Reflexes from the Aortic Baroreceptor Fibers in the Cervical Vagus of the Cat and the Dog

By Cyril S. Ito and Allen M. Scher

ABSTRACT

The baroreceptor fibers which arise from the aortic arch course centrally within the vagus nerve in the dog, and they usually follow this path in the cat. Near the origin of the superior laryngeal nerve, a separate branch of the cervical vagus (the cervical aortic nerve) arises. Previously, it was thought that this nerve contained all the important baroreceptor afferents. Aortic baroreceptor fibers that are not within the cervical aortic nerve were studied in the anesthetized cat and dog after cervical aortic and carotid sinus nerves had been sectioned. Some experiments were acute, but most were conducted 13-60 days after nerve section (to allow transected nerves to degenerate). After degeneration, baroreceptor activity was found in the peripheral aortic nerves in most animals. The sensory terminals of the surviving baroreceptor fibers were on the aortic arch on the left side and at the root of the right subclavian artery on the right side. In one of four chronic cats, four of eight chronic dogs after degeneration, and one of three animals in acute experiments a depressor response (8-70 mm Hg in chronic and 10 mm Hg in acute experiments) followed stimulation of the peripheral aortic nerve. The surviving aortic baroreceptor fibers coursed centrally in the cervical vagus.

KEY WORDS aortic depressor reflex aortic arch deafferentation aortic baroreceptor sites electrical stimulation baroreceptor electroneurogram baroreceptor fiber pathways neurogenic hypertension vagal baroreceptor fibers

Hypertension induced by surgical section of the four major baroreceptor nerves in the neck has been studied for a number of years (1). The severity of hypertension produced by this procedure is variable (2-5). Baroreceptors and other peripheral receptors at sites other than the systemic arterial vessels, i.e., cardiac (6) and pulmonary receptors (7), might be responsible for most of this variability. However, the variability might be due in part to systemic arterial baroreceptors that continue to make synaptic connections in the medulla despite the surgical procedures. Section of the carotid sinus nerves presents no problem. However, the anatomy of the aortic baroreceptors and their connection to the central nervous system show some variability in different species. Aortic baroreceptor fibers reach the central nervous system via the cervical aortic nerve and the cervical vagus in the dog and rabbit (8, 9), but they are also present in the recurrent laryngeal nerve in the rat (10-12).

To avoid confusion, we will refer to all baroreceptor fibers and nerves from the aorta and its intrathoracic branches as aortic baroreceptor fibers and peripheral aortic nerves, respectively (Fig. 1). The branch of the cervical vagus which contains many or most of the aortic baroreceptor fibers and which separates from the main vagal trunk near the root of the superior laryngeal nerve will be called the cervical aortic nerve. Those aortic baroreceptor fibers that remain in the cervical vagus will be referred to as vagal aortic baroreceptor fibers.

The existence of aortic baroreceptor fibers that are not part of the cervical aortic nerve does not prove that such aortic fibers are functional, i.e., that changes in their firing rate can elicit a reflex. It has been assumed that reflex effects from aortic baroreceptors can be effectively eliminated by bilateral section of the cervical aortic nerve in the cat (13) and the dog (14, 15). If a reflex change in arterial blood pressure can be elicited by stimulation of the peripheral aortic nerve after such section, this assumption is invalid.

The present study was undertaken to test the validity of the above assumption; two experimental procedures were used. The first procedure attempted to (a) ascertain (by recording nerve activity) whether some aortic baroreceptor fibers survive after the cervical aortic nerve has degenerated following section and (b) obtain a reflex...
Methods

Ten cats (2.5-5.0 kg) and 14 dogs (6-16 kg) of both sexes were studied. In 6 of the cats and 9 of the dogs, the cervical aortic nerves were surgically sectioned and the animals were then allowed to recover. In 2 of the chronic dogs, once on the left side and once on the right, the cervical aortic nerve could not be located and the entire vagosympathetic bundle was severed. No prior surgery was performed on the remaining 4 cats and 5 dogs; they were studied in acute experiments. In these animals, the cervical aortic nerves were sectioned during the experiment.

