Whatever the underlying mechanisms, the study reported here furnishes evidence that recovery properties in the intact ventricle are subject to the influence of excitation sequence. This supports previous evidence obtained by Cranefield and Hoffman that ventricular repolarization has features of a propagated process. It also provides a possible explanation for some features of the body surface electrocardiogram. The magnitude of the alteration in refractory period which is caused by activation sequence was small in this study but represents only alterations at the test sites. Alteration of recovery properties at other sites by activation sequence is probable and the cumulative effect of such alterations is likely to be capable of affecting the electrocardiographic waveform. In particular, the failure of the QRS-T area to be independent of activation sequence may reflect the failure of recovery properties to remain independent of activation order.  

**SUMMARY** Relaxation of rabbit and rat aorta by isoproterenol decreases with increasing age, whereas such responses caused by nitroglycerin or sodium nitrite are not age-dependent. In the present study, we sought to determine whether this relationship also exists in pulmonary arteries and portal veins. As was the case with the aorta, isoproterenol-induced relaxation of pulmonary arteries decreased as the animal aged; relaxation by nitroglycerin was minimally altered. Aging did not influence responses of rabbit and rat portal veins to isoproterenol or nitroglycerin. If the responses of these blood vessels are characteristic of the responses of other vascular smooth muscles to vasodilators, then this study suggests a difference in the manner by which arteries and veins age. We also confirmed that isoproterenol-induced relaxation of rabbit and rat aorta markedly decreases with increasing age and that the responses of rat aorta to nitroglycerin are independent of age. Because of the agonist used to contract the tissues before drug-induced relaxation, the results of the first series of experiments with nitroglycerin on rabbit aorta were at variance with our earlier findings. When KCl was used to contract the aorta, the mean effective dose (ED₅₀) obtained for nitroglycerin for tissues from 2-year-old rabbits was 8 to 19 times larger than that obtained from 2-month-old rabbits. This ratio dropped to 4 when the tissues were contracted with histamine. Since KCl and histamine contract rabbit aorta by different mechanisms, this finding suggests that, in addition to a specific loss in β-receptor activity, increasing age results in an alteration in the contraction-relaxation process of rabbit aortic tissue.

**REFERENCES**


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**The Relationship between Age and Relaxation of Vascular Smooth Muscle in the Rabbit and Rat**

**Jerome H. Fleisch, Ph.D., and Carol S. Hooker, M.S.**

**RELAXATION** of rabbit and rat thoracic aorta mediated by β-receptors decreases with increasing age of the animal. The biochemical mechanism responsible for this phenomenon is unknown, although Ericsson and Lundholm have presented evidence suggesting that, at least in rat aorta, the defect is in the adenylate cyclase-AMP system.

Our present experiments began with the idea of defining the relationship between vascular relaxation and aging in blood vessels other than the aorta. Relaxation of rabbit and rat pulmonary arteries induced by isoproterenol decreased with increasing age, whereas responses to nitroglycerin did not depend on the age of the animal. In contrast, the responses of rabbit and rat portal veins to both isoproterenol and nitroglycerin were not related to the age of the animal. This suggests that at least one facet of the aging process may differ in arterial and venous smooth muscle.

During the course of this investigation we reexamined the relationship between age and drug-induced aortic relaxation. This reexamination was important because we used animals obtained from colonies other than those used for our earlier studies. As the rabbits and rats aged, their aortas lost the ability to relax in response to isoproterenol; sodium nitrite, as well as nitroglycerin, produced maximal relaxation which was independent of age. These findings were in agreement with our previous observations. In addition, we now have demonstrated that the mean effective dose (ED₅₀) of nitroglycerin for aortas from older but not younger rabbits is...
dependent on the agonist used to first induce contraction of the muscles.

