

## Dynamic contrast-enhanced MR imaging of the stimulated pituitary gland

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Received 3 September 2003; revised 9 December 2003; accepted 5 January 2004

**Apoplexy due to infarction and/or hemorrhage is a frequent complication of pituitary adenoma, occurring either spontaneously or precipitated by several factors, among them pituitary function test with hypothalamic releasing hormones. The mechanism by which releasing hormones cause pituitary apoplexy is unclear. It has been proposed that increase in pituitary size and/or alterations in blood flow could be responsible. The aim of this study was to explore the effects of intravenous administration of hypothalamic releasing hormones on pituitary size and hemodynamics in healthy subjects. Gadolinium-DTPA-enhanced dynamic magnetic resonance imaging (MRI) was performed in eight healthy volunteers under basal conditions and 20 min after injection of releasing hormones. Mean upslopes of Gadolinium-DTPA enhancement curves showed good correlation between basal and stimulated conditions ( $R = 0.89$ ) and were significantly steeper after stimulation ( $P = 0.017$ ). In contrast, pituitary height, width and length did not differ significantly between basal and stimulated conditions. In conclusion, the pituitary does not swell in healthy subjects in response to stimulation with hypothalamic releasing hormones, whereas transfer of contrast agent to tissue (blood flow and/or vessel permeability) is enhanced.**

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*Keywords:* Apoplexy; Gadolinium; Pituitary adenoma

### Introduction

Pituitary apoplexy is a clinical syndrome characterized by sudden headache, visual impairment and hormonal dysfunction due to infarction and/or hemorrhage of a pituitary adenoma (Cardoso and Peterson, 1984; Randeve et al., 1999). The outcome is often permanent pituitary insufficiency requiring hormone replacement therapy (Lamberts et al., 1998; Vance, 1994). Hemorrhage is a frequent complication of pituitary adenomas, reported to occur in up to 10% of adenomas (Fraoli et al., 1990). Apoplexy may be the first sign of pituitary adenoma and in most

cases occurs spontaneously (Bills et al., 1993). However, several predisposing factors have been described, including pituitary function tests with hypothalamic releasing hormones (e.g., Drury et al., 1982; Masago et al., 1995; Riedl et al., 2000; Rotman-Pikielny et al., 2003).

Since pituitary apoplexy after combined pituitary stimulation has only been reported in patients with macroadenomas so far, it has been proposed that the stimulation could cause an increase in pituitary volume which in turn would lead to infarction due to the limited space in the rigid walls of the sella (Riedl et al., 2000).

Dynamic contrast-enhanced magnetic resonance imaging (MRI) using exogenous contrast agents like Gadolinium-DTPA is a non-invasive tool for studying functional parameters. Pituitary enhancement patterns have been studied mainly during and immediately after the first pass of Gadolinium-DTPA (Bartynski and Lin, 1997; Kanou et al., 2002; Miki et al., 1990; Tabarin et al., 1998; Yuh et al., 1994). The main information provided by the contrast agent enhancement curve is tissue vascularization and perfusion. It is also influenced by capillary permeability and the volume of interstitial space (Roberts, 1997). Dynamic Gadolinium-DTPA-enhanced MRI imaging is widely used in the diagnosis of pituitary adenomas (Patronas et al., 2003) and is especially useful for detection of microlesions (Bartynski and Lin, 1997; Patronas et al., 2003). The normal pituitary gland typically enhances within the first 1–2 min after contrast injection. The enhancement pattern is consistent with the vasculature architecture of the pituitary with the posterior lobe enhancing earlier than the anterior lobe (Sakamoto et al., 1991; Yuh et al., 1994). Delayed enhancement is found in patients with arteriovenous fistulas in the cavernous sinus (Shigematsu et al., 2003) and hypopituitarism (Sato et al., 1998).

