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Evaluation of Ischemia and Myocardial Viability in Patients with Coronary Artery Disease (CAD) with Iodine-123-Labeled 15-(p-Iodophenyl)-3-R,S-methylpentadecanoic Acid (BMIPP)

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Abstract

Twenty patients with coronary artery disease (CAD) controlled by coronary arteriography (CA) and biplane left ventricular cineventriculography (LVCV) were investigated with the 15-(p-[I-123]iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) fatty acid analogue. During maximal symptom limited exercise 5 mCi (200 MBq) of BMIPP were injected followed by two SPECT studies within three hours. After another 30 min, with the patient at rest a third SPECT was performed after reinjection of 3 mCi (100 MBq) BMIPP. Visual inspection of the short and long axis slices and quantitative comparison of the short axis slices of the tomograms were performed to grade BMIPP uptake and refill and detect turnover abnormalities. These were addressed either as scar or as ischemia and compared to CA and a graded score of regional wall motion by LVCV which provided values for sensitivity (SE) and specificity (SP) to detect CAD. By visual inspection, SE and SP values were 71% and 94%, respectively. SE could be improved by quantification to 86%. Fifteen infarctions had correspondend clinical, angiographic and scintigraphic findings in 93%. Our results of this study demonstrate that BMIPP scintigraphy is able to diagnose CAD and viability of the myocardioum with great reliability. Furthermore, BMIPP seems to have advantages compared to the straight chain IPPA analogue because of its longer retention.

Introduction

The metabolic integrity of the myocardial cell forms the basis to maintain contractile function, which represents viable myocardium. An indirect index of viability is the evaluation of oxygen consumption or metabolism. For these reasons PET-techniques in conjunction with C-11 acetate (1) or F-18 deoxyglucose (2) serve as the "gold" standard for the detection of viability.

A corollary for the demonstration of viability is the substantiation of the deterioration of flow which might lead to impairment of metabolism which can non-invasively be reliably detected with PET and C-11 palmitate (3).

Because PET techniques are costly and will probably continue to be limited to only a few centers, alternative substrates were developed to transfer this concept to the more widly used SPECT techniques.

Tracers of oxidative metabolism such as 15-(p-[I-123]iodophenyl)pentadecanoic acid (IPPA) or 15-(p-[I-123]iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) have been developed as candidates for this purpose (4, 5). It has been shown that IPPA reliably detects patients with coronary artery disease (CAD) (6, 7) and that the uptake is linearily correlated with flow (8). BMIPP and IPPA follow the initial biochemical pathways of uptake, transport and activation within the myocardial cell (9) and IPPA behaves similar than the physiologic tracer palmitic acid, were metabolism is directly linked to oxygen consumption (10).

One major disadvantage of IPPA is its rapid turnover, which requires short SPECT rotation times (15 minutes) and only limited investigation times are feasible (45 minutes). 15-(p-[I-123]iodophenyl)-3-R,S-methylpentadecanoic acid (BMIPP) was developed in an attempt to overcome these shortcomings and appears to be a more attractive fatty acid tracer for such studies because the methyl group somehow interferes with ß-oxidation so that the compound remains in the myocardial cell for a significantly longer period (11).

BMIPP, as a further development of fatty acid tracers for SPECT, showed similar properties as IPPA (12). The prolonged kinetics of BMIPP promise better imaging modalities and thus advantages for diagnosis.

Material and Methods

Patient population

Governmental permission and approval of this study by the local ethical committee was obtained and all fully informed patients gave their written consent. We investigated 20 patients with CAD substantiated by quantitative coronary arteriography (CA) and left ventricular cineventriculography (LVCV) in the right and left anterior oblique projections. There were 5 female and 15 male patients with a mean age of 54.7 years (range 31-68 years). A narrowing of a coronary artery over 50% was considered significant for CAD.

Radiopharmaceutical

The iodine-123-labeled BMIPP was prepared by the thallation-iodination exchange reaction of 15-(p-[I-123]iodophenyl)-3-R,S-methylpentadecanoic acid (BMPP) substrate as described previously (13, 14). The highly pure iodine-123 was produced by the (p,2n) reaction on enriched xenon-124 and was obtained from Cygne, Eindhoven/Netherlands. The total synthesis, purification, and formulation time was about 2 hours. The product showed a single, homogenous radioactive component on TLC analysis. Radiolabeling yields averaged about 85% for all formulations. The I-123 BMIPP was dissolved in a small volume of absolute ethanol (100 µl), complexed to 10% human albumin solution (5-10 ml) and then filtered through a 0.22 micron millipore filter. The product was sterile and pyrogen-free and no adverse reactions were observed in any patients.

Myocardial scintigraphy

The patients were strictly fasted for at least 12 hours and underwent a maximal symptom-limited exercise. At maximal workload, 200 MBq BMIPP was administered intravenously. After a period of two minutes to recover, the patient was positioned under a large-field-of-view gamma camera (Elscint, Apex 409) and a planar sequential scan was achieved in the anterior view for a 15' period in 19 patients. In one patient this initial period was used to acquire an "early" whole body scan (ADAC, Genesys). In one patient a "late" whole body scan was

performed three hours p.i..

After the planar scan, the first tomogram (STRESS) was acquired. Acquisition was achieved by a 180° rotation for a 25' period with 30 projections in a 64x64 matrix. SPECT was repeated after three hours with the same acquisition parameters (3 H. P.I.). After a second injection (reinjection) of another 100 MBq BMIPP at rest a third SPECT was achieved (REINJECTION). All SPECT acquisitions were performed by the Elscint camera.

