VPH2

Virtual Pathological Heart of the Virtual Physiological Human

Grant Agreement Number 224635

– Deliverable –

D1.5.3 – Updated Dissemination Plan, including report of activities

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Version 1.0	20/06/2011	Deliverable refinement	Sorin
Version 1.1	17/10/2011	updating from partners	Sorin & partners
Version 2.0	21/10/2011	Final version	Sorin

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1. Executive Summary

Deliverable 1.5.3 contains the report of dissemination activities done by the Consortium during the third year.

SORIN, the Task responsible, coordinate the dissemination activities along with the Scientific Dissemination Board.

All the partners involved in the Dissemination activities have participated to the writing of D1.5.3 and to the identification of the dissemination events and actions.

2. Introduction

VPH2 aim is to develop ICT-based tools for modelling and simulation of human cardiac physiology and disease-related process that will help cardiologists and cardiac surgeons in the definition of the severity and extent of the disease in patients with post-ischemic left-ventricular dysfunction (LVD).

VPH2 technology will be useful for application in intelligent medical simulation environments for surgery training, planning and interventions providing tools in support of Risk Assessment, Decision Making and allowing the optimisation of cardiovascular departments and hospital resource usage with a consequent reduction of costs for the NHSs.

The importance of a dissemination strategy and plan for the VPH2 project is to inform and involve the general public as well as the specific clinical and scientific targets potentially interested in the Project's outcomes and results.

The present updated dissemination plan presents the report of activities carried out by the Consortium during the third year of project duration.

2.1. Task 1.5: Dissemination Plan

The VPH2 Dissemination Plan has been very useful during the entire project for the coordination and monitoring of the partners' participation to events (as international Conferences and workshops) in the relevant domains and areas with the aim of presenting the Project's results and achievements.

The Plan also reported the submission and publication of consolidated results to selected journals and magazines and the organisation of dissemination events (workshops) targeted to the VPH2 end-users.

The web has been considered as a privileged tool for the dissemination of VPH2. A Project Website has been developed and has a specific Dissemination section (Public area). Dissemination through the website has allowed a wider access to information about the project, the related events and news, as well as the direct contact with the project Coordinators for stakeholders.

Leaflets and posters have been produced taking into account the relevant target groups and audiences. The promotional and informational materials have been made available on the website for download thus enhancing their efficacy through an enlarged diffusion.

2.2. Deliverable structure

D1.5.3 presents the report of activities carried out by the Consortium during the third year of project.

Chapter 4 presents the report of dissemination actions divided in 4 groups based on the typology:

- Bring about approval
- Poster
- Conferences, exhibitions, Workshops, seminars
- Press releases and Publications

Chapter 5 presents the Scientific Dissemination Board and the responsible for dissemination for each partner.

Chapter 6 presents the individual dissemination actions carried out by each partner during this third year of project duration.

3. Dissemination Strategy

During the third year of activities both the Scientific Dissemination Board and the Consortium decided to not modify the Dissemination Strategy decided previously and written in the Deliverable D1.5 Dissemination Plan submitted at M3.

4. Report of activities

4.1. Phase 3: Pre-product and product launch

Four distinct phases were envisaged:

- Phase 1: Initial awareness.
- Phase 2: Bring about approval.
- Phase 3: Pre-product launch.
- Phase 4: Product launch.

During the third year of project duration, Phase 2 was finished, and Phase 3 is in closure. The project hasn't entered yet the Phase 4, since the prototype (i.e. the Product) needs more validations and development.

The Scientific Dissemination Board and the Consortium have defined the role of each partner (from the dissemination point of view) and decided a dissemination plan and a series of tools to use.
The following paragraphs contain the report of activities divided in 3 groups (different tools used).

4.1.1. Monitoring literature

In the third year, **PoliMI** went on monitoring the literature relevant to WP5 with the aim of gathering information to improve FAT and FPT functionalities and predictive capabilities. This activity was carried out in collaboration with IFC-CNR and SCS. The monitoring activity was mainly focused on the identifications of clinical papers reporting studies involving large populations of ischemic patients treated with surgical techniques. The activity was conducted mainly by making use of "pubmed" and "scopus", two internet research motors specific for medical research. In particular pubmed is a free service of the US National Library of Medicine that includes over 18 million citations from MEDLINE and other life science journals. Scopus is a subscription-based abstract and citation database and web-based research tool provided by Elsevier in cooperation with a number of university research libraries.
Other PoliMI activities included google search and participation top conferences, workshops and meeting with other experts in the field of Cardiovascular Engineering.

Relevant bibliography

- Witkowski TG, ten Brinke EA, Delgado V, et al. Surgical ventricular restoration for patients with ischemic heart failure: determinants of two-year survival. Ann Thorac Surg 2011;91(2):491-8.
- ten Brinke EA, Klautz RJ, Tulner SA, et al. Clinical and functional effects of restrictive mitral annuloplasty at midterm follow-up in heart failure patients. Ann Thorac Surg 2010;90(6):1913-20.
- Auger D, van Bommel RJ, Bertini M, et al. Prevalence and characteristics of patients with clinical improvement but not significant left ventricular reverse remodeling after cardiac resynchronization therapy. Am Heart J 2010;160(4):737-43.
- Van Bommel RJ, Delgado V, Schalij MJ, Bax JJ. Critical appraisal of the use of cardiac resynchronization therapy beyond current guidelines. J Am Coll Cardiol 2010;56(10):754-62.
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- ten Brinke EA, Bertini M, Klautz RJ, et al. Noninvasive estimation of left ventricular filling pressures in patients with heart failure after surgical ventricular restoration and restrictive mitral annuloplasty. J Thorac Cardiovasc Surg 2010;140(4):807-15.

- Ciarka A, Braun J, Delgado V, et al. Predictors of mitral regurgitation recurrence in patients with heart failure undergoing mitral valve annuloplasty. Am J Cardiol 2010;106(3):395-401.

- Di Donato M, Fantini F, Toso A, Castelvecchio S, Menicanti L, Annest L, Burkhoff D. Impact of surgical ventricular reconstruction on stroke volume in patients with ischemic cardiomyopathy. J Thorac Cardiovasc Surg. 2010;140(6):1325-31.e1-2.

- Di Donato M, Castelvecchio S, Menicanti L. End-systolic volume following surgical ventricular reconstruction impacts survival in patients with ischaemic dilated cardiomyopathy. Eur J Heart Fail 2010;12(4):375-81.

- D'Onofrio A, Cugola D, Bolgan I, Menicanti L, Fabbri A, Di Donato M. Surgical ventricular reconstruction with different myocardial protection strategies. A propensity matched analysis. Interact Cardiovasc Thorac Surg 2010;10(4):530-4.

- Suma H, Tanabe H, Uejima T, Isomura T, Horii T. Surgical ventricular restoration combined with mitral valve procedure for endstage ischemic cardiomyopathy. Eur J Cardiothorac Surg 2009;36(2):280-4.

- Yoon DY, Smedira NG, Nowicki ER, Hoercher KJ, Rajeswaran J, Blackstone EH, Lytle BW. Decision support in surgical management of ischemic cardiomyopathy. J Thorac Cardiovasc Surg 2010;139(2):283-93, 293.e1-7.

- Isomura T, Hoshino J, Fukada Y, et al. Volume reduction rate by surgical ventricular restoration determines late outcome in ischaemic cardiomyopathy. Eur J Heart Fail 2011;13(4):423-31.

- Sénéchal M, Lancellotti P, Magne J, et al. Impact of mitral regurgitation and myocardial viability on left ventricular reverse remodeling after cardiac resynchronization therapy in patients with ischemic cardiomyopathy. Am J Cardiol 2010;106(1):31-7.

- Kalogeropoulos A, Savoye LP, Georgiopoulou V, et al. Long-term response of the left ventricle to cardiac resynchronization therapy: insights from standard and strain echocardiography. Congest Heart Fail 2011;17(2):71-9.

- McLeod CJ, Shen WK, Rea RF, et al. Differential outcome of cardiac resynchronization therapy in ischemic cardiomyopathy and idiopathic dilated cardiomyopathy. Heart Rhythm 2011;8(3):377-82.

- Ciampi Q, Pratali L, Citro R, Villari B, Picano E, Sicari R. Clinical and prognostic role of pressure-volume relationship in the identification of responders to cardiac resynchronization therapy. Am Heart J 2010;160(5):906-14.

- Shanks M, Delgado V, Ng AC, et al. Clinical and echocardiographic predictors of nonresponse to cardiac resynchronization therapy. Am Heart J 2011;161(3):552-7.

IFC-CNR: The literature concerning the topics of VPH2 project has been monitored by Pubmed search engine site using the following key words: heart failure, post ischemic ventricular dysfunction, biomarkers, ventricular remodelling, imaging and cardiovascular disease, ischemic mitral regurgitation and surgical ventricular restoration. We report a selected bibliography of some very interesting papers related to these fields.

- van den Broek KC, Defilippi CR, Christenson RH, Seliger SL, Gottdiener JS, Kop WJ. Predictive value of depressive symptoms and B-type natriuretic peptide for new-onset heart failure and mortality. Am J Cardiol. 2011 Mar 1;107(5):723-9.

- Manzano-Fernández S, Januzzi JL Jr, Boronat-Garcia M, Bonaque-González JC, Truong QA, Pastor-Pérez FJ, Muñoz-Esparza C, Pastor P, Albaladejo-Otón MD, Casas T, Valdés M, Pascual-Figal DA. β-Trace Protein and Cystatin C as Predictors of Long-Term Outcomes in Patients With Acute Heart Failure. J Am Coll Cardiol. 2011 Feb 15;57(7):849-58.