Methods

Male and female New Zealand rabbits (Sweetwater Farms Rabbitry; Hillsboro, Ohio, and Camm Research Institute, Inc., Wayne, New Jersey) and male Sprague-Dawley rats (Harlan Industries, Cumberland, Indiana) of known age were used. Rabbits were killed by an air embolism and rats by a blow to the head. Helically cut rabbit and rat aortas and rabbit pulmonary arteries (1-2 cm distal to the right ventricle) were prepared by the method of Furchgott and Bhadrakom. Since rat pulmonary arteries cut in a similar manner were not very reactive, a ring of this circular smooth muscle was used. Rabbit and rat portal veins were prepared as described by Hughes and Vane. Tissues were cut to approximately the same size regardless of age and then suspended in isolated organ baths holding a volume of 10 ml of a modified Krebs-bicarbonate solution (pH 7.4) of the following composition (millimoles per liter): KCl, 4.6; CaCl2·2H2O, 2.3; KH2PO4, 1.2; MgSO4·7H2O, 1.2; NaCl, 118.2; NaHCO3, 24.8; and dextrose, 10.0.

Rabbit portal veins, aortas, and pulmonary arteries were subjected to tensions of 2, 4, and 8 g, respectively, whereas rat portal veins were kept at 1 g and rat aortas and pulmonary arteries at 2 g. These initial tensions were determined by length-tension analysis; the preparation was set at that resting length which resulted in maximal contractions with respect to the tension applied to the tissue.

Contractions were measured isometrically with a Grass FT-03 force-displacement transducer and recorded on a Grass polygraph as changes in grams of tension. The muscles were aerated with 95% O2 and 5% CO2 and the temperature was maintained at 37.5°C by means of a constant temperature circulating unit. All tissues were kept in the organ baths for 1-2 hours before exposure to drugs, which were prepared in the Krebs-bicarbonate solution. The drugs, except for KCl, were kept on ice throughout the experiment. Isoproterenol, nitroglycerin, and NaNO2 were added to the baths in cumulative doses until complete relaxations with respect to the tension applied to the tissue.

Relaxation of the various blood vessels was measured after the tissues had been contracted to an extent which, in preliminary experiments, permitted a large relaxation on application of isoproterenol. KCl was used to contract rabbit aorta (ED50), rabbit pulmonary artery (ED50), rabbit portal vein (ED50), and rat pulmonary artery (ED50). In a separate series of experiments, histamine was used to contract the rabbit aorta (ED50). The best relaxation was obtained in the rat aorta after a serotonin-induced contraction (ED50). Relaxant responses were plotted as percent of the maximal possible relaxation, that is, relaxation of the contracted tissue back to the baseline tension. The effect of isoproterenol on the rat portal vein was measured most conveniently by first exaggerating its inherent rhythmic activity with serotonin (1 x 10^-4 M) and then monitoring the dose-dependent decrease in the amplitude of contraction on application of isoproterenol. All responses were obtained in the presence of phentolamine (1 x 10^-4 M), an a-receptor blocking agent. This procedure was necessary to avoid the stimulating effects of isoproterenol on the a-receptors. In experiments using Ca2+-free medium, CaCl2·2H2O was omitted from the Krebs-bicarbonate solution and ethylene glycol-bis(beta-aminoethyl ether)-N,N'-tetraacetic acid (EGTA) (1.0 mM) was added to sequester all other Ca2+.

The following drugs were used: L-isoproterenol d-bitartrate dihydrate (Winthrop); potassium chloride (reagent grade, Mallinckrodt); serotonin creatinine sulfate, histamine dihydrochloride, and EGTA (Sigma); nitroglycerin (Eli Lilly); sodium nitrite (J.T. Baker); and phenolamine mesylate (Ciba-Geigy).

Results

THE INFLUENCE OF AGING ON RELAXATION OF THE THORACIC AORTA

The degree of relaxation caused by isoproterenol markedly decreased with increasing age. Aortas from 2-year-old rabbits relaxed to only 17% of maximum, whereas tissues from 2-month-old rabbits produced a relaxation equivalent to 85% of maximum (Fig. 1, lower panel). Responses to nitroglycerin also were age-related (Fig. 1, upper panel). Unlike the case with isoproterenol, the major effect of aging on the action of nitroglycerin was on the ED50. Compared to the ED50 for nitroglycerin in aortas from 2-month-old rabbits, the ED50 in aortas from 6-month-old rabbits was 4 times larger; from 1-year-old rabbits, 13 times larger; and from 2-year-old rabbits, 19 times larger.

