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BACKGROUND AND PURPOSE: **First pass contrast-enhanced MR imaging using gradient-echo acquisitions is commonly used to assess cerebral blood flow, despite the confounding signal from large blood vessels. We hypothesized that removal of this unwanted intravascular signal using independent component analysis would result in a more accurate depiction of cerebral blood flow.**

METHODS: **Images of 11 patients, acquired with our acute stroke imaging protocol, were post processed to produce images of relative cerebral blood flow (rCBF). The same images were processed with independent component analysis to identify and remove the signal from large blood vessels, with a second set of rCBF images produced. Both sets of rCBF maps were pooled, randomized in order, and read in a blinded fashion by two neuroradiologists to assess the level of large artery artifact and overall image quality. Significance was determined using a Wilcoxon signed rank test.**

RESULTS: **Results from both readers indicated that the level of large artery artifact was significantly reduced in the images processed using independent component analysis component removal ($P < .05$). In addition, both readers indicated significantly ($P < .05$) improved image quality of the images processed using independent component analysis.**

CONCLUSION: **The removal of the signal resulting from large blood vessels before calculation of rCBF resulted in images with significantly less artifact and higher image quality.**

MR imaging techniques to study cerebral perfusion have been developed and used clinically to detect ischemic stroke (1). On the basis of tracer kinetics, perfusion parameters are derived from the signal intensity changes in the brain after the IV injection of a bolus of gadolinium-based contrast agent. Typically, multi-phase T2*- or T2-weighted sequences, such as gradient-echo or spin-echo echo-planar images, are used to acquire a time series of images and parametric maps of relative cerebral blood flow (rCBF), mean transit time, and relative cerebral blood volume are derived (1–3). In these acquisitions, spatial resolution is limited because of the high temporal sampling rate. Low spatial resolution results in partial volume effects where an image voxel contains both brain parenchyma and a large blood vessel. Because of partial volume effects, the large signal intensity variations in the vicinity of the larger blood vessels may result in an overestimation of perfusion in the voxel. Spin-echo acquisitions have less sensitivity to these effects, but gradient-echo acquisitions are commonly used for perfusion studies because of their sensitivity to a larger range of vessel size (4). Recently, some authors have advocated the use of combined spin-echo and gradient-echo sequences, which exhibit mixed vessel sensitivity (5).

The purpose of this study was to attempt to remove partial volume effects from perfusion data using independent component analysis (ICA). ICA is a method of identifying independent signal sources from a mixture of signals without a priori knowledge of the sources (6, 7). ICA has previously been used with functional MR imaging to identify regions of activation (8–11). We report our results using ICA to identify and remove the dynamic signature of large vessels from parametric maps of relative cerebral blood volume, rCBF, and mean transit time.

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Methods

To determine the effectiveness of ICA in MR perfusion imaging, we compared parametric images of cerebral blood flow derived from raw MR images and those pre-processed using ICA component removal. Eleven consecutive patients (four men and seven women; median age, 49.3 ± 26.4 years; age range, 10–80 years) underwent imaging using the clinical acute stroke imaging protocol routinely performed at our site (12). Perfusion-weighted images were acquired in the axial plane with 2D, gradient recalled, single shot, echo-planar imaging (2000/60 [TR/TE]; flip angle, 60 degrees; field of view, 24 cm; readout resolution, 128; phase-encoding values, 64; 10 to 14 7-mm interleaved sections per phase; 36 consecutive phases; total imaging time, 73 s). Contrast agent (gadodiamide, 0.1 mmol/kg of body weight) (Omniscan; Nycomed-Amersham, Princeton, NJ) was injected at 2.0 to 4.0 mL/s using a power injector (Spectris; MEDRAD, Indianola, PA) 13 s after imaging initiation. This protocol produced a set of 36 image stacks; each stack of images represented a "snapshot" of the patient's head as the bolus of contrast agent passed**.** This allowed for the determination of 36 independent components.

Relative regional cerebral blood flow (rCBF) was calculated using the singular valued decomposition deconvolution presented by Ostergaard et al (2). An arterial input function was chosen by inspection and used to deconvolve each voxel in the time series of images. The arterial input function was derived by placing a single region of interest over the middle cerebral artery. A single arterial input function was used to deconvolve voxel-by-voxel contrast curves from both hemispheres. A resulting stack of 2D images was produced in which signal intensity was proportional to cerebral blood flow. The arterial input function used in the singular valued decomposition deconvolution was written to disk and used as input to the deconvolution of the ICA-processed images. All post processing was performed on an offline workstation (Impact 1000; Silicon Graphics, Mountain View, CA), using software that was developed in house.

