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The effects of nitroglycerin, norepinephrine and aminophylline on intrapulmonary arteriovenous anastomoses in healthy humans at rest

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ABSTRACT

We have investigated the effects of the intravenous infusion of nitroglycerin (NTG), norepinephrine (NE) and aminophylline (AMP) on the opening and recruitment of intrapulmonary arteriovenous anastomoses (IPAVA) in healthy humans at rest. In ten volunteers saline contrast echocardiography was performed during administration of two doses of the NTG (3 $\mu g\,kg^{-1}\,min^{-1}$ and 6 $\mu g\,kg^{-1}\,min^{-1}$) and NE (0.1 $\mu g\,kg^{-1}\,min^{-1}$ and 0.25 $\mu g\,kg^{-1}\,min^{-1}$) as well as 30 min following the administration of AMP at rate of 6 $mg\,kg^{-1}$. Echocardiography was used to assign bubble scores (0–5) based on the number and spatial distribution of bubbles in the left ventricle. Doppler ultrasound was used to estimate pulmonary artery systolic pressure. Using a Finometer the following hemodynamic parameters were assessed: heart rate, stroke volume, cardiac output, total peripheral resistance as well as systolic, diastolic and mean arterial pressure. The most important finding from the current study was that nitroglycerin, norepinephrine and aminophylline in the applied doses were not found to promote IPAVA opening in healthy humans at rest.

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1. Introduction

Human lungs have a primary function in gas exchange. In addition to that primary function, pulmonary microvasculature has a role as a blood filter trapping thrombi, platelet aggregates, gas and various other emboli before these potential infarcting agents can reach the arterial system (Butler and Hills, 1979). Pulmonary capillaries are a highly effective sieve since their mean diameter is 6.5 μm and can be maximally expanded to 13 μm (Glazier et al., 1969). Intrapulmonary arteriovenous anastomoses (IPAVA) are blood vessels present in humans and other species (Cheney et al., 1978; Galambos et al., 2013; Lovering et al., 2007; Muneyuki et al., 1971; Tobin, 1966) and coexist with pulmonary capillaries responsible for gas exchange. Since IPAVA are 15–500 μm (up to 1000 μm) diameter vessels, their opening presents a possible pathway for systemic microembolisation (Tobin and Zariquiey, 1950; Tobin, 1966). However, this potential pathway of embolization of vital organs (cerebral and coronary vasculature) is poorly perfused, or closed at rest in humans (Elliott et al., 2013). The mechanism(s) causing IPAVA opening or closure are still unknown. Recently, increases in pulmonary artery systolic pressure (PASP) and/or cardiac output (QT) have been shown to promote their opening and recruitment: during exercise (Eldrige et al., 2004; Kennedy et al., 2012; Lovering et al., 2008a,b, 2009; Stickland et al., 2007), at rest when breathing hypoxic mixtures (Laurie et al., 2010) and during intravenous infusion of inotropes (Bryan et al., 2012; Laurie et al., 2012), using a technique called saline contrast echocardiography. The closure of these vessels by breathing 100% oxygen appears to be due to a different mechanism because in exercising subjects and subjects receiving intravenously inotropes pressures and flows were equally elevated, yet IPAVA remained closed (Laurie et al., 2012; Lovering et al., 2008b).

In the present study we planned to investigate the effects of nitroglycerin (NTG), norepinephrine (NE) and aminophylline (AMP) on IPAVA opening and recruitment. We hypothesized that NTG, as a well known dose dependent venous and arterial vasodilator (Imhof et al., 1982), could have a direct dilating effect on IPAVA. When administered at higher rates, NTG increases QT, and an increase in QT has been reported to promote IPAVA opening. NE increases both systemic and pulmonary artery pressure (Cudkowicz, 1968), and slightly alters QT. While it was demonstrated that combination of

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PASP and QT promotes IPAVA opening an effect of increased PASP during unchanged QT on IPAVA opening needs to be addressed. Finally, the pulmonary vasodilator APM was previously shown to open IPAVA in dogs (Butler and Hills, 1979), but not in pigs (Vik et al., 1991), while what happens in humans is presently unknown.

The purpose of this study was to investigate whether the intravenous infusion of NTG, NE and AMP (all common used drugs worldwide) promotes opening and recruitment of these large-diameter dynamic vessels in healthy humans during rest, thus creating possibility of systemic embolization of vital organs such as the brain and heart.

2. Methods

2.1. Subjects

Ten male subjects were enrolled in this study. Nine subjects completed the protocol with administration of all three drugs. One subject completed the NE and NTG protocol, and was excluded prior the AMP administration due to headache and nausea after higher intravenous NTG dose (otherwise common NTG side effects). At the time of the study all subjects were apparently healthy. All of the subjects were experienced technical divers, screened for the presence of a patent foramen ovale within past three years using previously described methods (Eldrige et al., 2004). All subjects showed transpulmonary passage of bubbles from the right to left heart through IPAVA during participation in previous studies (Ljubkovic et al., 2012; Madden et al., 2013). Age, height, weight, body mass index (BMI), and body fat (BF) percentage were determined before the inclusion in study as well as spirometry, maximum voluntary ventilation and single-breath diffusing capacity for carbon monoxide, all determined using a pulmonary function testing unit (Quark b^2, Cosmed, Rome, Italy). Percent body fat was estimated by measuring subcutaneous skinfold thickness with a caliper (Harpenden skinfold caliper, Baty National, West Sussex, UK) at the three sites according to the Jackson Pollock equations for males. One subject reported mild smoking habits. All subjects were provided with a detailed description of all methods used and provided written informed consent before inclusion in the study. All experimental procedures were conducted in accordance of the Declaration of Helsinki, and were approved by the Ethics Committee of the University of Split School of Medicine.

