11 octylamine in rabbit and human lungs. Syrota et al. (*9*) have reported on the uptake of C-11 chlorpromazine in human lungs. In the present study, we have used N-isopropyl-p-[I-123]iodoamphetamine (I-123 IMP), which several groups are currently investigating as a brain-imaging agent (*10-14*). A high lung uptake of I-123 IMP has been reported (*11,15-17*).

Clinical and experimental application of I-123 IMP to the study of pulmonary physiology requires quantitative techniques for measuring its uptake in the lungs. We now report on our experience in quantifying the uptake of I-123 IMP in the dog lung by a modification of external counting techniques that were developed to study lung water and pulmonary edema (*18-21*). The feasibility of applying these methods to the study of pulmonary physiology and disease in man is discussed.

MATERIAL AND METHODS

In the present study, six dogs were used in 30 experiments. The animals were of mixed breeds weighing between 30 lb and 40 lb, three female and three male. None had been used for other procedures for at least a week before participation in one of the present studies, and none received any medication during this rest period. Approximately 20 min before beginning the study, the animals received a light anesthetic dose of the short-acting barbiturate, thiamylal.

Preliminary experiments were performed to determine the temporal behavior of I-123 IMP over periods of 20–30 min. In six animals, 2.5 to 4 mCi of I-123 IMP (1.5 mCi/ml, 0.45 mg/mCi) were injected as an intravenous bolus through a small catheter, and data were recorded in 20-sec frames. A large-field-of-view camera interfaced to a digital computer was used to acquire data. These preliminary studies demonstrated a prominent retention of I-123 IMP in the lungs, and excellent camera images of the lungs were obtained, but the uptake of I-123 IMP was so rapid that clearly data acquisition using more rapid framing rates would be necessary to study the pulmonary uptake of this agent.

In order to measure the uptake of I-123 IMP, we adopted a modification of the multiple-indicator techniques of Chinard and Enns (22) and Crone (23) for measuring capillary permeability. Three radiotagged tracers were injected as separate boluses into a peripheral vein within a period of 10 min. A 2-mCi bolus of Tc-99m micro SC was followed by a bolus of 2 mCi of I-123 IMP. A final bolus of 2 mCi of In-111 DTPA was administered in most experiments. The same site and technique were used for each bolus. For 30 sec after each bolus injection, data were acquired at five frames/sec in 64 × 64 matrices. Twenty percent windows were used: at 140 keV for Tc-99m micro SC, at 159 keV for I-123 IMP, and at 247 keV for In-111 DTPA.

In the present study, Tc-99m micro SC was used as the vascular (reference) tracer. It was chosen for its availability, compatibility with current gamma cameras, and its physiologic properties. When made by the hydrogen sulfide process, Tc-99m micro SC has a particle size of <200 mμ (24) and remains almost entirely within the vascular space during its first transit through the lung. It is then rapidly cleared from the vascular space by the liver and spleen. As test tracers, I-123 IMP or In-111 DTPA were used. In four experiments, In-111 DTPA was also used as a reference tracer and I-123 IMP as the test tracer, in order to evaluate the extraction of I-123 IMP over and above that expected on the basis of extracellular diffusion alone.

DATA ANALYSIS

When applied to the lung, previous indicator-dilution techniques call for injection of two tracers in a single bolus into the right heart. One, a reference vascular tracer, is assumed to stay within the vascular system for the duration of the study; the other is a test tracer whose extraction is to be evaluated. In the original Chinard-Crone technique (22,23), the lung retention or extraction ratio for the test tracer is calculated from the difference between the fractional recoveries of test and reference vascular tracers in the left heart.

Although simultaneous injection of two boluses of test and reference tracers into the same vessel was used in the original Chinard-Crone technique, the camera-computer system available for our study is not interfaced for simultaneous dual-nuclide recording. We therefore used separate injections of tracers under stable physiologic conditions. Rapid sequential boluses have been used by several investigators studying lung water with external counting techniques in both dogs and man (18–21).

