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Handedness in man: The energy availability hypothesis

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SUMMARY

More than 90% of the human species are right handed. Although outwardly our body appears symmetrical, a 50/50% lateralization in handedness never occurs. Neither have we seen more than 50% left handedness in any subset of the human population. By 12–15 weeks of intrauterine life, as many as 6 times more fetuses are noted by ultrasound studies to be sucking on their right thumbs. Distinct difference in oxygenation leading to dissimilar energy availability between right and left subclavian arteries in place by week 9 of life may hold the clue to the lateralization of hand function and eventually, the same in the brain. We know there is a higher incidence of left handedness in males, twins, premature babies and those born to mothers who smoke. They may represent a subset with less distinct difference in oxygenation between the 2 subclavian arteries during the fetal stage. This hypothesis if correct not only closes the gap in understanding human handedness and lateralization but also opens a vista for new research to focus on in utero tissue energy availability and its impact on outcome in life.

Introduction

Many theories have been put forth to explain why more than 90% of the human species are right handed [1]. None however, has adopted an energy driven approach to look at the subject. Over the last few decades detailed research has given us new insights and a better understanding of embryogenesis and fetal growth [2]. We now understand that the low levels of oxygen in the developing embryos stimulate the production of hypoxia inducible factors which can impact the development of organ structure including blood vasculature [3]. The difference seen in the vasculature between both subclavian arteries in early fetal stage may hold the clue to the phenomenon.

Difference in oxygenation between the right and left subclavian arteries

The fetus gets its oxygen and energy supply through the mother via the placenta and umbilical vein. The oxygen and energy are then pumped out by the fetal heart to the various organs. By 9 weeks of gestation, the 6 pharyngeal arches are already reduced to the adult form where the 4th arch predominates [4]. The left ventricle by then is in place to pump the slightly more oxygenated blood to the aorta preferentially perfusing the coronary arteries and the three great vessels of the aorta. The right subclavian being part of the first offshoot of the great vessels, gets the full force of this oxygenation. The left subclavian artery however has deoxygenated blood (from the right ventricle discharging blood into the aorta through the ductus arteriosus) emptying in close proximity to the run off to this particular vessel - a situation that places the tissues perfused by the left subclavian artery slightly more disadvantaged compared to that covered by the right subclavian artery [5] (see Fig. 1).

By 10–15 weeks of gestation, this difference in oxygenation and energy availability between the right and left side has produced visible results. Fetuses are noted to be moving more of their right arm [6] and six times more fetuses are found in ultrasound studies [7] to be sucking on their right thumb compared to their left during this stage of life in utero. This observation according to Hepper in his comments in the New Scientist is true even for anencephalic babies [7] and hence debunks the often held theory that it is the asymmetrical and better brain development on the left side that initiates the right handed predominance. In addition, definitive brain development does not occur until much later [7,8] and cannot possibly explain the phenomenon of right-handed dominance seen from 10 weeks onwards. The hand movements may ultimately be responsible for the brain development and this aligns well with the literature that demonstrates how a change in handedness produces concomitant changes in the brain [9,10].

