Comparison in Man of Adrenergic Blockade Produced by Dibenzyline, Ildar, Priscoline, and Regitine

By Harold D. Green, M.D.

A method is presented for analyzing the probable effectiveness of blocking drugs in relieving vasospasm in the extremities, and comparison is given of the relative potency and side effects of 4 adrenergic blocking drugs and of their effects on heart rate, arterial pressure, and cardiac output, as estimated from a "circulatory index." Data are also given on the use of these drugs in evaluation of the circulation in patients.

In evaluating the status of the peripheral circulation in man, it is necessary to differentiate between the impairment of blood flow due to organic obstructive disease and that due to excessive vasospasm. This differentiation can be accomplished by determining the maximal peripheral flow after relaxation of all vasospasm. Drugs capable of relaxing vasospasm are also potentially useful in the therapy of vasospastic conditions. In a similar previous study it was shown that tolazoline hydrochloride (Priscoline hydrochloride) and phentolamine methanesulfonate (Regitine) were effective vasodilators but that beta-pyridyl carbinol (Roniacol) was practically ineffective. In this paper we compare the effectiveness of 2 new drugs, azapetine phosphate (Ildar phosphate) and phenoxybenzamine hydrochloride (Dibenzyline), and a tolazoline-phentolamine combination with that of tolazoline alone used as a reference standard.

Methods

Peripheral circulation was evaluated by placing subjects in a constant temperature room under controlled conditions and recording temperatures of the skin of 2 fingers on each hand, 3 toes on each foot, and the forehead with a 12-point Brown potentiometer. Copper-constantin thermocouples were held in contact with the skin by means of cellophane strips placed 1 cm. from the thermocouple tip. The wires were curved in such a way that the tip was held firmly against the skin without being covered at the tip by the cellophane. The recorder required 2½ min. to complete each cycle of 12 readings. Blood flow and vasoconstriction were estimated from the relationship of the temperatures of the skin to room and forehead temperatures. Minimal blood flow, due to maximal vasoconstriction, was considered to exist when the skin temperatures approximated room temperature, and maximal blood flow, due to maximal vasodilatation, when the skin temperatures approximated the forehead temperature. Approximately a 15 C. differential existed between room and forehead temperatures.

The studies, conducted on 10 volunteer normal medical students, were carried out in a room in which the temperature was maintained at 19.5 to 20.5 C. The air in this room circulated at a velocity of approximately 120 feet/min. and varied in humidity between 44 and 72 per cent of saturation (average: for summer, 66; for winter, 48). Exposure to this environment, while clad only in shorts, induced strong vasoconstriction in all the subjects as indicated by the progressive decline of the temperatures of the fingers and toes to 19 to 24 C. during the 45 to 90 min. of initial cooling prior to administration of the drug. The subjects were maintained in the same environment and degree of exposure throughout the study; no warming was applied to any part of the body.

The 4 adrenergic blocking agents used to induce vasodilatation in this study were tolazoline hydrochloride, used for comparison with the previously reported studies, and azapetine phosphate, phenoxybenzamine, and a tolazoline-phentolamine combination. The structural formulae of these drugs have been presented elsewhere.

Each drug was diluted in 200 ml. of 0.9 per cent saline and administered intravenously over a period of 30 to 45 min., zero time on the chart being the beginning of the drug administration. The 10 subjects received each of the 4 drugs in turn on separate days. No vasodilator drug was administered until maximal vasoconstriction was induced. During administration of the drugs the blood pressure and pulse rate were recorded at least every 5 min.

Before the drugs were used for these studies, ex-
periments were performed on dogs to evaluate the dose needed to produce any toxic effects. The minimal toxic dose was divided by 10 and used as the starting dose for this study. In the preliminary studies on the students the dose was increased cautiously until a desired effect was obtained or until toxic effects were produced. The dose used in these studies was considered to be either an effective dose or the maximum safe dose to be used by this method of administration.

Results

Tolazoline (Priscoline). Tolazoline was given to each subject in a dose of 2 mg./Kg. of body weight. The results obtained with this drug were comparable to those reported previously when body warming was not used. Figure 1 shows the temperature responses in 1 finger and 1 toe of each of the 10 subjects. In the fingers, an excellent response occurred in 3, a fairly good response in 6, and a poor response in 1 subject. In the toes, excellent responses occurred in all but 3 subjects. The mean maximal responses are given in table 1A and C.

The average heart rate increased 12 per cent (table 1G), which was significant at the 5 per cent level. The incidence of changes of arterial pressure is summarized in table 2.

