Univerzita Karlova v Praze

1. lékařská fakulta

Autoreferát disertační práce

Úloha foramen ovale patens v patofyziologii vzniku dekompresní choroby

The Role of Patent Foramen Ovale in the Pathophysiology of Decompression Sickness

MUDr. Jakub Honěk

2017

Doktorské studijní programy v biomedicíně

Univerzita Karlova v Praze a Akademie věd České republiky

Obor: Fyziologie a patofyziologie člověka

Předseda oborové rady: Prof. MUDr. Jaroslav Pokorný, DrSc.

Školicí pracoviště: Ústav patologické fyziologie, 1. LF UK

Školitel: RNDr. Luděk Šefc, CSc.

Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

Obsah

Abstrakt

Foramen ovale patens (PFO) je spojováno se zvýšeným rizikem vzniku dekompresní choroby potápěčů (DCS). Patofyziologicky je tento jev vysvětlován paradoxní embolizací dusíkových bublin do systémového oběhu s následnou obturací kapilár vedoucí k ischemickému poškození tkání. Tato hypotéza, ač vyslovena již v 80. letech 20. století, je stále diskutována a doposud chyběla experimentální a prospektivní klinická data, která by ji podporovala. Její význam přitom není zdaleka jen teoretický. Průkaz PFO jako etiologického faktoru vzniku DCS a zejména nevyprovokované DCS (bez porušení dekompresních pravidel), by mělo zásadní význam i v terapii a prevenci této choroby, která představuje potenciální riziko pro miliony potápěčů na celém světě.

V našem výzkumu si klademe za cíl ozřejmit úlohu PFO v patofyziologii vzniku DCS a zjistit, zda prevence paradoxní embolizace dusíkových bubIin, povede k snížení incidence nevyprovokované DCS. Provedli jsme screening přítomnosti PFO pomocí transkraniální duplexní ultrasonografie u 489 potápěčů. V retrospektivní analýze jsme zjistili, že incidence nevyprovokované DCS byla 7% a že PFO bylo jediným rizikovým faktorem.

V dalším výzkumu jsme se zaměřili na detekci venózních a arteriálních dusíkových bublin po simulovaných ponorech v hyperbarické komoře. Zjistili jsme, že ponory provedené podle Bühlmannova dekompresního režimu (doporučeného pro rekreační potápěče v Evropě) byly spojeny s nižším výskytem jak venózních tak arteriálních bublin, než ponory provedené podle režimu US Navy. V jiné studii jsme zjistili, že katetrizační uzávěr PFO vedl k eliminaci arteriálních bublin po dvou profilech ponoru (do 18 m a do 50 m), po kterých byla v minulosti prokázána vysoká incidence žilních bublin. Konzervativní profily ponoru (omezení expozice zvýšenému parciálnímu tlaku dusíku, prodloužení dekompresního postupu), testované v dalším experimentu, vedly k významné redukci výskytu venózních bublin, ale ne k úplné eliminaci arteriálních embolů. Při přímém srovnání s katetrizačním uzávěrem PFO byly v eliminaci arteriálních bublin méně efektivní.

Na základě našich výsledků navrhujeme uzavřít, že PFO je spojeno se zvýšeným výskytem arteriálních dusíkových bublin po ponoru a se zvýšeným rizikem vzniku DCS u potápěčů. Našimi originálními výsledky pak je skutečnost, že i) PFO byl jediným rizikovým faktorem vzniku nevyprovokované dekompresní příhody, ii) katetrizační uzávěr PFO a konzervativní profily ponoru vedly k redukci výskytu arteriálních bublin po ponoru a mohou tak předcházet vzniku DCS u potápěčů s PFO. Klinická efektivita těchto postupů však musí být ověřena v dalších experimentálních a zejména longitudinálních klinických studiích.

Abstract

Patent foramen ovale (PFO) has been associated with an increased risk of decompression sickness (DCS) in divers. Pathophysiologicaly this has been ascribed to paradoxical embolization of nitrogen bubbles from venous blood to systemic circulation, resulting in obstruction of peripheral capillaries and ischemic injury. However, the role of PFO has been largely debated and experimental and prospective clinical data has been missing. It is of note, that this hypothesis is not only of theoretical importance. The proof of PFO as a causative factor of DCS and, importantly, of unpredictable events (unprovoked DCS) could affect millions of divers worldwide through improved therapy and prevention.

In our research we aimed to describe the pathophysiological role of PFO in decompression sickness and to determine whether the prevention of arterialization of post-dive venous gas emboli (VGE) would decrease the incidence of unprovoked DCS in divers. We have screened 489 scuba divers for the presence of PFO by means of transcranial color-coded Doppler ultrasonography. In a retrospective analysis we found that the incidence of unprovoked decompression sickness was 7% among these divers and that PFO was the only risk factor.

Subsequently, we have studied the occurrence of VGE and arterial gas emboli (AGE) in divers with large PFOs or after catheter-based PFO closure in a series of experimental studies in hyperbaric chamber. We found that Bühlmann regimen dives (recommended for recreational divers in Europe) were associated with lower occurrence of VGE than US Navy decompression regimen dives. In another study we demonstrated that after two provocative dive profiles, that generated significant number of VGE, catheter-based PFO closure led to elimination of post-dive AGE and DCS symptoms. In a following study conservative dive profiles (limited depth-time nitrogen exposure and prolonged decompression) led to decreased occurrence of VGE, but not to complete elimination of AGE. When compared with catheter-based PFO closure, conservative dive profiles were less effective in AGE reduction after a single simulated dive.

Based on our results, we suggest that the presence of a PFO is associated with increased post-dive occurrence of AGE and an increased risk of DCS in divers. Our original findings are that i) PFO was the only risk factor for unprovoked DCS, ii) catheter-based PFO closure and conservative dive profiles reduced post-dive AGE occurrence and might thus prevent DCS in divers with a PFO. However, the clinical efficacy of DCS prevention using these measures needs to be confirmed in further experimental and, importantly, in long-term clinical follow-up studies.

1. Introduction

The exposure to the hyperbaric environment during scuba (self-contained underwater breathing apparatus) diving is associated with unique effects on human physiology and with specific pathophysiologic consequences. In divers, PFO is associated with the increased risk of decompression sickness (DCS) (Bove A.A., 2014). Despite the high prevalence of PFO (25-30% in adults) (Hagen P.T. et al., 1984) and the existence of millions of divers worldwide (Vann R.D. et al., 2005), many questions regarding the role of PFO in the pathophysiololgy of DCS remain to be answered.

