Influence of Gravity Compensation on Muscle Activation Patterns During Different Temporal Phases of Arm Movements of Stroke Patients

G. B. Prange, MSc, M. J. A. Jannink, PhD, A. H. A. Stienen, MSc, H. van der Kooij, PhD, M. J. Ilzerman, PhD, H. J. Hermens, PhD

Background. Arm support to help compensate for the effects of gravity may improve functional use of the shoulder and elbow during therapy after stroke, but gravity compensation may alter motor control. Objective. To obtain quantitative information on how gravity compensation influences muscle activation patterns during functional, 3-dimensional reaching movements. Methods. Eight patients with mild hemiparesis performed 2 sets of repeated reach and retrieval movements, with and without unloading the arm, using a device that acted at the elbow and forearm to compensate for gravity. Electromyographic (EMG) patterns of 6 upper extremity muscles were compared during elbow and shoulder joint excursions with and without gravity compensation. Results. Movement performance was similar with and without gravity compensation. Smooth rectified EMG (SRE) values were decreased from 25% to 50% during movements with gravity compensation in 5 out of 6 muscles. The variation of SRE values across movement phases did not differ across conditions. Conclusions. Gravity compensation did not affect general patterns of muscle activation in this sample of stroke patients, probably since they had adequate function to complete the task without arm support. Gravity compensation did facilitate active arm movement excursions without impairing motor control. Gravity compensation may be a valuable modality in conventional or robot-aided therapy to increase the intensity of training for mildly impaired patients.

Keywords: Stroke rehabilitation; Upper extremity; Muscle activity; Motor control; Arm support

A majority of patients have impaired arm and hand function after a stroke, causing difficulties in activities of daily living. To achieve as much functional independence as possible, restoration of arm function is one of the main objectives of stroke rehabilitation. For optimal results, functional exercises with active participation of the patient are incorporated in an intensive and motivating training program.

Improvement of functional use of the arm can be related to restoration of neural function within affected tissue and incorporation of pathways that may not usually contribute to reaching, as well as to behavioral adaptations and compensatory strategies. Specific interventions aimed at each of these potential mechanisms, however, have not been determined so that patients can obtain the best gains in arm function.

Recent technological developments have led to the use of robotic devices for the application of active and intensive training for the affected arm. In a recent systematic review, we concluded that neurophysiologic aspects of arm function of stroke patients improve after robot-aided therapy, but the effect on functional use of the arm in activities of daily living is less distinct. Such limited generalization of training to increased functional use of the arm is not only noticed after robot-aided therapy, but also in many conventional interventions in stroke rehabilitation. More insight into the working mechanisms of individual training interventions is needed to allow better planning of the timing and content of rehabilitation.

Concerning the content of robot-aided therapy, our systematic review indicated that different training modalities, such as passive movement, active movement with robotic assistance, and active movement with robotic resistance are applied simultaneously in a robot-aided training session. Besides these training modalities, arm support is incorporated in the design of many robotic devices to compensate for the influence of gravity on the arm. However, the individual contribution of each of those modalities to the improvement of arm function after robot-aided therapy is largely unknown.

Regarding the contribution of arm support to restoration of arm function, initial results of an exercise therapy program applying gravity compensation by sling suspension showed an improvement of arm function of stroke patients after 9 weeks of training. This suggests that the application of gravity compensation alone may be a valuable tool to stimulate functional improvement in poststroke rehabilitation.

Research into the instantaneous influence of gravity compensation on arm movements after stroke has been mainly focused on kinematics of arm movements. Beer and colleagues showed that the active range of elbow extension increases during 2-dimensional planar reaching movements at shoulder height with...
arm support when compared to similar unsupported movements. Results along the same lines were found during reaching movements in more functional circumstances. Maximal reaching distance during a 3-dimensional movement, starting with the hand at waist height and reaching to a target at shoulder height, as if reaching for a cup in a drawer, is slightly larger when gravity compensation is applied to the arm of stroke patients.12

Insight into underlying working mechanisms of the influence of gravity compensation on arm function can be obtained by studying muscle activation patterns. In previous research, we found that in healthy persons the level of muscle activity in muscles counteracting gravity during reaching movements decreased with gravity compensation.13 At the same time, gravity compensation did not affect the general pattern of muscle activity during functional, 3-dimensional reaching movements at table height,13 even though the gravitational force is taken into account in internal models when planning and executing movements.14

