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# Technology Update

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## Differentiating Vascular Pathophysiological States by Objective Analysis of Flow Dynamics

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### ABSTRACT

*Background and Purpose.* There is an unmet need to classify cerebrovascular conditions physiologically and to assess cerebrovascular system performance. The authors hypothesized that by simultaneously considering the dynamic parameters of flow velocity, acceleration, and pulsatility index (PI) (impedance) in individual Doppler spectrum waveforms, they could develop an objective method to elucidate the pathophysiology of vascular conditions and classify cerebrovascular disorders. This method, dynamic vascular analysis (DVA), is described. *Methods.* First, a theoretical model was developed to determine how any vascular segment and the ensemble of intracranial vascular segments could be defined according to its dynamic physiological characteristics. Next, the DVA method was applied to 847 anonymous serial complete clinical transcranial Doppler (TCD) studies of patients without regard for their diagnosis to ascertain actual reference ranges and the normality of the distribution curves for each dimension of the 3-parameter nomogram. The authors applied DVA to 2 clinical cases to see if they could track the changes in vascular performance of 2 known progressive diseases. *Results.* The theoretical analysis identified 295,245 possible vascular states for the ensemble of vascular segments in the cerebral circulation. When applied to clinical TCD data, DVA revealed continuous, normally distributed data for the velocity, PI, and logarithm of the

acceleration. *Conclusions.* DVA is proposed as a method for monitoring the physiological state of each cerebral artery segment individually and in ensemble. DVA evaluates the relationship among acceleration (force or pressure), velocity, and PI and provides an objective means to evaluate intracranial vascular segments using the paradigm of the well-described pressure-perfusion autoregulation relationship. DVA may be used to study cerebrovascular pathophysiology and to classify, evaluate, and monitor cerebrovascular disorders or systemic disorders with cerebrovascular effects.

Key words: Dynamic vascular analysis, transcranial Doppler ultrasound, arterial-venous malformation, arteriosclerosis, small vessel disease, sleep apnea, congestive heart failure.

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### Background and Introduction

There is a need for an objective, systematic, scalable, and automated process by which information known to exist in transcranial Doppler (TCD) data can be extracted to determine the physiological state of each cerebral artery segment and express the information in an objective, clinically valuable form.<sup>1</sup> The presently proposed method, dynamic vascular analysis (DVA), is a way to physiologically differentiate factors that affect arterial wall performance. The information gained by DVA may be used as a basis for contrast in graphical representations of vascular functional states.

Experienced TCD interpreters review waveform morphology<sup>2</sup> to guide the final clinical interpretation, as the

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information content of any parameter considered individually is limited. For example, the assessment of vascular spasm, stenosis, or hyperemia cannot be inferred from mean flow velocity (MFV) alone unless a certain threshold value is attained, increasing specificity at the risk of diminishing sensitivity. One must evaluate time-dependent MFV changes or the dynamic properties of waveforms, that is, waveform analysis, to ascertain useful information about such vessel properties as spasm,<sup>3</sup> stenosis, or hyperemia. Nevertheless, some parameters in select conditions have been proven useful. MFV has been shown to be a marker of stroke risk in sickle-cell disease.<sup>4</sup> With DVA, segmental waveform morphology may be objectively measured and viewed in the context of the overall pattern of cerebral hemodynamics.

#### *DVA Analysis of Doppler Ultrasound Data*

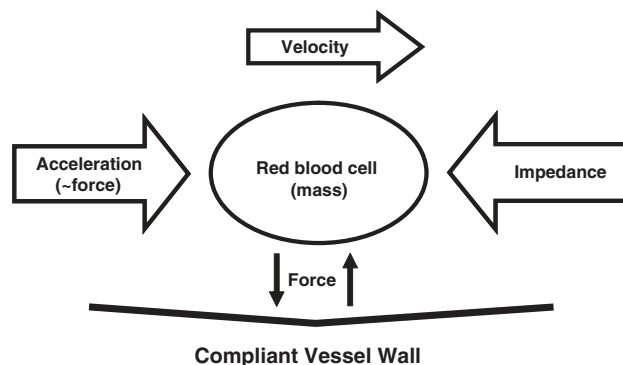
The cerebrovascular pressure-perfusion curve describes the autoregulation of cerebral blood flow.<sup>3,5-7</sup> This phenomenon occurs segmentally, regionally, or globally. We have developed a way to produce an equivalent of the pressure-perfusion relationship using data derived from standard TCD waveforms. DVA is a method to evaluate the pressure-perfusion relationship in each segment and the relationships among the ensemble of segments in the cerebral vascular system. By determining the physiological state of each cerebral vascular segment and then the overall pattern, valuable insights regarding the cerebrovascular system may be discerned.

Flow dynamics result from the force and counterforce of blood pressure and vessel wall tension, respectively, and those of blood pressure and flow impedance. The Doppler spectral waveform is rich in information regarding the vessel wall—this information is found in the distribution of red blood cell velocities provided by the technique and in the dynamic changes of these velocity distributions. Velocity is a measure of blood movement. Dynamic changes of velocity, such as systolic acceleration (SA) and pulsatility index (PI) considered together with MFV in a 3-parameter nomogram, robustly characterize the physiological state of the vessel through which the blood flows (Fig 1).

### **Patients and Methods**

#### *Patients*

The purpose of the present study was to use the DVA method to collect and evaluate the reference data needed to prospectively evaluate cerebral hemodynamics using the same method. We performed a retrospective analysis of TCD data by applying DVA methodology to patients referred for any clinical reason to undergo a TCD study.