The diver is exposed to a hyperbaric environment during submersion. At depth, gases dissolve in tissues in a rate, that is dependent on the chemical composition and density of capillaries (Doolette D.J., Mitchell S.J., 2001). As the diver ascends, a pressure gradient drives the dissolved gases to venous blood and ultimately to the alveolar space from where it is expired. If the pressure drops too quickly, the tissues become supersaturated with gases not utilized by the body (nitrogen, inert gases) and gas bubbles form (Papadopoulou V. et al., 2013). These bubbles may cause either local tissue damage or embolize through venous blood (Vann R.D. et al., 2010). Small quantities of venous gas emboli (VGE) were confirmed by Doppler studies after most scuba diving (Dunford R.G. et al., 2002; Ljubkovic M. et al., 2011). Most divers with VGE, however, remain asymptomatic, as these are effectively filtered by pulmonary circulation. Symptoms may occur either with high bubble load (i.e. pulmonary gas embolism in case of severe violation of the decompression regimen) or due to paradoxical embolization (arterialization of bubbles) in a diver with a permanent or transient right-to-left shunt. In divers with a PFO, if paradoxical embolization occurs, arterialized bubbles lodge in peripheral capillaries. Furthermore, excess gas from supersaturated tissues promotes further growth of these bubbles. The resulting obstruction of capillaries causes local ischemia (Vann R.D. et al., 2010).

The connection between PFO and DCS was first described in the 1980s (Wilmhurst P.T. et al., 1986; Moon R.E. et al., 1989). Since then, a high prevalence of PFO has been repeatedly reported in divers with the neurological or cutaneous form of DCS (Torti S.R. et al., 2004; Wilmhurst P.T. et al., 2001; Cantais et al., 2003; Gempp al., 2012). Additionally, it has been suggested that repeated exposure to asymptomatic arterial embolisms could lead to chronic sequelae (Knauth M. et al., 1997). Bearing in mind the high prevalence of PFO, these reports raise concern among divers and involved medical professionals. Moreover, in divers with a PFO, a paradoxical embolization to the systemic circulation may cause various symptoms, even after a dive with an appropriate decompression regimen (Germonpré P., 1998). This unpredictable event has been coined “unprovoked DCS“.

Paradoxical embolization results from increased right atrial pressure due to hemodynamic changes that occur in divers. After submersion, blood redistributes from the periphery to the thorax, which results in an increased right atrial pressure (Marabotti C. et al., 2013). Moreover, divers may perform a Valsalva maneuver during or after the dive (to equalize pressure in the middle ear or while lifting heavy diving equipment), which further contributes to the increased right atrial pressure and might lead to transient right-to-left shunting through the PFO. It is important to note, that shunt size might influence the risk of decompression sickness. The prevalence of large PFOs is estimated to be 6-10% in general population (Kerut E.K. et al., 2001). Also, the prevalence of PFO was reported to decrease with age in a large autopsy study of normal hearts (Hagen P.T. et al., 1984), on the other hand, there is some evidence for increasing patency of the foramen ovale in divers over years (Germonpré P. et al., 2005).

Theoretically, a PFO could contribute to the increased risk of DCS by other mechanisms than paradoxical embolization of nitrogen bubbles. Increased right atrial pressure in divers (Marabotti C. et al., 2013) might lead to significant shunting of hypersaturated blood through the PFO. This would lead to slower nitrogen desaturation and increased local bubble production in peripheral tissues. This mechanism was proposed by Bove (Bove A., 2015), but experimental data are still lacking.

There is still a large knowledge gap with regards to the optimal risk stratification and management strategy in divers with a PFO and routine screening for PFO in divers is currently not recommended in most countries (Undersea and Hyperbaric Medical Society, 2011; Torti S.R. et al., 2007). Suggested recommendations for divers with diagnosed PFO and a history of DCS include the cessation of diving, a conservative approach to diving, and PFO closure. However, to date there were no data that could guide our clinical decisions. So far there was no evidence to support the efficacy of catheter-based PFO closure on neither the reduction of arterial bubble counts nor the incidence of clinical overt DCS.

Similarly, although often advised, there were no data that would prove the efficacy of conservative dive profiles (CDP) for divers with a PFO. Conservative dive profiles are measures aiming to lower the probability of nitrogen bubble formation in order to decrease the risk of DCS. The probability of tissue supersaturation and subsequent bubble formation can theoretically be lowered by both minimizing tissue saturation (i.e. limiting nitrogen exposure) and allowing more time for the desaturation of tissues. To lower nitrogen exposure, various CDP recommendations limit maximum depth, dive time, number of dives per day or advise the use of mixtures with lower nitrogen content (enriched air nitrox) (Gempp E. et al., 2012; Klingmann C. et al., 2012). Similarly, to allow more time for desaturation, a slower ascent rate and performing longer safety stops is recommended (Klingmann C. et al., 2012). There is some evidence that pre-dive hydration and pre-dive exercise reduce the risk of DCS (Gempp E., Blatteau J.E., 2010).

2. Hypothesis, Aims and Objectives

Hypothesis

Arterialization of post-dive VGE through a PFO plays an important role in the pathophysiology of DCS and its prevention will decrease the incidence of unprovoked DCS.

Aims and objectives

The aim of our research is to elucidate the pathophysiological role of PFO in decompression sickness.

In order to achieve the aims of the project we will:

1) Perform screening for the presence of PFO in a large population of Czech professional and recreational divers and asses their risk of unprovoked DCS.
2) Perform simulated dives in a hyperbaric chamber to compare the occurrence of venous and arterial gas emboli while using different decompression regimens in divers with a PFO.
3) Perform simulated dives in divers with a PFO and after catheter-based PFO closure in order to determine the effect of PFO closure on the occurrence of venous and arterial gas emboli.

4) Perform simulated dives with conservative profiles in divers with a PFO in order to determine the effect of these procedures on the occurrence of venous and arterial gas emboli.
5) Compare the efficacy of conservative dive profiles and catheter-based PFO closure in reduction of post-dive AGE.

