Potential and Limitations of Echocontrast-Enhanced Ultrasonography in Acute Stroke Patients
A Pilot Study

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Background and Purpose—Ultrasonography (US) is a well-established method used to assess the brain-supplying arteries in the acute stroke setting. However, several technical and anatomic limitations are known to reduce its diagnostic accuracy and confidence level. Echocontrast agents (ECA) are known to improve the signal-to-noise ratio by enhancing the intensity of the reflecting Doppler signal. We undertook this prospective study to evaluate the diagnostic value of ECA in a consecutive, nonselected cohort of acute stroke patients with insufficient native US investigations.

Methods—During a 1-year period, 25 patients were examined within 48 hours of the onset of stroke. The need for ECA was due to an insufficient transtemporal (n=18), transforaminal (n=4), or extracranial (n=3) imaging of arteries potentially involved in the ischemic event. In 12 patients, a diagnostic suspicion could natively be raised, whereas in the other 13 patients, the strongly reduced image quality did not allow for any neurovascular conclusions. Four grams of Levovist was injected at a concentration of 200 mg/mL and 400 mg/mL for the extracranial and transcranial insonations, respectively. The effect of the echocontrast enhancement was assessed with respect to (1) signal enhancement, (2) image quality, (3) final diagnostic confidence, and (4) the need for additional neurovascular imaging methods.

Results—In all but one patient (96%), a strong signal enhancement was noted, leading to a moderate (n=11) or strong improvement (n=10) of the transcranial image quality. Thus in a total of 18 patients (72%), the echoenhancement provided a neurovascular diagnosis of sufficient confidence. This led to the confirmation of the previously suspected findings and disclosed three further occlusions and four stenoses of the intracranial arteries. In contrast, for the three extracranial examinations the image quality was not sufficiently improved because of persistent color artifacts derived from adjacent neck vessels. Besides the seven patients with inconclusive examinations, five patients with conclusive echoenhanced US studies (48% in total) demanded additive neurovascular imaging studies, based on the clinical decision of the attending physicians. This led to confirmation of all high-confident sonographic diagnoses.

Conclusions—In summary, in approximately three fourths of our acute stroke patients with insufficient native US investigations, echocontrast enhancement enabled a reliable neurovascular diagnosis, allowing the cancellation of additive neurovascular imaging procedures in half of our cohort. Our preliminary results suggest that ECA can reasonably support the early cerebrovascular workup in the acute stroke setting. (Stroke. 1998;29:949-954.)

Key Words: contrast media ■ ultrasonics ■ stroke ■ cerebral arteries

Evaluation of the brain-supplying arteries is an important diagnostic procedure in acute stroke patients. Early knowledge of the cerebral circulation can provide crucial pathophysiological as well as prognostic information to guide therapeutic decisions in the acute stroke setting. Extracranial and transcranial Doppler ultrasonography (US) is a well-established noninvasive method for the assessment of the cerebral vasculature on an emergency basis. The development of the color-coded duplex imaging technique has led to further diagnostic refinements. It allows for the reliable identification of the target vessels without potential harmful compression maneuvers, exact localization of the Doppler sample volume, and angle-corrected measurements of blood flow velocities. However, there are still well-known diagnostic limitations of this imaging technique. Extracranially, severe obesity, echodense plaques, vessel elongation, and an extremely reduced blood flow velocity constitute major restrictions. Transcranially, the insufficient transtemporal bone window due to hyperostosis of the skull is the most important obstacle. In the acute stroke setting, the examiner is further faced with a disease-related, reduced patient compliance and with the well-recognized difficulty in distinguishing high-grade artery stenosis from complete occlusions.

Recently, transpulmonary echocontrast agents (ECA) have been developed to overcome some of these limitations. Several recent studies have demonstrated the physicochemi-
Echocontrast Agents in Acute Stroke

E. M. Kaps, D. W. D. et al.

1. Introduction

Echocontrast agents (ECA) are microbubble suspensions that improve diagnostic potential and limitations of ECA application in a nonselected, consecutive series of acute stroke patients. During a 1-year period, 25 patients (12 women, 13 men), 32 to 83 years old (mean age, 61±13 years), were enrolled in this study. All patients had had acute cerebral ischemia within 48 hours before the US investigation. In 15 patients the anterior circulation and in 9 patients the posterior cerebral circulation was clinically affected. In 1 patient who had hemiparesis and hemianopia, the affected vessel territory could not clinically be defined.