**Fig 1.** Dynamics of flow velocity changes reflect impedance and wall compliance. During each pulse, energy is absorbed and then released by the vessel. The smooth muscle in the vessel wall may contribute energy to the forward movement of blood at that point. The relationships among the force vectors are reflected in the dynamic changes of velocity during each pulse. The dynamics of flow changes, therefore, reflect properties of the vessel such as compliance and downstream impedance.

Participants were 847 symptomatic patients referred to 2 community hospital noninvasive cerebrovascular laboratories for a TCD study. The raw data were measured directly from the TCD waveforms by the interpreting clinician (KC).

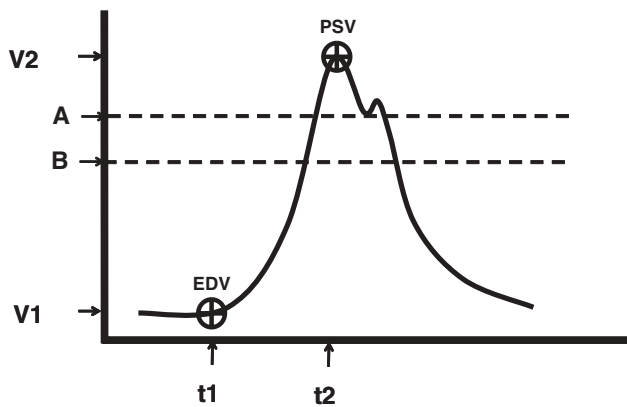
#### *TCD*

An EME-Nicolet Pioneer or a Multigon Multidop TCD instrument was used to perform traditional handheld TCD studies according to well-published techniques.<sup>8,9</sup> A sweep speed of 5 seconds per screen yielded 4 to 5 quality waveforms per page. The displayed screen was saved when the technologist identified at least 1 clear waveform (among several contiguous waves) per screen. The depths of the points of insonation were grouped according to corresponding vessel segments.

#### *DVA Process*

##### *Best Wave Selection*

The best wave Doppler spectrum waveform at each point of insonation was selected from the waves in the 5-second sweep screen and saved using the TCD instrument's built-in software. Waves occurring immediately after any premature beat or in the middle of any irregular beat were eliminated from consideration. Waves with the strongest overall signal (as determined by visual inspection of the color spectrum related to intensity of signal) and with maximum amplitude (velocity) were selected. This technique minimizes technologist error related to angle of insonation. Signal intensity and amplitude diminish as a function of the cosine of the angle of insonation. Viewed



**Fig 2.** Coordinates measured on waveform. The onscreen cursor is placed at the end of diastole of the preceding waveform (end diastolic velocity [EDV]) and the maximal point of systolic velocity (peak systolic velocity [PSV]) in the ensuing wave. These cursor points are each represented by absolute values on the corresponding axes. (A) Measured mean flow velocity (MFV). (B) Calculated MFV.

from the perspective of information theory, the selected best waves were those with the greatest content of information regarding vessel properties, including the highest intensity of Doppler spectrum, maximum MFV, and an uncorrupted TCD waveform envelope.

#### *Cursor Placement*

A single reviewer (author KC) used the instrument software to manually place a cursor on the computer screen at the end diastolic and peak systolic (highest velocity attained during systole) points of the representative best waveform (Fig 2). The x- and y-axis values for each cursor position yielded, respectively, the time and velocity. These numbers were displayed on the screen and manually transcribed to a computerized spreadsheet. From these data, peak systolic velocity (PSV,  $v1$ ), peak systolic time (PST,  $t1$ ), end diastolic velocity (EDV,  $v2$ ), and end diastolic time (EDT,  $t2$ ), the systolic upstroke acceleration [ $SA = (PSV - EDV)/(PST - EDT)$ ], mean flow velocity [ $MFV = (PSV - EDV)/3 + EDV$ ], and PI [ $PI = (PSV - EDV)/MFV$ ] were calculated for each vessel segment.

#### *Statistical Methods*

The objectives of analysis were to characterize the data, evaluate the distribution function, examine for correlations, and determine if the data were biologically clustered or represented a continuum of physical measurements. This forensic statistical analysis was undertaken blindly; the statistician was not provided any knowledge of the origin of the data or the relationships among the parameters. The statistician was asked to analyze the data knowing only that it was ultrasound data and the names of the parameters. For the purposes of statistical analysis,

depth ranges corresponding to a particular vessel segment were grouped together.

Statistical methods included an assessment of normality in the reference data and cluster analyses to determine if the data represented a continuum of physiological measurements or represented biologically clustered traits. Cluster analyses were performed using an agglomerative hierarchical method that begins with every observation being separate; each data element was assumed to represent its own cluster. In the first step, the 2 observations closest together were joined. Next, either a third observation was joined to the first 2 or other observations were joined into a different cluster. This process was continued until all clusters joined into one. After standardizing variables to a common scale, each set of parameters was subject to the single linkage method of analysis, which led us to conclude that we were dealing with only 1 group of data.

The MiniTab software package (MiniTab, State College, PA) was used to perform normal probability and cluster analyses of the data. The significance of any change over time in the clinical cases presented was analyzed by ANOVA, Student's  $t$  test, and the  $z$  test.