During the administration of this drug, shivering sensations, rather severe flushing of the skin of the face, neck, and back, and redness of the eyes were noted (table 3). The flushing of the skin disappeared within 1 hour after completion of the drug administration and the redness of the eyes within 2 to 3 hours. The shivering stopped upon cessation of the drug administration. With the completion of the studies, all subjects were able to arise and to continue their work or studies with no discomfort.

Azapetine (Ilidar). Each subject received 1 mg./Kg. of this drug. The temperature responses of the fingers were significantly better than, and those of the toes slightly less than, those noted with tolazoline (fig. 1A and C).

No sudden or immediate drop in the arterial blood pressure occurred while the drug was being administered. In a small number of the subjects there was a gradual decline in arterial pressure; in others it remained stable (table 2). The heart rate increased slightly but not significantly (table 1G).

Nasal congestion was noted during the drug
Table 1.—Mean and Variability of Responses in Ten Normal Medical Students

<table>
<thead>
<tr>
<th></th>
<th>Mean, standard error,† probability</th>
<th>Azapetine</th>
<th>Tolazoline</th>
<th>Tolazoline-phenolamine</th>
<th>Phenoxy-benzamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal skin temperatures</td>
<td>Index finger</td>
<td>A</td>
<td>Mean 30.8</td>
<td>28.2</td>
<td>26.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>S.e. 1.3</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p† 0.017</td>
<td>—</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Great toe</td>
<td>C</td>
<td>Mean 26.1</td>
<td>27.0</td>
<td>23.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D</td>
<td>S.e. 1.7</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p‡ 0.41</td>
<td>—</td>
<td>0.0001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>Control</td>
<td>E</td>
<td>Mean 67.2</td>
<td>64.6</td>
<td>66.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F</td>
<td>S.e. 1.6</td>
<td>3.2</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Exp. per cent of control</td>
<td>G</td>
<td>Mean 105.9</td>
<td>112.2</td>
<td>106.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H</td>
<td>S.e. 10.4</td>
<td>4.9</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I</td>
<td>p§ 0.55</td>
<td>0.035</td>
<td>0.035</td>
</tr>
<tr>
<td>Control arterial pressure</td>
<td>Systolic</td>
<td>J</td>
<td>Mean 112.9</td>
<td>112.9</td>
<td>114.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K</td>
<td>S.e. 2.0</td>
<td>2.7</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td>L</td>
<td>Mean 70.5</td>
<td>69.9</td>
<td>68.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>S.e. 2.7</td>
<td>1.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Corrected pulse pressure*</td>
<td>Control</td>
<td>N</td>
<td>Mean 63.7</td>
<td>63.6</td>
<td>67.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>O</td>
<td>S.e. 3.0</td>
<td>2.7</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>Exp. per cent of control</td>
<td>P</td>
<td>Mean 113.0</td>
<td>114.1</td>
<td>106.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q</td>
<td>S.e. 5.4</td>
<td>5.4</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>p§ 0.04</td>
<td>0.0255</td>
<td>0.35</td>
</tr>
<tr>
<td>Circulatory index (H.R. ×</td>
<td>Control</td>
<td>S</td>
<td>Mean 4308</td>
<td>4129</td>
<td>4406</td>
</tr>
<tr>
<td>corrected P.P.)</td>
<td></td>
<td>T</td>
<td>S.e. 280</td>
<td>333</td>
<td>259</td>
</tr>
<tr>
<td></td>
<td>Exp. per cent of control</td>
<td>U</td>
<td>Mean 120.4</td>
<td>129.7</td>
<td>113.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V</td>
<td>S.e. 8.4</td>
<td>10.8</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W</td>
<td>p§ 0.04</td>
<td>0.023</td>
<td>0.125</td>
</tr>
</tbody>
</table>

* Corrected pulse pressure was calculated as:

\[ \text{Corrected pulse pressure} = \frac{\text{Measured pulse pressure} \times \text{cycle length (seconds)}}{\text{Diastolic length (seconds)}} \]

The cycle length was computed from the heart rate, and the diastolic length from the data of Katz and Feil.1

† S.e. = Standard error of mean based on N = 10 observations in all cases.

‡ The likelihood that the difference between the indicated mean and the mean for tolazoline could occur by chance.

§ The likelihood that the difference between the indicated per cent of control and 100 per cent could occur by chance.

Both sets of probability values were read from a chart of t vs. probability, prepared by James F. Crow, which may be obtained from the Department of Zoology, Dartmouth College.

administration and for 1 to 2 hours following (table 3); drowsiness and slight vertigo persisted for about 24 hours and redness of the eyes for 1 to 2 hours.