The size of the pituitary has been studied in healthy subjects using MRI and CT measurements and is reported to be 4–7 mm (height), 10–15 mm (width) and 7–11 mm (length) (see Kato et al., 2002 and references therein). Different formulas have been used for calculating pituitary volume of the three parameters, but none seemed to be superior. Overall, pituitary height has been proposed as the best single surrogate parameter of pituitary size (Lurie et al., 1990). Height is maximal in young adults (Kato et al., 2002; Lurie et al., 1990) and changes with chronic functional alterations. For example, pituitary height has been shown to

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correlate with gestational age during pregnancy (Dinc et al., 1998; Elster et al., 1991).

Acute changes of the pituitary gland in different activity states have not been studied *in vivo*, and it is not known if and how the pituitary gland is altered upon activation. The goal of this study on young healthy volunteers was the comparison of pituitary size and Gadolinium-DTPA enhancement patterns under basal conditions and after stimulation with hypothalamic-releasing hormones.

## Methods

### Subjects

Ten young (aged  $27.3 \pm 5.6$  years), healthy subjects (5 male, 5 female) with a body mass index of  $22.7 \pm 3.6$  were included in the study. Mean blood pressure was  $117 \pm 11/75 \pm 8$ . None of the volunteers had a history of metabolic, gastrointestinal, liver or kidney disease or did take any medication (including hormonal contraception). Routine blood chemistry, peripheral blood count and basal hormone levels were normal. The study was approved by the local institutional review board, and written informed consent was obtained from all subjects.

Two of the subjects (one male, one female) had abnormal findings in the basal MRI scan (pituitary microadenoma and pituitary hypertrophy) on study day 1 and were excluded from further analysis.

### Study protocol

For each subject, 2 study days were scheduled with intervals of 7 days. On both study days subjects arrived between 7.30 a.m. and noon after an overnight fast. An intravenous cannula was placed in an antecubital vein on both study days for Gadolinium-DTPA injection and collection of blood samples, and for intravenous injection of releasing hormones on study day 2.

On study day 1, MRI scans were performed under basal conditions.

On study day 2, MRI scans were performed 20 min after intravenous injection of hypothalamic releasing hormones—the time point when the pituitary would be expected to be most active as judged by peak concentrations of most pituitary hormones. TSH, ACTH and GH reach their peak values in the circulation after 20–30 min, Prolactin earlier (10–20 min) and FSH and LH later (30–45 min) (Cohen et al., 1986).

### Stimulation tests

On study day 2, a combined pituitary stimulation test was performed with intravenous injection of hypothalamic releasing hormones (corticotropin-releasing hormone, CRH, 100  $\mu$ g; thyrotropin-releasing hormone, TRH, 200  $\mu$ g; growth hormone-releasing hormone, GHRH, 100  $\mu$ g; gonadotropin-releasing hormone, GnRH, 100  $\mu$ g; CRH and GHRH: Ferring Pharmaceuticals, Berlin, Germany, TRH and GnRH: Aventis, Frankfurt, Germany).

Blood samples for determination of ACTH, cortisol, TSH, GH, LH, FSH and prolactin were drawn before (basal) and 10 min (before start of MRI), 45 min (after MRI) and 60 min after injection of hypothalamic releasing hormones.

### Hormone assays

Hormone levels were determined with commercially available assays and analyzed on automated immunoassay-analyzers. LH, FSH, TSH and prolactin were assayed with an Elecsys 2010<sup>®</sup> (Roche-Diagnostica, Germany), cortisol and GH with Auto-DELFIA<sup>®</sup> (Wallc Oy, Finland) and ACTH with an Advantage<sup>®</sup>-System. Day to day imprecision of analyses was determined by Lyphocheck three level control material (Bio-Rad, USA), except for ACTH, for which Nichols three level controls (Nichols Institute Diagnostics, USA) were used. The coefficients of variation were 4–5% (LH), 2–3% (FSH), 4% (prolactin), 3–4% (TSH), 3% (GH), 3–5% (cortisol) and 3–9% (ACTH).

