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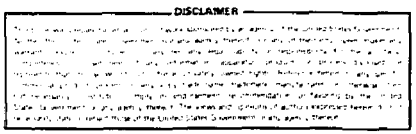

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REGIONAL MYOCARDIAL BLOOD FLOW, METABOLISM AND FUNCTION ASSESSED NONINVASIVELY BY POSITRON EMISSION TOMOGRAPHY

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ABSTRACT

Positron emission computed tomography is a new technique for the noninvasive measure of myocardial blood flow, mechanical function and, in particular, metabolism. The capability of this new study means is due to the technological innovations of the imaging device and the availability of radioactive tracers that are specific for blood flow and metabolism The device permits recording of cross-sectional images of the left ventricular myocardium that reflect quantitatively regional tracer tissue concentrations. By employing tracer kinetic models this new technique permits the measurement of regional glucose and fatty acid metabolism of the heart. While already an important new tool for investigative studies into cardiac physiology and pathophysiology the clinical utility of positron emission tomography remains to be defined.

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Among the techniques that are available for the noninvasive study of the heart, positron computed tomography (PCT) occupies a unique position: not only does it provide a means for the assessment of regional myocardial blood flow and regional mechanical function but also of regional myocardial metabolism. Each segment of cardiac performance can be evaluated either individually or in combination with this new imaging modality which therefore offers the potential for an improved understanding of global and regional myocardial physiology in health and disease. PCT has entered the field of cardiology only very recently. The following discussion intends to provide a basic understanding of the technical aspects of this new device, to describe approaches that are employed for quantitative assessment of cardiac performance and, lastly, to discuss its potential future use and clinical implications.

TECHNICAL CONSIDERATIONS

What accounts for the unique capability of this new imaging modality? There are two primary reasons, one, the technological innovations of PCT, and two, the availability of radioactive labeled tracers that are specific for metabolic pathways. Technically, PCT overcomes many of the limitations of conventional gamma camera or planar imaging[1,2,3]. The distribution of the labeled tracers in organs is displayed in a 3-dimensional fashion and three-dimensional information is no longer compressed into planar images. Spatial resolution is depth-independent, i.e. structures deep in the body are imaged with the same spatial resolution as those close to the surface. Finally, the effect of varying attenuation of photons as they travel through tissue prior to reaching the detector can be removed. In their design, state-of-the-art positron tomographs are similar to the now conventional x-ray transmission (or CAT) scanners[1] and both employ similar algorithms for image reconstruction. However, x-ray tomographs apply external radiation and determine its attenuation across the body whereas in PCT the source of radiation resides

within the body and its emissions are collected for subsequent reconstruction of tomographic images. The former technique produces a cross-sectional image of the interactions of x-rays with tissue as opposed to the latter, PCT, which provides images of the cross-sectional distribution of tracer tissue concentrations.

Positrons are particles with a mass equal to that of electrons but an opposite charge. As they loose their kinetic energy, they interact with an electron and are annihilated. Their mass is converted into two 511 keV photons or x-rays that leave the site of interaction in diametrically opposed directions. The simultaneous emission of the 511 keV x-rays is detected by pairs of opposing scintillation detectors connected by an electronic "coincidence" circuitry (Figure 1). Only interactions in the well defined "field-of-view" between two detector pairs are recorded. This unique electronic collimation forms the basis of the depth independent resolution. Like other photons, the two 511 keV x-rays are attenuated as they travel through tissue, yet the degree of attenuation can easily be measured and, hence, corrected for appropriately. Employing these two principles the distribution of tracers labeled with positron emitting radioisotopes in the body can be determined by collecting data at multiple angles through a 180° arc. At present this is accomplished best by tomographs employing hexaganol, octagonal or circular arrays of detectors[1-3] (Figure 2). From the collected data cross-sectional or tomographic images are reconstructed that display the distribution of radioactive labeled tracers in a quantitative manner, i.e. in terms of mCi per picture element or gram tissue. Therefore, these images resemble autoradiographs that are obtained in vivo or provide an in vivo capabilitity that is analogous to in vitro tissue counting (Figure 3).

