



Cerebral hemodynamic changes during motor imagery and passive robot-assisted movement of the lower limbs

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ABSTRACT

Background: Neurovascular Coupling is the cerebral mechanism responsible for linking neuronal activity, cerebral metabolism and regional cerebral blood flow (CBF). The direct relation between functional brain activity during active, passive and motor imagery paradigms and changes in CBF has been widely investigated using different techniques. However, CBF changes have not been investigated beat by beat during robot assisted passive movement (PM) and motor imagery (MI) of lower limb, yet.

Materials and methods: We investigated beat-to-beat hemodynamic changes in 8 healthy subjects using TCD during MI and robot-assisted PM of lower limb.

Results: The results showed that MI and PM induce a significant CBFv increase and that PM and MI lead to similar hemodynamic changes in healthy subjects.

Conclusions: The findings may be useful to better understand the variation of CBFv in brain pathology and to develop more specific and efficient rehabilitation therapy protocols in neurological diseases, such as stroke.

1. Introduction

Cognitive and sensorimotor tasks activate different areas of the brain, leading to an increase in regional metabolic demand through the dilatation of cerebral arterioles and capillaries to provide O₂, glucose and other metabolites. Therefore, there is a close link between neuronal function and activity-induced hemodynamic response with local increase in cerebral blood flow (CBF) [1].

A direct relation between functional brain activity during active and passive movement and motor imagery paradigms and changes in CBF have been widely investigated using different techniques such as functional magnetic resonance imaging (fMRI) [2,3], positron emission tomography (PET) [4], single photon emission computed tomography (SPECT), transcranial Doppler (TCD) ultrasound [5,6], magnetoencephalography (MEG) [7], and electroencephalography (EEG) [8,9]. However, only few of these studies are focused on beat-to-beat CBF activity-related changes. TCD is an easy to perform and widely available tool which evaluates dynamic adjustment in CBF accompanying cerebral activation. Previous TCD studies showed a CBF velocity rise during sensorimotor paradigm and these changes appeared to be task-specific [10–13].

Neurovascular coupling is compromised in different diseases involving the nervous system like cerebrovascular, autonomic, and cognitive dysfunctions, as well as in systemic diseases. The study of hemodynamic changes during active and passive movement and motor imagery in healthy subjects could contribute to get a clearer picture of these phenomena in patients with neurological diseases. Such changes might be particularly relevant in ischemic stroke, in which the regional hypoperfusion is related with the neurological deficit [14–16]. In rehabilitation practice, active and passive movements are widely used in stroke patient recovery in order to improve sensorimotor function. Moreover, motor imagery – a structured repetition of a cognitive imagination task – is adopted in patients with stroke-induced limited mobility to promote the activation of the cerebral cortex even in the absence of a physical movement [17].

Robot-assisted therapy has also shown to be an effective and reliable method to deliver highly repetitive, progressive, and engaging training to trigger neuroplasticity following a stroke [18,19]. Compared with conventional rehabilitation therapy, robot-assisted therapy holds clear advantages such as precisely controlled force feedback, automated movement control, objective, and quantifiable performance measurement [20,21]. Recently, brain oscillatory activity changes were

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investigated by EEG during passive movement administered by robotic devices and during motor imagery, both in healthy subjects and in stroke patients [22–24]. However, there is a lack of knowledge in hemodynamic changes in robotic assisted therapy, which was investigated only in relation to passive movement of upper limb [5]. The present study aimed at investigating the task-related hemodynamic beat-to-beat response to Passive robot-assisted Movement and to Motor Imagery paradigms of lower limb in healthy subject by means of TCD.

2. Material and methods

2.1. Study population

The study was conducted at the Clinical Unit of Neurology of University Hospital of Trieste, Italy, and it included 8 healthy volunteers, selected between students and residents that were working in our neurological center. The inclusion criteria were young healthy subjects (age 20 to 30 years), right footed, without history of cardiovascular and cerebrovascular disease, in particular without impaired motor functions. Heart rate and blood pressure were recorded for each subject at baseline and at the end of the experimental protocol. Subjects with blood pressure values higher than 140/90 mmHg and cardiac frequency over 100 bpm were excluded.

The research was conducted according to the principles of the Declaration of Helsinki. All participants released their informed consent to participate in the study after all procedures had been fully explained. Approval for the study had been previously obtained from the local ethics committee.

