IMAGING TECHNIQUES

Positron emission tomography and myocardial imaging

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Imaging with positron emission tomography (PET) offers unrivalled sensitivity and specificity for research into biochemical pathways and pharmacological mechanisms in vivo. Cardiac and neurological research with PET has flourished over the past 20 years, but it is only more recently that cardiology has begun to benefit from the advantages provided by PET. From the physical point of view, scanning of the heart presents a challenge because of greater complications in correcting for photon attenuation and scattered radiation, and because of movement of the heart and lungs.

Methodological background

The success of PET is based on the properties of the isotopes used (table 1). Their short physical half lives make it possible to administer a tracer dose high enough to obtain useful data, but such that the radiation burden to the patient is acceptably low. Positron emitters do not exist in nature and they must be produced artificially by means of a particle accelerator (generally a cyclotron).[1] Production of isotopes with the shortest half lives has to be carried out in the vicinity of the scanner and necessitates the installation of cyclotron and radiochemistry facilities. However, ^{18}F compounds can be delivered from a relatively remote site of production. The commercial success of PET has been driven by ^{18}F labelled fluorodeoxyglucose (FDG) which is used to measure glucose metabolism in tissues. Because of the longer half life of ^{18}F (table 1), many centres rely on production from a centralised cyclotron, thus avoiding the expense of individual facilities. However, research centres aiming to derive most from the power of PET require on site production of a range of tracers.

Unique features of PET

- Positron annihilation/coincidence detection
- Short physical half life/lower radiation dose to patients
- Attenuation correction
- Correction for partial volume effect
- Capability of making absolute measurements of tracer concentration
- Multiple physiological tracers

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Table 1 Properties of isotopes used in PET imaging

Isotope	Half life (min)	Positron energy (MeV)		Mean range in tissue (mm)	Examples of labelled compounds
		Mean	Maximum		
^{15}O	2.03	0.74	1.74	2.97	$H_2{}^{15}O$— blood flow $^{15}O_2$—oxygen consumption $C^{15}O$—blood volume
^{13}N	10.0	0.49	1.20	1.73	$^{13}NH_3$—blood flow
^{11}C	20.4	0.39	0.97	1.23	^{11}C-HED—presynaptic catecholamine reuptake (uptake 1) ^{11}C-CGP 12177—β adrenoceptors ^{11}C-MQNB—muscarinic receptors ^{11}C-acetate—oxygen consumption
^{18}F	109.8	0.25	0.64	0.61	^{18}F-FDG—glucose metabolism ^{18}F-FDopa—dopamine storage

Positron emission and detection

Positrons are emitted with a continuous range of energies up to a maximum, which is characteristic of each particular isotope (table 1). The positron is successively slowed down by Coulomb interaction with atomic electrons and "annihilates" with an electron when its energy has been reduced close to zero, resulting in a pair of photons flying off in opposite directions with an energy of 511 keV. Positrons emitted from a tracer injected into the body are not measured directly, but indirectly from the photons emitted when the positron annihilates with an electron (fig 1). Detectors placed on either side of the active volume are connected in a so called coincidence circuit so that if both detectors record an event within a very short interval (about 10^{-8} seconds), it is assumed that a positron annihilation has taken place.

Attenuation correction: a main feature of PET

The distance between the emitting atom and the point of annihilation depends on positron energy (table 1). This distance, together with the photon angular spread, "blur" the true tracer distribution slightly and, depending on the type of PET detector and the radioisotope used, can lower the resolution by 1–3 mm. This small loss of resolution, however, is relatively minor compared to the consequences of photon scattering. Photons of 511 keV travelling through a composite medium such as the thorax will be scattered by interaction with atomic electrons and undergo change of direction and loss of energy. If a photon is scattered it is "lost" to the original line of response (the

