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Sequential MR Enhancement Pattern in Normal Pituitary Gland and in Pituitary Adenoma

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PURPOSE: To measure and evaluate the temporal enhancement characteristics of the normal pituitary gland and pituitary adenoma. METHODS: Thirty healthy subjects and 10 patients with sellar pituitary adenomas were studied prospectively using dynamic MR imaging with a 5- or 10-sec temporal resolution during a bolus injection of gadolinium. RESULTS: Qualitative visual analysis demonstrated a consistent sequential pattern of pituitary enhancement in which the posterior lobe enhanced earlier than the anterior lobe by approximately 35 sec. Quantitative analysis revealed that posterior lobe enhancement occurred 9.8 ± 1.5 sec (mean ± SEM) before the anterior lobe in healthy subjects, whereas tumor enhancement occurred significantly before the anterior lobe but only slightly before the posterior lobe in patients with adenomas. CONCLUSION: The sequential enhancement pattern of the normal pituitary gland was found to be consistent with its vascular anatomy. In contrast to previous reports, pituitary adenomas were found to enhance earlier than the anterior lobe. These results suggest that pituitary adenomas have a direct arterial blood supply, similar to that of the posterior pituitary lobe.

Index terms: Pituitary gland, magnetic resonance; Pituitary gland, neoplasms; Adenoma; Magnetic resonance, contrast enhancement


Temporal enhancement patterns of the normal pituitary gland and pituitary adenomas have been studied previously with magnetic resonance (MR) image-acquisition-time intervals between 14 and 60 sec (1, 2). Using 60-sec image-acquisition-time intervals and visual analysis, Miki et al (1) noted that the normal pituitary gland enhances maximally on the first or second image (60–120 sec) after contrast administration, whereas pituitary adenomas enhance maximally in later images. In two recent studies that analyzed a limited number of patients using region of interest (ROI) analysis techniques and shorter image-acquisition times, the posterior lobe was found to enhance 14 sec (2) or 30 sec (3) before the anterior lobe. In each of these studies, however, the time difference between the anterior and posterior lobes was equal to the image-acquisition time between successive images. These studies investigating the temporal pattern of pituitary enhancement were constrained by limited temporal resolution and the lack of a sensitive objective means to detect the onset of parenchymal enhancement.

The purpose of our work was to assess the pattern of enhancement in the normal pituitary gland and pituitary adenomas using an image-acquisition process with increased temporal resolution (5–10 sec) and an automated method of time-intensity curve analysis that allows relative enhancement time to be calculated quantitatively at fractional temporal resolutions.

Materials and Methods

Thirty healthy subjects and 10 patients with sellar pituitary adenomas (macroadenomas) were prospectively studied with dynamic-contrast MR. Dynamic-spoiled gradient-echo imaging with flow compensation (25/13/1–2 [repeti-
tion time/echo time/excitations]) (50° flip angle) was performed in a sagittal plane through the pituitary stalk with a 5- or 10-sec temporal resolution and 10-mm section thickness. Dynamic MR imaging was initiated 30 to 45 sec before a bolus injection of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) and continued for a total of 180 sec. Images were acquired using a 1.5-T imager (Signa, General Electric Medical Systems, Milwaukee, Wis). The bolus was delivered either by hand injection or with an MR-compatible power injector (Medrad, Pittsburgh, Pa) at a rate of 5 to 9 ml/sec. The images were reviewed visually and analyzed quantitatively.

**Qualitative Visual Analysis**

The enhancement sequence of various pituitary regions (posterior lobe, anterior lobe, and pituitary stalk) was assessed independently by two radiologists. Each investigator viewed the dynamic MR study as a cine loop at various speeds and noted the frames in which individual structures were best delineated. Using the differences in imaging frames, relative times of maximal enhancement for each structure were estimated.

**Quantitative Analysis**

Our quantitative analysis method estimated the relative time difference between two time-intensity curves using the following steps: 1) image transfer to a microcomputer; 2) ROI delineation; 3) generation of time-intensity curves; 4) expansion of the data set using interpolation; and 5) optimal fitting of one time-intensity curve to another using a three-variable unconstrained optimization technique.

Image analysis and quantification of the relative enhancement time between time-intensity curves was performed on a Macintosh IIfx microcomputer (Apple Computer, Cupertino, Calif). Dynamic study images were transferred from the MR imager to the microcomputer over an ethernet computer network. Time-intensity curves were generated for the posterior and anterior lobes of the pituitary as well as for the straight sinus and tumor using ROI analysis. These structures were traced manually in the image frame identified by the qualitative visual analysis as having optimal delineation of the anterior lobe, posterior lobe, stalk, and adenoma. The regions were then duplicated in all images in the series, and time-intensity curves were generated for each structure.