Image analysis

After a filtered backprojection and reorientation of the heart the short and long axis slices were reconstructed with a thikness of two pixels. The slices were first read visually and blindly in comparison to the other diagnostic modalities to analyze the uptake and refill of BMIPP. The myocardium was divided into ten segments (anterior: basal, middle, distal; posterolateral: basal, middle, distal; inferior: basal, distal; septum; apex) to score the BMIPP uptake using a three-point grading system (3=normal, 2=reduced with refill, 1=absent). Each segment was represented by a minimum of two slices.

The short axis slices were than quantified with the "bull's-eye" technique. The regional comparison of the slices of the STRESS and REST tomogram provided values for turnover of BMIPP and the comparison of the STRESS and REINJECTION SPECT for "refill" values.

Wall motion analysis

Left ventricular cine ventriculography in two planes was scored blindly in comparison to the other diagnostic modalities in the ten segments using a three-point grading system (3=normal, 2=hypokinesia, 1=akinesia). We had no dyskinetic segments in our patient group.

Blood analysis

Blood samples were withdrawn at three and 20 minutes and three hours p.i.. Lipids were extracted from the serum by a modified Folch method and an aliquot was analyzed by thin layer chromatography (TLC) in two different solvent systems (A: petroleum ether/ether/acetic acid, 69:30:1, v/v/v; B: benzene/dioxane/acetic acid, 80:18:2, v/v/v). This method was recently described in detail (15). Standards (iodobenzoic acid (IBA), cold iodinatd BMIPP, and tripalmitin (TG)) were also spotted on the plates as reference points. After analysis the TLC-plates were cut into 15 segments which were counted. The measured activities were expanded to the blood volume which was calculated from weight and height (16) of the patient and this value was compared to the injected activity. This analysis provided an estimate of the percent injected dose in each radioactive peak in the whole blood volume.

In addition, blood samples were withdrawn at rest and at the maximal stage of exercise to provide values for the lactate serum level as the main competing substrate for free fatty acids.

Results

CA revealed in our patients 12 LAD (left anterior descending artery)-, 6 LCX (left circumflex artery)-, and 11 RCA (right coronary artery)-stenoses. There were 11 patients with one vessel, 3 with two vessel, and 4 with three vessel disease. Two patients had a normal coronary artery system.

The average stage of exercise was 138 watts. The mean heart rate was 135.4 beats/min at a predicted age-related heart rate of 149.5 beats/min for maximal exercise.

In LAD-, LCX-, and RCA supplied regions with non-stenosed arteries we calculated "normal" values for BMIPP turnover which are summarized in Table 1, along with the values for refill. Turnover values in regions supplied by a stenosed artery were considered significantly decreased if they differed from the normal mean value by more than one standard deviation.

Figure 1 shows the early (Fig. 1 A) and late (Fig. 1 B) whole body scans. In the late scan we calculated the background corrected uptake of BMIPP as the percent of the whole body activity and the mean counts per pixel for the thyroid (0,3%; 8,0), heart (1,5%; 28,2), urinary bladder (4,0%; 22,2) and liver (3,0%; 23,9).

Figure 2 shows an example of the grouped frames of the sequential planar scintigram (Fig. 2 A) and the derived time activity curves (Fig. 2 B). The upatke ratios calculated from 19 patients of the heart to liver, lungs, and background were 1.18±0.15, 2.0±0.21, and 2.5±0.18, respectively.

Figure 3 A illustrates four short axis slices of the complete set of tomograms of a patient with an occluded LAD. Fig. 3 B shows the computer printout of the CA of this patient who had an infarction in the distal anterior wall with akinesia in this region (Fig. 3 C). In the exercise ECG, ischemia could not be substantiated although the patient exercised maximally.

In the STRESS slices there is a reduced uptake in the anterior wall matching the arteriography. The uptake in the 3. H. P.I.-SPECT shows no major uptake differences compared to the STRESS tomogram. In the REINJECTION tomogram there is normal uptake (refill) in the non-infarcted regions of the anterior wall (arrows) indicating ischemic but viable myocardium. In addition, there is a persistent defect in the distal anterior wall matching the LVCV or the infarcted area.

There were 15 infarctions proven anamnestically, typical enzyme changes, ECG signs and by LVCV either by a- or hypokinesia (Table 2). In 14 cases (93%) BMIPP-SPECT corresponded with the clinical findings. The infarction which was not detected by BMIPP was for a patient with a non-transmural infarction of the anterior wall with normal regional wall motion in the questionable area. We had one patient with absent uptake in all three sets of slices in the inferior wall perfused by a normal coronary artery, but there was no regional wall motion abnormality and no infarction in this area in the history of the patient. On the other hand, we had two anamnestically proven infarctions in the posterolateral

wall with hypokinesia in this area but normal coronary arteries and normal BMIPP uptake.

Figure 4 summarizes our results concerning the diagnosis of ischemia with regard to the findings in CA and the mode of analysis of the BMIPP scans. Infarcted areas were excluded in this analysis. Because of the small numbers of stenosed vessels it seemed statisticaly of no value to separate this analysis into the three main territories. In the case of the analysis based on turnover values, specificity could not be calculated due to the mode of calculation of the normal values.

The two patients with no evidence of stenoses in CA had normal homogeneous uptake of BMIPP in all tomogramms.