The results with nitroglycerin were not in complete
TABLE 1  Age-Related Changes in Nitroglycerin- and NaNO₂-Induced Relaxation of Rabbit Aorta

<table>
<thead>
<tr>
<th>Nitroglycerin</th>
<th>NaNO₂</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2 months</td>
<td>2 years</td>
<td>2 months</td>
<td>1 year</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ED₅₀ (M)*</td>
<td></td>
<td>0.5 ± 1.0 Ma</td>
<td>1.0 ± 2.0 Ma</td>
<td>0.8 ± 1.0 Ma</td>
<td>1.2 ± 1.5 Ma</td>
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<td></td>
<td></td>
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<tr>
<td>% maximal response</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>No. of rabbits</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
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Responses to nitroglycerin and NaNO₂ were obtained after a contraction produced by KCl. α-Receptor sites had been blocked by 1 x 10⁻⁶ M phentolamine.

† Values represent mean ED₅₀ ± SE.

agreement with those in our previous experiments. In that study, relaxation produced in rabbit thoracic aorta by NaNO₂, another "nonspecific" smooth muscle depressant, was not greatly influenced by the age of the animal. Therefore, the possibility arose that aging might affect the actions of these two vasodilators differentially. We compared the effects of these two agents on aortas from 2-month-old and 2-year-old female rabbits and those from 2-month-old and 1-year-old male rabbits. (These animals were readily available from our supplier.) Table 1 shows that the aging process equally increased the ED₅₀ for nitroglycerin and for NaNO₂; the ratio of ED₅₀ for old to that for young rabbits was smaller for tissues from female than male rabbits.

Experiments with rat aortas demonstrated that isoproterenol-induced relaxation of these tissues progressively decreased with increasing age. When compared with aortas from 7- to 8-week-old rats, maximal relaxations resulting from isoproterenol declined by 80% in tissues from 9- to 10-month-old rats. Responses to nitroglycerin remained constant over this period although reduced at 1 x 10⁻⁷ M (P < 0.01) (Fig. 2, upper panel).

THE INFLUENCE OF ANIMAL SOURCE AND THE CONTRACTILE AGONIST ON RELAXATION OF RABBIT AORTA

The above data were collected from a colony of rabbits different from that used in our earlier experiments. Since there is evidence to suggest that this type of aging phenomenon may be dependent on the source, and therefore the genetic makeup, of the animals, we performed a series of experiments on aortas from rabbits purchased from another colony. The ED₅₀ of nitroglycerin for aortas from 1½- to 2-year-old rabbits was 8.4 times larger than that obtained for aortas from 2-month-old rabbits (n = 5). Although higher, this value was closer to our original observation. As anticipated, the response to isoproterenol was markedly reduced. In our earlier work, histamine was used to contract the aortas. Therefore, in the present experiments some of the aortic contractions were induced with histamine (to the same ED₅₀ as KCl), and their responsiveness to isoproterenol and nitroglycerin was determined as a function of age. The ratio of the average ED₅₀ of nitroglycerin for aortas from old to young rabbits fell to 4 (n = 4). The same experiments then were repeated with aortas from rabbits acquired from the first colony, and identical results were obtained (Table 2). Analysis of these data revealed that the relaxation of aortas from the young rabbits produced by either isoproterenol or nitroglycerin was the same whether KCl or histamine was the contracting agonist. Although the response to isoproterenol was substantially reduced when aortas from the older animals had been contracted by histamine this reduction was less than when KCl was the stimulating agent. More importantly, the ED₅₀ of nitroglycerin for aortas from the older animals contracted by histamine was smaller than when similar tissues were first contracted with KCl.

