Effect of Aging on Myocardial Perfusion Reserve

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Myocardial perfusion reserve (hyperemic ÷ basal myocardial blood flow) describes vasodilator responsiveness of coronary-resistive vessels. The effect of aging and gender on myocardial perfusion reserve remains controversial. **Methods:** We studied 56 normal volunteers (21 women, 35 men; aged 50 ± 20 yr, range 21–86 yr) with ^{15}O-water PET to measure myocardial blood flow during basal and hyperemic states with intravenous dipyridamole (0.56 mg/kg, n = 46) or adenosine (140 μg/kg/min, n = 10). For comparative analysis, patients were grouped according to age: <30 yr (n = 11), 30–49 yr (n = 18), 50–69 yr (n = 15) and ≥70 yr (n = 12). **Results:** Overall, basal flow was 1.00 ± 0.26 ml/min/g and hyperemic flow was 3.31 ± 1.38 ml/min/g, resulting in a myocardial perfusion reserve of 3.38 ± 1.35. There was an increase in basal flow with age (r = 0.45, p < 0.025), although hyperemic flow was only lower in patients ≥70 yr, causing a significant reduction in myocardial perfusion reserve: 3.54 ± 0.96 in <30 yr, 4.23 ± 1.35 in 30–49 yr, 3.51 ± 1.21 in 50–69 yr and 1.94 ± 0.46 in ≥70 yr (p < 0.05 versus all groups <70 yr). **Conclusion:** Myocardial blood flow during basal and hyperemia conditions are roughly comparable up to 60 yr of age. Above this age, there is significant increase in basal flow associated with an increase in systolic blood pressure. Above 70 yr, there is a significant reduction in hyperemic flow, and thus myocardial perfusion reserve independent of hemodynamic response to vasodilator stress.

Key Words: myocardial perfusion reserve; dipyridamole; oxygen-15-water; positron emission tomography

J Nucl Med 1995; 36:2032–2036

Ideally, coronary vasodilator reserve, defined as the ratio of maximal to basal coronary blood flow, for a given perfusion pressure (1) may be used as an objective measurement of vasodilatory capacity of coronary circulation (2,3). Thus, it has been used extensively to document functional severity of epicardial coronary stenoses (4–7). Given that coronary blood flow is determined predominantly by vasodilatation in coronary-resistive vessels in the absence of flow-limiting epicardial disease coronary vasodilator reserve is also a measure of resistive-vessel function (1–6).

The effect of aging on coronary-resistive vessel function is poorly understood. In atherosclerosis, there is increasing evidence suggesting that coronary-resistive vessel dilatation may be impaired early before the development of significant epicardial coronary disease (8,9), probably due to endothelial cell dysfunction (10). Given the increase in systolic blood pressure with the time associated with reduction in compliance of large systemic arteries (11), and possible changes vascular endothelium integrity (12), it is possible that coronary-resistive vessel function declines along with the general age-related decline in cardiovascular performance. The age of onset and the time course of this potential change are not clearly defined, which has important implications in subject selection for studies on coronary flow and myocardial perfusion.

The aim of this study was to use dynamic PET to measure myocardial blood flow in normal male and female subjects of different ages to document any changes in coronary-resistive vessel function occurring as a function of aging.

METHODS

Subjects

Fifty-six normal subjects (21 women, 35 men; mean age 50 ± 20 yr, range 21–86 yr) were studied. All subjects were at low risk for coronary artery disease (CAD) at the initial screening. None of the subjects had a clinical history of CAD and all had a normal physical examination. All subjects were nonsmokers with no evidence of valvular or primary myocardial disease, no history of diabetes, systemic hypertension or a family history of coronary disease. Subjects were enrolled either by contact as relatives of patients or, in the case of subjects over 60 yr, from a ballroom dancing class. None were on any cardiovascular medication. All subjects had a normal resting electrocardiogram, a negative treadmill exercise test for ischemia at high workload and underwent PET scanning.

The PET imaging protocol was approved by the Research Ethics Committee of Hammersmith Hospital, London and the Hospital Ethics Committee of the Cliniques Universitaires Saint-Luc, Brussels. All subjects gave written informed consent.