The TLC's of the serum lipids showed an increasing fraction of radioactivity which was more polar than the cold iodinated BMIPP standard (Figure 5 A-C). The results are summarized in Table 3. There was statistically no difference between the two solvent systems.

Lactate serum levels at rest and at maximal exercise were 1.6±0.6 mmol/l and 4.3±1.8 mmol/l, respectively, at a normal range for our institution of 0.6 - 1.8 mmol/l. The increase was statistically highly significant ($p < 0.001$).

Discussion

The results of this study demonstrate that imaging of the left ventricular myocardium with BMIPP and tomographic technique reveals reliable information about the ischemic but viable

myocardium with good correlation with the results of regional wall motion studies and the anatomy of the coronary artery system. With regard to the detection of ischemia rather than infarcted areas, semi-quantification could improve the accuracy of the method.

Our experiences (17) in the diagnosis of coronary artery diesease (CAD) using 15-(p-[I-123]iodophenyl)pentadecanoic acid (IPPA) encouraged us to investigate the usefulness of an optimized compound like BMIPP. The rapid metabolism of IPPA (18) permits only short rotation times for SPECT. This limits the statistics of the tomogramms and thus image quality and the possibility of quantification. It was expected that ß-oxidation of BMIPP is inhibited somehow by the methyl-branching (11) so that the myocardial residue should be prolonged. Our results show that this is in agreement with the in vivo situation. The average activity loss over three hours is only 18.7±5.1 % in regions perfused by non-stenosed coronary arteries. Thus, prolonged imaging periods are possible but the lack of redistribution of BMIPP makes a second injection (reinjection) necessary to detect ischemic but viable myocardium. However, this is not a disadvantage with regard to the low radiation dose.

The whole body distribution shows that the initial uptake of BMIPP is mainly restricted to the heart and liver. The uptake ratio of heart/liver is slightly greater compared to IPPA and was always greater than unity in our patient group. Therefore "bulls-eye" quantification could be achieved by simple sub-

traction of decay corrected tomograms.

The attempt to diagnose ischemia by using semi-quantification of the tomograms (turnover rates) was based on the assumption that the metabolism of BMIPP is, at least in part, dependent on oxygen supply and consumption. Because the usual ß-oxidative process is apparently inhibited by the methyl group, an alternative metabolic pathway is suggested which might involve α-oxidation as discussed by several authors (19, 20, 21, 22) forming ß-hydroxy analogues or another process which has not yet been elucidated.

Our data clearly demonstrate that BMIPP is metabolized either by the heart or other organs because there is activity detectable in the urine bladder which must be due to a urine excreted metabolite. Because the iodine uptake in the thyroid three hours p.i. is about four times less than the activity concentration in the bladder, from which the activity additionally was partly excreted during that time, it would seem unlikely that deiodination of the tracer is occuring. This is supported by the analysis of the urine of patients (12) after administration of BMIPP. After lipid extraction a high amount of the radioactivity was found in the organic phase and TLC and HPLC analysis revealed a polar component which was adressed as a metabolite of BMIPP. However, the increasing uptake of activity in the thyroid over time (Fig. 1) indicates a small amount of deiodination of BMIPP but the metabolic pathway responsible for that finding remains unclear.

TLC analysis of blood lipids showed a metabolite more polar than the BMIPP standard and even more polar than iodobenzoic acid which is assumed to be the principal metabolite of IPPA (23), although recently (p-iodophenyl)propenoic acid was proposed to be the main metabolite (24). The polar fraction from BMIPP metabolism increased slowly with time implying a low rate metabolic pathway. The polar component observed in TLC analysis appears to correspond with the same metabolite of BMIPP found in isolated heart experiments (15) because both compounds had the same R_f-value (0.20). This correspondence indicates that also the in vivo metabolite in man is primarily generated by metabolism in the heart.

This metabolite might be a product resulting from α-oxidation, since is known to occur in ischemic conditions (21). Because this metabolite was detected also in patients without stenoses and a normal scan, this metabolic pathway might be at least partly an alternative to ß-oxidation in the normal perfused myocardium, too.

Experimental data have suggested that this metabolite is a short chain hydroxy carboxylic acid (25), but this result is in contrast to chemical analyses by other investigators of the metabolic compounds in the blood and urine of patients (26) which suggested iodophenylacetic acid and their conjugates as the major metabolites. In summary, the chemical structure of the BMIPP-metabolite(s) still remains unclear but all investigators agree that degradation of BMIPP takes place by some oxidative process which may be α-oxidation as the first

step followed by ß-oxidation.

Our data are consistent with the results of several other groups that demonstrate that BMIPP or similar derivatives are useful in the diagnosis of various diseases of the heart (27, 28, 29). Visual inspection of the scans with regard to infarcted areas reveals high accuracy and correlation to clinical findings, including regional wall motion, as found in another study (27). We missed only one infarction but this was non-transmural, and there was only one false positive defect in which the whole inferior wall showed a persistent defect in all three tomograms. The large size of this defect should result in a hypo- or akinesia, but CA demonstrated a normal artery and LVCV revealed normal wall motion. In addition, there was no infarction in the history of the patient so that the presence of infarction in the questionable area was very unlikely, so this case remains unclear. In contrast, we had two myocardial areas where infarction was suspected by anamnesia and ECG but CA had no signs of CAD, although there was hypokinesia in the questionable area. In these cases the normal uptake of BMIPP represented the clinical situation more precisely compared to the other diagnostic tests if CA is considered as the "gold" standard.

