Non–super-selective Venous Sampling for Persistent Hyperparathyroidism Using a Systemic Hypocalcemic Challenge

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ABSTRACT

Purpose: To describe a new protocol employing an acute systemic hypocalcemic challenge (SHC) aimed at augmenting the parathyroid hormone (PTH) gradient to enable non–super-selective venous sampling (VS) in patients with persistent primary hyperparathyroidism (PHPT).

Materials and Methods: In a retrospective study, 37 patients (39 studies—20 SHC, 19 super-selective VS) who underwent VS for persistent or recurrent PHPT were examined. Study patients were pretreated with intravenous hydration, diuretics, and bicarbonate to induce temporary relative hypocalcemia and then underwent non–super-selective VS targeted at large vessels within the neck and chest with rapid PTH testing. The traditional VS protocol involved super-selective VS with arteriography.

Results: SHC decreased ionized calcium by 0.098 mmol/L ± 0.18 ($P = .07$) and increased peripheral PTH by 10.2 pg/mL ($P = .58$). Positive VS gradients, defined as a ≥ 1.4-fold difference from baseline to after SHC, were detected in 95% of patients. VS findings guided successful surgery in 77% of SHC cases and 90% of super-selective VS cases; the peak gradient site was concordant with operative findings in 46% of SHC cases and 80% of super-selective VS cases. Avoidance of super-selective sampling decreased mean fluoroscopy time from 91 minutes to 33 minutes and decreased contrast material administered from 204 mL to 63 mL (both $P < .0001$).

Conclusions: The SHC protocol to enable non–super-selective VS in patients with persistent PHPT had the same ability as super-selective VS to detect a positive (≥ 1.4-fold) PTH gradient, was associated with decreased accuracy in identifying the site of the adenoma compared with super-selective VS, and significantly decreased contrast material used and fluoroscopy time.

ABBREVIATIONS

IJ = internal jugular vein, PHPT = primary hyperparathyroidism, PTH = parathyroid hormone, SHC = systemic hypocalcemic challenge, VS = venous sampling

Primary hyperparathyroidism (PHPT) is a common clinical condition, affecting 1 in 700–1,000 patients (1,2). Definitive cure is achieved only through successful surgery (3). In experienced hands, initial parathyroid surgery is associated with success rates of ≥ 95% and complication rates of approximately 1%–2% (4,5). Patients whose initial surgery is unsuccessful often do not undergo reoperation (6). Patients with persistent PHPT (defined as hypercalcemia within 6 months after initial surgery) or recurrent PHPT (hypercalcemia occurring ≥ 6 months after a postoperative period of eucalcemia), should be evaluated for reoperation at an expert center (7).

Remedial parathyroid surgery is frequently challenging. Compared with initial surgery, it is associated with substantial increases in morbidity, mortality, risk of operative failure, and cost (8). Given these increased risks, the decision to reoperate is driven to a large degree by the ability to localize accurately the hyperfunctioning parathyroid lesion preoperatively (9–11). First-line noninvasive imaging fails to locate the lesion in a significant fraction of

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None of the authors have identified a conflict of interest.

J Vasc Interv Radiol 2012; 23:1191–1199

http://dx.doi.org/10.1016/j.jvir.2012.06.005

patients who are candidates for reoperation (12). Use of ultrasound, computed tomography (CT), magnetic resonance (MR) imaging, and technetium-99m (^{99m}Tc) sestamibi scintigraphy for noninvasive localization has yielded variable results, with agreement between two imaging modalities reported to be only 30% in the reoperative setting (13–15).

Super-selective venous sampling (VS), performed via dual central venous and arterial catheterization to measure parathyroid hormone (PTH) gradients across inflow and outflow regions of the thyroid, can localize the side of the hyperfunctioning gland in 39%–93% of patients with persistent or recurrent PHPT (15–17). We implemented a new protocol for VS in which an acute systemic hypocalcemic challenge (SHC) was induced with diuresis followed by primarily large vein sampling with rapid PTH assessment. We hypothesized that VS with SHC protocol would be equivalent to traditional, super-selective VS with arteriography in its ability to detect a PTH gradient. In addition, we hypothesized that the SHC protocol would decrease fluoroscopy time and volume of contrast material administered.