The original Chinard-Crone method used two indicators: a diffusible test tracer and a nondiffusible vascular reference indicator injected into the afferent vessel of the organ being studied. Venous outflow was then sampled and analyzed for the two indicators, and fractional extraction (E) of the diffusible indicator in a single passage through the capillaries was calculated as

$$E(t) = \frac{C_R(t) - C_T(t)}{C_R(t)}, \qquad (1)$$

where $C_R(t)$ and $C_T(t)$ are, respectively, the normalized concentrations of the reference and test indicators at time t in the venous effluent. Concentrations are normalized to total amount of respective reference or test tracer injected. Extraction of the tracer substances is taken to be relatively constant in time during their first pass through the capillary bed of the organ under study.

In the present studies we have used a computer-assisted gamma camera system and the following method of data analysis. To obtain fractional extraction by noninvasively monitoring the capillary bed itself, the following modifications of the original Chinard-Crone method have been made.

The area weighted extraction, E(t), is calculated from:

$$E(t) = \frac{\int_0^t C_R(\tau)d\tau - \int_0^t C_T(\tau)d\tau}{\int_0^t C_R(\tau)d\tau}, \qquad (2)$$

where $C_R(\tau)$ and $C_T(\tau)$ are the concentrations of reference and tracer activity in the effluent at time τ, each normalized to total dose injected at time zero.

When calculating extraction using Eq. (2), we must know the concentrations of test and reference tracers in the venous effluent of the organ being studied. In this study of the lungs such an approach would require either invasive sampling of effluent blood in the pulmonary

veins or left heart, or noninvasive external monitoring of uncontaminated regions of interest over the left heart. We used neither of these approaches. The first was rejected because it is invasive, the second because overlying lung makes accurate counting over the left heart difficult in the dog, especially in the presence of high lung extraction. Instead, Eq. (2) was modified so that residue activity in the lung itself, rather than effluent concentrations from the lung, could be used to calculate extraction.

Assuming rapid (instantaneous) injection, the normalized residue function H(t) at any time, t, can be described as:

$$H(t) = 1 - F \int_0^t C(\tau)d\tau \qquad (3)$$

where F is the blood flow to the organ, $C(\tau)$ is the normalized concentration of test or reference tracer at time τ in the venous effluent, and H(t) is a unitless residue function that represents the fraction of tracer remaining in the organ at time t following an impulse arrival of tracer.

Combining Eqs. (2) and (3) yields

$$E(t) = \frac{H_T(t) - H_R(t)}{1 - H_R(t)}. \qquad (4)$$

T and R indicate test and reference tracers, as before, and the residue functions, $H_R(t)$ and $H_T(t)$, assume fractional values of the injected doses.

The observed pulmonary time-activity curves obtained by externally monitoring the lungs after a peripheral bolus injection cannot be directly substituted for the pulmonary impulse response functions $H_R(t)$ and $H_T(t)$. The shape of the raw curves represents the effects of transit of tracer through the peripheral venous system and the right heart as well as the lungs, even if the dose could be injected as a perfect bolus peripherally. The pulmonary impulse response functions $H_R(t)$ and $H_T(t)$ must therefore be obtained by deconvolving the observed pulmonary curves by the observed right-heart curves. Once the impulse response functions are thereby determined by deconvolution, the extraction of radiotracers within the lung can be calculated using Eq. (4).

In the set of experiments used for determining first-pass pulmonary uptake of tracers, data were analyzed as follows:

1. Using areas of interest over the right heart and the lateral aspects of the lung fields, two time-activity curves were generated for each injected tracer. Right heart and lung curves were corrected for background.

