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Assessment of the effect of percutaneous ethanol injection in autonomously functioning thyroid nodules by colour-coded duplex sonography

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Abstract. Percutaneous ethanol injection (PEI) is an effective treatment for autonomously functioning thyroid nodules (AFTNs). The aims of this study were to assess: (1) the ultrasound (US) and colour-coded duplex sonography (CCDS) baseline and post-therapy patterns of AFTN, and (2) the contribution of CCDS in determining the efficacy and optimum duration of PEI. Forty AFTNs were evaluated by US and CCDS before, during and 6 and 12 months after PEI. Four grades of increasing vascularity were arbitrarily identified at CCDS (O-1-2-3). These data were compared with thyroid scintiscan and hormonal findings. All nodules showed a striking volume decrease. After treatment a hypoechoic pattern and blurred outlines on US were associated with a higher percentage volume reduction. Soon after PEI a reduction in the vascularity score was noticed in 29 of 40 of AFTNs. Pre- and post-treatment vascular score distributions were significantly different. It is concluded that a vascular score decrease to grade 0–1 at the end of PEI is an index of successful treatment.

Key words: Hyperthyroidism – Thyroidnodule – Alcohol-ethyl – Doppler sonography – Ultrasonography – Ultrasonography interventional

Introduction

Ultrasound (US)-guided percutaneous ethanol injection (PEI) has recently been proposed [1] as a new treatment for autonomously functioning thyroid nodules (AFTNs). Previous reports have demonstrated the feasibility, safety and clinical effectiveness of this procedure [2–4], which appears to be a possible substitute, in selected cases, for surgery or radioiodine therapy. US is the technique of choice both for guiding the needle inside the AFTN to be treated and for monitoring ethanol diffusion within the lesion. In recent years, however, colour-coded duplex sonography (CCDS) has become available in most diagnostic departments and seems to increase the accuracy of US scan of the thyroid [5–13]. As has been demonstrated in experimental studies and in operative specimens from humans, alcohol produces tissue damage by both a direct coagulative necrosis and a partial or complete small vessel thrombosis. Thus CCDS could be useful in demonstrating PEI-induced vascular damage during and after the procedure [14–17]. PEI treatment is usually stopped after the attainment of serum T_3 and T_4 normalisation. However, at the end of the treatment serum thyroid stimulating hormone (TSH) is still undetectable and the thyroid scintiscan is still suppressed. Hence, further diagnostic tools are needed for an early assessment of the completeness of treatment and to exclude a relapse of hyperthyroidism.

Therefore, the aims of the present study were: (1) evaluation by US and CCDS of AFTN baseline and post-therapy patterns and their correlation with hormonal and scintigraphic data, and (2) assessment of the contribution of CCDS in determining precociously the efficacy of PEI and its optimum duration. To effect this goal, we studied a homogeneous group of 40 AFTNs, cause of hyperthyroidism, which were treated with PEI and subsequently followed for a 12-month period. The US and CCDS results were compared with clinical, hormonal and scintiscan findings.

Methods

Subjects: enrolment criteria

From January 1991 to September 1992, 40 consecutive patients were enrolled in our study: 37 women and 3 men, from 24 to 73 years of age (mean 51 years). All the patients had solitary AFTNs and presented a clinical and laboratory pattern of hyperthyroidism (in-

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creased serum free thyroxine (FT_4) and/or free triiodothyronine (FT_3) and undetectable TSH levels). Fine needle aspiration biopsy (FNA) [18] was performed on all patients to rule out malignancy.

All patients had refused surgery and radiometabolic therapy and gave their informed consent to this therapeutic procedure. The study was conducted in accordance with the Helsinki Declaration and was approved by the Bio-ethics Committee of the hospital.