3. Material and Methods

Patients

A total of 489 consecutive divers were screened for PFO at our center. TCCS was used for screening, the diagnosis of PFO was confirmed by TEE. The right-to-left shunt was graded by means of TCCS according to the International Consensus Criteria (Jauss M., Zanette E., 2000): (grade 1) 1-10 bubbles, (grade 2) >10 bubbles but no curtain (uncountable number of bubbles), (grade 3) curtain. Baseline data (demographic data, diving experience, DCS history) were collected from all divers in the time of the screening examination.

Simulated Dives

Simulated dives were performed in a hyperbaric chamber according to the Bühlman (Bühlman A.A., 1983) or US Navy decompression regimen (United States Navy, 2008), respectively. Various dive profiles were used to test the effect of catheter-based PFO closure and the efficacy of CDP on reduction of AGE and VGE.

Post-Dive Bubble Detection and Symptom Assessment

Venous and arterial gas emboli were monitored within 60 min after surfacing (Carturan D. et al., 2002). In all divers the incidence of DCS symptoms was evaluated. Venous gas emboli were assessed by TTE in the right ventricular outflow tract, AGE were detected by means of TCCS in the middle cerebral artery (Blersch W.K. et al., 2002).

Catheter-Based Patent Foramen Ovale Closure

The PFO closure procedures were performed in a single center (with the exception of two divers) between February 1, 2006 and April 30, 2013. The Amplatzer septal occluder (AGA Medical Corporation, Golden Valley, MN) was used in 5 (25%) divers. In the remaining 15 (75%) cases, the Occlutech Figulla PFO Occluder N (Occlutech GmbH, Jena, Germany) was used. In all divers, the indication for the procedure was a history of unprovoked DCS and the presence of a grade 3 PFO. There were no major complications, bleeding at the puncture site with no need of intervention occurred in one patient (5%).

Definitions

Arterial gas emboli were defined as HITS in the Doppler spectrum detected by TCCS in the middle cerebral artery (Blersch W.K. et al., 2002). Venous gas emboli were defined as HITS in the Doppler spectrum detected by TTE in the right ventricular outflow tract. Neurological symptoms of DCS were defined as headache, unusual fatigue, visual problems, limb weakness or paralysis, dizziness and paresthesia reported by the patient ≤24 h after the simulated dive. A history of unprovoked DCS was defined as any DCS symptoms that originated ≤24 h after a dive that complies to all rules advised to recreational divers (no decompression air dive performed within the limits of any commercially available recreational diving table or computer, maximum depth 40 m, maximum ascent rate 10 m/min, safety stop performed as advised by computer/table).

Statistical Analysis

The distribution of data was evaluated by the Kolmogorov-Smirnov test. For categorical variables Fisher's test or $\chi 2$ test were used when appropriate. For continuous variables the Kruskal-Wallis test and the Mann-Whitney U test were used when appropriate. Normally distributed data are presented as mean ± standard deviation (SD) and non-normally distributed data as median with interquartile range (IQR). A p-value of ≤ 0.05 was considered to indicate a statistically significant difference.

To assess for risk factors of unprovoked DCS the associations between variables and DCS endpoint were evaluated using survival analysis techniques. We used Cox proportional hazards models to compute a hazard ratio (HR) with 95% confidence interval (CI), both unadjusted and adjusted, for the potential confounding covariates. Total sum of dives value was used as a measure of time.

Due to the possibility of numerically unstable estimates and large standard error, we did not include all available covariates in the final Cox proportional hazards model. Therefore, a backward stepwise elimination algorithm with a likelihood ratio statistic to minimize the exclusion of predictors involved in suppressor effects was used. Variables with a p value ≤ 0.1 on univariate testing were included in the elimination algorithm. Goodness of fit of the model was tested with the Grønnesby and Borgan test for the Cox proportional hazards model, with the number of risk groups based on May and Hosmer.

Additionally, Kaplan-Meier survival curves were created and log-rank statistics were calculated. Schoenfeld residuals were calculated for all models to assess a significant departure from the model assumption.

All statistical analyses were done using GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA) and IBM SPSS Statistics 23.0 (IBM, USA).

4. Results

Risk Factors of Unprovoked Decompression Sickness

A total of 489 divers were screened for the presence of a right-to-left shunt from January 2006 to January 2014 by means of TCCS. The screening program was offered to all registered Czech diving clubs, to professional police and firefighter divers and was regularly promoted through diving magazines, websites, instructor courses and diving and hyperbaric medicine meetings. Baseline data (demographic data, diving experience, DCS history) were collected from all divers in the time of the screening examination. The screening program is the main focus of the doctoral thesis of co-author Martin Šrámek, MD, who is also preparing the data for publication. Here we analyze the risk factors of unprovoked DCS. Survival analysis was used to identify the risk factors for unprovoked DCS.

Of the 489 divers (35.53 ± 8.95 years, 86.5% men) screened, 36 (7%) suffered from unprovoked DCS. The risk of unprovoked DCS was significantly higher in divers with a PFO according to the results of the log-rank test of the Kaplan-Meier analysis: $\chi 2\ (1) = 49.068$, $p < 0.001$ (Fig. 4). Hazard ratio (HR) for unprovoked DCS in divers with a PFO was 52.371 (95% CI 7.173 - 382.382, $p < 0.001$). The prevalence of PFO was 97.2% in divers with a history of unprovoked DCS and 35.5% in controls ($p < 0.001$). There was no difference in sex, age, body mass index, and total number of dives between the respective groups.