2.2. Subject preparation and experimental protocol

The study was executed in the laboratory of Department of Integrative Physiology over a single visit. Subjects were placed in left lateral decubitus position for the duration of the entire protocol, and instrumented with a 20 G intravenous catheter in antecubital vein of the left arm. Two three way stopcocks (Lakhani Medicare Private Limited, Faridabad, Haryana, India) were connected to the catheter. The proximal stopcock was used for drug infusion, while through the distal stopcock a bolus comprised of 1 mL of air, 1 mL of the subject's blood, and 4 mL of saline was applied. All drugs were administered using an infusion pump (B. Braun, Infusomat® Space, Breinigsville, USA). Two doses of the NTG as well as NE were administered for 3–4 min: NTG at a rate of 3 $\mu g\,kg^{-1}\,min^{-1}$ and 6 $\mu g\,kg^{-1}\,min^{-1}$, and NE 0.1 $\mu g\,kg^{-1}\,min^{-1}$ and 0.25 $\mu g\,kg^{-1}\,min^{-1}$, respectively. AMP was administered at rate of 6 $mg\,kg^{-1}$ over a period of 30 min. Drugs were subsequently administered after a 15 min resting baseline period. Wash-out between different drug protocols lasted 30–45 min in order to reach baseline hemodynamic values. The first two administered drugs, NTG and NE, were randomized due to their short half-life (NTG $t_{½} \sim 3$–4 min; NE $t_{½} \sim 1$–2 min), while AMP was administered last due to half-life of $t_{½} \sim 8$ h.

2.3. Echocardiography measurements

An apical four chamber view was obtained *via* a phase-array ultrasonic probe (1.5–3.3 MHz) connected to a Vivid q ultrasonic scanner (GE, Milwaukee, USA). High quality images were obtained in all subjects and recordings were made for further analysis. Venous gas bubbles were seen as high density echoes in the heart cavities. For each bubble injection the apical four chamber view was recorded for 20 cardiac cycles after the initial appearance of bubbles in the right ventricle. A previously published subjective scoring system, ranging from 0 to 5 (Lovering et al., 2008b), was used to determine the bubble grade in the left ventricle more than 3 cardiac cycles after their appearance in the right heart. Bubble grade was determined by a consensus of the same two experienced observers throughout the entire study. A bubble grade ≥ 2 was considered a significant indicator for IPAVA opening. Pulmonary artery systolic pressure (PASP) was determined by measuring the peak velocity (υ) of the tricuspid regurgitation jet and applying that to the modified Bernoulli equation $4\upsilon^2 + 3$ (Rudski et al., 2010).

2.4. Assessment of hemodynamic parameters

All records were obtained in a quiet environment with an air temperature of $23 \pm 1\,^{\circ}C$. Subjects were placed in a supine (left lateral decubitus) position and rested for at least 15 min prior to recording. Systolic and diastolic blood pressure (SBP, DBP) were continuously and noninvasively monitored using finger photoplethysmography on the middle finger (Finometer, TPD Biomedical Instrumentation, Amsterdam, The Netherlands) and verified using a mercury manometer on the brachial artery before the scheduled drug protocol started. Stroke volume (SV) was estimated using Modelflow analysis (Wesseling et al., 1993) and verified using echocardiographic Teichholz's method subsequently after BP was calibrated. Cardiac output was calculated as SV × heart rate (HR), while total peripheral resistance (TPR) was derived from mean arterial pressure (MAP)/QT. All recordings were made *via* PowerLab/16_{SP} data acquisition system (ADI Instruments, Sydney, Australia) and were transferred and stored on a PC for further analysis (ADInstruments, Chart™ 5, Colorado Springs, USA), which included 1 min ± 1 s data segments. Peripheral oxygen saturation (SpO2) was monitored continuously by pulse oximetry (Poet II, Criticare Systems, Waukesha, WI), with the probe placed on the forefinger of the left hand.

2.5. Statistical analysis

Data are presented as mean ± standard deviation (SD). Normality of the distribution was confirmed for all parameters using the Shapiro–Wilk test. All of the comparisons of parameters measured for NTG and NE (baseline *vs.* drug infusion) and baseline values reached prior the each intravenous drug infusion were performed by repeated-measurements ANOVA using the *post hoc* Bonferroni test. Comparison of parameters measured for an AMP (baseline *vs.* drug infusion) was performed using Student's *t*-test for dependent samples, respectively. Bubble scores are presented as median (25–75% quartile range) and were compared using nonparametric Friedman analysis of variance. Analyses were done with Statistica 8.0 software (Statsoft, Inc., Tulsa, USA), and significance was set to $p < 0.05$.

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