Leftward Bulging of Atrial Septum Is Provoked by Nitroglycerin and by Sustained Valsalva Strain

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Background: The motion of the interatrial septum primum (septum) is dependent on the interatrial pressure relation, normally with slightly higher pressure in the left atrium and the septum bulging toward the right atrium. The aim of this study was to explore the physiologic mechanisms that reverse interatrial pressures and provoke leftward bulging of septum (LBA). The hypothesis was that both left ventricular unloading with nitroglycerin and sustained Valsalva strain would independently provoke LBA and that their combination would further intensify the effect.

Methods: Prospectively collected transesophageal echocardiography recordings from 13 patients with obstructive sleep apnea were retrospectively analyzed for the presence or absence of LBA during resting respiration and during Valsalva strain. In each condition, LBA beats were counted at time points before and after nitroglycerin spray had been administered, which enabled a comparison of the independent effects and the combined effect of the nitroglycerin and the Valsalva maneuver. An LBA beat was defined as a heartbeat displaying any LBA during the cardiac cycle.

Results: Nitroglycerin increased the proportion of LBA beats significantly during resting respiration, from 21 ± 27% to 54 ± 43% (P = .008). During Valsalva strain, the proportion increased with nitroglycerin spray from 48 ± 21% to 80 ± 17% (P = .001). After nitroglycerin administration, LBA occurred in at least three beats during strain in all Valsalva periods.

Conclusions: Unloading of the left ventricle by nitroglycerin administration and by sustained Valsalva strain independently provoked LBA. The combination of these two interventions further intensified the effect. (J Am Soc Echocardiogr 2014;27:1120-7.)

Keywords: Echocardiography, Patent foramen ovale, Nitroglycerin, Diastolic function, Septum primum motion

The motion of the interatrial septum primum (hereafter called the septum) is dependent on the interatrial pressure relation, normally with slightly higher pressure in the left atrium. The septum is then bulging toward the right atrium, with a short reversal only in early systole during inspiration.[1,2] The bulging of the septum can therefore be seen as a marker for the interatrial pressure difference.[2-4]

The Problem

It is established that the release of a powerful Valsalva maneuver induces leftward bulging of the septum (LBA), but there is only limited understanding of most other aspects of the physiology controlling the interatrial pressure relation.[5] In this study, we explored the mechanisms of the interatrial pressure relation, as expressed by the presence or absence of LBA.

Present Knowledge

Because bulging reflects interatrial pressure, LBA implies that right atrial pressure exceeds left atrial pressure. In the case of a patent foramen ovale (PFO), this pressure gradient opens the PFO, which would otherwise be functionally closed, and drives blood from the right atrium through to the left atrium. Absent LBA is the most common cause of false-negative results when attempting to detect PFO via contrast transesophageal echocardiography (TEE),[6-9] and reduced Valsalva strain due to sedation is a common explanation for the absence.[10-12] Another explanation for absent LBA may be elevated left atrial pressure with continuous rightward bulging of the septum.[1,4,13,14] Elevated left atrial pressure may occur in patients with diastolic dysfunction due to left heart disease secondary to hypertension, diabetes, or ischemic heart disease.[15] Left atrial pressure increases further with stress and increasing systolic blood pressure,[16] and TEE is a stressor that often increases blood pressure and pulse.[17] The increase in atrial pressure may be rapid and greater in the left than in the right atrium.[18] Nitroglycerin administration reduces both systemic pressure and left atrial pressure.[19]

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Abbreviations
LBA = Leftward bulging of the septum
OSA = Obstructive sleep apnea
PFO = Patent foramen ovale
RWT = Relative wall thickness
TEE = Transesophageal echocardiography

Furthermore, right atrial inflow is reduced during the Valsalva strain period[20]; when strain is sustained for five beats, the interatrial pressure gradient seems to equalize or even intermittently reverse[5] and might thus provoke LBA.

Hypothesis

We hypothesized that left ventricular unloading with nitroglycerin would provoke LBA and that sustained Valsalva strain would also achieve this effect. We further hypothesized that the combination of these two interventions would intensify the effect.

METHODS

Study Population

Thirty patients with obstructive sleep apnea (OSA) were previously screened for the presence or absence of PFO with contrast TEE. As previously published, PFOs were detected in 14 of these patients.[8,9,21] The 30 examinations have now been analyzed for interatrial septal motion, and the highest value was noted. Patient examinations showing ≥10 mm of septal motion from one side to the other were included for analysis of LBA. This selection was made because we deemed it more feasible to evaluate bulging of the septum when there is some redundancy of the septum. In patients with only small motion of the septum from one side to the other, the curvature of the septum may be difficult to discern. The group consisted of 13 patients, with PFOs detected in nine of them. Hypertension was present in nine and diabetes in five patients. The mean age was 62.8 ± 5.6 years (range, 55–73 years). Left ventricular ejection fraction was ≥55% in all subjects. Right ventricular systolic pressure could be measured in 12 of the 13 patients and was 27 ± 6 mm Hg (range, 17–44 mm Hg).

