

Foramen Ovale and Ductus Arteriosus Patency in Neonatal Harbor Seal (*Phoca vitulina*) Pups in Rehabilitation

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Abstract

Twenty neonatal harbor seal (*Phoca vitulina*) pups in rehabilitation following maternal separation underwent serial echocardiographic studies to assess patency and subsequent age of functional closure of the *ductus arteriosus* (*d.a.*). B-mode, color-flow Doppler, and pulse and continuous wave Doppler were utilized to identify the *d.a.* and determine patency and directionality of blood flow. Seals were also evaluated for evidence of *foramen ovale* (*f.o.*) patency. B-mode ultrasound was used to evaluate the inter-atrial septum for abnormal (aneurismal) motion, a sign of *f.o.* patency in other species. In one harbor seal, this motion was confirmed as being consistent with *f.o.* patency by contrast echocardiography. Closure of the *f.o.* was not confirmed in any harbor seal prior to release back into the free-ranging population.

Data acquired indicate that there is patency of the *f.o.* and *d.a.* after birth for a longer period in phocids than in described terrestrial mammals. The *f.o.* may be patent up to 7 wks of age, and the *d.a.* may be patent up to 6 wks of age without evidence of clinical consequence. This difference in ontogeny between terrestrial mammals and harbor seals is presumptively a diving adaptation. Such an adaptation is counterintuitive given that humans with *f.o.* patency are at increased risk of stroke following the introduction or formation of intravascular gas bubbles and suggests that concurrent protective mechanisms may be present.

Key Words: echocardiography, echocardiology, harbor seals, *Phoca vitulina*, pinniped, congenital defect

Introduction

Neonatal harbor seals (*Phoca vitulina*) are one of the most common marine mammal species in rehabilitation facilities worldwide, with hundreds of individuals a year receiving intensive nutritional support

and clinical care. Patent *ductus arteriosus* (*d.a.*) and patent *foramen ovale* (*f.o.*) have been noted during necropsies in harbor seal pups under 1 mo of age that were presumed premature due to the presence of a lanugo coat *post partum* (Dierauf et al., 1986). In those animals, patent *d.a.* has been reported as a congenital defect in some; while in others, the cause of death has been attributed to unrelated pathology and the patent *d.a.* considered incidental (Colegrove et al., 2005). Patent *d.a.* has also been reported as a cause of death in Hawaiian monk seals (*Monachus schauinslandi*) (Banish & Gilmartin, 1992). The clinical significance of patency of these structures in neonatal harbor seals is thus unclear. To determine whether such patency was ontogenically normal, this study aimed to demonstrate the presence of *d.a.* and *f.o.* patency and to determine the approximate age of functional closure of the *d.a.* in neonatal harbor seals in rehabilitation.

Materials and Methods

Twenty harbor seals were recruited for the study. All of the harbor seals were considered clinically healthy with the exception of varying degrees of malnutrition from maternal separation that resulted in their rescue from along the northern California coast. Six harbor seals had full lanugo coats at admission (five males and one female), nine had partial lanugo coats at admission (four male and five female), and five had no evidence of lanugo coats at admission (two males and three females) (Dierauf et al., 1986). All harbor seals with full or partial lanugo coats were admitted between 27 February and 27 March. All harbor seals without evidence of lanugo coats were admitted on 1 April or later. All harbor seals with lanugo coats at admission completely lost their lanugo coats at varying times during the study period. Harbor seals had an estimated age of between 0 to 1 d and 7 to 10 d at admission (Dierauf et al., 1986). Seventeen harbor seals were born prior to 15 April and were thus considered premature (Greig et al., 2010);

three were born after 15 April. Admission weights ranged from 6.2 to 9.6 kg (mean 7.2 kg). All harbor seals were fed a formula of artificial milk and salmon oil by gavage (Walsh & Gearhart, 2001).

All harbor seals were weighed within 24 h of every echocardiogram being acquired. As patients became less easy to handle with increasing age, diazepam was administered IV at a dose rate of 0.20 to 0.25 mg/kg 5 to 10 min prior to examination to alleviate anxiety and facilitate manual restraint for echocardiography. Echocardiograms were produced from harbor seals admitted with evidence of lanugo coat (full or partial) weekly or biweekly depending on the clinical status of the patient. In harbor seals admitted without evidence of lanugo coat, a single echocardiogram was performed.