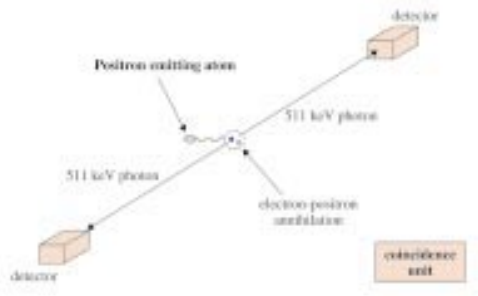

Figure 1: Physics of positron emission, annihilation, and coincidence detection. Adapted from Camici *et al*.[2]

line joining the two detectors depicted in fig 1), and the apparent radioactivity measured along that line of response will be reduced. This effect is known as "attenuation". Scatter and attenuation are problems common to all sorts of radionuclide imaging techniques and are responsible for most of the artifacts associated with single photon emission computed tomography (SPECT), particularly when low energy isotopes (for example, thallium-201) are used. In contrast to SPECT, correction for attenuation is relatively straightforward in PET because of the mechanism of coincidence detection. A radioactive source is placed in the detector field of view and measurements are taken with and without the inactive patient in position. The ratio of counts recorded for the two situations gives the total attenuation factor.[2]

Partial volume effect

The partial volume effect occurs whenever the dimensions of the object to be imaged are comparable to the resolution of the camera. Although the detector will accurately record the total activity in the object, it will distribute it over an area larger than the actual size of the object. Hence, the detected concentration of activity per unit volume will be less than the actual value. In PET (or SPECT) imaging, quantification of radionuclide concentration is complicated by partial volume effects caused by the small thickness of the ventricular wall relative to the spatial resolution of the cameras and the motion of the heart. In addition, because of the changes in wall thickness throughout the cardiac cycle, the recovery coefficient (the radioactivity concentration recorded relative to the actual concentration) will vary. The partial volume effect is therefore particularly important in patients with coronary artery disease who have regional motion abnormalities and thinning of the left ventricular walls.[3] A number of strategies have been developed to correct for it.

Tomographs and data acquisition

The earliest tomographs consisted of a single ring of detectors with thick lead shielding on either side to stop photons arising from outside the plane of the ring (which can only yield random or scattered coincidences). Most PET scanners consist of bismuth germanate detectors. The 511 keV photons have a high probability of being stopped by this high density material and then giving up their energy. This energy is transformed into visible light (scintillation) which is amplified by a photomultiplier tube, just as in a conventional nuclear medicine gamma camera. Data acquisition in such systems is organised as a series of planes or slices through the patient. A detector can also be in coincidence with detectors in other rings of a multi-ring scanner. Conventionally, the raw data are formatted into matrices known as sinograms, each element of which contains the number of events ("counts") recorded in each line of response. Each row of the sinogram represents a one dimensional view (or projection) of the patient at a given angle and the sinogram encompasses all angles around the patient. The standard process of image reconstruction extrapolates or back-projects the projection data into the "image space" (field of view) of the tomograph, as well as applying a spatial frequency filter to remove blurring.[1 2]

Most PET scanners operate in frame mode where a number of (usually) contiguous time frames are defined before acquisition commences. Frame lengths are chosen to try to accommodate the varying kinetic components at different times after injection. However, especially with rapidly decaying tracers (such as ^{15}O and ^{11}C), it is more efficient to store each event separately in list mode. List mode acquisition offers data of the highest possible temporal resolution which can be: (1) subsequently rebinned into different frame sequences, as desired, for image reconstruction; and (2) partitioned into different gates on the basis of cardiac and respiratory signals to reduce motion artifacts caused by cardiac and respiratory movement.

Positron labelled tracers

A tracer is a measurable substance used to mimic, follow or trace a chemical compound or process without disturbing the process under study. In the case of PET this is made possible by: (1) the high sensitivity of PET imaging which enables the measurement of radiolabelled tracers administered in picomolar concentrations which are sufficiently low so as not to disturb the processes under study; and (2) the ability of current cameras to perform rapid dynamic imaging—that is, to provide good temporal resolution. Positron emitting radionuclides are incorporated into tracers by rapid radiochemical procedures. These can be administered to subjects either by intravenous injection or by inhalation. The tracer substitutes for the natural or endogenous substrate and gives information on the cellular pathway that would have been followed by that substrate.

