CHEST

Valsalva Maneuver in Pulmonary Arterial Hypertension

Susceptibility to Syncope and Autonomic Dysfunction

Philip L. Mar, MD, PharmD; Victor Nwazue, MD; Bonnie K. Black, RN, CNP; Italo Biaggioni, MD; André Diedrich, MD, PhD; Sachin Y. Paranjape, BS; James E. Loyd, MD; Anna R. Hemnes, MD; Ivan M. Robbins, MD; David Robertson, MD; Satish R. Raj, MD; and Eric D. Austin, MD

BACKGROUND: Patients with pulmonary arterial hypertension (PAH) are routinely instructed to avoid performing the Valsalva maneuver for fear of syncope or sudden cardiac death. The mechanism of this action has not been elucidated. We conducted a case-control trial of nine patients with PAH and 15 healthy control subjects to determine if systemic hemodynamic changes during the Valsalva maneuver in these patients invoke greater susceptibility to syncope than healthy control subjects. Metrics commonly employed in autonomic testing were used to assess the degree of autonomic failure.

METHODS: Common Valsalva parameters, including adrenergic baroreflex sensitivity, pressure recovery time, systolic BP (SBP) recovery, diastolic BP (DBP) recovery, mean arterial pressure recovery, and the Valsalva ratio, were calculated. Mann-Whitney *U* tests were used to compare continuous variables. The primary end point was adrenergic baroreflex sensitivity.

RESULTS: Patients with PAH had lower adrenergic baroreflex sensitivity (9.7 $\pm$ 4.6 mm Hg/s vs 18.8 $\pm$ 9.2 mm Hg/s; $P = .005$), longer pressure recovery time (3.6 $\pm$ 2.5 s vs 1.7 $\pm$ 0.8 s; $P = .008$), similar SBP recovery (–13 $\pm$ 11 mm Hg vs –12 $\pm$ 23 mm Hg; $P = .640$), less DBP recovery (–1 $\pm$ 12 mm Hg vs 13 $\pm$ 14 mmHg; $P = .025$), less mean arterial pressure recovery (–5 $\pm$ 11 mm Hg vs 5 $\pm$ 17 mm Hg; $P = .048$), and a decreased Valsalva ratio (1.25 $\pm$ 0.11 vs 1.60 $\pm$ 0.22; $P < .001$) compared with healthy control subjects.

CONCLUSIONS: Compared with healthy control subjects, patients with PAH are more susceptible to syncope during the Valsalva maneuver because of autonomic dysfunction causing cerebral hypoperfusion. These study patients with PAH exhibited a degree of susceptibility to syncope similar to a spectrum of patients with intermediate autonomic failure who typically experience a SBP drop of 10 to 30 mm Hg with standing. CHEST 2016; 149(5):1252-1260

KEY WORDS: autonomic function; autonomic nervous; pulmonary arterial hypertension; syncope

ABBREVIATIONS: BRS-a = adrenergic baroreflex sensitivity; DBP = diastolic blood pressure; HC = healthy control; HR = heart rate; MAP = mean arterial pressure; MSNA = muscular sympathetic nerve activity; PAH = pulmonary arterial hypertension; PRT = pressure recovery time; SBP = systolic blood pressure; VM = Valsalva maneuver

AFFILIATIONS: From the Autonomic Dysfunction Center, Division of Clinical Pharmacology, Departments of Medicine (Drs Mar, Nwazue, Biaggioni, Diedrich, Loyd, Hemnes, Robbins, Robertson, and Raj; Ms Black and Mr Paranjape), Pharmacology (Drs Biaggioni, Robertson, and Raj), Biomedical Engineering (Dr Diedrich), Neurology (Dr Robertson), and Pediatrics (Dr Austin), Vanderbilt University, Nashville, TN; Division of Cardiovascular Medicine, Department of Medicine (Dr Mar), University of Louisville, Louisville, KY; and Department of Cardiac Science (Dr Raj), Libin Cardiovascular Institute, University of Calgary, Calgary, AB, Canada.

FUNDING/SUPPORT: This study was funded by the National Institutes of Health [Grants P01 HL 108800 and K23 HL 098743].

CORRESPONDENCE TO: Eric D. Austin, MD, Vanderbilt University MCN, Room DD-2211, Nashville, TN 37232-2578; e-mail: eric.austin@vanderbilt.edu

DOI: http://dx.doi.org/10.1016/j.chest.2015.11.015

Pulmonary arterial hypertension (PAH) is a significant problem worldwide, with a high degree of morbidity and mortality within a few years of diagnosis.[1] Syncope in patients with PAH is thought to portend a poorer prognosis and is associated with sudden death.[2,3] The etiology of syncope in these cases has been associated with arrhythmias.[3,4] Patients with PAH are routinely counseled to avoid straining or other situations in which they would strain against a closed glottis, such as the Valsalva maneuver (VM), for fear of syncope.[5] The contribution of systemic hypotension to syncope in this setting has not been explored. Opotowsky et al[6] recently showed that a bedside VM may reliably differentiate between those patients with pulmonary hypertension with or without elevated pulmonary artery wedge pressure, and thus differentiate PAH from pulmonary hypertension due to left-sided heart failure. However, no studies have evaluated the hemodynamic changes in the systemic circulation during all four phases of VM in patients with PAH compared with normal subjects as they relate to BP and heart rate (HR).