- Babür Güler G, Karaahmet T, Tigen K. Myocardial fibrosis detected by cardiac magnetic resonance imaging in heart failure: impact on remodeling, diastolic function and BNP levels. Anadolu Kardiyol Derg. 2011 Feb;11(1):71-6.

- de Boer RA, Lok DJ, Jaarsma T, van der Meer P, Voors AA, Hillege HL, van Veldhuisen DJ. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. Ann Med. 2011 Feb;43(1):60-8.

- Watson CJ, Ledwidge MT, Phelan D, Collier P, Byrne JC, Dunn MJ, McDonald KM, Baugh JA. Proteomic Analysis of Coronary Sinus Serum Reveals LRG as a Novel Biomarker of Ventricular Dysfunction and Heart Failure. Circ Heart Fail. 2011 Jan 31.

- Delgado V, van Bommel RJ, Bertini M, Borleffs CJ, Marsan NA, Arnold CT, Nucifora G, van de Veire NR, Ypenburg C, Boersma E, Holman ER, Schalij MJ, Bax JJ. Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. Circulation. 2011 Jan 4;123(1):70-8.

- Jankowska EA, Filippatos GS, von Haehling S, Papassotiriou J, Morgenthaler NG, Cicoira M, Schefold JC, Rozentryt P, Ponikowska B, Doehner W, Banasiak W, Hartmann O, Struck J, Bergmann A, Anker SD, Ponikowski P. Identification of chronic heart failure patients with a high 12-month mortality risk using biomarkers including plasma C-terminal pro-endothelin-1. PLoS One. 2011 Jan 17;6(1):e14506.

- Adams KF Jr, Mehra MR, Oren RM, O'Connor CM, Chiong JR, Ghali JK, Lenihan DJ, Dunlap SH, Patterson JH, Schwartz TA, Felker GM. Prospective evaluation of the association between cardiac troponin T and markers of disturbed erythropoiesis in patients with heart failure. Am Heart J. 2010 Dec;160(6):1142-8.

- Takeda K, Matsumiya G, Hamada S, Sakaguchi T, Miyagawa S, Yamauchi T, Sawa Y. Left ventricular basal myocardial scarring detected by delayed enhancement magnetic resonance imaging predicts outcomes after surgical therapies for patients with ischemic mitral regurgitation and left ventricular dysfunction. Circ J. 2010 Dec 24;75(1):148-56.

- Eurlings LW, van Pol PE, Kok WE, van Wijk S, Lodewijks-van der Bolt C, Balk AH, Lok DJ, Crijns HJ, van Kraaij DJ, de Jonge N, Meeder JG, Prins M, Pinto YM. Management of chronic heart failure guided by individual N-terminal pro-B-type natriuretic peptide targets: results of the PRIMA (Can PRo-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) study. J Am Coll Cardiol. 2010 Dec 14;56(25):2090-100.

- deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA. 2010 Dec 8;304(22):2494-502.

- Kim HN, Januzzi JL Jr. Biomarkers in the management of heart failure. Curr Treat Options Cardiovasc Med. 2010 Dec;12(6):519-31.

- Aalbers J. Vitamin D is a prognostic marker in heart failure. Cardiovasc J Afr. 2010 Nov-Dec;21(6):348.

- De Lazzari C, D'Ambrosi A, Tufano F, Fresiello L, Garante M, Sergiacomi R, Stagnitti F, Caldarera CM, Alessandri N. Cardiac resynchronization therapy: could a numerical simulator be a useful tool in order to predict the response of the biventricular pacemaker synchronization? Eur Rev Med Pharmacol Sci. 2010 Nov;14(11):969-78.

- Arndt-Marić R, Nägele H, Schewe G, Kromminga A. Are autoantibodies against the beta1-adrenergic receptor markers for dilated cardiomyopathy? Clin Lab. 2010;56(11-12):519-26.

- Volpe M, Francia P, Tocci G, Rubattu S, Cangianiello S, Elena Rao MA, Trimarco B, Condorelli M. Prediction of long-term survival in chronic heart failure by multiple biomarker assessment: a 15-year prospective follow-up study. Clin Cardiol. 2010 Nov;33(11):700-7.

- Fertin M, Hennache B, Hamon M, Ennezat PV, Biausque F, Elkohen M, Nugue O, Tricot O, Lamblin N, Pinet F, Bauters C. Usefulness of serial assessment of B-type natriuretic peptide, troponin I, and C-reactive protein to predict left ventricular remodeling after acute myocardial infarction (from the REVE-2 study). Am J Cardiol. 2010 Nov 15;106(10):1410-6.

- Velagaleti RS, Gona P, Larson MG, Wang TJ, Levy D, Benjamin EJ, Selhub J, Jacques PF, Meigs JB, Tofler GH, Vasan RS. Multimarker approach for the prediction of heart failure incidence in the community. Circulation. 2010 Oct 26;122(17):1700-6.

- Boxer R, Kleppinger A, Ahmad A, Annis K, Hager D, Kenny A. The 6-minute walk is associated with frailty and predicts mortality in older adults with heart failure. Congest Heart Fail. 2010 Sep-Oct;16(5):208-13.

- Zabczyk M, Butenas S, Palka I, Nessler J, Undas A. Active tissue factor and activated factor XI in circulating blood of patients with systolic heart failure due to ischemic cardiomyopathy. Pol Arch Med Wewn. 2010 Sep;120(9):334-40.

- Hombach V, Merkle N, Bernhard P, Rasche V, Rottbauer W. Prognostic significance of cardiac magnetic resonance imaging: Update 2010. Cardiol J. 2010;17(6):549-57.

Sorin continued the monitoring through all the literature using public online database and the major scientific magazines it has subscribed. The news of highest interest for the project resulted to be the following:

- Agfa HealthCare and TomTec partner on Echocardiography analysis and Measurement solution, www.ehealthnews.eu, September 2010;

- Siemens introduces new solutions for the diagnosis and therapy of heart diseases, www.ehealthnews.eu, September 2010;

- Norwegian cardiologists use breakthrough technology to study heart remodelling after valve replacement in patients with blue-baby syndrome, www.qmed.com, April 2011;

- Implantable device provides a “guardian angel” to watch over your heart, www.qmed.com, April 2011;

- New MRI methodology revolutionizes imaging of the beating heart, www.sciencedaily.com, April 2011

During this third year of VPH2 project **CTI** allocated most of its effort in finalizing the data mining studies and in using the extracted knowledge as part of a decision support module. For that purpose several similar works were studied and the most interesting are presented in the following.

- Gary S. Francis and W.H. Wilson Tang, Histamine, Mast Cells, and Heart Failure: Is There a Connection? J. Am. Coll. Cardiol. 2006 48: 1385-1386.

- Kim J, Washio T, Yamagishi M, et al. A novel data mining approach to the identification of effective drugs or combinations for targeted endpoints—application to chronic heart failure as a new form of evidence-based medicine. Cardiovasc Drugs Ther 2004;18:483–9.

- Kirk T. Phillips and W. Nick Street, Predicting Outcomes of Hospitalization for Heart Failure Using Logistic Regression and Knowledge Discovery Methods. AMIA Annu Symp Proc. 2005; 2005: 1080.

WWU found interesting for the VPH2 project the following articles:

- Barth AS, Aiba T, Halperin V, DiSilvestre D, Chakir K, Colantuoni C, Tunin RS, Dimaano VL, Yu W, Abraham TP, Kass DA, Tomaselli GF. Cardiac resynchronization therapy corrects dyssynchrony-induced regional gene expression changes on a genomic level. Circ Cardiovasc Genet. 2009 Aug;2(4):371-8.

- Chemello D, Rohde LE, Santos KG, Silvello D, Goldraich L, Pimentel M, Rosa PR, Zimerman L, Clausell N. Genetic polymorphisms of the adrenergic system and implantable cardioverter-defibrillator therapies in patients with heart failure. Europace. 2010 May;12(5):686-91.

- Kusche-Vihrog K, Callies C, Fels J, Oberleithner H.The epithelial sodium channel (ENaC): Mediator of the aldosterone response in the vascular endothelium? Steroids. 2010 Aug-Sep;75(8-9):544-9.

- Molineris I, Grassi E, Ala U, Di Cunto F, Provero P. Evolution of promoter affinity for transcription factors in the human lineage. Mol Biol Evol. 2011 Feb 18. [Epub ahead of print]

- Sinzinger H, Derfler K, Laimer H, Seyfried H, Maier M. Risk charts--very popular but useless? Vasa. 2010 Nov;39(4):287-9.

- Uthoff H, Staub D, Socrates T, Meyerhans A, Bundi B, Schmid HP, Frauchiger B. PROCAM-, FRAMINGHAM-, SCORE- and SMART-risk score for predicting cardiovascular morbidity and mortality in patients with overt atherosclerosis. Vasa. 2010 Nov;39(4):325-33.

- van Leeuwen N, Caprio M, Blaya C, Fumeron F, Sartorato P, Ronconi V, Giacchetti G, Mantero F, Fernandes-Rosa FL, Simian C, Peyrard S, Zitman FG, Penninx BW, de Kloet ER, Azizi M, Jeunemaitre X, Derijk RH, Zennaro MC. The functional c.-2G>C variant of the mineralocorticoid receptor modulates blood pressure, renin, and aldosterone levels. Hypertension. 2010 Nov;56(5):995-1002.

