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Cardiac Fluid Dynamics Anticipates Heart Adaptation.

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14 **ABSTRACT**

15 Hemodynamic forces represent an epigenetic factor during heart development and are supposed to
16 influence the pathology of the grown heart. Cardiac blood motion is characterized by a vortical
17 dynamics, and it is common belief that the cardiac vortex has a role in disease progressions or
18 regression. Here we provide a preliminary demonstration about the relevance of maladaptive intra-
19 cardiac vortex dynamics in the geometrical adaptation of the dysfunctional heart. We employed an *in*
20 vivo model of patients who present a stable normal heart function in virtue of the cardiac
21 resynchronization therapy (CRT, bi-ventricular pace-maker) and who are expected to develop left
22 ventricle remodeling, if pace-maker was switched off. Intra-ventricular fluid dynamics is analyzed by
23 echocardiography (Echo-PIV). Under normal conditions, the flow presents a longitudinal alignment of
24 the intraventricular hemodynamic forces. When pacing is temporarily switched off, flow forces develop
25 a misalignment hammering onto lateral walls, despite no other electro-mechanical change is noticed.
26 Hemodynamic forces result to be the first event that evokes a physiological activity anticipating cardiac
27 changes and could help in the prediction of longer term heart adaptations.

28 INTRODUCTION

29 Mechanical forces have an active biological role during morphogenesis. They stimulate cellular growth
30 and multiplication at the microscopic level which eventually reflect on the macroscopic shaping of an
31 organ as a whole (Farge, 2011; Freund et al., 2012). The importance of hemodynamic forces for heart
32 morphogenesis was first demonstrated in the zebrafish, in which it was experimentally shown that
33 intracardiac stresses imparted by the blood flow lead the proper heart development (Hove et al., 2003).
34 Biological fluid forces are known to play a central role in the growth of the embryonic heart and
35 vasculature (Reckova et al., 2003; Santhanakrishnan and Miller, 2011) so that the phenotype of
36 congenital heart abnormalities was suggested to depend from the characteristics of blood flow forces
37 acting on the developing tissues (Gruber and Epstein, 2004). Along the same line, it is suggested that
38 hemodynamic forces should participate to pathological developments and therapeutic outcomes in the
39 grown heart, although evidences are still lacking (Pasipoularides, 2012; Pedrizzetti et al., 2014).

40 The clinical syndrome of heart failure (HF) is the principal social threatening cardiac progressive
41 dysfunction. It presents either as a primary pathology or because of a majority of primary diseases. The
42 salient feature of HF is the development of left ventricle (LV) remodeling: a geometric modification
43 and dilatation of the ventricular chamber that progressively reduce its muscular pumping ability.
44 Despite modern treatments, hospitalization and death rate remain high, with nearly 50% people
45 diagnosed with HF dying within 5 years (Levy et al., 2002).

46 The physiological causes that lead to LV remodeling are mainly ascribed to an increase of stresses on
47 the myocardial fibres (around a scar area, because of higher systemic pressure etc.), which stimulate the
48 growth and multiplication of cells and give rise to an increase of muscular thickness and then
49 dilatation. Current models of cardiac remodeling, however, are not consistently predictive and remain
50 rather primitive (Opie et al., 2006; Sengupta and Narula, 2008); although a variety of pathophysiologic

51 mechanisms have been suggested, there is paucity of methods capable of effectively forecasting the
52 future risk of cardiac remodeling (Wu et al., 2008; Nijveldt et al., 2009). All existing models, in
53 particular, do not account of the presence of hemodynamic forces that can trigger the sequence of
54 events leading to progressive LV remodeling and eventually to HF (Pasipoularides, 2012; Pedrizzetti et
55 al., 2014).