Study Protocol

PET. Imaging was performed at two centers: University of Louvain, Brussels, Belgium (10 subjects) using an ECAT 911/01 single-slice tomograph (CTI Inc., Knoxville, TN), which has been previously described (13) and MRC Cyclotron Unit, Hammersmith Hospital, London, UK (46 subjects) using an ECAT 931-08/12 15 slice tomograph (CTI) giving a 10.5-cm axial field of view (14). In both scanners, emission scans were reconstructed with a Hanning filter with a cutoff frequency of half maximum, resulting

TABLE 1
Hemodynamic Parameters at Baseline and Hyperemia

Age band	n	Baseline			Hyperemia		
		Heart rate	Systolic blood pressure	Rate-Pressure product	Heart rate	Systolic blood pressure	Rate-Pressure product
20–29	10	66 ± 12	120 ± 6	7990 ± 1630	95 ± 18	120 ± 114	11,200 ± 1920
30–39	9	62 ± 8	111 ± 10	6870 ± 980	89 ± 10	115 ± 13	10,250 ± 1580
40–49	10	60 ± 11	123 ± 27	7310 ± 1220	86 ± 15	131 ± 21	11,360 ± 3480
50–59	8	68 ± 6	128 ± 20	8629 ± 1763	88 ± 3	131 ± 23	11,760 ± 2440
60–69	7	64 ± 8	144 ± 13*†‡	9740 ± 1340†‡	88 ± 9	150 ± 10*†	13,260 ± 1820†
70–79	7	64 ± 6	140 ± 18*†‡	9070 ± 1950†‡	79 ± 9*	148 ± 18*†	11,730 ± 2210
80–89	5	58 ± 4	139 ± 29*†‡	8150 ± 2120	70 ± 10*†§	145 ± 20*†	10,180 ± 2460
Mean ± s.d.		64 ± 9	129 ± 21	8180 ± 1725	87 ± 14	133 ± 21	11,500 ± 2495

*$p < 0.05$ vs. 20–29 yr.
†$p < 0.05$ vs. 30–39 yr.
‡$p < 0.05$ vs. 40–49 yr.
§$p < 0.05$ vs. 50–59 yr.

in a transaxial resolution of 8 mm FWHM for the emission data at the center of the field of view (13,14).

Regional myocardial blood flow (milliliters per minute per gram) was measured on transaxial images using ^{15}O-water as a flow tracer given as an intravenous infusion (University of Louvain) or the ^{15}O-carbon dioxide inhalation technique (MRC Cyclotron Unit). Both techniques give comparable results (15,16) and have been validated in the respective centers (15,17). Measurements were made at rest and 2 min after the end of intravenous administration of dipyridamole (0.56 mg/kg over 4 min in 46 subjects) to cover the peak vasodilator effect or during intravenous adenosine infusion (140 μg/kg/min in 10 subjects) according to standard practice (15–17). In both centers, heart rate and systemic blood pressure measurements were obtained every minute during the infusion and acquisition protocol. Patient characteristics were similar at both study sites, with no significant differences identified in the hemodynamic response to either vasodilator in the subjects studied. Data analysis was performed as previously reported (15,17). Myocardial perfusion reserve was defined as hyperemic myocardial blood flow divided by basal myocardial blood flow.

Because basal myocardial blood flow is closely related to the rate-pressure product (18), an index of myocardial oxygen consumption, basal flow data were also corrected in each patient for the respective rate-pressure product by the following equation:

rate-pressure product − corrected basal flow

$$= \text{basal flow} \cdot \frac{[\text{mean of group rate-pressure product}]}{\text{individual rate-pressure product.}}$$

This correction assumes that there is homogenous myocardial perfusion in the subjects.

In addition to studying the effect of age on basal and hyperemic myocardial blood flow, a direct comparison was also made between men and women within a 40–70 yr age range to study any relationship between gender and blood flow.

Statistical Analysis

All data are expressed as mean ± s.d. Two-tailed paired and unpaired Student's t-tests were used to compare mean group values. Simultaneous comparison of more than two mean values was performed using one-way analysis of variance, and Fisher's

least significant difference method was subsequently applied to localize the source of the difference (19). Regression analysis was performed according to standard techniques on the myocardial blood flow data to achieve the best fit. A p value <0.05 was considered statistically significant.

