Respiratory Physiology & Neurobiology 188 (2013) 71–78

Contents lists available at SciVerse ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Prevalence of left heart contrast in healthy, young, asymptomatic humans at rest breathing room air

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ARTICLE INFO

Article history:
Accepted 23 April 2013

Keywords:
Transthoracic saline contrast echocardiography
Patent foramen ovale
Right-to-left shunt
Intrapulmonary arteriovenous anastomoses

ABSTRACT

Our purpose was to report the prevalence of healthy, young, asymptomatic humans who demonstrate left heart contrast at rest, breathing room air. We evaluated 176 subjects (18–41 years old) using transthoracic saline contrast echocardiography. Left heart contrast appearing ≤3 cardiac cycles, consistent with a patent foramen ovale (PFO), was detected in 67 (38%) subjects. Left heart contrast appearing >3 cardiac cycles, consistent with the transpulmonary passage of contrast, was detected in 49 (28%) subjects. Of these 49 subjects, 31 were re-evaluated after breathing 100% O_2 for 10–15 min and 6 (19%) continued to demonstrate the transpulmonary passage of contrast. Additionally, 18 of these 49 subjects were re-evaluated in the upright position and 1 (5%) continued to demonstrate the transpulmonary passage of contrast. These data suggest that ~30% of healthy, young, asymptomatic subjects demonstrate the transpulmonary passage of contrast at rest which is reduced by breathing 100% O_2 and assuming an upright body position.

1. Introduction

In the last decade, a number of studies using intravenously injected contrast in combination with echocardiography have investigated the relationships between the transpulmonary passage of contrast during exercise (and other conditions) and several physiologically important functions, including pulmonary gas exchange efficiency (Lovering et al., 2008a; Stickland and Lovering, 2006; Stickland et al., 2004, 2006) and pulmonary pressure regulation (La Gerche et al., 2010; Lalande et al., 2012; Stickland et al., 2004). The majority, but not all, of these studies (Eldridge et al., 2004; Elliott et al., 2011; Kennedy et al., 2012; Laurie et al., 2012, 2010; Lovering et al., 2008a,b; Stickland et al., 2004) using intravenously injected contrast sought to exclude subjects for the presence of an intracardiac pathway (i.e. PFO) because it is known that the prevalence of PFO has been reported in various populations to be ~25–40% and therefore should be a fairly common finding (Hagen et al., 1984; Marriott et al., 2013; Woods et al., 2010). Neglecting to exclude subjects for a PFO could result in ambiguous results as one would be unable to determine if the presence of left heart contrast was the result of contrast passage via a PFO or via an intrapulmonary pathway. Thus, excluding subjects with a PFO would ensure that any potential relationships between the transpulmonary passage of contrast and the physiological variable in question would be specific to contrast traveling through an intrapulmonary pathway, rather than a PFO.

Less well accepted is a rationale for screening and either including or excluding subjects without PFO but who demonstrate the transpulmonary passage of contrast at rest breathing room air prior to any intervention. Clearly, if subjects demonstrate the transpulmonary passage of contrast prior to the intervention (i.e. while at rest breathing room air) there is no baseline without the transpulmonary passage of contrast on which to form conclusions. Hence, this is one rationale for screening subjects and excluding those who demonstrate the transpulmonary passage of contrast at rest breathing room air. Recent work by Woods et al. is to our knowledge the only report of the prevalence of the transpulmonary passage of saline contrast in humans at rest (Woods et al., 2010). In this study it was determined that 29/104 (28%) subjects demonstrated the transpulmonary passage of contrast at rest, however this was

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http://dx.doi.org/10.1016/j.resp.2013.04.019

Table 1
Anthropometric and demographic data of all 176 subjects.

	Clear, $n = 60$	Transpulmonary, $n = 49$	PFO, $n = 67$
Height (cm)	175 ± 8	174 ± 10	172 ± 11
Weight (kg)	71 ± 12	68 ± 12	69 ± 12
BMI (kg/m^2)	23.1 ± 2.8	22.6 ± 2.9	23.2 ± 2.8
Age (yrs)	23 ± 4	24 ± 4	23 ± 3
Female (%)	43	47	51

Values are expressed as mean ± standard deviation.

not an asymptomatic population as the authors were investigating the potential relationship between left heart contrast and migraine headache. Also noted in the work by Woods et al. the transpulmonary passage of contrast in healthy humans at rest who do not have a PFO is conventionally assumed to be an uncommon finding. This is presumably because the prevalence of otherwise healthy, asymptomatic humans who demonstrate the transpulmonary passage of contrast is not well established. Previous work done in our laboratory using transthoracic saline contrast echocardiography (TTSCE) in healthy humans has meticulously screened for and excluded subjects with PFO, and for subjects without PFO who demonstrate the transpulmonary passage of contrast at rest breathing room air (Elliott et al., 2011; Laurie et al., 2012, 2010). Accordingly, our laboratory has accumulated a large data set of healthy, young, asymptomatic human subjects and is in a unique position to aid in establishing the prevalence of the transpulmonary passage of contrast at rest breathing room air in this population. Thus, the first aim of this study is to report a retrospective analysis of these data.