At first, each patient underwent a complete native US cerebrovascular workup. This included a continuous-wave and pulsed-wave Doppler sonography (MultiDop X, X2, DWL) as well as color-coded duplex imaging (HP Sonos 2500, Hewlett-Packard) of the extracranial and intracranial brain-supplying arteries. The extracranial color-coded duplex scans were performed with a 7.5/5.5-MHz linear scanner and a 5-MHz-sector scanner, respectively. The transtemporal and transfemoral color-coded duplex imaging were performed with a 2.0/2.5-MHz, 90 degree sector transducer. All US procedures were done in accordance with general accepted guidelines.

The decision toward the need for a subsequent ECA-enhanced US study was made with the agreement of at least two experienced investigators (D.G.N., D.W.D., V.K., G.S.A.). Only if these investigators were unable to sufficiently evaluate the arteries that potentially caused the acute ischemic event in order to reach a reliable neurovascular diagnosis, the presence of an insufficient precontrast image quality was stated. The latter procedure included the use of the lowest possible pulse repetition frequency, the highest possible power and gain settings, and the selection of the most appropriate wall filter with a still acceptable amount of color and Doppler signal artifacts.

The target vessels of the repeated examination using ECA were the middle cerebral artery (MCA, n=15) and the posterior cerebral artery (PCA, n=4) for an insufficient temporal bone window, the intracranial vertebral artery (VA-ic, n=1) and the basilar artery (BA, n=3) for insular insufficiency, and the internal carotid artery (n=1) and the extracranial vertebral artery (VA-ec, n=2) for insufficient extracranial investigations. In 13 patients (52%), the strongly reduced image quality did not allow any neurovascular conclusions. In the remaining 12 patients (48%), a diagnostic suspicion could be raised after native US investigations (Table).

No patient had a history of galactosemia or galactokinase deficiency. Levovist was injected through an antecubital vein with a 19 gauge needle. A dose of 4 g Levovist was injected at a concentration of 400 mg/mL for the transtemporal approach and in a concentration of 200 mg/mL for the extracranial color-coded duplex imaging. When the extracranial signal enhancement was too low, a second study with the higher Levovist concentration of 400 mg/mL was added. Half of the suspension was injected as a bolus over 5 to 10 seconds. The remaining dosage was slowly administered in two separate portions within the next minute. To provide the complete dosage entering the circulatory system, each ECA injection was immediately followed by an injection of 5 mL of saline (0.9% concentration). Relevant parts of the native US investigation and the complete procedure under echocontrast enhancement was documented on videotape for later reevaluation. To continuously provide optimal imaging properties, the investigator was free to adjust the settings of the US machine throughout the whole procedure. Mostly, during the early so-called “blooming phase” of the echoenhancement, only subtle changes were made, and a maintenance of an optimized insonation position was provided. A few seconds later, the effect of the ECA could then efficiently used. Criteria for an occlusion of an intracranial artery were in accordance with those described by Kaps et al. Diagnosis of an intracranial stenosis was made if a focal increase of the systolic blood flow velocity >160 cm/s or a relative increase of >50% compared with the prestenotic and poststenotic vessel segments was present, together with low-frequency noise caused by vessel wall cakovations.

The effect of the echocontrast enhancement was assessed in agreement of at least two experienced US investigators (D.G.N., D.W.D., V.K., G.S.A.) after an additional off-line reevaluation of the videotape. The investigators were aware of the clinical status of the patient but blinded to other neuroimaging studies that were performed later. Three categories of the ECA effect were defined previously:

1. Doppler Signal Enhancement

The pure ECA effect of signal enhancement was quantified. We distinguished (a) very weak or no signal enhancement, (b) moderate, and (c) strong signal enhancement.

