Asymmetric redirection of flow through the heart

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Through cardiac looping during embryonic development[1], paths of flow through the mature heart have direction changes and asymmetries whose topology and functional significance remain relatively unexplored. Here we show, using magnetic resonance velocity mapping[2–5], the asymmetric redirection of streaming blood in atrial and ventricular cavities of the adult human heart, with sinuous, chirally asymmetric paths of flow through the whole. On the basis of mapped flow fields and drawings that illustrate spatial relations between flow paths, we propose that asymmetries and curvatures of the looped heart have potential fluidic and dynamic advantages. Patterns of atrial filling seem to be asymmetric in a manner that allows the momentum of inflowing streams to be redirected towards atrio-ventricular valves, and the change in direction at ventricular level is such that recoil away from ejected blood is in a direction that can enhance rather than inhibit ventriculo-atrial coupling[6]. Chiral asymmetry might help to minimize dissipative interaction between entering, recirculating and outflowing streams[7]. These factors might combine to allow a reciprocating, sling-like, 'morphodynamic' mode of action to come into effect when heart rate and output increase during exercise[6].

Although flow in the human heart, particularly the left ventricle, has been investigated by physical and computational modelling[8–10], and by invasive and non-invasive imaging[11,12], there is still only limited understanding of changes in direction and asymmetries of flow through heart cavities, or of their potential significance in relation to function. Vertebrates show cephalo-caudal and dorso-ventral asymmetries of body plan with respect to which lateral asymmetries of the heart and other internal organs occur[13,14]. Cardiac looping involves the ventral displacement of a ventricular relative to an atrial 'loop' in a ventrally located, cephalically directed flow path. Lateral displacements of parts of this sinuous path result in chiral, quasi-helical asymmetries. Plurality of venous inflows and septation of systemic from pulmonary flow paths complicate the picture further, but for the purposes of this paper, attention is focused on asymmetries and changes in direction of flow in heart cavities, subordinate to asymmetries of the heart as a whole.

We used magnetic resonance phase-velocity mapping[3,4] to investigate patterns of flow in human heart cavities, aiming at visualizing cavity filling patterns and elucidating major changes in direction of blood. The technique, besides using transiently applied magnetic gradients to locate signal from nuclei in three-dimensional space, uses gradient applications to encode velocity in the phase of the radio signal received back from energized nuclei. The nuclei in question are those of hydrogen in water, so no contrast agent or marker is needed for this non-invasive flow-imaging technique. The flow images, reconstructed from the signal received over many heart cycles, record large-scale flow features that recur repeatedly through successive beats. Figure 1 shows systolic and diastolic streamline maps[5] computed from mid-systolic and early diastolic frames of 16-phase cine magnetic resonance velocity acquisitions[4] in a healthy 34-year-old man in planes located through the cavities of the right atrium, the left atrium and the left ventricle. Corresponding animated streamline maps were also made (see Supplementary Information). For assessment of consistency of major flow features between subjects, velocity maps were acquired in 21 additional healthy volunteers (see Tables 1 and 2 of Supplementary Information). Topologies and orientations of large-scale intra-cavity flow features