However, after stroke, limitations in motor planning, integration of sensorimotor information, generation, and coordination of muscle activity, both within and between muscles, may reduce functional use of the arm.15 Therefore, it is unclear how the application of gravity compensation affects motor control of arm movements in stroke patients. In the light of the increased range of motion with arm support,11,12 we expect that gravity compensation may influence motor control of stroke patients positively by inducing changes in muscle activation patterns. These changes may suggest a potential for neurological recovery in the case of more normal muscle activation patterns, or may indicate that behavioral adaptation takes place in the case of new patterns of muscle activation. Insight into the nature and direction of changes in motor control, due to gravity compensation, is essential to determine optimal application of this intervention in stroke rehabilitation in terms of content and timing.

Therefore, the objective of the present explorative study was to obtain quantitative information on how gravity compensation influences muscle activation patterns of stroke patients during functional, 3-dimensional reaching movements.

Method

Participants

After selection by a rehabilitation specialist, 10 stroke patients were recruited from a local rehabilitation center. Inclusion criteria for participation were that stroke patients had to be: (1) at least 4 weeks poststroke; (2) able to lift their arm (partly) against gravity; (3) free from additional orthopedic, neurological, or rheumatologic disease of the upper extremities; (4) not suffering from shoulder pain either in rest or during movement; and (5) able to understand and follow instructions. Patients provided written informed consent before being admitted to the study. The medical ethics committee of the institution approved the study.

Procedure

The current arm function of each participant was assessed at the start of the experiment using the upper extremity portion of the Fugl-Meyer assessment (maximal score of 66).16 Participants performed 2 movement series with the affected arm, once with and once without gravity compensation. The sequence of movement, with or without gravity compensation, was randomized across participants to reduce the potential effect of learning or adaptation. Participants had a 15-minute practice period prior to the actual measurements to get accustomed to movements with gravity compensation.

Participants sat in front of a height adjustable table and were secured to the chair with straps to limit compensatory trunk movements. The wrist was fixated by a splint in as neutral a position as possible, midway between flexion/extension and radial/ulnar abduction. Two targets with a diameter of 10 cm were located on the table surface. The first target was located at a position such that when the hand touched the target, the upper arm was parallel to the trunk and the elbow was flexed at approximately 90°. The second target was 35 cm from the first target, allowing participants to reach forward in a sagittal plane using both the shoulder and the elbow (Figure 1). Participants started with their hand on the first target and performed repeated multijoint reach and retrieval movements for 30 seconds, alternating between the 2 targets at a self-selected speed, to match movement paths and movement speeds commonly used in exercises during poststroke rehabilitation.

Gravity Compensation

The influence of gravity on the upper extremity was counteracted by a custom-made mechanical, passive device (Freebal; Figure 1). This device provided a constant amount of gravity compensation throughout the entire workspace of approximately 1 m³ via 2 independent ideal springs, enabling fully compensated 3-dimensional arm movements. Compensating forces from the springs, located in the base of the device, are transferred to the arm of the participant by 2 cables running overhead, which are attached to the wrist and elbow by 2 pliable joint braces. By varying the tension of the springs, the amount of gravity compensation is easily adjustable to the arm weight of the participant. A more detailed description of the specifications of Freebal is published elsewhere.17

Measurements

Muscle activity and joint angles of shoulder and elbow were recorded and displayed synchronously to relate muscle activity to movement direction, using software written in Labview (National Instruments, Austin, Texas). Minimum and maximum elbow joint angles (hand on first and second target, respectively), as determined by zero crossings of the elbow angular velocity, defined reversals in movement direction. The phase from one maximal elbow extension to the next was defined as a movement cycle, divided in a retrieval (maximal
using Ag/AgCl-electrodes (Neuroline, type 720 00-S; Medicotest A/S, Ølstykke, Denmark) and according to the guidelines of the SENIAM project. The EMG signals were amplified using a K-Lab amplifier (K-Lab, Haarlem, the Netherlands), high-pass filtered (third order Butterworth filter, cut-off frequency 20 Hz), and digitized by a 12-bit analog-to-digital converter (integrated in the VICON data station) with a sample rate of 1000 samples per second. These EMG signals were then band-pass filtered (second order zero-phase shift Butterworth, cut-off frequencies 20-400 Hz) and converted to smooth rectified EMG (SRE) signals (using a second order zero-phase shift Butterworth low-pass filter at 25 Hz for smoothing) for each muscle per participant. Figure 2 shows examples of EMG recordings of BIC of several reach and retrieval movements with and without gravity compensation of a single participant, before and after conversion to SRE signals.