- Munshi A, Sharma V, Kaul S, Rajeshwar K, Babu MS, Shafi G, Anila AN, Balakrishna N, Alladi S, Jyothy A.Association of the -344C/T aldosterone synthase (CYP11B2) gene variant withhypertension and stroke. J Neurol Sci. 2010 Sep 15;296(1-2):34-8.

- Pfeufer A, Sanna S, Arking DE, Müller M, Gateva V, Fuchsberger C, Ehret GB, Orrú M, Pattaro C, Köttgen A, Perz S, Usala G, Barbalic M, Li M, Pütz B, Scuteri A, Prineas RJ, Sinner MF, Gieger C, Najjar SS, Kao WH, Mühleisen TW, Dei M, Happle C, Möhlenkamp S, Crisponi L, Erbel R, Jöckel KH,

Naitza S, Steinbeck G, Marroni F, Hicks AA, Lakatta E, Müller-Myhsok B, Pramstaller PP, Wichmann HE, Schlessinger D, Boerwinkle E, Meitinger T, Uda M, Coresh J, Kääb S, Abecasis GR, Chakravarti A. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. Nat Genet. 2009 Apr;41(4):407-14.

- Olsson S, Melander O, Jood K, Smith JG, Lövkvist H, Sjögren M, Engström G, Norrving B, Lindgren A, Jern C; International Stroke Genetics Consortium (ISGC). Genetic variant on chromosome 12p13 does not show association to ischemic stroke in 3 Swedish case-control studies. Stroke. 2011 Jan;42(1):214-6.

- Marques FZ, Campain AE, Yang YH, Morris BJ. Meta-analysis of genome-wide gene expression differences in onset and maintenance phases of genetic hypertension. Hypertension. 2010 Aug;56(2):319-24.

- Holmen OL, Romundstad S, Melien O. Association between the G protein β3 subunit C825T polymorphism and the occurrence of cardiovascular disease in hypertensives: The Nord-Trøndelag Health Study (HUNT). Am J Hypertens. 2010 Oct;23(10):1121-7.

EPFL found that the following articles are of VPH2 interest:

- M Astorino. Interaction fluide-structure dans le système cardiovasculaire. Analyse numérique et simulation. PhD thesis, Université Pierre et Marie Curie Paris VI, 2010.

- F. Liang and H. Liu. A closed-loop lumped parameter computational model for human cardiovascular system. JSME International Journal Series C, 48(4):484–493, 2005.

- J.T. Ottesen and M. Danielsen. Modeling ventricular contraction with heart rate changes. Journal of Theoretical Biology, 222(3):337–346, 2003.

- B. Quatember, M. Mayr, W. Recheis, S. Demertzis, G. Allasia, A. De Rossi, R. Cavoretto, and E. Venturino. Geometric modeling and motion analysis of the epicardial surface of the heart. Mathematics and Computers in Simulation, 2010.

- P. Reymond, F. Merenda, F. Perren, D. Rüfenacht, and N. Stergiopulos. Validation of a one-dimensional model of the systemic arterial tree. Am. J. Physiol.-Heart C, 297(1):H208, 2009.

- P. Segers, N. Stergiopulos, N. Westerhof, P. Wouters, P. Kolh, and P. Verdonck. Systemic and pulmonary hemodynamics assessed with a lumped-parameter heart-arterial interaction model. Journal of Engineering Mathematics, 47(3):185–199, 2003.

- Y. Sun, M. Beshara, RJ Lucariello, and SA Chiaramida. A comprehensive model for right-left heart interaction under the influence of pericardium and baroreflex. American Journal ofPhysiology-Heart and Circulatory Physiology, 272(3):H1499, 1997.

- G. Szabo, D. Soans, A. Graf, C.J. Beller, L. Waite, and S. Hagl. A new computer model of mitral valve hemodynamics during ventricular filling. European Journal of Cardio-thoracic Surgery, 26(2):239–247, 2004.

- Z. Virag and F. Lulí c. Modeling of aortic valve dynamics in a lumped parameter model of left ventricular-arterial coupling. Annali dell'Universita di Ferrara, 54(2):335–347, 2008.

NIGUARDA in the last year continued to monitor literature concerning the topics of VPH2 project (surgical ventricular restoration, surgery of ischemic mitral regurgitation, coronary artery bypass surgery and concomitant other surgical options of post ischemic ventricular dysfunction) using Pubmed search engine site. We report a selected bibliography of some papers related to these fields.

- Adhyapak SM, Parachuri VR. Architecture of the left ventricle: insights for optimal surgical ventricular restoration. Heart Fail Rev. 2010 Jan;15(1):73-83. Review.

- Zhong L, Su Y, Gobeawan L, Sola S, Tan RS, Navia JL, Ghista DN, Chua T, Guccione J, Kassab GS. Impact of surgical ventricular restoration on ventricular shape, wall stress, and function in heart failure patients. Am J Physiol Heart Circ Physiol. 2011 May;300(5):H1653-60.

- Isomura T, Hoshino J, Fukada Y, Kitamura A, Katahira S, Kondo T, Iwasaki T, Buckberg G; RESTORE Group. Volume reduction rate by surgical ventricular restoration determines late outcome in ischaemic cardiomyopathy. Eur J Heart Fail. 2011 Apr;13(4):423-31.

- Castelvecchio S, Menicanti L, Donato MD. Surgical ventricular restoration to reverse left ventricular remodeling. Curr Cardiol Rev. 2010 Feb;6(1):15-23.

- Silberman S, Eldar O, Oren A, Tauber R, Fink D, Klutstein MW, Bitran D. Surgery for ischemic mitral regurgitation: should the valve be repaired? J Heart Valve Dis. 2011 Mar;20(2):129-35.

- Murphy MO, Rao C, Punjabi PP, Athanasiou T. In patients undergoing mitral surgery for ischaemic mitral regurgitation is it preferable to repair or replace the mitral valve? Interact Cardiovasc Thorac Surg. 2011 Feb;12(2):218-27. Review

- Bouma W, van der Horst IC, Wijdh-den Hamer IJ, Erasmus ME, Zijlstra F, Mariani MA, Ebels T. Chronic ischaemic mitral regurgitation. Current treatment results and new mechanism-based surgical approaches. Eur J Cardiothorac Surg. 2010 Jan;37(1):170-85. Review.

- Fattouch K, Sampognaro R, Speziale G, Salardino M, Novo G, Caruso M, Novo S, Ruvolo G. Impact of moderate ischemic mitral regurgitation after isolated coronary artery bypass grafting. Ann Thorac Surg. 2010 Oct;90(4):1187-94.

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- Dor V, Civaia F, Alexandrescu C, Sabatier M, Montiglio F. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatments for Ischemic Heart Failure (STICH) trial. J Thorac Cardiovasc Surg. 2011 Apr;141(4):905-16, 916.e1-4.

4.1.2. Website

The VPH2 Project Website, administered by SORIN, is available on-line at www.vph2.eu and it is contains both a public and a private area (accessible to Partners by means of User ID and Password authentication).

The website is divided in several sections and related categories that can be intuitively browsed through the main menu.

The Website has been continuously updated and maintenance was done in order to rationalize it, to improve its performance, to share documents among partners and to disseminate the major results of the project.

4.2. Poster

POLIMI presented the poster "Mitral Valve Modelling in Ischemic Patients: Finite Element Analysis from Cardiac Magnetic Resonance Imaging" at Computing in Cardiology 2010 (Belfast September, 26th-29th).

POLITECNICO DI MILANO

Mitral Valve Modelling in Ischemic Patients: Finite Element Analysis from Cardiac Magnetic Resonance Imaging

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Introduction

Background

Ischemic mitral regurgitation (IMR) is a common and important complication of ischemic heart disease, associated with excess mortality independently of baseline characteristics and degree of ventricular dysfunction. Because altered annular geometry often contributes to leaflet malcoaptation in IMR, surgical correction is required to restore proper mitral valve (MV) function. Current standard treatment for IMR is the implantation of an annuloplasty ring that downsizes the mitral annulus to increase leaflet coaptation. However, residual or recurrent mitral regurgitation frequently appears after ring annuloplasty, as a consequence of a poor prognosis.

Aim of the study

We aim at developing a novel approach to the finite element (FE) modeling of the MVs, which merges a realistic morphological description of the valve, a sophisticated modeling of the response of its tissues and dynamic boundary conditions derived from *in vivo* data acquired non invasively via cardiac magnetic resonance (CMR) imaging. Furthermore, our long-term goal is to use these pathological valve models as a baseline condition to be compared with different post-operatory scenarios.

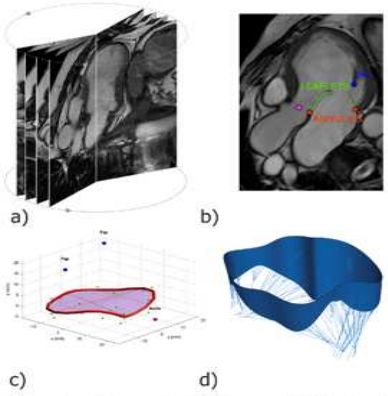

Figure 1. a) Long-axis CMR images, b) Tracing of annulus (red), leaflet (green), papillary muscle (blue) and position of the aorta (pink), c) Annular profile and papillary muscles detected on the ED frame and d) valve geometrical model.

Materials and Methods

Three models were built using our in home software: model A for a healthy MV, models B and C for two regurgitant MVs associated to ischemic diseases. Moreover, the patient whose dataset was used to build model B showed also dilated cardiomyopathy.

