Fourier Analysis of the Cerebrovascular System

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We performed Fourier analysis of the middle cerebral artery blood flow velocity waveform envelope in 14 normal subjects (group A) and 15 patients, of whom five had arteriovenous malformations (group B), five had cerebral vasospasm (group C), and five had arterial hypertension (group D). Measurements were obtained under conditions of normocapnia, hypercapnia, and hypocapnia. The Fourier coefficients measured in the first five harmonics of the Doppler waveforms of group A were used as the reference baseline and were compared with the coefficients found in the other three groups. Group B showed significantly lower Fourier coefficients, while groups C and D showed higher coefficients (p<0.05). The elevation of the Fourier coefficients occurred in an alternating pattern in group C and a decremental pattern in group D. This distinction was attributed to possible differences in the underlying pathophysiological processes. The degree of vascular distensibility of the cerebral arterioles, inferred from the shape of the Fourier analysis curves, was compared in all four groups. Vascular distensibility was characterized as abnormal in arteriovenous malformations, vasospasm, and arterial hypertension. Fourier coefficients may be better indicators of cerebrovascular abnormalities than mean blood flow velocity in hypertension and pulsatility index in arteriovenous malformations, vasospasm, and hypertension. (Stroke 1991;22:721–726)

Analysis of the hemodynamic characteristics of arterial systems is based on the idea that, following each cardiac systole, waves are reflected toward the heart from the distal arteriovenous junctions. Having arrived at the aortic valve, these waves are then reflected away from the heart, thus retraversing the system. This sets up a condition of resonance and forms the basis of the "windkessel" hypothesis, which compares the arterial system with a short, purely elastic chamber into which blood is abruptly ejected with each heart beat and from which blood is drained at a rate proportional to the instantaneous pressure difference determined by the arteriolar resistance. This model oversimplifies the actual situation, and a more in-depth analysis is needed if theoretical concepts are to have practical applications in the understanding of circulatory hemodynamics in normal and pathological states.

It is obvious that complex waveforms can be resolved into simple waves. In turn, the latter can be resynthesized to form the original wave, analogous to obtaining white light from a mixture of colored lights. A mathematical approach to carry out such analysis was developed by J. Fourier. This mathematical approach can be used to express a complex pulse wave as a series of sine waves characterized by amplitude, phase, and time period. The sine waves in turn, if resynthesized, reproduce the original waveform. For example, in a subject with a heart rate of 60 beats/min there are 60 pulse cycles each in 1 second, so the fundamental frequency is 1 Hz. This is the frequency of the first sine wave or the first harmonic. The second harmonic is twice the frequency of the first sine wave, and so on. We can quantify the amplitude of each sine wave, which can be designated as the amplitude of the Xth harmonic. The mathematical expression referred to as the Fourier series is given below. Attinger et al. have evaluated its applicability in the cardiovascular and respiratory systems, concluding that its two basic postulates, namely, periodicity and linearity, are usually satisfied for the oscillatory components of these systems. Fourier coefficients of the first to the tenth harmonics have also been shown to differentiate blood flow in normal and pathological vessels. This analysis was used by Aaslid in an attempt to relate pulsatility of
the flow velocity in the middle cerebral artery (MCA) to cerebral perfusion pressure. Woodcock et al. have applied Fourier analysis of Doppler flow velocity waveforms in femoral artery obstruction for the assessment of damping phenomena. The aim of this work is to explore the basic application of Fourier analysis in the study of hemodynamic changes occurring in the cerebrovascular bed of normal subjects, as well as of patients with arteriovenous malformations (AVMs), vasospasm after aneurysmal subarachnoid hemorrhage, and hypertension.

