Effect of microbubble contrast on intracranial blood flow velocity assessed by transcranial Doppler

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Abstract

Purpose Ultrasound contrast agents (UCA) salvage a considerable number of transcranial Doppler (TCD) exams which would have failed because of poor bone window. UCA bolus injection causes an undesirable increase in measured blood flow velocity (BFV). The effect of UCA continuous infusion on measured BFV has not been investigated, and some in vitro experiments suggest that gain reduction during UCA administration may also influence measured BFV. This study aimed to investigate the effect of UCA continuous infusion on BFV measured by TCD and the influence of gain reduction on these measurements in a clinical setting.

Methods The right middle cerebral artery of ten patients with optimal bone window was insonated using a 2 MHz probe. UCA were administered using an infusion pump. BFV was measured (1) at baseline, (2) during UCA infusion, (3) during UCA infusion with gain reduction, and (4) after UCA wash-out phase. Gain reduction was based on

the agreement between two neurosonographers on the degree of gain reduction necessary to restore baseline Doppler signal intensity (DSI). Actual DSI was estimated offline by analysis of raw data.

Results BFV measured during UCA infusion with no gain adjustment was significantly higher than baseline BFV [peak systolic velocity (PSV): 85.1 ± 19.7 vs. 74.4 ± 19.7 cm/s, $p < 0.0001$; Mean velocity (MV): 56.5 ± 11.8 vs. 50.2 ± 12.3 cm/s, $p < 0.0001$]. BFV measured during UCA infusion with gain reduction was not significantly higher than baseline BFV (PSV: 74.3 ± 18.9 vs. 74.4 ± 19.4 cm/s, $p = 0.8$; MV: 49.4 ± 11.0 vs. 50.2 ± 12.3 cm/s, $p = 0.8$). Actual DSI during UCA infusion with gain reduction was not significantly higher than baseline DSI (13 ± 1 vs. 13 ± 1 dB).

Conclusion This study shows that UCA continuous infusion leads to an increase in measured BFV which may be counteracted by reducing Doppler gain thus restoring pre-contrast DSI.

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Keywords Blood flow velocity · Transcranial Doppler ·
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Riassunto

Scopo L'uso del mezzo di contrasto ecografico (UCA) rende possibile l'esame Doppler transcranico (TCD) in pazienti con finestra ossea inadeguata. L'iniezione in bolo di UCA provoca un aumento indesiderato nella misurazione della velocità del flusso sanguigno (BFV). L'effetto di UCA, iniettato per infusione continua, sulla misurazione del BFV non è stato studiato ed esperimenti in vitro suggeriscono che anche la riduzione del guadagno durante la somministrazione UCA può influenzare la misurazione del BFV. Questo lavoro ha lo scopo di studiare l'effetto di UCA iniettato per infusione continua sulla BFV misurato

mediante TCD e l' influenza della riduzione del guadagno su queste misure, nella pratica clinica.

Metodi È stata insonata l'arteria cerebrale media destra di dieci pazienti, con finestra ossea ottimale, usando una sonda da 2 MHz. Sono stati somministrati UCA mediante una pompa per infusione. È stata misurata la BFV (1) basale, (2) durante infusione di UCA, (3) durante infusione di UCA con riduzione del guadagno, (4) dopo la fase wash-out del UCA. La riduzione del guadagno è stata basata sull'accordo tra due neuro-ecografisti riguardo alla riduzione del guadagno necessaria per ristabilire l'intensità del segnale Doppler (DSI) presente all'inizio dell'esame (baseline). Il valore attuale del DSI è stato calcolato mediante l'analisi a posteriori dei dati grezzi.

Risultati Il BFV misurato durante l'infusione di UCA senza regolazione del guadagno era significativamente più alto rispetto al BFV basale [picco velocità sistolica (PSV): 85.1 ± 19.7 vs. 74.4 ± 19.7 centimetri/s, $p < 0.0001$; velocità media (MV): 56.5 ± 11.8 vs. 50.2 ± 12.3 centimetri/s, $p < 0.0001$]. Il BFV misurato durante infusione di UCA con riduzione del guadagno non era significativamente superiore alla BFV basale (PSV: 74.3 ± 18.9 vs. 74.4 ± 19.4 centimetri/s, $p = 0.8$; MV: 49.4 ± 11.0 vs. 50.2 ± 12.3 centimetri/s, $p = 0.8$). Il valore attuale della DSI durante l'infusione di UCA e riduzione del guadagno non era significativamente superiore a quello basale (13 ± 1 vs. 13 ± 1 dB).