A second set of rCBF images was produced after applying a locally developed ICA program to the raw perfusion-weighted images (13). A detailed description of ICA is presented as an appendix to this report. ICA identified 36 independent components and mapped these to their corresponding spatial locations, with the signal intensity of each voxel reflecting its *z* score for the particular component. The resulting component maps were inspected, and arterial components were identified manually by a trained operator (T.J.C.) based on morphology and temporal features. Components corresponding to the middle cerebral artery, circle of Willis, sylvian fissure, and sagittal sinus were identified. Typically, four to six components were required to completely remove the unwanted signal associated with these large vessels. Once these components were identified, the time course information corresponding to these components was removed as described in the appendix and a new time series of images was produced. Because the arterial component of these images had been removed by the ICA, the previously calculated arterial input function was used in the calculation of rCBF. Therefore, each voxel's concentration curve was deconvolved with the arterial input function determined by inspection, as described above, resulting in a second set of ICA-processed rCBF images.

The rCBF images created with the conventional singular valued decomposition program were filmed nine per sheet, with patient and acquisition information removed. The most proximal and/or most distal images in the stack were not filmed when they contained little anatomic information or suffered from severe signal loss due to field inhomogeneities near air-tissue interfaces. The rCBF images created after removal of arterial components with ICA were filmed identically to the unprocessed perfusion maps. The 22 image sets were randomized in order and presented to two experienced neuroradiologists (V.M.H., H.A.R.) who graded the images on a 4-point scale (0–3 points) based on the level of observed large artery artifact (0 = artifact not present, 1 = artifact questionably present, 2 = artifact present but not severe, 3 = artifact present and severe) and the overall quality of the perfusion map (0 = robust CBF map, 1 = CBF information present, 2 = CBF information questionably present, 3 = no CBF information evident). Differences between ICA and raw perfusion maps in observed large vessel artifacts and overall image quality were evaluated with the Wilcoxon signed rank test at a 5% level of significance.

Results

Technically satisfactory raw echo-planar imaging flow data were acquired for each of the 11 patients, and rCBF maps were produced. In each case, ICA identified components with time characteristics and spatial localization typical of arterial blood flow (Fig 1). The time course of the arterial components showed earlier arrival time and a less broad peak than those of other components. In particular, the component associated with the sagittal sinus was both delayed with respect to the arterial components and more distributed in time. In each case, rCBF maps were obtained by singular valued decomposition after the removal of the arterial flow component from the data.

The conventional singular valued decomposition maps of perfusion showed areas of excess vascular signal. They showed flow in cerebral gray matter and similar or greater magnitude of flow in the interhemispheric fissure, sylvian fissure, and perimesencephalic cisterns. The rCBF maps created after removal of arterial components showed flow in gray matter with little or no flow in the interhemispheric fissure, sylvian fissure, and perimesencephalic cistern (Fig 2). In cases in which cerebral infarcts were present, the region of diminished perfusion was better shown with the maps after removal of the arterial component than in the conventional singular valued decomposition maps (Fig 3).

The results of the blinded readings of the rCBF maps are shown in the Table. Both readers found significantly less artifact ($P < .05$) and significantly higher image quality ($P < .05$) after removal of the arterial component.

Discussion

Removal of the arterial component with ICA results in disappearance of essentially all the signal intensity with a hemodynamic profile characteristic of large blood vessels, leaving the capillary flow intact. These results show an improvement in the rCBF maps created by singular valued decomposition after the removal of arterial components from the data. The conventional rCBF images have a confounding effect of large vessels, or an "arterial shine through" effect. These results suggest that post processing perfusion data with ICA may effectively remove the unwanted arterial signal from gradient-echo echo-planar perfusion-weighted images. To our knowledge, this is the first demonstration of a technique to remove the unwanted signal intensity associated with