Subjects and Methods

We included 14 normal subjects and 15 patients. The normal subjects were 18-27 years old, had no neurological, cardiovascular, or respiratory diseases, and comprised group A. The patients comprised groups B, C, and D. Group B included five normotensive patients, ages 31-35 years, with a cerebral AVM at least 4 cm in size as determined by computed tomography, magnetic resonance imaging, and cerebral angiography. Two of these patients had neurological deficits (one had a hemiplegia and the other a mild sensory loss) contralateral to the AVM; the other three patients were neurologically intact. Group C included five normotensive patients, ages 22-35 years, with vasospasm, diagnosed by transcranial Doppler ultrasonography (TCD) and cerebral angiography, following aneurysmal subarachnoid hemorrhage. Computed tomography did not show enlarged ventricles, nor were there any clinical symptoms suggesting raised intracranial pressure at the time of the study. These patients had various degrees of weakness in the extremities contralateral to the MCA in which vasospasm occurred. For groups B and C, only the waveforms clearly consistent with AVM-feeding or vasospasm-affected vessels were further analyzed. Finally, group D included five patients, ages 65-67 years, with a long-standing history of hypertensive cardiovascular disease (mean arterial blood pressure of 110-130 mm Hg). The hypertension had been diagnosed 5-10 years earlier, and these patients' brachial blood pressures were >160/95 mm Hg at the time of the study. Three patients had been treated with the antihypertensive drug propranolol and the other two with methyldopa. None of the group D patients showed evidence of other cardiovascular disorders. All participants gave consent for the procedure in accordance with ethical research committee requirements. All participants were instructed to refrain from medications, smoking, and ingesting caffeine for at least 24 hours before the studies.

All TCD studies were performed using examination techniques similar to those previously published and a three-dimensional TCD instrument (Transcan, Eden Medical Electronics [EME], Oberlingen, Germany). The subject was first placed in a supine horizontal posture with the head within a stereotactic headpiece, which was secured in the position to be maintained throughout the examination. Head holders made of expanded polystyrene were used to prevent any additional movement. A specific point in the main stem of the MCA was located through the transtemporal window using a 2-MHz transducer, which was then secured in place. A similar procedure was used for the contralateral MCA. Five measurements of the mean blood flow velocity were obtained on each side. Measurements were then repeated under conditions of hypercapnia and hypocapnia. The end-tidal carbon dioxide volume percentage (% vol CO2) was measured using an infrared CO2 analyzer (223 CO2 Monitor, Datex Instrumentarium Corp., Helsinki, Finland). Breathing room air was considered the normocapnic condition and corresponded to approximately 5% vol CO2. In turn, hypercapnia corresponded to ≥6% vol CO2 and was induced by breath-holding while the patient's nostrils were clamped. Hypocapnia was induced by hyperventilation, with a concurrent drop to ≤4% vol CO2.

Each Doppler waveform envelope was analyzed at 64 points, always using the "foot-to-foot interval," and obtaining Fourier coefficients for the first 10 harmonics (Figure 1; note that coefficients are labeled "pulsatility indices" by EME software). Such analysis is performed directly by the TCD computer as $F = F_0/F_m$, where $F$ is the Fourier coefficient, and allows demonstration of the various sine waves that comprise the original blood flow velocity waveform.

Analysis is based on the expression

$$ F(t) = F_m + \sum_{X=1}^{N} F_x \cos(\omega t + \phi_x) $$

where $F(t) =$ blood flow velocity signal subjected to Fourier analysis, $F_m =$ mean value of $F(t)$, $X =$ harmonic number, $N =$ number of harmonics included in the analysis, $F_x =$ amplitude of the $X$th harmonic, and $\phi_x =$ phase angle.

The analysis was repeated for 10 consecutive similar waveforms. In Figure 1, waveforms obtained from the MCA in a hypertensive patient were subjected to Fourier analysis. Only the amplitudes of the Fourier coefficients for each harmonic were calculated and used in further analysis. Since the TCD computer superimposes a resynthesized waveform envelope (red tracing) on the original waveform (gray tracing), a perfect match of the two waveforms validates the computer's calculations.

Means and standard errors of the derived Fourier coefficients were calculated, and differences among coefficients for the 10 harmonics were determined using analysis of variance (ANOVA). Fourier coefficients for the first five harmonics of group A were compared with those for groups B, C, and D individually using a two-tailed $t$ statistic to test the hypothesis that findings in the normal state differed from those in the pathological states. The Gosling pulsatility index
(calculated as the difference between the peak systolic and end-diastolic velocities divided by the mean velocity) and the mean blood flow velocity were also used in comparing the normal and pathological states.

**Results**

Mean blood flow velocities in group A were within the range established for normal subjects in prior studies. The Fourier coefficients obtained were considered representative of the normal state and were used as the reference baseline for further analysis. In Figure 2, standard errors from these baselines (lines above and below the x axis) show the normal range of variation. Typical findings for groups B, C, and D (shaded bars) are also displayed as mean percentage change from baseline calculated as \((F_b - F_A)/F_A \times 100\), where \(F_A\) = mean reference Fourier coefficient and \(F_b\) = measured Fourier coefficient. In group B, there were significant decreases in the Fourier coefficients for the first four harmonics \((p < 0.05)\). In groups C and D, on the other hand, there were significant increases in the coefficients \((p < 0.05)\). In group C the increases noted for the first four harmonics followed an alternating pattern, while group D displayed increases for only the first three harmonics and the changes followed a decremental pattern.

