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Genetic variation and patent foramen ovale: approaches to management through exercise and sports medicine

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ABSTRACT

The non closure of foramen ovale has been held responsible for increased risk in several pathologies. The patent foramen ovale is an abnormality of the interatrial septum, present in 20 30% of the general population. It has been associated with several causes of morbidity such as strokes, migraine, paradoxical embolism. In exercise and sports medicine, it is associated with extra risk of pathologies in all sports in particularly in high altitude excursions and trekking or underwater activities (decompression sickness).

To provide better recommendations for doctors managing patients with this pathology, we first aimed to verify both risk factors and hereditary aspects. Initially, we tested these two hypotheses:

Does the presence of a patent foramen ovale in a patient increase the risk of a desaturation accident?

Is the persistence of the foramen ovale inherited?

To facilitate improved clinical decision making for physicians managing patients with patent foramen ovale, we developed decision trees based on common clinical scenarios. These tools are intended to help assess the suitability of individuals for participation in hyperbaric activities, whether recreational or professional. The decision trees also address the management of patients who have experienced saturation accidents and offer guidance to support their families.

- Evaluate whether there are contraindications for patients considering hyperbaric activities, either for leisure or work purposes.
- Provide case by case recommendations in which patients suffered from saturation accidents.

Offer support and information to the families of affected patients.

Keywords: patent foramen ovale, diving, decompression sickness, inheritage.

Abbreviations

HDL: high density lipoprotein
LDLR: Low Density Lipoprotein Receptor
NKK2 5: NK2 homeobox 5
PFO: Patent foramen ovale
SDHC: Succinate dehydrogenase complex subunit C
TCD: transcranial Doppler
TEE: transesophageal echocardiography
TTE: transthoracic echocardiography

Introduction

Patent Foramen Ovale is a known risk factor for cryptogenic stroke, paradoxical embolism, migraines with aura, atrial or atrioventricular rhythm disorders, desaturation incidents, mountain sickness.

In the fetus, the foramen ovale is essential because it diverts oxygenated umbilical venous blood away from the nonfunctioning lungs. After birth, rising intrathoracic pressure helps seal this opening. However, a patent foramen ovale persists in about 25% of adults and may, in some circumstances, cause a right to left atrial shunt.

In hyperbaric and underwater medicine since the 1980s, PFO is considered a risk factor, with positivity rates found by various authors ranging between 50 and 80% in cases of decompression sickness[1,2].

Decompression sickness risk depends on the nitrogen load in tissues and blood. Divers learn basic physics (gas dissolution and basic physiology) to understand how dive profiles (depth, time, and stops) reduce this risk. Nevertheless, decompression sickness can follow any dive. In severe neurological cases (brain, cerebellar, or inner ear involvement), a patent foramen ovale is often considered an aggravating factor.

The search for a familial component for PFO dates to the 2000s, with stroke or migraine. In hyperbaric medicine, we found only one study on the inheritance of the patent foramen ovale in a work by Wilmshurst in 2004[3], during a study of migraine with aura and PFO. Of the 19 patients in his study, 11 were divers and had experienced a desaturation sickness. Our work is therefore the first to specifically focus on practitioners of underwater and hyperbaric activities and therefore outline relevant decision making scenarios regarding such activities.

Genetic variants affecting cardiac development and the non closure of the foramen ovale should be considered when deciding on underwater and hyperbaric activities. We outline relevant decision making scenarios.

We propose a practical approach for physicians caring for divers. Because routine screening is not warranted, we provide guidance on when to refer a patient for PFO assessment, based on current evidence regarding familial predisposition.

Patients and methods

We retrospectively reviewed 104 medical records from hyperbaric and underwater medicine consultations conducted after decompression illness, for post incident evaluation, or for fitness to dive assessment.

Each consultation included a clinical interview (diving and sports history), assessment of relevant personal history (e.g., migraine with aura, atrial arrhythmias) and family history, and a physical examination for signs of right to left shunt. Transthoracic and/or transesophageal contrast echocardiography for patent foramen ovale (PFO) assessment was routinely prescribed. Records were eligible if the PFO evaluation was performed according to international standards, regardless of the result.

We also analyzed a patient with persistent neurological sequelae to investigate familial transmission of this cardiac anomaly.

