Anesthesiology
56:444–448, 1982

# *Cardiovascular and Regional Blood Flow Changes during Halothane Anesthesia in the Aged Rat*

*William E. Hoffman, Ph.D.,* David J. Miletich, Ph.D.,† Ronald F. Albrecht, M.D.‡*

*Chres Seals§ and Anita Jozefiak§*

**The authors investigated the cardiovascular and regional hemodynamic changes that occur in the aged rat under unanesthetized control conditions and during the induction of halothane anesthesia. Regional blood flow changes were measured in young (4-month-old) and aged (27–29-month-old) F-344 rats using radioactive microspheres under unanesthetized conditions and during three levels of halothane anesthesia. Blood halothane levels were measured at each anesthetic level. The inspired concentrations of halothane were adjusted in young *vs.* aged rats so that each group was tested at the same depth of anesthesia. Results indicate that aged rats had significantly lower blood pressures than young rats in an unanesthetized state and at all levels of halothane anesthesia. Tissue blood flow was similar between young and aged rats in skeletal muscle and skin, while blood flow to renal and small intestinal tissues was consistently higher in young rats. Heart blood flow was initially 100 per cent higher in young rats but decreased to similar levels as aged at the highest levels of halothane anesthesia used. Cerebral blood flow was similar initially in young *vs.* aged, but increased in young rats with deeper levels of halothane anesthesia while decreasing in aged rats. These results indicate significant regional hemodynamic differences in young compared to aged rats under unanesthetized conditions as well as in response to halothane anesthesia. (Key words: Age factors. Anesthetics, volatile: halothane. Brain: blood flow. Heart: blood flow.)**

ANESTHETIC MANAGEMENT of the geriatric patient, although not a new problem, is one of increasing importance to the anesthesiologist. The per cent of population over 59 years of age has increased from 6.5 per cent in 1900 to 13.2 per cent in 1970.[1] An increased incidence of hypertension, diabetes, arthritis and other problems with aging often results in the need for surgical care in the elderly.[1] It is apparent that physiologic changes occur in the aged subjects which make them more susceptible to the effects of anesthetics such that circulatory homeostasis is more difficult to maintain during surgery.[1–4] In these experiments the rat was used as an experimental model and the regional vascular effects of halothane anesthesia were examined in young *vs.* aged subjects. Blood pressure and regional blood flow were examined in young and aged rats in an unanesthetized state and with three different levels of halothane anesthesia.

## Methods

### Anesthetic Level

In order to test young and aged rats under equal anesthetic levels of halothane, initial experiments were carried out to determine the inspired halothane concentration necessary to produce loss of reflex response to tail pinch. Four-month and 27–29-month-old male Fischer F-344 rats were ventilated artificially during these experiments; body temperature was maintained at 37°C and arterial blood $P_{CO_2}$ was adjusted to 35–40 mmHg. The inspired halothane concentration was adjusted to 1 per cent in $O_2$ initially and maintained at this level for 15 min. If the rat responded to tail pinch the halothane concentration was increased 20 per cent and maintained for 15 min before the next test. This process was continued until the rat failed to respond to tail pinch. The inspired halothane anesthetic concentration was determined as the average between the level at which the rat did not respond to tail pinch and the last concentration at which the animal responded. If the rat did not respond to tail pinch initially the inspired halothane concentration was decreased 20 per cent and the process was reversed. The inspired halothane concentration required to produce loss of reflex response to tail pinch was $0.78 \pm 0.03$ per cent in aged ($n = 7$) and $0.95 \pm 0.05$ per cent in young rats ($n = 5$). The difference between the groups was significant ($P < 0.05$).

### Microsphere Injections

Four and 27–29-month-old F-344 rats were also used for cardiovascular measurements during halothane anesthesia. These animals received no drug treatment prior to the day of the experiment. Rats were tested with radioactive microspheres under unanesthetized conditions and at inspired halothane anesthetic concentrations of 0.39, 0.78, and 1.56 per cent in aged and 0.48, 0.95, and 1.90 per cent in young rats. These levels corresponded to 0.5, 1, and 2 times the halothane concentration necessary to produce anesthesia in young and aged rats, as indicated above. In the young and aged rats to be tested in an unanesthetized state catheters were implanted in a femoral artery and vein and the left ventricle under

* Assistant Professor, Director of Research Labs.
† Assistant Professor, Director of Research.
‡ Professor and Chairman.
§ Technical Assistant.