56 The distinguishing feature of cardiac blood flow is the presence of vortices. The sinuous flow paths
57 around the vortex in the human heart were elegantly described by magnetic resonance visualization
58 (Kilner et al., 2000). It was suggested that the asymmetric vortical arrangement was the flow functional
59 counterpart of the looped heart structure that enhances the conservation of momentum from the entry
60 jet to the ejected flow. It ensures an energetic balance of the longitudinal function during the filling-
61 emptying mechanism with left ventricle asymmetry and vortex formation (Pedrizzetti and
62 Domenichini, 2005). In recent years, numerous results about vortex dynamics in the human LV were
63 produced using different techniques, from numerical simulations to magnetic resonance, to
64 echocardiography (Markl et al., 2011; Sengupta et al., 2012). All these studies evidenced the presence
65 of an intimate relationship between cardiac function and quality of intra-ventricular fluid dynamics.

66 A firm evidence of the relevance of LV fluid dynamics to the development and progression of a cardiac
67 pathology, however, is still lacking. This is partly imputable to the difficulty of building comprehensive
68 mathematical or experimental models capable of accounting of the complex transduction mechanism,
69 where the large scale flow forces are sensed at the microscopic level, turn into cellular multiplication,
70 and lead to alterations at the organ level (Pasipoularides, 2012). Here, we present an initial evidence
71 that the quality of cardiac fluid mechanics could be a participating factor of heart adaptation
72 mechanisms, namely adverse or reverse remodeling. These results may provide an interpretative
73 ground for future clinical studies.

74 **METHODS**

75 We consider an *in vivo* model made of formerly HF patients with dilated LV that were subjected to
76 cardiac resynchronization therapy (CRT, implant of bi-ventricular pace-maker) and that returned (after
77 at least six months of therapy) to a stable condition with a LV of normal dimension and functional
78 parameters. These subjects represent a special prototype model with a stably normal cardiac function
79 with the support of the CRT. The same subjects, whether CRT is switched off, are expected to turn into
80 an unstable state undergoing heart adaption and, within a few weeks, falling back into LV remodeling.
81 The realization of both stable and unstable states on a same subject, at few seconds of distance, permits
82 a deterministic one-to-one comparison.

83 These subjects were selected from a population of 30 (age 58 ± 11 years old) who underwent CRT device
84 implant according to the in use guidelines for a non-ischemic and non-valvular dilated cardiomyopathy.
85 Exclusion criteria were atrial fibrillation, severe renal insufficiency, acute coronary syndrome, cardiac
86 insufficiency of advanced grade (NYHA IV), severe either pulmonary hypertension or obstructive
87 pulmonary disease, uncontrolled systemic hypertension. At follow-up, all patients were in sinus rhythm
88 with spontaneous atrio-ventricular conduction. In this population we identified a sub-group of 6
89 patients who presented a high response to the therapy (super-responders). This sub-group was
90 characterized by a pre-CRT dilated LV with large volumes (end-systolic volume >160 ml, end-diastolic
91 volume >200 ml) and reduced ejection fraction ($EF < 30\%$). The high response to the therapy, was
92 defined by a reduction of more than 40% in both LV volumes and an EF above 40%. In the same
93 population, as counter-examples, we also identified 2 subjects presenting the opposite outcome and did
94 not get any benefit from the CRT (non-responders) whose LV volumes were not significantly reduced
95 ($<10\%$) after six months of therapy. The selection of extreme sub-groups (super-responders and non-
96 responders) was driven by the objective of developing a deterministic biomechanical interpretation at
97 an individual level and avoiding the statistical analysis typical for clinical results that are not the scope

98 of the present study. All subjects underwent echocardiographic examination. Cardiac mechanical
 99 contraction was evaluated by the global longitudinal strain (GLS) while its synchronicity was evaluated
 100 by the standard deviation of time to peak of transversal strain (SD-TTS) (Knappe et al., 2011) assessed
 101 in bi-plane recordings (2- and 4-chambers apical views). Intra-cardiac fluid dynamics was measured
 102 using an echographic adaptation of the optical particle image velocimetry, widely validated in clinical
 103 applications (Echo-PIV) (Sengupta et al., 2012), on a longitudinal plane containing both the inlet and
 104 outlet valves (3-chambers view). Echo-PIV permits a good temporal resolution but presents some
 105 limitations in the quality of spatial distribution (noise) and in the detection of high velocities
 106 (Kheradvar et al., 2010). For these reasons velocity information was here employed in averaged and
 107 normalized terms only, that are less affected by local and instantaneous inaccuracies.