The distal main pulmonary artery proximal to the bifurcation was evaluated using B-mode ultrasound to locate the region of the *d.a.* Once identified, color-flow Doppler and pulse wave or continuous wave Doppler were used to document the presence or absence of flow (patency) and direction of blood flow within patent *d.a.* Measurements of the left atrium, aortic root, and main pulmonary artery were made. A left atrial to aorta ratio (LA:Ao) was calculated to determine if evidence of progressive left atrial enlargement was present as an indicator of significant volume overload. All seals were evaluated for evidence of *f.o.* patency by observing the inter-atrial septum for abnormal (aneurismal) motion during the cardiac cycle (Vittoria Mattioli et al., 2003). One harbor seal with abnormal septal motion was then anesthetized with isoflurane by mask and contrast echocardiography performed by

the administration of 10 mls of agitated saline into the subclavian vein as a bolus.

Results

A total of 53 echocardiograms were produced from the 20 harbor seals ranging from one to five studies per harbor seal (median three). Both the pulmonary artery and inter-atrial septum were best identified in all animals from the right parasternal approach in short axis. Data are presented in Table 1 for each group. Data for the groups demonstrated complete overlap; thus, they were batched for statistical analyses.

When considering all data, the LA:Ao ranged from 1.00 to 1.67 (mean 1.23, s.d. 0.21). For any individual harbor seal, the LA:Ao never varied more than 11% among measurements, a figure below the accepted margin of error of up to 30% for serial echocardiography measurements on the same individual (Simpson et al., 2007). The main pulmonary artery data across all groups ranged from 1.2 to 1.5 cm in diameter (mean 1.33, s.d. 0.12). The measured diameter did not alter by more than 15% (0.2 to 0.3 cm) among serial echocardiograms in any individual.

Ductus Arteriosus

Figures 1 through 3 show representative images of echocardiograms produced from one harbor seal. At admission, *d.a.* patency with left-to-right shunting was observed in all 20 harbor seals. Age and weight findings among groups of harbor seals with different stages of lanugo coat loss are summarized in Table 1. These data overlapped among groups, and all data were batched for calculation of confidence

Table 1. Summary of data for harbor seals grouped by presence of lanugo coat at admission into rehabilitation

	Full lanugo coat at admit (<i>n</i> = 6)	Partial lanugo coat at admit (<i>n</i> = 9)	No lanugo coat at admit (<i>n</i> = 5)
Estimated age at closure of <i>d.a.</i> (d)	Range = 28-54 Mean = 36.5 s.d. = 10.6	Range = 20-49 Mean = 33.3 s.d. = 9.4	N/A*
Weight (kg) at closure of <i>d.a.</i>	Range = 6.3-7.8 Mean = 7.5 s.d. = 1.27	Range = 6.3-12.1 Mean = 8.1 s.d. = 1.34	N/A*
LA:Ao ratio	Range = 1.13-1.58 Mean = 1.37 s.d. = 0.18	Range = 1.00-1.75 Mean = 1.20 s.d. = 0.21	Range = 1.10-1.72 Mean = 1.40 s.d. = 0.22
PA diameter (cm)	Range = 1.2-1.5 Mean = 1.33 s.d. = 0.12	Range = 1.2-1.5 Mean = 1.34 s.d. = 0.07	Range = 1.2-1.5 Mean = 1.33 s.d. = 0.09
Maximal age (d) <i>f.o.</i> observed patent	Maximum = 46	Maximum = 51	Maximum = 29

* Non-lanugo coat patients underwent echocardiography only once during which patency of the *d.a.* was documented in four of five harbor seals in this group. As serial echocardiography was not performed, closure was not observed and closure date and weight were not recorded.

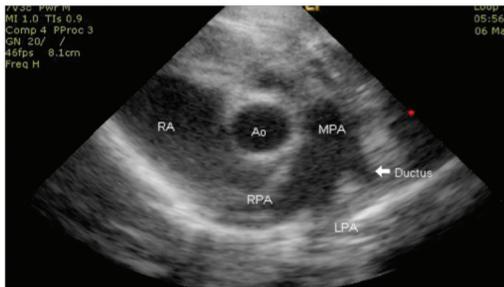


Figure 1. B-mode image of the heart base in short axis, demonstrating the position of the *ductus arteriosus* (labeled with white arrow and “Ductus”) along the main pulmonary artery; RPA = right pulmonary artery, LPA = left pulmonary artery, Ao = aorta (in short axis), and RA = right atrium.

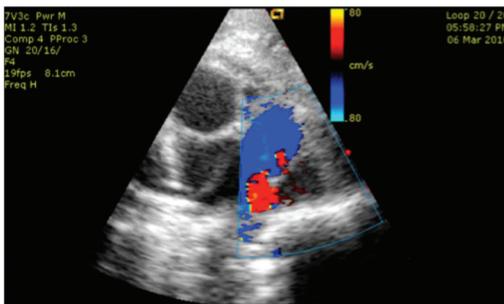


Figure 2. Color flow Doppler image of abnormal blood flow toward the transducer (red) via the patent *d.a.*; the blue blood flow represents normal blood flow directionality through the main pulmonary artery.