From counts to physiological parameters

After administration of a known amount of the tracer, its myocardial and arterial concentrations can be measured as a function of time using the PET camera. Measurement of the radiotracer concentration in arterial blood can be made from regions of interest positioned in either the left atrium or ventricle and provide information on the supply of tracer to the myocardium over the time course of the PET study. This measurement is termed the "arterial input function". The myocardial uptake of the tracer over time is termed the "tissue response" and can also be determined from analysis of the PET images. The tissue response to an arterial input function can be quantified using a tracer kinetic model, which describes the dynamic biological behaviour of the tracer in tissue in mathematical terms. These kinetic models are based upon careful validation in animal studies utilising both in vitro and in vivo models. The application of these models to the raw data allows transformation of the initial radioactivity

Cardiac applications of PET

- Myocardial blood flow
- Free fatty acid, glucose, and oxygen metabolism
- Identification of hibernating myocardium
- Cardiac autonomic function:
  - –postsynaptic β adrenoceptors
  - –presynaptic nerve terminals
  - –cholinergic receptors

measurements (counts) into absolute units (for example, myocardial blood flow in ml/minute per gram of tissue). This ability to provide accurate measurements per unit mass of tissue is a major advantage of PET imaging.

Applications of PET to cardiology

There has been much discussion about the dual roles of "research" and "clinical" PET. A number of centres have installed PET systems purely for clinical diagnosis, mainly in the determination of myocardial viability, but also for applications in oncology and neurology. Diagnostic testing of this kind is clearly derived from original work carried out at research establishments. The terms "research" and "clinical" should, therefore, be regarded as complementary. In the author's institution the balance between research and diagnosis is approximately 80% versus 20%.

Myocardial blood flow

Oxygen-15 labelled water ($H_2{}^{15}O$) and nitrogen-13 labelled ammonia ($^{13}NH_3$) are the tracers most widely used for the quantification of regional myocardial blood flow with PET. Tracer kinetic models have been successfully validated in animals against the radiolabelled microsphere method over a wide flow range for both $H_2{}^{15}O$ and $^{13}NH_3$.[4] Assessments of myocardial blood flow in normal volunteers using either tracer at rest or during pharmacologically induced coronary vasodilatation are similar (table 2).[5] $H_2{}^{15}O$ is theoretically superior to $^{13}NH_3$ in that water is a metabolically inert and freely diffusible tracer which has a virtually complete myocardial extraction independent of both flow rate and myocardial metabolic state.[4] On the other hand, the quality of myocardial $^{13}NH_3$ images is superior to that of $H_2{}^{15}O$. Both tracers have short physical half lives (table 1) which allow repeat measurements of myocardial blood flow in the same session.

Before the advent of PET technology, investigations of regional coronary blood flow in man were restricted to measurements in the epicardial coronary arteries. However, it is well established that the major regulatory site of tissue perfusion is at the level of the microcirculation which is not amenable to catheterisation.[4] With the development of quantitative myocardial blood flow measurement using PET, it is possible to challenge the function of the coronary microvasculature by measuring the coronary vasodilator reserve (CVR), calculated as the ratio of near maximal flow during pharmacologically induced coronary vasodilatation to baseline flow. PET studies in healthy human volunteers have established that CVR in response to intravenous dipyridamole or adenosine is 3.5–4.0 (fig 2A) (table 2).[5] These data are similar to those reported using the Doppler catheter technique for measuring epicardial coronary flow velocity.[4]

Use of PET in normal volunteers has highlighted the effects of age, sex, and alteration in sympathetic tone on myocardial blood flow and CVR. Thus, it has been shown that myocardial blood flow at baseline and at hyperaemia remains relatively constant up to 60 years of age. Above this age, there is a significant increase in basal flow associated with an increase in systolic blood pressure and a significant reduction in hyperaemic myocardial blood flow and CVR.[6]

The measurement of CVR is useful for the assessment of the functional significance of coronary stenoses in patients with coronary artery disease (fig 3).[7] In addition, PET is particularly helpful in those circumstances where the CVR is diffusely (and not regionally) blunted, for example, hypertrophic cardiomyopathy or hypertensive heart disease caused by a widespread abnormality of the coronary microcirculation (fig 2B, C).[8] It may aid in the differentiation of pathological from physiological left ventricular hypertrophy and in the exclusion of myocardial ischaemia in patients with chest pain and angiographically normal