2. Image Quality

The color-coded image and the Doppler signal quality of the target arteries was assessed separately. We differentiated among (a) a low quality, if only minor or no parts of the target arteries were visible after echocontrast-enhancement, (b) moderate image quality, if a considerable part but not the total length of the target segment could sufficiently be depicted, and (c) high image quality, if the target vessel was sufficiently visualized on the echocontrast-enhanced scans.

3. Diagnostic Confidence

To clearly evaluate the diagnostic benefit of the ECA application, the final diagnostic confidence was only divided into two categories: There was either (a) a conclusive US study of sufficient diagnostic confidence or (b) an inconclusive examination with too-low diagnostic confidence. Sufficient diagnostic confidence was indicated when a reliable neurovascular diagnosis (eg, “normal,” “stenosis,” or “occlusion”) of a given artery could be deduced by means of the postcontrast scans, and no confirmative neuroimaging studies had to be recommended by the US investigators. Alternatively, the diagnostic confidence was stated as insufficient if the diagnostic reliability was absent or too low to completely eliminate the demand for additional neurovascular imaging procedures. Thus the latter group was composed of cases without any diagnostic benefit and those in which at least a diagnostic suspicion could be raised after ECA application.

All patients without a conclusive echocontrast US study underwent at least one further neurovascular imaging procedure such as intraarterial digital subtraction angiography (DSA), magnetic resonance angiography (MRA), or computed tomographic angiography (CTA). An attempt was made to perform the additional imaging studies within 24 hours after the US examination. In patients with a conclusive US investigation, a decision toward further neurovascular imaging studies was made by the attending in-hospital physicians. Beforehand, all physicians had received a detailed report of the native and the echo-enhanced US investigations. A positive decision was either made to obtain a second confirmative neuroimaging study (eg, before initiation of long-term anticoagulation in patients with a symptomatic intracranial artery stenosis) or to provide more clinical information of vascular territories not assessable with current US methods (eg, small penetrating and leptomeningeal arteries, or the venous circulation). The results of these imaging procedures were correlated to the postcontrast ultrasonicographic diagnoses.

Results

In all 25 subjects, the ECA application was well tolerated without serious or persistent side effects. Four patients
complained of transient and mild adverse experiences: Two patients had pain at the injection site lasting several seconds, one patient felt taste sensations, and one patient experienced mild headache.

### Signal Enhancement

In all but one patient (96%), the ECA application led to a strong (n=16) or moderate (n=8) signal enhancement compared with the native scans. This increase was observed for the Doppler signal as well as for the color-coded images. In one patient, in whom the MCA was transtemporally examined, the ECA injection did not lead to any transcranial blood flow visualization. In this particular patient, intracranial structures were completely absent on the previous US B-mode scan, indicating an extremely bad transtemporal bone window with a low amount of US transduction.

### Image Quality

For the transcranial approach, the image quality of the echocontrast-enhanced US investigations was closely correlated to the amount of signal enhancement. Thus in 10 of the 13 patients (77%) with strong signal enhancement, a likewise strong improvement of the vessel imaging was noted (Figure 1 and Table). Furthermore, all 11 patients with moderate transcranial signal enhancement had moderate improvement of the image quality. In contrast, the image quality of the extracranial target vessels was not (n=1) or only slightly improved (n=2) by the ECA injection despite strong signal enhancement in all cases. In these individuals, visualization of these vessels was hampered by color artifacts derived from adjacent extracranial neck vessels, for example, the jugular vein or the cervical arteries. In one patient with difficult differentiation between internal carotid artery (ICA) occlusion, the ECA injection did not lead to any transcranial blood flow visualization. In this particular patient, intracranial structures were completely absent on the previous US B-mode scan, indicating an extremely bad transtemporal bone window with a low amount of US transduction.
sion and filiform stenosis, artificial signals under echocontrast were directly projected into the distal lumen of the ICA (Figure 2). By means of the pulsed Doppler, only venous flow signals were noted in the distal postocclusive part of the ICA.