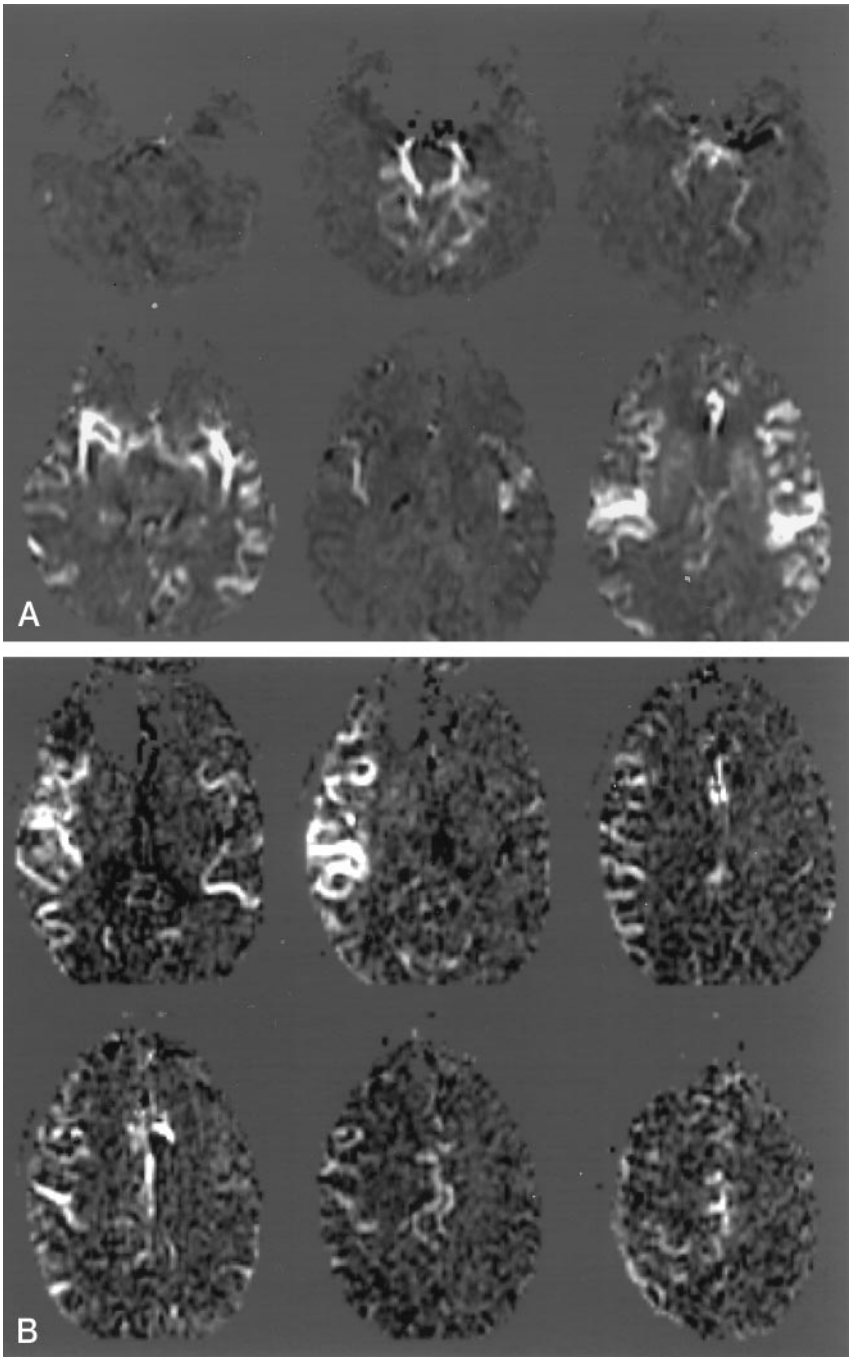

FIG 1. ICA identified components with time characteristics and spatial localization typical of arterial blood flow.

A, Images from the case of a 10-year-old male patient with thrombotic thrombocytopenic purpura and seizures. Examples of the spatial localization of components identified by ICA as arterial components are shown. Note that the signals identified correlate with the locations of large blood vessels in the sylvian fissure, interhemispheric fissure, and peri-mesencephalic cistern.

B, Examples of the spatial localization of components identified by ICA as arterial components in a 65-year-old female patient with left hemispheric border zone ischemia after embolization of a cavernous carotid aneurysm. Note the markedly reduced large vesssel flow components in the left hemisphere. Signals that correlate with the location of large blood vessels in the sylvian fissure, inter-hemispheric fissure, and peri-mesencephalic cistern were identified.

large blood vessels from perfusion-weighted MR images using ICA.

Perfusion images contain data on the capillary, arterial, and venous flow. For clinical use, maps of tissue perfusion without the confounding effects of arterial and venous flow are optimal. The presence of an effect due to large blood vessels, or the arterial shine through, effectively adds a low resolution cerebral angiogram to the perfusion data and tends to obscure the tissue perfusion. The most important application of perfusion imaging is to detect tissue that is underperfused or hyperperfused. The presence of arterial shine though may simulate hyperperfusion or mask hypoperfusion.