Conclusioni Questo studio dimostra che l'utilizzazione di UCA per infusione continua porta ad un aumento del BFV misurato, che può essere neutralizzato attraverso la riduzione del guadagno, il quale ripristina l'intensità del segnale Doppler al livello presente prima della somministrazione dell'UCA.

Introduction

Transcranial Doppler (TCD) examination is inadequate or impossible in 5–25 % of patients [1, 2] due to excessive signal attenuation by the skull. Ultrasound contrast agents (UCA) overcome this limitation by enhancing the returned signal and thus increasing the signal-to-noise ratio [3]. Clinical neurosonographic studies have shown that UCA bolus injection causes a 20–24 % increase in measured peak systolic velocity (PSV) [4, 5], but there are no available data about the influence of continuous UCA infusion on measured PSV. One in vitro study suggests that the UCA-related increase in PSV may be avoided by gain reduction [6], but this has not yet been confirmed in clinical studies. The aim of this study was to investigate (1) the effect of continuous UCA infusion on PSV and mean velocity (MV) measured with TCD, and (2) the influence of gain reduction on these measurements.

Materials and methods

Patient population

Study subjects were selected among patients admitted to the stroke centre with suspected ischemic stroke. Inclusion criteria were (1) ability to cooperate and remain at ease during the study procedure, (2) a good temporal bone window on routine transcranial duplex ultrasound, and (3) normal intracranial arteries on CT angiography. The regional ethics committee approved the study and all patients gave their informed consent.

TCD protocol

All examinations were performed by two experienced neurosonographers (NL, LT). The examination room was kept quiet and light was dimmed throughout the examination. With the patient in supine position, the right MCA was insonated using a 2 MHz probe (Companion III Nicolet Vascular, Madison, WI, USA) secured to the patient's head using a head band. Sample volume length was 15 mm and was centred at 52 mm insonation depth. An initial 5 min resting period was included to reach a stable state before the start of recordings. SonoVue (Bracco, Italy), a microbubble contrast agent containing sulphur hexafluoride gas stabilized by phospholipids, was administered via antecubital fossa venous access using an infusion pump (VueJect, Bracco, Italy). The trend curves of blood flow velocity (BFV: PSV and MV) were measured throughout the examination and analyzed offline. The baseline gain was set at the lowest level providing optimal Doppler signal based on the agreement between the two operators. The gain was the only parameter which was changed during the examination. The protocol steps were as follows (Fig. 1): The baseline Doppler signal was recorded for 1 min (R1), UCA infusion set at 0.3 ml/min was started (wash-in phase), and the time to stable contrast enhancement was noted. When the contrast-enhanced Doppler signal was considered stable, recording was performed for 1 min (R2). The gain was thereafter reduced until the intensity of the contrast-enhanced Doppler signal matched the baseline Doppler signal. The degree of gain reduction was based on the agreement between the two operators blinded to the measured velocity values. The contrast-enhanced Doppler signal after gain reduction was recorded for 1 min (R3). The UCA infusion was then stopped and the gain was progressively increased to keep the Doppler signal matched to the baseline Doppler signal (wash-out phase). When the gain level was back to baseline, the contrast enhancement was considered minimal, and the Doppler signal was recorded for 1 min (R4). BFV

Fig. 1 Schematic representation of study method and results

measurements and data analysis PSV were defined by the software of TCD machine as the highest value of the envelope curve during a cardiac cycle. MV was defined by the software of TCD machine as the mean of the values of the envelope curve during one spectral sweep. PSV and MV values were then averaged over one minute time period, i.e. over each of the four 1 min recordings. The Doppler signal intensity (DSI) was estimated after exporting XML report of each examination and offline reading of raw ultrasound data. DSI was defined as the mean of a 10 s random selection of each recording (*R1*, *R2*, and *R3*). Statistical power calculation was based on the results from an earlier study [4]. One-sample comparison of mean was used. The estimated sample size required to provide a test power of 0.90 was 1. Two patients were required to provide a test power of 0.99. The number of patients to be included in the study was arbitrarily set to 10. For statistical analysis paired two-sample mean-comparison Student test was used.

