Ipsilateral Motor-Related Hyperactivity in Patients With Cerebral Occlusive Vascular Disease

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Background and Purpose—Cerebral occlusive vascular disease is an established risk factor for ischemic stroke; however, little is known about its effects on brain function in patients without stroke. To detect possible functional alterations, we used magnetoencephalography and evaluated cerebral cortical activity during hand motor tasks in a group of such patients.

Method—Event-related desynchronization (ERD) during hand-grasping and self-paced finger-tapping tasks was examined in 38 right-hand-dominant patients with occlusive disease of the internal carotid or middle cerebral artery caused by diverse pathologies (atherosclerosis, 28; others, 10) and in 8 control subjects. All patients had no apparent motor impairments. The spatial distribution and the intensity (t value) of ERD in the beta band were analyzed with synthetic aperture magnetometry. According to the laterality index calculated from the ratios of peak t values on ipsilateral vs contralateral (with respect to the hand movement) hemispheres, the distribution of ERD was classified into 3 patterns: contralateral, bilateral, and ipsilateral.

Results—Abnormal ipsilateral dominant distribution of beta ERD was observed significantly more often during contralesional hand grasping in patients with atherosclerotic vascular lesion. It was accompanied by significantly higher t values on the ipsilateral hemisphere, without a decrease in those on the contralateral side. The age, the rating scores of periventricular hyperintensity, and ventricular size were all significantly higher in patients who showed the ipsilateral-dominant pattern.

Conclusion—Abnormal ipsilateral hyperactivity may indicate the presence of subclinical functional alterations related to atherosclerotic occlusive vascular disease. (Stroke. 2008;39:2769-2775.)

Key Words: carotid stenosis ■ functional imaging ■ ischemia ■ neurophysiology

Severe stenosis, or occlusion, of the internal carotid artery (ICA) or middle cerebral artery (MCA) is an established risk factor for stroke and a target for neurosurgical procedures aimed at its prevention. Although cerebral blood flow (CBF), metabolism, and morphological changes in this pathology have been evaluated in some detail using modern neuroimaging techniques, little is known if brain function itself is altered under such ischemic conditions, particularly when infarction is absent. It is a common observation that patients with cerebral occlusive vascular disease show no apparent neurological symptoms, even in a state of severe hypoperfusion called “misery perfusion.” Nevertheless, some decline in cognition has been detected in asymptomatic as well as symptomatic patients with carotid artery stenosis, which indicates that brain function can be altered even without any history of stroke. Because cognitive function reflects activity of the whole brain, it is not easy to distinguish the contributions from left and right hemispheres in cognitive tests. Hence, development of a more objective and quantitative measure could greatly help in early diagnosis and treatment of functional alteration accompanying ischemic cerebrovascular disease. The objective of this study was to evaluate subclinical alterations in motor-related brain function in patients with cerebral occlusive vascular disease who showed no apparent motor impairments.

Attenuation of the electroencephalographic power in the central brain region during hand movement or sensory stimulation was quantitatively defined as event-related desynchronization (ERD) and thought to reflect a correlation between an activated cortical area and an increased level of neuronal excitability. Because of its consistent relation to the movement, ERD in the beta band (βERD) has been considered a physiological phenomenon caused by activation of the sensorimotor cortex. Moreover, it has been shown that βERD represents execution as well as programming or control of the movement. In this study, we have chosen βERD as a parameter of brain
function and analyzed it using magnetoencephalography (MEG) with synthetic aperture magnetometry (SAM). In particular, we were interested in the behavior of βERD during movement of the hand contralateral to the occlusive vascular lesion (contralateral hand), because such movements could activate the hemisphere of the lesion. The superior spatial resolution of MEG allows identification of the anatomic location of cortical activity with enhanced accuracy. The spatial filtering technique using an adaptive beam-forming method (SAM) is a unique modality for estimating the tomographic distribution of the power or its change within a selected band frequency from MEG data. Using SAM, the regions with significant oscillatory change are displayed on individual MR images; recently, that imaging has been clinically applied as functional neuroimaging.