2. Time-activity curves for the right heart and lung were fitted with a gamma variate of the form $C(t) = Kt^\alpha e^{-t/\beta}$ (25). The first point for the fitted segment was chosen at approximately 10% of the peak on upslope, and the last point was at 50-70% of the peak on the downslope of the respective curves. These segments of the

heart and lung curves are largely free of problems of contamination from adjacent structures and from recirculation, and hence data were fitted over them. Lung curves of I-123 IMP were fitted somewhat differently; gamma variates were fitted over segments extending from ~10% of the plateau to just beyond the beginning of the plateau, since a significant downslope is not present for these curves. This yielded good fits of the data over the indicated segment. Calculations involving these curves were carried out only over the approximate fitted segments.

3. Gamma-variate fits of the right heart and pulmonary curves of the reference and test vascular tracers were deconvolved using a least-squares procedure to yield the pulmonary impulse response functions, $H_R(t)$ and $H_T(t)$, of the reference and test tracer substances, respectively. The impulse response functions H(t) were constrained to be monoexponential functions of the form $H(t) = Ae^{-k(t-t_a)}$ where A and k are scalar parameters and t_a is the lag time between lung and right heart. Although other more complicated models for the pulmonary impulse response function could be used, this single-exponential, single-compartment model was chosen for purposes of computational and conceptual clarity in this initial study. Data for the least-squares normal equations were taken from the onset of the right-heart and lung curves up to the time that the pulmonary curve of the reference tracer had fallen to between 50% and 30% of its peak value.

The pulmonary impulse response functions, $H_R(t)$ and $H_T(t)$, are normalized to peak values of 1.

5. E(t) is determined from Eq. (4). Reported extraction values were mean E(t) from time zero to one pulmonary transit time.

RESULTS

In the preliminary set of experiments used to study the pulmonary washout of I-123 IMP, sequential images of the lungs were made at 10- 20-sec intervals following a rapid i.v. injection of 2 to 4 mCi of I-123 IMP. There was a high initial uptake of the tracer in the lungs, followed by slow washout (see Fig. 1). Delayed uptake in the liver and other organs is probably related to this slow washout from the lung (Figs. 1 and 2).

In the first-pass experiments, the pulmonary uptake of I-123 IMP was determined six times in five different dogs. The extraction of In-111 DTPA was determined four times in three dogs. The differences in first-pass handling of I-123 IMP, In-111 DTPA, and Tc-99m micro SC by the lung are shown in Fig. 3, where the fitted right-heart and pulmonary curves for the three tracers are plotted. Figure 4 shows the transfer functions or impulse response functions, H(t), from which the extraction fractions were calculated using Eq. (4). The impulse response function of I-123 IMP showed the
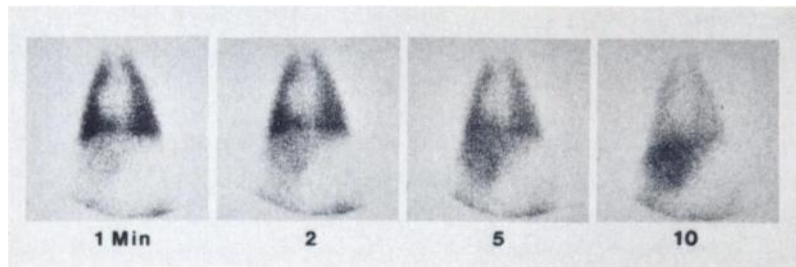
FIG. 1. Images of chest and upper abdomen of dog given 2.5 mCi of I-123 IMP as intravenous bolus. Note initial rapid pulmonary uptake of tracer, followed by slower uptake in liver and other organs as pulmonary washout occurs.
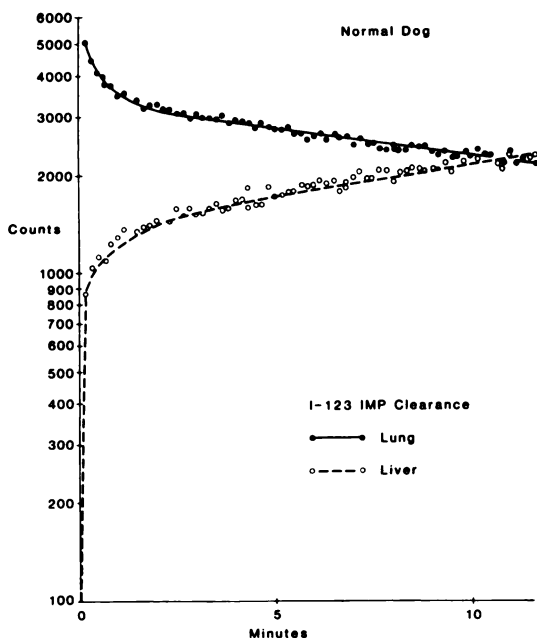
greatest lung retention, followed by In-111 DTPA and Tc-99m micro SC (Fig. 4). The extraction fraction for I-123 IMP using Tc-99m micro SC as the reference tracer was 0.92 ± 0.04 (mean ± s.d.).