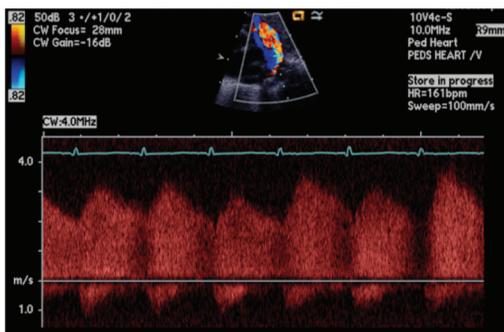


Figure 3. Continuous wave Doppler evaluation of the abnormal blood flow shows a characteristic pattern of continuous high-velocity flow through the *d.a.* in a left to right direction (toward the transducer).

intervals (CI). Age at functional closure ranged from 20 d to 54 d (mean 33.6 d, s.d. 10.6), resulting in a calculated 95% CI of 27.9 to 39.2 d for functional closure. Weight at functional closure ranged from 6.3 to 12.1 kg (mean 7.9 kg, s.d. 1.27), resulting in a calculated 95% CI of 7.0 to 8.7 kg.

Foramen Ovale

The inter-atrial septum was adequately identified and evaluated in 16 of 20 harbor seals. Fifteen of 16 harbor seals evaluated had aneurismal atrial septal motion observed on echocardiography. The inter-atrial septum could not be adequately imaged in four harbor seals on any occasion. In one harbor seal, a partial lantago, the inter-atrial septum was identified, and aneurismal motion was not present (presumptive *f.o.* closure).

Contrast echocardiography was performed in one harbor seal with aneurismal inter-atrial septal motion and patency demonstrated by the appearance of microbubbles in the left-sided cardiac chambers following opacification of the right-sided chambers. This information was applied to observations of aneurismal motion of the atrial septum in the other harbor seals as presumptive *f.o.* patency. Data are provided in Table 1. Closure of the *f.o.* was not confirmed in any harbor seal prior to release back into the free-ranging population (maximum estimated age: 51 d).

Discussion

The *d.a.* is anatomically located between the main pulmonary artery and the proximal descending aorta. It forms from the 6th aortic arch during embryologic development. It functions to permit the majority of the circulating blood to bypass the fetal lungs while the fetus is *in utero* and the lungs are not functional in gas exchange. The *d.a.* is a muscular blood vessel that is kept patent *in utero* by circulating prostaglandins (House & Ederstrom, 1968; Momma et al., 1980; Smith, 1998) and low oxygen tensions of the blood traveling through the *d.a.* (Smith, 1998). In terrestrial mammals, increases in systemic oxygen tensions are believed to stimulate *d.a.* constriction at birth along with alterations in prostaglandin levels (Kittleson, 1998a; Smith, 1998), and administration of prostaglandin to human infants with patent *d.a.* has resulted in constriction in some cases (Ivey & Srivastava, 2006). Trials using prostaglandin therapy in canines with patent *d.a.* have shown limited effects (Bakirel et al., 2007). In certain canine breeds, patent *d.a.* is hereditary, and failure of *d.a.* closure is due to hypoplasia of the musculature (Buchanan, 2003). Recent research in mice (*Mus musculus*) has suggested that an appropriate drop in prostaglandin levels is required, rather than an elevation, for closure of the *d.a.* to occur (Chang et al., 2009). During closure, the *d.a.* musculature contracts then undergoes fibrosis, resulting in permanent and irreversible closure and the resultant structure, the *ligamentum arteriosus*, persists throughout adult life (Smith, 1998; Kittleson, 1998a). Failure of *d.a.* closure can have

serious consequences that are not conducive to survival (Kittleson, 1998a).

The *f.o.* is located within the atrial septum. Persistent patency occurs when the *septum primum* and *septum secundum* fail to fuse and a small communication between the right and left atria persists (Kittleson, 1998b). This defect is identified in approximately 30% of humans by probe *post mortem* but is often functionally closed *in vivo* as the flap of the *septum secundum* is held in place by appropriate pressure differentials (Vick & Titus, 1990). Patent *f.o.* is an uncommon finding in terrestrial animals such as dogs and cats. In canines, it is most commonly seen in combination with congenital pulmonic stenosis (Kittleson, 1998b). Clinical consequence as a result of atrial septal defects without concurrent cardiac disease in animals is minimal (Kittleson, 1998b); however, patent *f.o.* has been associated with stroke in humans (Vittoria Mattioli et al., 2003).