**Tolazoline-phenolamine (Priscoline-Regitine) Combination.** Two subjects received 0.5 mg./Kg. of each drug and the other 8 received 0.75 mg./Kg. The temperature responses in the fingers were on the average less than those noted with tolazoline alone and were significantly less than those noted with azapetine. In the toes there was a significantly smaller response than that to either tolazoline or azapetine (fig. 1; table 1A and C).

Except for 2 subjects there was no change in arterial pressure (table 2). There was a small but significant increase in heart rate.

**Phenoxybenzamine (Dibenzyline).** Phenoxy-
benzamine was given to all subjects in a dose of 0.2 mg./Kg. There was no response in the toes of any subject, the temperatures continuing to drop slightly during the drug administration. In the fingers, there was a slight response in 3 and a good response in 2 (fig. 1); on the average, however, the responses were significantly poorer than those to tolazoline or azapetine (table 1A).

The systolic arterial pressure dropped in 2 subjects (table 2). The pulse rate was unchanged by the drug.

Nasal stuffiness, noted during the drug administration, lasted 4 to 8 hours afterwards and was not relieved by nose drops. Upon completion of the studies, all students were able to get up and walk about with no untoward symptoms. Approximately 1/2 to 1 hour after the study, 3 of the subjects noted shortness of breath and tiredness after slight exertion and 1 noted a definite palpitation of the heart with rapid pulse; all 4 found it necessary to lie down for 1 to 2 hours.

**Circulatory Index.** To obtain a measure of the change in cardiac output we computed a "circulatory index," which, for this paper, is defined as the product of the heart rate and a corrected pulse pressure. It is based on the assumption that the stroke volume roughly parallels the corrected pulse pressure. The corrected pulse pressure was computed from the heart rate and recorded pulse pressure according to the simple equation given in the legend to table 1. In this equation it is assumed that the pressure drop during diastole is proportional to the diastolic "run off" and that, if all the blood were ejected during the first instant of systole, the systolic pressure would rise to some value higher than that recorded and that the pressure drop during the entire cycle would then be proportional to the "run off" during the whole cycle, which would in turn be proportional to the stroke volume. This circulatory index increased significantly with both azapetine and tolazoline.

**DISCUSSION**

Relatively speaking, all the drugs were pushed to a reasonably safe maximum level. Under these conditions the best responses were obtained with tolazoline and azapetine, which compared favorably in this series of studies. Both drugs increased the temperatures in the fingers and toes approximately equally in all subjects and both caused a minimum of discomfort accompanying and following the administration. The tolazoline-phen tolamine (Priscoline-Regitine) combination, which has a smaller dosage of tolazoline than the tolazoline alone, was less effective in overcoming vasospasm and caused considerably more severe nasal stuffiness than either azapetine or tolazoline alone. In the dosage used, phenoxybenzamine was not effective in overcoming vasospasm in the lower extremities and only slightly effective in the fingers. The dosage was not increased because of the unpleasant side effects, particularly the delayed symptoms that suggested postural hypotension.
In general the subjects who responded well with tolazoline were likely to respond better with the other drugs, and those who responded poorly with tolazoline usually also did poorly with the other drugs. In a given subject a good response in the toes was usually accompanied by a good response in the fingers and, conversely, a poor response in the fingers was almost always accompanied by a poor response in the toes.

The data in table 1 suggest that, in the doses given, tachycardia was produced most consistently by tolazoline, +12 per cent, and by the tolazoline-phentolamine combination, +6 per cent; the other drugs caused little or no significant increase in heart rate. On the average, pulse pressure tended to be increased with all 4 drugs, but significant increases were seen only with tolazoline and azapetine. Cardiac output per minute, as estimated from the "circulatory index," was increased significantly only with azapetine and tolazoline.

In animals, phenoxybenzamine and phentolamine seemed to be 3 to 10 times as potent as tolazoline and azapetine in blocking adrenergic stimulation. From the present studies it would appear that, in man, they are more nearly of equal potency, although phenoxybenzamine was not given in a dose large enough to produce effects comparable with those of the other drugs.

Mosher and co-workers studied the blockade of vasospasm induced by exposure to temperatures of 19 to 22 C. and found that they had to use 0.7 to 1.0 mg./Kg. of phenoxybenzamine. They noted that their subjects had to be kept flat for 2 to 3 hours after the test and had to be very careful for 24 to 48 hours afterwards to avoid postural hypotension. We deliberately used smaller doses in order to avoid such delayed symptoms. Doses of tolazoline, azapetine, tolazoline-phentolamine, and phentolamine alone, which caused much better blockade, did not have this prolonged, delayed effect.