RESULTS

Hemodynamic Variables during PET

Overall, there was an increase in heart rate from baseline to hyperemia, 64 ± 9 to 87 ± 14 bpm (p < 0.001) but no significant change in systolic blood pressure from baseline to hyperemia, 129 ± 21 to 133 ± 21 mmHg, in the subjects studied. The rate-pressure product, however, increased from 8180 ± 1725 mmHg/min at baseline to 11,500 ± 2495 mmHg/min at hyperemia (p < 0.001), a mean increase of 41.9% ± 28.8% (Table 1). Diastolic blood pressure and mean arterial pressure were not significantly different at baseline and hyperemia. A weak relationship was demonstrated between the basal rate-pressure product and increasing age, which was due to an increase in systolic blood pressure at rest with increasing age (Fig. 1). A direct relationship was also seen between the rate-pressure product and basal myocardial blood flow (Fig. 1).

A comparison was made between male and female study subjects aged 40 to 70 yr. The mean age in the 13 men was 52 ± 9 yr (range 41–70 yr) and 57 ± 8 yr (range 47–70 yr, p = ns) in the 14 women. At baseline, the heart rate was 63 ± 8 and 65 ± 9 bpm, systolic pressure was 130 ± 17 and 138 ± 26 mmHg and the rate-pressure product was 8204 ± 1566 and 8867 ± 1676 mmHg/min (all p = ns). At hyperemia, the heart rate was 83 ± 12 and 90 ± 11 bpm, systolic pressure was 138 ± 19 and 142 ± 22 mmHg and the rate-pressure product was 11,677 ± 3037 and 12,784 ± 2491 mmHg/min (all p = ns).

Myocardial Blood Flow by Age

Myocardial blood flow and myocardial perfusion reserve according to age bands are shown in Table 2. Basal flow was higher with increasing age, which occurred because of the
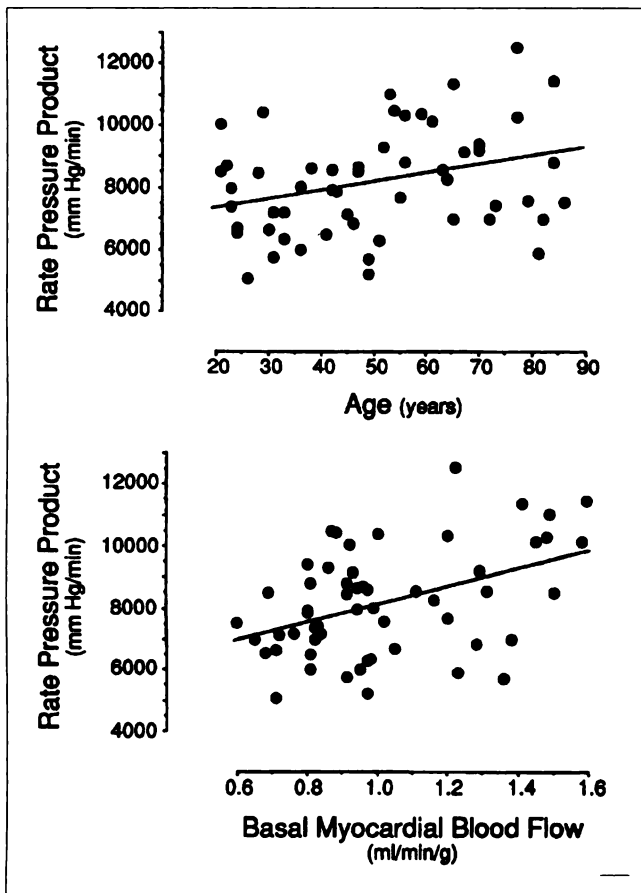
FIGURE 1. Scatterplot shows the relationship between (top) age and basal rate-pressure product (y = 6756 + 28.4x; r = 0.32, p = 0.016) and (bottom) basal myocardial blood flow and rate-pressure product (y = 5260 + 2881x; r = 0.44, p < 0.001).

increase in systolic blood pressure and, thus, the rate-pressure product. This increase was abolished when basal flow was corrected for the rate-pressure product. A reduced hyperemic response was seen in subjects over age 70 yr (Fig.