2.2. Brain activation paradigms and procedure

The experimental protocol consisted of six unilateral and bilateral lower limbs tasks performed by robot-assisted passive movement and by motor imagery separately. The tasks included dorsi-plantar flexion of tibio-tarsal joint and knee flexion-extension, as described below:

1. Right knee flexion-extension movement;
2. Left knee flexion-extension movement;
3. Bilateral knee flexion-extension movement - bicycle movement;
4. Right tibio-tarsal joint dorsi-plantar flexion movement;
5. Left tibio-tarsal joint dorsi-plantar flexion movement;
6. Bilateral tibio-tarsal joint dorsi-plantar flexion movement.

Each task, lasting one minute, was performed randomly alternating with rest.

The Passive movement (PM) was performed using the robot-assisted single-joint cyclic ankle movement of the BTS ANYMOVE robotic hospital bed (BTS Bioengineering, Milan, Italy) [23]. The proximal section of the bed was reclined at 60° above the horizontal. The knee and ankle movements were assisted by two dedicated engines placed in the lower limb support section. The ankle movement was set to 15° of dorsi-flexion and 30° of plantar-flexion and the cyclic ankle movement had a frequency of 0.2 Hz.

During the Motor Imagery (MI), participants were instructed to imagine the kinesthetic experience of movement of lower limbs described above. An acoustic signal was used to guide participants in performing the different tasks. Before the experiment, each subject was trained to perform the task correctly.

The subject was instructed to keep their eyes closed to avoid external stimuli. EMG signals in this study were acquired to assure the absence of active movement during Motor imagery, Robot Assisted Passive Movement paradigms, as well as during rest. The surface EMG were measured from left and right quadriceps and anterior tibial in each task. The signals were acquired using Be light (EBNeuro, Florence, Italy) amplifier at a sampling frequency of 512 Hz sampling frequency. EMG data were filtered with the 10–250 Hz 2nd order Butterworth

bandpass filter. The experiments were conducted in a climatic chamber to maintain stable environmental conditions. We maintained the room temperature at 23 °C with 50% relative humidity. Before the measurements, the experimental protocols were explained in detail to the participants. Prior to the study, the participants were instructed to abstain from alcohol and from smoke for 12 h, not to eat a meal within 90 min, and to get enough sleep.

2.3. TCD acquisition and analysis

Cerebral blood flow changes were evaluated with TCD by the same researcher (P.C.) with extensive experience in ultrasounds. Baseline values were collected at resting state (RS), 3 min average, prior to experimental procedure. Bilateral cerebral blood flow velocity of the middle cerebral artery (MCA) using TCD signal was constantly recorded. TCD data acquisition analysis was based on: TCD measurements with the DWL Embo-Dop device, with hand-held transducer; Pulsed-wave mode at a frequency of 2 MHz; bilateral intonation of MCA through the temporal window at a depth of 50 to 64 mm. Continuous recording of CBFv and PI of the MCA, alternating the right and left MCA at least for 30 s each; 4 repetitions of each task of 30 s alternated with 30 s runs of rest. Medians (ranges) of measured Vmean (mean velocity), Vmax (systolic pick velocity) and PI values (pulsatility index: measure of the variance of the blood velocity within the vessel through the cardiac cycle, calculated as: pick systolic velocity-diastolic velocity, divided by the mean velocity during the cardiac cycle) were calculated. CBFv signal was visually inspected to identify artefacts and noise, and narrow spikes were removed by linear interpolation. The CBFv channels were subjected to a median filter and all signals were filtered by a low pass filter with a cutoff frequency of 100 Hz. CBFv values were calculated for each beat.

2.4. Statistical analysis

Differences in Vmax and Vmean values among the resting state, PM and MI, for left and right MCA recorded separately for each task were assessed by Kruskal-Wallis test followed by multiple pairwise comparisons using the Dunn-Bonferroni approach. A value of $p < .05$ was considered as statistically significant.

3. Results

All 8 recruited subjects (3 M/5F) completed motor tasks. Mean age was 28 ± 3 years, while mean height, weight, and body mass index were 165 ± 8 cm, 54 ± 8 kg, and 20 ± 2 kg/m², respectively. Median blood pressure was 120/60 mmHg and median heart rate (HR) was 80 bpm. Medians (ranges) of measured Vmean and Vmax are reported in Table 1, while Table 2 reports results of comparison of Vmean and Vmax among RS, PM and MI tasks. Vmax measured values were significantly higher both during PM and MI compared to RS in each task for left and right MCA. These measurements did not differ between PM and MI, although slightly higher for MI than PM in most of cases. The same significant differences were observed in Vmean during PM and MI compared to RS, with the exception of right MCA for Right Foot task and of both MCAs for Alternating foot task, where PM differed from MI, too. Our results show an increase of MCA main velocity bilaterally with slightly higher values of Vmax and Vmean on the dominant left hemisphere but they did not differ significantly between left and right MCA. TCD raw data (TCD tracings, Vmax and Vmean) of a representative single case that reflects the trend of changes in the flow identified in our cohort are reported in Fig. 1.