Results

A patent foramen ovale was detected in 79 patients (76%) and excluded in 24 (24%). In the general population, PFO affects approximately 20% 25% of individuals (4) and is a recognized risk factor for decompression illness.

CLINICAL CASE:
Mister X, 42 years old and father of three, has a history of decompression illness and patent foramen ovale. He began diving at 24 and holds a Niveau 3 certification from the Fédération Française d'Études et de Sports Sous Marins. He has completed more than one hundred sea dives, with a maximum depth of sixty nine meters. After a 49 meter dive lasting 15 minutes, he developed tingling in his left leg despite appropriate decompression stops recorded by his computer (4 minutes at 6 m and 14 minutes at 3 m).

The patient was quickly referred to the hyperbaric medicine department, where decompression sickness with neurological symptoms affecting the left lower limb was diagnosed. Upon clinical examination, findings included muscle weakness, heightened and overactive reflexes, abnormal superficial sensation, an epileptoid tremor in the foot, and a positive Babinski sign.

Contrast transesophageal echocardiography showed right to left bubble passage in the patient

and two of his sons, consistent with PFO; the third son had no PFO. Overall, 3 of 4 family members (75%) were affected, compared with an expected prevalence of ~25%. In some families, PFO has been reported to follow an autosomal dominant inheritance pattern.

PFO is considered as a risk factor:

Figure 1 displays the pedigree of family x. The proband, a diver, experienced decompression illness once. Two sons had a large right to left shunt with features of a PFO.