MATERIALS AND METHODS

Patients

Institutional review board approval was obtained for this retrospective study. After the development of the SHC protocol in May 2008, consecutive patients with persistent or recurrent PHPT who were referred from an endocrine surgeon were assigned to undergo VS after SHC. All procedures were performed by a single interventional radiologist with > 10 years of interventional experience. Eligible patients had a biochemically confirmed diagnosis of PHPT (ionized calcium > 2.5 mmol/L or total calcium > 10.5 mg/dL and PTH > 65 pg/mL) (18), which persisted or recurred after previous surgery. Data from this cohort of consecutive SHC patients (August 2008–November 2010) and a group of consecutive historical controls who underwent super-selective VS (July 1996–May 2008) were reviewed retrospectively. The historical control sampling procedures were performed by a single operator with > 20 years of interventional radiology experience. There was no change in technique over the study period. Patients were not eligible to undergo VS if they had a previous allergic reaction to iodine contrast medium or had a creatinine level > 2.0 mg/dL.

Systemic Hypocalcemic Challenge Protocol

The SHC protocol was instituted by a specially trained staff member on the patient's arrival at the hospital on the day of the procedure (**Fig 1**). Using a transfemoral route, blood samples were taken from individual large veins within the neck and chest. The vein sampling locations were the superior vena cava, bilateral internal jugular (IJ), bilateral subclavian, bilateral brachiocephalic, and azygos veins. Upper, middle, and lower location samplings were obtained in the superior vena cava and IJ. Samples were collected in groups of four and sent to the laboratory for rapid PTH serum measurements. PTH levels were measured using a Roche rapid PTH platform (< 20-minute turnaround time; Elecsys 2010; Roche, Basel, Switzerland). When a PTH gradient was identified in a large vein, super-selective sampling was directed in the area of the gradient if deemed necessary by the interventional radiologist. A VS gradient was considered positive if the ratio of serum PTH in the sampled specimen to baseline serum PTH level was ≥ 1.4 (19).

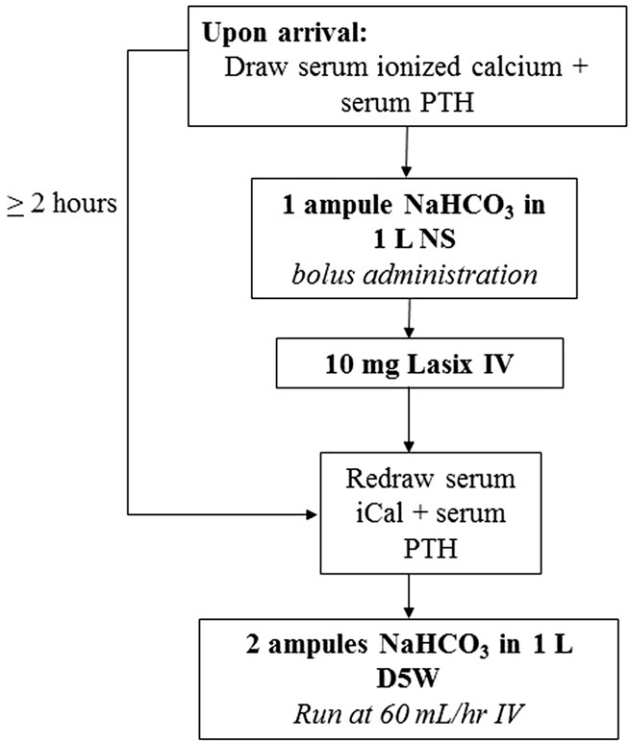

Figure 1. Eligible patients (persistent or recurrent PHPT without renal failure or contrast allergy) were scheduled to undergo SHC with semiselective VS. The protocol before initiating the VS is shown. Sampling was initiated within 1 hour of completion of the SHC protocol. Bicarbonate ($NaHCO_3$) infusion continued throughout the VS procedure. D5W = 5% dextrose in water, iCal = ionized calcium; NS = normal saline.

Remedial Parathyroidectomy

Patients were referred for VS after consultation with an endocrine surgeon or after an outside referral from an endocrinologist. Our protocol for work-up of persistent or recurrent PHPT included reimaging with surgeon-performed ultrasound and ^{99m}Tc sestamibi scan. If nonlocalizing or discordant studies had been performed at outside institutions before referral, they were repeated at our institution. Most surgical cases were performed by a fellowship-trained endocrine surgeon who performs > 200 parathyroid operations each year. Other surgical cases were performed