

Is Thyroid Stunning a Real Phenomenon or Just Fiction?

Thyroid stunning is usually defined as decreased uptake or trapping of radioiodine ^{131}I by normal thyroid tissue or differentiated thyroid cancer after diagnostic administration of ^{131}I . As simple as this definition might be, it is as important to understand the mechanisms by which this phenomenon, if real, is caused. There are 2 possible explanations: Stunning may result either from a reduction of the number of functional thyroid cells simply caused by cell death due to the β -radiation of ^{131}I (this would be, rather, a partial ablation) or from a decreased ability of viable thyroid cells to trap or retain radioiodine for a more-or-less specific time interval. The first explanation for stunning—that is, a partial ablation caused by activities administered diagnostically in cancer patients that are comparable with activities used therapeutically for thyrotoxicosis—would indicate therapeutic effects comparable with a fractionated therapy. Another possible ablation mechanism could be intratherapeutic necrosis due to high radiation doses of ^{131}I within the first 24–48 h, as observed by Guiraud-Vitaux et al. (1), resulting in a reduced number of cells and, thus, reduced uptake when intratherapeutic imaging or uptake measurements are usually performed after 48 h or later. However, the second explanation for stunning—a radiation-induced reduction of iodine uptake or metabolism in viable cells—would imply a potential reduction of the therapeutic efficacy of radioiodine treatment after diagnostic ^{131}I imaging, raising the question of whether the

management of patients has to be changed.

Since the first report on intratherapeutically reduced uptake of ^{131}I after diagnostic studies with this radioisotope by Rawson et al. (2) in 1951, the phenomenon of thyroid stunning has been investigated by several authors, who have reported contradictory findings. Interestingly, most of the articles using a quantitative approach did show evidence for stunning, whereas the reports dealing with qualitative methods (i.e., visual assessment of scans or assessment of the therapeutic outcome of patients) yielded conflicting results. For example, Leger et al. (3) and Kao and Yen (4) described a visually reduced or suppressed uptake of radioiodine in thyroid remnants after scanning with 185 and 111 MBq ^{131}I , respectively, whereas other authors, such as McDougall (5) or Cholewinski et al. (6), found no changes of the ^{131}I uptake pattern when diagnostic and subsequent therapeutic scans were compared. Contradictory results were also obtained in studies on ablation rates of thyroid remnants. For example, Muratet et al. (7) detected a significantly higher ablation rate of postsurgical remnants in patients after a diagnostic scan with 37 MBq ^{131}I (76% vs. 50%; $P < 0.001$). On the other hand, Morris et al. (8) reported on the non-impact of thyroid stunning for the remnant ablation rates in nonscanned and scanned patients using 111–185 MBq ^{131}I . However, quantitative studies by Leger et al., Huic et al. (9), and Sabri et al. (10) always proved a reduced therapeutic versus diagnostic ^{131}I uptake. Furthermore, data indicate that stunning, as expected from a radiobiologic point of view, is related to dose: Sabri et al. clearly showed that stunning ex-

ists in benign thyroid disease and that there was a significant correlation between thyroid stunning and the first absorbed energy dose. Jeevanram et al. (11) observed a reduction in uptake that was proportional to the calculated radiation dose, ranging from 31 to 73 Gy in postthyroidectomy patients, and Medvedec (12) reported on significant stunning effects above doses as low as 10 Gy. On the basis of clinical papers providing quantitative data, Coakley (13) recently concluded in his editorial: “Evidence that stunning is a real phenomenon is now strong, albeit not yet conclusive.”

Besides the aforementioned clinical studies, few experimental studies dealing with radiation-induced changes and thyroid stunning have been published (1,14). Guiraud-Vitaux et al. (1) observed morphologic and ultrastructural changes in rat thyroid cells after administration of diagnostic and therapeutic amounts of ^{131}I typical for necrosis of the cells with no signs of apoptosis. Thereby, the effects of ^{131}I varied only in quantity, with a much higher number of damaged cells in the therapeutic group. Furthermore, in the diagnostic group the damage was observed only at 24 h but not at 48 h, whereas in the therapeutic group changes were found at any time. In 2 animals that received 9 MBq ^{131}I 8 d after injection of 0.45 MBq ^{131}I (1.85 MBq/g of thyroid tissue), radioiodine uptake per gram of thyroid was similar to that obtained in the therapeutic group.