The relative enhancement time between two time-intensity curves was estimated using a three-parameter least-squares numerical optimization technique (Fig 1). The distance between the two curves (the cost function) was minimized with respect to three independent unconstrained variables, each applied to a single curve: 1) a constant amplitude offset; 2) a linear amplitude gain factor; and 3) a constant time offset. Curves were initially interpolated to twice the number of original data points using a four-point interpolation. Subsequent subframe increments were computed using a two-point linear interpolation. The Nelder-Mead simplex algorithm (4) was used to minimize the distance between the two curves with respect to the three design variables. The time-offset parameter at the point of minimum cost represents the relative time difference to enhancement between the two curves.

The time-difference analysis was applied to the following curve pairs: 1) anterior versus posterior lobes; 2) straight sinus versus anterior lobe; 3) straight sinus versus posterior lobe; and 4) straight sinus versus adenoma. The accuracy of our analysis was confirmed by comparing the directly measured relative time delay between anterior and posterior lobe enhancement with an indirect measure using the straight sinus as a baseline.
Results

Of the 30 healthy subjects studied, 20 were imaged using a 10-sec image-acquisition time, and 10 were imaged using a 5-sec acquisition time. A 5-sec acquisition time was used in eight of the 10 patients with pituitary adenomas.

Visual Analysis

Normal Subjects. Qualitative visual analysis of the pituitary gland in 30 healthy subjects revealed a consistent sequential pattern of enhancement in which the posterior lobe enhanced earlier than the anterior lobe by an average of 35 sec (Figs 2 and 3). In the two patients whose stalks were visualized throughout the entire dynamic study, the stalks were found to enhance 10 sec after the posterior lobes and 10 sec before the anterior lobes (Fig 2).

Patients with Sellar Adenomas. In the 10 patients with sellar pituitary macroadenomas, lobar anatomy was disrupted by the tumors. Thus, a comparison between the adenomas and the remaining normal pituitary lobes was not possible. Also, because bolus arrival time could not be accurately controlled, a quantitative comparison with healthy control subjects using an internal reference was necessary.

Quantitative Analysis

Our quantitative analysis method estimated relative-enhancement-time differences with respect to the midpoints of the time-intensity curves (Fig 1). The results are illustrated in Figure 4.

Normal Pituitary Gland. Relative-enhancement-time analysis of 30 subjects with normal pituitary glands demonstrated that posterior lobe enhancement occurred $9.8 \pm 1.5$ sec (mean $\pm$ SEM) before anterior lobe enhancement ($P < .0001$, paired, two-tailed, Student $t$ test) (Figs 2 and 3). In the subset of healthy subjects imaged using a 10-sec temporal resolution, the posterior
Fig. 3. Sequential enhancement of normal pituitary gland: visual analysis. Sagittal dynamic study of the pituitary was performed using spoiled-gradient-echo imaging (25/13) (50° flip angle) with 10-sec intervals between successive images.

A, Image obtained before the arrival of the gadolinium bolus shows a slightly hypointense oval-shaped pituitary gland (arrows). The linear structure within the pituitary gland may represent the partial volume of a blood vessel.

B, Image obtained 60 sec after image A shows initial enhancement of the posterior lobe (arrow) and absence of enhancement of the anterior lobe.

C, Image obtained 70 sec after image A shows evidence of anterior lobe (small arrows) and posterior lobe (large arrows) enhancement.

D, Image obtained 100 sec after image A shows homogeneous enhancement of the entire gland. The pituitary stalk is poorly visualized throughout the entire dynamic study.

lobe was found to enhance 11.7 ± 2.1 sec before anterior lobe enhancement (n = 20; P < .0001). In the two patients whose stalks were visualized throughout the entire examination, the onset of pituitary stalk enhancement was 3.7 sec after the posterior lobe and 7.4 sec before the anterior lobe.

Straight Sinus: Internal Reference. Both the posterior and anterior lobes were found to enhance after the straight sinus with a consistent time interval (11.0 ± 1.1 and 21.9 ± 1.5 sec, respectively) (Fig 4). Posterior-to-anterior lobe differences, when measured relative to the straight sinus, were consistent with the direct measures (10.6 ± 1.5 sec versus 9.8 ± 1.5 sec; paired comparison was not statistically significant). The time course of straight-sinus enhancement, therefore, may serve as a reliable internal reference when pituitary lobar anatomy cannot be confidently identified, such as in a large adenoma.