CHRONIC STUDIES

Denervation Procedures.—Under sodium pentobarbital anesthesia (35 mg/kg, iv) a 5-cm midline skin incision was made rostral from the middle of the larynx. Under a stereomicroscope (6 x), the cervical aortic nerve was sectioned bilaterally near its junction with the superior laryngeal nerve, and the distal segment was ligated and reflected caudally. In three of the cats and eight of the dogs, the carotid sinus nerve was also sectioned bilaterally (to eliminate its buffering action [19]) (20); a short length of the sinus nerve was removed, and the distal segment was ligated and reflected toward the carotid sinus. Before each nerve was sectioned, its identity was confirmed by recording action potentials. After the nerves had been sectioned, the incision was closed and the animal was allowed to recover.

Surgical Preparation for Experimentation.—Studies on chronically denervated animals were conducted 13-34 days after surgery in cats and 21-60 days after surgery in dogs. Cats were anesthetized with chloralose (60 mg/kg, ip); dogs were medicated with ketamine hydrochloride (20 mg/kg, im) and anesthetized with chloralose (60 mg/kg, iv) supplemented as needed. A midline skin incision was made from the sternal margin of the neck to the larynx, and the trachea was cannulated. The vagosympathetic bundle and the common carotid artery were dissected free for 2-3 cm just below the larynx on both sides. Arterial blood pressure was recorded from a cannula inserted into the left femoral artery and advanced to the aortic arch. The left side was usually studied first. Only one side was studied in some animals for technical reasons.

The animal was supported on a respirator, and the left chest was opened. As in our earlier study (8), occluding snares were placed on the ascending aorta at its origin and the descending aorta at the level of the fifth rib. A trough was fashioned out of the pleural sheath, a length of the peripheral aortic nerve was exposed and desheathed, and warm mineral oil was poured into the trough to cover the nerve.

The peripheral aortic nerve on the right was exposed using a supraclavicular approach. The midline incision was extended caudally from the cervical margin of the sternum diagonally about 5 cm over the right ribs. A trough was fashioned out of the pleural sheath, a length of the peripheral aortic nerve was exposed and desheathed, and warm mineral oil was poured into the trough to cover the nerve.

depression in arterial blood pressure by stimulating those aortic baroreceptor fibers which survive the degeneration. The degenerating segment of a crushed peripheral nerve ceases to conduct action potentials 5 days after section in the cat’s popliteal nerve (16) and the dog’s phrenic nerve (17). The distal segment of the baboon’s peripheral nerve can conduct action potentials up to 9 days after section (18). The second procedure examined the reflex changes in arterial blood pressure in response to stimulation of the peripheral aortic nerve immediately before and shortly after transection of the cervical aortic nerve.

Circulation Research, Vol. XXIV, January 1974
Experimental Procedure.—The experiment began with a search for baroreceptor activity in the peripheral aortic nerve; nerve recording followed by electrical stimulation of the nerve through platinum electrodes was used. When more than one branch of the peripheral aortic nerve was located (Fig. 1) each branch was stimulated, and then all branches were stimulated simultaneously. If a response was obtained, the question of whether it was mediated reflexly or directly was then investigated as follows. Either the peripheral aortic nerve was sectioned distal to the point of stimulation (eliminating direct effector connections) or the vagosympathetic bundle was severed at the larynx (eliminating connections to the central nervous system). The response to stimulation of the peripheral aortic nerve was again examined.

Stimulation (Grass SD-5) at 100 Hz with pulses 0.1 msec in duration and 4 v in amplitude was satisfactory for eliciting an aortic depressor response. These stimulus parameters are within the effective range found by Edis and Shepherd (15) in the dog and by Douglas and Schaumann (21) in the cat.

Following stimulation, the peripheral aortic nerve was severed and the distal segment placed on platinum electrodes. If baroreceptor activity was found, the site of the baroreceptor nerve endings was localized by occluding the aorta with the snare connections to the cervical aortic nerves. The experimental protocol was slightly altered from that followed in the chronic animal studies; the response to stimulation of the central segment of the sectioned peripheral aortic nerve was noted before and after the cervical aortic nerve was sectioned. Reflex effects from aortic fibers coursing centrally in the cervical aortic nerve would have been eliminated by sectioning the nerve. Since vagal aortic baroreceptors are indistinguishable within the chest from other aortic baroreceptors, a search for baroreceptor sites was not performed in these acute studies. The experiments were not completed in two of the dogs because of technical difficulty.

