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Research article

On the form problem of embryonic heart loops, its geometrical solutions, and a new biophysical concept of cardiac looping

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ABSTRACT

Background: Cardiac looping is an essential process in the morphogenesis of embryonic hearts. Unfortunately, relatively little is known about the form and biophysics of embryonic heart loops. Thompson regarded the form of an object as "*a 'diagram of forces' . . . from it we can . . . deduce the forces that are acting or have acted upon it*." Therefore, the present study was conducted to uncover the best geometrical solution of the form problem of embryonic heart loops. This approach may help to identify the biophysics of cardiac looping.
Results: Analysis of the tendrils of climbing plants disclosed striking resemblance between the configurations of embryonic heart loops and a form motif named helical perversion. Helical perversion occurs in helically wound objects where they connect two helical segments of opposite handedness (two-handed helix). Helical perversion evolves in living and non-living filamentary objects such as the tendrils of climbing plants and helical telephone cords.
Conclusions: Helical perversion may be the best geometrical solution of the form problem of embryonic heart loops. The dynamics and mechanics of the emergence of helical perversions are relatively well known. The behavior of looping embryonic hearts may be interpreted in light of this knowledge.

1. Introduction

1.1. Looping morphogenesis

The embryonic vertebrate heart precedes all other organs in the onset of function. In human beings, for example, cardiac contractions start around the 21st embryonic day (Britten et al., 1994; Wisser and Dirschedl, 1994), which is only 7-days after the first missed period. At this early developmental stage, the heart is seen as a simple tubular pump, which generates a unidirectional blood flow although it lacks valves (Männer et al., 2010). The tubular embryonic heart is not only the first organ to function, but is also the first organ to develop a bilateral asymmetric form. Vertebrates belong to the so-called *bilateria*, which are animals having a bilateral symmetry. In adult vertebrates, the bilateral symmetry is usually confined to the outer form of the body whereas the situs of their inner organs usually show bilateral asymmetries in form and/or position, which normally occur in species-specific conserved patterns named *situs solitus*. The developing heart acquires its asymmetric form during a morphogenetic process named *cardiac looping* (for reviews see Männer, 2000, 2009). During this process, the initially straight and bilaterally almost symmetric heart tube becomes transformed into a convoluted heart loop, the topology of which, defines the future positional relationships of the developing heart chambers and the stems of the arteries and veins (Fig. 1). Experimental data have shown that the heart loop of vertebrate embryos can principally occur in two form variants, each of them being the mirror image of the other one. The vertebrate heart is, therefore, regarded as a handed structure. Based on the spatial orientation of its main bend – which can be directed either to the right or the left of the embryo's body – the handedness of the heart loop is traditionally classified as *D-loop* (dextral-loop) or *L-loop* (levo-loop), respectively (Fig. 2). In all vertebrate species studied so far, the D-loop configuration is the normal variant, whereas L-loop hearts are extremely rare findings, suggesting a strong genetic background for the looping morphogenesis of the vertebrate heart (for review see Palmer, 2004).

1.2. Genetic background for looping morphogenesis of the embryonic heart

Since the 19th century, morphologists and embryologists, such as the Nobel laureate Hans Spemann (*1869–1941†), have tried to uncover the genetic background for bilateral asymmetric development of the inner organs of vertebrates (for a review see Blum

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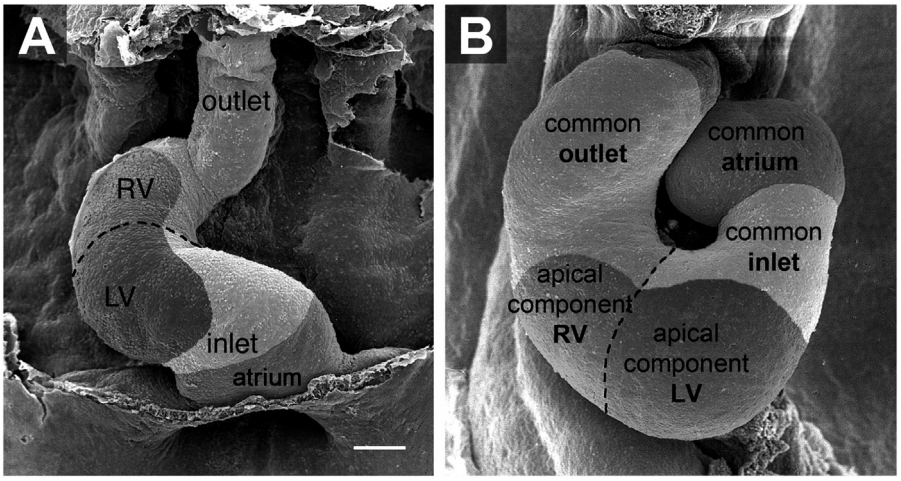