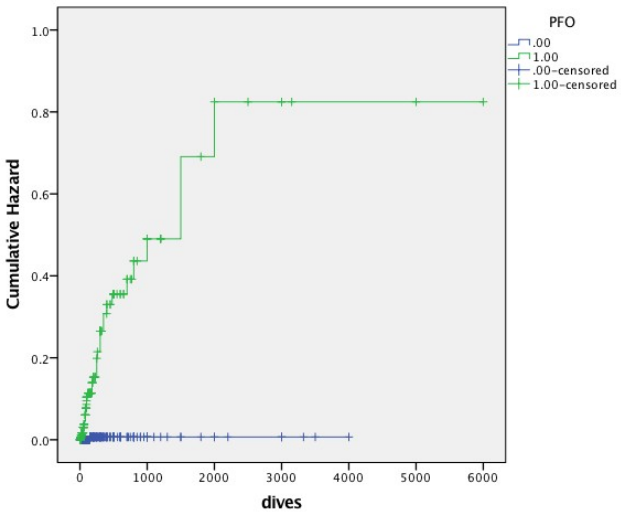

Fig. 1 Kaplan Meier analysis - cumulative hazard of unprovoked decompression sickness in divers with and without a PFO

Study 1 – Comparison of Bühlmann and United States Navy Decompression Regimen

The aim of the study was to test the risk of paradoxical embolism of nitrogen bubbles after simulated dives in divers with a patent foramen ovale (PFO), and to compare the safety of commonly used decompression regimens. In 31 divers we detected ultrasonographically VGE and AGE after surfacing from simulated dives. Three different decompression procedures were compared – Bühlmann 18 m, US Navy 18 m and US Navy 50 m (Bühlman A.A., 1983; United States Navy, 2008).

In the Bühlmann 18m regimen VGE were detected in 3 (21%) divers, no AGE (0%) were detected. In the US Navy 18 m regimen VGE were detected in 6 (67%) divers, AGE in 2 (22%) divers. In the US Navy 50 m regimen VGE were detected in 7 (88%), AGE in 6 (75%) divers. Significantly lower number of VGE was detected after Bühlmann regimen dives (recommended for recreational diving in the Czech Republic) compared with the US Navy regimen dives (21% vs. 76%, $p = 0.004$).

Study 2 – Efficacy of Catheter-Based Patent Foramen Ovale Closure

In this study VGE and AGE were assessed by means of ultrasound in 47 divers (35±8.6 yrs, 81% males) after surfacing from a simulated dive in hyperbaric chamber. The divers chose between two dive profiles (Dive A to 18 m, or dive B to 50 m). All divers had a grade 3 PFO and previously suffered from DCS; in 20, the PFO was occluded with a catheter-based device (closure group), the other 27 divers did not undergo any closure procedure (PFO group).

There was no difference in VGE occurrence between the closure and PFO groups, but no divers in the closure group had post-dive AGE after both dives (Figs. 2 and 3). Also, none of the divers in the closure group had DCS symptoms. In the PFO group neurological symptoms of DCS were observed in 21% and 25% of divers in dive A and B, respectively.

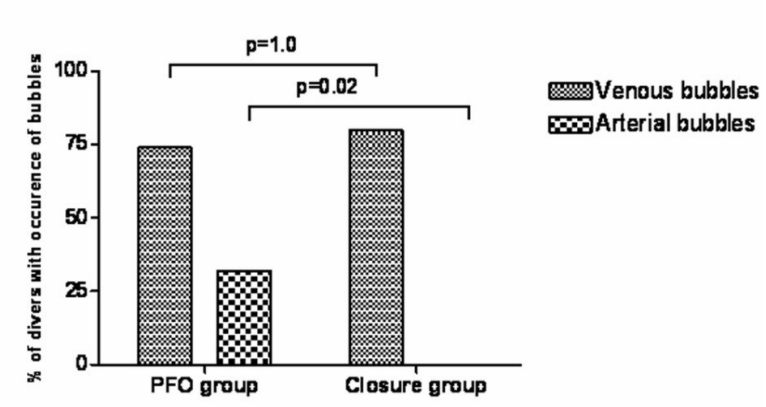

Fig. 2 – Occurrence of Arterial and Venous Gas Emboli after Dive A

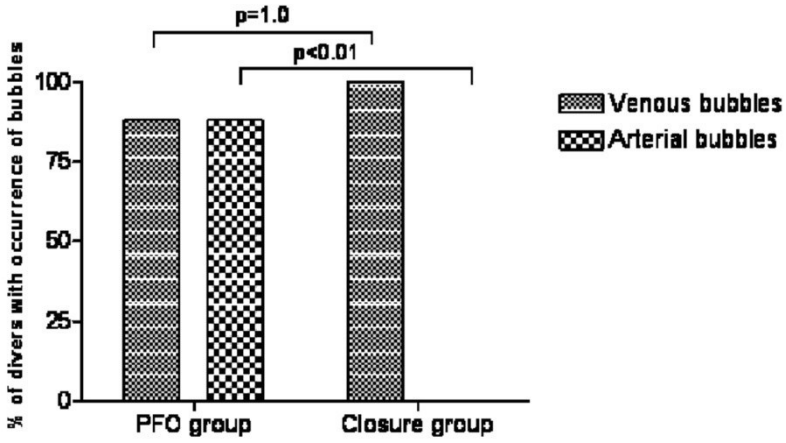

Fig. 3 – Occurrence of Arterial and Venous Gas Emboli after Dive B

Study 3 – Efficacy of Conservative Dive Profiles

In this study VGE and AGE were assessed by means of ultrasound in 46 divers (36.4 ± 10 years; 72% men) with a grade 3 PFO. All divers performed a simulated dive to 18 m in a hyperbaric chamber. Divers were randomized into three groups: group A (n = 13; 36.5 ± 9 years; 77% men) performed a standard Bühlmann regimen no-decompression dive (dive time 51 min, ascent rate 10 m/min), group B (n = 14, 40.9 ± 12 years; 64% men) performed the same regimen with a slower ascent (51 min, 5 m/min), and a control group (n = 19; 33.0 ± 8 years; 74% men) performed a staged-decompression dive according to the US Navy decompression regimen (80 min, 9 m/min, decompression stop 7 min at 3 m). The occurrence of arterial and venous gas emboli is summarized in Fig. 4.

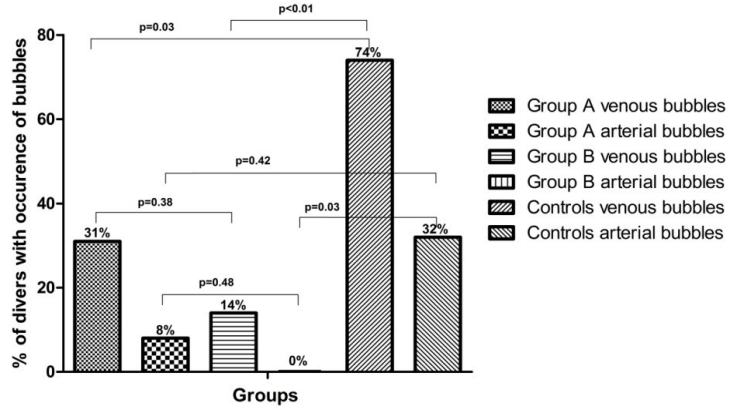

Fig. 4 – Summary of the Occurrence of Post-Dive Venous and Arterial Gas Emboli.