Data Analysis

Parameters of movement performance were determined using the kinematic data. Movement time was defined as the movement cycle duration averaged over all movement cycles per participant (in milliseconds). Movement symmetry was defined as the relative duration of reach with respect to the average movement cycle (in percentages). Joint excursions of elbow and shoulder angles were defined as the difference between minimal and maximal joint angles (in degrees), averaged over all movement cycles.

Averaging the SRE values and joint angles over the repeated movement cycles, during one 30-second series of reach and retrieval movements, provided an average muscle activation pattern (MAP) for each participant. The first 3 movement cycles were excluded from analysis to take intraparticipant and interparticipant differences in movement time into account. The average
A linear mixed model was used to test differences in average SRE values per participant due to gravity compensation (2-level factor “compensation”) in each muscle (6-level factor “muscle”) per movement part (3-level factor “part”). To account for the correlation of multiple measurements within one participant, the intercepts of the model equation were treated as random factors per participant. The factors—compensation, muscle, and part—were treated as fixed effects, since these effects were considered to be similar between participants. The 2-way interactions (muscle × part, compensation × muscle, and compensation × part) were included in the model. For all significant effects and interactions post hoc tests (with Sidak adjustment) were performed.

Furthermore, differences in movement performance parameters between movements with and without gravity compensation were tested using either paired-sample t tests or Wilcoxon signed ranks tests as a nonparametric equivalent.

To detect potential effects of learning or adaptation, muscle activity and movement performance parameters of the 2 groups performing movements, with and without gravity compensation, in reversed order, were compared using a t test for independent samples in the case of normally distributed parameters and a nonparametric equivalent, the Kolmogorov-Smirnov test, for parameters deviating from the normal distribution. For all tests the significance level was defined as 0.05.

**Results**

**Participants**

A total of 10 individuals participated in this study, but because of missing data of markers defining the elbow joint angle we had to exclude 2 participants from further analysis. EMG data of BIC of 1 participant was not recorded due to technical problems during data acquisition; however, since the remaining EMG signals and kinematic data were complete, this participant was not excluded. Physical characteristics of the participants are displayed in Table 1.

Five participants started the experiment with gravity compensation, whereas 3 participants performed first movements without gravity compensation. Comparison of differences in parameters related to gravity compensation revealed no consistent differences in movement performance parameters and EMG parameters between the groups starting the experiment with different conditions of gravity compensation. Therefore, data of all participants were pooled in subsequent analyses.

**Movement Performance**

A mean (±SD) of 12 (±4) movement cycles per participant were used for analysis. When comparing movement performance, with and without gravity compensation (Table 2), no differences were observed for movement symmetry and joint excursions of elbow, shoulder plane, and shoulder elevation angles between both conditions (P = .590, P = .386, P = .626, P = .499, respectively). When looking at specific arm orientations only minor
observed across movement parts, while during retrieval, muscle activity decreased slightly across movement parts (ie, from movement initiation to termination) in the majority of muscles. Several general aspects of muscle activation were identified when MAPs of all participants during movement without gravity compensation (Figure 4) were compared. All muscles were persistently active without periods of relaxation, except TRI, which had very low levels of activity during both reach and retrieval. The SRE values changed very little across movement parts during reach ($P = .547$), which was consistent for all muscles as supported by a nonsignificant interaction of “muscle × part” ($P = .054$). On the other hand, SRE values generally decreased across movement parts during retrieval ($P = .006$). This decrease was not different between muscles, as shown by a nonsignificant interaction of “muscle × part” ($P = .491$).