### MRI

MR-examinations of the pituitary were performed on a 1.5 T MR unit (Siemens Vision, Siemens, Erlangen, Germany) with a gradient strength of 23 mT/m. Using a circularly polarized head coil three localizer sequences in axial, coronal and sagittal plane were obtained to provide reproducible imaging planes for the second intraindividual examination. Based on this localizer sequences, the pituitary was examined on the coronal plane pre- and postcontrast and in the sagittal plane postcontrast. The following sequences were applied: a standard T1-weighted spin echo (SE) sequence (TR/TE: 450/14 ms) before and after intravenous administration of a double dose (0.2 mmol/kg body weight) of gadolinium-DTPA (Magnevist, Schering, Berlin, Germany). The field of view (FOV) was  $173 \times 230$  mm, the matrix size  $284 \times 512$ , the slice thickness was 2 mm and 2 acquisitions were collected. Immediately after i.v. administration of gadolinium-DTPA, a dynamic contrast study was performed using a standard T1-weighted 2D Gradient-echo (GRE) sequence (TR/TE/Flip angle: 30/4 ms/30°). Three coronal slices best covering the pituitary were selected from the native study and the GE sequence was repeated every 20 s over a total examination time of 3 min. From these data, a time vs. signal intensity curve was constructed using the scanner software.

### Matching of MRI scans and pituitary size measures

For the second MR examination in each volunteer the selection of the same coronal and sagittal slices was performed by three localizer sequences and anatomical landmarks. Based on these images, maximal height and width (from coronal planes) and length (from sagittal planes) of the pituitary were measured using a workstation (Magic View Siemens). Measuring was performed by a single radiologist (S.T.) blinded to the study days of the images. An example for midlevel slices used for measurements is given in Fig. 1.

### Gadolinium-DTPA enhancement curves

Each time vs. signal intensity curve generated by the scanner software was converted into the related enhancement curve according to the equation

$$y(t) = (S_t - S_0)/S_0 \times 100\%$$

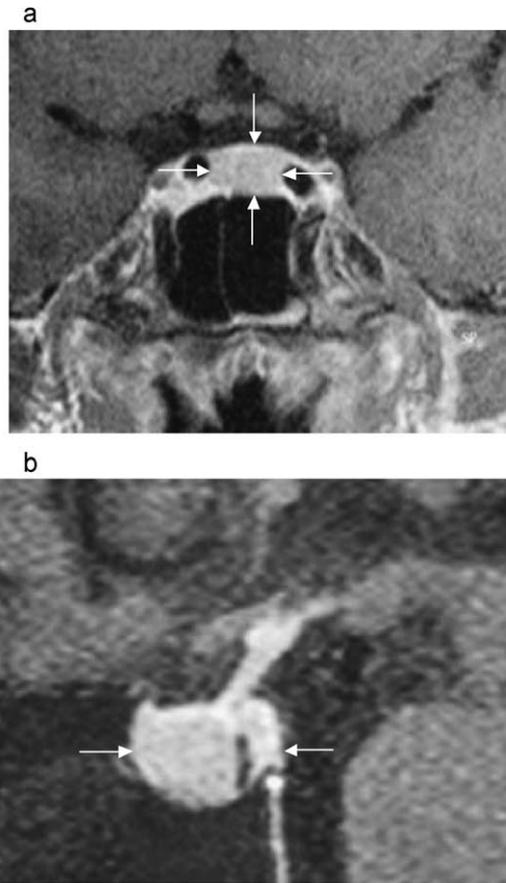


Fig. 1. T1-weighted midlevel slices of pituitary MRI in (a) coronal plane and (b) sagittal plane. Arrows indicate maximal width and height (a) and length (b).

where  $y(t)$  is enhancement at time point  $t$ ,  $S_0$  the signal intensity of the first time point (baseline) and  $S_t$  are signal intensities taken from subsequent images acquired every 20 s.

