Jpn Circ J 1999; **63:** 407–411

Improvement of Regional Myocardial and Coronary Blood Flow Reserve in a Patient Treated With Enhanced External Counterpulsation

— Evaluation by Nitrogen-13 Ammonia PET —

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Enhanced external counterpulsation (EECP) is a noninvasive treatment for chronic stable angina, which works by recruiting and developing the coronary collateral vessels. Coronary perfusion and coronary flow reserve (CFR) were evaluated by nitrogen-13 (^{13}N) ammonia positron emission tomography (PET) in a patient who had undergone EECP. The patient, who had 3-vessel coronary artery disease, required a percutaneous transluminal coronary angioplasty (PTCA) for the right coronary artery. The PTCA was successful, but 6 months later he again felt chest oppression. The coronary angiography showed re-stenosis at the PTCA site, and other progressive coronary stenosis. The patient was again treated with EECP for 35 h. The ^{13}N-ammonia PET was performed both at baseline and during dipyridamole provocation, before and after EECP treatment. Coronary perfusion of each myocardial wall increased at the baseline (anterior: 0.52–0.75; septal: 0.48–0.66; lateral: 0.61–0.68; inferior: 0.46–0.57 ml min^{-1} g^{-1}), and the CFRs in the septal and inferior walls (septal: 2.07–2.15; inferior: 1.99–2.06) also increased after the treatment. Thus, the EECP treatment improved both coronary perfusion at baseline and CFR, which suggests that it may be one of the choices for treatment of angina. (*Jpn Circ J* 1999; **63:** 407–411)

Key Words: Enhanced external counterpulsation (EECP); Ischemic heart disease; ^{13}N-ammonia PET

About 40 years ago, a surgeon proposed and tested methods that could both augment the function of the failing heart and assist the circulation.[1] Synchronous counterpulsation was proposed for decreasing the afterload during systole and augmenting coronary blood flow during diastole. As the result of many mechanical developments and clinical studies, external counterpulsation demonstrated improved survival in patients with cardiogenic shock[2] and significantly reduced the mortality rate during the acute period after myocardial infarction.[3] Enhanced external counterpulsation (EECP) was modified to its present form, as reported by Zheng et al in 1983.[4] Lawson et al, in 2 previous studies, reported that EECP therapy was effective in the treatment of chronic stable angina[5,6] and that the benefit continued for 3 years.[6] How exactly EECP produces this sustained benefit in patients with chronic stable angina is unknown, but it is considered that it recruits and develops the coronary collateral vessels. At the 70th American Heart Association Scientific Sessions in 1997, the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) reported a reduction of angina episodes and an increase in both exercise time and onset time of ischemic ST depression by EECP.[7] We previously reported a patient treated with EECP for 13 h,[8] during which we evaluated the patient's hemodynamics with a Swan-Ganz catheter. During the EECP treatment, the pulmonary capillary wedge pressure and cardiac index were increased compared with before the treatment, and the ^{201}Tl-single photon emission computed tomography (SPECT) image after EECP treatment was improved compared with that before treatment.

But no previous study has investigated quantitative coronary perfusion and coronary flow reserve (CFR). We evaluated both these aspects using nitrogen-13 (^{13}N) ammonia positron emission tomography (PET) in association with EECP treatment and this report is the first to prove an increase in coronary perfusion and CFR with EECP.

Methods

Patient Profile

The patient, a 50-year-old man, had a history of mild, well-controlled hyperlipidemia, no obesity and he did not smoke. His father had both diabetes mellitus and hypertension, and his mother had myocardial infarction, cerebral infarction and diabetes mellitus. The patient was well until September 1996 when he felt chest discomfort, which at first continued for 5–10 s and then appeared once weekly. The effect of nitroglycerin was uncertain. In May 1997, the patient was discovered to have an inferior myocardial infarction on ECG, and visited the Department of Cardiovascular Surgery of Kyoto University Hospital in June. The

(Received October 21, 1998; revised manuscript received January 11, 1999; accepted January 28, 1999)