Since I-123 IMP has a small molecule, it might be retained in the lung partly on the basis of diffusion into extravascular spaces. To estimate the extent of this potential diffusion, an extracellular trace of similar molecular weight was studied. In-111 DTPA extraction was measured four times in the same group of dogs, and its extraction ratio was 0.17, using Tc-99m micro SC as the reference tracer. Since future studies on the quantification of lung receptors may require a correction for extracellular uptake, in four experiments In-111 DTPA was used as the reference tracer and I-123 IMP as the test tracer. The lung extraction ratio of I-123 IMP under these conditions was 0.72. This is 80% of the value obtained with Tc-99m micro SC as a vascular tracer.

Although the mechanism of lung uptake remains to be established, uptake by amine receptors on the endothelial cells is a likely possibility, based on current evidence. To test this hypothesis further, the extraction fraction of I-123 IMP was determined before and after pharmacological intervention with a second amine. In three experiments, 100 mg ketamine (which can be given intravenously with minimal cardiovascular response in the anesthetized dog) was injected 10 min before measuring the I-123 IMP extraction ratio against Tc-99m micro SC. After this intervention, the extraction ratio of I-123 IMP was 0.67, representing an average decrease of 27% from I-123 IMP extraction ratios obtained in the studies without ketamine. This reduced extraction was also illustrated by the more rapid decay of the pulmonary impulse response function of I-123 IMP after ketamine administration (Fig. 5).

On the other hand, the slight change observed in the In-111 DTPA extraction ratio in the two experiments done after ketamine administration was in the opposite direction. These experiments with ketamine suggest that the decrease observed in the I-123 IMP extraction ratio was not due to changes in blood flow (26,27) or vascular recruitment induced by the ketamine, but rather to alterations in the uptake capacity of the lung endothelium for the I-123 IMP.

DISCUSSION

Investigations of the metabolic functions of the lung have demonstrated that it performs important functions involving peptides, prostaglandins, and amines that are basic to homeostasis of the cardiovascular and central nervous systems. Unfortunately, extension of these studies to clinical problems has been severely limited, since the methods used to study these functions are usually invasive or involve radiopharmaceuticals that have undesirable radiation properties. In this study we eliminated some of these undesirable features as they pertain to the dual-nuclide method, while retaining the basic principles. We have made appropriate modifications of instruments, replacing probes and well counters with gamma cameras, radiopharmaceuticals, and techniques of data analysis.

To make use of readily available instrumentation, we have injected the tracers sequentially rather than as a single bolus. To make the method more suitable for clinical use, we also used peripheral rather than central bolus injections and thereby derive pulmonary impulse response functions. This is made possible by the tech-

FIG. 2. As pulmonary I-123 IMP decreases, rise in liver activity occurs. Half-time for slow phase of lung washout ranges from 15–20 min in different dogs.