The problem of arterial shine through may be addressed by changing the acquisition strategy. Some authors advocate the use of spin-echo acquisitions to minimize the effect of large blood vessels on the flow data. Spin-echo acquisitions are less susceptible to local field transient signal fluctuations in the vicinity of large vessels as the contrast bolus passes. Therefore, they do not suffer from the arterial shine through to the same extent as do gradient-echo acquisitions. However, the use of a spin-echo acquisition with inherently less T2* weighting results in a much smaller change in signal intensity in response to the passage of the bolus and therefore a smaller signal-to-noise ratio of the perfusion-weighted images. In addition, spin-echo sequences are sensitive

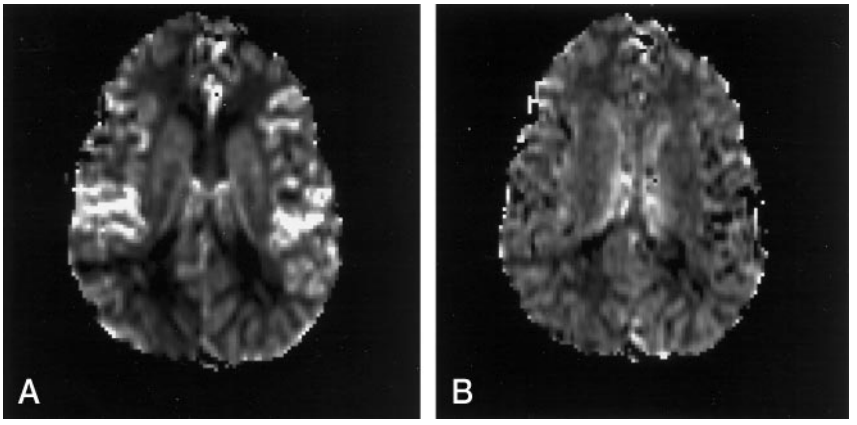

FIG 2. Normal rCBF maps of the 10-year-old male patient shown in Figure 1A.
A, Before ICA component removal.
B, After ICA component removal. Note the reduction in the arterial shine through that is the effect of large vessels confounding the tissue perfusion map. There is a subtle decrease in flow in the paramedian right parietal cortex.

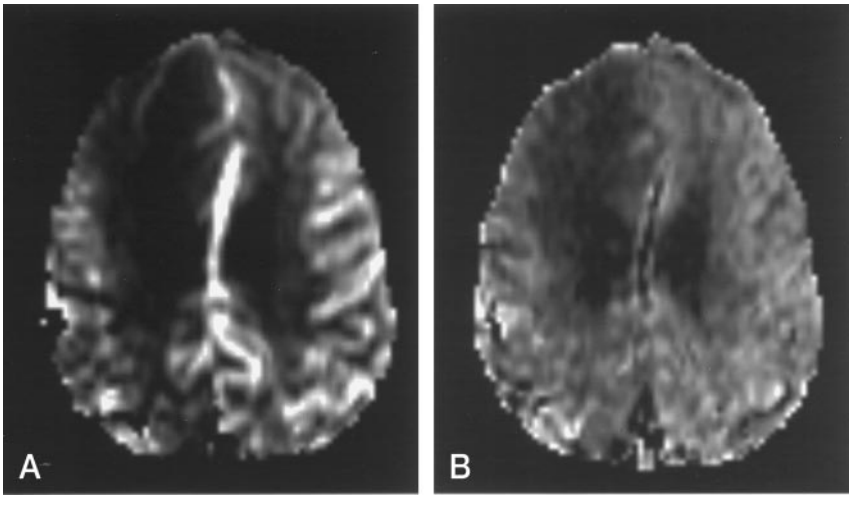

FIG 3. rCBF maps of an 80-year-old female patient with large cell lymphoma of the right frontal lobe.
A, Before removal of arterial shine through.
B, After removal of arterial shine through using ICA. Reduction of arterial shine through improves definition of poorly perfused region.

Results of a blinded reading of the parametric maps of cerebral blood flow

	Reader 1			Reader 2		
	Raw Mean (σ)	ICA Mean (σ)	*P*	Raw Mean (σ)	ICA Mean (σ)	*P*
Artifact severity	2.5 (0.7)	1.3 (1.1)	<0.05	2.8 (0.4)	1.0 (0.9)	<0.05
Image quality	1.1 (0.5)	0.5 (0.8)	<0.05	1.3 (0.5)	0.4 (0.5)	<0.05

Note.—ICA indicates independent component analysis. A Wilcoxon signed rank test comparing the severity of the artifact and image quality before (raw) and after (ICA) independent component removal of arterial components showed that component.

primarily to blood vessels in the size range of 1 μm to 10 μm (4). Therefore, spin-echo acquisitions in perfusion imaging may underestimate cerebral blood flow and vascular volume.