Methods

Patients

From April 2005 to June 2007, 62 adult patients with ICA/MCA stenosis, or occlusion, without ischemic stroke during the past 3 months, were admitted to the Department of Neurosurgery of Osaka University Hospital for a surgical procedure or clinical evaluation. Occlusive disease was defined as an obstruction >60% according to the criteria of the North American symptomatic carotid endarterectomy trial for cervical ICA and narrowing of >50% on angiography for intracranial ICA or MCA. For the current MEG study, we excluded the following categories of patients: those who showed motor symptoms or who had infarction around the motor-related regions, and those in whom large magnetic artifacts were detected in MEG recordings. After selection, 38 patients were enrolled in this study prospectively. All of them were right-hand-dominant, as determined with the Edinburgh handedness inventory, and presented with no apparent motor symptoms in a routine neurological examination. In 11 patients, MRI revealed previous infarctions located in the frontal lobe (anterior to premotor cortex), occipital lobe, and in the basal ganglia, but no infarction was detected around the sensorimotor or premotor cortices, internal capsule, or corona radiata. Twenty-eight patients had atherosclerotic lesions (cervical ICA stenosis in 16, cervical ICA occlusion in 4, intracranial ICA stenosis in 2, and MCA occlusion/stenosis in 6), and the other 10 had lesions not related to atherosclerosis (intracranial ICA occlusion/stenosis attributable to moyamoya disease in 4, intracranial ICA stenosis attributable to encasement by meningioma in 1, cervical ICA occlusion attributable to Takayasu disease [occlusion from common carotid artery] in 1, occluded ICA for the treatment of tumor, giant aneurysm, and traumatic arterial dissection, respectively, in 3, and an incidental finding in 1).

Control Subjects

Eight right-hand-dominant control subjects (5 men and 3 woman), with a median age of 66 (range 55 to 79), were used as controls.

MEG Study

Motor-related magnetic field was recorded using a helmet-shaped 64-channel SQUID system (NeuroSQUID Model 100; CTF Systems Inc) in a magnetically shielded room. The patients/subjects were seated in a comfortable chair with their eyes open and were asked to stare blankly at a point in front of the chair. The MEG data were acquired with a 625-Hz sampling rate and filtered with a 200-Hz on-line low-pass filter.

After a brief explanation, the patients/subjects were asked to perform 2 kinds of hand motor tests: a hand-grasping task and a self-paced finger-tapping task. Because the latter is relatively more complex and requires greater concentration, the tasks were performed in the following order: (1) right finger tapping; (2) left finger tapping; (3) right hand grasping; and (4) left hand grasping. During performance of these tasks, subjects/subjects were monitored continuously on a video camera and checked for the absence of an apparent mirror movement in the other (resting) hand. The ongoing waveform (MEG) results were displayed on a monitor and stored in the workstation memory. Each examination session was begun and terminated by measuring the head position of the patient. Before the acquisition of the actual results, 1 or 2 preliminary trials were performed to ensure that the patient performed the task correctly.

Task 1, the hand-grasping task (not a tonic sustained grasp), involved grasping with 1 hand weakly at a constant rate while the other hand was resting. The working hand was supinated while the resting hand was pronated and placed on an arm rest. The data for each trial were collected relative to the trigger (sound cue or time “0”) for 20 seconds and consisted of 2 periods: the “control” state in the time window −10 to 0 seconds, in which the patient remained still, and the “active” state in the time window 0 to +10 seconds, which involved grasp and release movements (Figure 1A). Six such trials, with 5-second intervals between them, were collected as an “examination,” first for the right hand. Then, the positions of the hands were changed and an identical examination was performed for the left hand.

Task 2 was a self-paced index-finger-tapping test using a nonmagnetic fiber optic response keypad (LUMItouch; Photon Control Inc), which was placed on either side of the arm rest. The patients were instructed to press the keypad with their index finger, with intervals of ~5 seconds (but without counting the time) between the taps. The data from 3 seconds before to 1 second after the key input were collected as a trial, and 60 trials were collected for each examination (Figure 1B).

Individual anatomic MR images were acquired using a 1.5-T imaging systems (Magnetom Impact; Siemens). For all measurements, fiducial skin markers were placed on the patient’s nasion and at bilateral preauricular points to establish common coordinate systems for MR images and MEG. This MEG protocol was approved by the ethics committee of the Osaka University Hospital. Informed consent for MEG recording was obtained from all patients and control subjects.