2). Thus, myocardial perfusion reserve was preserved in patients up to the age of 70 years but reduced progressively in older subjects (Fig. 2), irrespective of the basal flow corrections by the rate-pressure product (Table 2).

Myocardial Blood Flow by Gender

A significant difference was noted in basal myocardial blood flow (0.98 ± 0.28 and 1.19 ± 0.21 ml/min/g, p = 0.039) in men and women, respectively. This apparent difference was no longer significant after basal flow correction for the rate-pressure product (0.99 ± 0.25 and 1.14 ± 0.34 ml/min/g, p = ns) in men and women, respectively. Furthermore, no differences were found between hyperemic flow (3.73 ± 1.47 and 3.69 ± 1.66 ml/min/g), myocardial perfusion reserve (3.88 ± 1.54 and 3.18 ± 1.48) or corrected myocardial perfusion reserve (3.88 ± 1.59 and 3.55 ± 1.98) in men and women. These findings are consistent with those in previous studies (18).

DISCUSSION

In this study, systemic hemodynamic response at hyperemia was demonstrated mainly as an increase in heart rate, with a lesser heart rate response in older subjects. Myocardial blood flow at baseline, when corrected for workload, at hyperemia and, thus, myocardial perfusion reserve, were not significantly different in patients under age 70 yr. Above age 70, after correcting for rate-pressure products, there was no change in myocardial blood flow at baseline compared to younger subjects. In subjects older than 70 yr, however, there was still progressive reduction in hyperemic flow response, independent of hemodynamic response to vasodilatation. Thus, the myocardial perfusion reserve remained unchanged up to this age threshold and was subsequently reduced, independent of the increased systolic pressure at rest in older subjects.

Senneff et al. used ^{15}O-water PET and demonstrated similar basal myocardial blood flows in two groups of sub-

TABLE 2
Myocardial Blood Flow and Myocardial Perfusion Reserve

| Age band	MBF$_{basal}$	Corrected MBF$_{basal}$	MBF$_{hyperemia}$	Myocardial perfusion reserve	Corrected myocardial perfusion reserve
20–29	0.86 ± 0.13	0.91 ± 0.19	2.95 ± 1.04	3.41 ± 0.92	3.42 ± 1.44
30–39	0.88 ± 0.10	1.07 ± 0.18	3.66 ± 0.89	4.20 ± 0.80	3.51 ± 0.95
40–49	1.03 ± 0.27	1.19 ± 0.39	3.72 ± 1.40	3.88 ± 1.87	3.58 ± 1.96
50–59	1.05 ± 0.23	0.95 ± 0.24	4.12 ± 1.36	3.96 ± 1.09	4.63 ± 1.74
60–69	1.24 ± 0.28*†	1.09 ± 0.16	3.83 ± 1.84	3.07 ± 1.15†‡	3.42 ± 1.32
70–79	1.15 ± 0.27*†	1.07 ± 0.30	2.16 ± 0.84†‡§¶	1.84 ± 0.40*†‡§	2.02 ± 0.53*†‡§
80–89	1.00 ± 0.42	1.02 ± 0.42	1.97 ± 0.64†‡§¶	2.09 ± 0.54*†‡§	2.02 ± 0.48‡§

