Regional distribution and kinetics of [^{18}F]6-flurodopamine as a measure of cardiac sympathetic activity in humans

Geoffrey Coates, Raman Chirakal, Ernest L Fallen, Günter Firnau, E Stephen Garnett, Markad V Kamath, Anita Scheffel, Claude Nahmias

Abstract

***Objectives*—To determine whether an increase in cardiac sympathetic activity produced by exercise or sublingual glyceryl trinitrate causes an increased rate of loss of fluorine-18 from the myocardium after intravenous [^{18}F]6-fluorodopamine ([^{18}F]F-DA) in normal volunteers. In addition, to determine the contribution of non-specific uptake of [^{18}F]F-DA in the myocardium in patients with recent heart transplant.**

***Protocol*—[^{18}F]F was prepared by direct electrophilic fluorination of dopamine. Nine healthy volunteers each received 1·85 × 10^8 Bq (168–250 μg) [^{18}F]F-DA over a period of 3 min and were scanned for 2 h in an ECAT 953/31 tomograph. Three controls were scanned before and after vigorous cycle exercise and two were scanned before and after sublingual glyceryl trinitrate. In addition, two patients (1 and 2 years post-heart transplant) underwent a myocardial perfusion study with ammonia labelled with nitrogen-13 followed by an [^{18}F]F-DA study.**

***Results*—There was intense uniform uptake of [^{18}F]F-DA throughout the myocardium in the healthy volunteers. The time course of ^{18}F in the myocardium under resting conditions fitted a biexponential function with mean half-times of 8·0 and 109 min. Vigorous exercise produced a three to fivefold increase in the rate of loss of ^{18}F compared with that when resting. After glyceryl trinitrate, one control had a profound reduction in blood pressure (23%) and twofold increase in the rate of loss of myocardial ^{18}F. The other control had no physiologically significant change in blood pressure, heart rate, or rate of loss of myocardial ^{18}F. Uptake of [^{18}F]F-DA in the two post-transplant patients was confined to a small anterobasal region adjacent to the atrioventricular groove, while blood flow, as measured with [^{13}N] ammonia, was uniformly distributed throughout the myocardium. Partial reinnervation of the myocardium was confirmed by the presence of distinct low frequency spectral peaks of the heart rate power spectrum in both patients.**

***Conclusions*—These results suggest that the uptake of [^{18}F]F-DA reflects the distribution of cardiac sympathetic innervation and that the rate of loss of ^{18}F from the myocardium partially reflects spill over of noradrenaline. The technique may be useful in investigating various cardiac conditions in which the sympathetic system is compromised.**

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Keywords: cardiac sympathetic system; dopamine labelled with fluorine-18; regional distribution and kinetics of [^{18}F]6-fluorodopamine in myocardium; noradrenaline

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There is growing evidence that heightened cardiac sympathetic activity has a role in the pathogenesis of heart disease. For example, Meredith *et al*[1] used noradrenaline (NA labelled with tritium and simultaneous sampling from artery and coronary sinus to demonstrate a fivefold increase in cardiac (NA) spill over from the hearts of patients who had had recent life threatening ventricular arrhythmias. Moreover, spill over studies by Brush *et al*[2] demonstrated reduced neuronal uptake of NA in patients with hypertrophic cardiomyopathy. Such direct measurements of NA in the coronary sinus and arterial blood are important in investigating cardiac sympathetic activity in humans. However, the measurements, besides being invasive, cannot provide information about the regional distribution of sympathetic innervation, for example, in patients with segmental myocardial ischaemia or infarction.

In recent papers Goldstein *et al* have demonstrated uptake of dopamine labelled with fluoride-18 at position 6 ([^{18}F]F-DA) into cardiac sympathetic neurones in animals[3] and humans.[4] They suggest that analyses of the accumulation and decline of myocardial ^{18}F can provide information about the turnover of vesicular amines in the human heart. The objectives of this paper are to describe the [^{18}F]F-DA technique and to provide further evidence that the technique, at least in part mesures NA turnover in humans. In addition, we provide evidence that uptake of [^{18}F]F-DA by the myocardium is specific with only minimal non-specific uptake in denervated myocardium.