Based on these qualitative and quantitative data, general aspects of muscle activation patterns can be identified for unsupported functional reach and retrieval movements of stroke patients. Muscle activity of BIC lifts and holds the lower arm above the table and aids in anteflexion of the shoulder. TRI is active to contribute to extension of the elbow toward the target, although at a very low level. DA and DM are active to maintain a certain degree of shoulder abduction during movements, to anteflex the shoulder during reach and to decelerate retroflexion of the shoulder during retrieval. Activity of DP decelerates anteflexion of the shoulder during reach and retroflexes the shoulder during retrieval. TRA is active to elevate the upper arm and to position the scapula correctly during reach and retrieval movements.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Physical Characteristics of Stroke Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n = 8)</td>
<td></td>
</tr>
<tr>
<td>Sex (men/women)$^a$</td>
<td>4/4</td>
</tr>
<tr>
<td>Arm dominance (right/left)$^a$</td>
<td>6/2</td>
</tr>
<tr>
<td>Affected side (right/left)$^a$</td>
<td>4/4</td>
</tr>
<tr>
<td>Dominant side affected (%)$^a$</td>
<td>50</td>
</tr>
<tr>
<td>Age (years)$^b$</td>
<td>63.0 (±12.0)</td>
</tr>
<tr>
<td>Height (m)$^b$</td>
<td>1.75 (±0.12)</td>
</tr>
<tr>
<td>Weight (kg)$^b$</td>
<td>81.4 (±24.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)$^b$</td>
<td>26.3 (±4.3)</td>
</tr>
<tr>
<td>Time poststroke (months)$^b$</td>
<td>3.5 (1-42)</td>
</tr>
<tr>
<td>FM score (max 66 points)$^b$</td>
<td>43.5 (33-60)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; FM, Fugl-Meyer assessment
$^a$Absolute numbers.
$^b$Mean ± standard deviation.
$^c$Median and range.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Movement Performance Parameters$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Compensation</td>
<td>With Compensation</td>
</tr>
<tr>
<td>Elbow excursion (degrees)</td>
<td>45.8 (±7.1)</td>
</tr>
<tr>
<td>Shoulder plane excursion (degrees)</td>
<td>52.5 (±12.3)</td>
</tr>
<tr>
<td>Shoulder elevation excursion (degrees)</td>
<td>17.1 (±5.0)</td>
</tr>
<tr>
<td>Movement time (seconds)$^b$</td>
<td>2.13 (±0.67)</td>
</tr>
<tr>
<td>Movement symmetry (%)</td>
<td>58.3 (±6.6)</td>
</tr>
</tbody>
</table>

$^a$Mean ± standard deviation is shown from 8 participants, except for shoulder plane excursion, where n = 6.
$^b$Significant difference between movements with and without gravity compensation ($P < .05$).

Differences were observed. Shoulder elevation was somewhat larger at the start of reach with gravity compensation than without gravity compensation (59 ± 4º and 53 ± 5º, respectively; $P = .021$). This resulted in a slightly larger extension of the elbow to reach the target with gravity compensation (137 ± 7º and 132 ± 8º, respectively; $P = .001$). Besides this, movement times were slightly larger with gravity compensation than during unsupported movements ($P = .017$), which was mainly related to a lower movement velocity and not to a larger movement distance. However, the actual difference was very small when movement velocities were calculated (0.03 m/s). Therefore, movement performance was regarded to be comparable for both conditions.

**General Aspects of Muscle Activation**

A typical example of a MAP of movement without gravity compensation is displayed in Figure 3. In this subject, most muscles displayed activity throughout reach and retrieval, with the exception of TRI, which showed very little or no muscle activity. During reach, a consistent level of muscle activity was observed across movement parts, while during retrieval, muscle activity decreased slightly across movement parts (ie, from movement initiation to termination) in the majority of muscles.

Several general aspects of muscle activation were identified when MAPs of all participants during movement without gravity compensation (Figure 4) were compared. All muscles were persistently active without periods of relaxation, except TRI, which had very low levels of activity during both reach and retrieval. The SRE values changed very little across movement parts during reach ($P = .547$), which was consistent for all muscles as supported by a nonsignificant interaction of “muscle × part” ($P = .054$). On the other hand, SRE values generally decreased across movement parts during retrieval ($P = .006$). This decrease was not different between muscles, as shown by a nonsignificant interaction of “muscle × part” ($P = .491$).