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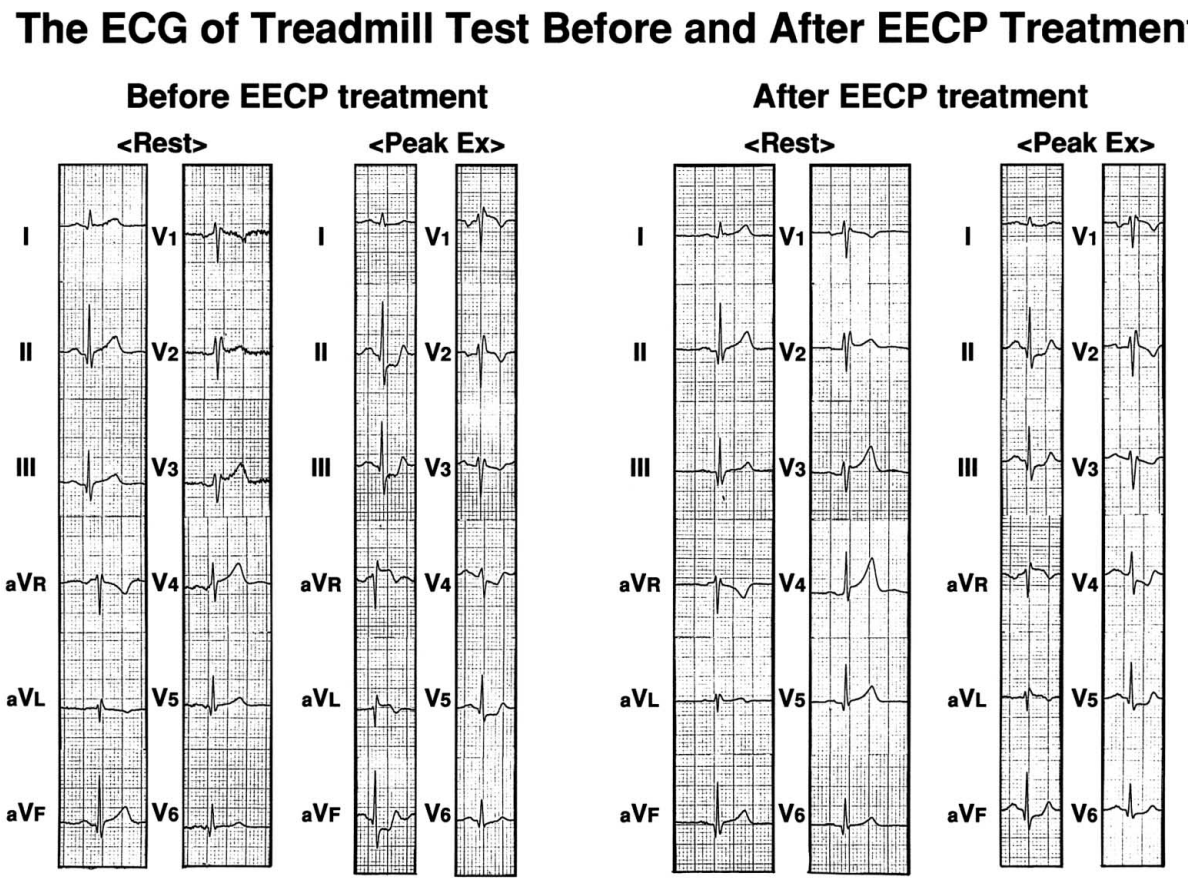

Fig 1. The ECG from the treadmill test before (left) and after EECP treatment (right). The ECG at rest, both before and after EECP treatment, shows normal sinus rhythm, incomplete right bundle branch block and no significant ST-T change. No significant ECG change at rest was observed either before or after EECP treatment. At peak exercise, both before and after EECP treatment, the ECG showed ST depression in II, III, aV_F and V_{4-6} (horizontal-down slope type). An impression was gained of exercise-induced ischemia in the inferolateral wall. However, the degree of ST depression in the II, III and aV_F leads after EECP treatment improved compared with before treatment, in spite of increaesd exercise time and no change in the peak double products. The improved exercise ECG suggested that the exercise-induced ischemia of the inferior wall improved after EECP treatment.