In our small patient group the analysis of turnover rates improved the sensitivity for the detection of ischemia in patients with CAD, compared to the visual inspection if a greater than 50% narrrowing of an artery was considered

significant and CA as the "gold" standard for CAD. This result implies that the degradation of BMIPP is oxygen-dependant and the rate of turnover is decreased under ischemic conditions which are assumed under maximal stress in myocardial regions supplied by a stenotic artery. Our data suggest that the differences between normal and ischemic areas are small, however, resulting in an interval of only one standard deviation. This might be improved by a greter than three hour time period between the STRESS and delayed tomogram.

A refill value of about 10% in the REINJECTION slices compared to the STRESS tomogram in non-ischemic areas (Table 1) might be due to "back diffusion" of unmetabolized tracer under stress. This fraction is assumed to be enhanced in ischemic areas (30), especially under maximal stress. Such kinetic behaviour of the BMIPP tracer was also found in isolated heart experiments (31) and occured in our patient group in normal perfused segments, indicating that ischemia is not a necessary supposition for back diffusion and might result from increased lactate serum levels which interfere with fatty acid metabolism.

In conclusion, the results of BMIPP-scintigraphy are in close correlation to coronary arteriography and left ventricualr cineventriculography in patients with CAD. As a tracer of fatty acid catabolism our preliminary results suggest that BMIPP SPECT holds promise as a method for the specific detection of ischemic but viable myocardium. Due to the physiologic properties BMIPP has major advantages over e.g.

IPPA but further experience is required to substantiate our results, especially if semiquantification of the tomograms is considered.

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Legends

Figure 1. A: Early (5-20 min. p.i.) whole body scan after administration of BMIPP. B: Late (three hours p.i.) whole body scan.

Figure 2. A: Grouped frame of the initial planar sequential scintigraphy. B: Time activity curves for the various organs derived from the sequential scan of the same patient as in Fig. 2 A normalized to the ROI size.

Figure 3. A: Four slices of the complete set of a BMIPP-tomography. There is decreased uptake in the anterior wall in the STRESS and 3 H. P. I. slices. In the REINJECTION tomogramm a fillin is clearly visible in the anterior wall (arrows) except in the very distal portion indicating infarction in this area. B: Computer printout of the findings of CA revealing an occluded LAD in the mid portion of this artery. C: Computer printout of the analysis of LVCV revealing an akinetic segment in the distal region of the anterior wall and the apex.

Figure 4. Sensitivity (SE) and specificity (SP) for the diagnosis of ischemia with regard to the mode of analysis of the BMIPP-scans. The CA findings were taken as the "gold" standard and a greater than 50 % narrowing of an artery was regarded significant for coronary artery disease.

Figure 5. TLC analysis of blood lipids of one patient in solvent system A consisting of pet ether/ether/acetic acid (69:30:1, v/v/v). A: three minutes p.i. B: 20 minutes p.i. C: three hours p.i. There is an increasing percentage of a very polar component indicating a metabolite of BMIPP.

Table 1. Mean "normal" values of turnover (T) and their standard deviations calculated by the comparison of decay corrected slices from the STRESS and 3 H. P.I. tomograms. Mean values of refill calculated by the comparison of the STRESS and REINJECTION tomogram (Rf1) and from the 3 H. P. I. and REINJECTION SPECT (Rf2). The latter values were corrected for the assumed fraction of backdiffusion of BMIPP from Rf1. LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery,

Table 3. TLC analysis of blood lipids. Values are expressed as the mean and their standard deviations and are expanded to the blood volume of the patient.

Table 1. Values of turnover and refill in non-ischemic myocardial areas

	LAD	RCA	LCX
T*	21.9±6,4	17.42±4.5	16.8±4.2
Rf1*	11.6±2.6	10.9±3.8	10.0±4.2
Rf2*	-1.7±0.6	2.5±1.0	1.8±1.7

* T= turnover; Rf1=Refill one; Rf2=Refilltwo2

Table 2. Scores of BMIPP uptake in relation to wall motion in 180 segments

BMIPP score	Wall motion score			Total
	3	2	1	
3	97	9	2	108
2	10	30	2	42
1	2	18	10	30
Total	109	57	14	180

Table 3. Results of the analysis of blood lipids

	% injected dose	
Time p.i.	BMIPP	Metabolite
3 min.	26.5±4.8	0
30 min.	2.8±0.5	5.2±1.8
3 hours	0	7.7±2.1

A B

Figure 1.