Results

Baroreceptor fibers that did not degenerate after section of the cervical aortic nerve were found in both the left and the right peripheral aortic nerves in most of the chronic animals studied. Baroreceptor activity was barely detectable in the intact peripheral aortic nerve in the chronically denervated animal, but it usually became clear after the peripheral aortic nerve was cut, desheathed, and split. This situation contrasts with the great ease with which baroreceptor activity could be recorded from the same branches in the animals studied acutely, even with the sheath intact.

A summary of the number of animals in which surviving baroreceptor fibers were found and a reflex effect to stimulation of the peripheral aortic nerve was obtained is shown in Table 1. The ventromedial cervical cardiac branch of the vagus nearly always (six of eight dogs, four of six cats) showed baroreceptor activity in the chronically denervated animals, and usually (three of six dogs) it produced a reflex response when it was stimulated. Each branch of the peripheral aortic nerve shown in Figure 1 exhibited baroreceptor activity at least once in eight dogs and six cats. The number of surviving baroreceptor fibers found on the left side and the right side varied. In the dog, surviving baroreceptor fibers were found more frequently on the left side. When surviving baroreceptor fibers were found on one side, at least three fibers were found and about six fibers were usually found. No association was apparent between the number of surviving fibers and the number of days after the nerve section.

In the two cats in which surviving baroreceptor
fibers were not found in the left peripheral aortic nerve (Table 1), the nerve was unbranched and ran

as a separate nerve to its junction with the superior laryngeal nerve. In the two dogs in which the vagosympathetic bundle was chronically severed on one side, no surviving baroreceptor fiber was found on that side. These results are not included in Table 1.

The greatest number of surviving baroreceptor fibers found in a peripheral aortic nerve after degeneration was in a dog. The record from this dog (Fig. 2) was obtained from the distal segment of the cut left peripheral aortic nerve 29 days after the carotid sinus and cervical aortic nerves had been transected bilaterally. From the decrease in baroreceptor activity as aortic arch pressure fell (Fig. 2A) and the increase in activity as aortic pressure rose (Fig. 2B), the baroreceptor endings were on or above the aortic arch. Adaptation of the baroreceptor activity following rapid, sustained increases in aortic pressure is apparent in Figure 2A and B. The sensory endings of most of these baroreceptor fibers were precisely located (Fig. 2C) by the marked increase in baroreceptor activity (at the arrows) produced by mechanically depressing the caudal margin of the aortic arch at its apex.

The response of surviving aortic baroreceptors to occlusion of the ascending and descending aorta is more clearly shown in Figure 3. This record was obtained from the cut left peripheral aortic nerve of a dog 28 days after the cervical aortic nerves had been sectioned. Occlusion of the ascending aorta (Fig. 3A) and of the descending aorta (Fig. 3B) clearly produced a decrease and an increase in baroreceptor activity, respectively. In this case, the sensory nerve endings were localized to the middle of the ventral wall of the aortic arch. Similar results were obtained on the left side in four of six chronic cats.

Figure 4 shows an electroneurographic recording from the cut right peripheral aortic nerve of a cat 17 days after the cervical aortic and carotid sinus nerves had been sectioned bilaterally. In this

<table>
<thead>
<tr>
<th></th>
<th>Surviving baroreceptor fibers</th>
<th>Aortic reflex response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Cat</td>
<td>4 (6)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Dog</td>
<td>7 (8)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

Total number of animals tested is given in parentheses.