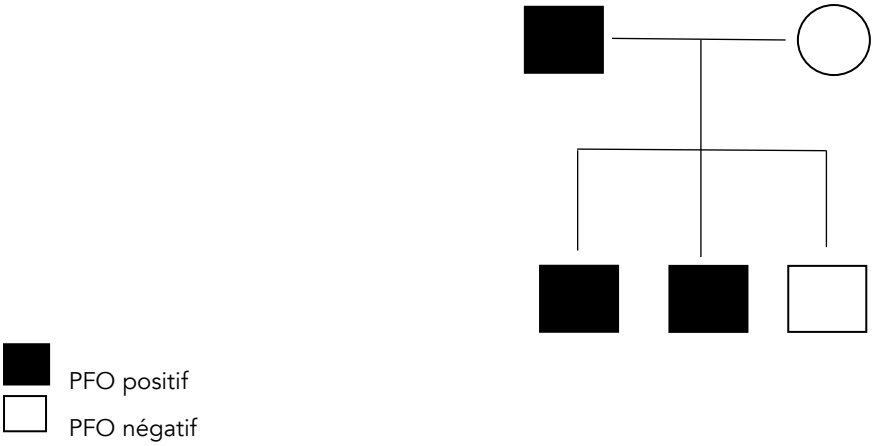


Figure 2. Management of consultant presented a decompression sickness

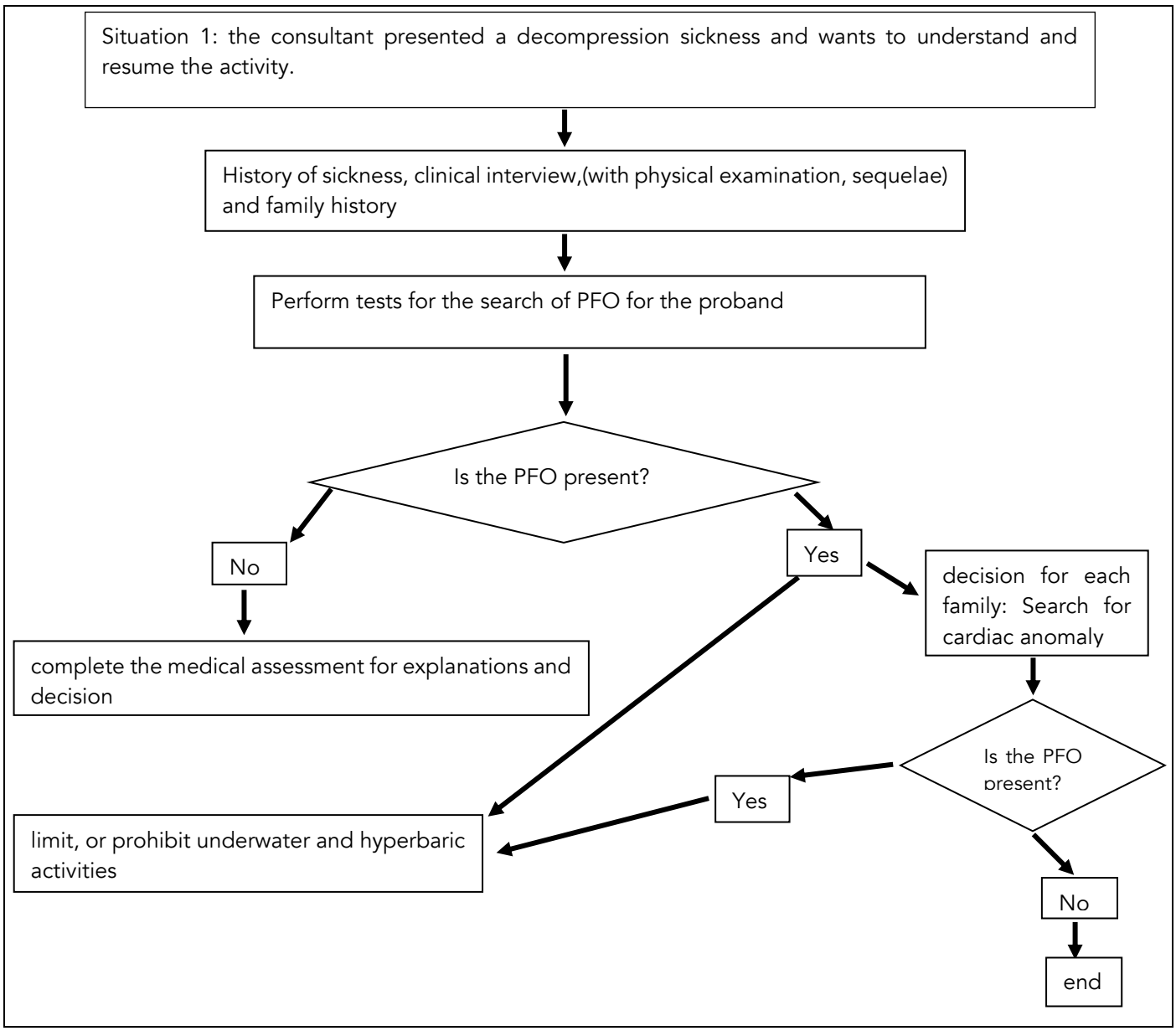


Figure 3. Management of a consultant with is relative of a patient in whom a PFO was found.