Study 4 – Comparison of Conservative Diving and Catheter-Based Patent Foramen Ovale Closure

In this study we pooled and analyzed data from our previous studies (study 2 and 3) in order to compare the efficacy of conservative diving and catheter-based PFO closure. This yielded a total of 47 divers with a PFO. Nineteen divers with a PFO performed a decompression dive to 18 m for 80 min (control group), 15 divers after a catheter-based PFO closure performed the same dive (group 1) and 13 divers with a PFO performed a dive to the same depth for a non-decompression time of 51 min (group 2). The results are summarized in Fig. 5.

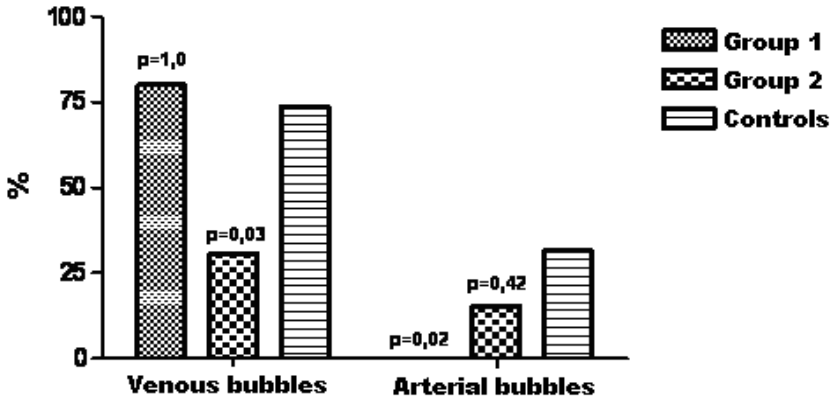

Fig. 5 - Summary of the Occurrence of Post-Dive Venous and Arterial Gas Emboli.

5. Discussion

Decompression sickness is known to be caused by nitrogen bubble formation during the diver's ascent (Vann R.D. et al., 2010). The diver is exposed to an elevated pressure of nitrogen when breathing compressed air. This excess nitrogen dissolves in all tissues. The total nitrogen load is determined by the depth profile and the duration of the dive. During the ascent and after the dive, the excess gas is transported from the tissues back to the alveoli and exhaled. If the diver reaches the surface too early, the tissues get hypersaturated and intravascular and extravascular bubbles form and increase in size (Vann R.D. et al., 2010). To prevent DCS, divers perform the ascent according to decompression tables or a decompression algorithm implemented in a diving computer.

Despite these preventive measures, small numbers of intravascular bubbles can be ultrasonographically detected in venous blood even after a properly performed dive (Dunford R.G. et al., 2002). These bubbles are usually asymptomatic because most of the time, they are effectively filtered by the pulmonary circulation (Vann R.D. et al., 2010). However, some divers experience a DCS without any violation of the decompression regimen, an event that has been termed unprovoked DCS.

The concept, that a small number of bubbles embolizing to the systemic circulation through the PFO could cause DCS was mentioned already in the 1980s (Wilmhurst P.T. et al., 1986; Moon R.E. et al., 1989). Several restrospective studies confirmed higher incidence of PFO in symptomatic divers (see table 1) in the two following decades. However, the role of PFO in the pathophysiology of DCS has since then been largely debated. To date there were no studies that would confirm the hypothesis that the reduction of the number of AGE would decrease the risk of DCS. Also, to date no studies focused specifically on unprovoked DCS.

We screened a relatively large population of Czech divers (N=489) and found that the prevalence of unprovoked DCS was 7%. The prevalence of PFO and, importantly, high-grade

PFO was high in patients with a history of unprovoked DCS. There was no difference in sex, age, body mass index and total number of dives between the respective groups. Patent foramen ovale was found to be the only risk factor of unprovoked DCS using Cox proportional hazards model. To our knowledge, this is the first study to asses for risk factors of unprovoked DCS.

Traditionally, age, body mass index and repetitive diving were considered risk factors of DCS. Carturan and colleagues monitored 50 divers after two dive profiles and found ascent rate, age, aerobic fitness, and adiposity to be associated with higher post-dive VGE occurrence (Carturan D. et al., 2002). In a study performed by the Divers Alert Network 67 recreational divers were monitored for two years for Doppler-detected VGE (Dunford R.G. et al., 2002). The incidence of high-bubble grade was approximately 20% higher for repetitive dives than for first dives, approximately 20% higher for males than females, also increased with age (by 25% in male and 55% in female divers, respectively). In a retrospective observational study male divers were also in higher risk of DCS, although this might have been influenced by their diving habits (St Leger Dowse M. et al., 2002). On the other hand, Gempp and colleagues found results similar to ours in a small case-controlled study of divers with recurrent DCS (Gempp E. et al. 2012). They found right-to-left shunt and lack of changes in the way of diving after prior DCS as the only predictors of neurological DCS recurrence. Age, gender and diving experience were not associated with recurrent neurological DCS. Together with our results this suggests that PFO might play a more important role in at least a subset of DCS such as the neurological form or in unprovoked episodes.

In our experimental studies we focused on divers with a PFO in whom we assessed for post-dive VGE and AGE after various simulated dives in a hyperbaric chamber. In the first experimental study we assessed for post-dive VGE and AGE in divers with a PFO after Bühlmann and US Navy decompression regimen dives. Significantly lower number of VGE was detected after the Bühlmann regimen (recommended for recreational diving in the Czech Republic) compared with the US Navy regimen. The US Navy decompression regimen is characterized by a higher nitrogen exposure and a shorter decompression procedure. This led to a higher percentage of divers with venous and arterial emboli, as expected. Importantly however, even after the very conservative 18m Bühlmann dive, that would typically be performed by recreational divers, bubbles were found in 21% of the participants. Ljubkovic and colleagues found VGE in 75% of divers after an 18m dive with a slightly longer bottom time (60 min) and shorter decompression (no safety stop at 3 meters) performed according to the Norwegian Diving Tables (Ljubkovic M. et al., 2011). Similarly, Dunford and colleagues found VGE in 91% recreational divers (Dunford R.G. et al., 2002). However, in this study the divers participated in a multi-level multi-day repetitive recreational diving activity.