Received from the Department of Anesthesiology, Michael Reese Hospital and Medical Center, 29th Street and Ellis Avenue, Chicago, Illinois 60616. Accepted for publication November 19, 1981. Supported by NIH grant #HL25399 and RCDA #HL/AG 20336 to WEH.

Address reprint requests to Dr. Hoffman.

halothane anesthesia as reported previously.[5] Following completion of all surgical procedures the rats were allowed three hours to recover from the effects of the anesthetic before the experiment was started. During the experiment each unanesthetized rat was placed in a 30 × 15 × 10 cm plastic box. This box was airtight except for an inlet from the gas anesthetic machine, an outlet to a scavenger system and a small hole to accomodate the implanted catheters. Rats were tested with one microsphere injection while breathing 100 per cent oxygen (turnover rate = 3 times/min). Each rat received up to three microsphere injections using each of three labeled 15 μm microspheres, cobalt-57, ruthenium-103, or scandium-46 (New England Nuclear). Microspheres were suspended in stock solutions containing 10–20 ml isotonic saline and 0.01 per cent Tween-80® in concentrations of 500,000 microspheres/ml. With each microsphere injection the stock solution was vortexed for 2 min; thereafter, a 0.2-ml sample was withdrawn and injected immediately into the left ventricle and flushed in with 0.2-ml isotonic saline. The injection procedure was carried out in 15 s. The volume of the ventricular catheter was 0.06 ml. During microsphere injection, arterial blood samples were withdrawn from the femoral artery at a rate of 0.4 ml/min using a Harvard® withdrawal pump starting immediately before and ending 45 s after the microsphere injection. A 0.5-ml sample of arterial blood was taken after the microsphere injection in order to measure blood gases, *p*H, and blood halothane concentration. Donor rat blood was used to replace samples taken during testing. The 13 young and 10 aged rats tested under unanesthetized conditions also were tested later during halothane anesthesia.

Young and aged rats tested during halothane anesthesia were prepared surgically as above. A tracheostomy tube also was inserted and the animals were ventilated using a Harvard® small animal respirator. These rats included those tested initially unanesthetized above as well as rats anesthetized with halothane for all microsphere tests. For each test, the inspired halothane concentration was adjusted randomly to one of three anesthetic levels of halothane as indicated above, according to the age of the rat. Twenty minutes were allowed after adjustment of the halothane concentration in order to achieve a near steady state. A microsphere injection was then given and an arterial blood sample taken for measurement of blood gases, *p*H, and blood halothane concentration. Blood pressure was monitored continuously using a Hewlett-Packard® pressure transducer and chart recorder. Heart rate was measured immediately before each microsphere injection. The inspired halothane concentration then was adjusted randomly to another anesthetic level and the procedure was repeated. A differently labeled microsphere was used for each test condition. When each rat had received up to three microsphere injections they were killed with an infusion of saturated KCl and the following tissues were removed or sampled: brain, heart, kidneys, forelimb skeletal muscle, small intestine, and skin. The activity of each microsphere in blood and tissue samples was analyzed using a Nuclear Chicago 1085® gamma counter and a Nuclear Data 600® multi-channel analyzer.[5] Whole tissue samples were analyzed for brain, heart, kidney, and foreleg skeletal muscle but not small intestine or skin tissues. Skin and skeletal muscle samples contained 200–400 microspheres from each microsphere injection and all other tissues contained over 400 microspheres.

Whole arterial blood samples for blood halothane measurements were taken in heparinized glass capillary tubes sealed with clay. Samples were analyzed using a Packard Series® 428 gas chromatograph using a modification of the methods of Lowe.[6] One-microliter whole blood samples were injected directly onto an 80–100 mesh chromosorb P® column maintained at 40°C. The flame ionization detector and injection port were maintained at 150°C. Standards were prepared by adding 5 μl halothane to 20 ml water in a capped syringe. The specific gravity of halothane at room temperature was used to calculate the concentration, given as mg/100 ml. Data reported in these experiments are reported as mean ± SE. Statistical tests between animal groups were made with unpaired *t* tests at each experimental data point. A linear model analysis of variance (BMDP, Biomedical Computer Programs, UCLA) was used to test the treatment effects of increasing halothane doses between young and aged rats.