Table 1. Mean value of FT_3, FT_4 and TSH before and after treatment in all patients

	Before PEI	After PEI	6 months later	12 months later
FT_3	11.8 ± 2.3	5.36 ± 1.65	5.32 ± 1.5	6.2 ± 1.8
FT_4	19.2 ± 3.5	12.28 ± 4.1	11.4 ± 3.6	12.8 ± 4.4
TSH	0.02 ± 0.03	0.023 ± 0.02	1.07 ± 0.8	1.3 ± 0.8

PEI: percutaneous ethanol injection
Data are expressed as the mean ± 1 SD in SI units. Normal range are: TSH, 0.2–4.0 mU/l; FT_3, 4.7–9.5 pmol/l; FT_4, 8.5–18.0 pmol/l

Procedure

PEI was performed on an outpatient basis once or twice a week and completed within 4–6 weeks according to a technique described elsewhere [3]. Each patient received 4–10 injections. Multiple treatments were performed during the same session in different nodular sites in thyroid lesions greater than 20 ml. The treatment was ended when serum FT_3 and FT_4 values, monitored every 2 weeks, were found to be normal.

US and colour Doppler assessment

The US and CCDS examinations were performed with a real-time apparatus equipped with "pulse" Doppler and colour-coded Doppler (Ansaldo Esaote AU 590 Asynchronous, Genoa, Italy). A 7.5 MHz linear probe was used for morphological and CCDS evaluation. US and CCDS study comprised three phases: (1) preliminary examination, (2) final examination at the end of PEI, (3) follow-up controls at 6 and 12 months.

At every US evaluation the volume and US pattern of the nodules were assessed. Nodule volume was calculated using the two-plane technique according to the $(D1 \times D2 \times D3) \times 0.523$ formula. CCDS evaluation was performed with axial and sagittal scanning. After a wide-window panoramic assessment, vascular structures were examined with narrower windows in order to obtain a greater sensitivity of CCDS by increasing the scanning line density. The amplifier gain was individually established in each case so as to situate it at a level immediately under the point of appearance of random colour noise. Ultrasound output power, colour write/echo priority and pulse repetition frequency (velocity range ± 5.9 cm/s; minimum frequency shift colour-encoded 50 Hz) were maintained at constant values. Vascularity was evaluated on sagittal and transverse scans, obtained along the maximum AFTN diameters. On the maximum diameter scan the nodule perimeter and the peripheral vessels were measured and the lengths compared. In this way, four grades of vascularity were arbitrarily identified: grade 0, no sign of increased vascularity; grade 1, a few clusters of vessels at peripheral sites on less than 30.0 % of the peripheral rim; grade 2, coarse and > 30.0 % peripheral vascular images; grade 3, grade 2 findings together with central vascular areas.

US and CCDS assessments were performed separately by three radiologists for independent interpretation and scoring. After all evaluation sheets were completed, the co-authors met to determine the "truth" regarding qualitative parameters. For quantitative parameters the mean was obtained from the data of different observers.

Scintiscan and hormonal assessment

Thyroid scintiscan (^{99m}Tc) and 24-h ^{131}I uptake were performed before, at the end of, and 3 and 6 months after PEI (Gamma Camera, Philips, The Netherlands; GE-Medical Systems, Milwaukee, WI). Each patient was clinically evaluated at the beginning, every 2 weeks during treatment and at the end of PEI. Patients were re-evaluated 6 and 12 months later. Serum FT_3, FT_4 and TSH were determined at the same times. The peripheral thyroid pattern was evaluated by specific radioimmunoassay (FT_4 and FT_3, Lisophase, Recordati, Milan, Italy). TSH was determined by immunoradiometric assay (Radim, Pomezia, Italy).

Hormonal data are expressed in SI units. Normal ranges for our laboratory are 0.2–4.0 mU/l for TSH, 8.5–18.0 pmol/l for FT_4, and 4.7–9.5 pmol/l for FT_3.