We hypothesized that patients with PAH will have hemodynamic profiles consistent with a significantly higher vulnerability to presyncope or syncope compared with healthy control (HC) subjects. To test this hypothesis, a case-control study was conducted to evaluate the hemodynamic changes that occur during VM in patients with PAH and HC subjects. The study used validated Valsalva metrics to assess orthostatic hypotension in patients referred for evaluation of syncope.

Materials and Methods

Patient Population

Between August 2013 and December 2013, patients with PAH cared for by the Vanderbilt Pulmonary Hypertension Center and age-/BMI-matched HC subjects recruited from the Vanderbilt University Clinical Research Center volunteer database and local advertisements were enrolled in the study.[7] Patients with PAH were diagnosed according to accepted international criteria, including a mean pulmonary arterial pressure $>$ 25 mm Hg and pulmonary artery wedge pressure $<$ 15 mm Hg.[8] Subjects were excluded if they had a square root sign on their VM tracing or were classified as New York Heart Association functional class III or higher. Patients with a square root sign were excluded because it invalidates Valsalva metrics.[9] Patients were neither included nor excluded based on history of syncope or BP ranges. HC subjects had no cardiovascular disease or other major illnesses, and none were current smokers. Pregnancy was excluded in female subjects on the basis of a urine or serum pregnancy test result.

The Vanderbilt University institutional review board approved this study (study no. 9401), and each subject gave his or her written informed consent for participation. Study investigations were performed at the Elliot V. Newman Clinical Research Center at Vanderbilt University. Pulmonary hypertension medications were not held prior to testing.

PAH Patient Data

Nine patients with PAH were enrolled in the study, and their pertinent clinical information, including right heart catheterization (RHC) and transthoracic echocardiogram (TTE) data, are listed in Table 1. RHC and TTE data were that most proximate to the Valsalva study. In eight of nine subjects, RHC was performed within 4 weeks of the study; the exception was subject 5, whose most proximate RHC was performed 8 months later. TTE was performed within 6 months of the Valsalva study for seven of nine subjects; the exceptions were subjects 2 and 3, who underwent TTE 7 and 10 months prior, respectively. These values are only meant to provide insight into the PAH patient population that was studied. Because neither TTE nor RHC was part of the study protocol, their significance in this setting is unclear, and statistical analyses were not performed on these data.

Data Acquisition During VM

Systolic BP (SBP) and diastolic BP (DBP) were measured continuously by using the finger volume clamp method (Nexfin; BMEYE) and intermittently with an automated oscillometric brachial cuff (Vital-Guard 450C, Ivy Biomedical Systems). HR was determined by using continuous ECG monitoring (Vital-Guard 450C, Ivy Biomedical Systems). ECG and BP data were digitalized with 14-bit resolution at a 500- and 1,000-Hz sample frequency by using a WINDAQ data acquisition system (DI720; DATAQ) and processed off-line by using custom software in PV-Wave language (PV-Wave; Visual Numerics Inc) written by one of the study authors (A. D.).

Valsalva Maneuver

Baseline HR, SBP, and DBP were obtained just prior to initiation of VM. Patients were asked to maintain an expiratory pressure of at least 40 mm Hg for 15 s. VM (Fig 1) can be divided into four phases.[10] Phase 1 and phase 2 are the "strain phases" of VM, with a Valsalva-induced reduction in cardiac venous return and relative hypotension. Phase 3 and phase 4 are the "recovery phases" of VM, when cardiac venous return normalizes to baseline levels. Phase 1 includes the period from the onset of VM until the SBP peak. Phase 2 lasts from the end of phase 1 until the release of the VM. Phase 4 begins after the nadir SBP of phase 3 and lasts until the end of the overshoot of SBP (if present), or when SBP returns to baseline if no SBP overshoot in phase 4 is present. DBP was recorded immediately preceding the relevant SBP.

Various Valsalva metrics (Table 2) have been reported as useful in characterizing the severity of sympathetic nervous system dysfunction and were measured in this study. These include total BP recovery[9] (Fig 1), pressure recovery time (PRT),[11] and the adrenergic baroreflex sensitivity index (BRS-a).[12] Total BP recovery is defined as the change in BP from baseline until the end of phase 2, and it can be further divided into systolic, diastolic, and mean arterial pressure (MAP) components. PRT is defined as the amount of time required for the SBP to recover from the nadir of phase 3 to the baseline SBP level in phase 4.[11] BRS-a is defined as the BP drop between baseline and the nadir of phase 3 divided by the PRT.[12] The lowest SBP during phase 3 was used to calculate the starting point for the PRT and BRS-a. Other recorded Valsalva parameters included baseline HR, maximum HR during VM, and the Valsalva ratio, which is