Radioactive indicators specific for various metabolic pathways have been mentioned as the second reason for the potential of PCT[1-3]. For example,

the radioactive isotopes of oxygen (^{15}O), carbon (^{11}C) and nitrogen (^{13}N) can be labeled to physiologic compounds without altering their biologic properties. Fluorine-18 also can be used to label chemical analogs of substrates by H or OH replacement. At present, the short physical half time of these isotopes (2 to 110 minutes) limits a more widespread use of PCT because it requires on-site production of isotopes and thus an on-site accelerator. Major efforts are therefore devoted to the development of compact and dedicated cyclotrons that are relatively inexpensive, reliable and can be operated like generator systems by technicians for fully or semi-automated production of labeled compounds. On the other hand, there are significant advantages to the short physical half-time of these isotopes, namely lower radiation doses to the patient and repeat studies at short time intervals.

Keeping in mind the two key elements of PCT, the autoradiographic nature of the images and the availability of physiologic tracers, how can this new imaging modality be utilized for the measurement of regional myocardial metabolism? There are several conditions that must be met before this new modality can be employed as a true and heretofore unknown "physiologic tomography"[4,5]: Rigid characterization of the analytical capabilities of the imaging device for quantification of labeled tracer concentrations in tissue; delineation of the manner in which these tracer mimic a physiologic process; and, finally, physiologic modeling or mathematical formulation of tracer kinetic models so that physiologic variables can be derived from the imaging data.

Research efforts in our laboratory have indeed stressed the study and solution of these conditions in order to develop a truly physiologic tomography. In the discussion below we will closely evaluate each aspect or condition required for physiologic tomography and how it can be applied to study of the three main segments of myocardial performance, i.e. flow, mecha-

nical function and metabolism.

MEASUREMENT OF REGIONAL MYOCARDIAL BLOOD FLOW

Earlier, we emphasized the autoradiograpic nature of the cross-sectional images. In other words, the tomographic images reflect the distribution of tracer tissue concentrations in a quantitative manner and, hence, could be used to measure in-vivo indicator tissue concentrations in terms of mg per gram tissue. However, there are limitations in this capability in that the measured concentrations in structures that are small compared to the image resolution will be underestimated. This partial volume effect was recently demonstrated by Hoffman et al[6] in phantom studies and amounts to the fact that if two objects with equal indicator concentrations but of considerably different volumes were imaged quantitatively, the concentration measured for the smaller object would be artificially low if its size is approximately 2 times less than the image resolution. When applied to the heart with its 0.8 to 2.0 cm thick left ventricular myocardium PCT would underestimate true tissue concentrations by nearly 50%. Nevertheless, by establishing a quantitative relationship between concentration recovery and object size, the loss of concentration recovery can be adequately corrected for if the object size is known. Wisenberg et al[7] in our laboratory have recently demonstrated that this is indeed possible for the heart. In animal experiments regional myocardial tracer tissue concentrations could be measured in-vivo with a high degree of accuracy after the image concentrations were corrected for wall thickness determined post-mortem and/or by echocardiography. By correcting for tissue concentrations in this manner, Wisenberg and et al[7] further confirmed the capability of PCT for the in vivo quantification of regional myocardial blood flow. Employing Ga-68 labeled albumin microspheres injected into the left atrium and the arterial reference technique[8], regional myocardial blood flow was accurately measured in-vivo from ECG gated

cross-sectional images of the left ventricle over a flow range from near zero to 500 ml/min/100gm. The standard error of the estimate over this large flow range was only 12 ml/min/100gm and the slope of the regression line between the in vivo and in vitro measurements was near unity (0.99).