Statistical analysis

Volume and hormone data are expressed as the mean ± 1 SD. Statistical evaluation of mean nodule volume changes and of modifications of the serum parameters was carried out by Student's t-test for paired data and Bonferroni's t-test for multiple comparisons. Relationship between changes in nodule volume, vascularity and the other parameters were evaluated by linear regression analysis. Differences in vascular score distribution before and after treatment were evaluated by chi-squared test.

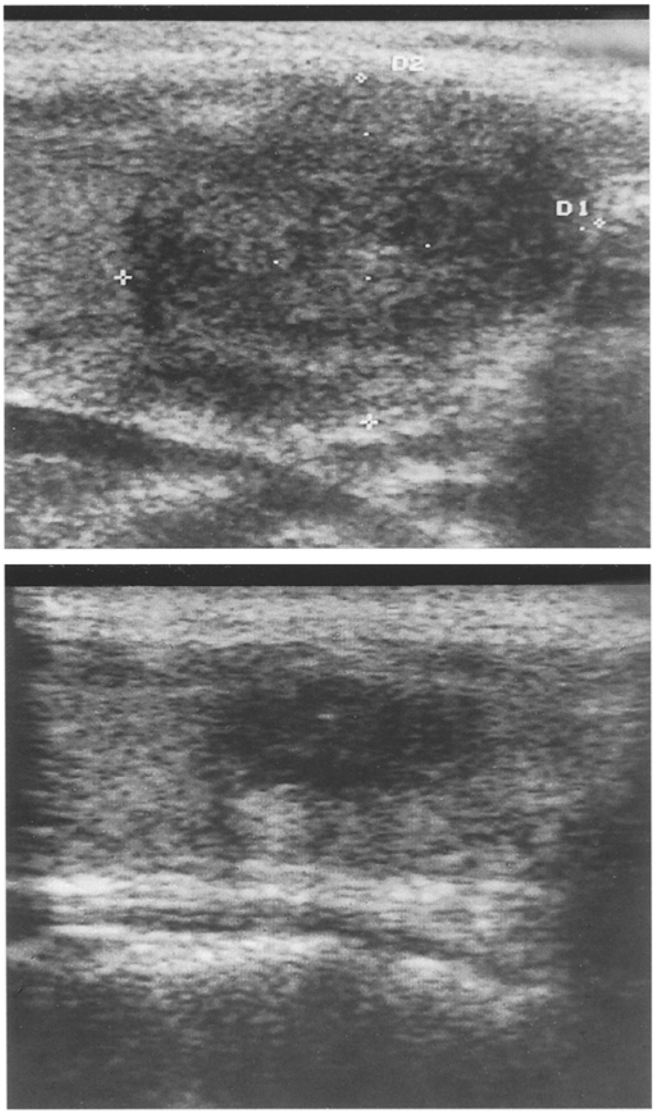
Results

Preliminary examination

Scintiscan and hormonal assessment
At baseline all patients showed increased serum FT_3 (11.8 ± 2.3), and 28 of 40 (70.0 %) also had high FT_4 (19.2 ± 3.5) levels. All patients had undetectable TSH values (Table 1). At baseline thyroid scintiscan, all nodules were hyperfunctioning, with complete suppression of extranodular parenchyma.

Table 2. Vascular changes in AFTN after PEI in all patients

Vascular score	Before PEI	After PEI	6 months later	12 months later
0	0	10	10	10
1	2	13	13	13
2	17	12	10	9
3	21	5	7	8



a

b

Fig. 1 a, b. Sagittal scan of the right thyroid lobe with 7.5 MHz linear array probe. AFTN before PEI **a** and 6 months after PEI **b**. Note the shrinkage of the nodule along with the reduced echogenicity and blurred margins

Cytological evaluation
Preliminary FNA ruled out malignancy, showing cytological findings consistent in all cases with "colloid nodule".