Table 2 PET measurements of myocardial blood flow in normal subjects

Author	*Tracer*	*Agent*	*Number subjects*	*Age*	MBF_{bas}	MBF_{hyp}	$MBF_{hyp/bas}$
Bergmann *et al*	$H_2{}^{15}O$	Dip	11	25	0.9 (0.2)	3.6 (1.2)	4.1 (1.2)
Geltman *et al*	$H_2{}^{15}O$	Dip	16	25 (4)	1.2 (0.3)	4.6 (1.6)	3.8 (1.1)
Camici *et al*	$^{13}NH_3$	Dip	12	51 (8)	1.0 (0.2)	2.7 (0.9)	2.9 (1.0)
Sambuceti *et al*	$^{13}NH_3$	Dip	14	49 (7)	1.1 (0.3	3.7 (0.8	3.6 (0.9
Chan *et al*	$^{13}NH_3$	Ado	20	35 (16)	1.1 (0.2)	4.4 (0.9)	4.4 (1.5)
Chan *et al*	$^{13}NH_3$	Dip	20	35 (16)	1.1 (0.2)	4.3 (1.3)	4.3 (1.9)
Araujo *et al*	$C^{15}O_2$	Dip	11	26 to 42	0.8 (0.1)	3.5 (1.1)	4.2 (1.2)
Merlet *et al*	$H_2{}^{15}O$	Dip	6	51 (5)	0.9 (0.1)	3.5 (0.8)	4.0 (0.7)
Muzik *et al*	$^{13}NH_3$	Ado	6	26 (3)	0.8 (0.2)	3.6 (1.0)	
Uren *et al*	$H_2{}^{15}O$	Dip/Ado	43	47 (20	1.0 (0.2)	3.2 (1.3)	3.4 (1.3)
Radvan *et al*	$C^{15}O_2$	Dip	8	27 (5)	0.8 (0.2)	3.1 (08)	3.8 (0.8)
Czernin *et al*	$^{13}NH_3$	Dip	18	31 (9)	0.8 (0.2)	3.0 (0.8)	4.1 (0.9)
Czernin *et al*	$^{13}NH_3$	Dip	22	64 (9)	0.9 (0.3)	2.7 (0.6)	3.0 (0.7)

Ado, adenosine; Dip, dipyridamole; MBF_{bas}, baseline myocardial blood flow; MBF_{hyp}, hyperaemic myocardial blood flow; $MBF_{hyp/bas}$, coronary flow reserve. Data are mean (SD). Adapted from Camici *et al*.[5]