## Results

Arterial blood pressure, blood gases, and heart rate of unanesthetized and halothane anesthetized young and aged rats are shown in table 1. Blood pressure decreased with increasing halothane concentrations in both young and aged rats. Blood pressure and heart rate were decreased significantly in aged rats at each anesthetic concentration compared to young rats. Tissue blood flow changes are shown in figure 1. A linear model analysis of variance indicated that skeletal muscle and skin blood flow were decreased as a function of halothane concentration in young and aged rats with no significant difference between groups. Intestinal and renal blood flow were decreased significantly in aged compared to young over all halothane anesthetic levels ($P < 0.05$). Intestinal and renal blood flow did not change significantly in both groups with increasing halothane concentration. Cerebral blood flow (CBF) was similar between young and aged rats under unanesthetized conditions but increased significantly in young rats with increasing halothane concentrations ($P < 0.05$). By contrast, CBF did not increase

TABLE 1. Mean Blood Pressure, Cardiac Output, Heart Rate Blood Gases, pH, and Halothane Concentration in Young and Aged Rats

| | Young (4-month) | | | | Aged (27–29 month) | | | |
|---|---|---|---|---|---|---|---|---|
| | Inspired Halothane Concentration (Per Cent) | | | | Inspired Halothane Concentration (Per Cent) | | | |
| | 0 | 0.46 | 0.95 | 1.90 | 0 | 0.39 | 0.78 | 1.56 |
| Mean blood pressure (mmHg) | 122 ± 3 | 125 ± 3 | 87 ± 7 | 66 ± 9† | 109 ± 4* | 87 ± 7* | 55 ± 7* | 45 ± 4*† |
| Heart rate ($min^{-1}$) | 382 ± 12 | 386 ± 10 | 323 ± 11 | 307 ± 9† | 304 ± 18* | 292 ± 12* | 234 ± 16* | 242 ± 11*† |
| Arterial $P_{CO_2}$ (mmHg) | 37 ± 2 | 39 ± 1 | 41 ± 1 | 38 ± 1 | 38 ± 3 | 40 ± 1 | 40 ± 3 | 36 ± 1 |
| Arterial $P_{O_2}$ (mmHg) | 232 ± 28 | 297 ± 19 | 318 ± 20 | 332 ± 18 | 196 ± 22 | 293 ± 14 | 265 ± 23 | 245 ± 27 |
| Arterial pH | 7.39 ± .02 | 7.39 ± .03 | 7.40 ± .04 | 7.40 ± .04 | 7.42 ± .02 | 7.35 ± .03 | 7.38 ± .04 | 7.39 ± .04 |
| Blood halothane (mg/100 ml) | 0 | 11.6 ± 1.0 | 21.2 ± 2.1 | 35.4 ± 2.9† | 0 | 9.8 ± 1.9 | 16.3 ± 4.2 | 23.8 ± 1.7*† |
| n | 13 | 17 | 20 | 10 | 10 | 14 | 15 | 11 |

* $P < 0.05$, aged compared to young rats.
† = a significant trend ($P < 0.05$) as analyzed by analysis of variance over the four treatment procedures within each group.

in aged rats with increasing halothane anesthesia and decreased at the highest concentration ($P < 0.05$). Myocardial blood flow was significantly decreased in young but not aged rats with increasing levels of halothane anesthesia. Myocardial blood flow was increased significantly in unanesthetized young compared to aged rats but flow decreased to comparable levels in both groups as halothane concentration was increased to the highest level. Finally, no young rats died during testing but four aged rats died during halothane anesthesia with the highest inspired halothane concentration.

## Discussion

These results indicate distinct differences in young and aged rats uder unanesthetized conditions and during halothane anesthesia. The average life span of the rats used for these studies is 23.5 months.[4] By previously reported standards of gerontological research, the 27–29-month-old rats which we used are considered aged rats. It was observed that the aged rats required a significantly lower inspired concentration of halothane than young rats to produce anesthesia. This is consistent with similar data in humans in which Gregory *et al.*[7] reported decreased alveolar halothane concentrations were necessary to maintain anesthesia in the aged subject.

The changes observed in regional blood flow during halothane anesthesia agree qualitatively with those reported earlier by Miller *et al.*[8] They observed a 23 per cent decrease in cardiac output in rats during anesthesia with 1.3 per cent inspired halothane concentration. The per cent of cardiac output distributed to renal, brain, and small intestinal tissues increased during halothane anesthesia with the largest percentage change apparent in cerebral tissue. The per cent of cardiac output distributed to heart, skin, and skeletal muscle either increased or did not change during halothane anesthesia. Overall these data indicate that halothane induces blood flow decreases in skeletal muscle, skin and heart tissues while maintaining flow in brain, intestine and renal vascular beds. Amory *et al.*[9] have also studied regional blood flow in young rhesus monkeys during halothane anesthesia using radioactive microspheres. They reported that increasing levels of halothane anesthesia produced a decrease in heart, skin, and skeletal muscle blood flow while renal blood flow was unchanged. In young men, Eger *et al.*[10] reported that halothane anesthesia produced a decrease in both skin and skeletal muscle blood flow. These results are similar to those reported here. Results reported by Deutsch *et al.*[11] indicate that renal blood flow decreases during halothane anesthesia in humans. This suggests that the effect of halothane on renal vasculature in humans may be different from that observed in rat and monkeys.