SAM Analysis of Motor-Related Field

Details of SAM algorithm have been described previously. In the present study, a volumetric image of root mean square source activity in the beta band with 5-mm voxel resolution was generated for each “control” and “active” time window: −9 to −1 and 1 to 9 seconds for task 1, and −3.0 to −2.7 and −0.3 to 0 seconds for task 2, relative to the trigger onset, respectively (Figure 1). The statistical imaging was computed subsequently by comparing the powers of the beta band (13 to 30 Hz) in both time windows on a single voxel basis over all trials using the Student t test with Jackknife statistics. The t value of each voxel was displayed in a color scale on individual MR images using the MRIviewer (CTF Systems Inc). The decrease of

![](image-url)
power that indicates ERD was displayed in blue, whereas the power increase that indicates event-related synchronization (ERS) was shown in red. SAM statistical images were created for grasping and tapping tests with each hand giving 4 (2 for each task) images for each patient. Before SAM analysis, all trials were inspected visually. Data with sensors located in the most anterior or lower part of the helmet were excluded from analysis if they were accompanied by large artifacts caused by the presence of metal in the oral cavity (dental problems) or movements of eyeballs.

Patterns of Distribution of Beta Band Desynchronization
The laterality index (LI) was calculated using the peak t values around the sensorimotor area on contralateral and ipsilateral hemispheres with respect to the examined hand as follows: LI = (Tc - Ti)/(Tc + Ti), where Tc is the highest peak t value on the contralateral hemisphere and Ti is that on the ipsilateral hemisphere. Based on the behavior of LI, we classified the spatial distribution of βERD into 3 types: contralateral-dominant (LI > 0), bilaterally spread (−0.1 ≤ LI ≤ 0), and ipsilateral-dominant (LI < −0.1).

Evaluation of Sulcal Atrophy, Ventricular Size, and Periventricular White Matter Hyperintensity
The morphological changes in MR images of sulcal atrophy, ventricular size, and periventricular hyperintensity (PVH) of the hemisphere with the vascular lesion were assessed using a semiquantitative 10-point visual scale introduced by Manolio et al. Three scorers, without any clinical information for patients, evaluated these 3 parameters. Sulcal atrophy and ventricular size were scored on T1-weighted images, and PVH was evaluated on FLAIR images (and not the proton images as in the original method of Manolio et al). Before analyzing the actual results, the 3 scorers performed a trial rating using MR images from a nonstudy patient and unified the scoring procedure. The variance in the visual scales among the 3 scorers was within 1 point for all parameters; hence, median values were calculated.

CBF Study With SPECT
Depending on their clinical conditions, the patients underwent 123I N-isopropyl-p-iodoamphetamine single-photon emission computed tomography (123I-IMP SPECT) with or without an acetazolamide challenge test. The details of SPECT procedure were reported previously.16 The results of 16 examinations (2 × number of patients) are presented.

Table 1. Motor Magnetic Field Properties and βERD Distribution Patterns in Control Subjects

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Tc, range</th>
<th>Ti, range</th>
<th>LI, range</th>
<th>Contra-dominant</th>
<th>Bilat-spread</th>
<th>Ipsil-dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>13.6, 6.8–24.9</td>
<td>9.2, 6.0–14.2</td>
<td>7.5, 3.8–14.7</td>
<td>7.3, 3.2–11.0</td>
<td>0.22, *</td>
<td>0.05–0.38</td>
</tr>
<tr>
<td>Hand Grasping</td>
<td>Finger Tapping</td>
<td></td>
<td></td>
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</tbody>
</table>

*P = 0.07 with Mann-Whitney U test.

![Figure 2](http://stroke.ahajournals.org/)

Figure 2. Voxels exhibiting statistically significant decrease in the power of β band (t value) are displayed in a blue scale. The images from a control subject (66-year-old woman) are shown as (A) (right hand grasping; Tc, 17.6; Ti, 11.3; LI, 0.22) and (B) (right finger-tapping; Tc, 7.3; Ti, 6.3; LI, 0.07). Both are classified as contralateral-dominant pattern. C, The angiogram showing left carotid artery stenosis (80%) in patient 2 (65-year-old man). D, During right hand grasping in the same patient, the distribution pattern was classified as "ipsilateral-dominant" (Tc, 16.8; Ti, 24.8; LI, −0.18). E, In the same patient, a contralateral-dominant pattern (Tc, 7.5; Ti, 7.1; LI, 0.04) was seen during a right self-paced finger-tapping task.