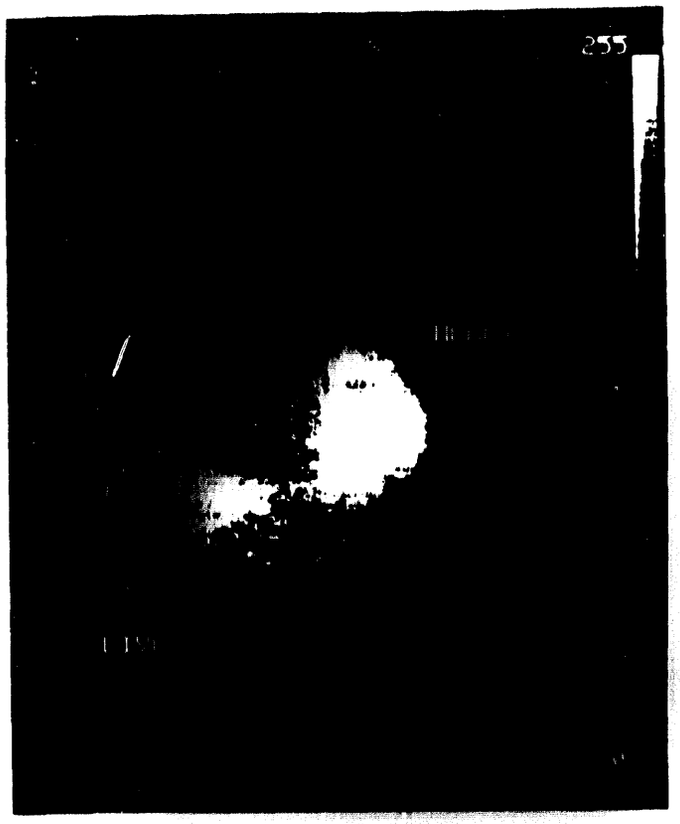

Figure 2a.

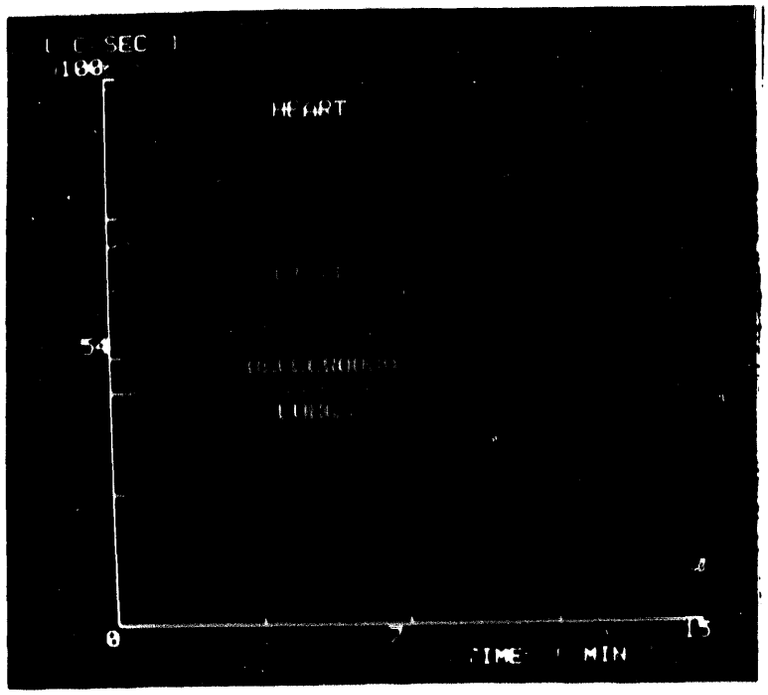

Figure 2b.

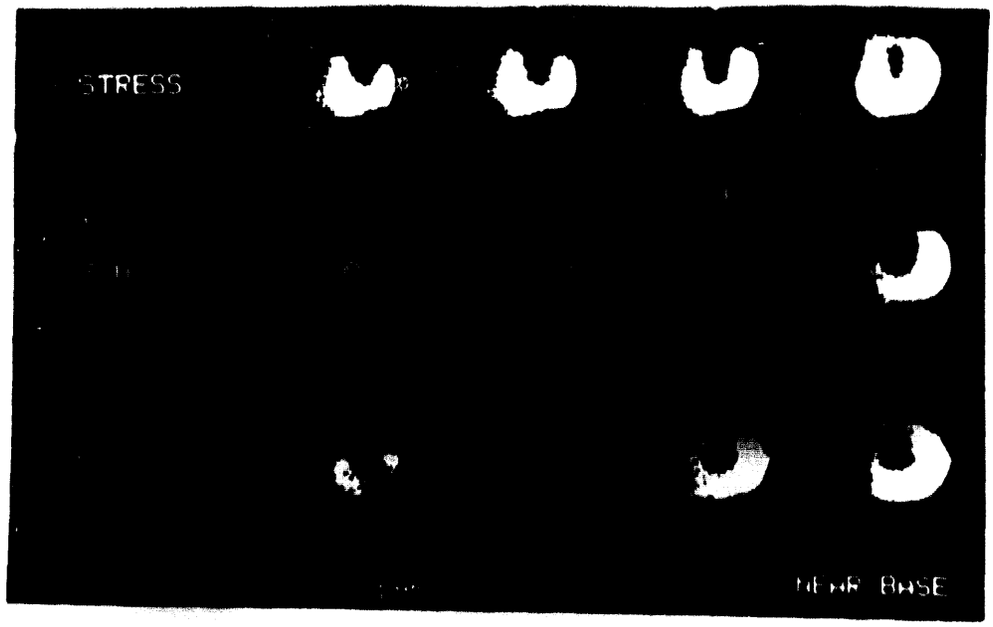

Figure 3a.

