Effects of carbogen breathing on tissue oxygenation and perfusion in head and neck tumors as measured by MRI

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Introduction

Recent studies have shown that treatment response in advanced head and neck tumors can be improved by accelerated radiotherapy with carbogen and nicotinamide (ARCON) [1]. Breathing carbogen can induce both increased tissue oxygenation and blood flow [2]. Insight in these conditions may be provided by MRI measurement of susceptibility (T2*) and Gadolinium (Gd) contrast enhancement respectively. For instance, in subcutaneous tumors in animals during carbogen breathing usually a signal increase is observed on T2* weighted images [2,3], whereas Gd uptake may be reduced under these conditions [4]. In this study measurements of T2* and Gd uptake were combined to investigate the effect of carbogen breathing on tumor oxygenation and tumor perfusion.

Patients and Methods

MR imaging was performed on a 1.5 T Siemens Vision system. Ten patients (5 hypopharynx carcinoma; 5 larynx carcinoma) were each studied twice, with and without carbogen breathing (2% CO_2; 98% O_2). In the first session Gd-DTPA was administered by intravenous bolus injection (0.5 mM, 2.5 ml/s) and tissue uptake of the contrast medium was monitored with a temporal resolution of 2 seconds (FLASH, TR=50 ms, TE=4.4 ms, 7 mm slice) for 90 seconds. In the second session T2* weighted images (16 echo FLASH, TR=65 ms, TE=6-51 ms, 5 mm slice) were recorded for 14 minutes whilst breathing air. Then carbogen breathing was started and the same images were recorded for another 6 minutes, followed by Gd contrast enhanced imaging as in the first session.

From the T2* weighted imaging data values of T2* (ms) and R2* (R2*=1/T2*) were calculated.

The dynamic Gd contrast image data was combined with PD weighted images to calculate Gd concentration (a.u.) [5] and analyzed using the compartmental model of Larsson [6]. The arterial input function was obtained from pixels in the internal carotid artery and the vertebral artery. The rate constant of Gd uptake k_{ep} (s^{-1}) [7] was calculated on a pixel-by-pixel basis. The k_{ep} values of pixels in Gd enhancing tumor regions were averaged to obtain the mean k_{ep} of the tumor.

Results and Discussion

The values of k_{ep} and T2* during air breathing and the changes in these parameters due to carbogen breathing are listed in tables 1 and 2 for all patients.

In none of the patients a statistically significant difference in k_{ep} was found between air breathing and carbogen breathing (Student's t-test, $p<0.05$). Also, the average change in k_{ep} of all tumors (1.3% ± 9%) was not significant. Although the rate constant k_{ep} is dependent on several physiological parameters (e.g. perfusion, vascular permeability), no changes in perfusion are assumed to be present when no changes in the value of k_{ep} are observed. However, since this kind of tumor seems to be well perfused, Gd uptake may be mainly permeability-limited and possible perfusion effects may induce only small changes in the value of k_{ep}.

The values of T2* during air breathing as shown in table 2 correspond well to previously reported measurements of T2* [8]. All patients showed a carbogen-induced increase in T2* which was statistically significant in 7 of 10 patients (Student's t-test, $p<0.05$). The average T2* of all tumors was 33.9 ms (± 3.8 ms) and 35.8 ms (± 4.1 ms) whilst breathing air and breathing carbogen respectively. This increase of T2* was shown to be significant (ANOVA, split plot design; $p<0.05$) and may account for the signal increase observed in T2* weighted imaging [2,3]. As the value of T2* reflects the oxygenation status of haemoglobin, the T2* increase can be interpreted as an improved tissue oxygenation.

Conclusion

In conclusion, the results show that breathing carbogen improves the oxygenation status of head and neck tumors. No carbogen-induced perfusion changes were detected by Gd contrast enhanced MR imaging.

References

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Table 1. Mean values of k_{ep} (s^{-1}) of the tumor during air breathing for all patients. Changes in k_{ep} due to carbogen breathing are expressed as Δ: carbogen - air. N.S.: not significant.

	k_{ep} (air) (s^{-1})	Δk_{ep} (%)	
1	0.039 ± 0.011	-7.7 ± 4.2	N.S.
2	0.050 ± 0.022	6.0 ± 6.1	N.S.
3	0.047 ± 0.015	12.8 ± 11.0	N.S.
4	0.022 ± 0.010	4.5 ± 8.3	N.S.
5	0.021 ± 0.012	-14.3 ± 8.2	N.S.
6	0.044 ± 0.015	-11.4 ± 6.6	N.S.
7	0.024 ± 0.009	8.3 ± 6.6	N.S.
8	0.030 ± 0.007	6.7 ± 4.5	N.S.
9	0.039 ± 0.017	-5.1 ± 7.1	N.S.
10	0.040 ± 0.043	10.0 ± 21.8	N.S.

Table 2. Mean values of T2* (ms) of the tumor during air breathing for all patients. Changes in T2* due to carbogen breathing are expressed as Δ: carbogen - air. N.S.: not significant; *: p<0.05; **: p<0.01.

	T2* (air) (ms)	ΔT2* (%)	
1	29.1 ± 1.8	8.2 ± 2.8	*
2	31.2 ± 2.0	0.6 ± 2.6	N.S.
3	32.5 ± 2.8	6.9 ± 3.4	N.S.
4	26.9 ± 0.9	7.5 ± 1.9	**
5	37.3 ± 1.5	5.9 ± 1.1	**
6	38.2 ± 1.1	6.1 ± 1.6	**
7	31.1 ± 2.1	5.9 ± 1.9	*
8	36.6 ± 2.6	7.9 ± 3.5	*
9	37.2 ± 1.3	3.1 ± 1.3	*
10	34.2 ± 2.7	7.4 ± 6.7	N.S.