Fig. 4. Quantitative analysis. Mean relative-enhancement-time difference with respect to the straight sinus is plotted with 95% confidence intervals. The asterisk indicates that the anterior lobe of the pituitary enhances significantly later than either the posterior lobe or pituitary adenomas (Scheffé f test, significant at P < .001).
Sellar Adenomas. In 10 patients with pituitary adenomas, tumor enhancement occurred consistently 9.3 ± 1.5 sec after straight-sinus enhancement (Fig 5). A one-factor analysis of variance showed that tumor enhancement occurred significantly before anterior-lobe enhancement (12.0 sec, Scheffe f test significant at \( P < .001 \)) and slightly (1.1 sec) but not significantly before posterior lobe enhancement (Fig 4).

Discussion

By using a reduced image-acquisition time interval and a quantitative computer analysis technique, the temporal-enhancement patterns of the anterior and posterior lobes of the normal pituitary glands were found to be consistent with the anatomic and physiologic constraints of the pituitary blood supply (5-7). The posterior lobe and part of the pituitary stalk have a direct arterial blood supply, whereas the anterior lobe is predominantly supplied by the portal venous system. Thus, if an intravenous contrast agent is given, it should arrive first at the posterior lobe, then at the stalk, and finally at the anterior lobe (Fig 6). It is generally believed that this vascular architecture allows for neurohormonal control of the pituitary by the hypothalamus (6). The posterior lobe was found to enhance before the anterior lobe in each of our 30 subjects. The stalk was found to enhance shortly after the posterior lobe and before the anterior lobe. This difference may reflect the distal branching of the superior hypophyseal arteries relative to the inferior hypophyseal arteries and/or drainage from the hypothalamus through the portal system.

Our data demonstrate that the straight sinus, a venous system, enhances consistently before the anterior and posterior lobes of the pituitary gland. One possible explanation for this counterintuitive observation is that larger-caliber vessels supply the brain parenchyma, whereas smaller-caliber vessels supply the pituitary gland; thus, blood may reach the cerebral sinuses faster, be-

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**Fig. 5. Enhancement pattern of pituitary adenoma.**

A, Image acquired with 5-sec intervals between successive images was obtained before the arrival of the gadolinium bolus. The pituitary adenoma (white arrows) is relatively isointense to the surrounding normal brain parenchyma. The deep venous structures, including the internal cerebral vein (black arrows), straight sinus, and transverse sinus (curved arrow), are not well seen.

B, Image obtained 15 sec after image A shows initial evidence of contrast enhancement with increased signal intensity in each of the deep venous structures as well as the superior-sagittal sinus. Note patchy areas of mild hyperintensity within the adenoma, indicating contrast enhancement of the adenoma at this time.

C, Image was obtained 10 sec after enhancement of the straight sinus (B). Initial enhancement of the adenoma is evident with signal intensity slightly higher than the surrounding brain parenchyma. This finding is consistent with measures made by quantitative analysis, in which adenoma enhancement followed enhancement of the straight sinus by approximately 9 sec. Note the improved visualization of the deep venous structures as well as the superior-sagittal sinus.

D, Image was obtained 50 sec after the enhancement of the straight sinus (B). Intense enhancement of the adenoma is evident.
The pituitary gland is a relatively small structure (12-15 mm in diameter); thus, delineation of the posterior lobe, anterior lobe, and pituitary stalk can be difficult. Although a 10-mm-thick sagittal section through the center of the pituitary gland was used in this study, delineation of the pituitary stalk was difficult even with the aid of image magnification. Previous dynamic MR studies of the pituitary gland have used manual ROI placement over the posterior lobe, stalk, and anterior lobe for each of the images in the series. Variations in ROI placement in successive images of the series may have contributed to variability in the resulting time-intensity curves. In our method of analysis, the image that best delineated the lobe of interest was first identified. This image was magnified, and the pituitary lobe was traced manually. The ROI was then duplicated for each image in the series; therefore, the variability of ROI placement between different images was greatly reduced.

In addition, our time-intensity-curve analysis estimates quantitatively relative enhancement delay at fractional temporal resolutions. The use of several data interpolation steps allows us to resolve differences in relative-enhancement delays between time-intensity curves that are less than our image-acquisition times of 5 or 10 sec. This method of analysis provides an objective measure of relative enhancement delay and is not limited by subjective bias and reduced sensitivity of visual-analysis methods. Differences between our visual and quantitative results are likely related to variations in detection methods. Visual analysis of enhancement depends on cumulative regional gadolinium concentration to produce a detectable signal-intensity change (increase), whereas the quantitative analysis detects the onset of en-
hancement. Visual analysis is less sensitive than quantitative analysis in evaluating the time course of enhancement.