THE INFLUENCE OF AGING ON RELAXATION OF THE PULMONARY ARTERY

To determine whether another artery displayed similar characteristics as a function of age, we investigated the
Table 2: Influence of Contracting Agonist on Drug-Induced Relaxation of Rabbit Aorta

<table>
<thead>
<tr>
<th>Contracting agonist</th>
<th>Age of rabbits</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>2 months</td>
</tr>
<tr>
<td>KCl</td>
<td></td>
</tr>
<tr>
<td>% maximal response to isoproterenol</td>
<td>87.1 ± 5.4</td>
</tr>
<tr>
<td>ED50 (M), nitroglycerin</td>
<td>2.8 ± 0.9 x 10^-9</td>
</tr>
<tr>
<td>No. of rabbits</td>
<td>6</td>
</tr>
<tr>
<td>Histamine</td>
<td></td>
</tr>
<tr>
<td>% maximal response to isoproterenol</td>
<td>85.2 ± 4.0</td>
</tr>
<tr>
<td>ED50 (M), nitroglycerin</td>
<td>2.1 ± 0.4 x 10^-9</td>
</tr>
<tr>
<td>No. of rabbits</td>
<td>7</td>
</tr>
</tbody>
</table>

Responses to isoproterenol and nitroglycerin were obtained after α-receptor sites had been blocked by 1 x 10^-6 M phentolamine. Values are expressed as the mean ± SE.

* Differs significantly from histamine-contracted aortas (P < 0.05).

The role of spontaneous tone and contractile tension in the drug-induced relaxation of arteries from young and old animals

Arterial responsiveness to isoproterenol could appear to decrease with increasing age if the arteries from older animals had an intrinsically greater spontaneous tone. After a drug-induced contraction, these tissues would have a greater total tension compared to those from the younger animals, and isoproterenol, not being as strong a vasodilator as nitroglycerin, might not be able to relax these tissues. An isometric recording system should eliminate such a variable, since the tissues are equilibrated at a set tension. To verify this we performed a series of experiments using aortas from rats (57-68 days, n = 6; 230-280 days, n = 6) and aortas and pulmonary arteries from rabbits (65-70 days, n = 4; 360-385 days, n = 4). The tissues were prepared as described above and equilibrated in the bath for 2 hours. Relaxant "dose-response curves" to isoproterenol and nitroglycerin were obtained without prior addition of a contracting agonist. To determine the degree of spontaneous tone, exposure for 1 hour to Ca^2+-free solution containing EGTA (1 mM) was instituted. That the tissues unquestionably were under the influence of Ca^2+-free medium was assured by the addition of a near-maximal contractile concentration of KCl to the bath. KCl-induced contractions of the aorta are exquisitely sensitive to extracellular Ca^2+. The arteries then were bathed in Ca^2+-containing Krebs-bicarbonate solution for at least 30 minutes, after which time the response to KCl was tested again. The results for all 20 tissues were identical. They are represented by the polygraph tracings from the two tissues shown in Figure 4. Isoproterenol and nitroglycerin did not relax the arteries that had not previously been contracted by a drug. The addition of Ca^2+-free medium did not measurably alter the resting tension of arteries from young or old animals. The slight response to KCl of the tissues exposed to this solution, followed by a complete restoration of the response to KCl when Ca^2+ was replaced, verified the efficacy with which the Ca^2+-free solution exerted its effect. Thus we conclude that, for this system, there is no difference in spontaneous tone between arteries from young and old animals.

The tension generated in response to KCl by young and old rabbit aortas used for the experiments described in Figure 1 were the same. Relaxation resulting from isoproterenol or nitroglycerin was therefore determined for tissues not only at the same ED50 but under the same contractile tension. This indicates that the absolute contrac-
Age and vascular relaxation/Fleisch and Hooker

Figure 4 Actual polygraph tracings from thoracic aortic strips from rats 68 (upper) and 280 (lower) days old. The records show the lack of effect of isoproterenol and nitroglycerin on tissues not previously contracted with a drug. Furthermore, Ca²⁺-free medium did not alter the baseline tension. KCl-induced responses verified that the aortas were under the influence of Ca²⁺-free environment.

Figure 5 Dose-response curves for the relaxant effects of nitroglycerin (top) and isoproterenol (bottom) on male rabbit portal veins during continued exposure to 1 × 10⁻⁴ M phenylephrine. Each point represents the mean value ± SE of the number of animals indicated.

Tile tension did not play a role in the marked decrease in responsiveness of these tissues to isoproterenol.