108 The dynamic interchange between flow and tissue was summarized by the rate of fluid momentum

$$109 \quad \mathbf{m}(\mathbf{x}, t) = \rho \left(\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} \right); \quad (1)$$

110 where $\rho=1050 \text{ Kg/m}^3$ is the blood density and $\mathbf{v}(\mathbf{x}, t)$ is the 2D velocity vector field. The field $\mathbf{m}(\mathbf{x}, t)$
 111 corresponds, by Navier-Stokes balance, to the sum of the pressure gradient and the viscous terms,
 112 where the latter is mostly negligible with the exception of the region next to the walls.

113 A measure of the global hemodynamic force (per unit depth) exerted by the fluid on the surrounding
 114 tissue is obtained after spatial integration of (1)

$$115 \quad \mathbf{M}(t) = \iint_{LV} \mathbf{m} dA. \quad (2)$$

116 taken over the image area contained inside the LV chamber. Directional distribution of hemodynamic
 117 forces during the entire heart cycle is summarized in terms of an intensity-weighted polar histogram
 118 (like that used for wind description). For this, the circumference is divided in 12 sectors, centered in

119 $\theta_i=(2i-1)\pi/12$, $i=1..12$, and the force moduli during all the time instants in the heartbeat are summed up
120 when the angle falls in a corresponding sector. The resulting values are normalized to unit sum to
121 provide an intensity-weighted angular frequency distribution.

122 **RESULTS AND DISCUSSION**

123 The intraventricular fluid dynamics under stable conditions (pace-maker ON), estimated from Echo-
124 PIV (one example is shown in Figure 1), agrees with what was previously described in literature: a
125 circulatory pattern forming during the LV filling (diastole) that accompanies blood from the inlet
126 toward the outflow where it converges like in a funnel during the ejection (systole) (Kilner et al., 2000;
127 Pedrizzetti and Domenichini, 2014; Markl et al., 2011; Sengupta et al., 2012). When the pace-maker
128 therapy is discontinued (pace-maker OFF), the LV mechanical function should manifest early signs of
129 mechanical dysfunction driving toward the spiral of events leading to remodeling and HF. However,
130 the overall fluid dynamics does not evidence qualitative alterations. Some minor differences are shown,
131 for example, in Figure 1 where the entering jet is slightly displaced toward the side wall, or the
132 converging motion during ejection presents sharper bends. Thesesmall changes, however, globally
133 reflect into large deviations of intraventricular momentum away from the normal, longitudinal base-
134 apex alignment.

135 The directional deviation on intraventricular forces becomes evident in Figure 2, where the polar
136 histogram of $\mathbf{M}(t)$ during the entire heartbeat is reported for 4 subjects. In the stable configuration
137 (pace-maker ON, left column in Figure 2) the momentum is well aligned along the base-apex LV axis,
138 in compliance with the dynamics of the filling-emptying process. Few seconds after the pacing is
139 switched off (right column), the LV enters into a physiologically unstable state whose dynamics
140 anticipates heart adaptation. In this condition, flow loses its natural alignment, intraventricular forces

141 develops transversal components, despite cardiac contractility and synchrony parameters (GLS, SD-
142 TTS) do not evidence noticeable (or measurable) changes.

143 As a counter-example we performed the same analysis on the non-responders subjects. Differently
144 from before, as summarized in Figure 3, in those subjects the flow was neither aligned when the peace-
145 maker was active nor when it was switched off. Their state was unstable (or meta-stable, given the
146 extreme deformation) and the therapy was not able to create longitudinal hemodynamic forces.