Patients and methods

FLUORINE-18

^{18}F labelled F_2 was produced in a Siemens RDS cyclotron (10·5 MeV protons) using the nuclear reaction oxygen-18 (p, n) ^{18}F on ^{18}O-gas.

SYNTHESIS OF [^{18}F]6-FLUORODOPAMINE

A mixture of ^{18}F labelled 2 and 6-fluorodopamine wás prepared by direct fluorination of dopamine in anhydrous hydrogen fluoride containing boron trifluoride.[5] [^{18}F]F-DA was separated from the reaction mixture by reverse phase high performance liquid chromatography (HPLC) (5 μ particle Vydac C-18 semipreparative column) using 0·1% trifluoroacetic acid in water containing 4·5% acetonitrile as the mobile phase with a flow rate of 1 ml/min. The final compound was characterised by its molecular ions using high resolution mass spectrometry and by hydrogen-1, carbon-13, and fluorine-19 nuclear magnetic resonance spectrometry. After isolation of the final product, it was evaporated to dryness, reconstituted in physiological saline, and sterilised by filtration through a 0·2 μm Millipore filter. The radiochemical and enantiomeric purity of [^{18}F]F-DA was determined by chiral HPLC and was greater than 96%. The specific activity of [^{18}F]F-DA at the end of synthesis was $6{\cdot}29 \times 10^{8}$–$1{\cdot}11 \times 10^{9}$ Bq/mg ($10{\cdot}73$–$18{\cdot}87 \times 10^{10}$ Bq/mmol) which corresponds to a dose of 168–250 μg of fluorodopamine for an injection of $1{\cdot}85 \times 10^{8}$ Bq.

RADIATION DOSE

The target organ for radiation absorbed dose for [^{18}F]F-DA is the bladder with a calculated dose of 8–10 mSv/mCi injected, depending on the frequency of voiding. Total body calculated radiation dose is 0·3 mSv/mCi.[4 6]

POSITRON EMISSION TOMOGRAPHY SCANNER

The scanner used in these experiments was an ECAT 953/31 tomograph that examines simultaneously 31 transaxial sections. The spatial resolution of the tomograph is 5 mm in all directions. Correction for attenuation is done using a rod source containing germanium-68/gallium-68 that can be extended into the field of view. With the rod source extended, an axial scan of the chest was performed before each study to identify the heart and centre it in the field of view.

UPTAKE AND WASH-OUT OF FLUORINE-18

In each study, we positioned the participant with the heart in the field of view of the positron emission tomography (PET) scanner and obtained a 30 min transmission scan for attenuation correction. We then infused $1{\cdot}85 \times 10^{8}$ Bq (168–250 μg) [^{18}F]F-DA in 10 ml saline over a period of 3 min. This was equivalent to 1·0–1·8 μg/kg/min. Dynamic images were collected at a frame rate of 10 s/frame for 12 frames, 30s/frame for six frames, and either 150 or 300 s/frame for the remainder of the study for a total scanning time of 2 h.

The following protocols were followed.

Firstly, nine healthy controls (aged 22–53) were studied at rest for 2 h after [^{18}F]F-DA injection.

Secondly, to determine whether the decline of ^{18}F in the myocardium was linked to NA turnover, we examined the effect of exercise. Three controls were studied at rest for 1 h. They then left the PET scanner and exercised on a bicycle ergometer for 30 min at approximately 60% of maximum predicted power output. After exercise they were repositioned in the PET scanner and the dynamic data were collected for a fujrther 1 h. Correct repositioning was confirmed with a laser beam system.

Thirdly, two of the volunteers were studied at rest for 1 h. Each was then given sublingual glyceryl trinitrate and data were collected for a further 1 h. The purpose of using glyceryl trinitrate was to elicit reflex cardiac sympathetic activation without a concomitant increase in myocardial blood flow.[7] Control 1 received 1·8 mg glyceryl trinitrate sublingually over 20 min and control no 2 received 0·6 mg glyceryl trinitrate sublingually. Blood pressure, pulse, and electrocardiogram (ECG) were monitored continuously for 5 min before glyceryl trinitrate and then every 3–5 min to the end of the study. Blood samples for plasma NA were taken at 5 min intervals starting immediately before administration of glyceryl trinitrate.