US assessment
The mean baseline volume of AFTNs ranged from 0.7 to 80 ml, with a mean value of 14.7 ml and median of 7.9 ml. The US characteristics were as follows: 33 nodules (82.5 %) displayed a solid echoic structure (21 hypoechoic, 2 hyperechoic, 4 isoechoic and 6 non-homogeneous) and 7 (17.5 %) showed a mixed pattern (solid and liquid components). A complete peripheral halo was observed in 21 cases (52.5 %); nodular edges appeared irregular and indistinct in 4 cases (10.0 %). Amorphous calcifications were present in 4 cases (10.0 %).

Colour Doppler assessment (Table 2)
At the beginning of treatment vascular scores were as follows: grade 0, no cases; grade 1, 2 cases (5.0 %); grade 2, 17 cases (42.5 %); grade 3, 21 cases (52.5 %).

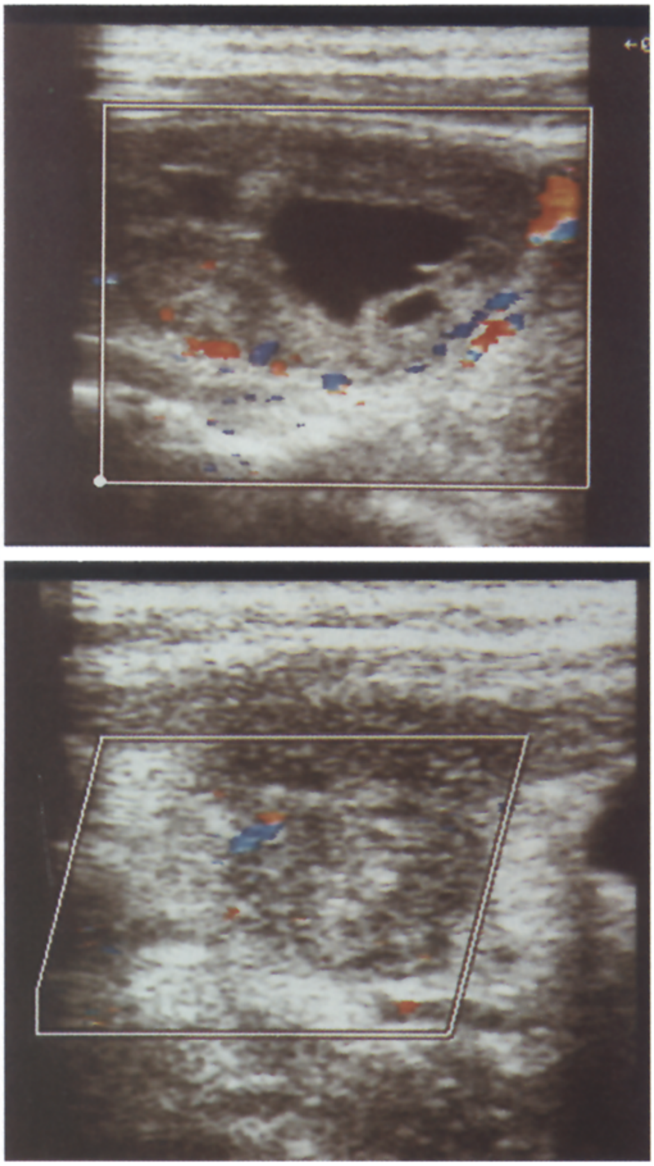
Examinations after treatment and during follow-up

Hormonal and scintigraphic assessment (Table 1)
At the end of treatment, 38 of 40 (95.0 %) patients were asymptomatic, with serum FT_3 and FT_4 normalisation but still undetectable TSH. The mean reduction in FT_3 was 6.44 ± 2.3 pmol/l (–54.5 %) and the mean FT_4 decrease was 6.92 ± 6.6 pmol/l (–36 %), both of which were statistically significant compared with baseline values ($P < 0.01$) (Table 1). Six months after PEI, TSH was again detectable in 34 of 40 patients (85.0 %), and remained suppressed in 6 patients (15.0 %). Two of these latter 6 (5.0 %) were still clinically and biochemically hyperthyroid. The mean serum TSH increase was 1.05 ± 0.64 mU/l (0.00–2.52 mU/l), which was statistically significant ($P < 0.01$) when compared with baseline values. In the 34 patients with normalised serum TSH, FT_3 and FT_4, hormonal levels remained within normal limits without further significant variations during the subsequent controls.

