similar to a death rate. Mathematically, it is the probability that a subject will die within an arbitrarily small interval of time (t, t + Δt), given that the subject has survived to time t. An assumption of the Cox model is that the hazard functions for any two subjects are proportional over time. From equation (A1) a likelihood function has been derived, and in any particular application, the regression parameters are estimated by maximizing the value of the likelihood function. To assess whether a particular characteristic is a significant independent predictor of survival, a test of significance is performed on the corresponding regression coefficient to determine if it is significantly different from zero. When many variables must be analyzed, the Cox model can be fitted in a stepwise fashion so that the first variable included is the single variable most important in explaining the survival pattern of the patients under study; the second is the variable which, when added to the first, gives the best pair of prognostic variables, and so on. Documentation of an efficient computer program that we use for performing these calculations will be furnished upon request.

The Mantel-Haenszel test, also applicable with variable-length follow-up and censored observations, is based on combining information from a set of contingency tables (one table for each time a failure occurs). A clear expository explanation with clinical examples is provided in part two of the excellent two-part series of papers in the British Journal of Cancer.23, 24

---

Spectral Analysis of Arterial Bruits
(Phonoangiography): Experimental Validation

ARNOLD MILLER, M.B.CH.B., ROBERT S. LEES, M.D., J. PHILIP KISTLER, M.D.

AND WILLIAM M. ABBOTT, M.D.

SUMMARY Turbulent flow in arteries produces sound recognized at the skin surface as a bruit. Spectral analysis of such bruits (phonoangiography) is the basis for a simple, noninvasive method of quantifying arterial stenosis. In human studies of carotid stenoses, the spectral break frequency of the bruit (f₀) (frequency beyond which bruit amplitude drops sharply) was directly related to the angiographic residual lumen diameter (d), i.e., d = U/f₀, where U is flow velocity. In the clinical situation, flow velocity remains relatively constant because of cerebrovascular autoregulation. In order to test the effects of flow velocity on bruit frequency, we have correlated, under controlled conditions, stenosis anatomy, blood flow, and the sounds originating from an abdominal aortic stenosis produced in adult mongrel dogs by external application of a 5-mm-wide Teflon band. Aortic flow was measured in arbitrary units with an electromagnetic flowmeter and varied by stepwise constriction of bilateral femoral arteriovenous fistulas. Bruits were recorded on tape and analyzed by computer.

The relationship between flow through the stenosis and break frequency of the bruit was linear (r = 0.89) in 10 dogs. Where d was altered in three other dogs, the relationship between flow and break frequency remained linear for each different d.

The data suggest that the relationship between break frequency, flow velocity and residual lumen diameter holds over a wide range of values of each of those variables.

ARTERIAL STENOSIS, when severe, produces turbulent flow distal to the stenotic site.1 This turbulence in turn produces pressure fluctuations that may be recorded as a bruit, either on the vessel wall or on the skin surface. The spectra of the turbulent pressure fluctuations have been shown to be similar to those of in vitro pipe turbulence.1 We have devised a method of arterial bruit analysis based on the analysis of turbulent flow that allows estimation of the extent of arterial stenosis at the site of origin of the bruit.2-5 This method is based on the algorithm d = U/f₀, where d is the residual lumen diameter at the stenosis, U is linear flow velocity and f₀ is the characteristic break frequency of the bruit, the frequency beyond which amplitude falls off with increasing frequency.3

The algorithm, although applied with significant accuracy to evaluate the degree of carotid artery stenosis in humans, has not been tested under controlled conditions in experimental animals.

We present here studies in the dog of the relationships among blood flow velocity, extent of stenosis and the characteristics of the sound produced.

Methods

Theoretical Background

Initial studies in our laboratory suggested a complex relationship between residual lumen diameter at a stenosis, flow velocity and the power spectrum of the sound produced,1, 2 but further theoretical analysis5 and a sizeable clinical experience3 has confirmed that the simple relationship f₀d = SU accurately describes the production of sound by a vascular stenosis, where f₀ is
the break frequency of the sound spectrum (fig. 1), d the residual lumen diameter at the stenosis, S the Strouhal number, an empirical constant, and U the linear flow velocity at peak systole distal to the stenosis. This relationship, based on human data, had not been validated in experimental animals, where both flow and stenosis size could be changed at will.