Most patients had no daytime sleepiness, because OSA was diagnosed as part of a population screening program, without considering any clinical symptoms of sleep apnea. Daytime sleepiness was assessed with the Epworth Sleepiness Scale, an eight-item self-administered questionnaire used for rating the likelihood of dozing off in eight daily situations, on a scale from 0 to 3. The final score may range from 0 to 24. We noted a mean score of 5.2 ± 3.5, with a maximum score of 10 in two patients, indicating only mildly increased sleepiness in these two patients. The apnea-hypopnea index was 29.8 ± 18.7, with a median of 21. Results of spirometry[21] were normal in all subjects. All participants gave written informed consent. The study was approved by the human research regional ethical review board in Gothenburg, Sweden.

TEE

Before the examination, the patients were thoroughly informed about the procedure, and they also practiced the Valsalva maneuver. All patients blew into a manometer at ≥40 mm Hg for ≥8 sec for standardization.[8] All patients received sedation with 2 mg midazolam before probe insertion. The protocol for TEE has been described elsewhere,[8,21] but the protocol in the present study contained some additional features, namely, recordings of septal motion, also without contrast injections.

The procedures were carried out in the following order: First, in the midesophageal view, septal motion was recorded at a typical angle of 50° to 100°, with both two-dimensional and M-mode imaging during resting respiration and during Valsalva strain. Second, multiple injections were given, with an accumulated volume of about 100 mL over a period of 20 min. Agitated polygeline (Aventis Pharma, Frankfurt am Main, Germany) creates effective contrast and was used for PFO detection.[22] A single contrast injection was considered positive when contrast appeared in the left atrium within three heartbeats of contrast filling of the right atrium, and the number of bubbles passing over to the left atrium during these three beats was estimated visually. Third, the septal motion was recorded during resting respiration. Fourth, nitroglycerin (0.4 mg × 2) was sprayed sublingually and the bed tilted constantly 10°, foot down. Fifth, the motion of the septum was registered during resting respiration and during Valsalva strain. Sixth, additional contrast injections were performed.

Blood pressure was measured manually in resting respiration, immediately before transesophageal echocardiographic probe insertion, before nitroglycerin administration, and 1 min thereafter. Images were stored digitally, and series of consecutive beats were recorded on video. Data were prospectively collected, but the analytic methodology was retrospectively applied. The video recordings were analyzed visually for the presence or absence of LBA, defined as a leftward shift and leftward convexity of the septum, as shown in Figures 1A and 1B and Videos 1 and 2 (available at www.onlinejase.com). When the septum is viewed as a part of the perimeter of a circle and the center of the circle is located on the right side of the septum, this indicates the presence of LBA. Analysis was made on a beat-to-beat basis, and an LBA beat was defined as a heartbeat with any period of LBA during the cardiac cycle. The analysis was made by two observers, independently of each other; discrepancies were then settled by consensus. The observers could not be blinded to the type of intervention, as the start and end of Valsalva strain were marked on the screen and information on nitroglycerin administration could be inferred from the time shown on the screen. The timing in relation to QRS complex and the duration of LBA were measured by one observer (M.C.J.), from digitally stored M-mode images, as shown in Figure 2, with commercially available software (EchoPAC; GE Healthcare, Fairfield, CT).

Transthoracic Echocardiography

Standard Doppler echocardiographic examinations were performed on the same day as contrast TEE, as previously reported.[21] All examinations were performed by the same experienced sonographer, and all the registrations that were included were also part of the standard clinical echocardiographic protocol at our institution. In accordance with the guidelines,[23] the images were analyzed offline with commercially available software (EchoPAC) by one person, who was blinded to the results of the interatrial septal motion analysis. Relative wall thickness (RWT) was calculated as (posterior wall thickness × 2)/left ventricular diastolic diameter.[23] In patients in sinus rhythm, elevated left ventricular diastolic pressure was assumed in the presence of all of the following factors: left atrial volume index > 34 mL/m^2, E/A ratio > 0.8, deceleration time < 200 msec, and pulmonary vein atrial reversal duration lasting 30 msec longer than mitral wave atrial duration.[24] In atrial fibrillation, left ventricular diastolic pressure was assumed to be elevated in the presence of a pulmonary vein diastolic flow deceleration time < 220 msec.[24]