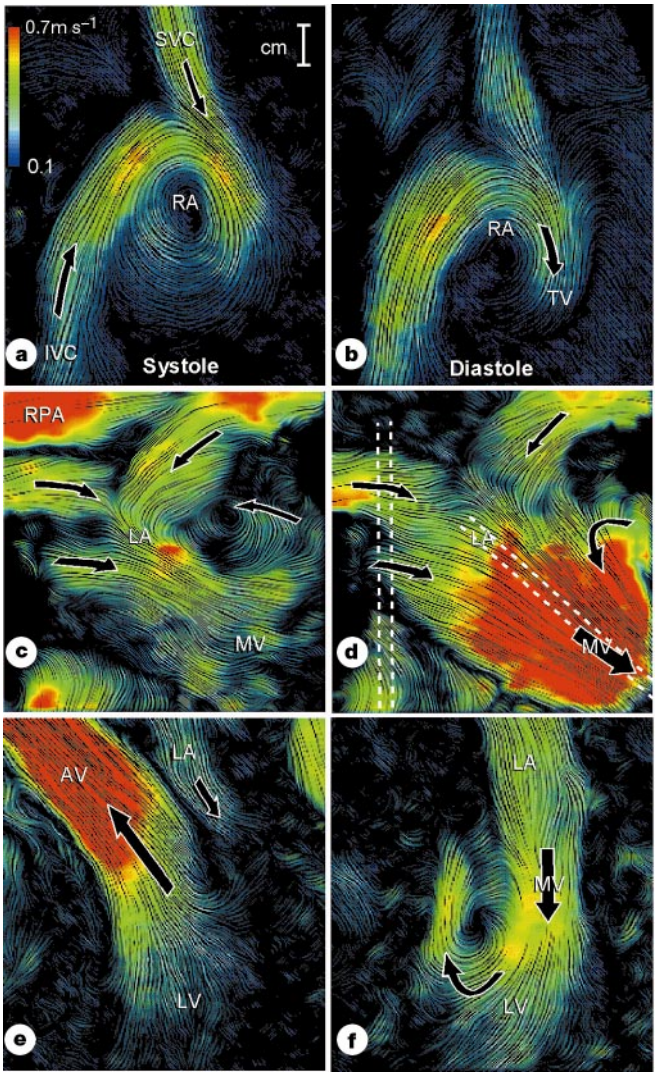

Figure 1 Asymmetric intracardiac flow patterns. **a**, In the right atrium in ventricular systole, viewed in a sagittal plane from the subject's right side, blood entering from superior and inferior caval veins contributes to the forward rotation of blood in the expanding chamber. Coloured streamlines computed from magnetic resonance velocity acquisitions show local speed, as indicated by the colour scale. **b**, In early ventricular diastole, further inflow of blood is again redirected forwards and down the front of the right atrium, and away from the viewer (out of plane) through the open tricuspid valve. **c**, In the left atrium in ventricular systole, blood enters from the upper and lower pulmonary veins on each side, indicated by arrows in this coronal plane viewed from the front (lower veins lie out of plane posteriorly). Streamlines are redirected asymmetrically round towards the mitral valve, which is closed, but pulled by contraction of the left ventricle. **d**, In early ventricular diastole, there is further inflow from veins while blood passes through the open mitral valve to the left ventricle. Vertical and oblique dotted lines indicate planes orthogonal to this panel represented by panels **a**, **b**, **e** and **f**. **e**, In the left ventricle in systole, streamlines pass from the left ventricle through the aortic valve, viewed here in an oblique long-axis plane from above left, the front of the subject being located to the left of the image. **f**, In early diastole, streamlines pass from the left atrium through the open mitral valve to the left ventricle, with asymmetric recirculation (curved arrow) round the anterior leaflet of the mitral valve. In **e** and **f** only, the colour scale is modified to reach red at 1 m s^{-1}. AV, aortic valve; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava; TV, tricuspid valve.

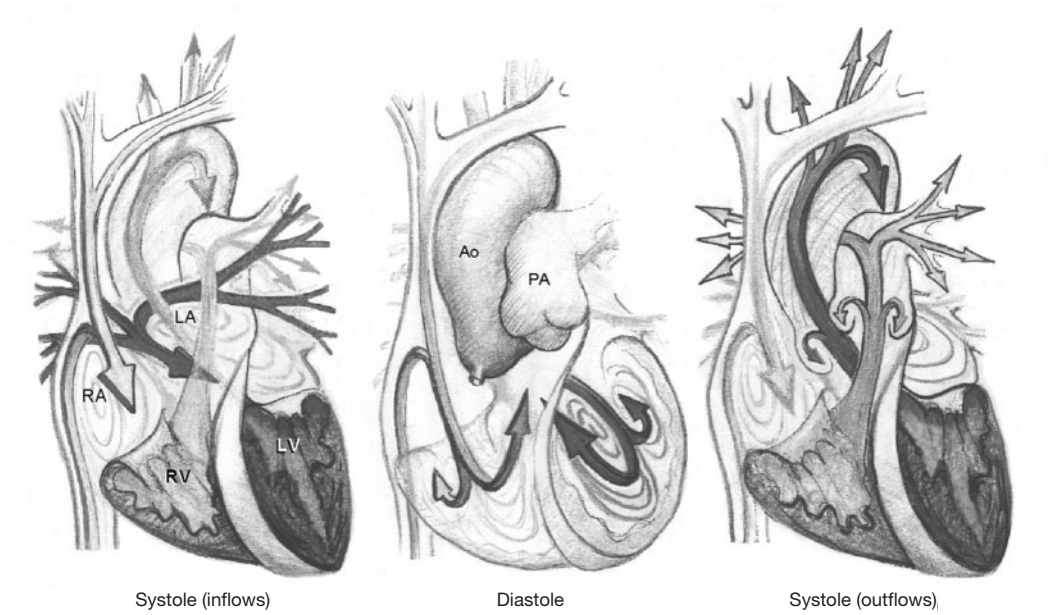

Figure 2 Changes in direction of blood through the heart. Main streams in systolic and early diastolic phases have been drawn as viewed from the front. Systole is shown twice so that the passage of blood can be followed from atrial inflows, to ventricles, to arterial outflows. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

were broadly similar between volunteers studied (see Supplementary Information).