CMR Imaging

CMR imaging of 18 evenly rotated long-axis cut-planeswas performed. Time resolution was equal to 55 frames/cardiac cycle, spatial resolution to 0.78 mm, and slice thickness was 8 mm (Fig. 1.a).

CMR Data Analysis and MV Geometrical Model

Dedicated custom software was developed in the Matlab environment (Mathworks Inc) and used for MV quantitative analysis. CMR data from a subset of three patients were selected for the reconstruction of the finite element models. The end-diastolic (ED) configuration was chosen as the reference one. The MV geometrical model (Fig. 1.d) was implemented defining:

i) the three-dimensional annular profile, by Fourier interpolation of the points selected on the MA in the ED frame (Fig. 1.b, 1.c)
ii) PMs tips, defined as the two points selected in the ED frame (Fig. 1.b)
iii) leaflets extent and inclination, consistently with the CMR-derived leaflets free-edge profile
iv) thirty-nine branched chordae tendineae of three orders; their number, the corresponding branched structure and insertion sites on the leaflets were defined in accordance to *ex vivo* findings [1].

Material Properties

All tissues were assumed non-linear and elastic. Leaflets behaviour was described through the hyperelastic and transversely isotropic constitutive model proposed by May-Newman and Yin [2].
Chordae tendineae response was assumed isotropic and described through a polynomial strain energy function [3].

Dynamic Boundary Conditions

Valve closure during systole was simulated. Blood pressure was accounted for via a time-dependent physiological pressure applied on the leaflets. The dynamic contraction of MA and PMs was modelled via kinematic boundary conditions.

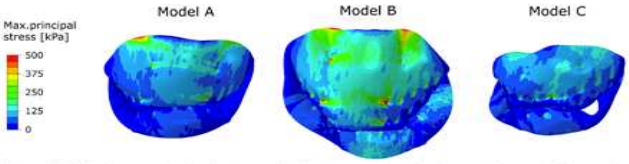

Figure 2. Maximum principal stress distribution on the leaflets at the systolic peak for the simulated healthy valve (model A) and regurgitant valves (models B and C).

Results and Discussion

In the healthy valve (model A) complete leaflet coaptation occurred at a very low value of transvalvular pressure drop (15 mmHg) consistently with *in vivo* findings [4]. In the ischemic patients' valves (models B and C), coaptation was incomplete: regurgitant areas were identified near the paracommissures. Peak stresses were computed next to the fibrous trigones on the annulus.

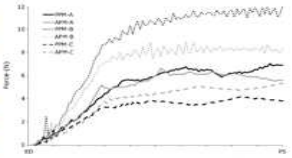

Figure 3. Time course of the reactions forces exerted on PMs.

In model B, both anterior and posterior leaflets (Fig. 2) were overall more stressed than in the other two cases.As regards the subvalvular apparatus, forces acting on the PMs are plotted in Fig. 3. Such tensions were unevenly transmitted to chordae tendineae throughout the simulated time-frame (Tab.1).
Computed results suggested that dilated cardiomyopathy following ischemic disease may alter the functioning of the valve not only in terms of loss of leaflets coaptation, but also increasing the stresses on the leaflets and the forces acting on the papillary muscles.

Table 1 Chordae tendineae forces (mean value ± standard deviation) obtained for different chordae types in the three simulated configurations. Values are expressed in N.

Chordae tendineae	Model A	Model B	Model C
marginal	0.162 ± 0.107	0.256 ± 0.156	0.109 ± 0.062
basal	0.157 ± 0.121	0.302 ± 0.248	0.143 ± 0.102
commissural	0.153	0.279	0.197
paracommissural	0.239	0.372	0.155
strut	0.898	1.197	0.355

Acknowledgements

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement No. 224635.

References

1.Lam JHC et al., Circulation 1970; 41:449-458.
2.May-Newman K and Yin FC, J Biomech Eng 1998; 120:38-47.
3.Kunzelman KS and Cochran RP, ASAIO Trans 1990; 36:M405-8
4.Timek T et al., J Thorac Cardiovasc Surg 2000; 119:774-783.

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CinC 2010

POLIMI presented the poster "Patient-specific CMR-based finite element model of the mitral valve" at the Second Italian Bioengineering Conference Torino, July 8th-10th 2010

POLITECNICO DI MILANO

Patient-Specific CMR-Based Finite Element Model of the Mitral Valve

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Introduction

Background

The mitral valve (MV) consists of two leaflets, inserted on the valvular plane through the mitral annulus (MA) and connected to underlying ventricular myocardium through a net of branched chordae tendineae that converge into two papillary muscles (PMs). Given the clinical impact of MV pathologies, MV biomechanics has been investigated through a variety of methods, including finite element (FE) modeling. However, none of the FE models currently available describes realistically the four aspects driving mitral function: valve morphology, tissues mechanical response, dynamic boundary conditions and interaction with the surrounding blood.

Aim of the study

We aim at developing a novel approach to the FE modeling of the physiological mitral valve, which for the first time merges a realistic morphological description of the valve, a sophisticated modeling of the response of its tissues and dynamic boundary conditions derived from *in vivo* data acquired non invasively via cardiac magnetic resonance (CMR) imaging.

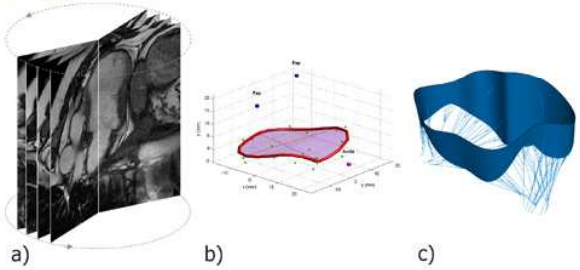


Figure 1. a) Long-axis CMR images, b) Annular profile and papillary muscles detected on the ED frame and c) valve geometrical model.

Materials and Methods

CMR Imaging

CMR imaging (Signa Excite, GE Medical Systems) of 18 long-axis planes (time resolution: 55 frames/cardiac cycle; spatial resolution: 0.78 mm; slice thickness: 8mm), evenly rotated (one every 10 degrees) along the left ventricular long-axis (Fig. 1.a), was performed in 12 patients with myocardial infarction using the SPSS sequence.

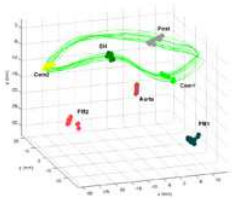
CMR Data Analysis and MV Geometrical Model

Dedicated custom software was developed in the MATLAB environment (The Mathworks Inc) and used for MV quantitative analysis. CMR data from a subset of three patients were selected for the reconstruction of the finite element models. The end-diastolic (ED) configuration was chosen as the reference one. The MV geometrical model (Fig. 1.c) was implemented defining:

i) the three-dimensional annular profile, by Fourier interpolation of the points selected on the MA in the ED frame (Fig. 1.b)
ii) PMs tips, defined as the two points selected in the ED frame (Fig. 1.b)
iii) leaflets extent and inclination, consistently with the CMR-derived leaflets free-edge profile
iv) thirty-nine branched chordae tendineae of three orders; their number, the corresponding branched structure and insertion sites on the leaflets were defined in accordance to *ex vivo* findings [1].

Material Properties

All tissues were assumed non-linear and elastic. Leaflets behaviour was described through the hyperelastic and transversely isotropic constitutive model proposed by May-Newman and Yin [2].



Chordae tendineae response was assumed isotropic and described through a polynomial strain energy function [3].

Dynamic Boundary Conditions

Valve closure during systole was simulated. Blood pressure was accounted for via a time-dependent physiological pressure applied on the leaflets. The dynamic contraction of MA and PMs was modelled via kinematic boundary conditions.

Figure 2. Reconstructed MA time-dependent profile and PMs position.

Results and Discussion

In the studied subjects, full valve closure occurred in a range of 15-20 mmHg transvalvular pressure drop, accordingly with *in vitro* observations [4].

Leaflets maximum principal stresses at systolic peak (SP) showed an asymmetric distribution (Fig. 3), in which the anterior leaflet resulted more stressed than the posterior one. Peak stresses were computed next to the fibrous trigones on the mitral annulus, and their values ranged from 300 kPa to 550 kPa.

As regards the subvalvular apparatus, forces acting on the PMs are plotted in Fig. 4. Peak values ranged from 4.5 to 8.4 N. Such tensions were unevenly transmitted to chordae tendineae throughout the simulated time-frame: the average load on a single chorda was highest in the strut chordae (up to 1.21 N at SP) and much lower in first order chordae (0.13 N at SP).

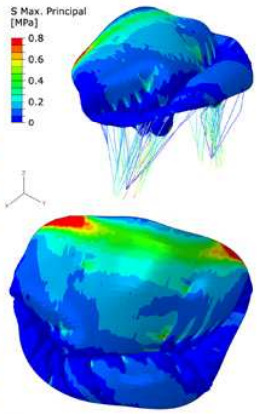


Figure 3. Leaflets maximum principal stresses.

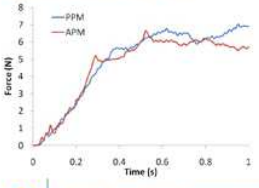


Figure 4. Time course of the reactions forces exerted on PMs.

In conclusion, the novel approach tested in this study allowed to obtain a MV FEM with beyond-state-of-the-art features. The use of CMR allowed overcoming many limitations of previous MV models and obtaining a more realistic FEM.

Acknowledgements

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement No. 224635.