*p < 0.05 vs. 20–29 yr.
†p < 0.05 vs. 30–39 yr.
‡p < 0.05 vs. 40–49 yr.
§p < 0.05 vs. 50–59 yr.
¶p < 0.05 vs. 60–69 yr.
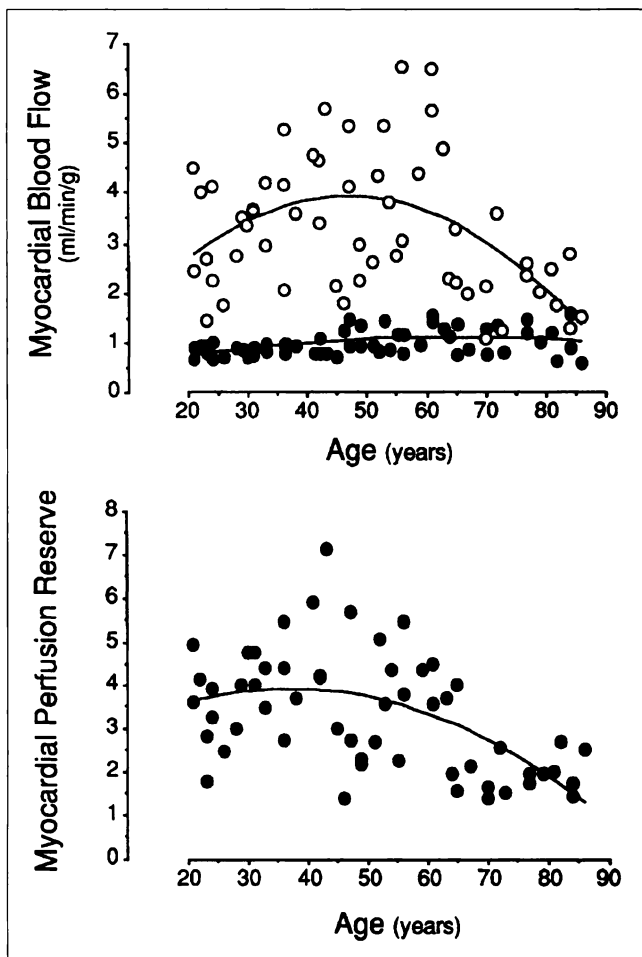
FIGURE 2. Scatterplot shows the relationship between (top) age and myocardial blood flow at baseline ($y = 0.33 + 0.025x - 0.00019x^2$; $r = 0.45$, $p = 0.025$) and hyperemia ($y = 0.22 + 0.16x - 0.002x^2$; $r = 0.49$, $p < 0.001$) and (bottom) age and myocardial perfusion reserve ($y = 2.41 + 0.08x - 0.001x^2$; $r = 0.55$, $p < 0.001$).

jects aged 25 and 55 yr), but a reduced flow response to dipyridamole in the older subjects, which they ascribed to reduced responsiveness to dipyridamole in the systemic and coronary vasculature (20). The latter finding agrees with our report finding, although no significant difference in hyperemic flow was seen between these two particular mean age groups. This may be because Seneff et al. found that a much lower mean heart rate response to dipyridamole was achieved in the older subjects. In addition, 4 of 11 older subjects had flow reserves ≤1.6, suggesting significant flow impairment (20).

In another study Czernin et al. used ^{13}N-ammonia and demonstrated increased basal flow with age that was directly related to higher systolic blood pressure (and thus rate-pressure product) in older subjects (mean age 25 and 55 yr) (18). Their finding is consistent with ours. In contrast to our study, however, no significant difference in hyperemic flow was seen in older subjects, implying that progressive reduction of coronary reserve was due predominately to the increase in basal flow alone. The reason for the differences in age-related hyperemic flow between the two

studies may be because we studied a larger number of subjects older than 70 yr (12 of 56 compared to 5 of 40), which allows greater discrimination of the extreme effects of age on hyperemic flow.

Although no gender difference was seen in hyperemic flow when age-matched men and women are compared, the women had a higher basal myocardial blood flow than the men, although this was no longer present after rate-pressure product correction. In our study, the majority of women were postmenopausal and we cannot address whether different hormonal states affect myocardial blood flow in normal controls.

Experimental studies show that there is a reduction in coronary flow per unit mass in different rat models of senescence but that, in the absence of macroscopic structural alterations in all sizes of coronary vessels, a change in vascular reactivity is the likely cause (21). In elderly subjects with risk factors for CAD, impaired vasomotor response to intracoronary administration of the endothelium-dependent vasodilator, acetylcholine, has been demonstrated in epicardial coronary arteries (23). Excluding such risk factors in patients with atypical chest pain, an age-related decrease in absolute coronary vasodilator reserve and dose response to acetylcholine still exist but with little reduction in flow reserve to endothelium-independent vasodilatation with papaverine. This suggests an intact vascular smooth muscle cell response (24). The fact that an attenuated response to dipyridamole occurs in patients over age 70 may be due to an inability of larger resistive vessels to respond to increased flow in the smaller arterioles, although this is only indirect result of impaired endothelial response to increased shear stress.