In addition, it has recently been demonstrated that breathing 100% O_2 prevents or significantly reduces the transpulmonary passage of contrast during exercise in healthy human subjects (Elliott et al., 2011; Lovering et al., 2008b). Furthermore, Stickland and colleagues reported that subjects who demonstrated the transpulmonary passage of contrast at rest breathing room air in the supine position (2/8), no longer did so after adopting an upright position (Stickland et al., 2004). Thus, if breathing 100% O_2 or changes in body positioning in healthy human subjects at rest prevented the detection of the transpulmonary passage of contrast, then this could potentially alter the findings from TTSCE studies in subjects breathing supplemental O_2 or in various imaging positions. Accordingly, the second aim of this study was to determine if breathing 100% O_2 or standing in the upright position would prevent the detection of the transpulmonary passage of contrast in a subset of healthy, young, asymptomatic human subjects at rest.

2. Methods

This study includes the retrospective analysis of echocardiographic screening data collected at the Cardiopulmonary and Respiratory Physiology Laboratory at the University of Oregon, between 2008 and 2012. This includes data from 179 healthy, asymptomatic, non-smoking subjects between the ages of 18 and 41 without a self-reported history of cardiopulmonary disease (Table 1). All 179 subjects have enrolled in an ongoing or completed study within our laboratory, and each subject provided verbal and written informed consent prior to participation. All studies received approval from the University of Oregon Committee for the Protection of Human Subjects Institutional Review Board and were conducted according to the Declaration of Helsinki.

The comprehensive echocardiographic assessment each subject underwent was performed to identify and exclude subjects from participating in studies within our lab on the basis of previously undetected cardiopulmonary disease, PFO, or if they demonstrated the transpulmonary passage of contrast at rest breathing room air. Accordingly, prior work published from our laboratory only includes subjects without cardiopulmonary disease, PFO or the transpulmonary passage of contrast at rest breathing room air (Elliott et al., 2011; Laurie et al., 2012, 2010). However, regardless of subjects inclusion or exclusion from prior work, the current report is inclusive of all healthy, asymptomatic subjects (i.e. without known lung disease) who have undergone this echocardiographic assessment in our lab. All sonography was performed using a Philips Sonos 5500, by a registered diagnostic cardiac sonographer in both adult and pediatric echocardiography with 25 years of experience using TTSCE. Of the 179 healthy subjects screened within our laboratory between 2008 and 2012, we identified and excluded one female subject with a small pericardial effusion and two male subjects with bicuspid aortic valves. The remaining 176 subjects with normal ventricular function, valvular function, great vessels, pericardium, and without evidence of myocardial ischemia or congenital heart disease are included in this analysis.

2.1. Transthoracic saline contrast echocardiography

Initial agitated saline contrast studies were performed with subjects breathing room air and reclined at 45° in the left lateral decubitus position where a clear apical, four-chamber view was obtained. Care was taken to optimally visualize all four chambers, interatrial septum and delineate myocardial and valvular structures by individually adjusting the receiver gain settings. Each saline contrast injection was created by manually agitating 3 ml of sterile saline with 1 ml of room air for 15 s between two 10 ml syringes connected in parallel to two 3-way stopcocks. The saline–air microbubble suspension was then immediately injected in a constant, forceful manner into a peripheral antecubital vein via an IV catheter (20–22 G). This mixture of saline and air provides excellent right sided contrast (Fig. 1). Following opacification of the right atrium and ventricle, the subsequent 20 cardiac cycles were recorded at >30 frames/s for further analysis.

The appearance of ≥1 microbubble in the left atrium or ventricle in any frame during the subsequent 20 cardiac cycles served as the criterion that subjects were either positive for an intracardiac right-to-left shunt (i.e. PFO) or demonstrated the transpulmonary passage of contrast (Freeman and Woods, 2008; Hlastala and Van Liew, 1975; Kjeldsen et al., 1999; Meerbaum, 1993; Meltzer et al., 1981; Nanthakumar et al., 2001; Roelandt, 1982; Tsujino and Shima, 1980; Woods et al., 2010; Yang et al., 1971a,b). Saline contrast injections were performed during normal breathing, as well as immediately following the release of a Valsalva maneuver in order to transiently elevate right atrial pressure and create conditions optimal for the detection of an intracardiac right-to-left shunt. Effective Valsalva maneuvers were confirmed by a transient leftward shift of the interatrial septum. Valsalva maneuvers do not increase left heart contrast in the absence of a PFO. An intracardiac right-to-left shunt was suspected if microbubbles appeared in the left heart ≤3 cardiac cycles following right heart opacification (Cabanes et al., 2002; Di Tullio et al., 1992; Lamy, 2002). Moreover, in all subjects careful color flow Doppler interrogation of the interatrial septum in multiple imaging planes was performed and additional evidence for an atrial septal defect (ASD) was ruled out, such as a dilated coronary sinus or right-heart chamber dilation and a normal and separate tricuspid annular plane from the mitral annulus was confirmed. The transpulmonary passage of contrast was positive if contrast appeared in the left heart >3 cardiac cycles following right heart opacification (Hlastala and Van Liew, 1975; Meerbaum, 1993; Meltzer et al., 1981; Roelandt, 1982; Tsujino and Shima, 1980; Yang et al., 1971a,b).

Following every saline contrast injection, the recording was meticulously reviewed frame-by-frame to ensure microbubbles were accurately differentiated from myocardial or valvular