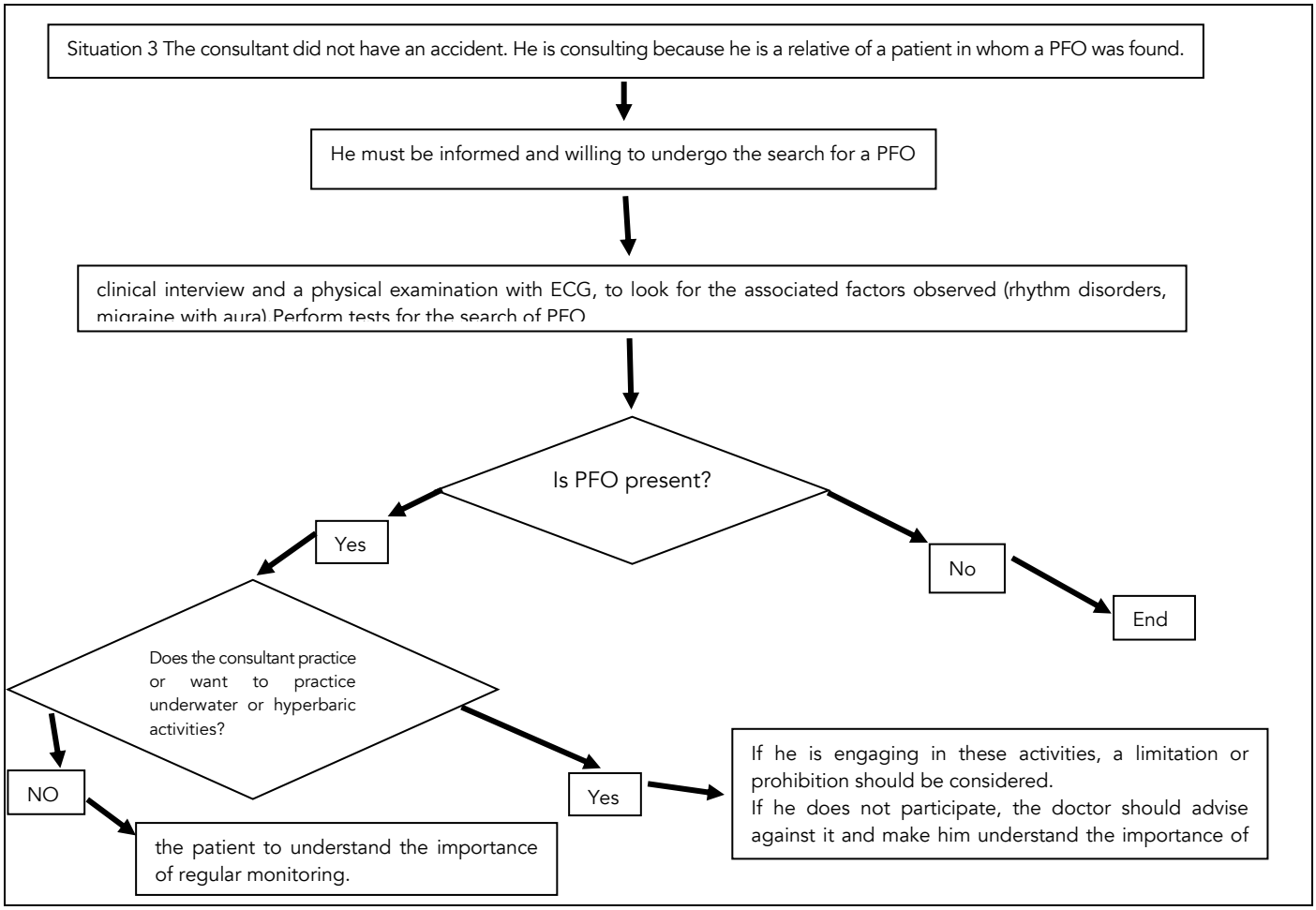
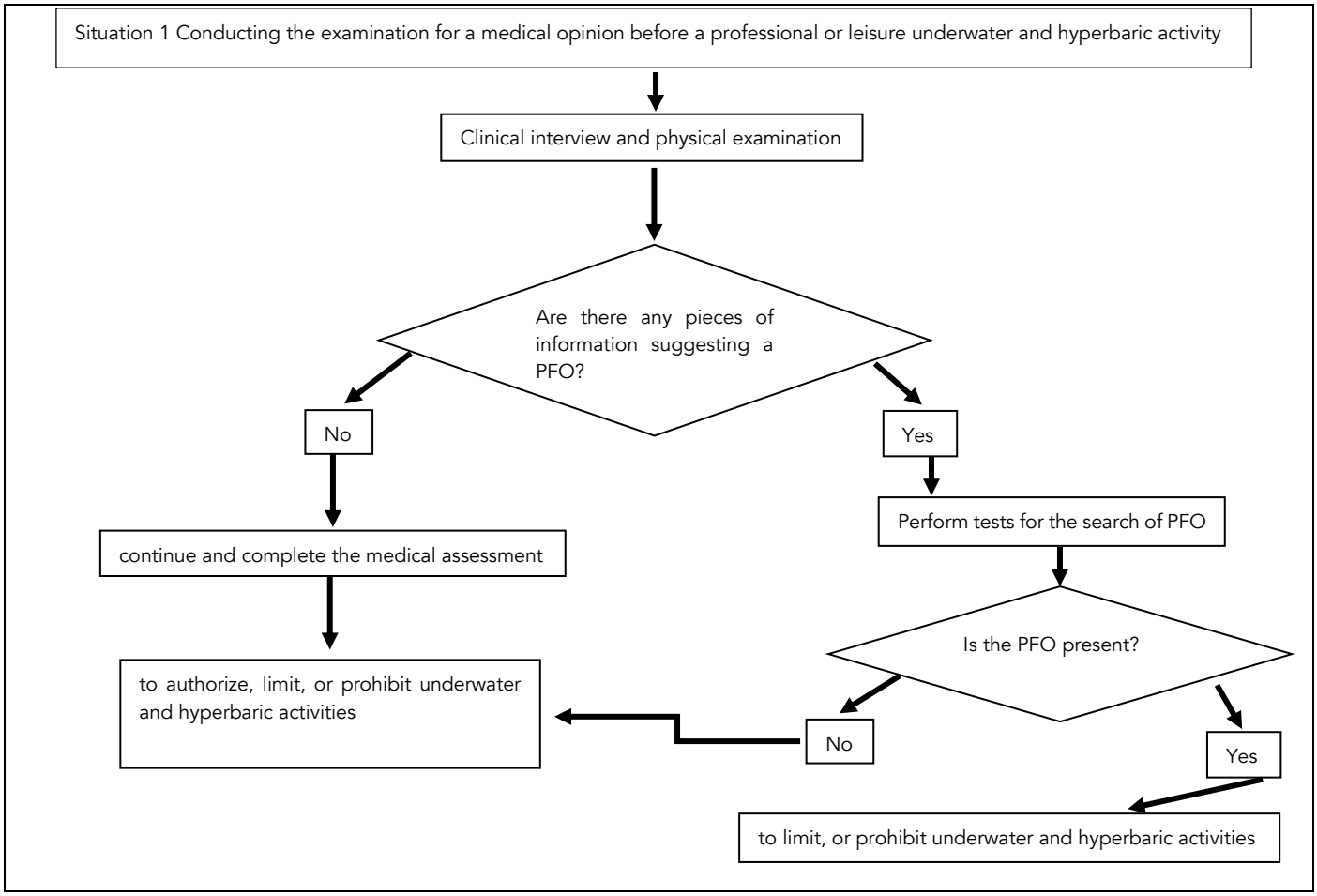