The effect of aging on the cardiovascular system is similar to that which occurs with hypertension. There is a tendency to develop cardiac hypertrophy, a reduction in left ventricular early diastolic filling rate, a reduction in arterial compliance and a diminished response to catecholamines (25). Irrespective of cardiac hypertrophy, there is also a reduction in basal and acetylcholine-induced release of endothelium-derived relaxing factors in resistive vessels in hypertension (26). Similarly, endothelial cells do become increasingly dysfunctional with age and, although there is frequent turnover in the vascular endothelium, the functional integrity of these cells is progressively weakened with increasing years (12,24).

Another explanation for the reduced vasodilator response may occur independent of the vascular endothelium. Dipyridamole is an adenosine deaminase inhibitor and by blocking local uptake of adenosine (27) potentiates the direct activity of adenosine on the P_1-purinergic receptor in vascular smooth muscle which is coupled to the adenylate cyclase enzyme. Given that systemic effects include a fall in arterial blood pressure and an increase in heart rate, the lesser increase in heart rate in the older subjects in this study may reflect an age-related decrease in response to the baroreceptor reflex (28).

There is also evidence of deficient neuroendocrine reg-

ulation of the cardiovascular system with advancing age (29). With beta-adrenergic receptor stimulation, older subjects have reduced heart rate response (30), lesser increase in left ventricular ejection fraction (independent of training (31)) and reduced relaxation of systemic vascular resistance compared to younger subjects (32). This appears to occur through multiple changes in molecular and biochemical beta-adrenergic receptor coupling (resulting in decreased affinity for agonists) and through postreceptor mechanisms such as altered activity of G-proteins and the adenylate cyclase catalytic unit (29). Adenosine may modulate the effect of beta-adrenergic receptor stimulation on cardiac contraction by reducing the receptor-mediated increase in intracellular cAMP, cAMP-dependent protein kinase and contractility (33). Given that in experimental models, there is greater local release of adenosine in the coronary microcirculation of older animals (34), it is possible that exogenous adenosine delivery has a lesser effect on vascular smooth muscle due to a process of desensitization. This is manifested in reduced myocardial perfusion reserve with extreme age.

CONCLUSION

Coronary-resistive vessel function and myocardial perfusion, as reflected in myocardial blood flow response to vasodilatation, is preserved to the end of the seventh decade. Thereafter, progressive reduction in vasodilatation occurs. These data have important implications for the selection of control subjects in coronary flow and myocardial perfusion studies.

ACKNOWLEDGMENT

REFERENCES

1. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Am J Cardiol 1974;33:87–94.
2. Hoffman JIE. Maximal coronary flow and the concept of coronary vascular reserve. Circulation 1984;70:153–159.
3. Klocke FJ. Measurements of coronary flow reserve: defining pathophysiology versus making decisions about patient care. Circulation 1987;76:1183–1189.
4. Gould KL, Kirkeeide RL, Buchi M. Coronary flow reserve as a physiologic measure of stenosis severity. J Am Coll Cardiol 1990;15:459–474.
5. Kirkeeide RL, Gould KL, Parsel L. Assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. VIII. Validation of coronary flow reserve as a single integrated functional measure of stenosis severity reflecting all its geometric dimensions. J Am Coll Cardiol 1986;7:103–113.
6. Wilson RF, Laughlin DE, Ackell PH, et al. Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. Circulation 1985;72:82–92.
7. Uren NG, Melin JA, De Bruyne B, Wijns W, Baudhuin T, Camici PG. Relation between myocardial blood flow and severity of coronary-artery stenosis. N Engl J Med 1994;330:1782–1787.
8. Zeiher AM, Drexler H, Wollschläger H, Just H. Modulation of coronary