Figure 3 shows typical Fourier coefficient curves found in the four groups under conditions of normocapnia, hypercapnia, and hypcapnia. The curves show peaks and troughs corresponding to maxima and minima Fourier coefficients, respectively. The most significant of these is the first minimum, defined as the first trough preceded and followed by higher points on the curve. This first minimum Fourier coefficient is probably analogous to that established for impedance curves. The first minimum was determined by first performing ANOVA, which showed significant variation of the Fourier coefficients for the 10 harmonics \((p = 0.0001)\). Those harmonics preceded and followed by others with higher Fourier coefficients were identified as minima. In the example shown in Figure 1, the first and second minima occurred at the fourth and seventh harmonics, respectively. The fact that the minima occur for successive waveforms rules out the influence of chance and artifact. For group A, the first minimum occurred at the fifth harmonic in normocapnia, the fourth harmonic in hypercapnia, and the seventh harmonic in hypcapnia (Figure 3, top). For group B, the first minimum occurred at the third harmonic in normocapnia, the fourth harmonic in hypercapnia, and the sixth harmonic in hypcapnia (Figure 3, top middle). Group C, on the other hand, showed the first minimum at the sixth harmonic in normocapnia and hypercapnia and the eighth harmonic in hypcapnia (Figure 3, bottom middle). Lastly, for group

**Figure 1.** Fourier analysis of right middle cerebral artery (RMCA) blood flow velocity waveform in hypertensive patient. Upper panel: raw spectra. Lower panel: waveform envelope (gray tracing) superimposed by resynthesized (red tracing) waveform. Fourier coefficients (pulsatility indices, PI) are given in all 10 harmonics for five successive waveforms. Markers are positioned at foot of each waveform envelope. Audio signal levels are color-coded. Note that fourth and seventh harmonics were preceded and followed by higher mean Fourier coefficients and therefore represent first and second minima, respectively.
Figure 3. Graphs of Fourier coefficients measured under conditions of normocapnia (a), hypercapnia (b), and hypocapnia (c) for 14 normal controls (top), five patients with arteriovenous malformations (top middle), five patients with vasospasm (bottom middle), and five patients with hypertension (bottom). In normal controls, first minimum occurs at fifth harmonic in normocapnia (straight arrow), fourth harmonic in hypercapnia (curved arrow), and seventh harmonic in hypocapnia (open arrow). In patients with arteriovenous malformations, first minimum is observed at third harmonic in normocapnia, fourth harmonic in hypercapnia, and sixth harmonic in hypocapnia. In patients with vasospasm, first minimum occurs at sixth harmonic in normocapnia and hypercapnia and eighth harmonic in hypocapnia. In patients with hypertension, first minimum is found at fourth harmonic in normocapnia and hypercapnia and eighth harmonic in hypocapnia.
D, the first minimum occurred at the fourth harmonic in normocapnia and hypocapnia and the eighth harmonic in hypocapnia (Figure 3, bottom).

Mean blood flow velocity, pulsatility index, and Fourier coefficients for the first five harmonics are compared between group A and the other groups in Table 1. Values were considered normal if they were not significantly different ($p > 0.05$) from those in group A. Most importantly, these comparisons showed no difference in mean blood flow velocity between groups A and D in normocapnia. Similarly, there was no distinction between group A and groups B, C, or D when pulsatility index was analyzed.

### Discussion

Although most previous studies have relied on impedance plots to demonstrate the reflection phenomenon,11 Wasterhof et al12 have shown that, in any pulsatile vascular system, the reflection phenomenon follows a pressure-to-pressure or flow-to-flow relation. Our results suggest that, under normocapnic resting conditions, Fourier coefficients vary within a narrow range. Pathological and physiological changes are accompanied by measurable deviations from this norm, as determined by Fourier analysis. In the case of AVM, where arterioles are not present and arterioles are connected directly to venous structures, the shunts that result from the anomaly characteristically display greatly reduced resistance. This is manifested by low Fourier coefficients, particularly in the lower harmonics, which contain the largest fraction of energy from left ventricular contraction.11 Patients with vasospasm or arterial hypertension both showed increased Fourier coefficients. There are differences in the patterns of Fourier coefficient abnormality observed in the two pathological states (Figure 2). Patients with vasospasm showed an alternating pattern, and those with hypertension showed a decremental pattern. In the case of vasospasm, the spastic segment of the MCA as seen on angiograms may be responsible for the alternating pattern based on its possible effect on the first minimum. This is similar to the phenomenon of the "single reflection site" described by O'Rourke and Taylor.13 On the other hand, in the case of hypertension, constricted arterioles in the distal vasculature may be responsible for the decremental pattern observed.