The results of these studies are to some extent dependent on the ability to measure cardiovascular and regional blood flow changes with repeated injections of microspheres. In other experiments, we have previously shown that repeated microsphere injections in rats, using similar methods as used here, will produce no significant change in blood pressure, heart rate, cardiac output, or tissue blood flow.[5] Random testing of the different halothane anesthetic levels in both young and aged rats would also tend to minimize any systematic treatment effects. These factors support the reliability of the cardiovascular changes observed as well as the observed differences between young and aged rats.

There are reports which indicate that vascular changes in the aged subject lead to changes in tissue blood flow and vascular reactivity.[12,13] Studies suggest that cerebral blood flow and neuronal density both decrease as a function of aging.[14,15] However, other authors found changes in cerebral blood flow with aging only when it was also accompanied by pathologic changes affecting the circu-

latory system.[16,17] In aged rats, Haining *et al.*[12] reported a reduced cerebrovascular response to increased $CO_2$ breathing and hypoxia, compared to young rats. Morita *et al.*[18] reported that halothane abolishes cerebral autoregulation and that changes in cerebral blood flow during halothane treatment are due to the direct cerebrovasodilator effect of the anesthetic. Data presented here suggest that the reported cerebrovasodilator effects of halothane[18-20] may be attenuated in aged rats, resulting in a decrease in cerebral blood flow in aged rats below control levels at the highest concentration of halothane anesthesia tested.

Under unanesthetized conditions, a decrease in myocardial blood flow was observed in aged rats compared to young. This appeared consistent with the observed decrease in blood pressure and heart rate in aged rats and possibly a lower myocardial oxygen demand under resting conditions. At an inspired halothane concentration of 0.95 per cent the rate-pressure product of young rats was similar to that observed in unanesthetized aged rats. At this level of anesthesia, myocardial blood flow was similar in young rats to that observed in unanesthetized aged animals. This suggests a correlation between myocardial oxygen demand and myocardial blood flow in young and aged rats. Halothane depresses left ventricular function in both humans and animals.[21,22] Myocardial blood flow and oxygen consumption are decreased during halothane anesthesia in young animals and humans and vascular resistance may actually increase.[23] These changes correlate well with halothane-induced depression of left ventricular function and the determinants of myocardial oxygen consumption. There is no evidence of anaerobic glycolysis or ischemic electrocardiogram changes with increasing halothane concentrations.[10,21] As the direct effects of halothane on coronary smooth muscle vaculature is dilatory,[24] the changes observed here and in other studies in young subjects[21,23] indicate a decrease in myocardial metabolic demand and normal metabolic control of coronary blood flow with respect to myocardial oxygen consumption. The depression in myocardial blood flow was attenuated significantly in our aged rats with increasing halothane concentrations in spite of similar decreases in blood pressure, heart rate, and rate-pressure product between young and aged test groups. The lack of depression in myocardial blood flow with increasing halothane anesthesia may be the result of increased sensitivity of the coronary vasculature to the vasodilatory effects of halothane or decreased responsiveness of the aged myocardium to the depressant effects of halothane. A decreased pharmacologic responsiveness in aged myocardial tissue would support the latter possibility.[25] Roberts and Goldberg[25] have reported that the depressant effect of quinidine on atrial and ventricular tissue is attenuated in the aged heart.