Fig. 1. These scanning electron micrographs of embryonic chick hearts (viewed from frontal) illustrate the main positional changes of the developing heart chambers of higher vertebrate embryos during cardiac looping. Heart loops at early stages ((A) 'C-shaped' loop; HH-stage 12) and advanced stages ((B) 'S-shaped' loop; HH-stage 17/18) of cardiac looping. The original position of the embryonic ventricles (anlagen of the apical trabeculated regions of the definitive ventricles) is cranial to the future atrial chambers and the two ventricles are originally aligned along the cranio-caudal body axis (right ventricle (RV) lies cranial to the left ventricle (LV)). During the transformation of the 'C-shaped' loop into an 'S-shaped' loop, the embryonic ventricles shift toward their definitive position caudal to the future atrial chambers and become aligned along the left-right body axis.

et al., 1999). Up to the end of the 20th century, however, only slight progress was made in this field. The scene then changed dramatically due to the rapid advancements in molecular biology. Thanks to molecular biologists, we now know that the handedness of the heart loop (D-loop or L-loop), and the bilateral asymmetries of other inner organs, is defined by a set of genes, which are normally expressed in bilateral asymmetric patterns within the lateral plate mesoderms of the embryo early in development (for reviews see Ibañes and Izpisúa Belmonte, 2009; Chen et al., 2010). We also know that the establishment of these left-right differences in gene expression patterns depends on a preceding process of breaking of the initially bilateral symmetry of the embryo, in which the directed movement of monocilia seem to play a prominent role (for a review see Hirota et al., 2009).

Molecular biologists have also found that the loss-of-function or gain-of-function of several genes, not involved in left-right patterning, lead to the development of abnormal heart loop phenotypes (e.g. Breckenridge et al., 2001; Risebro et al., 2006; Ribeiro et al., 2007; Brade et al., 2007). Examples from the list of such looping abnormalities are absent looping (straight heart tubes), incomplete D-looping, or excessive D-looping (highly convoluted loops). This shows that genes defining the handedness of the embryonic heart loop are not the only genes involved in the development of its form.

The progressive uncovering of the complex genetic background of cardiac looping poses the question how the genetic information is translated into mechanical forces that shape the developing heart. In some instances, the answer to this question may be deduced from the known functions of the genes. For example, the incomplete and excessive D-looping phenotypes, found in embryos with altered function of genes involved in myocardial proliferation, may be explained by altered growth of the heart tube (Risebro et al., 2006; Ribeiro et al., 2007). For the majority of genes, however, it may be difficult or nearly impossible to clarify, only on the basis of known gene functions, how their gene products physically act in cardiac looping. In these cases, knowledge of the biomechanics of the looping process may help to deduce how these genes contribute to the shaping of the embryonic heart. Unfortunately, however, the biophysical processes driving cardiac looping are not well known at the present time.

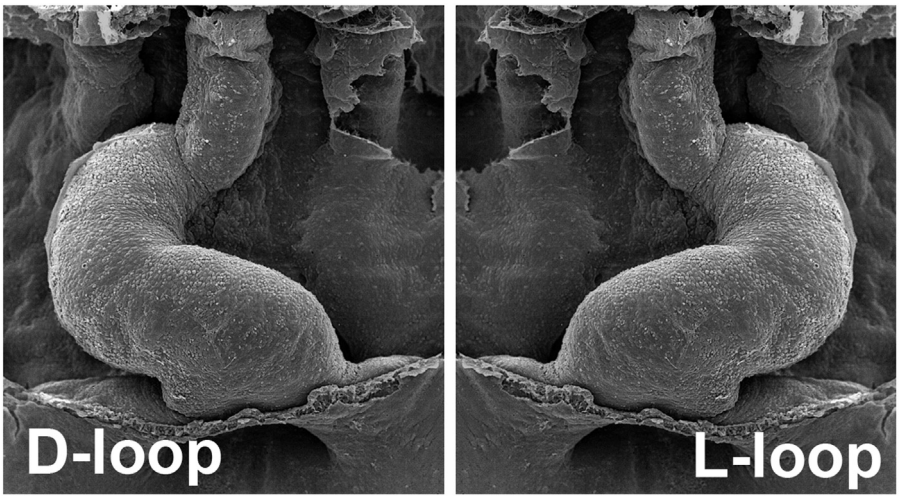

Fig. 2. These scanning electron micrographs of embryonic chick hearts (viewed from frontal) illustrate the so-called D-loop and L-loop configurations ('C-shaped' loops; HH-stage 12).

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