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Letters to the Editors

Impaired vascular reactivity in primary hyperparathyroidism may contribute to cardiovascular risk

Sirs, We read with interest the recent article by Neunteufl *et al.* (2000), which reported the effects of parathyroidectomy on vascular reactivity in patients with primary hyperparathyroidism (PHPT). Flow-mediated dilatation (FMD) of the brachial artery was assessed before and after parathyroidectomy. Previously, the same authors reported that despite similar FMD in PHPT and healthy controls (11·6 ± 4·6% *vs.* 12·6 ± 4·9%), glyceryl trinitrate (GTN)-mediated dilatation was blunted in the PHPT group (Neunteufl *et al*., 1998). Following parathyroidectomy, brachial artery responses to flow and GTN were unchanged. The authors conclude that vascular smooth muscle function is impaired in PHPT, resulting in altered vascular reactivity, which does not improve despite successful parathyroidectomy.

In our experience, increases from baseline arterial diameter of greater than 10%, following the stimulus of increased flow, are unusual even in young, healthy individuals. Therefore, the magnitude of dilatation in the present study is surprising, particularly given the prevalence of other cardiovascular risk factors (38% smokers, 27% hypertensive in study group) known to impair endothelial function. The failure to demonstrate an improvement in FMD after treatment would be expected because the dilatation observed at baseline probably reflects the near maximal response of flow-induced endogenous nitric oxide (NO) release. The authors' chosen methodology of placing the occluding cuff in the upper arm will lead to ischaemia of the brachial artery distal to the cuff and also to products of local ischaemia being washed over the segment of artery under study, following cuff release. It is to avoid such confounding variables that Celermajer *et al*. (1992) chose to place the occlusion cuff at the wrist. It is thus possible that cuff placement could have accounted for the relatively large responses reported in the current study. Support for this hypothesis comes from recent data demonstrating that, following release of an upper arm cuff, there is a greater hyperaemic stimulus than that observed with wrist cuff placement, leading to greater dilatation (Vogel *et al*. 2000). Furthermore, the increased dilatation may not be entirely NO-dependent as ischaemic, vasodilatory metabolites may have contributed. This confounding influence may have masked changes in the bioavailability of NO and thus endothelial function in the study.

The observation of impaired GTN-mediated dilatation in the presence of intact FMD is unusual given that GTN, acting as direct NO donor to vascular smooth muscle, is a considerably more potent stimulus than flow-induced changes dependent on endogenous NO (Bhagat *et al*., 1997). Both mechanisms rely on the presence of intact smooth muscle function as they share a final common pathway in initiating dilatation by relaxing smooth muscle in the media. In the presence of smooth muscle dysfunction, FMD would also be attenuated significantly. Thus, the observation of intact FMD in this study does not indicate smooth muscle dysfunction as Neunteufl *et al.* (2000) suggest. Indeed, at such high doses of GTN (0·8 mg) part of the response to GTN may also be flow-mediated and it is this component of the response which is impaired, suggesting endothelial dysfunction in PHPT as has been previously demonstrated (Nilsson *et al*., 1999). Impaired GTN-mediated dilatation reflects reduced distensibility in the large conduit vessels, suggesting arterial stiffening. We have recently demonstrated increased large artery stiffness in untreated mild PHPT (Smith *et al*. 2000). The haemodynamic consequences of arterial stiffening include the elevation of central aortic pressure, a key determinant of left ventricular afterload, and the subsequent development of left ventricular hypertrophy (LVH). Our observations may therefore explain the frequent finding of LVH in both hypertensive and normotensive PHPT patients.

The underlying mechanisms of arterial stiffening in PHPT, whether due to predominantly structural changes in the vessel wall such as media calcification or to functional abnormalities that include endothelial dysfunction have yet to be determined. Although Neunteufl *et al.* (2000) suggest that structural changes such as medial calcification are responsible, evidence for this hypothesis is lacking. Despite the undoubted association of intracardiac calcification, to our knowledge there is no clear evidence of an association between large vessel calcification and PHPT. A postmortem study reported coronary artery calcification in hypercalcaemic subjects (Roberts & Waller, 1981) but this study group was heterogeneous, containing individuals with uraemic hyperparathyroidism. Although vessel calcification is a well-recognized phenomenon in uraemic hyerparathyroidism, its pathogenesis in this condition is complex and inferences should not be extrapolated to PHPT. Rather than structural changes in the vessel wall, metabolic abnormalities, including insulin resistance, that are associated with PHPT (Valdemarsson *et al*., 1998) may provide an alternative explanation for impaired vascular reactivity in the condition (Smith *et al*. 2000). Although further studies are awaited, we agree with Neunteufl *et al.* (2000) suggestion that patients with both treated and untreated PHPT should be considered to be at increased cardiovascular risk.

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Antihypertensive drug urapidil metabolites interfere with metanephrines assays

Sirs, Hormonal overproduction assessment is mandatory to diagnose pheochromocytomas but urinary catecholamines or metabolites assays are prone to spectrophotometric analytical interferences (Rosano *et al*., 1991). Interferences are much less frequent although not unheard of using high pressure liquid chromatography coupled to electrochemical detection (HPLC/ED). We report here double interferences using both metanephrines assays in patients receiving the antihypertensive drug urapidil (Dooley & Goa, 1998).

Our attention was attracted by elevated total urinary metanephrines levels (spectrometric assays, Gardet *et al*.) in patients from an emergency cardiology ward. Patients receiving urapidil had higher metanephrines levels than other patients [median (min−max): 0·47 [0·15–1·01] *vs.* 1·2 [0·7–4·7] mg/d, N 12 *vs.* 10, nonurapidil *vs.* urapidil-treated patients, respectively, $P < 0{\cdot}0005$ Mann–Whitney test] despite similar blood pressure levels and urinary catecholamines excretion (not shown). We hypothesized that urapidil treatment generated interferences in this assay. Furthermore, about 2/3 of samples of urapidil-treated patients also had (i) an additional peak more or less merged with the normetanephrine peak (ii) a delayed (2 h) peak. Interestingly, the latter was visible even if the first peak was undetected. Undetected the early peak could lead to an overestimation of the normetanephrine level. Metanephrine, metoxydopamine, adrenaline, nor-adrenaline and dopamine were devoid of interference and within the normal range.

Did the additional peak reveal the presence of (i) urapidil itself (ii) a metabolite (iii) a compound formed after urine collection and extraction in an acidic medium? Chromatograms were obtained after diluting the drug in the vehicle phase or after processing and diluting the drug (10^{-5}-10^{-8} M) in a mock urine acidification. No peak was detected. The hypothesis of a metabolite-induced interference was confirmed when one of us self-administered a sustained-release 30 mg urapidil capsule. Both additional peaks were present 6 h after the administration.

Thus urapidil can induce interferences in 2 unrelated metanephrines assays. This can result in false positive diagnosis of pheochromocytoma, increasing anxiety and costs. Furthermore, as the HPLC column was ageing (2–3 weeks) it is less easy to diagnose the interference rendering the diagnosis very difficult or impossible. We are aware of an adrenocortical adenoma operated on the belief of (falsely) elevated normetanephrine. Keeping in mind this problem is especially important when dealing with urapidil-treated patients with adrenal incidentaloma and/or hypertensive crisis. Should the problem of urapidil-induced interferences arise, the determination of urinary catecholamines levels assay could help to avoid a misclassification of adrenal tumours.

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