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1.Lam JHC et al., Circulation 1970; 41:449-458.
2.May-Newman K and Yin FC, J Biomech Eng 1998; 120:38-47.
3.Kunzelman KS and Cochran RP, ASAIO Trans 1990; 36:M405-8
4.Timek T et al., J Thorac Cardiovasc Surg 2000; 119:774-783.

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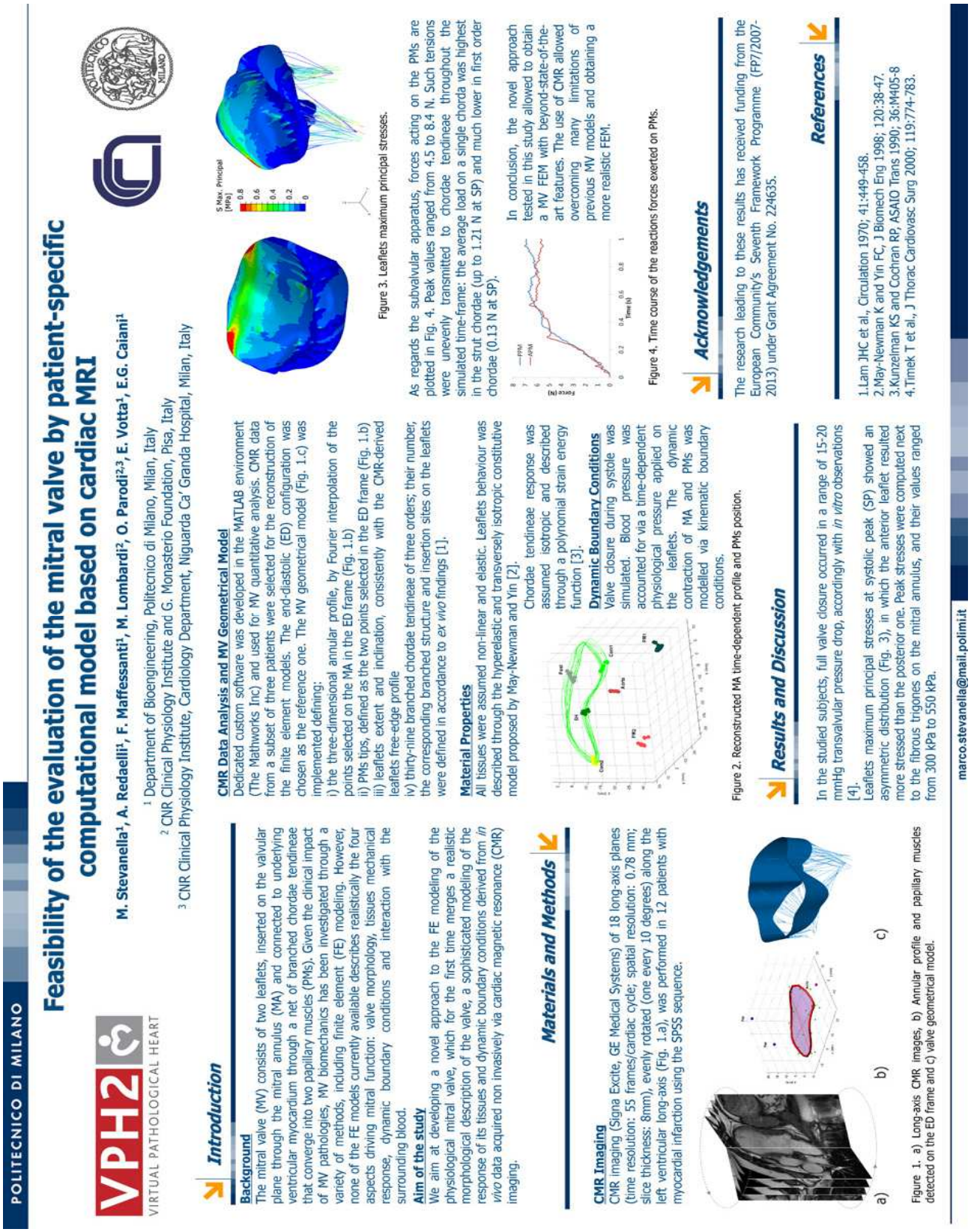
GNB 2010

POLIMI presented the poster "Feasibility of the evaluation of the mitral valve by patient-specific computational model based on cardiac MRI" at the European Congress ESC 2010, August, 28th – September, Stockholm, Sweden



POLIMI presented the poster "Annuloplasty ring assessment for the treatment of ischemic mitral regurgitation by patient-specific computational analysis from MRI images" at the ISMRM Italian Chapter Conference 2010, Rome, Italy, March 31th – April 1st, 2011

POLITECNICO DI MILANO

Annuloplasty ring assessment for the treatment of ischemic mitral regurgitation by patient-specific computational analysis from MRI imaging

M. Stevanella[1], C.A. Conti[1], E. Votta[1], F. Maffessanti[1], M.C. Carminati[1], M. Sotaquira[1], A. Roghi[2], O. Parodi[3], E.G. Caiani[1], A. Redaelli[1]

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[3] CNR Clinical Physiology Institute, Pisa, Italy

Introduction

Background

The mitral valve (MV) consists of two leaflets, inserted in the valvular plane through the mitral annulus and connected to underlying ventricular myocardium through a net of branched chordae tendineae that converge into two papillary muscles (PMs). Ischemic mitral regurgitation is usually treated through restrictive annuloplasty via rigid ring, which constrains the annular shape, or flexible ring, which preserves annular dynamics. The choice between these options is still debated and several methodologies have been adopted to identify the best solution.

We aimed at analyzing the effects of ring flexibility in restrictive annuloplasty through mitral valve (MV) patient-specific realistic finite element (FE) models based on cardiac magnetic resonance (CMR) imaging.

Materials and Methods

CMR Imaging

CMR imaging (Signa Excite, GE Medical Systems) of 18 long-axis planes (time resolution: 55 frames/cardiac cycle; spatial resolution: 0.78 mm; slice thickness: 8mm), evenly rotated (one every 10 degrees) along the left ventricular long-axis (Fig. 1.a), was performed in 5 patients with myocardial infarction using the steady-state free precession sequence.

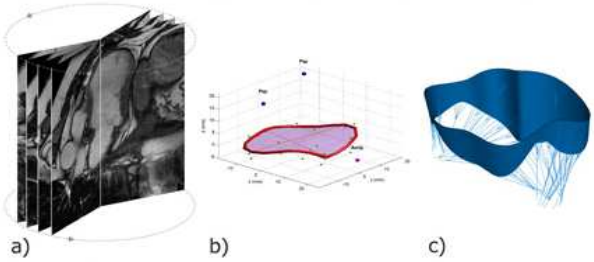

Figure 1. a) Long-axis CMR images, b) Annular profile and papillary muscles detected on the end-diastolic (ED) frame and c) MV geometrical model.

CMR Data Analysis and MV Geometrical Model

For every frame, in each cut-plane (Fig. 1a) the following valvular substructures were manually defined using custom software implemented in MATLAB (Natick, MA, United States):

1) two annular points at the level of leaflet insertions
2) multiple points defining leaflet profile connected through cubic splines
3) a point for each visible PM tip

The 3D coordinates of the points on each cut-plane were reconstructed from the position of the latter with respect to the rotation axis (Fig. 1b). The end-diastolic (ED) MV geometry was assumed as the reference configuration for the reconstruction of the FE model (Fig. 1c). A physiological transvalvular pressure was applied to the leaflets to simulate valve closure.

For each patient, three conditions were simulated: (i) pre-operative; (ii) after insertion of a specific ring with closed profile and regionally varying bending stiffness (CV ring); (iii) after implanting a specific rigid ring with partially open profile at saddle-horn (RO ring).

Material Properties

All tissues were assumed non-linear and elastic. Leaflets behavior was described through the hyperelastic and transversely isotropic constitutive model proposed by May-Newman and Yin [2].

Chordae tendineae response was assumed hyperelastic and isotropic [3].

Dynamic Boundary Conditions

Valve closure during systole was simulated. Blood pressure was accounted for via a time-dependent physiological pressure applied on the leaflets. The dynamic contraction of mitral annulus (MA) and PMs was modeled via kinematic boundary conditions.

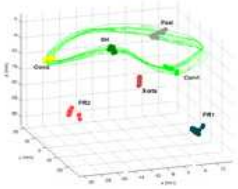

Figure 2. Reconstructed MA time- dependent profile and PMs position.

Results and Discussion

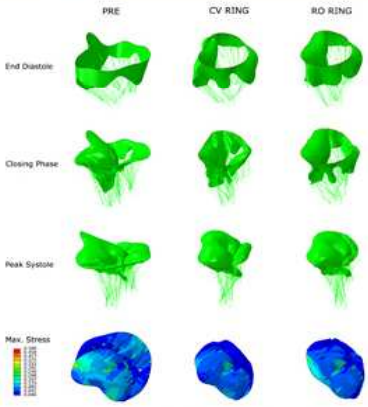

Figure 3. Representative FE simulations of the pre-operative scenario (PRE), and post operative outcomes with a flexible (CV) ring and with a rigid (RO) ring: closure dynamics and principal stress distribution on the leaflets (atrial view) are shown.

The RO ring restored MV competence in all patients resulting in higher coaptation length, while CV ring succeeded only in 5/7. Conversely, CV ring partially preserved annular dynamics, that was lost with the RO ring. Both rings significantly reduced leaflets stresses and tensions on chordae tendineae and PMs. While RO rings resulted in a good performance, flexible CV rings could not always guarantee to counterbalance the effects of leaflets tethering associated to ischemic regurgitation.