During vasodilation peripheral resistance is reduced, mean blood flow velocity increases, and reflection at the arteriolar terminations decreases; the reverse occurs during vasoconstriction. In normal subjects, the first minimum occurred at a lower harmonic during vasodilation (hypocapnia) than during rest (normocapnia) but at a higher harmonic during vasoconstriction (hypocapnia). This shift of the first minimum is probably governed by the inverse relation between frequency and wavelength. That is, the lower the harmonic frequency, the longer the wavelength, and vice versa. This is easily observed in the characteristic curve of group A (Figure 3, top). It is not clear how this relates to the reflection phenomenon described by O'Rourke and Taylor in the peripheral vasculature.13 There seems to be precedence for this relation, though this will require further proof. In group B (Figure 3, top middle), hypocapnia resulted in the expected response. During hypocapnia, however, the shift of the first minimum was opposite that observed in the normal subjects. Since it is not unusual to find increased blood flow within an AVM at the expense of flow in the surrounding normal vascular territories (a physiological phenomenon commonly referred to as the "steal effect"14), it is possible that vasodilation of normal intracranial vessels during hypocapnia induces an increment in blood flow to areas that surround the AVM. This may lead to partial collapse of the anomalous vessels and may result in an opposite phenomenon or "anti-steal" effect.15 The partially collapsed AVM vessels, in turn, may account for the shift of the first minimum to a higher harmonic, as explained above.

In more rigid vascular systems, as found in vasospasm and arterial hypertension (Figures 3, bottom middle and bottom, respectively), hypocapnia resulted in a shift of the first minimum to a higher harmonic as expected. During hypocapnia, on the other hand, the first minimum was encountered at the same harmonic as during normocapnia. These results suggest a state of decreased or absent distensibility with preserved contractility. Probably a greater degree of vascular stiffness in vasospasm is demonstrated by the near-superimposition of the three curves in Figure 3, bottom middle. Since we did not measure resistance changes, we cannot relate the
findings in vasospasm and hypertension to increased resistance in this study. Others have suggested increased cerebrovascular resistance in vasospasm.\textsuperscript{14} It has also been suggested that there is a marked increase in cerebrovascular resistance in hypertensive individuals.\textsuperscript{15} This was documented by Reimnuth and colleagues\textsuperscript{16} using the nitrous oxide method.\textsuperscript{17} Normotensive subjects age-matched to the patients in group D do not show any abnormalities of their Fourier coefficients (unpublished observations), suggesting that our findings do not represent an age-related effect.

Abnormalities of cerebrovascular CO\textsubscript{2} reactivity have been demonstrated in carotid atherosclerotic diseases by others using conventional TCD techniques.\textsuperscript{4,18,19} Fourier analysis, however, adds a new dimension to our understanding of the physiological changes in the cerebral vasculature in response to CO\textsubscript{2} and pathological states. Mean blood flow velocity could not separate hypertensive from normal subjects. Furthermore, the pulsatility index was not helpful in distinguishing the normal from the pathological groups ($p > 0.05$). This is not surprising since this index was proposed for use in peripheral vessels, where in the normal resting condition Windkessel effects dominate over resistance effects.\textsuperscript{4} This further emphasizes the potential application of Fourier analysis in these conditions.

The method for resolving bioelectric waveforms into their various frequency constituents is gaining wide acceptance and clinical application. This has been referred to as “spectral analysis” in electroencephalography\textsuperscript{20} and as “high-resolution EKG with frequency domain analysis” in electrocardiography.\textsuperscript{21} It is along these lines that we suggest the term “high-resolution TCD”\textsuperscript{13} for the technique we describe since it better distinguishes normal from pathological groups than conventional parameters such as mean blood flow velocity and the Gosling pulsatility index.

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References


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