Diagnostic Confidence
In 18 of the 25 patients (72%), the application of Levovist led to a reliable neurosonographic diagnosis of high confidence. In 9 of these patients, this revealed pathologic neurovascular findings closely related to the acute ischemia: Three natively suspected intracranial artery occlusions of the MCA (n=2) and distal VA (n=1) were confirmed, and 3 further occlusions of the MCA were disclosed (Figure 1 and Table). In the remaining 3 patients, 4 intracranial artery stenoses of the MCA (n=2), PCA (n=1), and BA (n=1) were detected. Only in one out of the latter cases a stenosis had been suspected natively. In the other 9 successful cases, the echocontrast-enhanced studies revealed completely normal findings enabling to exclude an arterial source of embolism.

In the remaining 7 patients (28%), no significant diagnostic benefit by echocontrast enhancement was achieved. In 4 of these patients, a diagnostic suspicion could be raised that still needed confirmation: Two normal findings of the MCA and
BA were assumed; in the other two patients, both with acute brain stem ischemia, occlusions of the BA and VA-IC were strongly suspected. In the remaining 3 patients, no clinical contribution at all was achieved by ECA-application. In one patient this was due to an extremely poor transtemporal bone window. In the other two patients, strong color artifacts from the adjacent neck vessels were responsible for these unsatisfactory results.

**Follow-up Examinations**

In 4 patients with ECA-confirmed occlusions (n=2) or stenoses of the MCA (n=2), echocontrast-enhanced follow-up examinations were performed. In the former two patients, a recanalization of the previously occluded MCA was demonstrated (Figure 1). In the other patients, unchanged focal increase of blood flow velocity was evident. This finding strongly supported the diagnosis of an atheromatous MCA stenosis rather than vasoparalytic hyperperfusion after spontaneous recanalization, which later was confirmed by MRA (Table).

**Additive Neurovascular Imaging**

In a total of 12 patients (48%), at least one additional neurovascular imaging procedure was performed. This group comprised the 7 patients with inconclusive examinations and 5 patients with conclusive US studies in whom the attending physicians decided to perform a further neurovascular investigation (Table). Whereas the 3 DSA and one MRA were done 2 to 3 days after the US examination, the remaining procedures were performed within 24 hours after the neurosonographic investigation. All neurosonographic diagnoses were unanimously confirmed. Thus no false-negative or false-positive diagnoses in this subgroup were made by echoenhancement. The four suspected diagnoses of the inconclusive examination group were also subsequently confirmed. In the patient without any signal enhancement (patient 19), an MCA stenosis was found by MRA. In the patient with the sonographically suspected pseudoocclusion of the ICA (patient 3), absence of flow was evident on MRA and occlusion was demonstrated by DSA 3 days later. Whether this occlusion already existed at the first US examination or was due to a progression of a former subtotal stenosis could not be clarified retrospectively. In the remaining 13 patients (52%), the high-quality echoenhanced US images allowed the cancellation of additive neurovascular imaging procedures.

**Discussion**

Echocontrast-enhanced US imaging is known to safely enhance the signal intensity and improve the image quality in patients with inadequate native insonation conditions.\(^{2,7,10–13}\) Its diagnostic potential has clearly been shown by increasing the number and the length of the cerebral arteries visible on color-coded imaging techniques after ECA application.\(^{14,15,19}\) To date, however, the true diagnostic value and therefore the cost-effectiveness of ECA in neurosonology has not been clarified. To substantiate this criterion, it has to be shown that (1) the use of echocontrast enhancement leads to a reasonable number of diagnostically successful US studies and that (2) the clinical demand for additional confirmative neurovascular imaging procedures, such as DSA and MRA, is considerably reduced after its application.

Since Levovist has been approved for routine clinical neurovascular diagnostics, we undertook this prospective study to address this issue in a consecutive nonselected patient series. We restricted our analysis to one of the most important target groups of neurovascular imaging, that is, acute stroke victims. Patients were enrolled irrespective of the location of the target vessel segment, for example, extracranially or intracranially. Our end point variables were improvement of image quality and gain of diagnostic confidence rather than duration or amount of signal enhancement. We further noted the frequency of cases in which further neurovascular imaging procedures were successfully canceled. To assess the clinical contribution of echocontrast enhancement, especially for the acute stroke setting, the indication for the echo enhancement was restricted to those cases in which potentially stroke-relevant arteries were inadequately assessable on the native scans.