Fourthly, two patients who received orthotropic heart transplants 14 and 27 months earlier were studied at rest for 2 h. This was done to determine non-specific [^{18}F]F-DA uptake in patients with partial or complete sympathetic denervation. Immediately before the [^{18}F]F-DA study, these patients were scanned after injection of $1{\cdot}85 \times 10^{8}$ Bq of [^{18}F]F-DA labelled with nitrogen-13 to determine the distribution of myocardial blood flow in relation to the distribution of [^{18}F]F-DA uptake.

These studies were approved by the Ethics Committee of the Faculty of Health Sciences, McMaster University. Each participant gave informed consent and signed an approved consent form.

SPECTRAL ANALYSES OF HEART RATE VARIABILITY

A power spectrum of heart rate variability was obtained in all participants. The ECG signals were sampled with a 12-bit analogue to digital converter. Data were processed on an IBM personal computer. Record lengths of 128 s of RR intervals were analysed sequentially for 15–30 min before and after infusion of [^{18}F]F-DA and before and after glyceryl trinitrate. A full description of this method is detailed in previous reports.[8 9]

DATA ANALYSIS

The time course of ^{18}F radioactivity from an annular region of interest in the myocardium halfway between the apex and base was fitted to the sum of two exponentials using non-linear least squares optimisation.[10]

The counts at each time point were normalised to the injected dose.

Results

There were no changes in pulse rate, blood pressure, or ECG in any participant during

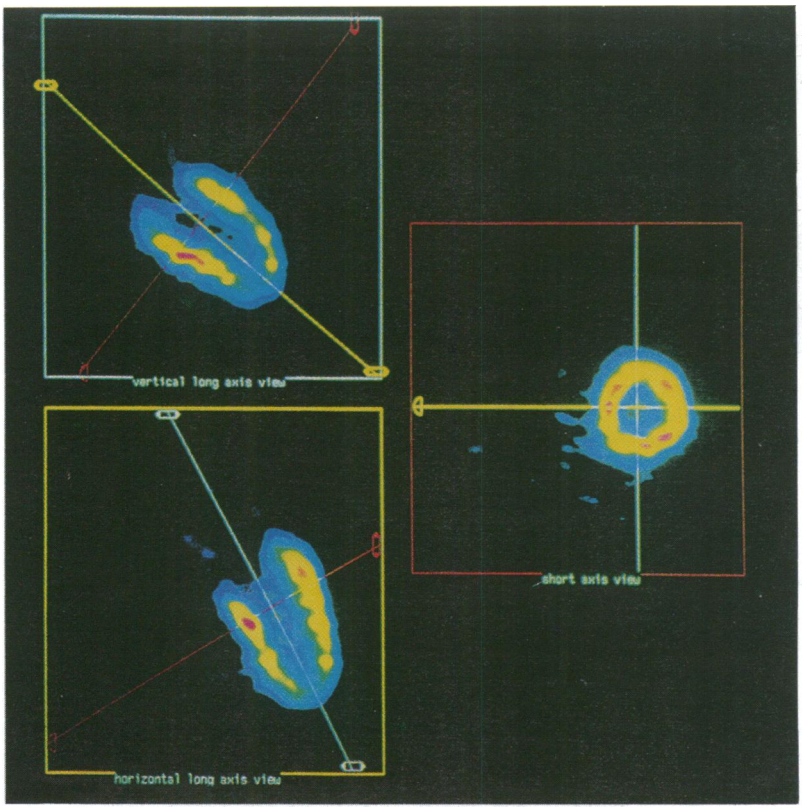

Figure 1 Distribution of [18F]F-DA in a healthy volunteer (control no 1). Data have been reconstructed to display 6 mm thick slices in the vertical and horizontal long axes and the short axis of the mid-left ventricle. The colour coding is such that red represents the areas of highest accumulation, followed by yellow, green, and blue.

and for 15 min after [18F]F-DA injection. There was intense, uniform uptake of [18F]F-DA in the left ventricle of healthy controls. Figure 1 shows data from control 1 reconstructed in vertical and horizontal long axes and in a short axis at mid-left ventricle. There was a homogenous distribution of 18F throughout the left ventricle with no detectable difference either visually or in count rate per unit volume of myocardium between the apex and base.