## **Results**

### *Statistical Analysis*

#### *Distribution of Measured Values*

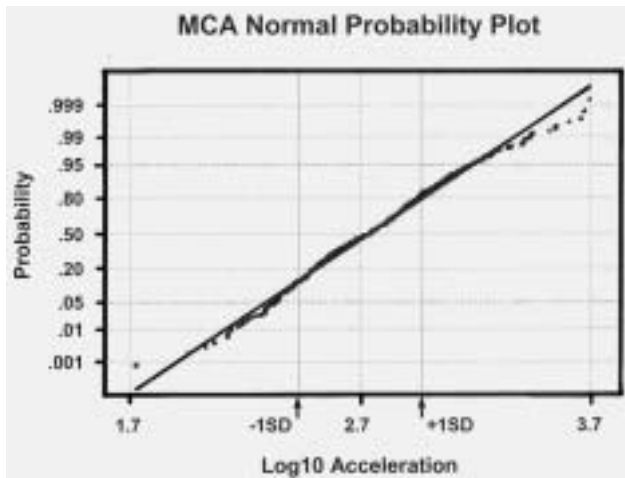
Normal probability plots indicated that velocity, PI, and logarithm of acceleration at each segment were nearly normally distributed in the central regions of the distribution (Fig 3). The Anderson-Darling normality test, which is especially sensitive to the shape of the tails of the distribution, indicated a slight but statistically significant nonnormality in the tails.

#### *Scatter Plots*

Standard plots of SA versus MFV (Figs 4a, 4b) and of PI versus MFV revealed only 1 cluster per vessel segment. Furthermore, the pattern of each scatter plot was distinct for the type of vessel it represented. For example, Figure 3a represents the data from the basilar artery, a major feeder artery. Figure 3b represents the measurements from the ophthalmic artery, an end artery, with characteristically higher accelerations and lower MFV.

#### *Cluster Analyses*

From cluster analysis, we learned that the data represented a continuum of physiological characteristics in a single cluster. This analysis was undertaken to see if observations should be considered as groups without prejudging if a particular cluster could be represented as more than 1 group. This process assumed no outside informa-



**Fig 3.** The logarithm of the acceleration is normally distributed. The logarithm (base10) of the left middle cerebral artery (MCA) systolic acceleration (SA) is distributed normally. The mean log SA for the left MCA was  $2.7 \pm 0.27$ . The arrows indicate the  $-1$  SD and the  $+1$  SD points.

tion about grouping. From these findings, we deduced that our measurements did not represent idiosyncratic biological clusters but rather represented a quantifiable continuum of physiological states.

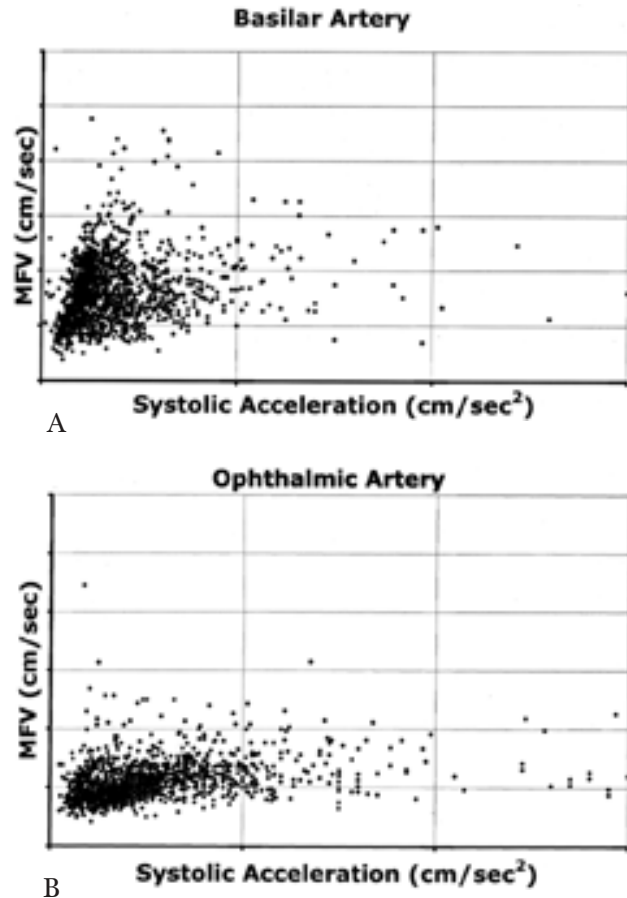
#### Ranges in the Reference Group

The symptomatic population was studied to evaluate the practicability of the DVA method and to allow prospective comparisons. The ranges for each parameter were determined during the same session for every vessel segment. Right and left segments were considered separately. Sample reference data are provided for 2 arterial segments. Examples of the ranges (mean  $\pm$  1 SD) for SA, MFV, and PI are provided for the right ophthalmic artery ( $557.7 \text{ cm/sec}^2 \pm 398.5$ ,  $22.2 \text{ cm/sec} \pm 6.45$ ,  $1.52 \pm 0.35$ , respectively) and for the basilar artery ( $365 \text{ cm/sec}^2 \pm 258$ ,  $38.43 \text{ cm/sec} \pm 13.55$ ,  $1.32 \pm 0.30$ , respectively) and are depicted in Figures 4a and 4b.