Data evaluation

Since in this small sample no normal distribution could be assumed, data are given as median  $\pm$  semi-interquartile range (SIR) unless stated otherwise and non-parametric tests were used for statistical evaluation. Statistical evaluation was performed using a commercially available software package (Statview, Abacus).

For basal and stimulated pituitary height, width and length, and the product of the three values (as a surrogate parameter for pituitary volume) linear regression analysis was performed to determine the accuracy of selection of matching MRI slices.

Basal and stimulated values of pituitary measures and basal and peak hormone levels were compared using Wilcoxon’s signed rank test.

For each enhancement curve peak value ( $y_{max}$ ) and peak time (time to reach the peak,  $t_{max}$ ) were determined (Fig. 2). Mean upslopes  $k$  were calculated for all enhancement curves according to the equation:

$$K = y_{max}/t_{max}$$

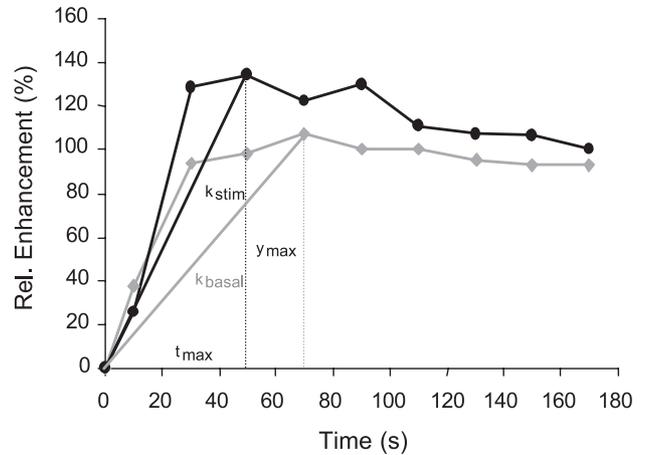


Fig. 2. Example of individual enhancement curves in basal (◆) and stimulated (●) conditions with peak values ( $y_{max}$ ), peak times ( $t_{max}$ ) and mean upslopes under basal ( $k_{basal}$ ) and stimulated ( $k_{stim}$ ) conditions.

The obtained basal and stimulated values were compared using linear regression analysis and Wilcoxon’s signed rank test.  $P < 0.05$  was considered statistically significant.

Results

Stimulation tests

An overview of basal and peak hormone concentrations is shown in Table 1. In each individual, pituitary hormones rose after injection of hypothalamic releasing hormones, and differences between basal and peak values were significant for all hormones (not shown).

Pituitary size

Mean values for pituitary height, length and width, and the product of the three parameters (as a surrogate for pituitary volume) are given in Table 2. Pituitary height was  $<0.9$  cm for all subjects in both basal and stimulated conditions.

Table 1  
Basal and peak hormone concentrations

Hormone	Units	Basal	Peak	Time point of peak values (min)
ACTH	Pg/ml	29.50 $\pm$ 6.25	51.00 $\pm$ 11.25	45
Cortisol	$\mu$ g/dl	14.80 $\pm$ 4.13	18.65 $\pm$ 2.20	60
TSH	$\mu$ U/ml	1.35 $\pm$ 0.34	12.45 $\pm$ 1.30	45
GH	ng/ml	0.40 $\pm$ 1.60	10.60 $\pm$ 2.50	45
FSH	mU/ml	4.25 $\pm$ 1.08	7.10 $\pm$ 2.23	60
LH	mU/ml	5.45 $\pm$ 3.00	26.20 $\pm$ 11.50	45
Prolactin	ng/ml	16.75 $\pm$ 6.38	100.20 $\pm$ 56.00	10

Hormone Concentrations of eight healthy subjects after combined pituitary stimulation test with hypothalamic releasing hormones. Data are given as median  $\pm$  SIR. ACTH, Corticotropin; TSH, Thyrotropin; GH, Growth hormone; FSH, Follicle-stimulating hormone; LH, Luteinizing hormone.