Moreover, despite CV flexibility, annular dynamics was not completely preserved. Our patient-specific FE approach could provide new insight in optimizing tuning of regional stiffness, thus potentially improving the performance of new ring design, as well as help in surgery planning [4].

Acknowledgements

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement No. 224635.

References

1.Lam JHC et al., Circulation 1970; 41:449-458.
2.May-Newman K and Yin FC, J Biomech Eng 1998; 120:38-47.
3.Kunzelman KS and Cochran RP, ASAIO Trans 1990; 36:M405-8
4.Stevanella M et al., Cardiovasc Eng Technol 2011; Epub.

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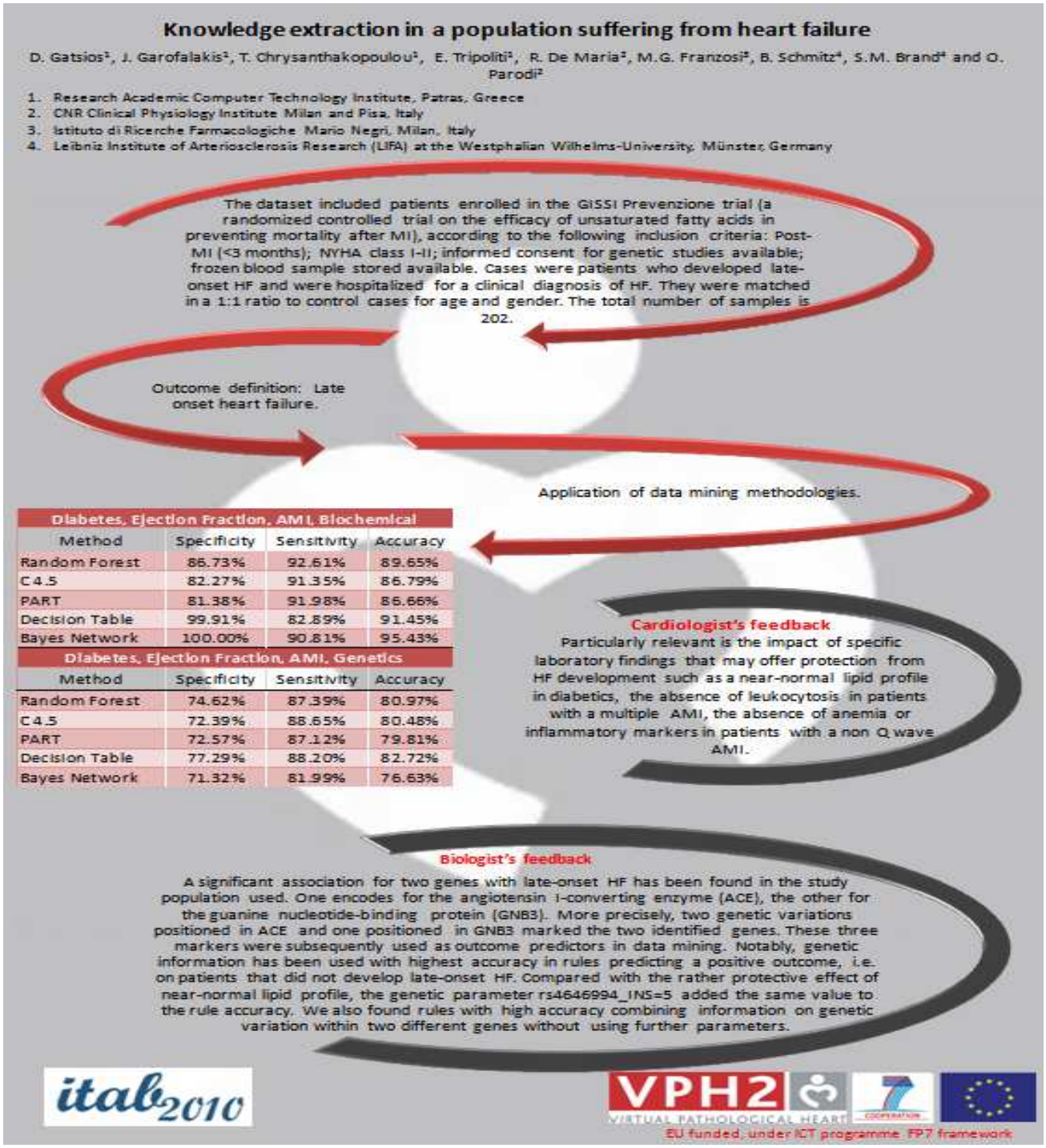
CTI presented the poster ”Knowledge extraction in a population suffering from heart failure” at the ITAB 2010 Conference in Corfu, Greece (November 2 – 5, 2010).



Knowledge extraction in a population suffering from heart failure

D. Gatsios[1], J. Garofalakis[1], T. Chrysanthakopoulou[1], E. Tripoliti[1], R. De Maria[2], M.G. Franzosi[3], B. Schmitz[4], S.M. Brand[4] and O. Parodi[2]

1. Research Academic Computer Technology Institute, Patras, Greece
2. CNR Clinical Physiology Institute Milan and Pisa, Italy
3. Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy
4. Leibniz Institute of Arteriosclerosis Research (LIFA) at the Westphalian Wilhelms-University, Münster, Germany

The dataset included patients enrolled in the GISSI Prevenzione trial (a randomized controlled trial on the efficacy of unsaturated fatty acids in preventing mortality after MI), according to the following inclusion criteria: Post-MI (<3 months); NYHA class I-II; informed consent for genetic studies available; frozen blood sample stored available. Cases were patients who developed late-onset HF and were hospitalized for a clinical diagnosis of HF. They were matched in a 1:1 ratio to control cases for age and gender. The total number of samples is 202.

Outcome definition: Late onset heart failure.

Application of data mining methodologies.

Diabetes, Ejection Fraction, AMI, Biochemical			
Method	Specificity	Sensitivity	Accuracy
Random Forest	86.73%	92.61%	89.65%
C4.5	82.27%	91.35%	86.79%
PART	81.38%	91.98%	86.66%
Decision Table	99.91%	82.89%	91.45%
Bayes Network	100.00%	90.81%	95.43%

Diabetes, Ejection Fraction, AMI, Genetics			
Method	Specificity	Sensitivity	Accuracy
Random Forest	74.62%	87.39%	80.97%
C4.5	72.39%	88.65%	80.48%
PART	72.57%	87.12%	79.81%
Decision Table	77.29%	88.20%	82.72%
Bayes Network	71.32%	81.99%	76.63%

Cardiologist's feedback

Particularly relevant is the impact of specific laboratory findings that may offer protection from HF development such as a near-normal lipid profile in diabetics, the absence of leukocytosis in patients with a multiple AMI, the absence of anemia or inflammatory markers in patients with a non Q wave AMI.

Biologist's feedback

A significant association for two genes with late-onset HF has been found in the study population used. One encodes for the angiotensin I-converting enzyme (ACE), the other for the guanine nucleotide-binding protein (GNB3). More precisely, two genetic variations positioned in ACE and one positioned in GNB3 marked the two identified genes. These three markers were subsequently used as outcome predictors in data mining. Notably, genetic information has been used with highest accuracy in rules predicting a positive outcome, i.e. on patients that did not develop late-onset HF. Compared with the rather protective effect of near-normal lipid profile, the genetic parameter rs4646994_INS=5 added the same value to the rule accuracy. We also found rules with high accuracy combining information on genetic variation within two different genes without using further parameters.

WWU presented the poster "Virtual Pathological Heart of the Virtual Physiological Human (VPH2)" at the Human Genome Meeting 2011, Dubai, United Arab Emirates, March 13th – March 17th, 2011.

Virtual Pathological Heart of the Virtual Physiological Human (VPH2)

Boris Schmitz[1,2], Renata DeMaria[4], Jonica Campolo[4], Marina Parolini[4], Stefan-Martin Brand[1,3], Oberdan Parodi[4].

[1]Medical Faculty of the Westphalian Wilhelms-University of Münster, Department of Molecular Genetics of Cardiovascular Disease, Münster; [2]University Hospital Münster, Department of Internal Medicine D, Nephrology and Hypertension, Münster; [3]Leibniz-Institute for Arteriosclerosis Research, Münster; [4]CNR Clinical Physiology Institute, Milan, Italy.

Background

VPH2 aims at developing a patient-specific platform improving the management processes of heart diseases classified by severity and extent of the disease in patients with post-ischemic left ventricular dysfunction (LVD). One major task is the integration of clinical, biological and genetic data, retrieved from medical records and laboratory research results. The project involves the development of tools for collecting, storing, analysing and linkage of heterogenic data. Here we present part of the genetic data generated for use within the VPH2 platform. We assessed the prevalence of genetic variants in patients with chronic systolic heart failure and different degrees of reverse LV remodelling after cardiac resynchronization therapy (CRT) in a multicentre case-control study. Information on genetic variants associated with CRT phenotypes were subsequently used for VPH2 data mining.