Based on these qualitative and quantitative data, general aspects of muscle activation patterns can be identified for unsupported functional reach and retrieval movements of stroke patients. Muscle activity of BIC lifts and holds the lower arm above the table and aids in anteflexion of the shoulder. TRI is active to contribute to extension of the elbow toward the target, although at a very low level. DA and DM are active to maintain a certain degree of shoulder abduction during movements, to anteflex the shoulder during reach and to decelerate retroflexion of the shoulder during retrieval. Activity of DP decelerates anteflexion of the shoulder during reach and retroflexes the shoulder during retrieval. TRA is active to elevate the upper arm and to position the scapula correctly during reach and retrieval movements.
Figure 5
Differences in Muscle Activity due to Gravity Compensation

![Graph showing differences in muscle activity due to gravity compensation.](image)

Note: Mean differences (±95% confidence interval) in smooth rectified electromyographic (SRE) values, averaged over all movement parts, due to gravity compensation (SRE with gravity compensation/SRE without gravity compensation), are displayed for reach (light symbols) and retrieval (dark symbols) per muscle. Asterisks represent significant differences between movements with and without gravity compensation (P < .05) according to the linear mixed model, taking intraparticipant correlation into account. BIC, biceps, long head; TRI, triceps, long head; DA, anterior deltoid; DM, middle deltoid; DP, posterior deltoid; TRA, upper trapezius.

Figure 6
Changes in SRE Values Across Movement Parts

![Graph showing changes in SRE values across movement parts.](image)

Note: Mean ± SD smooth rectified electromyographic (SRE) values per movement part are shown for movements without (cross markers) and with (circular markers) gravity compensation for each muscle during reach (upper panels) and retrieval (lower panels). BIC, biceps, long head; TRI, triceps, long head; DA, anterior deltoid; DM, middle deltoid; DP, posterior deltoid; TRA, upper trapezius; I, initiation; II, forward progression; III, termination of movement.

Discussion

Our hypothesis was that gravity compensation would influence muscle activation patterns of stroke patients in a positive manner. Knowledge of the nature and direction of these changes will enhance our understanding of underlying working mechanisms of the influence of gravity compensation on improvements in arm movement ability. General aspects of muscle activation during functional reach and retrieval movements, with and without gravity compensation, were identified. Persistent activity was a common aspect during the functional arm movements without gravity compensation in most muscles; there were no periods of complete muscle relaxation. An exception was TRI, which had very low levels of activity throughout the movement. The level of persistent activity did not vary much in muscles from movement initiation to termination during reach, while it decreased somewhat during retrieval. This general pattern was observed in all muscles. A comparison of muscle activation patterns during movements, with and without gravity compensation, showed that the pattern of muscle activity, as represented by the change of average SRE values across specific aspects of movement, was not influenced by gravity compensation, whereas the level of muscle activity was 25% to 50% lower with gravity compensation in all muscles, except in TRI during reach. At the same time, movement time, movement symmetry, and joint angle excursions were comparable in both conditions, although the arm was elevated slightly higher during movements with gravity compensation.
After stroke, muscle activation can be disturbed in many ways with respect to that of healthy persons. Despite this, few differences were observed in the general pattern of muscle activation during these functional reach and retrieval tasks (as indicated by the change of muscle activity level across movement parts) when the MAPs of stroke patients in the present study were compared to those of healthy elderly individuals performing similar movements in a previous study. It is remarkable that in both stroke patients and healthy elderly persons all muscles, except TRI, were persistently active without periods of muscle relaxation. A plausible explanation for this is that a rather continuous activation is needed to provide stabilization for the many degrees of freedom of the shoulder joint, and to facilitate control of the interaction torques acting on elbow and shoulder joints due to movements of the adjacent joint.

The similarity in MAPs between healthy elderly individuals and stroke patients may be related to the ability of the patients to complete the movement task without gravity compensation. The stroke patients included in the present study were mildly to moderately affected, with FM scores ranging between 33 and 60. The functional reach and retrieval movements were well below the maximal capacity of the stroke patients involved. The nature of these submaximal movements contributed to the observed persistent muscle activity, without clear phasic muscle activation, which limited the possibility of a detailed analysis of the timing of muscle activation.