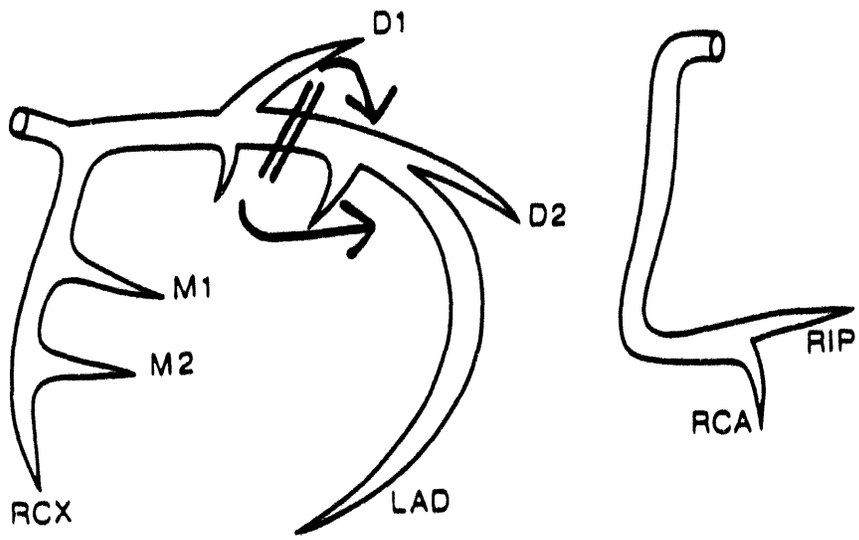

Figure 3b.

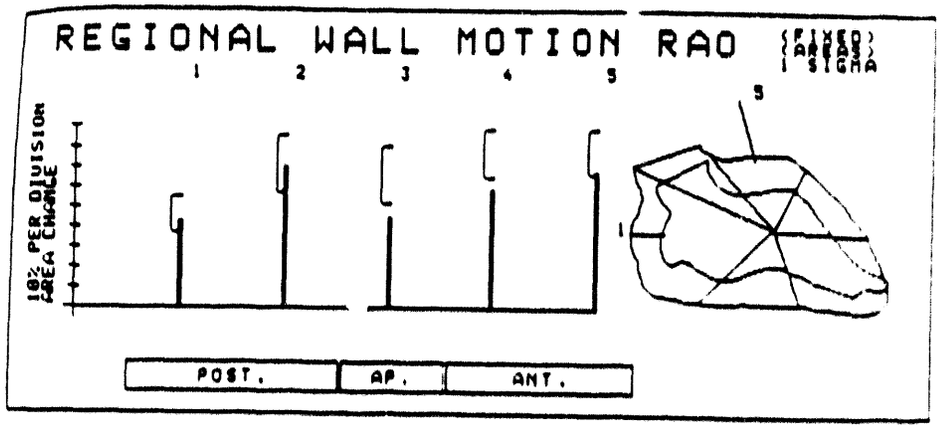

Figure 3c.

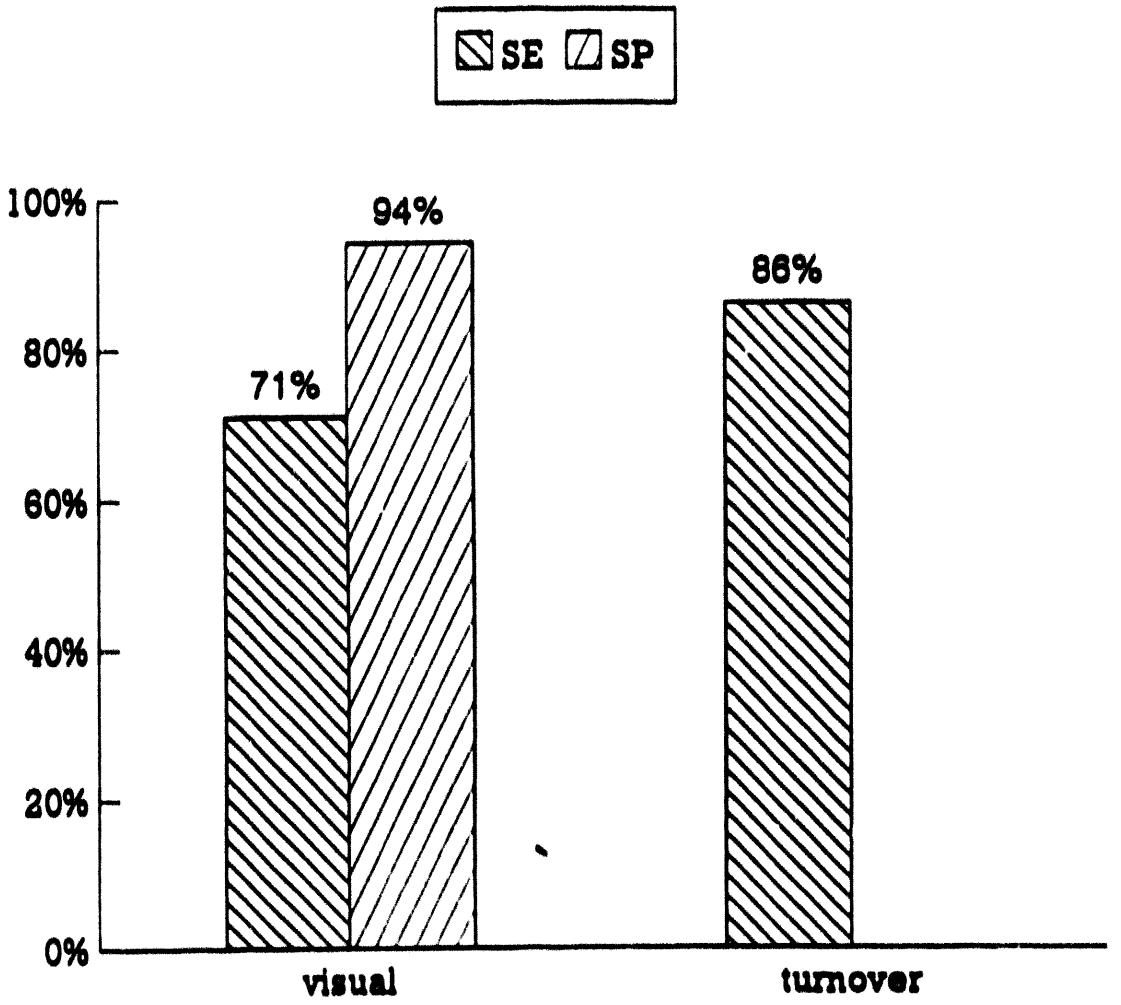

Figure 4.