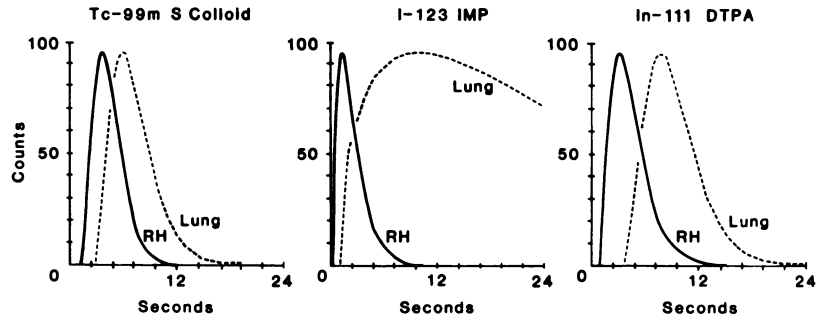Tc-99m S Colloid   I-123 IMP   In-111 DTPA

FIG. 3. Fitted time-activity curves over right heart (RH) and lung for first pass of Tc-99m micro SC, I-123 IMP, and In-111 DTPA.

nique of deconvolution described in the section on data analysis.

Our applications of this technique to the dog have yielded results consistent with those in the literature for similar compounds studied by invasive techniques or in perfused lung preparations. Several other potential advantages of this noninvasive approach include the following:

1. The measurement of the extraction fraction is relatively independent of pulmonary blood flow.

2. It is less affected by abnormalities in the left cardiac chambers, nonuniform mixing, and choice of sampling site than are techniques using catheter sampling (28).

3. Regional extraction fractions can be calculated.

4. The monitoring of the right heart's time-activity curve makes it possible to eliminate immediately a poor injection from further analysis.

As mentioned previously, the radiopharmaceuticals used in this study were Tc-99m micro SC (vascular), In-111 DTPA (extracellular), and I-123 IMP (amine). They were selected because most of the radiopharmaceuticals that have been used previously for dual-tracer dilution studies are not readily available for human use (including In-113m, $H_2^{15}O$, I-123 antipyrine, and I-123 albumin). Others that have been used for invasive methods in acceptable radiation doses would give unacceptably high radiation doses if given in the millicurie amounts required for accurate external counting. These

include I-131 albumin and Na-22. Tritium or C-14-labeled compounds cannot be measured with external counting. Thus, for one or more reasons, almost every other radiopharmaceutical or chemical used in the investigative laboratory is unacceptable for clinical use. To meet our clinical need for vascular and extracellular tracers, we have looked at radiopharmaceuticals that are currently available and approved by the FDA for other procedures.

Two radiopharmaceuticals, Tc-99m-labeled red blood cells and Tc-99m sulfur colloid, are available as potential vascular tracers. Red blood cells labeled in vitro with Tc-99m are probably the most physiological reference vascular tracer, but red-cell diseases and several drugs such as heparin may prevent satisfactory labeling. In this study we felt that a high level of Tc-99m activity in red blood cells in the heart would also interfere with the accuracy of counting the I-123 IMP bolus.

Technetium-99m micro SC has been used for several years in this clinic for liver and bone-marrow imaging; lung uptake is rarely seen and free Tc-99m is negligible. The particle size is less than 200 mμ. Binding to the pulmonary vasculature, if any, during the first-pass study does not appear to produce a measurable error, although this will require further study. Its rapid clearance from the blood by the liver makes it an ideal radiopharmaceutical when a second emitter of similar energy is to be used subsequently.
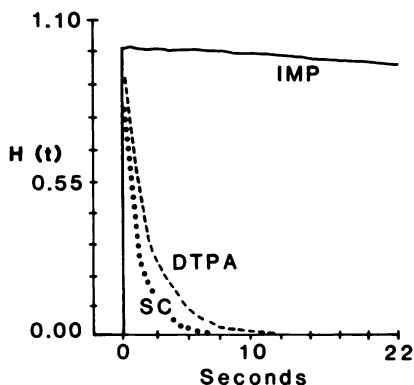
FIG. 4. Pulmonary impulse response functions, H(t), for Tc-99m micro SC, In-111 DTPA, and I-123 IMP. Note prominent retention of I-123 IMP.
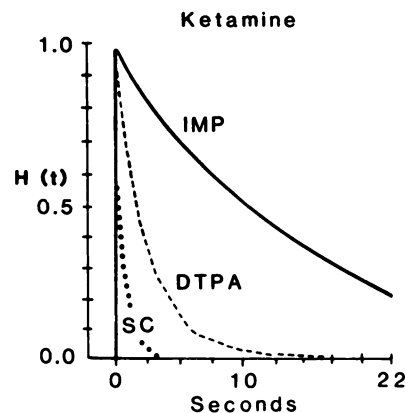
FIG. 5. Pulmonary impulse response functions, H(t), for Tc-99m micro SC, In-111 DTPA, and I-123 IMP following ketamine administration. Ketamine resulted in lower retention of I-123 IMP in lung, but little change in retention of In-111 DTPA.