Table 2  
Pituitary measures

Parameter	Basal	Stimulated	NR ↑/↓/–	P (diff)	R <sup>2</sup>
Height	6.30	6.55	5/2/1	0.11	0.965
Width	13.75	13.93	4/3/1	0.20	0.943
Length	10.29	9.99	3/4/1	0.67	0.604
Product	931	939	6/2/0	0.40	0.941

Mean pituitary measures (in mm) and their product (in mm<sup>3</sup>, as a surrogate parameter for volume) of matched MRI scans for eight healthy subjects at baseline and 20 min after stimulation with hypothalamic releasing hormones. The number of measures increasing (↑), decreasing (↓) or remaining the same (–) after stimulation are given for each parameter. Goodness-of-fit (R<sup>2</sup>) and P (diff) refer to comparison of basal vs. stimulated values.

None of the measured parameters was significantly different in the stimulated vs. basal pituitary, nor was the product of the three parameters. Changes in measures were inconsistent throughout the subjects. On the other hand, linear regression analysis revealed R<sup>2</sup> values > 0.9 for three of the four parameters reflecting excellent goodness of fit (i.e., matching of MRI sections).

An overview of the changes in measures and results of statistical analysis are given in Table 2 (although non-parametric statistical evaluation is used, data are presented as means for the sake of comparability).

Individual changes in pituitary size parameters are presented in Figs. 3a–d.

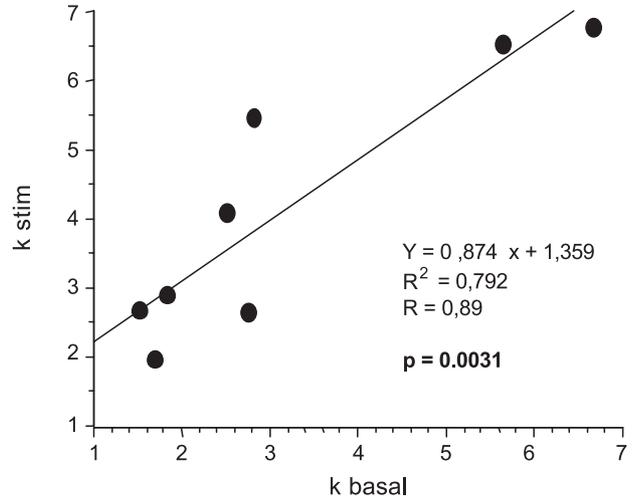


Fig. 4. Linear regression model of mean upslopes under basal ( $k_{\text{basal}}$ ) and stimulated ( $k_{\text{stim}}$ ) conditions in eight healthy volunteers.

Gadolinium-DTPA enhancement

An example for individual basal and stimulated Gadolinium-DTPA enhancement curves is given in Fig. 2.

Peak values were  $124 \pm 43$  and  $130 \pm 71$ , respectively ( $R^2 = 0.852$ ,  $P = 0.001$ ). They were reached after  $47.5 \pm 15$  (basal) and