The decline of 18F in the myocardium in the resting controls (study 1) was best fitted by two decaying exponential curves (fig 2(A)). The mean (range) half-time of the fast component in these controls had a half-time of 8·0 (5·4–8·8) min. The slow component had a mean (range) half-time of 109 (78–146) min.

Exercise caused the heart rate to increase from 60–70 to 135–150 beats per minute (study 2). There was a three to fivefold reduction in myocardial radioactivity concentration after the exercise period (fig 2(B)).

In control 2 0·6 mg of sublingual glyceryl trinitrate caused a profound decrease in systolic blood pressure from a mean of 111 mm Hg before glyceryl trinitrate to a low of 85 mm Hg systolic 9 min after administration (study 3). Systolic pressure returned to pre-glyceryl nitrate levels after 27 min. There was a statistically significant increase in the low frequency (sympathetic) component of the power spectrum of heart rate variability and a decrease in the high frequency (vagal) component (fig 3) starting 6 min after administration of glyceryl trinitrate. Plasma NA increased from 2·53 nmol/l before to 4·48 nmol/l 5 min after glyceryl trinitrate (the last sample taken). During the hypotensive period after glyceryl trinitrate the rate of decline in radioactivity concentration of 18F in the myocardium doubled.

In control 1 there was only a transient reduction in systolic pressure from 120 to 109 mm Hg after the third 0·6 mg tablet of glyceryl trinitrate. There was no change in the

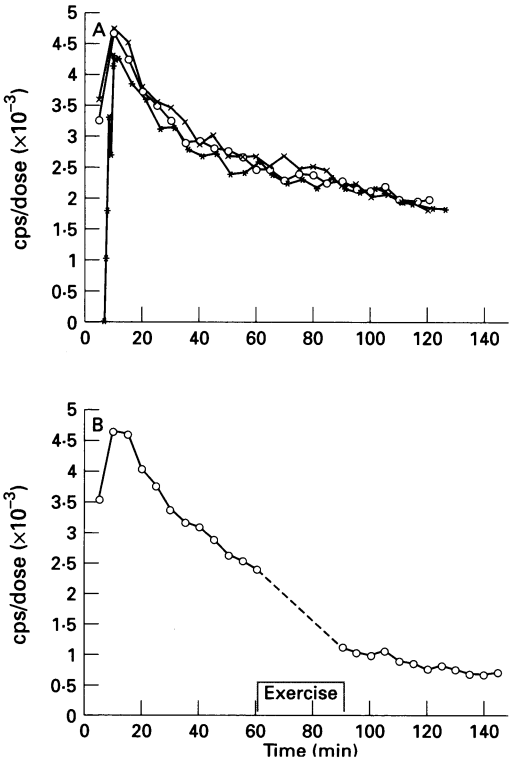

Figure 2 (A) Time course of fluorine-18 concentration in an annular region of interest in the mid-ventricular slice in the three healthy volunteers who exercised in study 2. Data were best fitted by two decaying exponential curves. (B) Time course of 18F concentration in the same region of myocardium as in fig 2(A). There was a marked reduction in radioactivity concentration in the myocardium with exercise in this control.

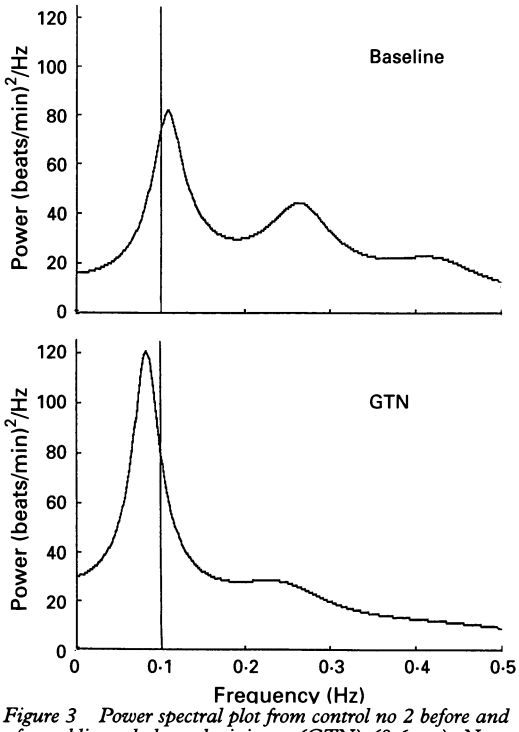

Figure 3 Power spectral plot from control no 2 before and after sublingual glyceryl trinitrate (GTN) (0·6 mg). Note a significant increase in the low frequency (sympathetic) component and a decrease in the high frequency (vagal) component with GTN.