Figure 4. Procedures for conducting a pre practice medical evaluation to obtain a professional opinion.



Discussion

GENETIC, HEREDITY AND PFO

Cardiac development from weeks 2 to 5 is shaped by molecular, cellular, and morphological processes, including mesoderm dynamic transformation into primitive endocardium This then transforms into cardiomyocytes. Variants are responsible for cardiac malformations such as valve malformations atrial septation, or disorganization of the conduction system, driven by complex genetic pathways or atrial septation, driven by complex genetic pathways[5,6].

the genes NKX2 5, SCN5A, MYH6, and GATA4 are the most important genes associated with PFO disease The Notch signaling pathway is implicated in heart development, with a member of the GATA transcription factor family (Binding Protein 4, GATA4), protein coding gene (like T Box Transcription Factor 20, TBX20), homeodomain transcription factor (including NKX2 5) and a Zinc Family Member 3(ZIC3)[7,8]. Particularly, NKX2 5 regulates the proliferation, migration, differentiation, and function of cardiomyocytes through signaling pathways[9]

And Xinyi Li[6] found mutations in Low Density Lipoprotein Receptor (LDLR), Succinate dehydrogenase complex subunit C (SDHC) and NK2 homeobox 5 (NKX2 5) associated with PFO. Low Density Lipoprotein Receptor variants are linked with familial hypercholesterolemia[10] has found changes in HDL (high density lipoprotein) and cholesterol following PFO closure. An interaction protein NKX2 5 and mutations may contribute to atrial septal defects and regulate cell proliferation, differentiation, and migration via signaling pathways.

Multiple mutation and transcription related pathway variants contribute to varying degrees, to failure of foramen ovale closure. Genetic risk is also shaped by interactions between these variants and environmental exposures such as elevated oxygen levels and hyperbaric pressure.

Identifying PFO associated mutations can clarify the mechanisms underlying PFO, although population specific penetrance remains poorly defined. Clinically, PFO is linked to decompression illness, migraine with aura and hypoxemia syndromes, and growing evidence suggests a role in atrial fibrillation.

In underwater and hyperbaric sports medicine, PFO presentations vary widely, and evidence on pathogenic PFO remains heterogeneous. The impact of genetic variants is still unclear, particularly regarding population specific penetrance. Clinically, PFO is associated with migraine and hypoxemia syndromes, and emerging data suggests a contribution to atrial fibrillation[12].