In the 10 patients with intrasellar pituitary macroadenomas, the tumor enhancement was noted to occur slightly, although not significantly, before the posterior lobes and significantly \((P < .001)\) before the anterior lobes. This finding contradicts previous studies (1, 3, 8) in which sellar pituitary adenomas were reported to enhance after the anterior lobes. This may be related to the temporal resolution and method of analysis used in our study, as well as tumor type (microadenoma versus macroadenoma). Sakamoto et al (3) reported one case of macroadenoma that enhanced slightly before the posterior lobe, whereas Miki et al (1) found adenoma enhanced after the anterior lobe and did not specify the tumor type. The early enhancement pattern from our findings suggests that sellar pituitary adenomas may have a direct arterial (neovasculature) supply and are consistent with previous angiographic and histopathologic studies of these tumors (9–17). It is unlikely that the adenoma vasculature would come from the portal system. Instead, the tumor may recruit new arterial blood sources through the release of angiogenesis factors (15). Gorczyca and Hardy (10) and others (15) have shown that there is a direct arterial blood supply to the anterior lobe in the normal pituitary, although it is not the primary source of blood to this lobe.

Two potential arterial blood sources have been identified: 1) the infradiaphragmatic supply from the capsular arterial rete and direct branches from the inferior-hypophyseal arteries; and 2) the supradiaphragmatic supply (also known as the trabecular artery) from branches of the superior-hypophyseal arteries. This has been demonstrated by Monnet et al (13), who showed that when the portal vessels are occluded partially or completely, a direct arterial supply to the anterior lobe is formed. This was illustrated by microsphere injection and vascular-cast studies. Racadot (15) showed that at least 80% of pituitary adenomas (both micro- and macroadenomas) have a direct arterial blood supply from arterial sources similar to those described by Gorczyca and Hardy (10).

Angiographic evaluation of pituitary adenoma vasculature has shown that a direct arterial blood supply is present, originating from the capsular arteries and branches of the inferior hypophyseal arteries (9, 14). Westberg and Ross (17) have reported that the arterial supply to these tumors may originate from any branches of the carotid siphon, but it most commonly arises from the capsular and inferior hypophyseal arteries. Further evidence of a new arterial blood supply in pituitary adenoma is the increased frequency of tumor-to-tumor metastases involving pituitary adenomas. Teears and Silverman (18) showed that most metastases to the normal pituitary gland are located in the posterior lobe (90%). The increased incidence of posterior-lobe metastases is thought to be related to the new arterial blood supply (19, 20). However, in cases of rare intracranial tumor-to-tumor metastases, the pituitary adenoma (18%) is second only to the meningioma (63%) as the most common site. A rich arterial supply to the pituitary adenoma (11, 16) and blood shunting from the posterior lobe (9) may create a suitable environment for metastatic cells to deposit in the pituitary adenoma.

Although our observations of the sequential pattern of enhancement in the normal pituitary and pituitary adenomas appear to be interesting, the clinical utility of such information requires further study. Potential uses of dynamic MR study may include location of normal pituitary tissue within pituitary macroadenomas and evaluation of cavernous sinus invasion by adenomas. Takahashi et al recently have presented data in 20 patients with surgically proved macroadenomas imaged using a 30-sec spin-echo technique (paper presented at the 30th Annual Meeting of the Radiological Society of North America, Chicago, Ill, November 29–December 4, 1992). They found that dynamic imaging was valuable in suggesting the location and size of the normal pituitary tissue in macroadenomas. Kawamura and Sze compared 30 patients using a half-dose (0.05 mmol/kg) gadopentetate dimeglumine dynamic study (fast spin-echo, 30-sec acquisition time) with 11 patients imaged using a standard dose (0.1 mmol/kg) of gadolinium (paper presented at 30th Annual Meeting of the Radiological Society of North America, Chicago, Ill, November 29–December 4, 1992). They found that the half-dose dynamic studies yielded superior contrast between the cavernous sinus and the pituitary. The technique was particularly useful in evaluating sinus invasion by adenomas. Additional potential uses of dynamic MR study might include assessment of response to therapy, both surgical as well as chemotherapeutic.

In summary, dynamic study of the normal pituitary gland in our patients demonstrates that
the posterior lobe enhances first, followed by enhancement of the stalk and then the anterior lobe. This is consistent with the normal pituitary blood supply. However, in patients with adenomas, the enhancement sequence is altered, with the tumor enhancing slightly before or simultaneously with the posterior lobe. This is likely because of a direct arterial blood supply (neovascuclature) to the tumor.

References