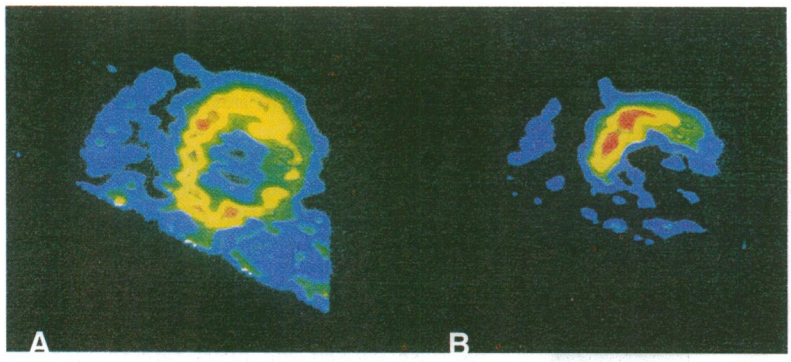

Figure 4 (A) Distribution of ammonia labelled with nitrogen-13 and (B) dopamine labelled with fluorine-18 at position 6([18F]F-DA) in a patient 2 years after heart transplant. Slices (6 mm) were taken close to the atrium. Uptake of [18F]F-DA is confined to the anterobasal region of the myocardium close to the left atrium. The colour coding is the same as in fig 1.

ratio of low/high frequency peaks in the power spectrum of heart rate variability and no change in the rate of decline in ^{18}F.

In both heart transplant patients (study 4) there was a uniform distribution of [^{13}N] ammonia in the myocardium reflecting a uniform blood flow to the myocardium (fig 4). In contrast, uptake of [^{18}F]F-DA was limited to a small region of the anterobasal myocardium subjacent to the atrioventicular groove (fig 4). Uptake in the rest of the myocardium was negligible and indistinguishable from background lung activity.

Discussion

We have demonstrated intense and uniform uptake of [^{18}F]F-DA in the myocardium of normal healthy volunteers under resting supine conditions. As in previous experiments in animals[3 4 11] and humans, our findings in humans suggest that there is specific retention of [^{18}F]F-DA by sympathetic neurones. Only minimal uptake was seen in the partially denervated heart and this finding was supported by partial sympathetic reinnervation seen on the power spectrum of heart rate variability.

The rate of wash-out of ^{18}F from the myocardium was increased in response to increased cardiac sympathetic activity as induced by exercise or sublingual glyceryl trinitrate. This increased wash-out of ^{18}F could be due to increased turnover in, and spill over of, NA labelled with ^{18}F([^{18}F]F-NA) formed from [^{18}F]F-DA in the cardiac sympthetic neurones.

Experiments in animals have established that after intravenous injection fluorodopamine behaves like endogenous dopamine in the heart. It is transported into sympathetic neurones, converted by dopamine β hydroxylase to fluoronoradrenaline and stored in sympathetic storage vesicles.[12–14] After intravenous injection of 6-fluorodopamine labelled with ^{3}H into rats, 40% of the ^{3}H in the heart after 1 h was in the form of [^{3}H] 6-fluoronoradrenaline.[13] Eisenhofer *et al*[13] also reported that, after correction for injected dose, the tissue content of [^{3}H]6-fluoronoradrenaline in the rat heart, although less than after dopamine, labelled with ^{3}H, was greater than with 2-fluorodopamine labelled with ^{3}H. For this reason, we have used 6-fluoro isomer of [^{18}F]F-DA. In normal volunteers Goldstein *et al*[4] reported a 50% reduction in myocardial uptake of [^{18}F]F-DA following blockage of neuronal uptake of catecholamines with desipramine. In addition, urinary excretion of vanillomandelic acid labelled with ^{18}F at position 6 was demonstrated. This provided the first direct evidence in humans for the specific neuronal uptake of [^{18}F]F-DA, its translocation into vesicles and conversion to [^{18}F]F-NA.