Statistical Analysis
The results for age, Tc, Ti, and LI were analyzed with nonparametric Mann-Whitney U test. To compare the 2 groups of patients with respect to the presence or absence of ipsilateral dominant pattern, we used χ² with Fisher exact probability test. P < 0.05 was considered as significant.

Results
Motor-Related Magnetic Fields in Control Subjects
In all control subjects, statistically determined regions of βERD with the highest t value were detected either on contralateral or ipsilateral sensorimotor, or premotor, cortex with respect to the examined hand (Figure 2A, B). The distribution patterns of βERD, peak t values (Tc and Ti), and LI during the 2 tasks are presented in Table 1. There was no evidence for the ipsilateral dominant distribution pattern of βERD, with the definition of LI < −0.1, in any individual in either of the tasks. Comparing the 2 tasks, the LI in hand grasping was larger than that in self-paced tapping, with an almost significant difference (P = 0.07, Mann-Whitney U test). With respect to the side (right or left) of the examined hand, there were no significant differences in Ti, Tc, and LI.
in either tasks, although there was a slight tendency (P=0.11, Mann–Whitney U test) for the higher median Ti during left hand-grasping (9.7; range 6.7 to 14.3) as compared to right hand-grasping (7.4; range 3.8 to 11.3).

Motor-Related Magnetic Fields in Patients With Occlusive Vascular Disease

In the group with atherosclerotic lesions (AS group), there were 21 men and 7 women, with an overall median age of 69 (range, 55 to 78) years; in that with nonatherosclerotic lesions (NAS group), median age was 48.5 (range, 21 to 73) and there were 4 men and 6 women. The age of the AS group was significantly higher than that of NAS (P<0.05, Mann–Whitney U test). According to the criteria for an “occlusive disease,” 9 patients in the AS group and 4 (all with moyamoya disease) in the NAS group had bilateral lesions. The symptomatic side and, if asymptomatic, the side of the more severe stenosis or CBF reduction are listed as “the site” in supplemental Table I (available online at http://stroke.ahajournals.org). The location of a previous infarction and the presenting ischemic symptom are also given in the same Table.

All 76 hand-grasping examinations in 38 patients (ie, 1 per hand) were performed successfully. In finger-tapping, trials that contained occasional large noise or inadequate signals (eg, double taps in a trial) were eliminated. The number of excluded trials was ∼5%, with a maximum of 8 eliminated tapping trials in a single patient. However, 9 examinations of finger tapping were not available because of unforeseen problems with the measuring device in 2, injury of the relevant finger in 1, and inadequate performance attributable to sleepiness, or too-fast pacing in 6 (supplemental Table II) attributable to an unavailable cause. Therefore, 67 tapping and 76 hand-grasping examinations were analyzed.

As in control subjects, regions with the highest t values were detected around the contralateral or ipsilateral sensorimotor, or premotor, cortex (Figure 2D, E). The distribution pattern of βERD and values of Ti, Tc, and LI for 38 patients are shown in Table 2. It can be seen that 20 of 76 examinations during hand grasping and 5 of 67 examinations during tapping exhibited an ipsilateral-dominant βERD pattern. Results from either tasks were then analyzed separately for each hand (supplemental Table II). In 38 grasping examinations with the contralesional hand (or the more severe side for bilateral lesions), an ipsilateral-dominant pattern was observed in 16 of 28 examinations in the AS group, and in 1 of 10 in the NAS group. In grasping with the “other” hand, 25 of 38 examinations were in patients who showed no detectable lesions on the contralateral side, whereas the remaining 13 were with the contralesional hand in patients with bilateral lesions. In this latter set, the ipsilateral pattern was seen in 3 examinations, all of which were in the AS group. Summing up these results, during grasping task, the ipsilateral-dominant βERD pattern was seen in 20 examinations, 19 of which were in patients from the AS group and 1 was in a patient from the NAS group.