The high incidence of VGE after repetitive dives and the relatively high incidence of VGE after a simulation of a single recreational dive, found in our study, might support the hypothesis that recreational scuba divers with a PFO might be susceptible to the occurrence of unprovoked DCS. On the other hand, we have not observed any arterial bubbles or DCS symptoms in this group. This could suggest that the amount of the bubbles formed is generally low and other factors might play role in the sporadic occurrence of unprovoked DCS, such as differences in the level of pre-dive hydration or pre-dive exercise (Gempp E., Blatteau J.E., 2010).

In the second experimental study we demonstrated the effect of catheter-based PFO closure on the occurrence of AGE after simulated dives to 18 and 50 meters, respectively. No difference was found in the occurrence of VGE between divers with a high-grade PFO (PFO group) and divers after trans-catheter PFO closure (closure group). However, only in the closure group no AGE were detected. Moreover, in the deeper dive, where the nitrogen load

was greater, AGE were observed in all divers with a PFO and detected VGE. Twenty-nine percent of these divers had cerebral DCS symptomatology. This is in agreement with a previous case-controlled study by Germonpré and colleagues (Germonpré P. et al., 1998), who found high prevalence of high-grade PFO in divers suffering from unprovoked cerebral DCS. In our study, no divers in the closure group had DCS symptoms after either the 18-m or the 50-m dive. It is plausible, therefore, that the presence of a PFO plays a key role in paradoxical embolization of venous bubbles after scuba dives and its catheter based-closure might have an effect in the prevention of unprovoked DCS recurrence in divers. This preventive strategy has previously been suggested by several authors (Billinger M. et al. 2011; Walsh K.P. et al., 1999; Lairez O. et al., 2009). However, to date there was a lack of any data in this field.

Other research groups have suggested that the transpulmonary passage might also play an important role in the occurrence of post-dive AGE. Ljubkovic and colleagues observed arterial bubbles in 9 of 34 divers who tested negative for PFO and argued that transpulmonary arterialization would occur if a large amount of bubbles were produced and an individual exhibited a higher susceptibility for the transpulmonary passage (Ljubkovic M. et al., 2012). This was not observed in the closure group in our study, where no arterial emboli were detected, despite the fact that the occurrence of VGE was not different from the PFO group. Also, clinical studies support the fact that PFO might be the major route of paradoxical embolization in divers. Torti et al. reported that the odds of suffering a major DCS were 5x higher in divers with a PFO and that the risk paralleled PFO size (Torti S.R. et al., 2004). Wilmhurst et al. found that the incidence of PFO was 77% among 61 divers who had suffered the cutaneous form of DCS, compared with 28% in control subjects (Wilmhurst P. T. et al., 2001).

Theoretically, a PFO could contribute to the increased risk of DCS by other mechanisms than paradoxical embolization of nitrogen bubbles. Increased right atrial pressure in divers (Marabotti C. et al., 2013) might lead to significant shunting of nitrogen hypersaturated blood through the PFO and thus slower nitrogen desaturation and increased local bubble production in peripheral tissues (Bove A.A., 2015). In our study there was no difference in VGE occurrence between the PFO and closure groups. However, our ultrasonographic methodology did not allow to asses venous bubble count as a continuous variable.

The absence of symptom-based clinical endpoints is the main limitation of this observational study. A randomized prospective follow-up trial would be necessary to assess the clinical relevance of catheter-based PFO closure in divers. Another potential limitation is the experimental setting of the study. There is some evidence that wet dives generate more venous bubbles than dry dives do (Møllerløkken A. et al., 2011). In our study, only the 18-m dive was a dry dive, in the 50-m dive, the divers were submersed in a water reservoir inside the hyperbaric chamber using their usual scuba equipment.

In the third experimental study we sought to determine the incidence of post-dive VGE and AGE after conservative dive profiles. We compared three different dives to a maximum depth of 18 m. Divers were randomized into three groups. The first dive represented usual recreational diving practice, the divers performed a standard Bühlmann regimen no-decompression dive (18 m, 51 min, ascent rate 10 m/min). The second group performed dive with the same depth and bottom time (18 m, 51 min) with a slower ascent rate (5 m/min). The control group performed a staged-decompression dive according to the US Navy decompression regimen (18 m, 80 min, 9 m/min, decompression stop 7 min at 3 m). This was a dive used in our previous experiments and generated significant amount of VGE.

There was significantly lower occurrence of venous bubbles in the Bühlmann regimen dives compared to controls. However, AGE were eliminated only in the conservative dive

with a slower ascent rate. Transient neurological symptoms (headache, unusual fatigue, transitory visual disturbances) were present only in the control group. This study is to our knowledge the first study to date to test the efficacy of conservative dive profiles on the reduction of arterial and venous gas emboli in divers with a PFO. It is plausible that slower ascent rate would decrease the incidence of unprovoked DCS in this group of divers as we have observed a significantly reduced occurrence of both VGE and AGE. However, we have to bear in mind that the incidence of unprovoked DCS is low and a larger-scale clinical study would be needed to confirm this hypothesis. In a small observational study by Klingmann and colleagues the incidence of DCS decreased after recommendation of conservative diving in divers with and without a right-to-left shunt (Klingmann C. et al., 2012). This study followed 27 divers with a history of previous DCS for a mean of 5.3 years.

The effectivity of conservative dive profiles and catheter-based PFO closure was compared in the fourth study. In this study we demonstrated that a conservative dive profile using the Bühlmann regimen does not lead to the complete AGE elimination, that can be achieved by PFO occlusion. This is in accordance with our clinical data showing an increased risk of unprovoked DCS in divers with a PFO and emphasizes the necessity of further studies that would confirm the safety of any conservative diving measures in divers with large PFOs. It is clear that modification of diving habits is the key to DCS prevention. However, the development of a clinically useful risk-stratification strategy and individualized diving tables require further experimental and clinical research. Similarly, catheter-based PFO closure seems to be a potentially highly effective measure but its precise role is to be determined.