#### Physiological States Derived

Three dynamic parameters, SA, PI, and MFV, were measured together on the same wave and then were considered together to define physiological vascular states. We know that a change in MFV correlates with a change in regional flow.<sup>10,11</sup> SA informs us about the force of blood flow, which is met with an equal opposing force created by the blood vessel wall,<sup>12-14</sup> and the PI informs us about the downstream or small vessel impedance to blood flow and represents, therefore, the force impeding the forward flow of blood.<sup>15,16</sup>

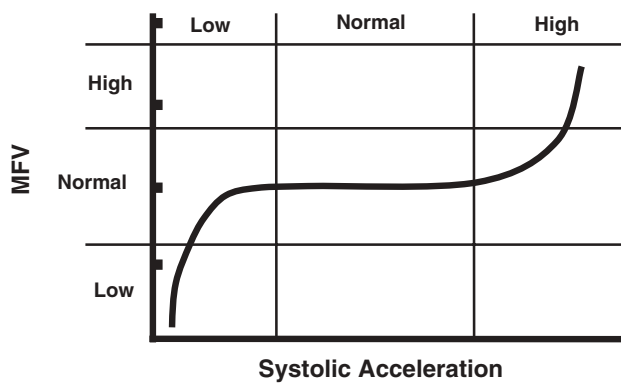
Whereas Force = Mass  $\times$  Acceleration ( $F = M \times A$ ) and Force = Pressure  $\times$  Area, we can assume that SA is propor-



**Fig 4.** Each vessel segment has characteristic flow dynamics. Shown are 2-dimensional. (a) All measurements taken from the basilar artery, a large conductance artery. (b) All measurements obtained from the ophthalmic artery, an end artery. In each plot, the y-axis represents velocity (cm/sec), the x-axis represents systolic acceleration (SA) ( $\text{cm/sec}^2$ ), and the z-axis, in 3-dimensional projections, represents the pulsatility index. For each projection, the axis scales are equal to allow visual comparison. MFV = mean flow volume.

tional to force and force is proportional to pressure; therefore, acceleration is also proportional to pressure (at the point of insonation in a vessel segment). Similarly, we can assume that the PI, an indicator of impedance, yields information about the resistance (related to compliance) of smaller capacitance vessels downstream from the segment in which the PI is measured.

The relationship between SA (which is proportional to force) and MFV is the clinical equivalent of the pressure-perfusion autoregulation relationship (Fig 5). The relationship between PI and MFV is similar, except that the compliance of the small vessels in that vascular distribution is represented. These 2 relationships, SA-MFV and PI-MFV, can be considered simultaneously, where the former describes the flow autoregulation at the point of



**Fig 5.** Pressure (acceleration)–velocity relationship. For every vascular segment, the classic cerebral pressure-velocity relationship can be expressed in terms of systolic acceleration (proportional to force or pressure) and mean blood flow velocity (MFV) (measured during the same pulse). This classification yields 9 sectors. Each vascular segment, therefore, can be classified (relative to its “normal” characteristics) into 1 of 9 sectors in the acceleration-velocity relationship. (A similar relationship can be expressed for a third parameter, the pulsatility index, which can be represented as a third dimension.)

measurement in medium-sized conductance vessels and the latter evaluates downstream vessel impedance in small or capacitance vessels. Thus, the effect of medium and small vessel characteristics on MFV can be measured segment by segment and in ensemble.

A fundamental assumption in DVA is that systolic acceleration is directly proportional to force ( $F = M \times A$ , therefore,  $F$  is proportional to  $A$ ). We recognized that

acceleration represents the force pushing blood forward and that vessel wall compliance is inversely proportional to the same force. Otherwise, the vessel wall would dampen that force by absorbing a fraction of the radial vector of that force. We appreciate, therefore, that the systolic acceleration is a measure of vessel wall compliance.

We defined at the segmental level, 3 states (high, normal, or low) for 3 parameters (acceleration, MFV, and PI) yielding a 27-element matrix ( $n = 3^3$ ). If we consider further 3 directions (states) of flow in each segment (forward, reverse, or no flow), then there are 81 ( $n = 3^4$ ) theoretically possible physiological states for each vessel segment (Table 1).

Regional or global physiological states result from compensatory autoregulation among segments. These patterns are characterized as distinct regional or global patterns of physiological states that enable the physiological differentiation of cerebrovascular disease states (Table 1). Thus, ensemble patterns are considered as global, regional, or segmental.

The number of ensemble states may be multiplied by the number of segmental states to yield the total number of theoretical vascular states. This physiological classification system yielded a sufficient number of vascular physiological states to classify the more limited number of conditions currently defined by clinical medical science. The data collected from actual cases can then be used to determine which of these theoretical states are compatible with life in homeostasis.

Table 1. Theoretical Physiological States Derived by Dynamic Vascular Analysis

State	Parameter	Number	Number of States for Each Parameter	Total
I. Insonation points	Vessel segments	15	15	15
II. Segment states	Flow direction	Forward/ $\phi$ /reverse	3	81
	Velocity	3	3	
	Acceleration	3	3	
	Impedance	3	3	
III. Ensemble states	Collateral flow			9
	Sidedness	R to L/NL/L to R	3	27
	Anterior versus posterior	A to P/NL/P to A	3	
Global patterns	Global	Homogeneous/NL/heterogeneous	3	27
	Regional	Anterior/NL/posterior	3	
	Hemisphere dominance	L/NL/R	3	

Insonation points include bilateral measurements of the ophthalmic arteries, middle cerebral arteries (M1 and M2), anterior cerebral arteries (A1), terminal internal carotid arteries (C1), posterior cerebral arteries (P1 and P2), carotid siphons (C2 and C4), vertebral arteries, and the basilar artery. The total number of states is determined by multiplying the total number of states identifiable with regard to each parameter. The product of the total number of states for each parameter equates to ( $3^9 \times 15$ ) or 295,245 theoretical physiological states.  $\phi$  = no flow, R = right, L = left, NL = normal, A = anterior, P = posterior.

