are no accurate or well validated methods for measuring blood pressure noninvasively *in vivo* in the aorta (10).

Notwithstanding this, driven it would seem by commercial claims (7) rather than evidence-based medicine, the Sphygmocor GTF approach now is being tried in all manner of disease states completely unrelated to the 14 subjects who provided data at cardiac catheterization for the original generation of the radial artery GTF (6). In this respect, even if one believes the claims that a single radial artery GTF can be used accurately and robustly to measure central aortic blood pressure noninvasively in all subjects of all ages, heights, weights, and blood pressures, both on and off medication (claims that are disputed because no evidence has, in fact, been published in the peer-reviewed literature), it seems completely implausible that this will work for all disease states as well.

Connected with this, a recent query about where is the evidence that the Sphygmocor system can be used to accurately and noninvasively predict central aortic blood pressure in patients with another endocrine disorder (diabetes; Ref. 11) was not able to offer any evidence or data to support the claims that were being made (12). Furthermore, a search on Medline up to September 2000 using "Sphygmocor" and "sphygmocardiography" as search terms confirms the absolute paucity of validation data that are available in the literature for the technique.

Other researchers have noticed this as well and have independently raised separate fundamental concerns about the use of the method, especially for the determination of the augmentation index (13–15) and central aortic blood pressure (16).

Unfortunately, citing papers from elsewhere in the field, which have not involved the Sphygmocor's radial artery GTF, as "validation" references, may make it appear on a cursory inspection that there have, in fact, been more validation studies using the device than are really the case.

Given all the above, Elsheikh *et al.* (1) may wish to exercise caution in making claims about the "validity" of the noninvasive approach they have adopted, which at present remains completely unproven, especially in endocrine disease.

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Homocysteine, Folate, Vitamin B12, and Transcobalamins in Patients Undergoing Successive Hypo- and Hyperthyroid States

To the editor:

In the March 2000 issue of this journal, Lien *et al.* (1) reported a transient increase in both plasma homocysteine and serum cholesterol during short-term iatrogenic hypothyroidism, which may confer increased cardiovascular risk. The observations of Lien *et al.* (1) are in accordance with the results of our previous preliminary study (2).

We now repeat plasma homocysteine, serum folate, and vitamin B12 in patients with successive hypo- and hyperthyroid states. Cobalamin-binding proteins, transcobalamins, were also determined to explain changes in vitamin B12 concentrations. Forty-five patients [age, 44.5 ± 12.3 yr (23–78); sex ratio M/F, 11/34] who had undergone total thyroidectomy for well-differentiated thyroid carcinoma were studied 4 weeks after the withdrawal of thyroïdal hormone therapy and then 14 weeks after the resumption of treatment to suppress the thyrotropin concentration. Hypo- and thyrotoxic states were evidenced by TSH concentrations (Table 1). Total EDTA-plasma homocysteine, serum folate, cobalamin, serum total B12 binding capacity, apo-haptocorrin, and apo-transcobalamin II were measured by methods described previously (4).

Homocysteine concentrations were significantly higher in hypo- than in hyperthyroid state (mean increase, 5.3 ± 4.6 μmol/L; Table 1). Furthermore, moderate hyperhomocysteinemia was observed for 10 of 45 patients (22%) with hypothyroidism [range, 17.5–27.2 μmol/L; reference range, 6.0–16.0 μmol/L (5)]. Homocysteinemia was normal in all patients in the hyperthyroid state. On univariate analysis, homocysteine was inversely related to folate (Rho, −0.33; $P = 0.02$). Our results suggested that folate levels may account in determining homocysteine as we confirmed the observation (1) of a moderate decline in serum folate in hypothyroid state, with a P value at the limit of significance ($P = 0.07$). Vitamin B12 was significantly higher in the hypothyroid state than in the hyperthyroid state, as found by Lien *et al.* (1). Transcobalamin levels were determined attempting to explain changes in vitamin B12 concentrations. Except in two cases, apo-haptocorrin was low in all patients in the two states whereas apo-transcobalamin II was not significantly decreased in hypothyroid patients. Vitamin B12 was not correlated to transcobalamins. We concluded that the increased vitamin B12 observed in hypothyroid state could not be explained by changes in transcobalamins.