Stimulation of the cardiac sympathetic system in animals by either application of electrodes to the stellate ganglia[15] or reducing blood pressure[16] causes release of NA from presynaptic storage vesicles. Most of this undergoes active reuptake by presynaptic neurones but some "spills" into the surrounding extracellular fluid and appears in venous blood.[1 2]

Sympathetic stimulation also causes release of stored fluoronoradrenaline from the hearts of intact animals. Chang *et al*[14] demonstrated release of stored [^{3}H]6-fluoronoradrenaline after increasing sympathetic nerve activity by injecting the α 2-adrenoreceptor blocker yohimbine. In this same study[14] they also recovered the expected metabolites of 6-fluorodopamine labelled with ^{3}H in plasma, namely 6-fluorohomovanillic acid and 6-fluoro-3, 4-dihydroxyphenylacetic acid. Goldstein *et al*[3] demonstrated in dogs that the rate of decline of ^{18}F in the myocardium after [^{18}F]F-DA increased when the sympathetic system was activated by nitroprusside.

These experiments in animals and humans and our own data in humans suggest that at least some of the injected [^{18}F]F-DA is converted to [^{18}F]F-NA and that the rate of ^{18}F decline represents in part [^{18}F]F-NA spill over from cardiac sympathetic neorones. If so, then PET imaging with [^{18}F]F-DA may help identify sites of sympathetic denervation as well as determining regional sympathetic activity.

The increased wash out of ^{18}F from the myocardium during exercise could be secondary to increased myocardial blood flow or increased plasma NA during exercise competing for reuptake with the [^{18}F]F-NA that has been formed from [^{18}F]F-DA. The results of the glyceryl trinitrate experiments, however, suggest that neither of these events caused the increased ^{18}F wash-out during exercise. Plasma NA concentration doubled in both controls after glyceryl trinitrate administration as would be expected in untrained individuals during exercise[17] but ^{18}F wash-out increased in only one participant. The increased rate of ^{18}F wash-out in control 2 after administration of glyceryl trinitrate is unlikely to be secondary to increased myocardial blood flow because this drug does not cause a global or regional increase in blood flow to the healthy myocardium.[7] It does, however, stimulate NA release from prejunctional neurones as a result of a reflex hypotensive response.

It is likely, then, that the increased wash-out rate of ^{18}F from the myocardium during exercise in the three controls and after glyceryl trinitrate in one healthy volunteer was due to increased cardiac sympathetic activity.

In the two patients with recent heart trans-

plants accumulation of [18F]F-DA was limited to a small region on the anterobasal wall near the atrioventricular grove. Our findings are similar to those reported by Schwaiger *et al*[18] with *m*-hydroxyephedrine labelled with carbon-11 in patients at various times after cardiac transplantation. In addition to the evidence from [18F]F-DA imaging, the appearance of the low frequency peak on the power spectra of heart rate variability of both these patients strongly suggests early partial cardiac sympathetic reinnervation post-transplantation.[19]

Other radiopharmaceuticals are being used to evaluate the distribution of sympathetic neorones in the heart. Schwaiger *et al*[18 20] have developed and used [11C] hydroxyephedrine for this purpose. This agent is a NA analogue with the same neuronal uptake mechanism as NA. Unlike NA however, [11C] hydroxyephedrine is not metabolised by monoamine oxidase and the wash-out rate does not reflect NA spill over.[21]

m-Iodobenzylguanidine (MIBG) labelled with iodine-131 or iodine-123 has been used for several years to image the adrenergic system including cardiac sympathetic innervation.[22-24] MIBG is an analogue of NA, which is taken up by sympathetic neurones and stored in neuronal storage vesicles. It has been used extensively to investigate cardiac sympathetic innervation in patients with heart failure,[25] cardiomyopathy,[26 27] and post-myocardial infarction.[28] Unfortunately, MIBG can only be produced with low specific activity. Therefore, amounts are given that exceed the B max for the uptake one system.[29] Consequently, at least in animals, a large fraction is taken up by non-neuronal uptake which has a very low affinity but a larger maximum binding constant than the uptake one system for catecholamines.[30] This may not be a problem in humans.[29] In addition, quantitation of regional uptake and wash-out in cross sectional images is not yet possible with single photon emitters such as 123I or 131I.