In right MCA, in all cases PI showed higher values during RS compared to MI or PM. It was statistically significant in RS compared to MI in all cases, while RS and PM differed significantly only for Alternating Leg and Left foot task. In left MCA, PI did not statistically differ among RS, PM, and MI.

Table 1
Median (range) values of Vmean and Vmax values among Resting state (RS), Passive Movement (PM) and Motor Imagery (MI) tasks.

		Vmean		Vmax	
		Right	Left	Right	Left
Resting state	RS	49 (30–64)	52 (30–60)	81 (59–115)	87 (56–106)
Right leg	PM	58.5 (43–88)	57 (48–92)	94 (80–131)	93.5 (70–136)
	MI	54 (43–89)	60 (40–86)	91 (73–135)	96 (78–127)
Left leg	PM	51 (45–86)	56 (47–84)	91 (73–133)	95 (80–130)
	MI	58 (40–83)	68 (45–87)	95 (65–132)	100.5 (77–127)
Alternating leg	PM	55 (44–89)	55 (34–88)	95 (78–130)	92 (81–128)
	MI	56 (42–92)	58 (46–89)	93 (68–126)	90.5 (74–130)
Right foot	PM	54 (45–77)	60 (40–91)	94 (74–123)	96 (71–132)
	MI	64 (51–79)	62 (44–82)	110 (76–126)	98 (73–125)
Left foot	PM	54 (44–84)	60 (36–93)	93 (76–129)	96 (65–131)
	MI	61 (41–79)	59 (47–93)	98.5 (69–118)	96 (80–128)
Alternating foot	PM	52 (41–85)	57 (44–91)	93 (56–137)	92 (75–134)
	MI	60 (46–79)	62 (44–88)	97.5 (73–122)	103 (75–133)

Table 2
Comparison of Vmean and Vmax values among Resting state (RS), Passive Movement (PM) and Motor Imagery (MI) tasks. P-levels (* - $p < .05$).

		Vmean		Vmax	
		Right	Left	Right	Left
Right leg	PM vs RS	< 0.001*	0.002*	< 0.001*	0.001*
	MI vs RS	< 0.001*	< 0.001*	< 0.001*	< 0.001*
	PM vs MI	0.119	0.870	0.406	0.591
Left leg	PM vs RS	0.002*	0.001*	< 0.001*	< 0.001*
	MI vs RS	< 0.001*	< 0.001*	< 0.001*	< 0.001*
	PM vs MI	0.158	0.126	0.816	0.430
Alternating leg	PM vs RS	< 0.001*	0.046*	< 0.001*	0.001*
	MI vs RS	< 0.001*	0.009*	< 0.001*	0.016*
	PM vs MI	0.808	0.324	0.537	0.342
Right foot	PM vs RS	< 0.001*	0.004*	< 0.001*	0.009*
	MI vs RS	< 0.001*	< 0.001*	< 0.001*	0.008*
	PM vs MI	< 0.001*	0.647	0.134	0.994
Left foot	PM vs RS	< 0.001*	< 0.001*	< 0.001*	< 0.001*
	MI vs RS	< 0.001*	< 0.001*	< 0.001*	0.001*
	PM vs MI	0.988	0.999	0.629	0.742
Alternating foot	PM vs RS	< 0.001*	0.008*	0.004*	0.014*
	MI vs RS	< 0.001*	< 0.001*	< 0.001*	< 0.001*
	PM vs MI	0.006*	0.007*	0.603	0.139

4. Discussion

This study reports the results of hemodynamic brain activity evaluated by TCD during robot-assisted cyclic lower limb movements and during motor imagery. The main new finding of this study is the significant increase of CBF in response to neural activation onset with Robotic Passive Movement from the lower limbs and Motor Imagery task. These findings may reflect the cerebral vasodilation in neurovascular coupling which is the cerebral mechanism responsible for linking neuronal activity, cerebral metabolism and CBF [25,26]. Neuronal activation of the primary sensory-motor cortex and supplementary motor area during robotic PM and MI induce CBFv increase in the middle cerebral artery that can be easily evaluated by TCD. Indeed, TCD monitoring allowed us to record the alterations in the MCA velocity, main vessel of the anterior circulation designated to provide oxygen and nutrients to the motor and sensory motor areas. The results are in line with those reported in studies that evaluated regional blood flow by different techniques (PET, fMRI, MEG, NIRS) [27–30]. Using PET, Weiller et al. showed a CBF increase during active and passive flexion

and extension of the right elbow of healthy subject in the contralateral sensorimotor cortex, supplementary motor area and inferior parietal cortex [27]. By means of fMRI, Boscolo Galazzo et al. demonstrated an activation of contralateral sensorimotor cortex, ipsilateral sensorimotor cortex, supplementary motor area, bilateral inferior parietal lobule bilateral cerebellum, and the basal ganglia during right-hand active and passive task in healthy subjects [28]. Recent fNIRS study reported an increased contralateral activation in response to active motor execution of finger- or toe-tapping tasks, while a bilateral activation pattern with motor imagery [30].