results of a complete medical examination (ECG, ^{201}Tl-SPECT, betamethyl-p-iodophenyl-pentadecanoic acid (BMIPP)-SPECT, etc) suggested an old myocardial infarction of the inferior wall and the patient underwent coronary angiography (CAG). The results of CAG were as follows: Seg 2: 99%; Seg 3: 50%; 4PL and 4PD: total with collateral filling from the left anterior descending coronary artery and the left circumflex coronary artery (grade III); Seg 6: 50%; Seg 7: 75%; Seg 13: 75%. It also revealed 3-vessel coronary artery disease, requiring a percutaneous transluminal coronary angioplasty (PTCA) for the right coronary artery, which was successfully done in August 1997. The patient no longer had chest symptoms and was discharged. Six months later, he felt chest oppression again, which became gradually worse. He was re-admitted in February 1998, and the second CAG showed re-stenosis at the PTCA site and other progressive coronary stenoses. After the second CAG, ^{201}Tl-SPECT was performed and showed anteroseptal hypoperfusion on exercise with redistribution at rest and an inferior perfusion defect, which suggested that the anteroseptal wall was viable but not the inferior wall. The indication for coronary artery bypass grafting (CABG) was discussed, but before enrolling in operating CABG, EECP treatment was suggested for the patient and was accepted. To ensure sufficient growth of the coronary collateral vessels, it was arranged that the patient be treated with EECP for 35 h.

Treatment

The EECP treatment was given in 1-h sessions, twice daily, and for a total of 35 h. During the treatment, the patient's medication was not changed. The EECP study was approved by the ethical committee of Kyoto University.

Tests

The patient underwent the treadmill test (Bruce method), exercise ^{201}Tl-SPECT (Bruce method) and ^{13}N-ammonia PET within 10 days before and after the EECP treatment.

Exercise ^{201}Tl-SPECT During the exercise ^{201}Tl-SPECT after EECP treatment, we stopped the exercise test at the same level of cardiac work done before treatment, and the image after treatment was acquired.

^{13}N-Ammonia PET The ^{13}N-ammonia PET was performed both at baseline and during dipyridamole provocation. At the baseline, both heart rate (HR) and blood pressure (BP) were measured. During the dipyridamole provocation test, measurement of HR and BP, and a 12-lead ECG, continued throughout the administration of dipyridamole (0.56 mg/kg iv for 4 min) and were terminated when the image was acquired. Three minutes after the administration of dipyridamole began, the ^{13}N-ammonia was injected intravenously. The image acquisition started

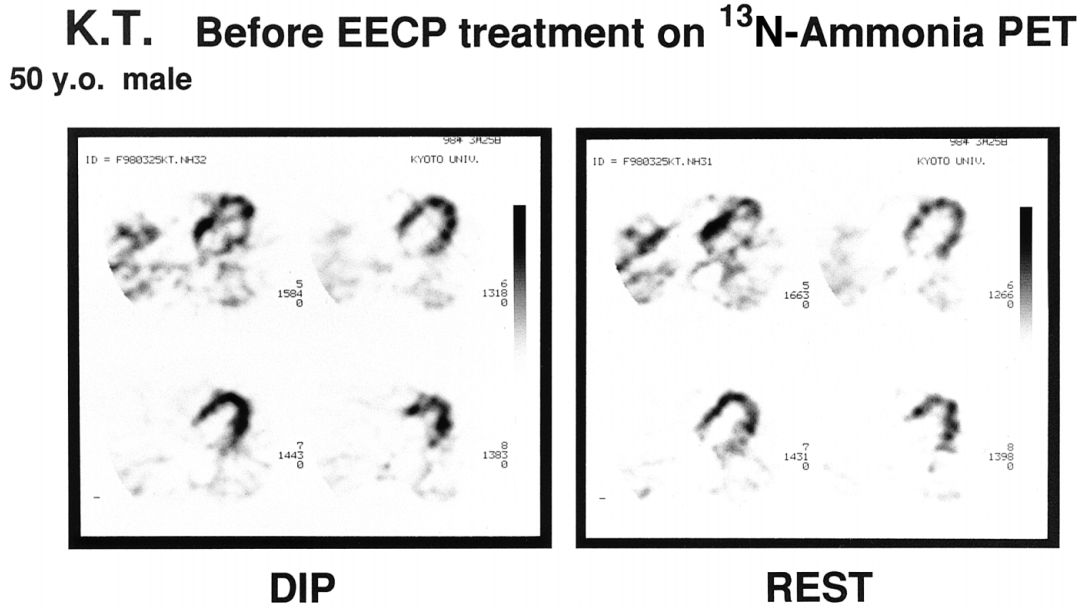

Fig 2. ^{13}N-ammonia PET before EECP treatment. A small infero-apical defect was visualized at rest and there was no change after dipyridamole provocation (DIP), so it was considered to be an old myocardial infarction.