**Design of Experimental Model**

The relationship SU = f_o: d cannot be tested by direct in vivo measurements, because there is no method available for accurate measurement of peak systolic midstream flow velocity and no accurate method for estimation of residual lumen diameters in the range encountered clinically, i.e., 1–3 mm. In addition, methods for creating a stenosis of known diameter in vivo have inherent error. Despite these problems, an electromagnetic flowmeter left in position for an entire experiment will give an accurate relative reading of volume flow in “flow units” and any change in true flow will be reflected by a proportionate change in “relative flow.” If vessel diameter and the flow profile across the vessel remain unchanged, as we believe was the case in these studies, the flowmeter readings are also proportional to linear flow velocity and may be used as a “relative” flow velocity.

Thus, even though U and d cannot be measured in absolute terms, if a fixed stenosis is made in an experimental animal (i.e., d is constant), then the relationship U/f_o: S should equal a constant as U is varied experimentally. Because S is constant, at least for each dog, any increase in U should produce a similar increase in f_o.

**Animal Model (fig. 2)**

Ten adult mongrel dogs were anesthetized with intravenous sodium thiopental. The jugular vein was carefully excised in its entire length, and all tributaries were ligated. The femoral artery and vein in both thighs were exposed. Using the jugular vein as a free graft, bilateral arteriovenous fistulas were created to increase the rate of aortic blood flow.

The abdomen was then entered through a midline incision and the abdominal aorta exposed. Catheters (PE-190) filled with heparinized saline and connected to strain gauges (Statham Model P23 pressure transducers) were inserted into the proximal aorta via the brachial artery and into the distal aorta via the median sacral artery to monitor proximal and distal blood pressure and heart rate so that a stable hemodynamic state could be maintained throughout the study. An electromagnetic flowmeter (Statham SP with 6-mm and 8-mm probes) was placed around the aorta just proximal to the bifurcation. Once in place, the flowmeter was not removed until the end of the experiment in order to minimize inaccuracy due to positional change. Basal peak systolic flow and pressure measurements were taken with the fistulas open and closed.

A stenosis was then created 6–8 cm proximal to the flowmeter by suturing a 5-mm-wide Teflon band around the aorta. An estimate of the degree of the luminal area reduction could be obtained by change in the distal flow and pressure measurements. The degree of stenosis was termed adequate if a bruit could be heard at the lowest aortic flow rate.

Screw clamps were then applied to the
arteriovenous fistulas to modify the flow through the fistulas in a graduated and controllable fashion. Flow through the fistulas was altered in 15–18 steps, from zero to maximal flow and back to zero. At each step, peak systolic aortic flow was measured with the flowmeter, and aortic pressures proximal and distal to the stenosis were measured and recorded.

At the conclusion of the experiment, the dog was sacrificed and the abdominal aorta, including the stenotic segment, was excised and filled with radiopaque resin (Microfil, Canton Biomedical Products, Inc.) at a pressure equal to the distal aortic pressure with the arteriovenous fistulas closed. The stenotic and distal aortic diameters were determined by both radiographic and direct cast measurements.

In three additional dogs, the same experiment was carried out for stenoses of different sizes in the same dog. The stenoses were created by external banding of the artery, as above. For each stenosis a fresh band was applied. The severity of the stenosis was determined by the change in distal flow and pressure measurements, as well as by direct measurement of the band. Flow measurements and bruit recordings were made in the stepwise fashion described above. In each dog, the same electromagnetic flowmeter probe was used for all stenoses. Once in position, the probe was not removed until the experiment was completed.

Recording, Analysis and Interpretation

Bruits were recorded at the site of maximal amplitude distal to the stenosis, with a piezoelectric displacement transducer (Hewlett-Packard 21050 B) whose frequency response was precalibrated. The transducer signal was filtered (band pass 100–2000 Hz), preamplified (Princeton Applied Research 113) and stored on magnetic tape (Tandberg 3000 X).