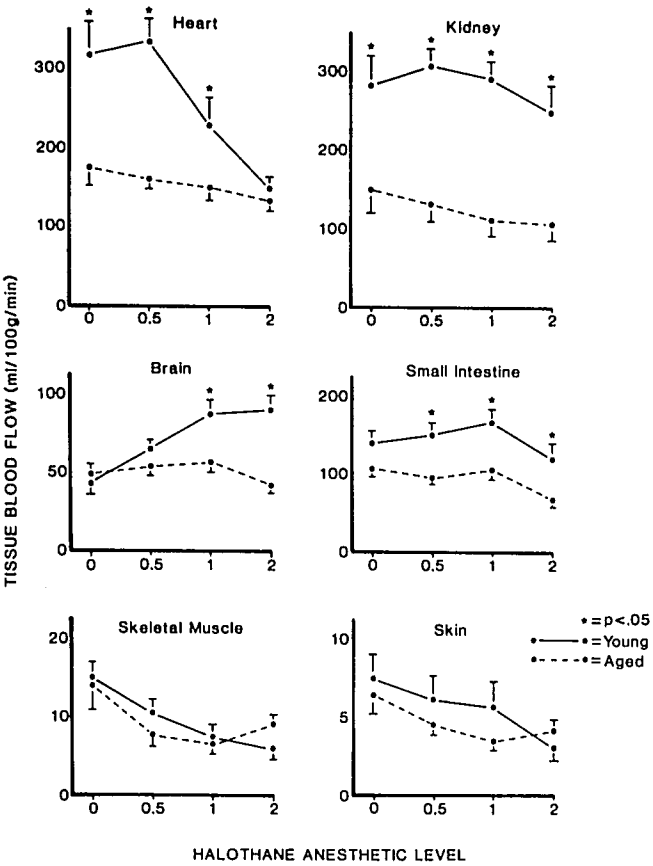


FIG. 1. Tissue blood flow in unanesthetized and halothane anesthetized young and aged rats. Inspired halothane anesthetic levels at each data point are as follows: 0 = unanesthetized control; 0.5 = 0.46 per cent for young, 0.39 per cent for aged; 1 = 0.95 per cent for young, 0.78 per cent for aged; 2 = 1.90 per cent for young, 1.56 per cent for aged. Number of rats tested at each anesthetic level are shown in table 1. Significance values indicate difference between young and aged rats at each anesthetic level as determined by *t* test. A linear model analysis of variance indicated that skeletal muscle and skin blood flow were decreased as a function of halothane concentration in young and aged rats with no significant difference between groups. Renal and intestinal blood flow were significantly different between young and aged rats with no difference in response to halothane anesthesia ($P < 0.01$). A significant difference between young and aged of tissue blood flow response to halothane was noted in heart and brain tissue ($P < 0.01$).

Both functional and morphologic renal changes have been reported in humans during aging.[26] Functionally, both a decrease in renal hemodynamics and renal tubular function have been observed. Davies and Shock[27] reported a decrease in p-aminohippurate clearance in aged subjects. Hollenberg *et al.*[28] demonstrated a decrease in renal blood flow per unit mass with advancing age. A decrease in renal blood flow was also observed here in aged rats under unanesthetized control conditions. At the same time, we found no change in renal vascular responsiveness in aged *vs.* young rats to the effect of increasing halothane concentration.

The extent to which these results relate to humans is uncertain. Cardiovascular changes and tissue vascular responsiveness may be different between humans and the rat during aging. An increased incidence of hypertension is apparent in humans during aging[1] but the rats studied here had lower blood pressures compared to young controls. Atherosclerosis occurs in aged humans but its presence in the aged rats of this study is doubtful. Wexler[29] reported that both aged senile and aged diabetic Sprague-Dawley rats will develop arteriosclerotic lesions but its presence in Fischer F344 rats is uncertain. There are similarities during aging between humans and the rat, however. First, a decrease in halothane anesthetic requirement occurs in both humans and the rat. In addition, tissue blood flow changes observed in aged rats in renal tissue agree with changes observed in humans.[27,28] Finally reflex cardiovascular responses are attenuated in aged humans and rats and vascular responsiveness to adrenergic and other pharmacologic stimuli are attenuated.[30,31] The regional vascular responses to halothane anesthesia are the result of several factors. These include the direct effects of halothane on smooth muscle contractility as well as central effects on cardiovascular control centers. Further studies are necessary to determine the extent to which regional vascular changes in aged rats during halothane anesthesia relate to humans.