While particulate indicators such as radioactive microspheres are most accurate for blood flow measurements their use in man is limited for obvious reasons. In the search for a diffusible flow indicator that can be administered intravenously we have extensively studied N-13 ammonia, an agent initially used as a myocardial imaging agent[9-11]. Administered intravenously, N-13 ammonia distributes in proportion to blood flow and rapidly and almost completely clears from blood into myocardium where it is trapped sufficiently long to permit quantitative imaging[11-13]. With these properties N-13 ammonia resembles to some degree a particulate indicator. At control flow (80 ml/min/100 gm) the extraction of N-13 ammonia during a single capillary transit approaches 90%[10] but decreases as flow increases[13]. Within the range of physiologically encountered flows (e.g. from near zero to 300ml/min/100gm) myocardial tissue concentrations are related to myocardial blood flow almost linearly (Figure 4). Except for extreme changes in arterial plasma pH levels, trapping of N-13 ammonia in myocardium remains unaffected by alterations in the metabolic and functional state of the heart(unpublished data). There is evidence that because of the rapid trapping and fixation in myocardium and the fast clearance from blood (blood N-13 ammonia levels are less than 2% of peak activity within 5 minutes of injection) noninvasive quantification of regional myocardial blood flow with this agent may be possible[14].

The suitability of this new agent for the assessment of regional myocardial blood flow with PCT has been demonstrated in the experimental animal[13,15] and, more recently, in man[16]. We have further shown the potential of N-13 ammonia and PCT for the detection of mild coronary artery

stenoses. At rest, even moderately severe coronary stenoses may not alter coronary blood flow yet limit coronary flow reserve. More importantly, coronary flow reserve can be reduced by even very mild stenoses, a phenomenon that can be demonstrated during maximum coronary vasodilatation[17,18]. Employing this principle in chronically instrumented animals we were able to detect less than 50% diameter coronary stenoses with N-13 ammonia and PCT during pharmacologically induced vasodilatation[15]. These findings are currently being tested in man (Figure 5). Our results in 10 normal volunteers and 29 patients with coronary artery disease appear to confirm our initial animal experimental findings and indicate that coronary stenoses as low as 40% diameter narrowing can indeed be identified[16].

ASSESSMENT OF REGIONAL MYOCARDIAL FUNCTION

Regional myocardial function traditionally has been determined from the extent and time course of regional systolic wall motion and thickening. These parameters conventionally are derived by contrast cineventriculography, echocardiography or gated blood pool imaging. Similar to ECG gated blood pool imaging the positron emission tomograph can be synchronized with the patients ECG and gated cross-sectional images obtained either at end-diastole and end-systole or as a sequence of images throughout the entire cardiac cycle[19].

From the gated cross-sectional images of the left ventricular myocardium or the cardiac blood pools - visualized after inhalation of small amounts of C-11 carbon monoxide that binds to hemoglobin and is an excellent blood pool imaging agent - quantification of left ventricular wall motion and measurement of global left ventricular function will become possible in the near future. Moreover, it appears that regional wall thickening as a highly sensitive index of regional function can be determined from gated cross-sectional images of the left ventricular myocardium. We mentioned earlier the difficulties in concentration recovery related to object size. While this dependency compli-

cates the quantification of tissue concentrations it actually can be utilized for the measurement of systolic wall thickening. As shown recently in our laboratory, the counts recovered from a given myocardial segment and expressed in counts/min/gram tissue increase from end-diastole to end-systole[7]. The increase is proportional to the degree of wall thickening as measured by echocardiography. If applied to man, regional myocardial blood flow measurements can be combined with determinations of regional mechanical function and both measurements easily be correlated. It would also seem feasible to expand this concept for comparing regional myocardial function with metabolism provided the myocardium is visualized with a metabolic tracer.

ASSESSMENT OF REGIONAL MYOCARDIAL METABOLISM

In the past numerous techniques have been developed and successfully employed for evaluating either invasively or non-invasively regional myocardial blood flow and function. However, the in-vivo study of regional myocardial metabolism thus far has remained unsatisfactory. As we will see, it is in this area where PCT shows the greatest promise and where its most unique potential lies.