The conventional methods of suppressing the unwanted arterial shine through signal from perfusion images include thresholding, which results in signal voids, or using spin-echo acquisitions that are insensitive to the signal changes in large vessels. Unlike these approaches, ICA identifies multiple components within a single voxel based on their time course information and not on the absolute flow or vessel size per se. ICA separates distinct temporal patterns that combine to produce the signal intensity changes observed within a voxel. For example, the peaked arterial component exhibiting an earlier arrival time is separated from the capillary component that is typically broader, or more "blunted," and arrives later in time.

Another potential advantage of ICA may be the ability to identify arterial components that are specific to different anatomic regions. In cases in which compromised flow affects one hemisphere, ICA could potentially be used to identify arterial components that more accurately represent the arterial input function of the affected region.

Perfusion-weighted images may also be acquired without the use of exogenous contrast agents. By means of alternating RF inversion pulses applied in the neck, a spin label is applied to blood within the carotid artery (14, 15). CBF is mapped by acquiring sections through the head and subtracting images acquired with and without the inversion pulse. This technique produces images less affected by arterial

shine through. Because the signal differences are inherently small (approximately 1%), substantial signal averaging and relatively long acquisition times are needed.

With the application of ICA to remove the confounding effects of arterial flow, the investigator has more flexibility in choosing the technical parameters and acquisition sequence. Gradient-echo sequences that have greater sensitivity to flow can be used advantageously. By using the gradient-echo sequence, the arterial input function can be characterized exactly, rather than estimated, for deconvolution analysis.

Our ICA implementation does have some potential limitations. Application of ICA component removal requires additional offline postprocessing of images. In the current implementation, to produce the ICA-processed images requires an addition 40 to 50 min of processing time**.** In the diagnosis of acute stroke, this additional time is undesirable in cases for which CBF maps are required to determine whether a patient is a candidate for thrombolytic therapy. Future work is aimed at streamlining this process to reduce the latency in the hopes of improving the delineation of perfusion deficits in cases of acute stroke.

Another potential limitation is the operator-intensive nature of the postprocessing. Because the number of components determined by ICA is equal to the number of time points, the system is over-determined. Multiple components are identified that have the same anatomic correlation or no anatomic correlation. Therefore, the removal of components requires some level of expertise and introduces an additional opportunity for human error into the miscalculation of rCBF maps. However, considering the improvement in image quality by the removal of the arterial shine through, determining the clinical significance of such postprocessing techniques warrants further study in a larger series of patients.

Conclusion

Initial results indicate that ICA can be used in post processing to remove unwanted arterial signal from gradient-echo echo-planar perfusion-weighted images, resulting in rCBF maps that show fewer artifacts and are of higher quality.

Appendix

The ICA method assumes that a dynamic MR signal is composed of a set of statistically independent components and attempts to separate these components without a priori knowledge of their characteristics (6–9). Each image in the perfusion study is modeled as a linear combination of static images or components (ie, sources) according to the following equation:

$$1) \qquad S_{ip} = \sum_t W_{it} X_{tp}$$

where S_{ip} is the i-th source of pixel p and X_{tp} is the measured signal intensity of pixel p at time t. The mean signal intensity over p has been subtracted such that the weighting matrix, W_{it}, defines the linear transformation between the sources, S_{ip}, and the measured signal intensities, X_{tp}. ICA is a method of calculating the weighting matrix, W_{it}. The elements of the inverse of the weighting matrix, W^{-1}, are the mixing coefficients of the sources. For each component, the mixing coefficients characterize the time courses.

For example, a given image acquired at time t may contain a mixture of images, or "components," of the middle cerebral arteries (MCA), the capillary bed (CB), and a draining vein (V). The signal intensity in a voxel located at position r is then as follows:

$$2) \quad X(r) = \alpha_1(t) \times MCA(r) + \alpha_2(t) \times CB(r) + \alpha_3 \times V(r)$$

The coefficients $\alpha_i(t)$ are related to W by the following equation.

$$3) \qquad \alpha_i(t) = (W^{-1})_{ti}$$

ICA determines component maps, $MCA(r)$, $CB(r)$, and $V(r)$, and the time-dependent mixing matrix by minimizing the mutual information contained in the component maps. This is achieved by formulating the algorithm in terms of a neural network. The update of the weighting matrix is calculated according to the method of steepest decent (7).

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