147 These observations suggest that a modification of the natural fluid dynamics pattern is the first
148 recognizable mechanical phenomenon associated with an unstable condition that anticipates LV
149 remodeling. Flow changes presumably are due to minor modifications in the synchrony of tissue
150 motion, like local and short-lasting accelerations, that are difficult to detect directly but that reflect on
151 the overall dynamic balance of the incompressible fluid contained in the LV chamber.

152 Hemodynamics forces, by themselves, are not able to provoke large stresses that may deform a tissue
153 by fatigue. However, during morphogenesis, endothelial cells are able to sense vorticity and loading
154 conditions via shear changes (mechano-sensing), transforming any abnormal condition into adaptive
155 responses (mechano-transduction) (Pedrizzetti et al., 2014). The presence of forces acting on
156 inappropriate regions at inappropriate timings presumably activates, through a plethora of intracellular
157 signaling pathways, a physiological adaption mechanism that under prolonged over-stimulation leads to
158 the development of LV adaptation.

159 **CONCLUSION**

160 These results provide initial evidence that the natural longitudinal alignment of hemodynamic forces is
161 a necessary condition for the presence of a physiologically LV stable state and to avoid heart
162 adaptation. By logical equivalence, the lack of flow alignment is a sufficient condition for
163 physiologically instability inducing heart adaptation.

164 Hemodynamic forces are known to participate to heart morphogenesis during the development of the
165 embryonic heart. This study suggests that they also participate to physiological adaptations in the
166 grown heart. In a more general perspective, large scale flow phenomena influence, through the
167 mediation of sensing and transduction at the cellular level, the long term shaping of the cardiac organ
168 as a whole.

169 Epigenetic mechanisms are a concurring factor in heart pathological adaptation and they are mediated
170 by mechanical forces. The deeper understanding of how physical phenomena are associated to
171 physiological outcomes could open a new comprehension about expression of phenotypes not revealed
172 by (and not written in) the genetic structure only.

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174 protection of human subjects. Informed consent for participation to this study was obtained from all
175 subjects.

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178 **Conflict of Interest:** none.