A completely new and functional approach dealing with thyroid stunning at the cellular level is presented by Postgård et al. (15) in this issue of *The Journal of Nuclear Medicine*. Porcine thyroid cells were cultured in a bicameral system in which the cell mono-

Received Feb. 5, 2002; accepted Feb. 22, 2002.
For correspondence or reprints contact: Winfried Brenner, MD, Universitätsklinikum Kiel, Arnold-Heller-Strasse 9, D-24105 Kiel, Germany.
E-mail: wbrenner@nuc-med.uni-kiel.de

layer divided 2 chambers according to the in vivo situation, which consists of 3 compartments: the follicular epithelium, the extrafollicular space (basal), and the follicular lumen (apical). This model allows measurement of the transepithelial iodine transport capacity, resulting in an iodine accumulation in the follicular lumen. After irradiation of the thyroid cells with different activities of ^{131}I for 48 h, corresponding to absorbed doses of 3–80 Gy, the iodine transport capacity was evaluated 3 d after terminating the irradiation period—that is, 5 d after ^{131}I application. In this experimental setting a reduction of the unilateral iodine transport from the extrafollicular space to the luminal space by nearly 50% was observed already at absorbed doses as low as 3 Gy, with a nearly complete blocking of iodine transport at 80 Gy, whereas an incubation with stable ^{127}I in the same iodine molarity revealed no significant differences compared with that of the control group. Significant cell loss, either by necrosis or apoptosis, did not occur, and the barrier function of the cell layer, as evaluated by measurements of the transepithelial resistance, did not change, even for an absorbed dose of 80 Gy.

Thus, according to the results of Postgård et al. (15), there is clear evidence that stunning is a real phenomenon, meaning a radiation-induced and dose-dependent reduction of the iodine transport capacity of viable thyroid cells, and that stunning is not the result of a significant cell loss caused by necrosis or apoptosis. These findings are in a line with the histomorphologic data of Guiraud-Vitoux (1) obtained in rat thyroid cells. However, their contradictory observation that radioiodine uptake 8 d after a diagnostic injection of ^{131}I is similar to that obtained in nonpretreated rats might be due to the longer interval (8 d vs. 5 d) between pretreatment and uptake measurement. Therefore, it is absolutely essential to perform further experimental studies to

learn more about thyroid stunning, such as the time of onset and the duration of this effect with respect to the absorbed doses and dose rates.

Furthermore, the results of Postgård et al. (15) do support all quantitative studies indicating a reduced iodine uptake after diagnostic irradiation with ^{131}I (3,9,16). The data imply a potential reduction of the therapeutic efficacy of radioiodine treatment after diagnostic ^{131}I imaging, even at low absorbed doses. Therefore, it is important to further investigate systematically the impact of thyroid stunning with respect to the administered activity or, rather, the absorbed dose for the various clinical situations in the treatment and follow-up of thyroid cancer patients and to clarify whether the management of patients must be changed, as discussed by several investigators (13,17–21). The most important aspect seems to be to reconsider if, and in which clinical situations, diagnostic studies with ^{131}I are necessary before radioiodine therapy besides for dosimetric purposes (which, in most cases, are not possible because of unknown lesion volumes).

In conclusion, thyroid stunning is a real phenomenon, as proven now at the cellular level. Much work remains to be done to fully understand this phenomenon in detail and to clarify the impact on diagnostic and therapeutic procedures to consequently improve and adjust the management of differentiated thyroid cancer for the patient's benefit.