At the end of PEI, the thyroid scintiscan showed a thyroid parenchyma that was still suppressed in all cases. Six months after PEI, the scintiscan yielded evidence of functional recovery of the extranodular glandular tissue in all the cases with detectable serum TSH (34/40; 85.0 %). In 11 cases (27.5 %) the lesion became "cold", and in 23 cases (57.5 %) the nodule was now not delineated. In the 6 cases (15.0 %) with suppressed TSH an hot localized area was still visible, with persistent functional suppression of the surrounding parenchyma.

US assessment
After PEI, the US study demonstrated progressive reduction over time of nodule volumes (Fig. 1). At the end of treatment the mean nodule volume reduction was 6.95 ml (14.7 ml vs 7.75 ml). The mean percentage volume reduction was 47.3 ± 19.6 %, ranging between 9.5 % and 92.9 %. At the 6- and 12-month controls, volumetric reduction was 61.6 ± 19.9 % and 70.3 ± 21.9 % ($P < 0.01$ vs baseline), respectively.

The initial volumes of the nodules were closely correlated with the volumes reached both at the end of treatment and in the subsequent follow-up ($r = 0.93$, $P < 0.01$). On the other hand, no correlation was found between baseline volumes and percentage volume de-



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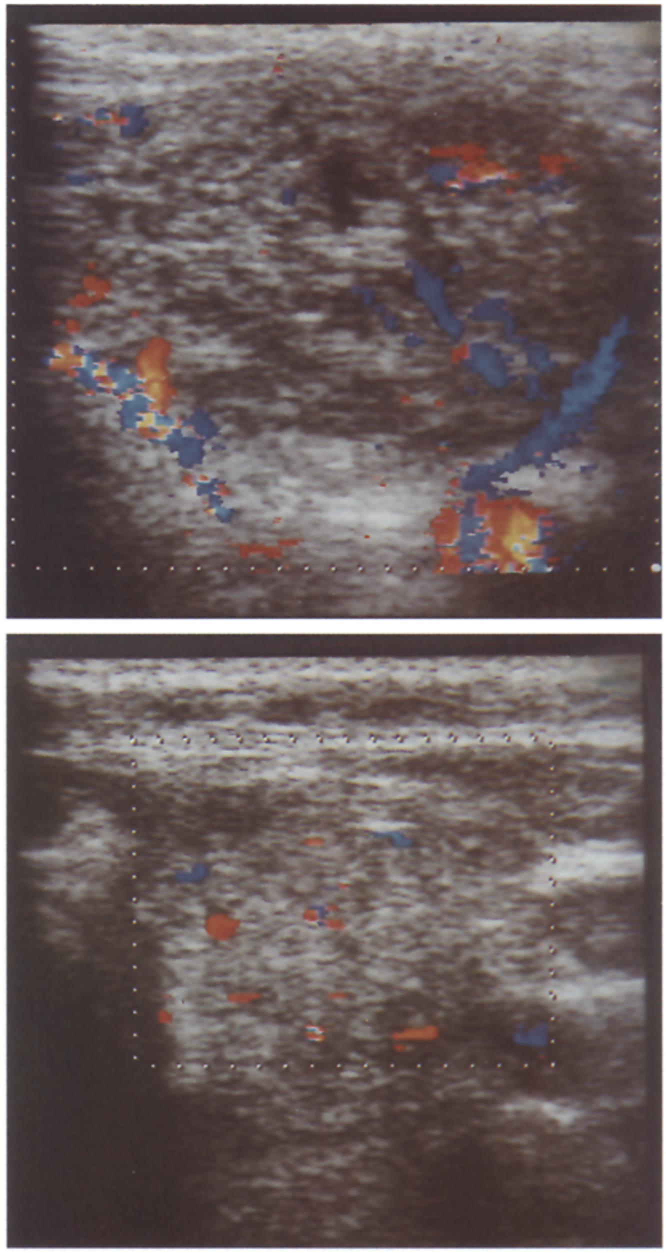