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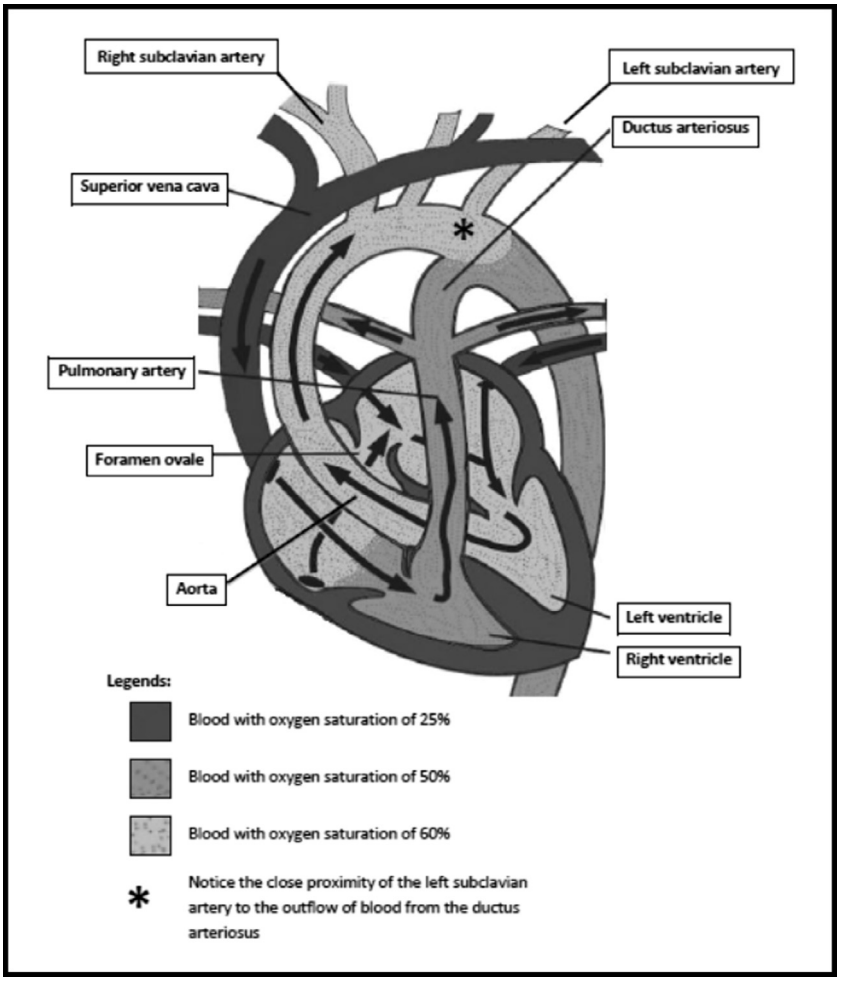

Fig. 1. The fetal circulation. (Adapted from Murphy, P.J. The fetal circulation. Continuing Education in Anaesthesia, Critical Care & Pain) [12].

The hypothesis

All fetuses go through the 9 months in a fairly hypoxic environment having to draw its oxygen supply from the outside environment through the mother. The longer journey for oxygen to arrive at the tissues of the fetus sees the death annually of approximately 3 million fetuses as stillbirths compared to half a million parturients during their pregnancies [11]. There are other evidences of the hypoxic environment – the two main ones are the high hemoglobin all babies are born with as part of the compensatory mechanism for the hypoxia, the other being the presence of fetal hemoglobin with its high affinity for oxygen to facilitate the uptake of oxygen from the parturient.

The postulate is, in spite of the generalized hypoxia, there is still a distinct difference between the oxygenation on the right and left (at least in the upper limbs) to move the proportion of handedness away from its expected 50% distribution on each side. If the difference in oxygenation is less distinct between the two sides one would logically see the proportion move back to the 50% distribution with a higher proportion of left handedness in the fetus/offspring than is currently seen in the general population.

In situations where there is worse hypoxia compared to what is usually the case, one would expect the right upper limb of the fetus not to be distinctly better oxygenated compared to the left. Such uterine environment is seen in the presence of male babies where testosterone increases metabolism and possibly reduces the difference between the 2 sides [13]. There is indeed a higher proportion of left handedness in male babies [14] and this therefore supports the hypothesis that the distribution should move towards the 50% proportion. Testosterone is already detectable in the maternal circulation at 7 weeks gestation in the presence of male fetuses reaching a peak in weeks 9–11 and can potentially have an influence on the energy state of the upper limbs to produce the hand dominance seen by 10 weeks of gestation [15]. The impact of testosterone increasing the hypoxia and decreasing the difference between the 2 sides is probably not great as the difference in left handedness between male and female offspring is just a matter of a few percentage points. Female babies of an opposite-sex twin pair does not have increased incidence of left handedness [16–18].

On the same token, mothers who are smokers [19], situations where there is maternal hypoxia decreases the right and left differential in oxygenation in the fetus, moving the proportion towards the 50% distribution. The higher proportion of twins with left handedness can also be explained by the increased hypoxia twins find themselves in. There is no significant difference in rate of left handedness between monozygotic and dizygotic twins [16,17,20] and this definitely does not provide strong support for the genetic influence theory. Preterm babies are often delivered prematurely by their care-providers when there are signs of threat to life due to worsening hypoxia in utero. The hypoxia in these babies may similarly explain the phenomenon of up to twice the incidence of non-right handedness preterm babies compared to normal term babies [21,22].