Results

Ten patients were included (8 male, median age 56.5 years, age range 35–67 years). Mean wash-in time was 3.2 ± 0.7 min. PSV values at baseline (*R1*), during UCA infusion with no gain adjustment (*R2*), during UCA infusion with gain adjustment (*R3*), and after UCA wash-out phase (*R4*) are shown in Table 1. BFV measured during UCA infusion with no gain adjustment was significantly higher than baseline BFV (PSV: 85.1 ± 19.7 vs. 74.4 ± 19.7 cm/s, $p < 0.0001$; MV: 56.5 ± 11.8 vs. 50.2 ± 12.3 cm/s, $p < 0.0001$), (Fig. 2a, b). The percent increase in measured PSV was 16 ± 9 % (6–33), and the

Table 1 Peak systolic velocity (PSV) and mean velocity (MV) measured at different recording phases

Patient (no.)	PSV (cm/s)				MV (cm/s)			
	<i>R1</i>	<i>R2</i>	<i>R3</i>	<i>R4</i>	<i>R1</i>	<i>R2</i>	<i>R3</i>	<i>R4</i>
1	56	65	54	54	39	44	37	38
2	85	96	87	82	55	61	56	53
3	70	75	70	70	47	50	47	47
4	112	125	110	106	70	77	65	67
5	84	102	85	84	57	67	58	57
6	46	61	48	45	30	40	32	30
7	81	89	80	82	57	62	54	58
8	53	69	54	52	36	46	37	37
9	72	76	71	73	50	52	49	51
10	85	93	84	86	61	66	59	60
Mean value	74.4	85.1	74.3	73.4	50.2	56.5	49.4	49.8
SD	19.4	19.7	18.9	18.7	12.3	11.8	11.0	11.7

R1 baseline Doppler signal

R2 UCA infusion with no gain adjustment

R3 UCA infusion with gain adjustment

R4 Doppler signal after wash-out phase

percent increase in measured MV was 14 ± 10 % (4–33) (Table 2). BFV measured during UCA infusion with gain reduction (*R3*) was not significantly higher than baseline BFV (PSV: 74.3 ± 18.9 vs. 74.4 ± 19.4 cm/s, $p = 0.8$; MV: 49.4 ± 11.0 vs. 50.2 ± 12.3 cm/s, $p = 0.8$), (Table 1; Fig. 2c). Relative reduction in Doppler gain is shown in Table 2. Mean DSI at baseline was 13 ± 1 , 25 ± 4 dB at *R2*, and 13 ± 1 dB at *R3* (Table 2). Mean wash-out time was 7.8 ± 3.4 min. No artefact hindering velocity measurement was noted during the recordings.

Fig. 2 Doppler signal at different recording phases
a $R1$ = Baseline
 PSV = 53 cm/s, **b** $R2$ = UCA
 infusion with no gain reduction
 PSV = 69 cm/s, **c** $R3$ = UCA
 infusion with gain reduction
 PSV = 54 cm/s

Discussion

To the best of our knowledge, this is the first transcranial ultrasonographic study which has investigated the effect of

continuous UCA infusion on measured PSV in a clinical setting. Earlier studies showed that UCA bolus injection can cause a 20–24 % increase in measured PSV [4, 5], and were not able to compensate for this change in measured

Table 2 Peak systolic velocity (PSV) and mean velocity (MV) percent variations and relative gain reduction during the different recording phases

Patient (no.)	PSV (cm/s)		MV (cm/s)		Reduction in Doppler gain dB ^c	Doppler intensity dB		
	R2	R3	R2	R3		R1	R2	R3
	vs.	vs.	vs.	vs.				
	RI ^a	RI ^b	RI ^a	RI ^b				
	(%)	(%)	(%)	(%)				
1	16	−4	13	−5	13	12	24	12
2	13	2	11	2	8	15	24	12
3	7	0	6	0	11	14	20	14
4	12	−2	10	−7	11	12	23	11
5	21	1	18	2	25	13	26	13
6	33	4	33	7	12	12	34	12
7	10	−1	9	−5	13	13	17	13
8	30	2	28	3	10	12	27	13
9	6	−1	4	−2	13	14	26	13
10	9	−1	8	−3	13	13	25	12
Mean value	16	0	14	−1	13	13	25	13
SD	9	2	10	4	5	1	4	1