Technetium-99m DTPA and In-111 DTPA have been widely used as agents to measure extracellular space, and they are commercially available. In the present study, In-111 DTPA was chosen because of its higher-energy peak, which can be measured in the presence of I-123 IMP.

Iodine-123 IMP has recently been investigated as a brain-imaging agent (*11–14*). Incidental to these studies has been the observation of a high lung uptake. Similar findings with carbon-11 chlorpromazine (*9*) have been reported in normal humans, while a much lower lung extraction of C-11 chlorpromazine was seen in patients with chronic obstructive airway disease. It seemed, therefore, to be an appropriate time to investigate I-123 IMP, which has the advantages of a more practical half-life and improved imaging characteristics.

Possible mechanisms of uptake of I-123 IMP by the brain have been discussed by Winchell et al. (*10,11*), who proposed that either the receptor-binding or the lipophilic properties of I-123 IMP could account for uptake by the brain. Similarly, uptake in the lung could result from several different mechanisms.

Studies using perfused, isolated lung preparations with low concentrations of amphetamine and halogenated amphetamines have demonstrated uptake kinetics consistent with the binding of these compounds by a transport system (*29*). Using lung membrane preparations, receptors have been demonstrated for several beta-adrenergic agonists, and it has been suggested that these receptors may be capable of binding a wide range of beta-1 and beta-2 amines (*30,31*). In the present studies, the suppression of extraction by pretreatment with ketamine is consistent with competition for a common amine receptor, since no such reduction of In-111 DTPA uptake was observed after ketamine. Demonstration of competition between I-123 IMP and nonradioactive amphetamine or iodoamphetamine would represent a stronger argument for a receptor mechanism, and these studies are now in progress in our laboratory.

On the other hand, the lipophilic properties of I-123 IMP, which might cause it to be taken up and held by lung lipids, have not been entirely excluded. This mechanism seems less likely, however, since substances with very similar lipophilic properties by the Oldendorf BUI criteria (*32*) have very different uptakes in the lung. [4-^{123}I]antipyrine with a BUI of 130, has a transit curve through the lung that is very similar to our DTPA curves (*20,21*) and that is distinctly different from the curves of high uptake and prolonged retention shown by the lung for I-123 IMP, which has a BUI of approximately 124 (*11*). Hence, although this finding does not provide a detailed mechanism for the observed pulmonary uptake of I-123 IMP, we believe there is evidence to support the position that pulmonary uptake is due to receptor binding of I-123 IMP rather than to its lipophilic properties.

In summary, we have developed a noninvasive modi-fication of the classic dual-tracer dilution technique for measuring lung extraction, using a gamma camera and computer system and compatible radiopharmaceuticals. In a pilot study, the method has been used to quantify the lung uptake of In-111 DTPA and I-123 IMP, with results that are consistent with known physiologic properties of DTPA and other vasoactive amines. This dual-tracer method provides a practical approach to the evaluation of tracer extraction, one that is applicable in a clinical environment.

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