Initially, the transducer was placed directly on the aorta, but it was damaged by the vibration of the arterial wall. Recordings were then made through a thin rubber Penrose tube filled with ultrasonic gel placed directly over the aorta. This filtered only the coarse, low-frequency vibrations of the arterial wall. Frequencies over 100 Hz were unaffected, as determined by multiple trials with and without the gel-filled drain. For each stenosis, 15–18 recordings were made and stored on magnetic tape. The recorded bruits were played back into a high-speed analog-to-digital converter (Analogic AN 5800) and then into a minicomputer (Data General Nova 1220). The digitized spectrum was displayed on a cathode ray tube, and a 40-msec segment at peak systole was isolated between cursors and subjected to fast Fourier transform spectral analysis. An amplitude-frequency plot was displayed on the cathode ray tube screen and a hard copy printout of each spectrum made. The characteristic peak frequency ($f_c$) was determined at each flow value. (fig. 1).

As described previously, when recordings were made in vivo directly on the exposed stenotic dog aorta, two superimposed spectra were found (fig. 3): the turbulent spectrum of the column of blood distal to the stenosis from which the peak frequency is determined, which varied as flow velocity varied, and a “resonant” spectrum from the vibration of the arterial wall itself, which remained relatively constant despite wide changes in flow. Because of the superimposition of these two spectra, it was sometimes difficult to distinguish the turbulent from the resonant peaks. Ideally, the “resonant” or flow-independent spectrum could be subtracted from the total sound spectrum of the recorded bruit. However, to do so would require definition and characterization of these resonances and the influence on them of the mechanical and structural properties of the arterial wall. Such data are, unfortunately, not available, and the turbulent peaks had to be recognized either by their greater amplitude or their movement up or down the sound spectrum as blood velocity was changed, or by both criteria. To test whether subjective bias occurred in selecting the correct peak, a system of weighting the data according to the ease of peak recognition was instituted and the results with weighted and unweighted data were compared.

In each experiment, half or more of the 15–18 spectra had an unequivocal turbulent peak and were designated as ideal readings and weighted with 3 points. In other spectra, the correct peak was less clear-cut but still easily distinguishable on one of the two spectra distal to the stenosis; these were weighted with 2 points. Finally, in those that remained there were multiple peaks and it was not evident which peak was associated with resonant and which with turbulent flow. The correct peak was determined by calculating its expected location from the relative flow velocity and break frequency seen in the unequivocal data. If a peak was present in the expected location, it was weighted with 1 point; if no peak was present, no weight was given. Only 1–5 spectra in any one experiment were weighted with 1 or zero.

An alternative, unweighted calculation was made,
using all the peaks, including those identifiable only by calculation, and the results with the two methods of analysis were compared.

Regression of break frequency upon flow velocity and the probability that the regression lines went through the origin were calculated as described by Snedecor and Cochran. The correlation coefficient between the measured parameters was also calculated.

Results

The results of the first 10 experiments show that with a constant diameter (d) of any given stenosis, the break frequency (f₀) was directly proportional to U. This relationship was linear through the entire range of flow velocities tested. The mean r value for both weighted and unweighted data was 0.88. Thus, the uncertainties introduced in detection of some peaks by the resonance of the aortic wall in the open-chest animal produced no significant bias in the data (table 1). A typical result from this experiment is shown in figure 4.

The results of the three experiments in which this relationship was tested in the same dog with stenoses of different sizes are tabulated in table 2. For a given stenosis the relationship U/f₀ remained constant, but the slope of the line varied with the degree of stenosis (fig. 5).

From examination of all the weighted results in tables 1 and 2, regression lines of the relationship U/f₀ for each stenosis were calculated and drawn to determine whether the line passed through zero. In 13 of 17 stenoses, the intercept was not significantly different from zero at the 5% probability level.

Estimation of the stenotic residual lumen diameter (d) of the externally banded artery by radiography and by casting proved inaccurate and inconsistent because application of the band produced multiple irregular invaginations of the arterial wall (fig. 6). However, using these results together with the distal flow and pressure changes, the relative effective severity of a particular stenosis could be approximated, allowing comparisons between stenoses to be made. This was particularly important where the diameter was varied in the same experimental animal (table 3).

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** The relationship in dog 1 between relative flow and break frequency. The broken line represents the calculated regression line, which in this case passes through the origin.