This capability is due in part to the quantitative capabilities of the imaging device and to the availability of radiopharmaceuticals that are highly specific indicators of metabolic pathways. We have discussed earlier the numerous isotopes that can be labeled to naturally occuring compounds without altering their biologic behavior. Among these, oxygen-15, carbon-11, nitrogen-13 and fuorine-18 have been employed most frequently in the past. While at first glance it would seem logical to label metabolic substrates with one of these isotopes, the difficulties encountered with this approach may be illustrated by the example of labeled glucose. Glucose as a primary energy substrate can be tagged with carbon-11 but its chemical state in myocardium at any time after intravenous administration remains unknown to the PCT. The

measured C-11 tissue concentrations represent a complex distribution of compounds that changes with time. Further, its rapid turnover rate in myocardium poses some limitations for obtaining high contrast cross-sectional images.

It thus would seem preferable to employ radioactive tracers that are not only specific for a given metabolic pathway but are also retained in myocardium sufficiently long to permit adequate external imaging and trace a metabolic process in a known and well defined manner, that is amenable to physiologic modeling[4,5]. Past research has therefore focused on two radiopharmaceuticals - Carbon-11 palmitate and Fluorine-18 deoxyglucose - both of which appear to largely fulfill the requirements of physiologic tomography. Moreover, they seem particularly intriguing for the study of the heart since the role of glucose and free fatty acids as the primary energy substrates of the heart has been well-established.

Carbon-11 palmitate has been described as a myocardial imaging agent suitable for PCT[20,21] and more recently been employed for sizing myocardial infarction in man[22]. Beyond the use for simple myocardial imaging this agent may eventually prove useful for assessing fatty acid metabolism of the heart. Because the carbon-11 label does not alter the biologic behavior of palmitate, the total uptake in myocardium or its turnover rates should in theory provide a measure of the rate of fatty acid metabolism. This in fact appears confirmed by Goldstein et al[23] and Klein et al who observed[25] in the isolated perfused rat heart an inverse relationship between myocardial half-times of C-11 palmitate and cardiac work. Further, its half-time was markedly prolonged under ischemic conditions[21]. While these results are encouraging their application to the in-vivo situation with indicator recirculation and flow dependency of indicator delivery and washout is highly complex and awaits further clarification.

Moreover, the intracellular kinetics of free fatty acids and hence of C-

11 palmitate are highly complex and exemplify the difficulties encountered for in-vivo measurements of regional myocardial metabolic rates. Upon entering the myocardial cell, free fatty acids are either channeled directly into beta-oxidative pathways, incorporated into phospholipids or stored in form of triglycerides. It appears that the major fraction of fatty acids is initially converted to and stored in form of triglycerides. External measurements of myocardial C-11 palmitate uptake would therefore not strictly reflect the rate of fatty acid utilization. Conversely, myocardial half-times of C-11 activity would indicate primarily the rate at which triclycerides are hydrolyzed. The rate of fatty acid utilization thus could be deducted only by inference, provided that all of the hydrolyzed fatty acids enter beta-oxidation without any loss into the blood. Accurate measurements of fatty acid utilization are therefore possible only if a) the various segments of the fatty acid metabolism can be identified and delineated; or b) when measuring total myocardial uptake, if the ratio of fatty acids entering beta-oxidation to fatty acids converted to triglycerides is constant; or finally, c) when measuring of myocardial half-times, if the rate with which fatty acids are oxidized is in constant proportion to the rate of triglyceride hydrolysis.

It is conceivable that the complex kinetics of natural compounds cannot be defined sufficiently to permit accurate measurements of myocardial metabolic rates and that substrate analogs must be developed that trace only one segment of a metabolic pathway, yet can be better delineated, their kinetics expressed in form of a physiologic model and formulated in mathematical terms.

Radioactive labeled 2-deoxy-glucose has become available as such a substrate analog for the measurement of regional glucose utilization rates. Sokoloff and associates[25] labeled this agent with C-14 and originated a physiologic model that permitted measurement of local cerebral glucose utilization in vitro. To adopt this technique for in-vivo PCT measurements the 2-

hydroxy group was substituted by a fluorine-18 atom to yield fluorine-18 2-fluoro-2-deoxyglucose (FDG)[26,27]. Further, the original physiologic model was modified in our laboratory by Huang et al[28] and measurements of regional cerebral glucose metabolism[30-32] by this technique validated by Phelps et al[29]. Once administered intravenously, exchange of FDG across capillary and cell membranes as well as initial metabolization is similar and in proportion to glucose. Like glucose, it is phosphorylated by hexokinase to FDG-6-PO_4 but then becomes metabolically trapped and is not a substrate for glycolysis, glycogen formation or the pentose shunt. Metabolically unbound FDG subsequently clears from myocardium and PCT images obtained at equilibrium reflect the regional utilization rates of exogenous glucose.