When comparing muscle activity during movements, with and without gravity compensation, we found that the level of muscle activity was lower during movements with gravity compensation, while movement performance was comparable. This reduction in level of muscle activity occurred in muscles that act against gravity (BIC, DA, TRA) in stroke patients, as well as in healthy elderly individuals. As observed in healthy elderly persons, the change of the level of muscle activity across movement parts did not differ between movements with and without gravity compensation. In other words, in both stroke patients and healthy elderly individuals, gravity compensation reduced the level of muscle activity needed to hold the arm in a certain orientation during reach and retrieval, while the general pattern of muscle activation for those movements was comparable. A study by Chabran et al on segmental postural control in healthy persons reported results along similar lines. While the presence or absence of an elbow support affects the level of activity of postural muscles (BIC, TRI, DA) during wrist flexion/extension, the timing of activity of the postural muscles is not influenced. Remarkably, gravity compensation influenced only the level of activity of BIC, DA, and TRA in healthy elderly persons, while in stroke patients the level of activity of DM and DP was also affected, with TRI to a lesser extent. This may be related to an inappropriate coupling of muscles after stroke, so that gravity compensation affected not only the anti-gravity muscles directly, but possibly also the coupled, coactivated muscles indirectly.

A limitation of the present study might be that, due to the rather coarse analysis of muscle activity during specific aspects of movement, we could not distinguish whether gravity compensation influenced the specific timing of muscle activation, as indicated by the onset and offset of phasic muscle activity. One could argue that to observe changes in timing, a more demanding task would be more suitable, for instance, by applying ballistic movements or by adding weights to the arm. However, such a fundamental approach was outside the scope of the present study, which focused on functional movements.

In the present study, visual inspection did not reveal any distinct differences in timing of muscle activity between movements with and without gravity compensation. Whether changes in timing would occur after an intervention in stroke patients is questionable, given the findings of Chabran et al, who noted no changes in timing of postural muscle contractions with varying elbow support conditions. In regard to the lower extremity, research by Buurke et al revealed that timing of muscle activity may not change during recovery of gait in stroke patients, although timing does differ instantaneously between walking with and without a walking aid.

Regarding movement performance, research indicates a positive influence of gravity compensation. In a previous study, our research group found that the active range of motion increases instantaneously with gravity compensation during multijoint maximal reaching movements in 3 dimensions with respect to movements without gravity compensation. Additional analyses showed a simultaneous decrease in the level of muscle activity with gravity compensation.

More fundamental research of Beer and colleagues identified an involuntary coupling between shoulder abduction and elbow flexion in stroke patients, which is less strong when the arm is supported, resulting in a larger elbow extension during maximal planar reach tasks with arm support. This abnormal coupling probably results from an increased use of alternative neural pathways to compensate for the damaged corticospinal tracts after stroke, which limit the selectivity of muscle activation.

Although gravity compensation did not affect motor control in the current sample of stroke patients as expected, the finding that gravity compensation did reduce the level of activity needed to perform the task indicates that active arm movements may be facilitated during stroke rehabilitation. In this sample of stroke patients with adequate function to complete the task, the facilitation due to gravity compensation occurred without impairing motor control. Due to the support of the arm, the need to generate muscle activity for the postural control of the arm is decreased and patients can use their remaining capacity for generation and coordination of a functional movement, such as reaching for a cup. This facilitating influence of gravity compensation implies that patients may start training of active movements at an early stage and to repeat more movements and/or attend longer or more frequent sessions than in a situation without gravity compensation. This would increase the intensity of therapy to stimulate restoration of arm function during poststroke rehabilitation.

Gravity compensation is not only applied in conventional rehabilitation, but is also often integrated into new approaches,
such as robot-aided therapy, to provide arm support during training of arm function. The findings from the present study suggest that the application of gravity compensation alone has the ability to influence the level of muscle activity generated during submaximal, functional arm movements, regardless of other potentially integrated training modalities that aim to change arm movement performance during therapy, or a research intervention. This supports the potential of the application of gravity compensation as a separate intervention during poststroke rehabilitation to stimulate restoration of arm function.

Acknowledgment

This research was supported by grant TSGE2050 from SenterNovem, the Netherlands. None of the authors had any conflicts of interest.

References