In the right atrium (Fig. 1a, b), streams from superior and inferior caval veins did not collide head on but turned forward, contributing to a forward rotation of blood, turning clockwise as viewed from the subject's right side. This filling pattern was associated with movement of the anterior part of the right atrial blood volume towards the inlet of the tricuspid valve. Inflows to both right and left atrial cavities showed peaks in two phases, coinciding with ventricular systole (Fig. 1a, c) and early ventricular diastole (Fig. 1b, d).

In the left atrium (Fig. 1c, d), imaging in a coronal slice showed that inflows from pulmonary veins, those on the left located slightly higher than those on the right, contributed to net rotational momentum—anticlockwise as viewed from the front. The asymmetric filling pattern was associated with leftwards and downwards movement of the inferior half of the contained blood volume, across towards the mitral valve, in systole as well as in diastole.

In the left ventricle, imaging in an oblique long-axis plane showed ejection of blood to the aorta in systole (Fig. 1e) and refilling from the left atrium in early diastole (Fig. 1f). There was a second, late diastolic phase of ventricular filling in the resting state[6], coinciding with atrial systole, not shown here. Inflow through the open mitral valve gave rise to recirculating flows beneath the valve leaflets, the dominant direction being under the free edge of the anterior mitral leaflet. Part of the blood volume was thus redirected towards the outflow tract (Fig. 1f). Transient recirculation was also seen beneath the posterior mitral valve leaflet. An almost complete change of direction between left ventricular inflow and outflow is shown by comparison of Fig. 1f and Fig. 1e.

In the right ventricle, inflow through the tricuspid valve also gave rise to recirculating flows beneath the leaflets, the dominant direction being towards the outflow region. The change in direction between inflow and outflow was less acute than that in the left ventricle. However, the right ventricle has a more marked chiral asymmetry than the left, its volume being indented by curvature of the septum, making the depiction of right ventricular flow in a single plane unsatisfactory.

Figure 2 gives an overview of systolic and early diastolic flows of the whole heart, gained from velocity map data acquired in five contiguous coronal planes covering the volume of the heart in the same subject. Flow paths were traced by hand on a transparent sheet taped to the computer screen as velocity maps were displayed one by one, working from the back of the heart to the front. The band-like depiction of principal flow paths allows overall spatial relationships and chiral asymmetries, not apparent in two-dimensional streamline maps, to be visualized. The drawing also permits recognition of potential continuity of momentum between chambers and between phases, which is relevant when, on exercise, systole and diastole alternate in rapid succession.

In a previous echocardiographic study[6], we documented a transition from biphasic left ventricular filling at rest, to rapid, monophasic filling during strenuous exercise. M-mode and Doppler echocardiographic traces showed evidence of enhanced, rapid reciprocation of atrial and ventricular action on exertion. During strenuous exercise, atrial systole came to coincide with early diastolic filling in a single short diastolic period of rapid ventricular filling. As the heart rate more than doubled, atrial systole (ventricular diastole) and ventricular systole (atrial diastole) alternated rapidly, peak velocities of ventricular inflow and outflow rising to about twice those of the resting state. These changes are compatible with the marked enhancement, during exercise, of exchanges of force associated with changes in momentum through curvatures of the heart.

Figure 3 shows drawings illustrating theoretical fluidic and dynamic consequences of looped as opposed to linear arrangements of deliberately simplified two-chamber heart models without chiral asymmetry. Whereas vertebrates have looped arrangements of juxtaposed atrio-ventricular cavities, a nearly linear arrangement occurs in dorsally located hearts of snails such as *Helix pomatia*—animals not noted for dynamic vigour. The depiction of intracavity recirculation patterns in Fig. 3 is based on the visualization of flow in symmetrical and asymmetric physical flow models (see animated images in Supplementary Information). The term 'fluidic' refers to the participation of the fluid's own dynamics in the control of direction and timing of flow through the system.