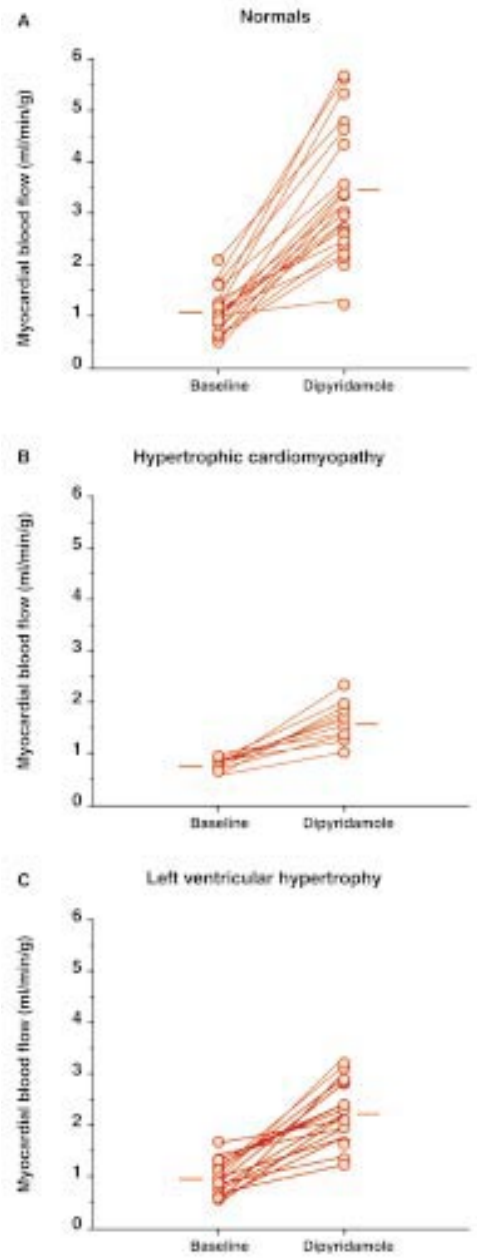

Figure 2: Myocardial blood flow under baseline conditions and during hyperaemia induced by intravenous dipyridamole in normal subjects (A), in patients with hypertrophic cardiomyopathy (B), and patients with left ventricular hypertrophy secondary to arterial hypertension or aortic stenosis (C). The diffuse blunting of flow reserve in these patients with angiographically normal coronary arteries is suggestive of widespread microvascular dysfunction. Adapted from Choudhury *et al*.[8]

coronary arteries.[4 5] Finally, the improved spatial resolution of the latest generation of PET cameras means that there is now a realistic prospect of quantification of transmural distribution of myocardial blood flow.

Myocardial metabolism

The utilisation of exogenous glucose by the myocardium can be assessed using PET with the glucose analogue FDG.[1] FDG is transported into the myocyte by the same transsarcolemmal carrier as glucose and is then

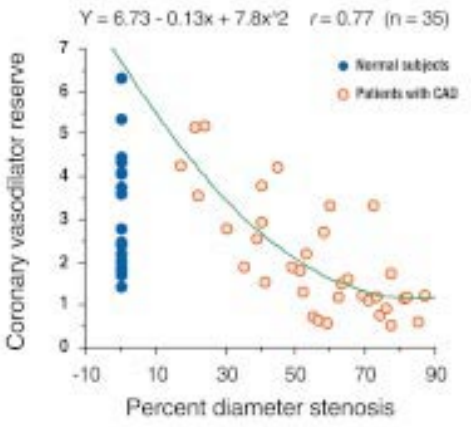

Figure 3: Coronary vasodilator reserve falls with increasing percent diameter stenosis and is exhausted for stenoses > 80%. Normal control values of coronary vasodilator reserve are shown at zero percent diameter stenosis on the left. CAD, coronary artery disease. Adapted from Uren *et al*.[7]

phosphorylated to FDG-6-phosphate by the enzyme hexokinase. This is essentially a unidirectional reaction and results in FDG-6-phosphate accumulation within the myocardium, as no glucose-6-phosphatase (the enzyme that hydrolyses FDG-6-phosphate back to free FDG and free phosphate) has yet been identified in cardiac muscle. Thus, measurement of the myocardial uptake of FDG is proportional to the overall rate of transsarcolemmal transport and hexokinase phosphorylation of exogenous (circulating) glucose by heart muscle.

A number of kinetic modelling approaches have been used for the quantitation of glucose utilisation rates using FDG.[1] The major limitation of these approaches is that quantification of glucose metabolism requires the knowledge of the lumped constant, a factor which relates the kinetic behaviour of FDG to naturally occurring glucose in terms of the relative affinity of each molecule for the trans-sarcolemmal transporter and for hexokinase. Unfortunately, the value of the lumped constant in humans under different physiological and pathophysiological conditions is not known, thus making precise in vivo quantification of myocardial metabolic rates of glucose practically impossible. Current measurements of the uptake of FDG (particularly if obtained under standardised conditions) allow comparison of absolute values from different individuals and may help to establish the absolute rates of glucose utilisation (in FDG units) in normal and pathologic myocardium.[9]

PET for the identification of hibernating myocardium

In the current era of coronary revascularisation and thrombolysis, it has become increasingly apparent that restoration of blood flow to asynergic myocardial segments may result in improved regional and global left ventricular function.[9–11] The greatest clinical benefit is seen in those patients with the most severe forms of dysfunction. Initial studies indicated that myocardial ischaemia and infarction could be

distinguished by analysis of PET images of the perfusion tracer $^{13}NH_3$ and the glucose analogue FDG acquired after an oral glucose load. Regions which showed a concordant reduction in both myocardial blood flow and FDG uptake ("flow-metabolism match") were labelled as predominantly infarcted, whereas regions in which FDG uptake was relatively preserved or increased despite having a perfusion defect ("flow-metabolism mismatch") were considered to represent jeopardised viable myocardium.[12] The uptake of FDG by the myocardium, however, depends on many factors such as dietary state, cardiac workload, response of the tissue to insulin, sympathetic drive, and the presence and severity of ischaemia. These factors contribute to variability in FDG imaging in the fasted or glucose loaded state, confusing data interpretation