Given the redundant supply and collateralization of the cerebral vessels, diagnostic information is derived by considering the ensemble of measurements from vessel segments in the cerebrum. In other words, if we look at adjacent and distant vessel segments and collateral flow patterns, we find supportive information that would help confirm the interpretation of Doppler data in a particular segment and could confirm the finding of distal dilation and/or contralateral collateral flow.

Patterns may be considered global if present in the majority of vessel segments. These global patterns of insonation include (1) increased acceleration that reflects diminution of compliance from increased intracranial pressure or extensive vasculopathy, (2) increased PI reflecting increased impedance from increased intracranial pressure or small vessel disease,<sup>17</sup> or (3) vasodilatation, reflecting sleep apnea<sup>18,19</sup> medication effect or low cerebral perfusion pressure (which exists also to some degree in apnea).<sup>18</sup> When considering the ensemble of vessels, this low perfusion pressure would be assumed to exist proximal to the point of insonation.

#### *Normal State Defined*

The DVA algorithm begins with quantitative data and relates this to physiological state according to standard deviation. The physiological state is defined with respect to each parameter being high, normal, or low, according to the standard deviation. The region between  $-0.5$  and  $+0.5$  SD is proposed as the range over which the physiological state is not only normally distributed but also unperturbed by local or systemic influences. The normal, unperturbed state of flow is defined as the region within 0.5 standard deviations of the mean of all 3 of the flow parameters (MFV, PI, and the natural log of SA).

#### **Case Studies**

To illustrate how DVA may be used in clinical and research studies, 2 exemplary cases are described presently.

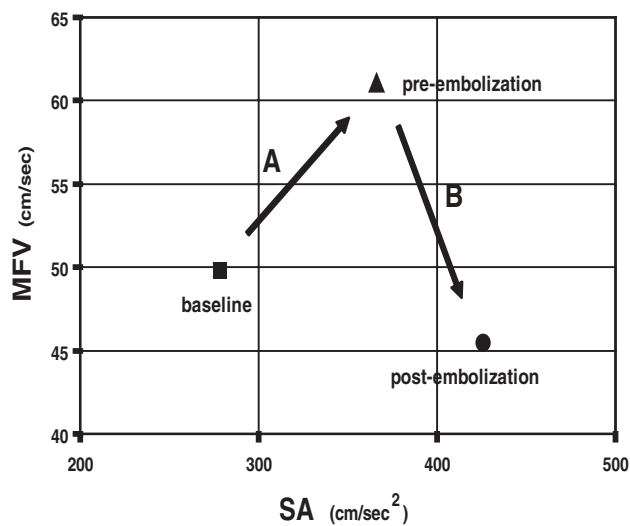
##### *Case of Thalamic Arterio-Venous Malformation (AVM)*

A 30-year-old woman presented with increased dystonia and focal seizures and has a diagnosed nonoperable, right thalamic AVM. She had been treated previously with gamma knife radiation and coil embolization. Examination revealed left homonymous hemianopsia, left hemiparesis with spasticity, and left-sided pathologic reflexes revealing upper motor neuron deficits corresponding to the right brain lesion. Her DVA revealed increased MFV into the right anterior circulation with pathologically low impedance. The left hemisphere was providing collateral support to the right hemisphere from the left an-

terior cerebral artery through the anterior communicating artery. The distal MFV was diminished in the left anterior, middle, and posterior cerebral arteries. An angiogram revealed that vessels fed the lesion from the right middle cerebral artery (MCA) (M1 segment), right anterior cerebral artery (A1 segment), and right posterior cerebral artery (P1 segment, proximal to the posterior communicating artery branch point) and revealed collateral support patterns. She was advised to undergo a repeat embolization procedure. She decided to wait. Her seizures became more frequent over the ensuing 6 months. A repeat angiogram revealed relatively no change and seemed to confirm the steal phenomenon. Her repeat DVA showed a clear increase in mean flow velocities through the conductance vessels and was angiographically shown to be the vessels from which the feeder vessels were derived. The same conductance vessels also showed a diminution of PI (impedance), suggesting an increasing vascular capacitance downstream from the conductance vessels. This suggested increasing stress and strain across these vessels as well as a further diminution of velocity to the contralateral hemisphere (Fig 6A). Another embolization procedure was performed. Two days following that procedure, the blood flow into the lesion had diminished (Fig 6B).

#### *Discussion of Case*

By understanding the dynamic changes and physiological characteristics in a growing vascular lesion,<sup>20</sup> the interventional radiologist might select vessels with highest velocity and lowest impedance for embolization therapy. Usually, the radiologist would embolize an AVM guided by an anatomic (not physiologic) approach. One would angiographically inspect the anatomy for arteries feeding the AVM. Given the difficulty and morbidity of the embolization procedure, it would seem prudent to guide the process of embolization using physiological information regarding the relative contribution of feeding arteries and real-time assessment of the process of embolization. Thus, it would seem possible to direct embolization therapy at feeder vessels believed to contribute most to the morbidity according to physiological characteristics. It is the exceptional deep AVM that can be evaluated directly by insonation of the feeder vessel when it extends directly from the circle of Willis. Traditional TCD is helpful in analysis of AVMs only when the feeder vessel can be directly insonated. By evaluating the ensemble of vessels, DVA may be better able to determine the compensatory patterns and global alterations of flow that allow the identification and localization of AVMs fed by deeper cerebral arteries that cannot be insonated.