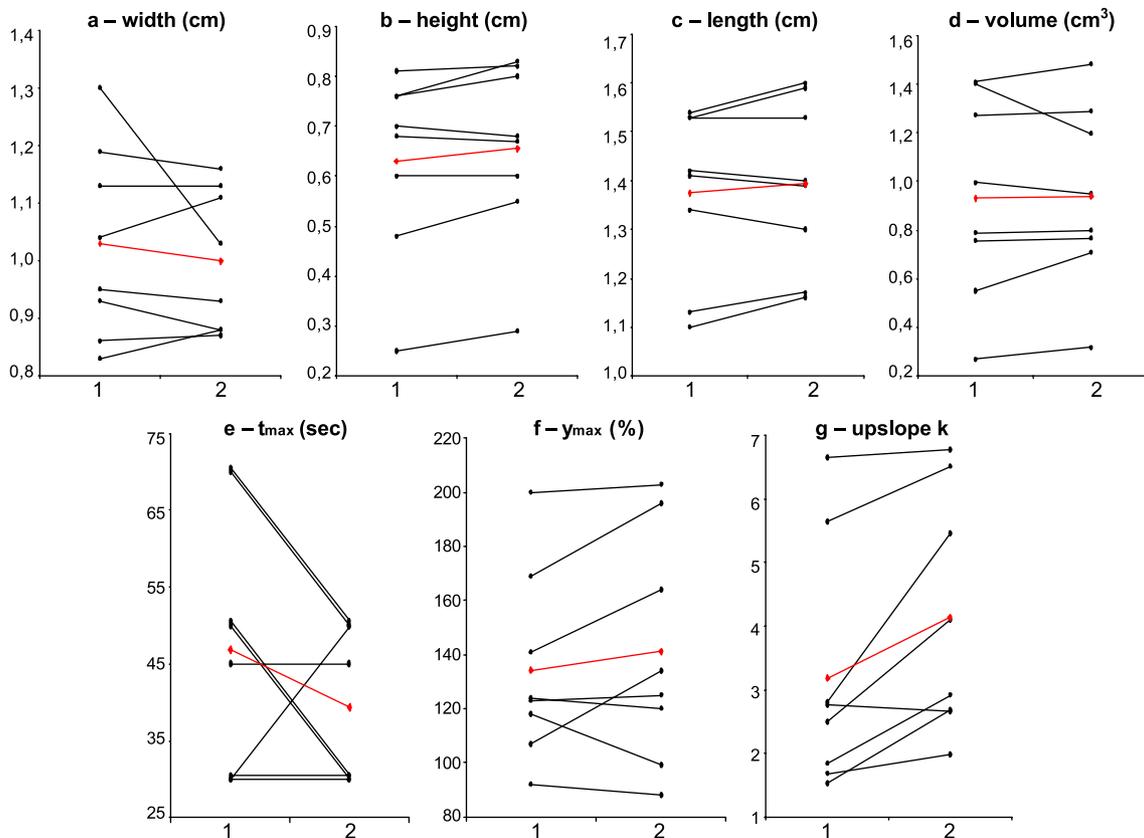


Fig. 3. Differences between pituitary size (a–d) and enhancement (e–g) values in eight individual subjects (black) and means (red) under basal conditions (1) and after stimulation (2). a, width; b, height; c, length; d, volume (width × height × length); e, peak time  $t_{\text{max}}$ ; f, peak value  $y_{\text{max}}$ ; g upslope k.

$37.5 \pm 10$  s (stimulated), respectively ( $R^2 = 0.223$ ,  $P = 0.24$ ).  $P$  values for the differences were not significant for both parameters.

Mean upslopes  $k$  were significantly steeper in stimulated than in basal conditions ( $3.51 \pm 1.66$  vs.  $2.63 \pm 1.24$ ,  $P = 0.017$ ). The individual upslopes showed large variations, but correlation between  $k_{\text{basal}}$  and  $k_{\text{stim}}$  was high with the resulting equation  $k_{\text{stim}} = 0.87 \times k_{\text{basal}} + 1.36$  ( $R = 0.89$ ,  $P = 0.003$ , Fig. 4).

Individual changes of the three parameters are given in Figs. 3e–g.

## Discussion

Two out of 10 young, apparently healthy adults turned out to have abnormal results on pituitary MRI scan and had to be excluded from the study. This finding in itself is remarkable and confirms the high frequency of pituitary pathologies in the general population (Burrow et al., 1981; Hall et al., 1994).