The above studies established that aging differentially alters the ability of aorta and pulmonary artery to relax in response to drugs. We then questioned whether the situation is comparable for venous smooth muscle. To reduce variations associated with different techniques (recording systems, buffers, etc.) and animal species, we chose a vein that appeared to be most suitable to meet this need, namely, the portal vein of rabbits and rats. It has the advantage of containing a relatively large amount of smooth muscle in comparison to other veins and enabled us to use our standard recording system and tissue baths. However, it must be noted that much of the smooth muscle is arranged longitudinally and, unlike most veins, it exhibits spontaneous rhythmic contractions.

Application of KCl (ED₅₀) to rabbit portal veins constricted the smooth muscle, with a concomitant decrease in rhythmic activity (both amplitude and frequency). Isoproterenol and nitroglycerin then produced dose-dependent relaxations which were not influenced by the animal’s age (Fig. 5). Similar experiments were performed on rat portal veins. Unlike the rabbit portal vein, responses of rat portal veins to isoproterenol were obtained best by first increasing the amplitude of the rhythmic contractions with serotonin. Figure 6 shows a tracing from an experiment in which the portal vein was obtained from a 9-month-old rat. Isoproterenol reduced the size of the contractions. This response was unrelated to the age of the animal (Fig. 7). Nitroglycerin, sodium nitrite, and papaverine proved ineffective “relaxants” of the rat portal vein. High concentrations of nitroglycerin produced a small effect which did not differ significantly (P > 0.05) between tissues from 7- to 8-week-old and 9- to 10-month-old animals (Fig. 7).

Discussion

β-Receptor-mediated relaxation of rabbit and rat thoracic aorta is age-dependent. In their study, Cohen and Berkowitz showed that 1 × 10⁻³ M cyclic AMP relaxed mesenteric arteries from 3- to 5-week-old but not from 9- to 13-week-old rats. Other tissues containing β-receptors also are influenced by the age of the animal. For example, relaxation of rat trachea by isoproterenol showed a small increase in the ED₅₀ with increasing age, and guinea pig trachea a moderate increase. More recently, Lakatta et al. described an age-sensitive component in the β-receptor system of rat heart. The inotropic response to norepinephrine or isoproterenol was smaller for hearts from 2-year-old rats than from 6-month-old rats, but the positive inotropic effect of Ca²⁺ was the same for hearts from both groups of animals.

From these studies we can conclude that, at least for some smooth muscles, and probably cardiac muscle, aging and...
The β-receptor function are related. A number of questions, however, remain unanswered. The first and foremost must be whether the loss in β-receptor-mediated responses with age extends to other arteries. This was partially answered by Cohen and Berkowitz, as pointed out above. Additionally, it is necessary to establish whether veins undergo this change in reactivity. A second major consideration involves the reproducibility of this phenomenon. Although verified by a number of laboratories, the loss in β-receptor activity at a known age in a particular species has been variable. This led to the hypothesis that this event was related to source and strain (or substrain) of the animals.

In our present study, isoproterenol-induced relaxation of thoracic aorta steadily decreased with increasing age: 20% of the maximal response to isoproterenol remained in aortas from 9-month-old rats and 2-year-old rabbits. Prior experiments indicated that aortic relaxation caused by isoproterenol would be negligible when rats reached 6 months of age. This is one indication of the significance that must be attached not only to species but to strain and substrain variations. Relaxation of rat aorta by nitroglycerin did not change with increasing age. In contrast, the ED₅₀ of nitroglycerin and of NaNO₂ was approximately 20 times larger in aortas from 2-year-old rabbits than in aortas from 2-month-old rabbits. Gross examination of aortas from the older rabbits did not reveal noticeable pathological lesions (e.g., atherosclerosis). Studies in which Ca²⁺-free medium was used to determine the spontaneous tone, likewise did not uncover differences between arteries from young and old rats and rabbits. Furthermore, variations in contractile tension of aortas from young and old rabbits and rats did not contribute to this apparent effect of aging.