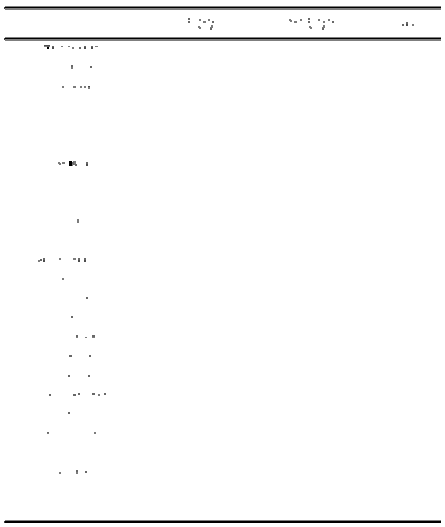
Cardiac resynchronization therapy (CRT)

CRT has been shown to reverse the remodelling process by improving ventricular size, shape, and mass and reducing mitral regurgitation. Reverse remodelling (RR+), defined in this study as a decrease >10% in left ventricular end systolic volume (LVESV) with respect to pre-procedural values, is associated to the delayed progression and reduced morbidity and mortality from heart failure (HF).

Lack of RR (RR-), found in over 30% of patients, is associated to hospital readmissions and death from progressive pump failure and represents therefore an important clinical issue with relevant prognostic implications.

Results

Table 1: Clinical characteristics of CRT patients



The average distance between blood sampling the CRT procedure was 44 [25-70] months. P-values are for chi-square or Fisher's exact test for categorical and Student's t or Mann-Whitney test for non-categorical variables. IHD, ischemic heart disease; IDC, idiopathic dilated cardiomyopathy; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end diastolic volume; LVESV left ventricular end systolic volume; MI, myocardial infarction; RAS, renin-angiotensin system; VHD, valvular heart disease.

Table 2: Genetic variants associated with CRT non-responder phenotypes

SNP	Test	Allele 1	Allele 2	Echo non-responders	Echo responders	P value
ATP1B1 (rs3766031)	GENO	C	T	52/9/0	39/21/1	0.013
	Allelic	C	T	113/9	99/23	0.006
GNB3 (rs5443)	GENO	C	T	34/21/4	20/33/8	0.022
	Allelic	C	T	89/29	73/49	0.013

Propensity score matching resulted in a balanced sample of 62 non-responders and 62 responders (Table 1). Clinical characteristics of the study population are consistent with current clinical practice, in terms of symptoms, etiology, electrocardiographic markers and drug treatment. Ventricular volumes were definitely enlarged in both groups as expected in a LV remodelling phenotype typical of HF. Despite matching RR- showed a higher prevalence of diabetes and less LV dilation than RR+. Two genetic variants, ATP1B1 (rs3766031 C/T, intron 2) and GNB3 (rs5443 C/T, exon 10), were detected within the CRT sample set (Table 2). For both variants, the C allele was significantly associated with the CRT non-responder phenotype (p-values 0.006 and 0.013, respectively).

Methods:

We enrolled 160 patients implanted with CRT at least 6 months before at 3 Italian centres.

Inclusion criteria were:
- NYHA class II – IV HF
- any aetiology of HF
- QRS duration on surface ECG >120 msec
- LVEF before CRT ≤ 35%
- LV end-diastolic diameter >55 mm at baseline
- stable left lead positioning
- ventricular volumes measured at follow-up echocardiography 6 to 12 months after CRT available

Exclusion criteria were:
- procedural failure (non functioning LV lead)
- death or loss to follow-up (as no blood sampling could be performed)

RR+ was defined as a decrease in LVESV >15%, at 6 to 12 months echo after CRT. All other changes classified the patient as RR-.

Genotyping of patients' DNA (2 ng) was performed using TaqMan analysis on ABI7900 for 44 genetic variants recently published to be replicatively associated with cardiac phenotypes.

Conclusion

We identified two genetic variants to be significantly associated with the CRT non-responder phenotype. ATP1B1 encodes the ubiquitously expressed β-subunit of Na^+/K^+-ATPase, an oligomeric protein necessary for the maintenance of Na^+- and K^+- electrochemical gradients across the plasma membrane. This transporter is involved in multiple physiological processes such as renal sodium reabsorption, vascular smooth muscle tone regulation, and cardiac muscle contraction. GTP-binding protein (GNB3) C825T is a functionally proven candidate polymorphism, the variant being associated with stimulation of the ubiquitously expressed Na^+/H^+ exchanger. Both variants reside within genes involved in signal transduction processes suggesting an impaired response of patients to the applied therapeutical treatment. The identified variants were used for data mining purposes within the VPH2 project.

Funding

VPH2 (Virtual Pathological Heart of the Virtual Physiological Human) is funded as an ICT project by the EU in the FP7-ICT-2007.2, project number 224635. Visit us at: http://www.VPH2.eu

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Chung ES et al., Circulation. 2008;117:2608-16.
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4.3. Conferences, exhibitions, workshops

The Research Direction involved in each dissemination action is reported in each table. The Research Directions are:

RD1 – Patient specific knowledge extraction and Disease Modelling

RD2 – Coupling genomics and biochemical markers for multiscale modelling

RD3 – Post ischemic left ventricular dysfunction and patient-specific treatment planning

RD4 – Imaging and visualisation techniques

4.3.1. Conferences and exhibitions

Event n.	1
Research Direction	RD3
Title	ESB2010 17th Congress of the European Society of Biomechanics
Date	July, 5^{th}-8^{th} 2010
Location	Edimburgh, UK
Type	Conference
Organizer	European Society of Biomechanics
Objective	The 2010 meeting had the ambition to cover the traditional core topics of the European Society of Biomechanics while including emerging areas in which much new and exciting biomechanics research is taking place.
Description	ESB2010 programme featured multiple tracks of presentations covering a broad range of biomechanics-related applications. Four plenary sessions tackled current key-topics in biomechanics research.
Target audience	Biomedical Engineers, Mathematicians
Participating partners	Polimi
Report	The work “Mitral valve finite element modeling from cardiac magnetic resonance imaging: patient-specific quantitative analysis”, by Stevanella M, Maffessanti F, Votta E, Caiani EG, Redaelli A, was presented in a podium presentation by M. Stevanella in the session “Cardiac: Flow Modelling & FSI”
Publishable summary	Finite element models (FEMs) has proven to be useful and accurate in the assessment of mitral valve (MV) biomechanics. Previously proposed MV FEMs, mostly based on animal or ex vivo measurements, lay over simplifying assumptions on MV symmetrical shape, idealize leaflets profile and disregard contraction. Thus, our goal was to develop a framework for the quantitative analysis of time-varying MV geometry from cardiac magnetic resonance (CMR) imaging, and to integrate these data in patient-specific simulations of MV closure from end diastole to peak systole. CMR imaging of 18 evenly rotated long-axis cut-planes (one every 10

	degrees) was performed on a healthy subject with a temporal resolution of 55 time-frames per cardiac cycle. Three-dimensional MV annulus geometry, leaflets surface and papillary muscles (PMs) position were manually obtained using custom software. Leaflets extent and 3-D orientation were set consistently with the MRI-derived leaflets free-edge profile. Thirty-nine branched chordae tendineae of three orders were defined in accordance to ex vivo findings. All tissues were assumed non-linear and elastic. Their mechanical response was described by means of proper strain energy potentials. Leaflets behaviour was described through the hyperelastic and transversely isotropic constitutive model proposed by May-Newman. Chordae tendineae response was assumed isotropic and described through a polynomial strain energy function, whose parameters were defined via interpolation of data from the literature. The dynamic contraction of mitral annulus and PMs was modeled via kinematic boundary conditions, i.e. imposing time-dependent nodal displacements, derived from annular nodes position at each time-frame. A physiological transvalvular pressure drop, up to 120 mmHg, was applied on the leaflets. In the studied subject, full valve closure occurred at a 15 mmHg transvalvular pressure drop, accordingly with in vitro observations. Leaflets maximum principal stresses were computed. The anterior leaflet resulted more stressed than the posterior one; peak values of 500 kPa were computed next to the fibrous trigones on the MA, consistently with their functional role of anchoring structures for the surrounding soft tissues. In this study, we introduced a novel approach for developing a FE model of the MV based on patient-specific data obtained from CMR. This technique allows for high time-resolution imaging in adequately large field of view, even in subjects with enlarged annulus due to MV pathologies. Although further tests on healthy and diseased subjects are mandatory, this approach could constitute the basis for an accurate evaluation of MV pathologic conditions and for the planning of surgical procedures.

Event n.	2
Research Direction	RD3
Title	2nd Italian Bioengineering Conference
Date	July, 8^{th}-10^{th} 2010
Location	Torino, Italy
Type	Conference
Organizer	GNB – National Bioengineering Group
Objective	The objective of GNB meetings is to represent the collect point of the national research activities in the field of Biomedical Engineering.
Description	The conference was structured into 6 plenary lectures, including one session focused on VPH2 research, 4 round tables, and 5 sessions of poster presentations (about 340 posters were presented as an overall).
Target audience	Bioengineers, Medical Doctors
Participating	Polimi

partners	
Report	The following plenary lecture was given by Alberto Redaelli: “Integrative Hybrid modeling”
Publishable summary	Computational biomechanics has undergone a tremendous evolution in the last ten years. Thanks to increasing computational resources and novel and sophisticated software tools, biomechanical problems, which could be hardly undertaken ten years ago, are now easily addressed. Indeed, simulations involving millions of unknowns can now be run on a desktop computer. As happens in these cases, borders are then moved farther and research explores new applications. Accordingly, in the last years the research interest has focused on new research topics in the areas of multiscale, multiphysics and heterogeneous integrative modeling (Siebes and Ventikos, 2010). Notably, we are witnesses of the concomitant great progress in imaging which is providing diagnostic possibilities that have not been available before. What described can have a deep impact on personalized healthcare, a paradigm based on the detailed comprehension of the patho-physiology of the tissue and/or organ under examination, with the aim of attaining a more efficacious treatment of the patient disease. Personalized healthcare requires realistic modeling tools able to tackle and couple all the relevant phenomena with sufficient detail and realism. The realistic description of the disease implies the ability to describe all the relevant physics involved in the disease at all the scale they occur. In fact, it is their interplay that determines the disease expression and progress. In this milieu, personalized healthcare can greatly benefit from imaging; the phenomenology of such complex biological behavior can be, at a large extent, caught through imaging; although currently limited by inadequate spatial and temporal resolutions, indeed, imaging can represent an important source of information, a sort of short cut, since it allows to describe the complexity of the phenomena as they are, rather than simulate them. Patient specific modeling can hence be approached by combining simulations and imaging, in a heterogeneous framework, what we define as integrative or hybrid modeling. Hybrids are mythological creatures combining body parts of more than one real species. In the general sense, a hybrid is the combination of two or more different things, aimed at achieving a particular objective or goal. The classical application of imaging in biomechanical modeling is the use of anatomical data to construct patient specific models. This is currently a widely used approach which allows to provide personalized evaluation of biomechanical tissue behaviors and fluid dynamics features. This is a first step, but still defective under many aspects. Indeed, computational models require assumptions also for physical properties and boundary conditions which can heavily affect the solution of the equations governing the tissue behavior. Imaging can help also in this case. Cine CT and Cine MRI, for example, can provide maps of the tissue motion, which can also be correlated to tissue mechanical properties.