GENETIC STUDIES

Patent foramen ovale (PFO) is a congenital cardiac defect that results from incomplete closure of the foramen ovale during embryonic development. In underwater and hyperbaric environments, it can have specific clinical implications. Decompression illness is a distinct condition in this setting.

PFO is a recognized risk factor for decompression illness.

PFO may show familial aggregation, suggesting a genetic contribution.

Based on these points, physicians assessing professional or recreational participants in underwater and hyperbaric activities typically consider three clinical scenarios.

PFO is suspected on history and physical examination and confirmed using transesophageal or transthoracic echocardiography (TEE, TTE) and/or transcranial Doppler (TCD)[11].

Situation 1: Medical evaluation prior to professional or recreational underwater and hyperbaric activities

The search for a possible PFO is mainly clinical.

The interview looks for factors that suggest the anomaly.

The evaluation focuses on cardiac history, particularly murmurs, and atrial or atrioventricular rhythm disorders reported by the patient or documented on EKG.

A murmur is characterized by its inconsistency. It is auscultated on the left edge of the sternal manubrium, at the level of the 4th intercostal space. It can be found at rest; but especially the patient will be asked to take hold of a forced inspiration and hold their breath with thoracic hyper pressure (Valsalva maneuver). This maneuver will increase the pressure in the right atrium[13]. It can cause audible blood flow from the right atrium to the left atrium. The absence of a murmur at rest

and its presence during the maneuver, or its presence at rest with amplification during the maneuver, practically indicates the PFO. It will need to be confirmed with additional examinations.

Heart rhythm disorder. The consultant should specify its knowledge, its frequency, nature, and any possible treatment that has been implemented. Attention is given to atrial arrhythmia (fibrillation or flutter) or even a nodal rhythm, or junctional extrasystoles, even in the absence of disorder under treatment.

Migraine with aura. It is a recurring headache accompanied by nervous system symptoms. They may include flashes of light, blind spots and other vision changes sensory or motor disturbances. The aura can also cause tingling in hand or face. Treatments for migraines with aura usually include medicines to prevent migraines with aura and medication to stop the headache once it has started. More than 70% of PFO was found in this pathology[2].

The assessment must be completed before issuing a certificate for practice. The diagnosis of PFO in humans is only possible using indirect techniques. Of the different techniques used, (transthoracic echocardiography or contrast enhanced transcranial Doppler) contrast enhanced transesophageal echocardiography is considered the "gold standard[11]."

If the search for PFO is negative, the certificate will be issued, depending on the results of the additional specific examination. If the search for PFO is positive, the decision will then be to prohibit or limit the practice of underwater and hyperbaric activities. It is also necessary to ask the consultant for the same search within the family, especially if they engage in this activity.

2nd situation: the consultant presented a decompression sickness and wanted to understand and resume the activity.

This is the case of Mister. X mentioned above.

It is mandatory to perform a search for the PFO before the decision of prohibition or limitation, and to explain the accident.

One must strongly insist on searching for cardiac anomalies in the family members, who practice this activity either for leisure or professionally.

3rd situation: the consultant did not have an accident. But he is relative of a patient in whom a positive PFO was found.

The patent foramen ovale being an anomaly with a familial, genetic component, it is necessary to insist that research be conducted on the proband's relatives. But this research can only be carried out with the voluntary approval of the consultant, after having given a presentation of the problem.

It is then recommended to conduct a clinical interview and a physical examination with EKG, to look for the associated factors observed (rhythm disorders, migraine with aura). The search for PFO is carried out using one of the classic techniques. If the result is negative, the issue is closed. If the test is positive, the patient must be made to understand the importance of regular monitoring. If they also engage in underwater and hyperbaric activities, a limitation or prohibition should be considered. If they do not engage in these activities, the doctor should advise against these and make him understand the importance of this decision.

Conclusion

There is a dominant transmission of the patent foramen ovale. This heart anomaly has a genetic component. It may be linked to the inheritance of migraine with aura and/or atrial arrhythmia. The subaquatic and hyperbaric activities is a pratique with risque factor. The presence of a PFO increases the risk. Our study proposes decisions trees for the care of patients and their families suspected of having a PFO. This should allow for better shared decision making by the physician.

The new knowledge about the genetic variants of FOP should thus make it possible to complete the practical guides for clinicians already published[14,15].

Conflict of Interest Statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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