Most of literature studies have focused on the latest period of each paradigm and not on dynamic changes. Active and passive motor paradigms seem to bring to similar CBF velocity response. Similar patterns of CBFv increase have been described in the literature after active movement, passive movement and cognitive paradigms [4,11,31]. Motor imagery shows a lesser contribution to the CBF response than the motor paradigm. No significant difference between contralateral and ipsilateral cerebral hemodynamic responses during each paradigm has been reported, albeit mutual consensus on prompt hemodynamic response in the dominant hemisphere [10].

TCD is a noninvasive method widely applied to assess cerebral hemodynamic variations during cognitive and action tasks allowing continuous measurements of CBFv in real time [5]. Measurement of blood flow velocity in the main arteries by TCD has been adopted in several studies to analyze brain activities during the performance of cognitive tasks, knowing that those paradigms have a positive influence on cerebral autoregulation. TCD is characterized by high temporal resolution, low cost, non-invasiveness, as well as ease of operation, and it may become one of the main tools to study flow-metabolic coupling in the human cerebral circulation. Salinet et al. conducted a TCD study demonstrating CBFv rise in ipsilateral and contralateral MCA arteries during the active/passive and motor imagery of flexion and extension of the elbow in healthy subjects [5,32]. In these studies, motor active task and passive motor task led to similar CBF responses. Moreover, our study assessed that, regardless from the movement task side, hemodynamic activation occurred similarly in both left and right MCA (Table 1). Although the dominant left side presented slightly higher values in all cases, PI modification didn't show any statistical significance level.

According to data from literature, in our study we found an increase of MCA main velocity bilaterally [33,34] with a slightly higher values of Vmax and Vmean on the dominant left hemisphere. Yet, they did not differ significantly between left and right MCA.

Our study, differently from previous TCD studies, investigates CBFv changes induced by robot-assisted passive movement. The robot assisted device may help physicians to improve standard rehabilitation treatments. Neuroscience studies indicate that repetitive movements may induce changes in the brain, retrain neural pathways and restore or improve motor skills lost as a result of stroke or spinal cord injuries due to neuroplasticity [33–36]. Recent neurological research indicates that the impaired motor skills of post-stroke patients can be restored and enhanced through task-oriented repetitive training [24]. Various rehabilitation processes have been developed to take advantage of neuroplasticity to retrain neural pathways and restore or improve motor skills lost as a result of stroke. Robot-assisted devices and the associated therapies for post-stroke rehabilitation have been given heightened attention in the research community in order to address the shortcomings of the conventional therapies [37,38].

In our study, MI and PM produced similar hemodynamic changes, indicating that they could have a similar impact on rehabilitation. Furthermore, these paradigms seem to lead to the activation of same brain areas as the active movements. However, robot-assisted passive movements could also be administered in patients with cognitive deficit as well as in cases of poor collaboration. MI and PM may represent an intriguing tool to understand motor system and its recovery after a brain injury, as well as to guide physicians in the draft of