TABLE 1
Number of Animals in which Surviving Baroreceptor Fibers Were Found and a Reflex Effect to Stimulating the Peripheral Aortic Nerve Was Obtained

![Figure 2](image-url)

**FIGURE 2**
Electroneurogram (ENG) from the distal segment of the cut left peripheral aortic nerve of a dog in which the cervical aortic and carotid sinus nerves had been transected bilaterally 29 days previously. Time marks are at 0.5-second intervals. In the middle of records A and B the time scale was expanded ten times. B is a continuation of A. C was obtained a few minutes later. The decrease in aortic arch pressure (AAP) in A was produced by occluding the ascending aorta at its origin for about 1.5 seconds. The elevation in blood pressure in B was caused by occluding the descending aorta at the level of the fifth rib; return of blood pressure to baseline followed release of this occlusion. The first two arrows in C indicate the result of briefly touching the caudal margin of the ventral surface of the aortic arch at the apex. At the third arrow pressure was maintained at this site for about 2 seconds. ECG = electrocardiogram.
case, it can be deduced from Figure 4A and B that the baroreceptor sensory endings were located on or above the aortic arch. These sensory endings were located at the root of the right subclavian artery. The bursts of action potentials at the arrows in Figure 4C were evoked by manipulating the junction between the right subclavian artery and the right common carotid artery. Figure 4C was obtained after the cat had been killed by asphyxiation. Activity from this peripheral aortic nerve was continuously recorded as asphyxiation progressed. The lack of chemoreceptor activity was typical of all such experiments.

In experiments in which the aortic nerve was stimulated electrically, an aortic reflex could be evoked from the left side in half of the chronically denervated dogs (Table 1). In chronic cats, a reflex response could not be evoked from the left peripheral aortic nerve in any of the four cats tested, but a response was evoked from the right side in one of two cats. Only one of six chronic dogs responded reflexly to electrical stimulation of the right peripheral aortic nerve. A discernible depressor response could not be elicited in any case when surviving baroreceptor fibers were not found in the peripheral aortic nerve.

Figure 5 shows the results of electrical stimulation of the right peripheral aortic nerve in the same cat used for the experiment illustrated in Figure 4. The depressor response in the left third of Figure 5 was elicited by stimulating the intact right peripheral aortic nerve. At the arrow, the right vagosympathetic bundle was sectioned just below the larynx. Thereafter, a depressor response could no longer be evoked, as shown in the right third of Figure 5. Essentially the same results were obtained on the left side in the chronic dog.

The largest aortic reflex response obtained following nerve degeneration was in a dog (Fig. 6). Both sinus nerves and both aortic nerves had been sectioned for 41 days. The response to stimulation of the intact left peripheral aortic nerve is shown in Figure 6A. Between A and B (Fig. 6) the main trunk of the left vagus was sectioned just cephalad to the aortic arch, all thoracic branches of the proximal vagal segment were severed, and the left cervical sympathetic trunk was sectioned at its origin. A depressor response could still be elicited by
stimulation of the proximal segment of the left peripheral aortic nerve (Fig. 6B and C).

In acute experiments, an aortic reflex from the left side could be evoked by electrical stimulation in one of three animals even after the cervical aortic nerves had been severed. Figure 7 shows the reflex response to electrical stimulation of the left peripheral aortic nerve in a cat studied acutely. Section of the left cervical aortic nerve (between Fig. 7A and B) substantially attenuated the aortic reflex but did not abolish it.

The magnitude of the reflex depression in mean arterial blood pressure at steady state ranged from 8 to 70 mm Hg in those chronic animals which showed a reflex response and was 10 mm Hg or less in acute studies. The magnitude of the aortic reflex elicited by stimulation of the surviving aortic baroreceptor fibers did not appear to depend on the number of surviving fibers (probably because we did not count the surviving fibers accurately). However, the magnitude of the reflex appeared to have been influenced by reinnervation of the carotid sinus. Although the small number of animals studied made a complete analysis impossible, the larger the magnitude of the reflex effect from the reinnervated carotid sinus, the smaller the magnitude of the observed aortic reflex. The period of complete denervation of the carotid sinus was variable; a small reflex response to carotid occlusion was noted in the cat as early as 17 days after nerve section. This rapid reinnervation probably resulted because of the short distance (about 1 cm) which separates the carotid sinus from the root of the sinus nerve.

**Discussion**

An assumption in this study was that the distal segment of the cut cervical aortic nerve ceases to propagate an action potential due to Wallerian degeneration by the thirteenth day after section for the cat and by the twenty-first day for the dog. This assumption is supported by our failure to find baroreceptor activity in the peripheral aortic nerve in the two dogs in which the vagosympathetic bundle was severed chronically just below the larynx and in the two cats in which the aortic nerve ran as a separate nerve to its junction with the superior laryngeal nerve. As mentioned earlier, 9 days is the longest that a cut peripheral nerve has been reported to conduct an action potential (18). Thus, the above assumption appears valid.