Lien *et al.* (1) have compared the results at 2-week intervals during two phases. We compared the results between two states, hypo- and hyperthyroidism, in a larger cohort of patients. The increase in homocysteine concentrations during hypothyroidism may be explained by changes in folate status and also by modifications in enzymes involved in homocysteine metabolism, distribution or clearance (1, 6), and/or by concurrent changes in renal function (1). Changes in activities of 5,10-methylenetetrahydrofolate reductase and methionine synthase have been reported during both hyper- and hypothyroid states in an animal model (7). Data about normalization of hyperhomocysteinemia with levothyroxine are conflicting. Normalization was obtained after 3–9 months in a study of 14 patients (8), but failed after 2 months in a cohort of 14 patients (9).

In conclusion, homocysteine was increased in 22% of our patients in the hypothyroidism stage. This mild hyperhomocysteinemia was rather explained by a modification of folates status, with a mild decrease of blood concentration and a negative correlation between folates and homocysteinemia, than by a modification of vitamin B12 status and transport.

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TABLE 1. Homocysteine, folate, vitamin B12, and transcobalamin results in patients undergoing successive hypo- and hyperthyroid states

	n	Hypothyroid state	Hyperthyroid state	*P*	Reference range
Serum TSH (mIU/L)	45	83.9 ± 52.5	0.03 ± 0.04	<0.001	0.25–4.0
Serum T_4 (pmol/L)	26	3.3 ± 1.5	19.5 ± 4.6	<0.001	11.0–25.0
Plasma homocysteine (μmol/L)	45	12.4 ± 5.8	7.1 ± 3.5	<0.001	6.0–16.0
Serum folate (nmol/L)	24	13.4 ± 6.0	15.5 ± 6.4	0.075	6.0–36.0
Serum vitamin B12 (pmol/L)	24	385 ± 102	313 ± 71	<0.001	180–810
Serum total B12 binding capacity (pmol B12/L)	27	464 ± 70	477 ± 67	0.35	
Serum apo-haptocorrin (pmol B12/L)	27	102 ± 24	102 ± 33	0.98	148–627
Serum apo-transcobalamin II(pmol B12/L)	27	362 ± 57	374 ± 50	0.069	295–1328

Results are expressed as the mean ± SD. Paired *t* test was used to evaluate plasma and serum data between hypothyroid and hyperthyroid states. Two-tailed at $P < 0.05$ was reported as statistical significance.

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Total Plasma Homocysteine in Hypo- and Hyperthyroidism: Covariations and Causality

To the editor:

There are consistent reports that patients with hypothyroidism have elevated total homocysteine (tHcy) in plasma and that tHcy is reduced following therapy with T_4 (1–5). The withdrawal of thyroid hormone replacement therapy before radioscintigraphy of thyroidectomized patients provides controlled conditions for the study of changes in tHcy under variable thyroid status. This strategy was adopted in a recent study from our group (5) and in the study on 45 patients reported by Barbé *et al.*

Barbé *et al.* found lower serum folate in the hypothyroid compared with the hyperthyroid state, and they observed the usual inverse relationship between folate and tHcy. From this observation they inferred that the changes in tHcy may be explained by altered folate status or by a modification of the activity of folate-metabolizing enzymes, as has previously been suggested (2). Like Barbé *et al.*, we found lower levels of serum folate during short-term iatrogenic hypothyroidism (5). We observed, however, that the changes in tHcy concentration during the hypothyroid phase were more strongly associated with changes in serum creatinine than in folate, suggesting a renal mechanism (5).

The covariation between tHcy and serum cholesterol was equally strong, but a mechanistic link between homocysteine and cholesterol metabolism is not readily apparent. The strong relation between tHcy and cholesterol should remind us that covariations certainly do not prove causality.

Thyroid status has a profound influence on a variety of biochemical processes (6–8), of which some may have secondary effects on homocysteine metabolism. For example, thyroid hormones markedly affect riboflavin metabolism, mainly by stimulating flavokinase and thereby the synthesis of flavin mononucleotide and flavin adenine dinucleotide (FAD; Refs. 7 and 8). Conceivably, these metabolic changes may affect homocysteine metabolism, because flavin mononucleotide and FAD serve as cofactors for enzymes involved in the metabolism of vitamin B6, cobalamin, and folate (9). Among these enzymes, the FAD-dependent methylenetetrahydrofolate reductase should be considered, because this enzyme is recognized as a possible mediator of changes in tHcy level according to riboflavin status (9).

In conclusion, the nice study of Barbé *et al.* provides longitudinal data in a large number of patients and brings strong support that thyroid status is an important determinant of plasma tHcy and affects serum folate levels. However, the question of the mechanism(s) behind hyperhomocysteinemia in hypothyroid patients remains to be elucidated.

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