**Fig 6.** Case 1: arterio-venous malformation at baseline, immediately before, and 2 days after embolization. Presented is a case of arterio-venous malformation (AVM) in a 30-year-old woman. The x-axis is the mean flow velocity (cm/sec) in the best wave measured for each insonated segment. The y-axis is the acceleration (cm/sec/sec) measured in the same wave. The geometric mean of every set of measurements made at each of 3 time points is represented: the square represents the baseline, the triangle represents preembolization, and the circle represents the measurements taken at 2 days postembolization. A 1-way ANOVA revealed a significant effect of acceleration,  $F(2, 65) = 4.565, P = .014$ , and velocity,  $F(2, 65) = 3.160, P = .049$ . MFV = mean cerebral blood flow velocity, SA = systolic acceleration. (A) Progressive increased acceleration (vessel tone) reflected a growing AVM (acceleration change significant,  $P = .02$ ; velocity change non-significant,  $P = .1$ , by both  $t$  and  $z$  tests). (B) After the procedure, velocity was reduced; however, as the change in acceleration (vessel tone) was not statistically significant, we concluded that the embolization was incomplete (velocity change significant,  $P < .01$ ; acceleration change non-significant,  $P = .07$ , by both  $t$  and  $z$  tests).

#### Case of Severe Sleep Apnea and Congestive Heart Failure

An 81-year-old gentleman who was repeatedly hospitalized for recurrent heart failure presented with increasing memory loss and ataxia. He had a low ejection fraction and a past history of hypertrophic cardiomyopathy. Previous evaluation by a neurologist was unremarkable, except for diffusely slowed and reduced electro-encephalogram waveforms. Magnetic resonance imaging reported age-related atrophy along with scattered periventricular white matter changes. He was told that his condition was related to his age and that there was nothing more that could be done. His family reported increased urinary urgency.

Neurological examination revealed marked subcortical abnormalities including sustention and intention

tremors, saccadic intrusions of his ocular smooth pursuit movements, and diminution of up-gaze and convergence movements. He walked with a wide-based gait that was shuffling. He turned around with multiple small steps. He had an axonal pattern neuropathy and a positive Romberg sign.

He was found to have on the DVA (Fig 7A) hemodynamics consistent with a proximal diminution of force of flow, related later to diminished cardiac output. Interestingly, the left MCA had the largest relative diminution of MFV. A detailed sleep history was consistent with apnea, although a polysomnogram 5 years earlier was unremarkable. A repeat study revealed severe sleep apnea. Following 2 months of continuous positive airway pressure (CPAP) therapy, the flow dynamics shifted toward normalized compliance (Fig 7A) with a dramatic reduction in hospitalizations for repeated congestive heart failure (CHF) and an improvement in cognition. Several months later, the patient experienced a very small infarct in the left MCA territory (which had been noted to have low flow dynamics on the previous DVA) and sustained a residual aphasia. His cardiac function continued to diminish despite maximal medical therapy, until he was admitted to the hospital again with CHF with an ejection fraction of less than 10% and dramatic reduction of cognitive and frontal lobe function. The DVA reflected worsening of cerebral flow dynamics (Fig 7B). Pre- and post-CPAP intervention DVAs demonstrated the change in cerebral hemodynamics. Eventually, the patient succumbed to his progressive disease.

#### Discussion of Case

The chronology of the DVA findings reflected initially the patient's response to CPAP and then reflected progressive terminal CHF.

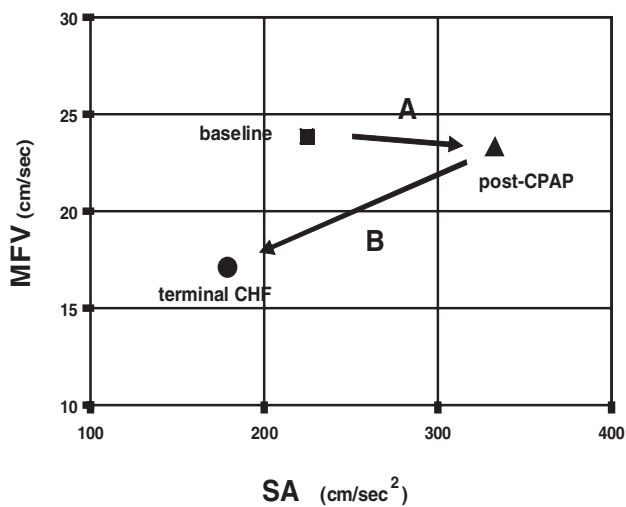
## Discussion

Physiological states may be defined at the segmental and ensemble levels for the purpose of categorizing vascular conditions. Different types of information may be observed at each level. The segmental and ensemble states defined by DVA are hypothetically related to known conditions as discussed below. Future studies will critically evaluate these hypotheses.

### Segmental States

#### Stenosis, Vasospasm, and Decreased Compliance

The example of stenosis is discussed to demonstrate how DVA may reveal and expand on the definition of an angiographically defined condition. Stenosis is a state of diminished compliance associated with an increase in the systolic acceleration of the blood in the same segment.