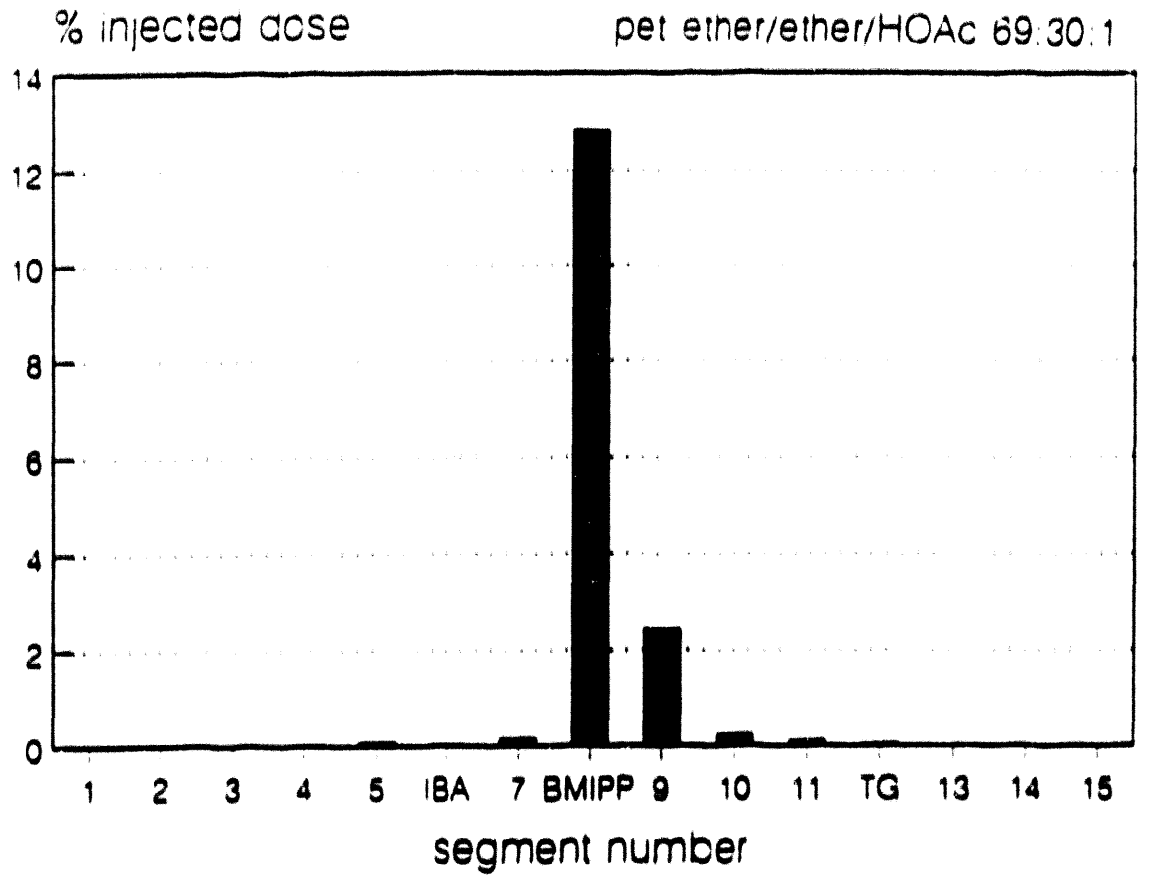

Figure 5a.

