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Adrenal vein sampling: Substantial need for technical improvement at regional referral centres

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ABSTRACT

Object: Adrenal vein sampling (AVS) is the gold standard for localization of aldosterone producing adenoma. The anatomy of the right adrenal vein makes this procedure technically demanding and it may yield no clinical information if the adrenal veins are not adequately cannulated. Having frequently observed the technical failure of AVS, we undertook a review of 220 procedures in British Columbia, Canada.

Design and methods: Subjects were retrospectively identified through the laboratory information system. The following were collected: demographics, screening aldosterone concentration and renin activity/mass, results of dynamic function tests, AVS aldosterone and cortisol results. Standard calculations were performed on AVS data and site-specific success rates were compared. The effect of adrenocorticotropin hormone (ACTH) stimulation on the selectivity index (SI) and lateralization index (LI) were explored.

Results: The overall technical success-rate of AVS procedures was only 44% in procedures where no ACTH-stimulation was used ($n = 200$) but this rose significantly ($p < 0.01$) to 82% for those employing ACTH ($n = 139$). ACTH-stimulation significantly increased the median SI (left: 5.8 vs 36.7, $p < 0.01$; right: 7.0 vs 51.2, $p < 0.01$), and salvaged 36 procedures from yielding no information, 21 of which demonstrated lateralization of aldosterone production. In 64 cases showing lateralization both pre and post-stimulation, ACTH significantly decreased the median LI from 5.4 to 2.2, $p < 0.01$, creating substantial risk for spurious loss of lateralization.

Conclusions: The technical success of AVS is lower than reported elsewhere. Provided that effects on the LI are considered, the use of ACTH-stimulation during AVS assists in the identification of unilateral forms of PA.

Introduction

Epidemiology

The prevalence of hypertension among adults in Canada and the US has been estimated at 22–23% with future increases forecast [1]. Consequences of untreated hypertension include: higher risk of coronary and peripheral vascular disease, left ventricular hypertrophy, congestive heart failure, and chronic renal impairment. Accordingly, identification and treatment of secondary hypertension is imperative to chronic disease prevention.

Clinical presentation

Approximately 11% of newly diagnosed hypertension is caused by primary aldosteronism (PA) [2]. PA is characterized by inappropriate adrenal production of aldosterone in the absence of renin-mediated stimulation [3]. Patients typically present with high-normal to overtly high serum aldosterone concentration (SAC), and low-normal to undetectable plasma renin activity (PRA) or plasma renin mass (PRM), treatment-resistant hypertension, and may also have hypokalemia and metabolic alkalosis. It is noteworthy that most patients are normokalemic [4,5].

Screening and confirmation

Biochemical screening for PA is undertaken in hypertensive individuals displaying any of the following: moderate to severe hypertension, early age of onset, treatment-resistance, concomitant spontaneous or diuretic-induced hypokalemia, or documented adrenal incidentaloma [3–6]. Screening is performed by analysis of SAC and PRA (or PRM) after appropriate patient preparation [3–6]. A positive screen for PA is constituted by a SAC:PRA ratio above a minimum threshold determined

Abbreviations: AVS, Adrenal Vein Sampling; ACTH, Adrenocorticotropin Hormone; APA, Aldosterone Producing Adenoma; BAH, Bilateral Adrenal Hyperplasia; BC, British Columbia; IVC, Inferior Vena Cava; LAV, Left Adrenal Vein; LI, Lateralization Index; LL, LifeLabs; PA, Primary Aldosteronism; PRA, Plasma Renin Activity; PRM, Plasma Renin Mass; RAV, Right Adrenal Vein; SAC, Serum Aldosterone Concentration; SI, Selectivity Index; SPH, St. Paul's Hospital.

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by the properties of the assays employed [5,6]. It has additionally been suggested that SAC should be above a minimum concentration before the SAC:PRA ratio is considered because suppressed PRA can lead to spuriously positive screens even in low-aldosterone states [3–5]. Diagnostic confirmation of PA is accomplished using one of several dynamic function tests: saline infusion, oral salt loading, fludrocortisone suppression, or captopril suppression followed by SAC or 24-h urine collections as appropriate [5–7].

Adrenal vein sampling

After diagnostic confirmation of PA, subtype classification is required to identify unilateral (surgically-curable) forms, most often aldosterone producing adenomas (APAs) [3–6], which represent 30–35% of cases [3,4]. Use of computed tomography imaging for subtype classification is unreliable because many APAs are too small to be detected and non-functioning incidentalomas may be mistakenly identified as causative. Therefore, the gold-standard for subtype classification is direct sampling and analysis of aldosterone and cortisol from adrenal vein effluent bilaterally, commonly referred to as adrenal vein sampling (AVS).

The AVS procedure is performed under fluoroscopic guidance by an interventional radiologist [8] and is technically demanding due to the anatomy of the right adrenal vein (RAV), which inserts directly into the posterior aspect of inferior vena cava (IVC) in proximity to a number of other veins of similar calibre. This can make anatomical identification of the RAV difficult. Furthermore, the RAV is usually shorter and narrower than the left adrenal vein (LAV) and may occasionally enter a common drainage with a small hepatic or renal capsular accessory veins [8]. It is important to avoid the incidental collection of hepatic drainage because it is aldosterone-deplete and may thereby confound calculations [9]. In contrast, the LAV drains into the superior aspect of the left renal vein, making it easier to locate. In an AVS procedure, the RAV and LAV are respectively or concomitantly catheterized, upon which samples from both are collected and analyzed for cortisol and aldosterone. It is important to collect samples from the RAV before the LAV because the former takes longer to identify and this order of collection helps ensure samples are drawn in close temporal proximity. This mitigates the risk of ACTH-mediated (stress-induced) fluctuations in the aldosterone/cortisol secretion which may confound interpretation.