6. Conclusions

In our research we aimed to describe the pathophysiological role of PFO in decompression sickness and to determine whether the prevention of arterialization of post-dive VGE would decrease the incidence of unprovoked DCS in divers. We have screened a large cohort of Czech divers for the presence of PFO and assessed for the incidence of unprovoked decompression sickness. Subsequently, we have studied the occurrence of venous and arterial gas emboli in divers with large PFOs or after catheter-based PFO closure using various simulated dives in a hyperbaric chamber. We have demonstrated that:

1) Patent foramen ovale was a risk factor for unprovoked DCS.
2) Bühlmann regimen dives were associated with lower occurrence of VGE compared to the US Navy air decompression procedure.
3) Catheter-based PFO closure led to complete elimination of post-dive AGE. The occurrence of VGE was not different between divers with a PFO and after catheter-based PFO closure.
4) Conservative dive profiles led to decreased occurrence of VGE, but not to complete elimination of AGE.
5) When compared with conservative dive profiles, catheter-based PFO closure was more effective in AGE reduction after a single simulated 18-meter dive.

Based on our results we suggest that PFO plays an important role in the patophysiology of DCS. The presence of a PFO is associated with increased post-dive occurrence of AGE and an increased risk of unprovoked DCS in divers. The most likely mechanism is paradoxical embolization of VGE, although decreased nitrogen desaturation due to right-to-left shunting might also play role. Catheter-based PFO closure and conservative dive profiles reduce post-dive AGE occurrence and might thus prevent DCS. The clinical efficacy of DCS prevention using these measures needs to be confirmed in further experimental and, importantly, also in long-term clinical follow-up studies.

7. References

Billinger M, Zbinden R, Mordasini R, et al. Patent foramen ovale closure in recreational divers: effect on decompression illness and ischaemic brain lesions during long-term follow-up. Heart 2011;97:1932-7.

Blersch WK, Draganski BM, Holmer SR, et al. Transcranial duplex sonography in the detection of patent foramen ovale. Radiology 2002;225:693-9.

Bove AA. The PFO gets blamed again…perhaps this time it is real. J Am Coll Cardiol Intv 2014;7:409-10.

Bove AA. in Denoble PJ, Holm JR, eds. Patent Foramen Ovale and Fitness to Dive Consensus Workshop Proceedings. Durham, NC, Divers Alert Network, 2015, 160 pp.

Bühlman AA. Decompression-Decompression Sickness. Berlin New York: Springer-Verlag, 1983. ISBN 0387133089.

Cantais E, Louge P, Suppini A, Foster PP, Palmier B. Right-to-left shunt and risk of decompression illness with cochleovestibular and cerebral symptoms in divers: case control study in 101 consecutive dive accidents. Crit Care Med 2003;31:84-8.

Carturan D, Boussuges A, Vanuxem P, et al. Ascent rate, age, maximal oxygen uptake, adiposity, and circulating venous bubbles after diving. J Appl Physiol 2002;93:1349-56.

Doolette DJ, Mitchell SJ. The physiological kinetics of nitrogen and the prevention of decompression sickness. Clin Pharmacokinet 2001;40:1-14.

Dunford RG, Vann RD, Gerth WA, et al. The incidence of venous gas emboli in recreational diving. Undersea Hyperb Med 2002;29:247-59.

Gempp E, Blatteau JE. Preconditioning methods and mechanisms for preventing the risk of decompression sickness in scuba divers: a review. Res Sports Med 2010;18:205-18.

Gempp E, Louge P, Blatteau JE, Hugon M. Risk factors for recurrent neurological decompression sickness in recreational divers: a case-control study. J Sports Med Phys Fitness 2012;52:530-6.

Germonpré P, Dendale P, Unger P, Balestra C. Patent foramen ovale and decompression sickness in sports divers. J Appl Physiol 1998;84:1622-6.

Germonpré P, Hastir F, Dendale P, et al. Evidence for increasing patency of the foramen ovale in divers. Am J Cardiol 2005;95:912-5.

Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17-20.

Jauss M, Zanette E. Detection of right-to-left shunt with ultrasound contrast agent and transcranial Doppler sonography. Cerebrovasc Dis 2000;10:490-6.

Kerut EK, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. J Am Coll Cardiol 2001;38:613-23.

Klingmann C, Rathmann N, Hausmann D, Bruckner T, Kern R. Lower risk of decompression sickness after recommendation of conservative decompression practices in divers with and without vascular right-to-left shunt. Diving Hyperb Med 2012;42:146-50.

Knauth M, Ries S, Pohimann S, et al. Cohort study of multiple brain lesions in sport divers: role of a patent foramen ovale. British Med J 1997;314:701-5.

Lairez O, Cournot M, Minville V, et al. Risk of neurological decompression sickness in the diver with right-to-left shunt: literature review and meta-analysis. Clin J Sport Med 2009;19:231-5.

Ljubkovic M, Dujic Z, Møllerløkken A, et al. Venous and arterial bubbles at rest after no-decompression air dives. Med Sci Sports Exerc 2011;43:990-5.

Ljubkovic M, Zanchi J, Breskovic T, et al. Determinants of arterial gas embolism after scuba diving. J Appl Physiol 2012;112:91-5.

Marabotti C, Scalzini A, Menicucci D, et al. Cardiovascular changes during SCUBA diving: an underwater Doppler echocardiographic study. Acta Physiol (Oxf) 2013;209:62-8.

Møllerløkken A, Breskovic T, Palada I, et al. Observation of increased venous gas emboli after wet dives compared to dry dives. Diving Hyperb Med 2011;41:124-8.

Moon RE, Camporesi EM, Kisslo JA. Patent foramen ovale and decompression sickness in divers. Lancet 1989;1:513-4.

Nagaraja V, Eslick GD. Stroke prevention by percutaneous closure of patent foramen ovale: a meta-analytic review. Int J Cardiol 2014;172:524–526.

Papadopoulou V, Eckersley RJ, Balestra C, Karapantsios TD, Tang MX. A critical review of physiological bubble formation in hyperbaric decompression. Adv Colloid Interface Sci 2013;191-192:22-30.

St Leger Dowse M, Bryson P, Gunby A, Fife W. Comparative data from 2250 male and female sports divers: diving patterns and decompression sickness. Aviat Space Environ Med 2002;73:743-9.