During a 1-year-period, 25 patients fulfilled these criteria. This represents approximately 15% of acute stroke victims entering our hospital within this time window. The echocontrast enhancement led to improvement of image quality in 84% of patients, enabling a neurosonographic diagnosis of sufficient diagnostic confidence in nearly three quarters of all cases. By this means, in 9 patients, arterial sources of cerebral ischemia were identified and in a further 9 patients this could be excluded. However, in 5 of these cases, the attending physicians decided to perform an additive neurovascular imaging procedure despite knowledge of a high-quality US investigation. Notably, in all of these patients, arterial obstructions were sonographically found. This reflects the strong requirements of diagnostic reliability and accuracy, especially for neurovascular investigations on acute stroke victims. This is due to the inherent prognostic and therapeutic consequences of some of these diagnoses (e.g., long-term anticoagulation in symptomatic basilar artery stenosis). It seems that a diagnostic redundancy despite high-quality US investigations cannot completely be prevented and is, in our opinion, justified in selected cases.

In all of these patients, confirmation of the high-confident, as well as of the suspected, US diagnoses was achieved. Thus no false-positive or false-negative diagnoses were made on the basis of the echocontrast-enhanced technique. In the other 13 acute stroke patients, representing roughly half of our cohort, the sufficient echocontrast images allowed cancellation of additional neurovascular imaging. Due to the limited number of patients in our series, the data must be interpreted with caution. However, it seems that for a subgroup of acute stroke victims, application of ECA is capable of replacing expensive, and potentially more invasive, neurovascular imaging methods.

Our results suggest a difference in the diagnostic value of ECA with respect to the insonation approach. Transtemporally, in 89% of all cases the target vessel—mostly the MCA—was sufficiently visualized. Thus for this approach, the use of ECA can be advocated in the acute stroke setting. The latter finding is in accordance with results on asymptomatic patients. Postert et al\(^{14}\) found a successful visualization of
the MCA in all 21 of their patients with insufficient trans-temporal bone window.

By contrast, 2 out of the 4 transforaminal, and all 3 extracranial target arteries were not depicted with high enough diagnostic confidence. For the transforaminal approach, this was due to the limited signal enhancement in the distal part of the basilar artery, which may constitute a principle limitation of this technique. In contrast, for the extracranial approach, the ECA application led unanimously to a strong increase in the signal intensity. However, the unsatisfactory results in these cases were due to persisting color artifacts derived from adjacent neck vessels. Specifically, in one patient with the presumed pseudoocclusion of the ICA, the ECA application did not lead to any image improvement. This occurred despite the use of a lower concentration, and gradual injection, of Levovist (Figure 2).

Because our experience with the extracranial and the transforaminal echoenhanced insonation is very limited and therefore preliminary, no definite conclusions can be drawn from our findings. However, it indicates the demand for further clinical studies to define more accurately the role of ECA for these sonographic approaches and delineate reasonable indications and diagnostic limitations more properly.

One limitation of our study is that we did not include the power-based duplex mode.22 The latter imaging technique has been suggested to be more sensitive for the visualization of flowing blood compared with the current mean frequency-based method.23,24 Thus it could be hypothesized that some of our unsatisfactory precontrast and postcontrast scans could have further been improved by this new procedure. Whether this would have led to completely successful investigations, for the transtemporal as well as for the transforaminal and extracranial approaches is unclear. Further clinical studies are required to address this issue.

In summary, in approximately three quarters of our acute stroke patients with insufficient native US investigations, echo contrast enhancement enabled a reliable neurovascular diagnosis, allowing the cancellation of further neurovascular imaging procedures in half of our cohort. Our preliminary results suggest that ECA can reasonably support the early cerebrovascular workup in the acute stroke setting.

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