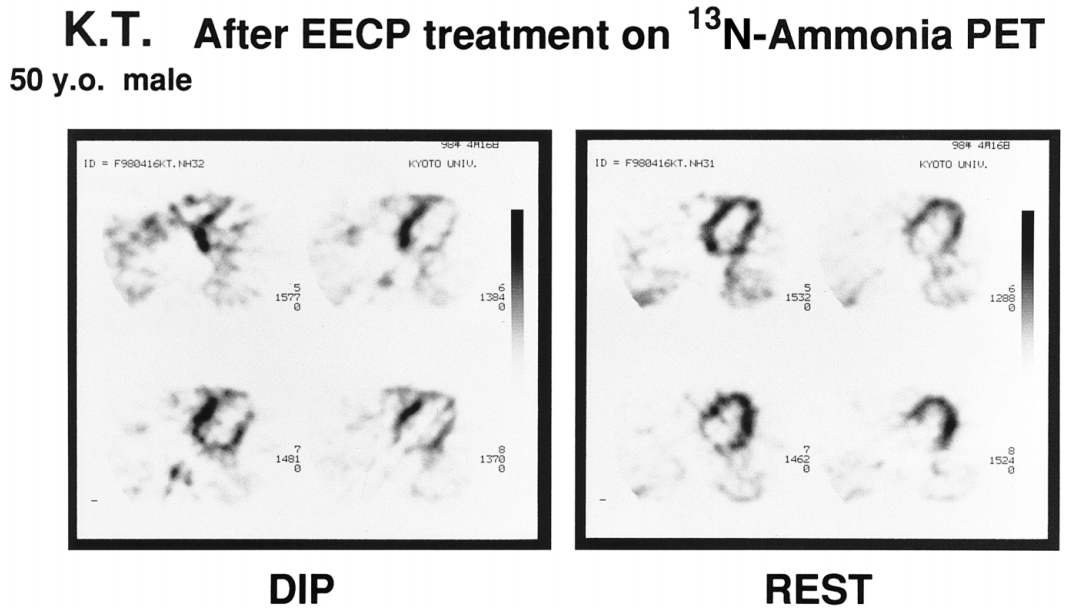

Fig 3. ^{13}N-ammonia PET after EECP treatment. A small inferior defect was visualized at rest, without any change after provocation (DIP), and an anterolateral hypoperfusion was visualized after provocation with redistribution at rest. The total impression was gained of a small scar on the inferior wall and a stress-induced ischemia of the anterolateral wall.

immediately after injection of the ^{13}N-ammonia, both at baseline and during dipyridamole provocation, before and after EECP treatment.

Interpretation of Images

All images from the exercise ^{201}Tl-SPECT and the ^{13}N-ammonia PET were interpreted by experienced observers, who have no prior information about the patient.

The regions of interest (ROI) on each myocardial wall were manually drawn on the ^{13}N-ammonia PET images taken at the baseline and during dipyridamole provocation both before and after EECP treatment. The coronary perfusions were calculated with the ROIs following Tadamura's method[9]. The CFR was calculated as that the coronary perfusion during provocation was divided by that on the baseline.

Results

During the treadmill test (Bruce method), the exercise time was prolonged from 500 s before to 619 s after EECP treatment. The onset time measured by 1-mm ST depression was also prolonged from 252 s before to 600 s after EECP treatment. However, the peak double products did not change significantly from 13,800 beats min^{-1} mmHg before to 14,124 beats min^{-1} mmHg after EECP treatment. No significant ECG change at rest was observed either

Table 1 Coronary Perfusion and Coronary Flow Reserve (CFR) in the Myocardial Walls

	Myocardial walls							
	Anterior		*Septal*		*Lateral*		*Inferior*	
	Coronary perfusion (ml min^{-1} g^{-1})	*CFR*	*Coronary perfusion (ml min^{-1} g^{-1})*	*CFR*	*Coronary perfusion (ml min^{-1} g^{-1})*	*CFR*	*Coronary perfusion (ml min^{-1} g^{-1})*	*CFR*
Before treatment	*0.48*	*1.76*	*0.52*	*2.07*	*0.61*	*1.50*	*0.46*	*1.99*
After treatment	*0.66*	*1.07*	*0.75*	*2.15*	*0.68*	*1.12*	*0.57*	*2.06*

before or after EECP treatment. At peak exercise, however, the degree of ST depression in the II, III and aVF leads after EECP treatment improved compared with that before treatment, in spite of the increased exercise time and no change in the peak double products (Fig 1).