With the recent suggestion that semiquantitative and quantitative analyses of FDG uptake may enhance detection of viable myocardium, there was an urgent need to standardise the study conditions rigorously. Furthermore, many patients with coronary artery disease are insulin resistant—that is, the amount of endogenous insulin released after feeding will not induce maximal stimulation owing to partial resistance to the action of the hormone. This may result in poor FDG image quality after an oral glucose load. To circumvent the problem of insulin resistance, an alternative protocol has been recently applied to PET viability studies. The protocol is based on the use of the hyperinsulinaemic euglycaemic clamp—essentially the simultaneous infusion of insulin and glucose acting on the tissue as a "metabolic challenge" and stimulating maximal FDG uptake.[9] This leads to optimisation of image quality and enables PET studies to be performed under standardised metabolic conditions, which allows comparison of the absolute values of the metabolic rate of glucose (μmol/g/min) among different subjects and centres (fig 4).

By comparing FDG images obtained under these conditions with regional wall motion information (derived from echocardiography or conventional radionuclide ventriculography), the need for a simultaneous flow scan is obviated. It is also possible to reduce the period of image acquisition to approximately 30 minutes, giving a total scan time of about an hour.

When to use PET for the identification of hibernation

Basically, three techniques are used to assess myocardial hibernation: dobutamine echocardiography, SPECT with thallium-201, and PET with FDG. These methods probe different aspects of myocyte viability, namely the presence of inotropic contractile reserve, sarcolemmal integrity, and preserved uptake of exogenous glucose, respectively. In patients with normal or moderate impairment of left ventricular function, their predictive value for the identification of hibernating myocardium appears to be similar (positive predictive value 69–83%, negative predictive value 81–90%).[11] Dobutamine stress echocardiography is the least expensive and most widely available technique for the detection of hibernating myocardium. Although it has good predictive accuracy in patients with mild to moderate left ventricular dysfunction, there is evidence that in patients with pronounced left ventricular dysfunction it has a higher false negative rate than nuclear techniques. In particular, PET is regarded as the method with the greatest predictive value in patients with heart failure and very poor ejection fraction.[13] Using PET with FDG during hyperinsulinaemic euglycaemic clamp, we have shown that a threshold value for the metabolic rate of glucose of 0.25 μmol/g/min allowed the best prediction of improvement in functional class of at least one grade after revascularisation.[14]

PET for the investigation of the autonomic nervous system

Several β blocker drugs have been labelled with carbon-11 to act as radioligands for imaging by PET.[1] The most promising of these is CGP 12177. This is a non-selective β adrenoceptor antagonist which is particularly suited for PET studies because of its high affinity and low lipophilicity, thus enabling the functional receptor pool on the cell surface to be studied. A graphical method for quantification of β