On the basis of mapped intracardiac flow patterns, we propose that curvatures and asymmetries of the heart confer potential functional advantages that could gain importance as flow velocities, heart rate and rates of change of momentum increase with exertion: eccentric alignments of venous inflows with respect to atrial cavities

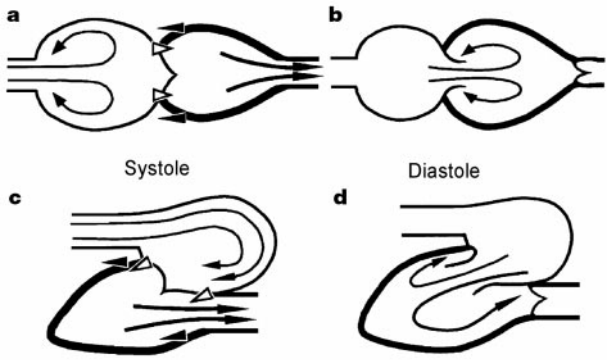

Figure 3 Comparison of linear and looped atrio-ventricular arrangements. **a**, In the linear arrangement in systole, contraction of the ventricle (thick boundary) pulls on the atrium (white arrowheads), contributing to atrial expansion. Inflow gives rise to recirculation bilaterally (thin arrows), a relatively unstable pattern of flow that redirects blood inappropriately for subsequent ventricular filling. Any recoil of the ventricle (black arrowheads) away from blood accelerated to the outflow (thick arrows) would push back against the atrium, counteracting atrial expansion. **b**, In diastole, recirculation in the expanding ventricle redirects fluid away from the outflow tract. **c**, In a sinuously looped arrangement in systole, ventricular contraction also expands the adjacent atrium (white arrowheads). Atrial filling is now asymmetric and more stable, streamlines being accommodated by wall curvatures in a way that redirects momentum towards the atrio-ventricular valve. Recoil of the ventricle away from ejected blood (black arrowheads) now adds to the pull on the atrio-ventricular junction, enhancing rather than suppressing atrial expansion. **d**, In diastole, redirected intra-atrial momentum can contribute to ventricular filling, which occurs with asymmetric recirculation, redirecting flow preferentially towards the outflow tract. Looped curvature thus allows the sinuous redirection of momentum and dynamically enhanced reciprocation between atrial and ventricular function.

predispose to asymmetry of intra-atrial flow, redirecting inflow towards rather than away from atrio-ventricular valves (Figs 1–3). Relatively coherent swirling of blood, although potentially associated with higher wall sheer stresses, might avoid excessive dissipation of energy by limiting flow separation and instability (see animated images in Supplementary Information). Chiral or non-planar asymmetry (Fig. 2) might also avoid instabilities by allowing entering, recirculating and outflowing streams to pass one another in three-dimensional space without collision[7]. At ventricular level, change in direction is such that recoil away from ejected blood is in a direction that can enhance rather than inhibit ventriculo-atrial coupling (Figs 1–3). Combining these effects, we propose that, during exercise, the looped heart is able to function 'morpho-dynamically', redirecting and slinging blood through its sinuous curvatures with minimal dissipation of energy and with dynamically enhanced reciprocation of atrial and ventricular function. Transition to this mode, in which forces associated with changes in momentum gain functional importance, can be likened to changes of whole-body mechanics when the actions of walking speed up to those of running. Dynamic exchanges and efficiency of the heart in this state could involve coupled interactions between contractility, elasticity and change in momentum, at atrial, ventricular and vascular levels. In health, auto-adjustments of contractility[15,16], compliance[17] and structure[18,19] might contribute to interrelations appropriate to morphodynamic heart action.

This interpretation has potential medical relevance where pathologies or interventions entail altered relations between form, flow, mobility and timing of the heart, especially in individuals who wish to maintain physically active lifestyles. In relation to heart surgery, the interpretation supports the proposition that spatial relations and mobility of cardiovascular tissues should be conserved or reinstated, if technically possible[20]. The relative stability of flow through the heart might have bearing on the avoidance of thrombosis, and, by affecting flow arriving at arterial branches, possibly on the avoidance of atherogenicity[21]. Our proposed functional interpretation is of interest in relation to research into the genetic[14] and phylogenetic origins of cardiac looping. Looped curvature of a ventrally located heart seems to be a feature confined to vertebrates, having apparently been retained and elaborated as classes evolved[22]. The ability of the looped heart to deliver enhanced output during strenuous exertion might have been a factor permitting the evolution of large, complex, dynamically active species characteristic of the vertebrate line. □

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Supplementary information is available on *Nature*'s World-Wide Web site (http://www.nature.com) or as paper copy from the London editorial office of *Nature*.

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