On the images from ^{201}Tl-SPECT, the myocardial perfusion after the EECP treatment improved compared with those interpreted before treatment. With particular reference to the inferior wall, the size of the perfusion defect on exercise did not show significant change; however, the minimal redistribution improvement was recorded at rest, after the EECP treatment.

On ^{13}N-ammonia PET before EECP treatment, BP was 118/73 mmHg and the HR was 50 beats/min at baseline. On dipyridamole provocation, the ECG showed no significant change and the patient felt no chest pain.

After the EECP treatment, BP was 95/55 mmHg and the HR was 49 beats/min and the patient had no chest pain at baseline. Just before the provocation, the ECG showed no significant change compared with the ECG done before treatment and the patient felt no chest pain. However, a few minutes after starting dipyridamole, he complained of chest oppression and a slight ST depression in leads II, III and aVF (horizontal type) was observed, but no significant change of either BP or HR was observed. His chest discomfort disappeared and the ECG change returned to the control level while the administration of dipyridamole was finished.

The ^{13}N-ammonia PET image before EECP treatment is shown in Fig 2, and that after the treatment in Fig 3. The finding before treatment was a small inferoapical defect at rest without any change on dipyridamole provocation, created the impression of a small inferoapical old myocardial infarction. After the treatment, however, the ^{13}N-ammonia PET image showed a small inferior defect at rest without any change on provocation, and an anterolateral hypoperfusion on provocation with redistribution at rest. The total impression was of a small scar on the inferior wall and a pharmacologically induced ischemia at the anterolateral wall.

The results of all coronary perfusions and CFRs are shown in Table 1. The coronary perfusions of each myocardial wall increased at baseline after the EECP treatment compared with those done before. The CFRs of the septal and inferior walls increased after the EECP treatment compared with those done before EECP. However, the CFRs of the anterior and lateral walls decreased after EECP treatment compared with the control.

Discussion

In the present patient, the exercise time and the onset time by 1-mm ST depression after EECP treatment were prolonged on the treadmill test (Bruce method) compared with those measured before EECP, but the peak double products did not change significantly. These findings were similar to previous studies.[4–7,10] The improved exercise ECG suggested that exercise-induced ischemia of the inferior wall improved after EECP treatment.

Lawson et al considered that the EECP effect was due to both cardiac and peripheral effects;[10] because in the improved patients, the peak double products after EECP treatment, although demonstrating a linear relation with exercise duration, did not increase significantly despite the increased exercise duration. This suggested that the increase in exercise duration after EECP treatment was due to both improved myocardial perfusion and altered exercise hemodynamics. Thus, they considered that EECP therapy appeared to exert a 'training' effect: decreasing peripheral vascular resistance and the heart rate response to exercise. We do not consider that the effect of EECP treatment was only due to recruitment and development of the coronary collateral vessels, but it is difficult to simultaneously evaluate both cardiac and peripheral effects. Therefore, in our first study we tried to prove that the cardiac effect of EECP treatment was due to recruitment and development the coronary collateral vessels. The CAG is useful for evaluating anatomical change, but the coronary arteries have autoregulation in controlling coronary blood flow. The CFR is measured using pharmacological provocation to evaluate the decreased coronary endothelial function, which is important to evaluate because it is not necessarily proportional to anatomical stenosis. Therefore, we chose the ^{13}N-ammonia PET to evaluate this coronary function and the cardiac effect of EECP treatment, because the EECP treatment is noninvasive and quantitative measurement is possible with the ^{13}N-ammonia PET.

The increase in all coronary perfusions of each of the myocardial walls at baseline suggested the development of coronary collateral vessels, and the subsequent increase in blood supply. However, the coronary perfusions measured in each myocardial wall at baseline after treatment were not considered to be increased enough compared with previous studies.[11–15] Nor was the recovery of CFR in the septal and inferior walls on dipyridamole provocation after EECP treatment enough compared with previous studies.[9,11–15]

We hypothesized that the decrease in the CFR at anterior and lateral walls was because the coronary perfusion at baseline after treatment increased compared with that done before treatment, and the blood steal from the anterior and lateral walls to the inferior wall might have been augmented with the developed collateral vessels. However, CAG was not performed after treatment, and so this hypothesis has not been proved yet. We must consider the difference between the exercise test and pharmacological provocation test. Pharmacologically induced steal may not affect perfusion much on exercise test. In spite of the relatively decreased flow reserve at the lateral wall (image visible on the ^{13}N-ammonia PET), the definite flow was not below the normal resting value.