3a b

Fig. 2 a, b. US with CCDS scan of the same AFTN before **a** and soon after **b** PEI. A clear decrease in vascular score can be noted (from grade 2 to grade 1), associated with changes in the US pattern

Fig. 3 a, b. US with CCS scan of an unsuccessfully treated AFTN before **a** and 6 months after **b** PEI. In this case there is no appreciable change in the vascular score, while a substantial volumetric reduction is present

crease after PEI ($r = 0.25$, $P > 0.05$). There was a significant correlation between the baseline AFTN volumes and the initial serum FT_3 values ($r = 0.52$, $P < 0.01$). No correlation was found between baseline volumes and FT_4 values.

At the end of treatment US pattern changes were observed in all nodules. A reduction in the initial echogenicity was observed in 22 nodules (55.0 %), 7 nodular lesions (17.5 %) with mixed echoic structure lost their liquid component and produced a solid hypoechoic US pattern, and 11 nodules (27.5 %) maintained a non-homogeneous solid pattern. After both 6 and 12 months, 23 of 40 nodules (57.5 %) showed a more defined hypoechogenicity. In the same cases nodular outlines had become blurred.

The 23 nodules that were clearly hypoechogenic with hazy edges in the follow-up study showed a significantly higher percentage volume reduction than the other nodules, which had a different US pattern (82 ± 8.40 % versus 54.5 ± 9.4 %; $P < 0.05$).

For US qualitative parameters there was full agreement between observers. Frequency distribution analysis of the US pattern showed a significant difference ($\chi^2 = 14.5$, $P < 0.01$) between successfully and unsuccessfully treated patients at 6 and 12 months.

Indeed, all 23 nodules with a hypoechoic pattern and blurred margins after PEI were found among the successfully treated patients (67 %). On the other hand, no unsuccessfully treated patient showed this pattern.

Table 3. Colour Doppler score in successful and unsuccessfully treated AFTN

Vascular score	Before PEI	After PEI	6 months later	12 months later
Successful treatment				
0	0	10	10	10
1	2	13	13	13
2	14	9	8	8
3	18	2	3	3
Unsuccessful treatment				
0	0	0	0	0
1	0	0	0	0
2	3	3	2	1
3	3	3	4	5

Colour Coppler assessment

The vascular scores at baseline, at the end of treatment and at the 6- and 12-months controls are summarised in Table 2. Inter-observer variation in masked assessment of the vascular score was seen in only in 2 of 40 (5 %) patients and in no case exceeded one degree.

At the end of treatment AFTN vascularity was reduced (Fig. 2) compared with baseline values in 29 of 40 cases (72.5 %); in 9 cases (22.5 %) (five grade 3 cases and four grade 2 cases) the vascular score was unchanged (Fig. 3) and in 2 cases (5.0 %) it was increased. The frequency distribution of vascular scores changed significantly after treatment ($\chi^2 = 37.5$; $P < 0.01$).

In the 34 (85.0 %) successfully treated patients, vascular score changes are summarised at the top of Table 3. Of the 6 (15 %) unsuccessfully treated AFTNs (bottom of Table 3) (i. e. patients still hyperthyroid or with undetectable serum TSH), there was no reduction in the baseline vascular score, but 2 cases showed a vascular score increase from 2 to 3.