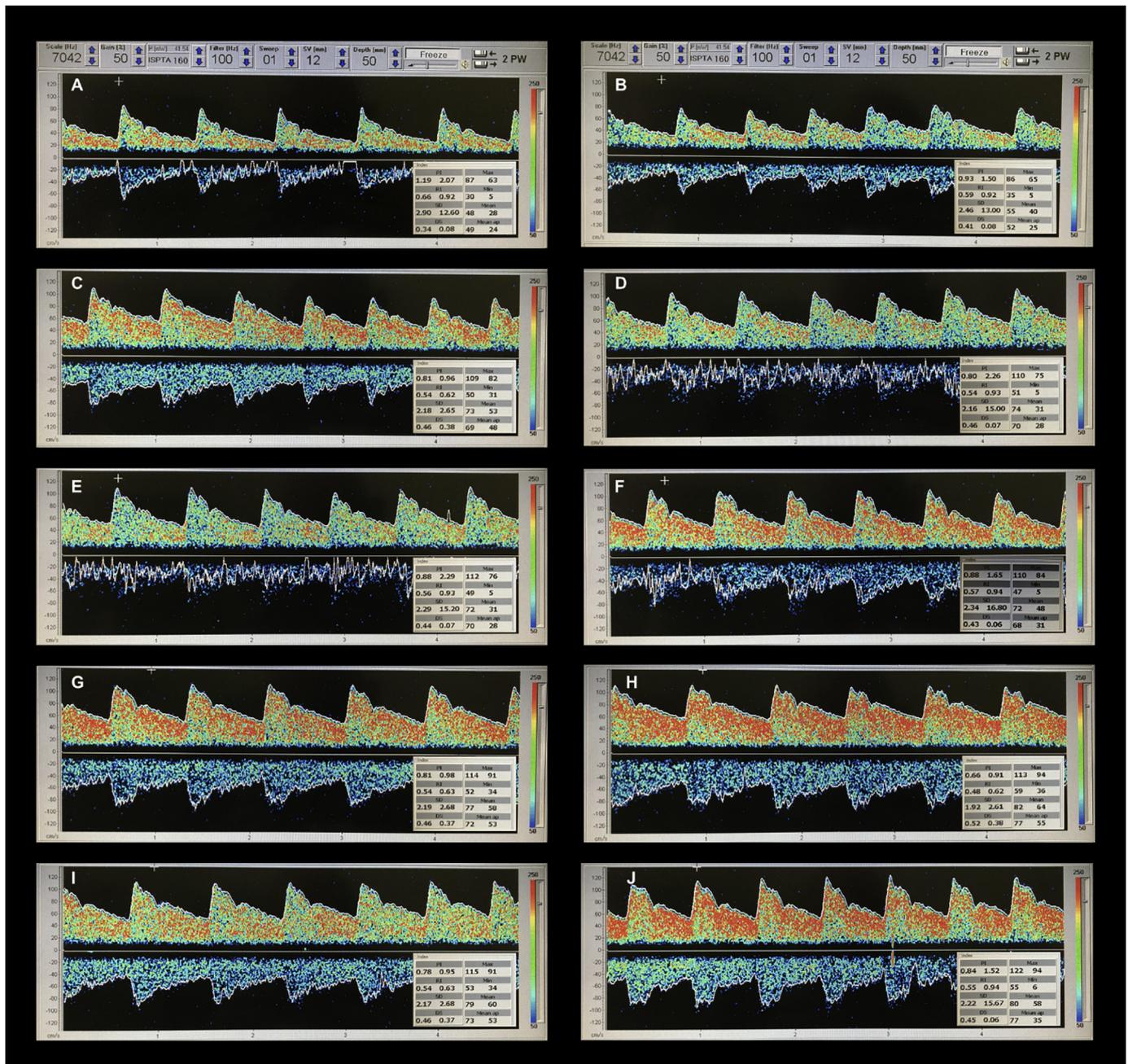


Fig. 1. TCD raw tracings and TCD velocimetric values. Resting state: (A) Right MCA, (B) Left MCA. Right Leg Passive Movement: (C) Right MCA, (D) Left MCA. Right Leg Motor Imagery: (E) Right MCA, (F) Left MCA. Alternating Leg Passive Movement: (G) Right MCA, (H) Left MCA. Alternating Leg Motor Imagery: (I) Right MCA, (J) Left MCA. Abbreviation. TCD: Transcranial Doppler. MCA: Middle Cerebral Artery.

neurorehabilitation protocols.

Our study has several limitations, first of all the small number of participants in the study leading to a potential lack of statistical power. TCD evaluation with hand-held probe performed in this study is more affected by the operator expertise than bob monitoring. Moreover, we recorded the changes in the MCA velocity, main vessel of the anterior circulation designated to provide oxygen and nutrients to the motor and sensory motor areas, but we couldn't judge the regional cortical activations. Future studies should also include fNIRS application. Finally, in our study we couldn't evaluate MCA velocity changes during active movement because the probe is very sensitive even to small movements, providing a reliable velocity value. However, We believe that analyzing active movement influence on MCA velocity and comparing it to passive movement and motor imagery would be an interesting

research area for a future study.

5. Conclusions

The significant CBFv increase assessed by TCD related to the neural activation during robot-assisted passive movement from the lower limbs is the intriguing and pivotal finding of this study. Furthermore, robotic passive movement and motor imagery induced similar hemodynamic changes. These findings increase knowledge on neurovascular coupling phenomena during sensorimotor paradigm in healthy subjects and may be useful to develop more specific and efficient rehabilitation therapy protocols in neurological diseases, such as stroke.

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Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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