The kinetics of FDG can be expressed by a three-compartmental tracer kinetic model with exchange between compartments that follows first order kinetics [28,29]. This is shown schematically in Figure 6, where the k_1* and k_2* are the rate constants for forward and reverse transport across the capillary membrane and k_3* and k_4* the rate constants for phosphorylation and dephosphorylation between FDG and FDG-6-PO_4. Our initial findings suggest that the rate constants of FDG in myocardium are of similar magnitude as those in the brain[30]. Once established they will be incorporated together with the physiologic model into the tomograph's systems program[30-32] so that regional myocardial utilization rates can be determined routinely and almost entirely by trained nuclear medicine technicians. For this measurement, FDG is administered intravenously and venous blood sampled serially. After forty to fifty minutes, when near steady state conditions are reached, cross-sectional imaging is performed, plasma glucose and FDG levels obtained and entered into the tomograph's systems computer; regional myocardial glucose utilization rates are then calculated automatically from selected regions of interest[31]. The accuracy of these measurements has been documented for the

brain, but awaits validation for the heart. Nevertheless, our initial experience has been encouraging. Regional glucose utilization rates calculated by this noninvasive approach ranged from 5 to 20 mg glucose/min/100gm and thus are in close agreement with data derived invasively in our laboratory in experimental animals using the Fick method (unpublished data).

CLINICAL CONSIDERATIONS

Thus far, we have discussed the technical aspects of PCT and its potential as a new means for the non-invasive study of regional myocardial blood flow, mechanical function and regional metabolism. Considering the complexities, effort and cost involved, the question as to whether this new study means will be clinically feasible and cost effective seems appropriate. Our initial clinical experience with this new tool in patients with cerebral disease is very encouraging and suggests that metabolic abnormalities of the brain detected by physiologic tomography provide an improved understanding of cerebral function and has a higher correlation to the clinical symptomatology than the structural or anatomical alterations discovered by CAT scanning[34]. To what degree this will apply to the heart is at present uncertain and will have to be answered in the near future.

Nevertheless, physiologic tomography offers a unique and heretofore unknown potential for the study of regional myocardial physiology and pathophysiology. We have mentioned earlier our initial observations on the detection of coronary artery stenoses in the experimental animal[16] and in man[17]. In these studies, detection of single vessel disease in man was highly accurate and appeared superior to conventional imaging. Stenoses with as little as 40% diameter narrowing by coronary arteriography were correctly identified yet in patients with triple vessel disease, the techique failed to detect in about half the patients the least severe stenosis. At present, image analysis in these studies is qualitative and the segment supplied by the

least severely stenosed coronary artery serves as reference. However, if the response to pharmocologic coronary vasodilatation is highly reproducible and consistent from patient to patient than the absolute increase in segmental myocardial blood flow should be a more superior index for the presence and severity of a coronary stenosis. Quantification of regional myocardial blood flow appears possible by measuring the arterial input function and the regional myocardial concentrations of N-13 ammonia obtainable by PCT.

As another example, this new study technique may permit for the first time characterization of the local metabolic alterations assosciated with acute myocardial ischemia. In a preliminary series of animal experiments[33] we applied a graded stenosis to the left anterior descending coronary artery and induced ischemia by pacing at high rates. Myocardial perfusion assessed with N-13 ammonia and PCT was reduced in the ischemic segment. FDG concentrations as an index of regional glucose utilization similarly were decreased in the ischemic segment, yet disproportionately less than the reduction in flow (Figure 7). Quantitative correlation between perfusion and the glucose uptake on the cross-sectional images demonstrated in the ischemic segments glucose uptake in excess of flow. If blood flow closely reflects the oxygen availability (i.e. if oxygen extraction does not significantly increase at low flows) then these observations suggest that in the ischemic segment energy is primarily derived from glucose either by residual oxidative capacity and/or anaerobic glycolysis. This is in agreement with earlier findings obtained in acute and destructive animal experiments[35]. Should this approach be applicable to man it then may become possible to identify ischemic myocardium, characterize its metabolic state, the degree of viability, and to assess the benefits of interventions designed to salvage injured myocardium. Since the severity of ischemia not only depends upon blood flow but also on the mechanical demand as well as on the duration of the insult - all of which are at