**Table 1. Correlation of Break Frequency with Blood Flow Through a Fixed Stenosis**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Flow Lowest (arbitrary units)*</th>
<th>Flow Highest</th>
<th>Break frequency Lowest (Hz)</th>
<th>Break frequency Highest</th>
<th>Correlation coefficient† Weighted</th>
<th>Correlation coefficient† Unweighted</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>250</td>
<td>2520</td>
<td>290</td>
<td>810</td>
<td>0.94</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>1000</td>
<td>1000</td>
<td>190</td>
<td>1900</td>
<td>0.80</td>
<td>0.88</td>
</tr>
<tr>
<td>3</td>
<td>1350</td>
<td>1350</td>
<td>200</td>
<td>550</td>
<td>0.76</td>
<td>0.75</td>
</tr>
<tr>
<td>4</td>
<td>2200</td>
<td>2200</td>
<td>250</td>
<td>600</td>
<td>0.88</td>
<td>0.85</td>
</tr>
<tr>
<td>5</td>
<td>5000</td>
<td>5000</td>
<td>220</td>
<td>1000</td>
<td>0.99</td>
<td>0.95</td>
</tr>
<tr>
<td>6</td>
<td>1230</td>
<td>1230</td>
<td>310</td>
<td>900</td>
<td>0.83</td>
<td>0.94</td>
</tr>
<tr>
<td>7</td>
<td>2720</td>
<td>2720</td>
<td>230</td>
<td>700</td>
<td>0.89</td>
<td>0.78</td>
</tr>
<tr>
<td>8</td>
<td>1880</td>
<td>280</td>
<td>280</td>
<td>620</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>9</td>
<td>2444</td>
<td>2115</td>
<td>210</td>
<td>700</td>
<td>0.79</td>
<td>0.89</td>
</tr>
<tr>
<td>10</td>
<td>2115</td>
<td>2115</td>
<td>300</td>
<td>750</td>
<td>0.92</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Mean 0.88 0.88

---

*Blood flow measured in arbitrary units with the electromagnetic flow meter. See text for details.
†The weighted correlation coefficient weights the data proportional to the observers assessment of the reliability of each data point. See text for details.
Table 2. Correlation of Break Frequency with Blood Flow Through Stenosis of Various Sizes

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Stenosis*</th>
<th>Flow</th>
<th>Break frequency</th>
<th>Correlation coefficient†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lowest (arbitrary units)</td>
<td>Highest (Hz)</td>
<td>Weighted</td>
</tr>
<tr>
<td>11</td>
<td>A</td>
<td>336</td>
<td>1260</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>987</td>
<td>4000</td>
<td>220</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>192</td>
<td>736</td>
<td>250</td>
</tr>
<tr>
<td>12</td>
<td>A</td>
<td>90</td>
<td>416</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>141</td>
<td>432</td>
<td>220</td>
</tr>
<tr>
<td>13</td>
<td>A</td>
<td>480</td>
<td>1072</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>320</td>
<td>752</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
</tbody>
</table>

*Stenosis was graded from A (least severe) to C (most severe).
†Blood flow measured in arbitrary units with the electromagnetic flow meter. See text for details.
‡The weighted correlation coefficient weights the data proportional to the observer's assessment of the reliability of each data point. See text for details.

Discussion

For any given arterial stenosis in the dog model, the break frequency ($f_b$) of the bruit produced was directly proportional to the peak systolic linear flow velocity. The relationship $U/f_b$ was linear, and thus constant and predictable through a wide range of flow velocities (i.e., $U/f_b = K$).

This confirms the work of Lees and Dewey, who showed that theoretical consideration of in vitro turbulent flow in pipes may be applied to pulsatile blood flow in vivo. It also confirms their practical conclusion that analysis of poststenotic turbulent blood flow could provide the basis for a method of quantitating arterial bruits.

The successful clinical application of this quantitative method to the evaluation of carotid stenosis has been reported. In a series of 175 carotid stenoses evaluated by both phonoangiograms and arteriography with independent interpretation, there was an 87% correlation to within 1 mm in the estimation of the residual lumen diameter of the stenosis.

Our results in the experimental animal have shown

![Figure 5](image1.png)

**Figure 5.** The relationship in dog 11 between relative flow and break frequency at three different residual lumen diameters. For a given stenosis, the relationship $U/f_b$ is linear, with the correlation coefficients indicated. The broken lines represent the extrapolation of the calculated regression lines and their proximity to the origin. The slope of the line varies with the severity of the stenosis: A is the least severe stenosis and C the most severe (see table 2).