In the study mentioned above and in another by Ford and associates rather large doses of phenoxybenzamine were used (in the latter a total dose of 95 mg. was given). These doses were sufficient to block the rise in arterial pressure that would normally follow an intravenous infusion of arterenol. Tests of adrenergic blockade per se were not carried out during our studies. A separate series of experiments suggests that the doses used in our study were sufficient to reverse the pressor response to 0.1 mg./Kg./min. of epinephrine but only reduced and did not abolish the pressor response when the same dose of arterenol was given intravenously. When we use the adrenergic blocking drugs in patients, we consider it important not to exceed the doses used in this study, since an occasional patient will show a considerable drop in arterial pressure with these doses. Moreover, it is important that the blockade be such that arterenol (Levophed) or phenylephrine (Neosynephrine) can be used by intravenous drip to restore and maintain the arterial pressure.

To date, 376 temperature studies have been made in patients, with the technic described in this paper for the drug administration plus body warming to enhance the dilator response: one hundred and two were done with tolazoline, 80 with phentolamine alone, and 194 with azapetine. There have been no serious complications in any of these patients. Phenoxybenzamine has not been used for temperature studies in patients because of the relatively poorer response noted at doses tolerated reasonably well in the 10 normal subjects. The tolazoline-phentolamine combination also has not been used in patients because of the relatively poor response and the relatively high incidence of side effects in the 10 normal subjects. It was not possible to repeat the studies on the same patient with all 3 of these drugs. In order to estimate the relative effectiveness of 3 of these drugs in patients, we have com-

Table 4.—Means of Maximum Temperatures Reached in Patients During Routine Studies, Body Warming Used in Addition to the Blocking Drug

<table>
<thead>
<tr>
<th></th>
<th>No. of studies analyzed</th>
<th>Finger</th>
<th>Toe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>A. Tolazoline</td>
<td>100</td>
<td>32.1</td>
<td>26.8</td>
</tr>
<tr>
<td>B. Phentolamine</td>
<td>79</td>
<td>32.8</td>
<td>27.0</td>
</tr>
<tr>
<td>C. Azapetine</td>
<td>194</td>
<td>32.4</td>
<td>28.5</td>
</tr>
<tr>
<td>D. Probability</td>
<td></td>
<td>0.12</td>
<td>0.8</td>
</tr>
<tr>
<td>A vs. B.</td>
<td></td>
<td>0.28</td>
<td>0.003</td>
</tr>
</tbody>
</table>
pared the maximal skin temperatures reached in all of these patients for each of the 3 drugs. Such comparison is valid only to the extent that in a large enough series of patients the proportion of severe obliterative disease will be the same for each group. The results of this analysis are reproduced in table 4, which shows that in the doses used the 3 drugs were essentially equally effective, although azapetine may be slightly better than tolazoline in the toes.

Early signs of impending fall of arterial pressure are nausea, pallor, tachycardia, and weakening of the radial pulsations. Any of these symptoms is an indication for stopping the drug and the institution of restorative procedures. The incidence of such side effects has been carefully analyzed for the first 143 of the patients receiving azapetine. In all these patients the calculated dose was 1.0 mg./Kg. of body weight. In 40 of them the azapetine had to be stopped after administration of one fourth to four fifths of the calculated dose because of the onset of dizziness, nausea, or hypotension. In 26 other subjects the drug was stopped after one fourth to four fifths of the calculated dose because a maximum response had been attained. In most of the 40 patients the symptoms were promptly relieved by elevation of the feet, administration of oxygen, and cessation of administration of azapetine. In 5 patients a small amount of phenylephrine (Neo synthephrine) was also given by slow intravenous infusion. This treatment promptly corrected any residual hypotension and abolished the symptoms. More recently we have given 50 mg. of Dramamine prior to the study, with considerable reduction in the incidence of nausea. As in the case of the medical students, very few of the ambulatory patients experienced any difficulty in standing after the customary period of half an hour after completion of the drug infusion during which they were left in the prone position.

If these precautions are followed, such temperature studies offer an excellent means of predicting the degree of vasospasm and the probable clinical effectiveness of these drugs in patients. If body warming is used in addition to the blocking drug, the technic is of considerable value in predicting the probable effect of sympathectomy in patients with peripheral vascular disease.11

Summary

In order to evaluate the possible effectiveness of a group of adrenergic blocking drugs used in treating peripheral vascular disease, the drugs were administered to a group of 10 normal subjects in whom vasospasm had been induced and the relative degree of relaxation of the vasospasm produced by each of the drugs was compared. Blood flow and the degree of vasoconstriction and vasodilatation were estimated from temperatures recorded from the skin of the tips of the digits. The vasospasm (reflex cutaneous vasoconstriction) was induced by exposure of lightly clad subjects to a room temperature of 20 C. for an initial period of 45 to 90 min. The 4 drugs used were tolazoline (Priscoline), azapetine (Ilidar), tolazoline-phenolamine (Priscoline-Regitine) combination, and phenoxybenzamine (Dibenzyline). Ten subjects were used, each subject receiving in turn each of the 4 drugs to make a total of 40 studies.