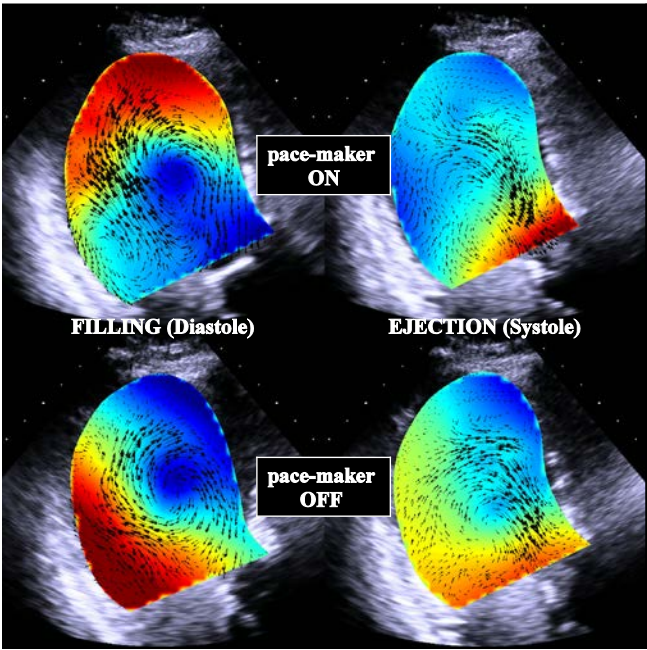
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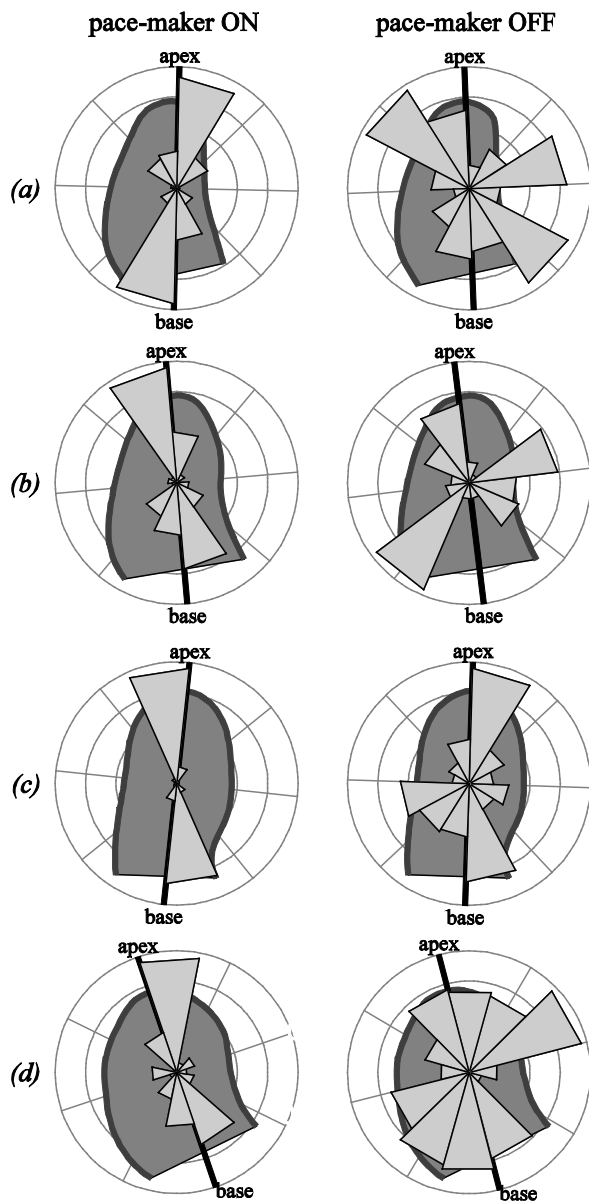
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231 **FIGURES**

232



233 **Figure 1.** Example of flow changes following deactivation of the pace-maker in a subject who
234 responded to the pacing therapy, during diastolic filling (left) and systolic ejection (right). The
235 colormap represents the intraventricular pressure with a scale from red (higher pressure, relative to the
236 mean value) to blue (lower).



237

238 **Figure 2.** Polar histogram of intra-cardiac momentum distribution during the heartbeat in 4 subjects
 239 who well responded to the pacing therapy (super-responders), (a) to (d), while the pacemaker is
 240 normally active and after a temporary deactivation.

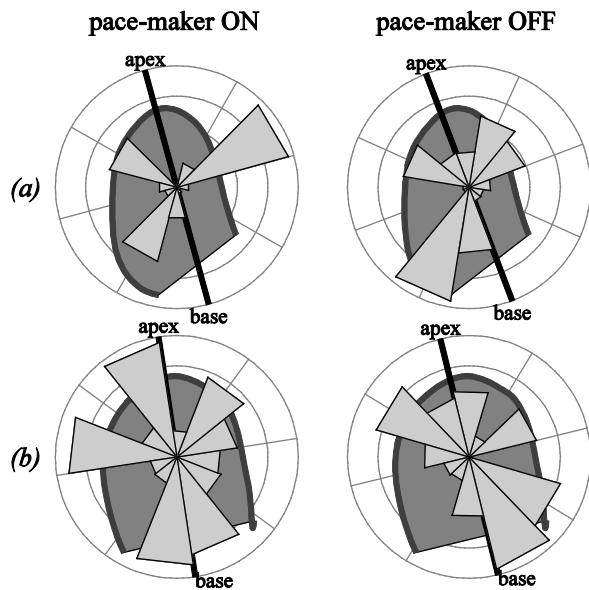


Figure 3. Polar histogram of intra-cardiac momentum

distribution during the heartbeat in 2 subjects who did not benefit from the pacing therapy (non-responders), (a) to (b), while the pacemaker is normally active and after a temporary deactivation.