In the tapping task, the ipsilateral dominant βERD pattern was observed only in 5 examinations; all were from patients of the AS group (3 were with the “contralesional” and 2 were with the “other” hand).

Table 3 recalcitrates the results described by taking into consideration the fact that only 25 of 38 patients had no detectable lesion on the side contralateral to the “other” hand, whereas 13 had bilateral lesions. This increased the number of “contralesional hands” to 51. The new calculation shows that in the case of grasping, 19 of 51 examinations with the “contralesional” hand (18 in the AS group and 1 in the NAS group) showed the ipsilateral dominant βERD pattern, whereas the figure was only 1 (a patient in the AS group) of 25 for the other hand. When calculated for each group of patients, 19 of 56 examinations in the AS group (18 with the contralesional and 1 with the “other” hand) and 1 (with the contralesional hand) of 20 examinations in the NAS group exhibited this same pattern. In relation to the self-paced tapping task, the occurrence of an ipsilateral-dominant βERD pattern bore no significant relation to either the hand (contralesional or other) or etiology (AS or NAS group). A representative case that exhibited an ipsilateral-dominant pattern in hand-grasping but not in tapping with contralesional hand is shown (Figure 2).

Factors Related to an Ipsilateral-Dominant βERD Pattern in the Grasping Task With the Hand Contralateral to the Atherosclerotic Occlusive Vascular Lesions

Because the ipsilateral-dominant βERD pattern was observed significantly more frequently in grasping with the contralesional hand than in tapping, the occurrence of this pattern was related to some characteristics of the patients. Table 3 shows a comparison of the number of examinations with an ipsilateral dominant βERD pattern with or without a detectable lesion on the side contralateral to the “other” hand (18 in the AS group and 1 in the NAS group) showed the ipsilateral dominant βERD pattern, whereas the figure was only 1 (a patient in the AS group) of 25 for the other hand. When calculated for each group of patients, 19 of 56 examinations in the AS group (18 with the contralesional and 1 with the “other” hand) and 1 (with the contralesional hand) of 20 examinations in the NAS group exhibited this same pattern. In relation to the self-paced tapping task, the occurrence of an ipsilateral-dominant βERD pattern bore no significant relation to either the hand (contralesional or other) or etiology (AS or NAS group). A representative case that exhibited an ipsilateral-dominant pattern in hand-grasping but not in tapping with contralesional hand is shown (Figure 2).

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sional hand in the AS group, we investigated the effect of several other “factors” on the frequency of this pattern (Table 4) in this same group. In 28 patients, 9 had bilateral lesions, resulting in 37 examinations of contralesional hand-grasping: 18 of these showed the ipsilateral βERD pattern, whereas 19 did not. Statistical analysis shows that the ipsilateral-dominant βERD pattern was seen more often in older patients and was accompanied by a higher Ti, but without a significantly different Tc. Scores for PVH and ventricular size on the side of the vascular lesion had higher values in cases that exhibited the dominant ipsilateral pattern. No significant relation was detected with respect to the incidence of “class C in CBF study,” “history of ischemic event,” “previous infarction” on the side of the vascular lesion, and the use of “left (nondominant) hand.” However, “MCA lesion” as compared with “ICA lesion” showed a significant correlation with the appearance of the ipsilateral-dominant βERD pattern. Individual data of morphological changes in MR images, CBF state, and other “factors” on the vascular lesion side can be found in supplemental Table I.

**Discussion**

A significant asymmetry in motor-related cortical activity was detected with MEG during grasping with the hand contralateral to the site of an atherosclerotic occlusive vascular disease. The ipsilateral-dominant distribution of βERD was present significantly more frequently in older patients and in those with more severe morphological changes. We feel that this phenomenon, which occurs without any identifiable motor symptoms, is abnormal and reflects subclinical alterations in brain function that accompany atherosclerotic occlusive vascular disease.

Enhanced ipsilateral motor activity has been seen previously during paralytic hand movement in patients with destructive lesions, such as occurring with brain tumor or after stroke, and was initially considered compensatory. It has been proposed recently that this activity has a hyperactive component attributable, in some cases, to interhemispheric disinhibition. Our results that show characteristic ipsilateral distribution of βERD during grasping with the contralesional hand, a significantly increased activity in the ipsilateral hemisphere without a decrease on the side of the vascular lesion, and a “normal” behavior in the tapping task indicate that hyperactivity on the ipsilateral hemisphere seen in patients with vascular lesions but without motor impairment is not compensatory. These same findings would argue against the possibility that the abnormal ipsilateral motor activity represents an involvement of symmetrical brain areas during the motor task and suggest that the phenomenon originates from other mechanisms.