It has been hypothesized that swelling of the pituitary gland triggers pituitary apoplexy after combined stimulation test with hypothalamic releasing hormones. Surprisingly, hypothalamic-releasing hormones did not lead to a statistically significant increase of pituitary size in the eight young healthy individuals in this study (Figs. 3a–d). Pituitary height, which has been proposed as the best single surrogate parameter for pituitary volume (Lurie et al., 1990), did increase in five of the eight subjects studied and decreased in two. Mean values differed by only 0.25 mm; certainly not enough to explain the precipitation of apoplexy by stimulation with hypothalamic hormones. We also used pituitary length and width and the product of the three parameters as measures of pituitary size with similar results. Observed changes were only small and inconsistent, although the matching procedure was accurate and the reproducibility of MRI scans was high, as shown by the high  $R^2$  (goodness-of-fit) values in linear regression analysis (Table 2). The only parameter that gave an unsatisfying  $R^2$  value was pituitary length, which was taken from sagittal images, whereas the other two parameters were taken from coronal images. All values were in the range reported (Kato et al., 2002 and references therein).

In contrast, Gadolinium-DTPA enhancement in the pituitary was altered significantly after injection of hypothalamic releasing hormones. In particular, mean upslopes of the enhancement curves were significantly steeper in stimulated than in unstimulated pituitary glands (Fig. 3g); thus, transfer of contrast agent to pituitary tissue is higher indicating increased blood flow and/or vessel permeability after stimulation with hypothalamic releasing hormones.

While no major hemodynamic effects of GHRH or GnRH have been reported TRH (Kondoh et al., 1989) and CRH (Grunt et al., 1993; Gutkowska et al., 2000) influence the systemic circulation. It has been shown that the endothelium-derived relaxant factor nitric oxide (NO) is involved in the vasodilatory effects of CRH (Gutkowska et al., 2000) and that NO is involved in hypothalamic (Prevot, 2002) and pituitary hormone release and blood flow (Duvilanski et al., 1995). The results reported here are the first indication of increased blood flow in pituitary portal vessels induced by hypothalamic releasing hormones.

Upslopes of Gadolinium-DTPA enhancement curves have been used successfully to characterize myocardial perfusion in rest and after adenosine challenge (Nagel et al., 2003; Panting et al., 2002). Although they cannot provide absolute values of blood flow mean upslopes are linearly related to perfusion data derived from

microsphere measurements (Klocke et al., 2001). In our small sample, individual upslopes of pituitary perfusion varied considerably (Fig. 3g) but the correlation of basal and stimulated upslopes was high (Fig. 4) and mean upslopes differed significantly ( $P = 0.017$ ). The absolute values (peak times and peak values) were less conclusive (Figs. 3e, f). It is possible that true peak times and values were missed despite the high temporal resolution of 20 s, which is in the range of most published dynamic MRI studies of the pituitary. In this study, a standard  $T_1$ -weighted 2D gradient-echo sequence has been used to acquire the enhancement curve. The high temporal resolution was achieved by selecting three coronal slices covering the pituitary gland from a native series. This approach would be practicable for routine clinical use.

Adenomas are thought to receive additional arterial blood supply (Yuh et al., 1994) which would certainly alter hemodynamics. Pituitary adenomas have shown maximum enhancement earlier (Miki et al., 1990; Sakamoto et al., 1991) and later (Bonneville et al., 1993; Finelli and Kaufman, 1993) than the normal pituitary tissue. In a recent dynamic MRI study (Kanou et al., 2002), the majority of pituitary adenomas reached peak enhancement earlier than or simultaneously with the normal pituitary glands, whereas microadenomas tended to have later enhancement patterns. The clinical significance of our study cannot not be tested in patients with pituitary macroadenomas due to their increased risk of pituitary apoplexy. However, it would be of interest to determine whether patients with microadenomas would react similarly to the administration of hypothalamic releasing hormones. This would challenge the hypothesis that changes in size are the underlying pathomechanism of pituitary apoplexy following pituitary stimulation tests.

In summary, different activity states of the pituitary gland were studied for the first time by contrast-enhanced dynamic MRI with high reproducibility. It is shown that pituitary glands of healthy subjects do not increase in size in response to intravenous administration of hypothalamic releasing hormones, whereas pituitary blood flow and/or vessel permeability is increased upon stimulation.

## Uncited reference

Holness et al., 1983

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