It is possible that the surviving baroreceptor fibers were fibers from the proximal stump of the cervical aortic nerve that had reinnervated the aortic arch. The distance between the cut proximal stump and the aortic arch was about 7 cm in the cat and 11 cm in the dog. Although axon regrowth within the sheath of a crushed nerve can occur at a maximal rate of about 5 mm/day (22), the rate of axon growth toward a target organ without a sheath to channel and guide the direction of growth is very much slower (23). When the site of the cervical aortic nerve section was examined after death, regrowth was not observed (16-25x magnification). In addition, the number of fibers found in the peripheral aortic nerve appeared to be independent of the time after the nerve section. These arguments, together with the finding that a depressor reflex response was evocable after section of the cervical aortic nerve in acute studies (Table 1, Fig. 7), indicate that aortic arch reinner-
AORTIC BARORECEPTOR REFLEX

RESP. = respiration, H.R. = heart rate, A.A.P. = aortic arch pressure, STIM. = stimulus, and ECG = electrocardiogram.

FIGURE 5

Response to stimulation of the right peripheral aortic nerve in the same cat used for the experiment illustrated in Figure 4. Stimulus: 100 Hz, 0.1 msec in duration, and 4 v in amplitude. The depressor response elicited by stimulation of the intact right peripheral aortic nerve could no longer be evoked after the right vagosympathetic bundle was sectioned at the arrow. RESP. = respiration, H.R. = heart rate, A.A.P. = aortic arch pressure, STIM. = stimulus, and ECG = electrocardiogram.

vation is a most unlikely reason for the reflexes observed in the chronic studies.

Our failure to find surviving baroreceptor fibers on a given side does not prove that none existed, since our search was not exhaustive. An exhaustive search would require a search of all the thoracic nerves joining the vagus nerve, since the depressor response usually elicited by electrical stimulation of the cervical aortic nerve was larger than that elicited by stimulation of the peripheral aortic nerve. Reliable estimates of the total number of surviving baroreceptor fibers are thus impractical.

Baroreceptor activity is a function of the static blood pressure, the rate of change of pressure, and the higher order time derivatives of pressure; baroreceptor adaptation is a transient response which is characteristic of baroreceptors (24). Adaptation of the nerve activity occurred following restoration of the aortic pressure in Figure 2A (right side) and in response to the sustained increase in pressure in Figure 2B (left side). It is probable that the adaptive characteristics of these baroreceptors were enhanced by the elevated blood pressure produced by the nerve section, since baroreceptor adaptation is less marked in the records in Figures 3 and 4.

Figures 5 and 6 show that a depressor response can be elicited by stimulation of the peripheral aortic nerve containing surviving baroreceptors. Figure 5 further shows that the vagosympathetic bundle is a vital link in the response, because the response was no longer evocable after the vagosympathetic bundle had been severed. Figure 6B and C shows that the vagus nerve conducts the afferent signal (from the stimulated peripheral aortic nerve) that causes the reflex depression in blood pressure, since the vagal trunk was connected to the central nervous system and all connections caudal to the clavicle were severed.

These findings indicate that reflexes elicited by electrical stimulation of the peripheral aortic nerve cannot be effectively eliminated in the cat and the dog by bilateral section of the cervical aortic nerve. More specifically, (a) the surviving baroreceptor fibers found in this study coursed centrally in the cervical vagus and did not join the cervical aortic nerve, thus confirming our earlier study (8), and (b) electrical stimulation of a very small number of aortic baroreceptor fibers can evoke a depressor reflex. Our findings also appear to invalidate the assumption (13, 14) that the completeness of aortic chemoreceptor denervation by cervical aortic nerve section is evidence for aortic baroreceptor deafferentation. We believe that our study indicates that, when bilateral section of the carotid sinus and cervical aortic nerves produces only a
Response to electrical stimulation of the left peripheral aortic nerve in a dog 41 days after transection of the four major baroreceptor nerves in the neck. Stimulus is the same as it is in Figure 5. A: Response of aortic arch pressure (A.A.P.) to stimulation of the intact left peripheral aortic nerve. B and C: Obtained by stimulating the proximal segment of the cut left peripheral aortic nerve after severing all connections of the left vagus caudal to the clavicle. STIM. = stimulus.