These results suggested that the shift to the right of the nitroglycerin and NaNO₂ dose-response curves, seen with aging in rabbit aorta, represented a subtle change. The reason was found to be related to the agonist used to bring the aorta to the tone required for testing vasodilators. Preliminary experiments showed that histamine did not maintain the pulmonary artery in a contracted state for sufficient time to complete a relaxant dose-response curve. KCl, on the other hand, was found to accomplish this for both the rabbit pulmonary artery and aorta. Relaxation of aortas from young rabbits caused by isoproterenol or nitroglycerin was virtually identical whether KC₃ or histamine was the stimulating agent. However, for aortas from older rabbits, these vasodilators did not relax KCl-contracted tissues as well as they relaxed histamine-contracted tissues. Since KCl and histamine contract rabbit aortas by different mechanisms, we conclude that, at least for rabbit aorta, the aging process changes the manner by which drug-induced contraction or relaxation, or both, take place. This is in addition to the specific loss in β-receptor activity.

As was the case with the aorta, relaxation of pulmonary arteries from rabbits and rats caused by isoproterenol decreased with increasing age. From these experiments, two facts emerged: aging can influence responses of an artery other than the aorta to isoproterenol, and the loss of ability to respond to vasodilators is not uniform from one artery to
another. As a result of the aging process, pulmonary arteries from both species lost about 50% of their responsiveness to isoproterenol. Unlike rabbit aortas, the ED$_{50}$ of nitroglycerin for pulmonary arteries from the oldest rabbits isoproterenol. Unlike rabbit aortas, the ED$_{50}$ of nitroglycerin for pulmonary arteries from the oldest rabbits isoproterenol. Unlike rabbit aortas, the ED$_{50}$ of nitroglycerin for pulmonary arteries from the oldest rabbits isoproterenol. Unlike rabbit aortas, the ED$_{50}$ of nitroglycerin for pulmonary arteries from the oldest rabbits isoproterenol. Unlike rabbit aortas, the ED$_{50}$ of nitroglycerin for pulmonary arteries from the oldest rabbits isoproterenol. Unlike rabbit aortas, the ED$_{50}$ of nitroglycerin for pulmonary arteries from the oldest rabbits isoproterenol. Unlike rabbit aortas, the ED$_{50}$ of nitroglycerin for pulmonary arteries from the oldest rabbits.

Future studies will have to be concerned with the influence of age on responses of small arteries to vasodilators to determine the degree of involvement of other segments of the arterial system. Despite the unique features of the portal vein, our results suggest that arteries and veins may adapt differently to this consequence of aging. The finding that age had no effect on responses of rabbit and rat portal veins to isoproterenol and nitroglycerin was surprising and perhaps within this finding lies the key to the biochemical lesion responsible for this event in aorta and pulmonary artery. Ericsson and Lundholm$^3$ have suggested that there is a change in $\beta$-receptor sensitivity which, presumably, is in part responsible for the inability of isoproterenol to increase cyclic AMP levels in aortas from older rats. This is in addition to the observation that cyclic AMP-induced relaxation of rat aorta decreases with increasing age.$^2,^3$ Another study that might have a bearing on this problem showed that large doses of epinephrine, administered intraperitoneally, increased free fatty acid production in rat aorta.$^{14}$ This cyclic AMP-mediated action is age-dependent and decreases in older animals. However, this change was not evident in animals less than 6 months old. It would be informative to conduct similar biochemical studies on portal veins to ascertain whether they undergo such changes with age.

Relaxation of the rabbit renal vein is being studied in our laboratory by a newly developed technique (C.S. Hooker and J.H. Fleisch, unpublished observations). Isoproterenol causes a moderate relaxation of this vein which appears to be independent of age. This lends support to our hypothesis that arteries and veins may age differently with respect to a loss in $\beta$-receptor activity.

There is no indication of what role a loss in $\beta$-receptor activity in the vasculature plays in either normal physiology or pathology. Strozzi et al.$^{15}$ demonstrated that vasodilation produced by metaproterenol, a $\beta$-receptor stimulant, decreased with increasing age in humans. Regardless of the actual significance of our findings, the present study dramatically points out that selecting animals by weight for certain studies is a meaningless exercise. Thus, we suggest that for greater uniformity from experiment to experiment, the age of the animals be given more attention.

Acknowledgments

We thank the Ciba-Geigy Corporation for the gift of phen tolamine mesylate used in this study.

References

The relationship between age and relaxation of vascular smooth muscle in the rabbit and rat.

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