Winfried Brenner, MD

*Clinic of Nuclear Medicine
University Hospital Kiel
Kiel, Germany*

REFERENCES

- Guiraud-Vitoux F, Feldmann G, Vadrot N, et al. Early ultrastructural injuries in the thyroid of the normal rat radioinduced by diagnostic and/or therapeutic amounts of iodine-131. *Cell Mol Biol.* 2001;47:495–502.
- Rawson RW, Rall JE, Peacock W. Limitations and indications in the treatment of cancer of the thyroid

- with radioactive iodine. *J Clin Endocrinol Metab.* 1951;11:1128–1131.
- Leger FA, Izembart M, Dagoussset F, et al. Decreased uptake of therapeutic doses of iodine-131 after 185-MBq iodine-131 diagnostic imaging for thyroid remnants in differentiated thyroid carcinoma. *Eur J Nucl Med.* 1998;25:242–246.
- Kao CH, Yen TC. Stunning effects after a diagnostic dose of iodine-131. *Nuklearmedizin.* 1998;37:30–32.
- McDougall IR. 74 MBq radioiodine ^{131}I does not prevent uptake of therapeutic doses of ^{131}I (i.e. it does not cause stunning) in differentiated thyroid cancer. *Nucl Med Commun.* 1997;18:505–512.
- Cholewinski SP, Yoo KS, Klieger PS, O'Mara RE. Absence of thyroid stunning after diagnostic whole-body scanning with 185 MBq ^{131}I . *J Nucl Med.* 2000;41:1198–1202.
- Muratet JP, Daver A, Minier JF, Larra F. Influence of scanning doses of iodine-131 on subsequent first ablative treatment outcome in patients operated on for differentiated thyroid carcinoma. *J Nucl Med.* 1998;39:1546–1550.
- Morris LF, Waxman AD, Braunstein GD. The non-impact of thyroid stunning: remnant ablation rates in ^{131}I -scanned and non-scanned individuals. *J Clin Endocrinol Metab.* 2001;86:3507–3511.
- Huic D, Medvedec M, Dodig D, et al. Radioiodine uptake in thyroid cancer patients after diagnostic application of low-dose I-131. *Nucl Med Commun.* 1996;17:839–842.
- Sabri O, Zimny M, Schreckenberger M, Meyer-Oelmann A, Reinartz P, Buell U. Does thyroid stunning exist? A model with benign thyroid disease. *Eur J Nucl Med.* 2000;27:1591–1597.
- Jeevanram RK, Shah DH, Sharma SM, Ganatra RD. Influence of initial large dose on subsequent uptake of therapeutic radioiodine in thyroid cancer patients. *Nucl Med Biol.* 1986;13:277–279.
- Medvedec M. Thyroid stunning [letter]. *J Nucl Med.* 2001;42:1129–1130.
- Coakley AJ. Thyroid stunning. *Eur J Nucl Med.* 1998;25:203–204.
- Yang T, Namba H, Hara T, et al. p53 induced by ionizing radiation mediates DNA end-joining activity, but not apoptosis of thyroid cells. *Oncogene.* 1997;14:1511–1519.
- Postgård P, Himmelman J, Lindencrona U, et al. Stunning of iodide transport by $^{131}\text{I}^-$ irradiation in cultured thyroid epithelial cells. *J Nucl Med.* 2002;43:828–834.
- Yeung HWD, Humm JL, Larson SM. Radioiodine uptake in thyroid remnants during therapy after tracer dosimetry. *J Nucl Med.* 2000;41:1082–1085.
- Dietlein M, Moka D, Scheidhauer K, et al. Follow-up of differentiated thyroid cancer: comparison of multiple diagnostic tests. *Nucl Med Commun.* 2000;21:991–1000.
- Hurley JR. Management of thyroid cancer: radioiodine ablation, “stunning,” and treatment of thyroglobulin-positive, ^{131}I scan-negative patients. *Endocr Pract.* 2000;6:401–406.
- Lind P. ^{131}I whole body scintigraphy in thyroid cancer patients. *Q J Nucl Med.* 1999;43:188–194.
- Reynolds JC, Robbins J. The changing role of radioiodine in the management of differentiated thyroid cancer. *Semin Nucl Med.* 1997;27:152–164.
- Cavalieri RR. Nuclear imaging in the management of thyroid carcinoma. *Thyroid.* 1996;6:485–492.