In this study, the improvement of chest symptoms, the ST depression on ECG, the ^{201}Tl-SPECT image, and the coronary perfusion and CFR on the ^{13}N-ammonia PET with dipyridamole, suggested that after EECP treatment myocardial ischemia recovered at the inferior wall. Although the patient did not feel any chest symptoms, and his exercise time and onset time by 1-mm ST depression were prolonged after EECP treatment, the coronary perfusions and CRFs were not enough to improve his quality of life and so we reconsulted the Department of Cardiovascular Surgery about performing CABG.

This report is the first to evaluate EECP treatment with ^{13}N-ammonia PET, and to prove that both coronary perfusion at baseline and coronary flow reserve improved. The result of EECP therapy should be not only to recruit and develop the coronary collateral vessels but also to improve the coronary artery function. Thus, EECP treatment is one of the choices for angina treatment.

References

1. Soroff HS, Hui JCK, Grion FG: Current status of external counterpulsation. *Crit Care Clin* 1986; **2:** 277–295
2. Soroff HS, Cloutier CT, Birtwell WC, et al: External counterpulsation: Managment of cardiogenic shock after myocardial infaction. *JAMA* 1974; **229:** 1441–1450
3. Amsterdam EA, Banas J, Criley JN, et al: Clinical assesment of external pressure circulatory assistance in acute myocardial infaction: Report of a cooperative clinical trial. *Am J Cardiol* 1980; **45:** 349–356
4. Zheng ZS, Li TM, Kambie H, et al: Sequential external counterpulsation (SECP) in China. *Trans Am Soc Artif Intern Organs* 1983; **29:** 599–603
5. Lawson WE, Hui JKC, Soroff HS, et al: Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. *Am J Cardiol* 1992; **70:** 859–862
6. Lawson WE, Hui JKC, Zheng ZS, et al: Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. *Am J Cardiol* 1995; **75:** 840–841
7. Arora RR, Chou TM, Jain D, et al: Results of Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): EECP reduces anginal episodes and exercise-induced myocardial ischemia (abstract). *Circulation* 1997; **96:** I-466
8. Masuda D, Nohara R, Fujita M, et al: A patient with silent myocardial ischemia successfully treated with enhanced external counterpulsation showing improved myocardial perfusion on ^{201}Tl-SPECT image. *Junkankika* 1998; **43:** 549–550
9. Tadamura E, Tamaki N, Yonemura Y, et al: Assessment of coronary vasodilator reserve by N-13 ammonia PET using the microsphere method and Patlak plot analysis. *Ann Nucl Med* 1995; **9:** 106–118
10. Lawson WE, John CK, Zhen SZ, et al: Improved exercise tolerance following enhanced external counterpulsation: Cardiac or peripheral effect? *Cardiology* 1995; **87:** 271–275
11. Krivokapich J, Huang SC, Shelbert HR: Assessment of the effects of dobutamin on myocardial blood flow and oxidative metabolism in normal human subject using nitrogen-13 ammonia and carbon-11 acetate. *Am J Cardiol* 1993; **71:** 1351–1356
12. Krivokapich J, Smith GT, Huang SC, et al: 13N ammonia myocardial imaging at rest and with exercise in normal volunteers: Quantification of absolute myocardial perfusion with dynamic positron emission tomography. *Circulation* 1989; **80:** 1328–1337
13. Chan SY, Brunken RC, Czernin J, et al: Comparison of maximal myocardial blood flow during adenosin infusion with that of intravenous dipyridamole in normal men. *J Am Coll Cardiol* 1992; **20:** 979–985
14. Czernin J, Muller P, Chan S, et al: Influence of age and hemodynamic on myocardial blood flow and flow reserve. *Circulation* 1993; **88:** 62–69
15. Iskandrian AS, Verani MS, Heo J: Pharmacological stress testing: Mechanism of action, hemodynamic response, and results in detection of coronary artery disease. *J Nucl Cardiol* 1994; **1:** 94–111