Similarly to our results, Krakauer et al using functional MRI observed abnormally increased ipsilateral activity during a contralesional hand movement in 6 patients with a unilateral ICA occlusion. The motor tasks they used had observation time windows of 20 seconds for the “active” and “control” states, comparable to those in the hand grasping of our study. However, when we analyzed with MEG during the self-paced tapping task (much shorter, 300-ms periods), we could not detect abnormal ipsilateral activity. This suggests that the different observation time windows record different brain activities.

During a voluntary hand motion, βERD is observed before and during movement execution and is followed by postmovement ERS. These frequency changes distribute on the sensorimotor area bilaterally but primarily on the hemisphere contralateral to the examined hand. The postmovement ERS is thought to reflect an inactive, “idling” state and shows an asymmetrical feature considered to be caused by a difference in handedness-related interhemispheric inhibition, “which is more prominent from the dominant than from the
nondominant hemisphere.” In our study, the “active” time window for hand-grasping was wide enough to encompass the whole of pre-, during-, and postmovement periods; however, that for the tapping task included premovement and motor execution, but less of the postmovement activity. If the postmovement ERS on the ipsilateral hemisphere, which is affected by the inhibition from the contralateral side, is decreased, then it would result in an increase of t value of ERD. Therefore, we propose that when 1 hemisphere activates, the impairment of its inhibitory function induces oscillatory change at the opposite side. For example, when during right hand-grasping in a patient with left ICA stenosis an impairment of the inhibitory function on the left hemisphere fails to deactivate the right hemisphere, this leads to a decrease of ERS on the right hemisphere, and we detect it as the ipsilateral dominant distribution of βERD. A statistically significant relation between the latter and the PVH in the AS group (Table 4) may indicate the contribution of the white matter damage to this phenomenon.

In the present work, we did not measure directly the postmovement ERS because of the difficulty in defining adequately the variation in time periods of post-tap finger movement and the influence of sensory input after the tap. Further studies using different tasks or other methods, such as transcranial magnetic stimulation, to measure cortical inhibitory function are required to confirm or refute our speculation. It should also be mentioned that measurements of motor activity that include pre- and postmovement time periods yield results for “activated areas” that might be strongly influenced by the inhibitory function of the primary activated hemisphere. It would be a great step forward if MEG could be used to evaluate brain activity of duration short enough to be less influenced by inhibitory functions.

Although the abnormal ipsilateral-dominant pattern was seen significantly more often in older patients and in those with higher scores for PVH and ventricular size, it is interesting that the clinically important indications for surgical intervention or stroke prevention, such as “impairment of vasoreactivity,” “presence of symptoms,” and “presence of an asymptomatic infarction,” showed no significant relation. It can be suggested that in addition to CBF impairment caused by occlusive lesions in large vessels, some other factors related to aging and systemic atherosclerosis, which accompany morphological changes such as PVH, may induce subclinical alteration in motor-related cortical activity. A significantly higher incidence of abnormal ipsilateral pattern in patients with MCA lesions might indicate that it reflects functional alterations in particular in this vessel’s territory.

In addition to stroke, atherosclerotic occlusive vascular diseases include slow but progressive pathological components that may induce atrophy or white matter change and result in functional impairments, such as vascular dementia. Detection with MEG of ipsilateral hyperactivity, an objective and quantitative measurement independent of CBF or metabolism, could greatly help in early diagnosis and treatment of functional alteration accompanying ischemic cerebrovascular disease.

**Summary**

We detected abnormal ipsilateral hyperactivity during a contralesional hand-grasping task in patients with atherosclerotic occlusive vascular disease. This phenomenon may represent an impairment of cortical inhibitory function caused by a vascular lesion. Evaluation with MEG could contribute to diagnosis and prevention of functional deterioration that accompany this class of diseases.

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**Disclosures**

None.

**References**


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