**Fig 7.** Case 2: congestive heart failure (CHF) complicated by hypertension and sleep apnea that progressed terminally to CHF. Presented is a case of CHF complicated by sleep apnea and hypertension in an 81-year-old male. The x-axis is the mean flow velocity (MFV) (cm/sec) in the best wave measured for each insonated segment. The y-axis is the acceleration (cm/sec<sup>2</sup>) measured in the same wave. The geometric mean of every set of measurements made at each of 3 time points is represented: the square represents the baseline, the triangle represents change with continuous positive airway pressure (CPAP), and the circle represents the measurements taken when the congestive failure was nearly terminal. Note that the flow rates are very low, indicating poor cardiac function in this patient. A 1-way ANOVA revealed a significant effect of acceleration,  $F(2, 63) = 6.730$ ,  $P = .002$ , and velocity,  $F(2, 63) = 5.910$ ,  $P = .004$ . MFV = mean cerebral blood flow velocity, SA = systolic acceleration. (A) Vasodilatation appeared to have corrected in response to CPAP therapy as evidenced by the normalization of acceleration (vessel tone) without a change of velocity (acceleration change significant,  $P = .04$ ; velocity change nonsignificant,  $P = .27$ , by both  $t$  and  $z$  tests). (B) Despite compliance with CPAP therapy, cardiac output diminished. This decreased the velocity and was associated with ineffective compensatory vasodilatation as evidenced by decreased acceleration (vessel tone). Overall flow rates and accelerations were worsening in this patient with hypertrophic cardiomyopathy (acceleration change significant,  $P < .01$ ; velocity change significant,  $P < .01$ , by both  $t$  and  $z$  tests).

Impedance may be elevated proximal to the region and diminished distal to the lesion. It is well known that stenosis in a segment is manifested as segmental increased velocity secondary to increased acceleration, indicating diminished compliance. This state may be characterized as relative segmental hyperemia with an increase in MFV because the flow rate (volume/time) through the stenotic segment is higher than would be expected in a normal vessel of the same dimensions or in a stenotic segment that was not contiguous with normal vessel segments. To maintain the volume flow rate beyond the area of stenosis

at the prestenotic volume flow rate, the velocity of blood passing through the stenotic region increases.<sup>21</sup> This relative hyperemia across the point of narrowing exists until the stenosis limits flow.

Much scientific and commercial effort is being made to identify the presence of atherosclerosis and atherosclerotic plaque using invasive procedures. Segmental diminished compliance, as evidenced by increased accelerations and increased velocities, may be consistent with but not limited to a site of arteriosclerosis, especially one that causes significant focal stenosis.<sup>22</sup> Diffuse arteriosclerosis can also affect the performance of vascular segments, with stiffening and decreased compliance,<sup>21</sup> and may be distinguished from that seen in hypertension by the segmental (focal) characteristic pattern of the former. Such changes could be identified by DVA as increased systolic acceleration with diminished impedance and may be used to assess preclinical, presymptomatic atherosclerosis and to follow potential changes associated with specific therapeutic interventions. Low compliance due to vasospasm could be distinguished from low compliance due to arteriosclerosis by considering vascular performance in the ensemble of cerebral vessels.

#### *Vasodilatation/Increased Compliance*

A state of vasodilatation is manifest as diminished acceleration. Low velocity represents, by definition, the failure of an otherwise healthy vessel segment at the point of insonation to dilate enough to compensate for the drop in force of flow from a proximal cause. Compensatory vasodilatation is a state of diminished acceleration with normal MFV. The differential diagnosis of low velocity, when considered alone and not correlated with any other parameter, includes cardiac disease, proximal stenosis, distal stenosis, or ectasia with normal flow volume.

#### *Small Vessel Disease/Increased Impedance*

Impedance is increased at the point of insonation secondary to a disease process that increases the resistance of distal capacitance arterioles either by causing them to narrow or diminish their compliance. This may be present in a local, regional, or widespread ensemble pattern. Diseases known to involve predominantly small vessels are associated with increased impedance.<sup>17</sup> The vasovascularum, consisting of small vessels, supports the metabolism of smooth muscle cells in the vessel wall in systemic arteries but is absent from the intracranial arteries<sup>23</sup> where metabolic support involves the astrocytes. The diminished vascular performance of the larger vessel would be expected to further compromise the perfusion of the distal diseased small vessel bed, leading to a progressive deterioration of vascular performance in a positive feedback cycle.

### *Ensemble States*

Although most of these physiological states will be familiar to the reader, it is important to appreciate that DVA makes it possible to define and ascertain these physiological states in the clinical setting.

Global low flow describes a state in which the velocity of flow is low in every vessel segment due to the failure of maximal compensatory dilation to maintain the velocity.<sup>6</sup> Global vasodilatation is a state of low acceleration in every segment secondary to diminished force exerted by the vessel wall or diminished blood volume presenting with the same flow dynamics. Hyperemia is a state of increased flow velocity secondary to true or perceived increase in metabolic substrate demand.<sup>6</sup> Hyperemic breakthrough is a state of such high force of flow that the limit of autoregulation is exceeded, increasing forces of stress and strain across the vessel wall.<sup>6</sup> Increased acceleration (right shifting) represents a state in which the acceleration is either in the normal range or increased, with diminished flow velocities. In this state, the vessel must transmit more force back into the vascular system with inefficient improvement in flow velocity. There also exists the possibility that there is a global force being applied to the vessel segments.<sup>24</sup> Increased impedance would<sup>17</sup> suggest that small vessel outflow is hampered either by small vessel disease or intracranial pressure.<sup>24</sup>

The DVA method provides quantitative physiologic information that represents a continuum of physiological states of vessel performance and that may be expressed also as semiquantitative states. DVA can characterize cerebrovascular dynamics in participants of clinical trials and enrich control treatment groups with respect to the condition targeted by therapies including clinical trials in primary and secondary stroke prevention, acute stroke, normal pressure hydrocephalus, sleep apnea, vascular dementia, vasculitis, and the selection of antihypertensive medications or other conditions with disordered cerebral hemodynamics or vascular responsiveness (eg, concussion, migraine).