vasomotor tone in humans. Progressive endothelial dysfunction with different early stages of coronary atherosclerosis. Circulation 1991;83:391–401.
9. Drexler HE, Zeiher AM, Meinzer K, Just H. Correction of endothelial dysfunction in coronary microcirculation of hypercholesterolaemic patients by l-arginine. Lancet 1991;338:1546–1550.
10. Kuo L, Davis MJ, Cannon S, Chilian WM. Pathophysiological consequences of atherosclerosis extend into the coronary microcirculation: restoration of endothelium-dependent responses by L-arginine. Circ Res 1992;70:465–476.
11. Learoyd BM, Taylor MG. Alterations with age in the viscoelastic properties of human arterial walls. Circ Res 1966;18:278–292.
12. Lüscher TF, Noll G. Endothelium-dependent vasomotion in aging, hypertension and heart failure. Circulation 1993;87(suppl VII):VII-97–VII-103.
13. Hoffman EJ, Phelps ME, Huang SC, Schelbert HR. Dynamic, gated and high-resolution imaging with the ECAT III. IEEE Trans Nucl Sci 1986;33:452–455.
14. Spinks TJ, Jones T, Gilardi MC, Heather JD. Physical performance of the latest generation of commercial positron scanner. IEEE Trans Nucl Sci 1988;35:721–725.
15. Araujo LI, Lammertsma AA, Rhodes CG, et al. Noninvasive quantification of regional myocardial blood flow in coronary artery disease with oxygen-15-labeled carbon dioxide inhalation and positron emission tomography. Circulation 1991;83:875–885.
16. Bergmann SR, Herrero P, Markham J, Weinheimer CJ, Walsh MN. Noninvasive quantification of myocardial blood flow in normal subjects with O-15-labeled water and positron emission tomography. J Am Coll Cardiol 1989;14:639–652.
17. Bol A, Melin JA, Vanoverschelde JL, et al. Direct comparison of ^{13}N-ammonia and ^{15}O-water estimates of perfusion and quantification of regional myocardial blood flow by microspheres. Circulation 1993;87:512–525.
18. Czernin J, Müller P, Chan S, et al. Influence of age and hemodynamics on myocardial blood flow and flow reserve. Circulation 1993;88:62–69.
19. Godfrey K. Comparing the means of several groups. N Engl J Med 1985;313:1450–1456.
20. Senneff MJ, Geltman EM, Bergmann SR, Hartman J. Noninvasive delineation of the effects of moderate aging on myocardial perfusion. J Nucl Med 1991;32:2037–2042.
21. Lakatta E. Cardiovascular regulatory mechanisms in advanced age. Phys Rev 1993;73:413–467.
22. Zeiher AM, Drexler H, Wollschläger H, Just H. Modulation of coronary vasomotor tone: progressive endothelial dysfunction with different early stages of coronary atherosclerosis. Circulation 1991;83:391–401.
23. Vita JA, Treasure CB, Nabel EG, et al. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. Circulation 1990;81:491–497.
24. Egashira K, Inou T, Hirooka Y, et al. Effects of age on endothelium-dependent vasodilation of resistance coronary arteries by acetylcholine in humans. Circulation 1993;88:77–81.
25. Lakatta EG. Similar myocardial effects of ageing and hypertension. Eur Heart J 1990;11(suppl G):29–38.
26. Panza JA, Quyyumi AA, Brush JE, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990;323:22–27.
27. West JW, Bellet S, Manzoli UC, Muller OF. Effects of persantine, a new coronary vasodilator, on coronary blood flow and cardiac dynamics in the dog. Circ Res 1962;10:35–42.
28. Gribbin B, Pickering TG, Sleight P, et al. Effect of age and high blood pressure on baroreflex sensitivity in man. Circ Res 1971;29:424–431.
29. Lakatta EG. Deficient neuroendocrine regulation of the cardiovascular system with advancing age in healthy humans. Circulation 1993;87:631–636.
30. Yin FC, Raizes GS, Guarnieri T, et al. Age-associated decrease in ventricular response to haemodynamic stress during beta-adrenergic blockade. Br Heart J 1978;40:1349–1355.
31. Stratton JR, Cerqueira MD, Schwartz RS, et al. Differences in cardiovascular responses to isoproterenol in relation to age and exercise training in healthy men. Circulation 1992;86:504–512.
32. van Brummelen P, Buhler FR, Kiowski W, Amann FW. Age-related decrease in cardiac and peripheral vascular responsiveness to isoprenaline: studies in normal subjects. Clin Sci 1981;60:571–577.
33. Dobson JG Jr. Mechanism of adenosine inhibition of catecholamine-induced responses in the heart. Circ Res 1983;52:151–160.
34. Dobson JG Jr, Fenton RA, Romano FD. Increased myocardial adenosine production and reduction of β-adrenergic contractile response in aged hearts. Circ Res 1990;66:1381–1390.