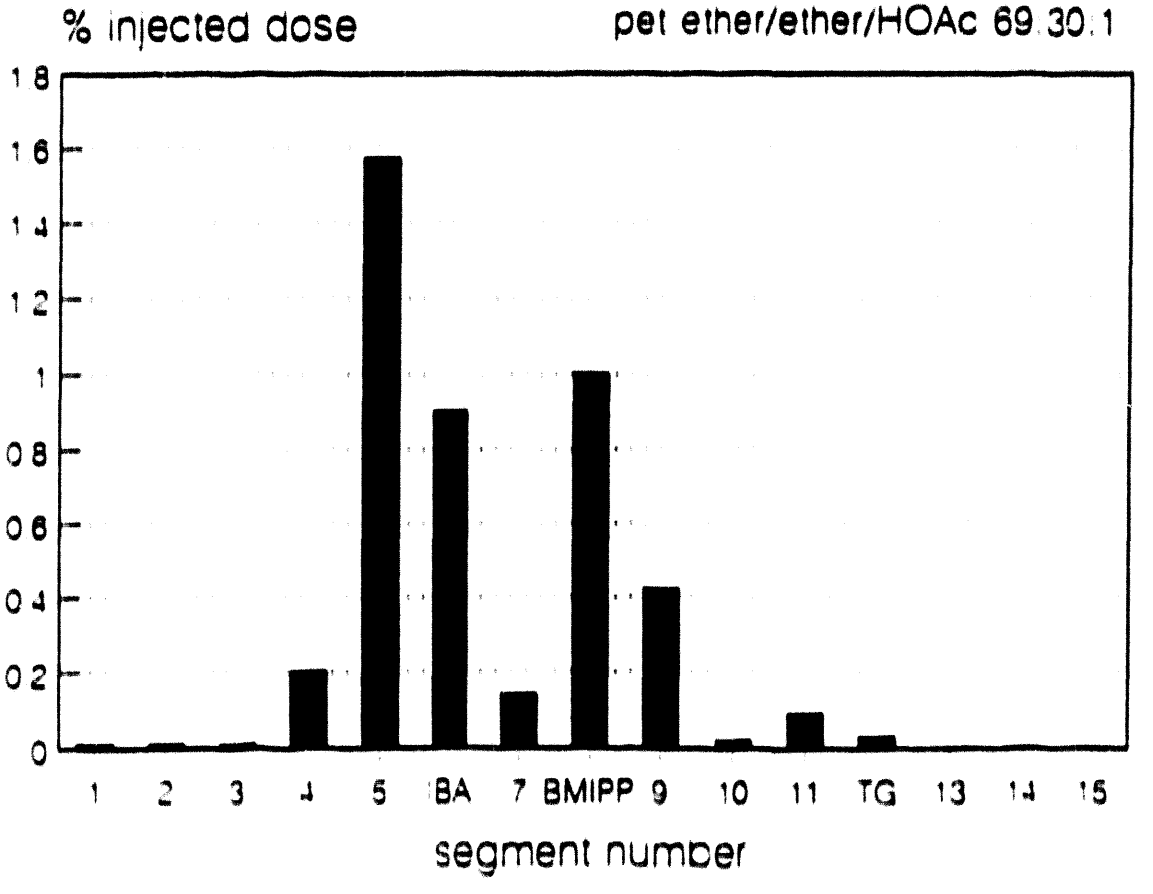

Figure 5b.

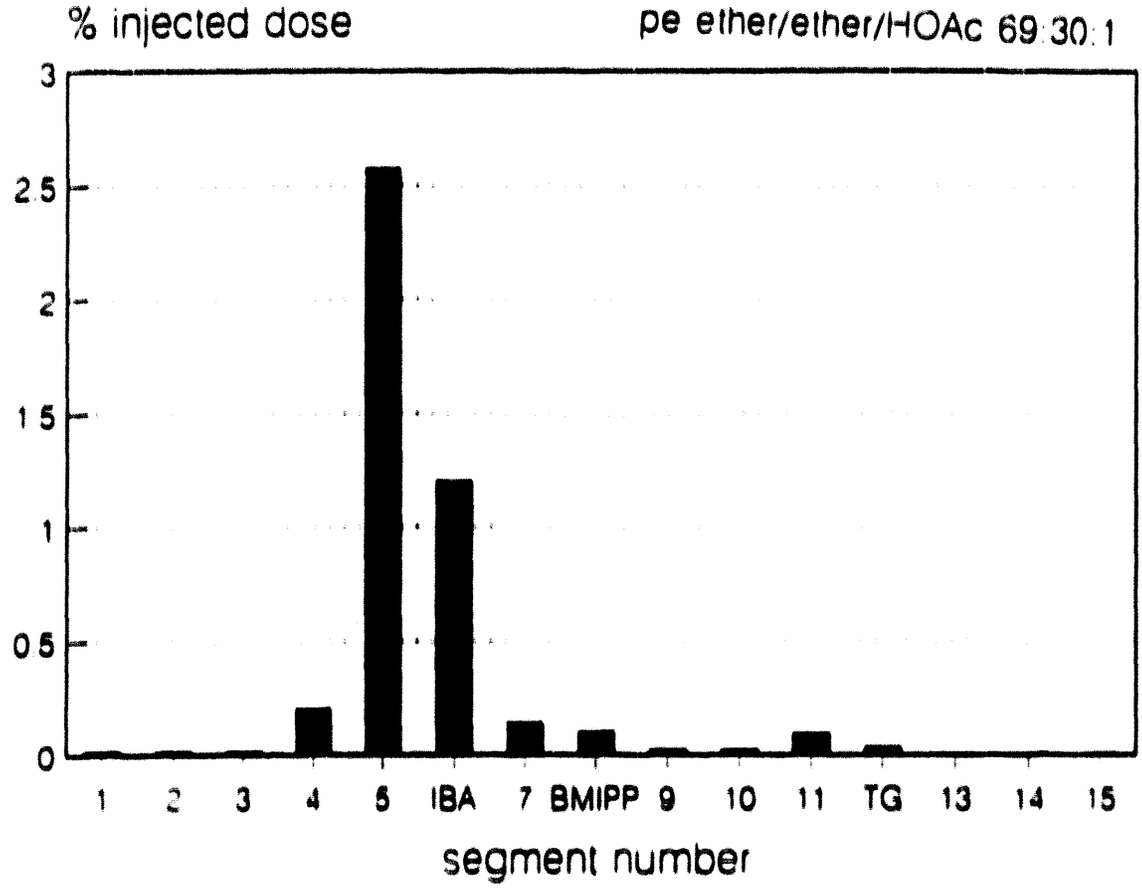
% injected dose
pe ether/ether/HOAc 69:30:1
3
2.5
2
1.5
1
0.5
0
1
2
3
4
5
IBA
7
BMIPP
9
10
11
TG
13
14
15
segment number

Figure 5c.

END

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