present difficult if not impossible to assess - physiologic tomography may indeed provide the most accurate means for estimating the severity of ischemia.

SUMMARY

The examples described above were intended to illustrate the potential of physiologic tomography and to describe the type of information that can be obtained with this new means for studying cardiac performance. It is conceivable that such data may prove to clinically useful and relevant. Nevertheless, and as mentioned earlier, the utility and ultimate role of this new imaging modality in health care delivery is difficult to assess at present and needs to be defined in the future. It would seem to us however that the current improvement in instrumentation and the development of compact, reliable and generator like cyclotrons will largely facilitate the use of physiologic tomography and make it attractive and accessible to a larger number of users. There can be however little doubt that physiologic tomography represents an important new tool for investigative studies to improve our understanding of cardiac physiology and disease. The quantitative aspects as well as simultaneous evaluation of more than one segment of myocardial performance, e.g. simultaneous study of mechanical function, blood flow and metabolism and their interdependency will provide a new and better understanding of myocardial physiology. Since many of the cardiovascular disorders originate at the cellular or metabolic level it is hoped that this technique may serve as a means for the early detection of cardiac disease, perhaps at a stage when it is still amenable to therapy.

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LEGENDS

Figure 1: Schematic representation of annihilation coincidence detection as the basis of PCT. As the positron interacts with an electron, their mass is converted into two 511 keV gamma rays which leave the site of interaction in diametrically opposed directions. The simultaneous emission of the 511 keV gamma rays is detected by a pair of opposing scintillation detectors in coincidence. Interactions only within the field of coincidence detection are recorded. Further, attenuation of the gamma rays by tissue is a function of the path length a and b and the attenuation coefficient (see text).

Figure 2: Whole body positron emission tomograph installed at the Nuclear Medicine Clinic at UCLA.

Figure 3: Typical cross-sectional images of the left ventricular myocardium obtained after intravenous N-13 ammonia. The cross-sections are spaced about one cm apart (ANT = anterior; LAT = lateral; and POST = posterior wall of the left ventricle; SEPTUM = interventricular septum). Levels 1 to 3 shows the high anterior wall, level 4 the mid left ventricle and levels 5 and 6 the lower and diaphragmatic portions of the left ventricle.

Figure 4: Relationship between myocardial N-13 ammonia tissue concentrations and myocardial blood flow measured in vitro by the microsphere technique and in vivo by PCT. The solid line represents the curve fit for N-13 ammonia concentrations measured in-vitro, the broken line the curve fit for N-13 ammonia concentrations measured in vivo by PCT. Note the near linear relationship over the flow range from 0 to 300 ml/min/100gm. Further, both curves are virtually identical except for the upward shift of the in vivo curve which is due to instru-

ment related background scatter and random coincidence (Schelbert, et al; Am. J. Cardiol. 43:209, 1979).

Figure 5: Cross-sectional myocardial perfusion images obtained with N-13 ammonia at control and during dipyridamole induced coronary vasodilatation. Only the high to mid anterior wall is shown (1 and 2). At control the images are normal, however during hyperemia, a defect is noted in the anterior wall (arrows) corresponding to a stenosis of the left anterior descending coronary artery.

Figure 6: Three compartmental tracer kinetic model for the kinetics of FDG (see text).

Figure 7: Cross-sectional images obtained in a dog during pacing induced ischemia of the anterior wall. Note the extensive perfusion defect on the perfusion images (arrows); a defect is also present on the glucose uptake images, but is considerably less pronounced and suggest glucose utilization in excess of blood flow (see text).