The age of *d.a.* functional closure in various terrestrial mammals varies from immediately following birth in rats (*Rattus norvegicus*) (Jarkovska et al., 1992), mice (Tada & Kishimoto, 1990), and rabbits (genus and species not provided in original manuscript) (Momma et al., 1980) to within the first couple of days *post partum* in humans (Drayton & Skidmore, 1987), lambs (*Ovis aries*) (Dawes et al., 1955), and guinea pigs (*Cavia porcellus*) (Fay & Cooke, 1972). In canines, patency may persist for 6 to 8 d (House & Ederstrom, 1968), and anatomic closure may take up to a month (Kittleson, 1998a). Our data indicate that functional *d.a.* closure in harbor seals occurs between 4 and 6 wks of age and between 7.0 and 8.7 kg body weight. Van Nie & Van der Kemp (1988) previously reported that anatomic *d.a.* closure occurs in *Ph. vitulina* when the heart reaches a weight of 120 g, and Slipjer (1961) correlated a cardiac weight of 120 g with a corresponding maximal body weight of 16.4 kg and an age of 6 to 9 wks in animals that underwent necropsy examination. The difference between these data and our data likely reflects the difference between functional and anatomic closure. One of our study animals that had attained functional closure died a week later from noncardiac causes. Anatomic *d.a.* patency was demonstrated at necropsy using a small probe reiterating the discrepancy between functional and anatomic closure.

Our data suggest that the *f.o.* can remain patent up to 51 d of age, but the approximate age of closure was not determined in this study and thus is an area warranting further work. Previously, Van Nie & Van der Kemp (1988) described necropsy proven anatomic *f.o.* closure in *Ph. vitulina* at a cardiac weight of 168 g and a corresponding age of 12 wks. Conversely, in the bearded seal

(*Erignathus barbatus*) functional closure of the *f.o.* was recorded via contrast echocardiography, with contrast medium injected into the epidural venous sinus of the lumbar spine. In that study, functional closure was recorded during the second week of life as the seals reached 60 kg in body weight (Lydersen et al., 2002). Again the differences between the Van Nie & Van der Kemp (1988) and Lydersen (2002) studies may be explained by the difference between functional and anatomic closure. Regardless, the functional closure data available for *E. barbatus* and the data we provide here for *Ph. vitulina* indicate that there is prolonged patency of the *f.o.* and *d.a.* compared to terrestrial mammals. The lack of variance over time in the LA:Ao and main pulmonary artery measurements indicated that there was no evidence of dilatation due to volume overload. Minimal if any hemodynamic consequences occurred in these patients, and patency was considered normal.

Prolonged patency of the *f.o.* and *d.a.* are important findings in this species as, similar to *E. barbatus*, *Ph. vitulina* pups enter the water almost immediately after birth to avoid predation (Lydersen et al., 2002; Burns, 2009), diving to a mean depth of 2.1 m (Greaves et al., 2005). Similar findings of prolonged patency compared to terrestrial animals have been briefly reported in cetaceans (Slipjer, 1961). Slipjer's necropsy findings demonstrated that anatomic *d.a.* patency in blue (*Balaenoptera musculus*) and fin whales (*B. physalus*) may persist up to 13 y of age and in delphinids up to 14 mo of age. Again, differences between functional and anatomic closure likely exist. Slipjer hypothesized that the persistence of patency was related to diving behavior during which intermittent elevations in pulmonary pressures and lowered oxygen tensions may maintain *d.a.* patency. Human divers with patent *f.o.* are considered to be at an increased risk of developing serious decompression sickness (Bove, 1998), and all humans with patent *f.o.* are at an increased risk of stroke following intravascular bubble formation (Vittoria Mattioli et al., 2003). Whether or not neonatal harbor seals form intravascular gas bubbles during these early shallow dives during which lung collapse is presumptively incomplete is unknown but should be considered and would suggest that concurrent protective mechanisms must be present. In the rehabilitation setting, neonatal harbor seals are prevented from diving until considered stable. This may take several weeks depending on the individual. If diving were the main mechanism for persistent patency, then the study data presented here should have demonstrated rapid closure rather than prolonged patency. Importantly, this may indicate that the timings described here are an underestimation of *d.a.* closure times for

the healthy, free-ranging population. Further work is necessary to determine whether or not there is a difference between animals that enter rehabilitation and those that develop normally in the wild under natural maternal care with a normal dive pattern. It would also be interesting to evaluate in the rehabilitation setting the effect of sub-atmospheric oxygen tensions, such as those that occur during diving, on the shunting profile through the patent *d.a.*

In conclusion, functional closure of the *d.a.* occurs at a later age *post partum* in harbor seals compared to described terrestrial animals, occurring between 4 and 6 wks of age and between 7.0 to 8.7 kg in harbor seal pups undergoing rehabilitation without evidence of clinically significant consequence. Patency of the *f.o.* persists up to at least 51 d of age without evidence of known clinical consequence. Patency should only be considered abnormal if there is evidence of cardiovascular enlargement or hemodynamic derangement.

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