Cortisol results from putative adrenal vein candidates are divided by those of the peripheral blood (lower-IVC, iliac or femoral vein) to calculate the so-called "selectivity index" (SI — see Table 1). The SI must exceed a pre-determined threshold in order to prove successful cannulation and appropriate sampling of adrenal effluent. An SI ≥ 2 is often considered evidence of adequate cannulation in the absence of ACTH-stimulation while levels ≥ 3 are used for AVS procedures augmented with ACTH [10]. If cannulation is successful for both adrenal veins, further calculations can be undertaken. In order to determine whether the cause of PA is unilateral (and therefore surgically treatable), the lateralization index (LI) is calculated dividing the larger ("dominant") venous aldosterone-to-cortisol (A/C) ratio by the smaller ("non-dominant") one (see Table 1).

There is no consensus on a minimum LI to diagnose lateralization [5–10]. Results from 3 to 5 are often considered specific to unilateral forms of PA, but use of higher values in this range increases the specificity for unilateral disease at the cost of diagnostic accuracy [11,12]. Results below 3 are often used to define bilateral disease and some authors propose a "gray" or indeterminate zone for results between 3 and 4 [10].

As mentioned, the stressful conditions placed upon patients during AVS are thought to be a risk for sporadic intraprocedural aldosterone/cortisol secretion, potentially confounding calculations. To overcome this effect, some sites use ACTH-infusion or bolus to overwhelm any physiological effects [5]. The use of ACTH also exaggerates cortisol secretion making biochemically-proven cannulation easier to attain [11].

Table 1
Definitions for the selectivity index, lateralization index, and thresholds for their interpretation which were employed in this study. "Periphery", in reference to the SI calculation, is understood to mean a collection from the infrarenal inferior vena cava, the iliac vein or the femoral vein.

Term	Definition
Selectivity index (SI)	$Cort_{(adrenal)}/Cort_{(periphery)}$
Successful catheterization pre-ACTH stimulation	SI ≥ 2
Successful catheterization post-ACTH stimulation	SI ≥ 3
Unsuccessful catheterization on the right (USCR)	SI < 2 (pre-ACTH) OR SI < 3 (post-ACTH)
Unsuccessful catheterization on the left (USCL)	SI < 2 (pre-ACTH) OR SI < 3 (post-ACTH)
Bilaterally unsuccessful catheterization (BUSC)	USCR AND USCL
Lateralization index (LI)	$[A/C_{(dominant)}]/[A/C_{(non\text{-}dominant)}]$
Aldosterone producing adenoma (LAA/RAA)	LI ≥ 4
Indeterminate diagnosis (IND)	3 < LI < 4
Bilateral adrenal hyperplasia (BAH)	LI ≤ 3

Screening in British Columbia Canada

In British Columbia (BC — population 4.6 million), PA screening is performed at two laboratories: LifeLabs (LL) in Victoria and St. Paul's Hospital (SPH) in Vancouver. The two laboratories use different approaches for PA screening: LL uses Siemens Coat-a-Count® radioimmunoassay for SAC and the Diasorin Liaison chemiluminescent sandwich assay for PRM. SPH uses liquid chromatography and tandem mass spectrometry for aldosterone [13] and an in-house radioimmunoassay (RIA) for PRA [14]. Notwithstanding the difference in renin determination, both strategies are known to be effective for PA screening [15].

Analysis of all AVS samples in BC occurs at SPH. When SPH protocolized the analysis and interpretation of AVS in 2006, it was apparent that rates of bilaterally successful cannulation of the adrenal veins were much lower than the >95% reported elsewhere [3]. Furthermore, there was disparity in success-rates between radiological operators. Because AVS exposes the patient to certain risks (infection, radiation exposure and rarely: adrenal vein rupture/thrombosis, or adrenal infarction) and because the procedure is costly from the perspective of consumables, radiologist/nursing time, use of the fluoroscopy suite, biochemical analysis, and interpretive time [16], a review of provincial AVS success was warranted as a quality-improvement initiative.

We have undertaken a 10 year retrospective review of AVS procedures in BC to investigate the site-specific success rates and to identify the practices of more successful sites.

Materials methods

Method of data collection

This study was approved by the SPH ethics board. One hundred and ninety-eight subjects who underwent 220 AVS procedures in BC over a 10-year period were identified through the laboratory information system at SPH. Extracted demographic information collected included: gender, age of initial screen, and age at AVS. Extracted biochemical data collected included: aldosterone and PRA/PRM results at the time of first screening, the dynamic function test employed (saline suppression or oral salt load) including the accompanying aldosterone results (serum/urine), and all collection dates. With respect to AVS, the following were extracted: hospital performing AVS and date of procedure, aldosterone and cortisol results for the LAV, RAV and peripheral vein. Results from all 6 institutions performing AVS (herein denoted A–F)