We envisage that the [18F]F-DA technique reported here will be useful in investigating various conditions in which the cardiac sympathetic system is compromised such as diabetes, cardiomyopathy,[31] recent myocardial infarction,[28] or heart failure.[25] The [18F]F-DA method, which measures the integrity of the presynaptic uptake and vesicular storage mechanisms, will also complement the existing techniques that measure post-synaptic β receptor density.[31 32]

In summary, we have demonstrated intense and uniform uptake of [18F]F-DA in the myocardium of normal volunteers. The rate of decline of 18F in the myocardium, in part, reflects NA spill over.

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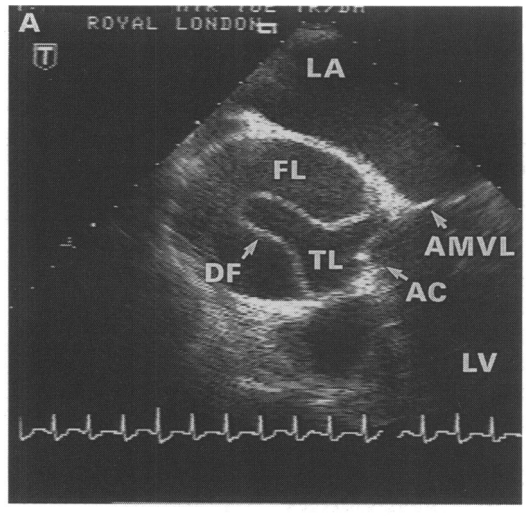
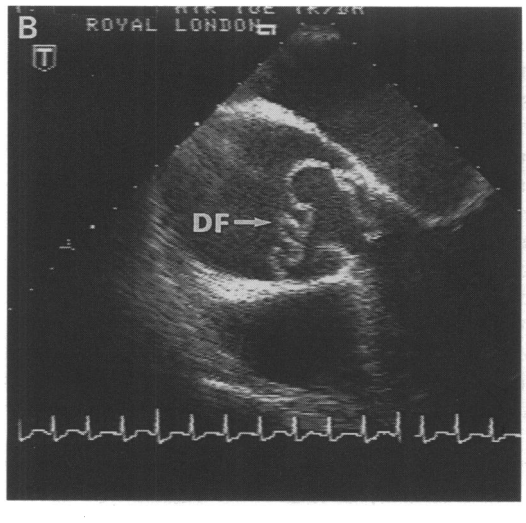
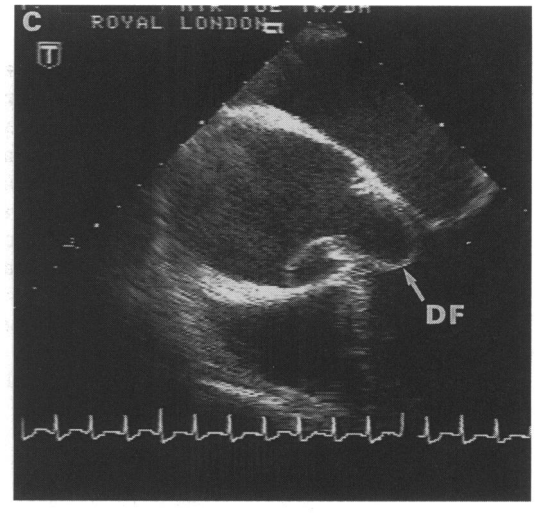
IMAGES IN CARDIOLOGY

Prolapse of an aortic dissection flap imaged by transoesophageal echocardiography







AC, aortic cusp; DF, dissection flap; FL, false lumen; TL, true lumen; LV, left ventricle; LA, left atrium; AMVL, anterior mitral valve leaflet.

This 66 year old farmer collapsed in a field while tending his sheep. On admission to hospital he complained of interscapular pain and was noted to have an early diastolic murmur. Here we present images obtained at subsequent transoesophageal echocardiography. These three sequential transverse views (A, B, and C) demonstrate a dilated aortic root and a proximal dissection flap prolapsing during diastole from aorta to left ventricle through the aortic valve.

The aortic valve was excised and the dissection resected down to the level of the valve. A 29 mm St Jude valved conduit was implanted, and the coronary arteries were anastomosed on aortic buttons. He left hospital at 14 days and was well six months later.

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