There was a positive correlation coefficient between the baseline vascular score and the initial nodule volume ($r = 0.41$, $P < 0.05$). However, vascular score was unrelated to hormonal parameters ($r = 0.23$, $P > 0.05$) and the US pattern of the nodules ($r = 0.21$, $P > 0.05$). The decrease in vascular score was significantly smaller in the patients where initial volume was > 20 ml than in nodules smaller than 5 ml (17 versus 11; $P < 0.05$).

Discussion

Clinical application of pulsed Doppler and, more recently, of colour-coded duplex sonography has been focused on the study of vascularity in different tissues, in both physiological and pathological situations [19–23]. Hence the present study was designed to assess vascular changes at CCDS examination in AFTNs treated by PEI, and their possible correlation with normalisation of nodular hyperfunction. CCDS vascular pattern before PEI confirmed the results of previous reports which had described the high-grade vascularity of AFTNs [5, 7–10, 12). Indeed, no grade 0 vascular score and only two grade 1 vascular scores were found in our population of 40 clinically and biochemically evaluated thyrotoxic patients.

A significant change in vascular score distribution was observed after treatment in the group of 34 successfully treated patients. No significant change was observed in the group of 6 thyroid nodules still hyperfunctioning after PEI. It is noteworthy that after treatment only 3 of 34 (7.5 %) successfully treated patients showed a persistent grade 3 score, while 5 of the 6 (80.0 %) unsuccessfully treated patients showed a grade 3 score. Therefore the finding of a high vascular score after PEI was, in our study, a clear (although not absolute) index of persistent nodular hyperfunction. On the other hand, the decrease to a low score (grade 0–1) was an early and almost absolute index of successful treatment, since no cases of persistent hyperfunctioning thyroid nodules showed this score after PEI. A US pattern characterised by hypoechogenicity and blurred margins was frequently observed in successfully treated patients and never in persistently hyperfunctioning AFTNs. So this finding should be considered a useful but late prognostic index, like TSH levels and the scintiscan results.

A significant correlation was found between the baseline volumes of AFTNs and serum FT_3 values, whereas there was no significant correlation with serum FT_4. This finding is in accordance with previous epidemiological reports [24], which have assessed the association between the clinical appearance of thyrotoxicosis and the progressive increase in AFTN volume during a prolonged follow-up period. The success rate of PEI was higher in smaller than in larger nodules. The failure of treatment in larger nodules can be explained by the relatively small volume of parenchyma damaged during each treatment, insufficient for a critical decrease in the mass of functioning tissue in large-volume nodules.

The presence of a correlation between the initial volume and the volume at the end of treatment suggests that PEI is not a substitute for surgery for aesthetic purposes in large AFTN. In fact, in these cases, a greater percentage volume decrease should be obtained, but this did not occur in our clinical experience.

In the future, it would seem worth while to make use of CCDS as a tool during PEI treatment of AFTNs. Inded, CCDS monitoring would enable:

1) Better visualisation of alcohol diffusion within thyroid tissue during ethanol injection when performing multiple alcohol injections during the same treatment. In fact, during PEI US visualises both stationary and flowing alcohol as hyperechoic area inside the thyroid tissue. On the other hand, CCDS allows the two components to be distinguished. This could be a useful aid in the prevention of recurrent nerve chemical damage, the most important of the potential complications of PEI [2, 3].
2) Needle insertion aimed specifically at the areas of the AFTN still vascularised after repeated treatments, thus improving the effectiveness of therapy. In fact, a high level of vascularity seems to be a sign of tissue areas still unaffected by direct ethanol da-

mage or by infarction due to the thrombogenic effect of alcohol. Hence, during each treatment, needle insertion should be directed towards the remaining well-vascularised areas of the nodule. In this way, CCDS monitoring could shorten the time required for successful treatment.

3) An early prognostic index of PEI efficacy at the end of treatment, when serum TSH levels are still undetectable, thyroid parenchyma is still functionally suppressed on the scintiscan and further criteria to assess the effectiveness of therapy are lacking.

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