RI baseline

R2 UCA infusion with no gain adjustment

R3 UCA infusion with gain adjustment

^a $[(R2/RI) - 1] \times 100$

^b $[(R3/RI) - 1] \times 100$

^c dB difference = $20 \times \text{Log}(\text{Gain}R1/\text{Gain}R3)$

PSV. This study shows that continuous UCA infusion increases measured PSV and MV, and that gain reduction may counteract the effect of UCA on measured BFV. UCA enhance the returned Doppler signal, and increase the signal-to-noise ratio [3]. There is no agreement on possible mechanisms by which UCA increase measured BFV, and several hypotheses have been proposed [6, 7]. First, the increase in measured BFV may be due to an increase in cardiac output induced by UCA. However, one animal study has shown that UCA lead to an increase in BFV without increasing the actual blood flow [8], and there is no clinical evidence that UCA have effects on heart rate or blood pressure [9]. Second, UCA may falsify the frequency of the back-scattered signal due to the different intrinsic properties of microbubbles compared with red blood cells (RBC). It is assumed that microbubbles move at the same velocity as the RBC [10], but in vitro studies [11, 12] have shown that acoustic radiation force may displace microbubbles in the ultrasound (US) wave propagation direction and that this can produce spectral broadening [12]. In vivo, however, this phenomenon is significantly reduced due to blood viscosity and low US intensity used for safety reason [13, 14]. Another characteristic of microbubbles is their

rupture induced by the insonation [15]. In vitro experiments have shown that a rupturing bubble leads to spectral broadening [13]. Although the effect of this phenomenon in vivo may be not as evident as in vitro [13], spectral broadening may represent the mechanism behind the UCA-related increase in measured BVF [8]. Third, UCA may lead to an increase in measured BFV by disclosing RBC which move at the highest velocity [6]. This flow lamina is represented by few RBC and thus hidden by background noise. UCA add scatterers moving at the highest velocity and may therefore disclose areas of the blood flow spectrum previously not measurable. This “disclosed high velocity lamina” may be suppressed by gain reduction restoring baseline DSI. This hypothesis is also supported by in vivo studies showing that UCA lead to increase in measured BFV only in deeply located vessels [16], but not in superficial vessels [17], suggesting that if optimal DSI is obtained, a further increase in the signal-to-noise ratio does not modify BFV, since the highest velocity lamina is already disclosed. This study does not answer the question about the mechanism behind the UCA-related increase in BFV. Several factors probably influence the measured BFV, e.g. type of contrast agent, degree of spectral broadening, gain settings and type and limitations of the maximum velocity estimator in addition to possible fluid dynamic effects of the contrast. In vitro experiments have shown that the increase in BFV can be caused by a combination of signal enhancement, limited frequency resolution and how velocity is read [18]. The results in this study are therefore valid only for the equipment and settings that are used. A study comparing different devices and settings should be carried out. Earlier clinical studies were not able to confirm that gain reduction may counteract the effect of UCA on BFV [4, 5], as previously suggested by an in vitro study [6]. The reason for this failure may be referable to the UCA administration method, i.e. bolus injection, used in those studies. UCA bolus provides a rapid signal enhancement followed by a short peak and decay after a few minutes, causing variations in the DSI and, hence, in the measured PSV [4]. Several gain adjustments are therefore required to keep a stable signal enhancement after UCA bolus injection. Continuous UCA infusion provides prolonged and uniform enhancement of DSI, avoids saturation artefacts [19], and requires only one gain reduction. Since TCD machines used in clinical practice are usually not equipped with software providing online quantitative DSI evaluation (dB), this was qualitatively evaluated by neurosonographers based on the Doppler spectrum intensity under each examination, and measurement of actual DSI was possible only offline after export of ultrasound raw data. Although a qualitative approach is subjective and therefore prone to error, the excellent agreement between offline estimation of DSI at baseline (RI) and during UCA

infusion with gain reduction (*R3*) suggests that qualitative evaluation of DSI is reliable.

Conclusion

This study shows that continuous UCA infusion leads to an increase in measured BFV, which may be counteracted by reducing Doppler gain thus restoring pre-contrast.

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Conflict of interest N. Logallo, A. Fromm, U. Waje-Andreassen, L. Thomassen and K. Matre declare that they have no conflict of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). All patients provided written informed consent to enrolment in the study and to inclusion in this article of information that could potentially lead to their identification.

Human and animal studies The study was conducted in accordance with all institutional and national guidelines for the care and use of laboratory animals.

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