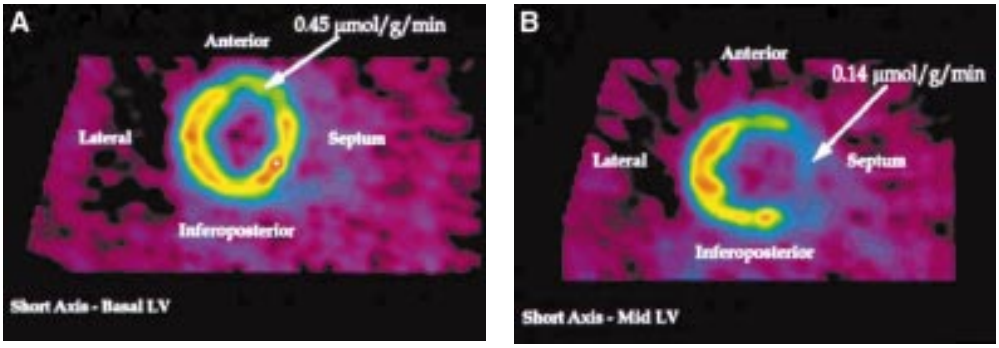

Figure 4: Myocardial viability in two patients with coronary artery disease and severe chronic left ventricular dysfunction assessed by PET with ^{18}F labelled FDG during hyperinsulinaemic euglycaemic clamp. Both patients had previous myocardial infarctions. The scan in panel A shows that FDG uptake in the previously infarcted anteroseptal segment is 0.45 μmol/g/min, suggesting the presence of viable myocardium. In the scan in panel B the uptake of FDG in the anterior wall and the interventricular septum is significantly reduced (0.14 μmol/g/min), suggesting absence of viability in this large area. A cut off point of 0.25 μmol/g/min is routinely used in our laboratory to differentiate between viable and non-viable myocardium.[13]

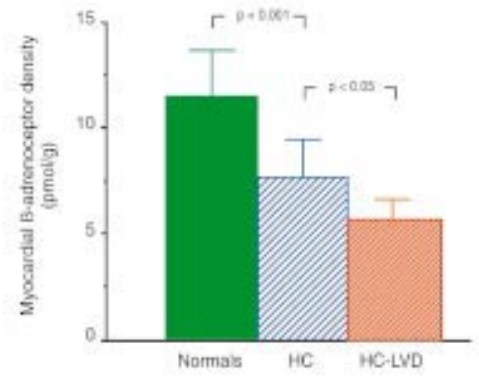

Figure 5: Mean left ventricular β adrenoceptor density in normal subjects and in patients with hypertrophic cardiomyopathy with preserved systolic function (HC) or with left ventricular dysfunction (HC-LVD). Adapted from Choudhury *et al*.[16]

adrenoceptor density (B_{max}, pmol/g) from the PET data has been developed. This approach requires two injections of ^{11}C-(S)-CGP 12177, one at a high specific activity followed by a second at a lower specific activity.[15] Studies in our institution in a group of healthy subjects over a broad range of ages have yielded mean (SD) B_{max} values of 8.4 (2.0) pmol/g, a figure which is comparable with the values measured using in vitro binding.[15] In addition, studies in patients have demonstrated diffuse down regulation of myocardial β adrenoceptors in hypertrophic cardiomyopathy and in congestive cardiac failure, two disorders in which there is a broad range of evidence for chronically raised levels of sympathetic nervous system activation. It has further been hypothesised that abnormal sympathetic activation may actually precede the development of systolic dysfunction in patients with hypertrophic cardiomyopathy. The relation between left ventricular function and myocardial β adrenoceptor density has been investigated and a significant correlation between left ventricular fractional shortening (echocardiography) and β adrenoceptor density (PET) was shown (fig 5).[16]

PET has also been used to investigate the integrity of pre-synaptic sympathetic innervation of the heart. Three tracers have been used for this purpose: ^{18}F labelled fluorometaraminol, ^{18}F labelled fluorodopamine and ^{11}C labelled hydroxyephedrine (^{11}C-HED). These tracers compete with endogenous noradrenaline for the transport into the presynaptic nerve terminal via the neuronal uptake-1 transport system. Once within the neuron these compounds are metabolised and trapped, and hence serve as markers of sympathetic innervation. Recent studies have demonstrated decreased retention of ^{11}C-HED in patients after cardiac transplant which is consistent with the heart being denervated. However, with time, some sympathetic re-innervation occurred particularly in the anteroseptal regions of the heart.[17] This has recently been correlated with recovery of the sensation of angina pectoris in these patients. Both pre- and postsynaptic myocardial autonomic function can be assessed non-invasively by combining different tracers—for example, ^{11}C-HED and ^{11}C-(S)-CGP 12177.[18]

PET studies using ^{11}C labelled MQNB have been used to quantify the density of myocardial muscarinic cholinergic receptors in both experimental animals and in man.[1] It would be desirable for these studies to be extended to patient groups given the possible pathophysiological role of muscarinic receptors in arrhythmogenesis and control of sympathetic nerve function.

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