## References


1. Ellison N: Problems in geriatric anesthesia. Surg Clin North Am 55:929–945, 1975
2. Miller R, Marlar K, Silvary G: Anesthesia for patients aged over ninety years. NY State J Med 77:1421–1425, 1977
3. Kohn P, Zerkert F, Vormitag E, et al: Risk of operation in patients over 80. Geriatrics 28:100–105, 1973
4. Masoro EJ, Bertrand H, Liepa G, et al: Analysis and exploration of age-related changes in mammalian structure and function. Fed Proc 38:1956–1961, 1979
5. Hoffman WE, Miletich DJ, Albrecht RF: Repeated microsphere injections in rats. Life Sci 28:2167–2172, 1981
6. Lowe HJ: Determination of all volatile organic anesthetics in blood, gas and tissue with or without chromatography. J Chromatogr 2:380–384, 1964
7. Gregory GA, Eger EI, Munson ES: The relationship between age and halothane requirement in man. ANESTHESIOLOGY 30:488–491, 1969
8. Miller ED, Kistner JR, Epstein RM: Whole body distribution of radioactively labelled microspheres in rat during anesthesia with halothane enflurane or ketamine. ANESTHESIOLOGY 52:296–302, 1980
9. Amory DW, Steffenson JL, Forsyth RR: Systemic and regional blood flow changes during halothane anesthesia in the rhesus monkey. ANESTHESIOLOGY 35:81–90, 1971
10. Eger EI, Smith NT, Stoelting RK, et al: Cardiovascular effects of halothane in man. ANESTHESIOLOGY 32:396–409, 1970
11. Deutsch S, Goldberg M, Steve GW, et al: Effects of halothane anesthesia on renal function in normal man. ANESTHESIOLOGY 27:793–804, 1966
12. Haining JL, Turner MD, Pantall RM: Local cerebral blood flow in young and old rat durng hypoxia and hypercapnia. Am J Physiol 218:1020–1024, 1970
13. Kuramoto K, Matsushita S, Kuwajima I, et al: Comparison of hemodynamic effects of exercise and isoproterenol infuson in normal young and old men. Jpn Circ J 43:72–76, 1979
14. Kety SS: Human cerebral blood flow and oxygen consumption as related to aging. Res Publ Assoc Res Nerv Ment Dis 35:31–45, 1956
15. Naritomi H, Meyler JS, Sakai F, et al: Effects of advancing age on regional cerebral blood flow. Arch Neurol 36:410–416, 1979
16. Sokoloff L: Cerebral circulation and metabolism in the aged, Aging. Edited by Gershon S, Raskin A. New York, Raven Press, 1975, pp 45–54
17. Birren JE, Butler R, Greenhouse SW, et al: Human aging: A biological and behavioral study. P.H.S. Pub. #986, U. S. Govt. Printing Office, Washington, D. C., 1963
18. Morita H, Nemoto EM, Bleyaert AL, et al: Brain blood flow autoregulation and metabolism during halothane anesthesia in monkeys. Am J Physiol 233:H670–H676, 1977
19. Morita H, Nemoto E, Bleyaert AL, et al: Brain blood flow autoregulation and metabolism during halothane anesthesia in monkeys. Am J Physiol 233:670–676, 1977
20. Michenfelder JD, Theye RA: Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimethaphan, halothane or nitroprusside. ANESTHESIOLOGY 46:188–195, 1977
21. Sonntag H, Merin RG, Donath U, et al: Myocardial metabolism and oxygenation in man awake and during halothane anesthesia. ANESTHESIOLOGY 51:204–210, 1979
22. Merin RG, Kumazawa T, Luka NL: Myocardial function and metabolism in the conscious dog during halothane anesthesia. ANESTHESIOLOGY 44:402–415, 1976
23. Smith G, Vance JP, Brown GM, et al: Changes in canine myocardial blood flow and oxygen consumption in response to halothane. Br J Anaesth 46:821–826, 1974
24. Domenech RJ, Macho P, Valdes J: Coronary vascular resistance during halothane anesthesia. ANESTHESIOLOGY 46:236–240, 1977
25. Roberts J, Goldberg PB: Changes in responsiveness of the heart to drugs during aging. Fed Proc 38:1927–1932, 1979
26. Epstein M: Effects of aging on the kidney. Feb Proc 38:168–172, 1979
27. Davies DF, Shock NW: Age changes in glomerular filtration rate, effective renal plasma flow and tubular excretory capacity in adult males. J Clin Invest 29:496–506, 1950
28. Hollenberg NK, Adams DF, Solomon HS, et al: Senescence and the renal vasculature in normal man. Circ Res 34:309–316, 1974
29. Wexler BC: Alloxan-induced diabetes in yong and old Sprague-Dawley rats. Exp Gerontol 16:47–58, 1981
30. Lakatta EG: Alterations in the cardiovascular system that occur in advanced age. Fed Proc 38:163–167, 1979
31. Fleisch JH: Age related changes in the sensitivity of blood vessels to drugs. Pharmacol Ther 8:477–487, 1980