![Figure 6](image2.png)

**Figure 6.** Sketch of the cross section of an externally banded artery. The multiple irregular invaginations of the arterial wall preclude accurate determination of the residual lumen diameter by casting or radiologic techniques.
Table 3. Relationship of Severity of Stenosis to Pressure and Flow

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Stenosis*</th>
<th>Flow difference† (arbitrary units)</th>
<th>Pressure difference‡ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>A</td>
<td>800</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>4140</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>4700</td>
<td>130</td>
</tr>
<tr>
<td>12</td>
<td>A</td>
<td>470</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>530</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>A</td>
<td>620</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>940</td>
<td>45</td>
</tr>
</tbody>
</table>

*Stenosis was graded from A (least severe) to C (most severe).
†Decrease in blood flow in arbitrary units, when the stenosis was imposed. See text for details.
‡Pressure difference across the stenosis.

This method of bruit analysis to be extremely sensitive in quantitating arterial turbulence when a bruit is present. Minor changes in blood flow are reflected in the bruit spectral analysis. The limiting factor when the recordings were made on the exposed, untethered vessel was the superimposition of the resonant spectrum of the vibrating arterial wall on the turbulent spectrum. Because of this resonance, a sound spectrum with multiple peaks was produced by the exposed vessel. Identification of the turbulent peak occasionally proved difficult. When recordings are made on the skin over a healed wound in the experimental animal (Miller A, Lees RS, Kistler JP, Abbott WM; unpublished data) or in the human with the stenotic vessel normally tethered, these resonant peaks are only occasionally seen and rarely of sufficient magnitude to cause difficulty in identifying the turbulent peak.3,5

We were able to discriminate resonant from turbulent peaks in two ways in the sound spectra recorded from exposed vessels. First, the turbulent peaks changed in frequency as flow velocity was varied, while resonant peaks remained virtually unaltered (Miller A, Lees RS, Kistler JP, Abbott WM; unpublished data). Thus a turbulent peak could be unequivocally identified by comparing two or more spectra recorded at different flow velocities. Second, in cases where a turbulent peak was thought to be one of several peaks of similar size, we calculated the ratio U/f0 for a given stenosis from several spectra obtained at flow velocities where the turbulent peak was clearly separated from any resonant peaks, and used the calculated f0 to identify the "buried" peak. In our analysis, peaks identified in this manner were down-weighted severely, as noted above.

In attempting to elucidate the mathematical equation SU = f0d where we were limited by a lack of independent means of measuring U and inability to create a stenosis of known diameter by external banding of arteries. The extent of infolding of the arterial wall beneath the constricting band precluded measurement in absolute terms (fig. 6).

By calculating the linear regression line of U vs f0 (fig. 4) for each diameter, we have shown that the y-intercept is approximately zero. This confirms that the equation given above is a reasonably accurate expression for turbulent flow. If we could determine clinically all the terms of the equation SU = f0d, several useful possibilities might follow. Not only would accurate determination of the residual lumen diameter in any situation, e.g., for heart valves and peripheral vessels, be feasible, but in a situation where this diameter was known, it might also provide a simple, practical, accurate and reproducible method for the determination of midstream peak systolic linear flow velocity in these situations. This method could be applied noninvasively, where the residual lumen diameter may be determined by independent means such as ultrasound imaging, as well as intraoperatively at the time of exposure of the artery or arterial prosthesis. In the latter situation, a known subcritical stenosis of sufficient degree to cause a bruit without change in distal flow could be imposed and U calculated from the equation.

In summary, our in vivo experiments confirm the validity of the relationship between break frequency, flow velocity and residual lumen diameter at a stenosis over a wide range of values for each of these variables. A simple microprocessor instrument for spectral bruit analysis and noninvasive estimation of the extent of carotid stenosis should become available in the near future at a cost of less than $10,000. Such an instrument would allow for easy testing of the applicability of bruit analysis in a wide range of clinical situations.

Acknowledgments

We thank Jeannie Friedman and Gilbert J. L’Italien and Brian Schaffer for technical assistance.

References

2. Fredberg JJ, Lees RS, Dewey CF Jr: How to listen to arteries (or what your doctor would hear if he were a fluid dynamician). AIAA Paper No. 70-144, AIAA 8th Aerospace Sciences Meeting, New York, January 19–21, 1970
Spectral analysis of arterial bruits (phonoangiography): experimental validation.
A Miller, R S Lees, J P Kistler and W M Abbott

Circulation. 1980;61:515-520
doi: 10.1161/01.CIR.61.3.515
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 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/61/3/515.citation

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/