Temporary hypertension, accessory fibers of the aortic nerve are present in the cervical vagus (4, 5, 25). Complete elimination of the aortic baroreceptors requires bilateral cervical vagotomy as well (2).

We are unable to explain why a reflex depression in arterial blood pressure was produced by electrical stimulation in only some animals (Table 1). The presence or the absence of aortic baroreceptor fibers coursing in the cervical vagus did not consistently explain this lack of effect, because a reflex response could not be obtained in some chronically denervated animals even though aortic baroreceptor activity was found in their peripheral aortic nerves. In unresponsive animals it is possible that the surviving baroreceptor fibers are too few to produce a detectable reflex response or that the surviving baroreceptor fibers do not synapse with other neurons in the central nervous system. Jewett (26) and Hillarp (27) have made similar suggestions. Also, the cell bodies of some of the aortic baroreceptor fibers could be caudal to the junction of the cervical aortic nerve with the superior laryngeal nerve; these distal fiber segments could survive following cervical aortic nerve section. Aberrant branches of baroreceptor fibers from the carotid sinus coursing peripherally in the peripheral aortic nerve (26, 28) could have produced the observed reflex changes. Since a reflex response was never obtained if active aortic baroreceptor fibers were not found in the distal segment of the cut peripheral aortic nerve and since the carotid sinus nerves were severed, this explanation is very unlikely. Finally, anesthesia may have depressed the reflexes in these animals.

In acute animal experiments only a small change
Aortic baroreceptor reflex

Response to stimulation of the left peripheral aortic nerve in a cat studied acutely after both carotid sinus nerves were severed. Stimulus is the same as it is in Figure 5. A: Reflex depressor response to stimulation of the intact left peripheral aortic nerve. B: After section of the left cervical aortic nerve and the left peripheral aortic nerve between A and B, a small reflex response could still be elicited by stimulation of the proximal segment of the cut left aortic nerve. See Figure 5 for definition of abbreviations.

in blood pressure (10 mm Hg) could be elicited by activating aortic baroreceptor fibers coursing in the cervical vagus. In a study of the rise in blood pressure produced by cold block of the cervical vagus in cats in which the cervical aortic nerves had been sectioned acutely, Oberg and White (29) found that a pressure rise of about 30 mm Hg was reduced to one of about 6 mm Hg after the cardiac branches of the vagal nerve had been sectioned close to the heart. The pressor response, which could still be produced by cold block, might have been largely due to block of tonic activity from vagal aortic baroreceptor fibers. The small reflex response in the acute animal in our study and the fact that it was not always present would make these reflexes from the vagal aortic baroreceptors easy to overlook. Hasimoto and Hirohata (30) reported no reflex changes in blood pressure in response to electrical stimulation of the peripheral aortic nerve in the dog after the cervical aortic nerves had been sectioned acutely, but their figure showed a small depressor response. In contrast, vagal aortic baroreceptor fibers can cause a large reflex change in arterial blood pressure in chronic animals following removal of the carotid baroreceptors and on section of the cervical aortic nerves (Fig. 6C).

The effectiveness of vagal aortic baroreceptors in controlling blood pressure in chronic cats and dogs after sinoaortic nerve section is open to speculation. The poor regulation of arterial blood pressure observed in chronic animals in which the carotid sinus and cervical aortic nerves have been sectioned bilaterally (3, 31) leaves the impression that the vagal aortic baroreceptors, cardiac baroreceptors, receptors of the pulmonary tree, and other unknown receptors may influence the blood pressure, but the precise role of each is unknown.

References

14. AVIADO, D.M., AND SCHMIDT, C.F.: Cardiovascular and


Reflexes from the Aortic Baroreceptor Fibers in the Cervical Vagus of the Cat and the Dog

CYRIL S. ITO and ALLEN M. SCHER

Circ Res. 1974;34:51-60
doi: 10.1161/01.RES.34.1.51

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/34/1/51

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research 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 Research is online at:
http://circres.ahajournals.org/subscriptions/