After maximum vasospasm was induced, the drugs were administered intravenously over a period of 30 to 45 min. in the doses: tolazoline, 2 mg./Kg.; azapetine, 1 mg./Kg.; tolazoline-phenolamine, 0.75 mg. of each/Kg.; and phenoxybenzamine, 0.2 mg./Kg.; each drug was diluted in 200 ml. of 0.9 per cent saline solution. Tolazoline and azapetine were found to be fairly good vasodilators in both the upper and lower extremities with the tolazoline-phenolamine combination producing somewhat less vasodilatation and phenoxybenzamine the poorest response. There were no dangerous or painful side effects to any of these drugs, but the phenoxybenzamine was followed, some time after the drug was administered, by symptoms that suggested postural hypotension.

Acknowledgment

Grateful acknowledgment is given to Mr. Mack Parsons and Mr. Don Hartzog, Jr., for assistance in the analysis of the data and to Mrs. Hannah Spencer, R. N., and Mrs. Mildred Kolb, R. N., who performed the temperature studies.

The azapetine PO4, Ilidar PO4, (RO 2-3248) was supplied by Hoffmann-LaRoche, Inc., Nutley, New Jersey. The phenoxybenzamine, Dibenzyline, was

**SUMMARIO IN INTERLINGUA**

Pro evaluare le efficaci possibili de un gruppo de agentes de blockade adrenergico usate in le tractamento de morbo periphero-vascular, illlos esseva administrate a un gruppo de 10 subjectos normal in que vasospasmo habeva esseite inducite, e le relative grado de relaxazione del vasospasmo effectuate per cata un del agentes esseva comparate. Le fluxo sanguinee e le grado de vasoconstringion e vasodilatazione esseva estimate super le base del temperaturas registrate al pelle del punctas digital. Le vasospasmo (reflexe vasoconstrictione cutanae) esseva inducitse per exponer le subjectos in leve vestimentos a un temperaturas de interio de 20 C durante un periodo initial de inter 45 e 90 minutus. Le quatro agentes usate esseva tolazolina (Priscolina), azapetina (Ilidar), tolazolina e phentolamina (Regitina) in combination, e phenoxybenzamina (Dibenzyline). Cata un del 10 subjectos recipieva cata un del 4 agentes, resultante in un total de 40 studios.

Post induction del vasospasmo maximal, le drogas esseva administrate intravenosemente in le curso de periodos de inter 30 e 45 minutus. Le doses usate esseva: tolazolina, 2 mg per kg de peso corporee; azapetina, 1 mg per kg; tolazolina-phentolamina, 0,75 mg per kg de cata un; e phenoxybenzamina, 0,2 mg per kg. Cata dose esseva diluite in 200 ml de solution salin de 0,9 pro cento.

Esseva constatatse que tolazolina e azapetina es satis bon vasodilataatore in le extremitates tanto superior como etiam inferior. Un vasodilatazione alique inferior esseva producite per le combination de tolazolina e phentolamina. Le pejor responsa esseva obtenite per phenoxybenzamina. Nulle periculolose o dolorose effectos lateral esseva notate pro ulle del drogas, sed le administration de phenoxybenzamina esseva sequite post un certe intervallo per symptomas que suggereva hypotension postural.

**REFERENCES**


5. **JOHNSON, H. D., GREEN, H. D., AND LANIER, J. T.: Comparison of adrenergic blocking action of Ildar (RO 2-3248), Regitine (C-7337), and Priscoline in the innervated saphenous arterial bed (skin exclusive of muscle) and femoral arterial bed (muscle exclusive of skin) of the anesthetized dog. J. Pharmacol. & Exper. Therap. 108: 144, 1953.**


11. **—: Correlation between vasodilation produced by thoracic or lumbar sympathectomy and vasodilation predicted from effects of blocking drugs in patients with peripheral vascular disease. Am. J. Physiol. 167: 789, 1951.**
Comparison in Man of Adrenergic Blockade Produced by Dibenzyline, Ildar, Priscoline, and Regitine

HAROLD D. GREEN

Circulation. 1957;15:47-53
doi: 10.1161/01.CIR.15.1.47

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1957 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/15/1/47

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/