Torti SR, Billinger M, Schwerzmann M, et al. Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. Eur Heart J 2004;25:1014-20.

Undersea and Hyperbaric Medical Society. UHMS best practice guidelines: prevention and treatment of decompression sickness and arterial gas embolism. Available at: https://www.uhms.org/images/DCS-AGE-Committee/dcsandage_prevandmgt_uhms-fi.pdf Accessed Dec 17, 2014.

United States Navy. US Navy Diving Manual Revision 6, 2008. Available at: http://www.usu.edu/scuba/navy_manual6.pdf Accessed November 12, 2013.

Vann RD, Butler FK, Mitchell SJ, Moon RE. Decompression Illness. Lancet 2010;377:153-64.

Vann RD, Freiberger JJ, Caruso JL. Divers Alert Network report on decompression illness, diving fatalities and project dive exploration: 2005 edition (based on 2003 data). DAN technical Report, 2005. Available at: http://www.diversalertnetwork.org/medical/report/2005DCIReport.pdf. Accessed February 24, 2015.

Vann RD, Lang M. Recreational diving fatalities. Undersea Hyperb Med 2011;38:257-60.

Walsh KP, Wilmhurst PT, Morrison WL. Transcatheter closure of patent foramen ovale using the Amplatzer septal occluder to prevent recurrence of neurological decompression illness in divers. Heart 1999;81:257-61.

Wilmhurst PT, Ellis PT, Jenkins BS. Paradoxical gas embolism in a scuba diver with an atrial septal defect. British Med J 1986;293:1277.

Wilmhurst PT, Pearson MJ, Walsh KP, Morrison WL, Bryson P. Relationship between right-to-left shunts and cutaneous decompression illness. Clinical Science 2001;100:539-42.

8. Seznam publikací doktoranda

1. publikace *in extenso,* které jsou podkladem disertace

a) s impact factorem

1. Honěk J, Šefc L, Honěk T et al. Patent Foramen Ovale in Recreational and Professional Divers: An Important and Largely Unrecognized Problem. Can J Cardiol. 2015;31:1061-6. (IF 3.940)
2. Honěk J, Šrámek M, Šefc L et al. Effect of Conservative Dive Profiles on the Occurrence of Venous and Arterial Bubbles in Scuba Divers: a Pilot Study. Int J Cardiol. 2014;176(3):1001-2. (IF 6.175)
3. Honěk J, Šrámek M, Šefc L et al. Effect of Catheter-Based Patent Foramen Ovale Closure on the Occurrence of Arterial Bubbles in Scuba Divers. J Am Coll Cardiol Intv. 2014;7:403-8. (IF 7.63)

b) bez IF

4. Honěk J. Katetrizační uzávěr foramen ovale patens u potápěčů. Kardiol Rev Int Med 2015;17:25-27.
5. Novotný Š, Honěk J, Januška J, et al. Patent foramen ovale: transcatheter closure or conservative dive profile in decompression sickness prevention in divers? Cardiology Lett. 2014;23:223-27.
6. Honěk J, Januška J, Novotný Š, et al. Detekce dusíkových bublin po simulovaném ponoru potápěčů s foramen ovale patens. Kdy doporučit katetrizační uzávěr? Interv Akut Kardiol. 2012;11:108-111.
7. Honěk J, Honěk T, Januška J et al. Perzistence foramen ovale patens a riziko paradoxní embolizace žilních bublin u potápěčů – cave pro sklerotizaci varixů pěnovou metodou. Rozhl Chir. 2012;91:378-380.
8. Honěk T, Tomek A, Šrámek M, et al. Foramen ovale patens jako příčina paradoxní embolizace u potápěčů. Možnosti screeningu, terapeutická a preventivní doporučení. Prakt Lék. 2007;87:48-51.

2. publikace *in extenso* bez vztahu k tématu disertace

a) s IF

9. Honěk J, Zemánek D, Veselka J. Left ventricular outflow tract obstruction after mitral valve repair treated with alcohol septal ablation. Catheter Cardiovasc Interv. 2013;82(6):821-5. (IF 2.396)

10. Bonaventura J, Alan D, Vejvoda J, Honěk J, Veselka J. History and Current Use of Mild Therapeutic Hypothermia after Cardiac Arrest. Arch Med Sci. 2016;12(5):1135-1141. (IF 2.030)
11. Horváth M, Hájek P, Štěchovský C, Honěk J, Špaček M, Veselka J. The Role of Near-Infrared Spectroscopy in the Detection of Vulnerable Atherosclerotic Plaques: State of the Art. Arch Med Sci. 2016;12:1308-16. (IF 2.030)
12. Veselka J, Krejčí J, Tomašov P, Durdil V, Riedlbauchová L, Honěk J, Honěk T, Zemánek D. Outcome of patients after alcohol septal ablation with permanent pacemaker implanted for periprocedural complete heart block. Int J Cardiol. 2014;171(2):e37-8. (IF 6.175)
13. Horváth M, Hájek P, Muller JE, Honěk J, Štěchovský C, Špaček M, Veselka J. First-in-Man Near-Infrared Spectroscopy Proof of Lipid-Core Embolization During Carotid Artery Stenting. Arch Med Sci. 2016;12(4):915-8. (IF 2.030)

b) bez IF

14. Honěk J, Veselka J. Varying Left Ventricular Outflow Obstruction Due to Atrio-Ventricular Dyssynchrony in a Patient with Hypertrophic Obstructive Cardiomyopathy. Cardiology Lett. 2015;24:25-27.
15. Honěk J, Veselka J. Intracardiac echocardiography-guided alcohol septal ablation, Cor Vasa. 2014;56:e411-12.
16. Horváth M, Hájek P, Štěchovský C, Honěk J, Veselka J. Intravascular Near-Infrared Spectroscopy: A Possible Tool for Optimizing the Management of Carotid Artery Disease. Int J Angiol. 2015 Sep;24(3):198-204.
17. Honěk T, Horváth M, Horváth V, Šlais M, Kneifl T, Honěk J, Vítovec M, fabián V, Slovák P. Catheter-based endovenous laser ablation of saphenous veins in the treatment of symptomatic venous reflux: Early results. Cor Vasa. 2016, in press.