### *Strengths and Limitations*

This retrospective study demonstrates that DVA can be applied to TCD data already obtained. This shows that the traditional technique of performing TCD yields data that may be analyzed by DVA. Although it may be possible to extract more dynamic information from the TCD data, we believe that the 3-parameter characterization of vascular states by DVA is sufficiently detailed to be able to physiologically characterize known cerebrovascular disorders with high resolution.

The data obtained in this study were from actual patients referred for a broad range of reasons. Although a typical patient referred for a TCD likely has an abnormality in at least 1 vessel segment, this abnormality is often not significant enough to influence the ensemble of insonated vessel segments. This means that the majority of segmental measurements analyzed in the present study represent the population at risk for a cerebrovascular event that is most likely to require a TCD and DVA. For research studies, asymptomatic control group patients will need to be studied using DVA to establish reference ranges.

The literature of vascular physiology and TCD ultrasound supports the logic in each step of the DVA process. To our knowledge, there is no other comparable means of simultaneously considering velocity along with 2 dynamic parameters (PI and SA) to physiologically classify cerebrovascular diseases according to the dynamic properties of vessel segments and the ensemble relationship of cerebrovascular segments. Currently, only Doppler ultrasound is able to provide information about the velocity distributions of blood cells in discrete vascular segments. Therefore, Doppler ultrasound is presently the only means (invasive or noninvasive) of collecting primary data to perform cerebrovascular physiological assessments. For example, invasive catheterization of a vessel would measure only the mean pressure in the vessel at any one time and cannot assess the peak velocities of the flowing blood. Furthermore, angiography would not be able to make measurements at all of the vessel segments insonated routinely using TCD. Traditional imaging modalities do not have the capability to measure the velocity distributions of moving blood cells in vivo. Although new techniques in CT angiography, magnetic resonance angiography, infrared spectroscopy, positron emission tomography, and single photo emission computer tomography scanning may claim to evaluate blood flow, these methods are intrinsically unable to measure the velocity distributions of moving blood cells as can be done readily using TCD ultrasound technique.

Because there may be interreader or intrareader variability related to cursor placement, it is important to be as precise as practically possible when positioning the cursor. Whereas subsequent steps of DVA analysis convert these readings to standard deviation scores, the method will be mathematically insensitive to variability in cursor positioning unless the values obtained are in the sigmoidal regions of the normal probability curve. The DVA method also converts standard deviation scores to a semiquantitative score of high, normal, or low, thereby reducing further the potential for cursor placement vari-

ability to introduce any significant error in the assignment of a DVA state to a particular segment. Finally, individual segmental states are then considered in ensemble to make the final assessment. These steps make it improbable that interreader or intrareader variability would be perpetuated into the final DVA assessment.

Vascular tone is sensitive to  $p\text{CO}_2$ . Individual TCD-derived parameters, such as velocity, are affected by vascular tone and therefore by  $p\text{CO}_2$ . However, velocity interpretations are assisted by correlation with  $p\text{CO}_2$ . DVA is sensitive to vascular tone and does intrinsically reflect the effect of  $\text{CO}_2$  on vascular tone. Future studies will relate DVA states to  $p\text{CO}_2$ ; meanwhile, we do believe that DVA produces a differential diagnosis that includes the effect of  $\text{CO}_2$ .

#### *Future Research Directions*

DVA makes it possible to monitor the cerebral circulation for the natural progression of a disease process or the reversal of a disease process in response to a therapy. Whereas systolic acceleration has been considered alone as an indicator of response to therapy,<sup>25</sup> DVA, which considers 2 parameters (MFV and PI) simultaneously with SA, will likely be more sensitive and specific in monitoring the response to drug therapy. As a quantitative classification system based on physiological principles, DVA suggests that the information content in velocity distribution information is substantial. Future work will incorporate new parameters as they are found to be clinically meaningful and will extend this form of analysis to the assessment of the entire vascular system.

Clinical studies may now be undertaken to ascertain reference ranges for different populations of humans. Reference ranges may be established for various species to support animal studies. Receiver-operator curves may be established for the diagnosis of particular disease conditions. Further research will establish the optimum thresholds of sensitivity and specificity in new algorithms that may be used to guide diagnosis and therapy of specific vascular disease states. DVA may also be used to study the safety of drugs early in the development phase and ascertain the efficacy and long-term safety of drugs in later phases. DVA may be used in clinical diagnosis, clinical monitoring, clinical trial selection, and risk stratification for prevention trials. One area of great research potential would be to differentially diagnose and monitor the progression and treatment of the dementias.<sup>26-29</sup>

DVA may be extended to the vasculature of every organ. DVA is a way to detect states of vascular disease, measure the performance of arterial systems, and classify the vascular diseases that progress to end-organ diseases. The DVA method may also include measurements made

in contiguous vascular segments, such as the carotid, brachial, or aortic root. DVA offers an objective, quantitative way to evaluate primary cerebrovascular disorders or systemic disorders with cerebrovascular effects.

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