	With reference to cardiac ejection mechanics, this approach is well known and was first applied by Schoephoster and co-workers in 1994 to calculate left ventricle fluid dynamics from 2D cineangiography (Schoephoster et al., 1994). Recently it has been extended to 3D datasets (see e.g. Schenkel et al., 2009). In this framework we are currently collaborating to a European project aimed at the development of patient specific models for cardiac surgical planning by merging modeling and imaging techniques. It focuses on the ischemic heart failure and has a twofold objective. Firstly, the simulation of the pathological heart from short axis MRI datasets for the assessment of the preoperative heart function and for the assessment of its modifications following surgical ventricle repair (offering a number of surgical options including ventricle restoration, resynchronization, revascularization and mitral valve repair); secondly, the simulation of the effects of mitral valve annuloplasty on heart function. This task is achieved using long axis MRI datasets to collect the mitral annulus and papillaries motion together with mitral leaflet morphology to construct patient specific mitral valve models. Another relevant ongoing work involving biomechanics and bioimaging experts that will be presented concerns the use of phase contrast MRI (PC-MRI) to disclose *in vivo* fluid dynamics behavior of arterial districts. PC-MRI is a specific MRI sequence, which can actually provide the three velocity components in a 3D domain, and allows for the integration in vivo of both anatomical and hemodynamic data (Morbiducci et al 2009). The main limitation to the use of PC-MRI is the space and, at a major extent, the temporal resolution of the dataset. The integration with CFD modeling can allow to attain acceptable spatial and temporal resolution. In general there is the need for new integrative instruments for the identification of patho-physiological data for diagnosis of several diseases. It is a call to overtake the current discipline borders, that wait to be caught.

Event n.	3
Research Direction	RD4
Title	7th International Conference on Biomedical Visualization, Medivis ‘10
Date	July 27th -29th, 2010
Location	London
Type	International conference
Organizer	GraphicsLink
Objective	Running alongside the broader conference on Information Visualisation, which attracts a large highly international audience, MediVis provides a concentrated focus purely on biomedical visualisation.
Description	Paper presented.
Target audience	Visualisation experts
Participating partners	BED, POLIMI
Report	MediVis is the longest running and most prominent European conference on biomedical visualisation. Its proceedings are published by IEEE

	Computer Society and are thus widely available to the visualisation community through the IEEE digital library. MediVis is a constituent conference of the annual Information Visualisation conference, which attracts about 30 participants from more than 20 countries worldwide.
Publishable summary	While there has been significant progress in the treatment of ischemic heart failure, it remains a significant health and economic problem worldwide. In this paper, we presented the challenges of modelling ischemic heart failure and introduced a user-friendly software system that forms a sub-set of the Virtual Pathological Heart environment, which is currently being developed in VPH2. The system will provide visualisation tools for surgical assessment and planning: the registration and display of necrotic and hypo-kinetic regions; simulated surgical restoration (cutting and patching); and finally post-operative functional prediction (volume, shape and mitral valve regurgitation).

Event n.	4
Research Direction	RD4
Title	VPH2010 Conference
Date	September 2010
Location	Brussels
Type	International conference
Organizer	VPH NoE
Objective	To raise awareness of VPH2 within the VPH community
Description	Paper presented.
Target audience	VPH community
Participating partners	BED, POLIMI, SCS
Report	The biennial VPH conference provides a focus for VPH activities and is an important medium for disseminating results across the whole VPH community.
Publishable summary	Ischemic heart failure remains a significant health and economic problem worldwide. The system described will provide visualisation tools for surgical assessment and planning: the registration and display of necrotic and hypo-kinetic regions; simulated surgical restoration and post-operative functional prediction.

Event n.	5
Research Direction	RD4
Title	European Congress ESC 2010
Date	August 28th - September 1st, 2010
Location	Stockholm, Sweden
Type	Congress
Organizer	European Society of Cardiology
Objective	The role of MRI on diagnostic assessment in cardiopathic patients.
Description	www.escardio.org

Target audience	World Cardiologist and cardiac basis researchers
Participating partners	Polimi, IFC CNR
Report	Abstract presentation: Feasibility of the evaluation of the mitral valve by patient specific computational model based on cardiac MRI. Stevanella M, Redaelli A, Maffessanti F, Lombardi M, Parodi O, Votta E, Caiani E.
Publishable summary	**Purpose.** Finite element models (FEMs) constitute an innovative approach for the biomechanical analysis of dynamic cardiac structures, and have been previously applied to analyse mitral valve (MV) behaviour with great benefits compared to animal studies. However, existing MV FEMs, based on animal or ex-vivo measurements, include important simplifications: valve symmetry and planarity, idealized leaflets free margin profile, and disregarded papillary muscles (PMs) contraction. Accordingly, our aims were: 1) to test the feasibility of extracting quantitative information about MV and PMs from cardiac magnetic resonance (CMR) imaging; 2) to design a realistic MV FEM by integrating quantitative information from CMR data, and simulate MV closure from end-diastole to systolic peak. **Methods.** CMR imaging of 18 long-axis planes, evenly rotated (one every 10 degrees) along the left ventricular long-axis, was performed in a healthy subject with a temporal resolution of 55 time-frames per cardiac cycle. In each plane and for each frame during systole, MV annulus and leaflets, and PMs tips (when visible), were manually identified using custom software. Then, 3-D MV annulus geometry, leaflets surface and PMs position were automatically computed for each frame, and used as input to the MV FEM. In addition, leaflets extent and 3-D orientation were set consistently with the MRI-derived leaflets free-edge profile. The MV tissue was modeled by hyperelastic anisotropic mechanical properties, and a physiological transvalvular pressure load curve was applied to the leaflets. **Results.** Preliminary results concerning different aspects of MV biomechanics, such as valve dynamics, leaflets coaptation, leaflets strains and chordae tendineae tensions, were in good agreement with in vitro observations and previous FEMs outcomes. Conclusion. Quantitative information on MV annulus and PMs morphology and dynamics can be extracted from CMR, when performed in multiple long-axis planes. These data potentially allow the implementation of a realistic and patient-specific MV FEM. This approach could overcome the limitations of previously proposed models and give new insight into the complex MV function. This approach could constitute the basis for accurate in-silico evaluation of MV pathologic conditions and for the planning of surgical procedures.

Event n.	6
Research Direction	RD3, RD4
Title	Computing in Cardiology Conference 2010
Date	September, 26th - 29th 2010
Location	Belfast, Ireland
Type	Conference

Organizer	Computing in Cardiology
Objective	Providing a forum for scientists and professionals from the fields of medicine, physics, engineering and computer science to discuss their current research in topics pertaining to computing in clinical cardiology and cardiovascular physiology.
Description	Computing in Cardiology (formerly Computers in Cardiology) is an international scientific conference that has been held annually since 1974. Meeting topics are: cardiovascular Imaging (echocardiography, angiography, SPECT and PET, MRI, CT, 3D imaging, multimodality imaging, knowledge-based image processing, new imaging modalities), cardiovascular mechanics (contractile and valvular function, arterial biomechanics, coronary artery measurements, instrumentation, blood pressure), ECG (repolarization, ischemia, high-resolution ECG, arrhythmia, diagnostic ECG, apnea detection from the ECG), electrophysiology (mapping, ablation, fibrillation/defibrillation, implantable devices), medical informatics (intranet/internet, DICOM and communication standards, automated decision support, telemedicine, PACS, databases, systems and instrumentation), modeling and simulation (cellular models, forward and inverse solutions), molecular techniques in cardiology and system study (heart rate variability, baroreflex control of circulation, methods and applications, nonstationarity and nonlinearity)
Target audience	Bioengineers, Medical Doctors, physicists, ICT experts
Partners involved	Polimi
Report	The following oral presentations were given: • F. Maffessanti: "Feasibility of a novel approach for 3D mitral valve quantification from magnetic resonance images", by Maffessanti F, Stevanella M, Votta E, Lombardi M, Parodi O, De Marchi D, Conti CA, Redaelli A, Caiani EG • C. Corsi: "Development and validation of automated endocardial and epicardial contour detection for MRI volumetric and wall motion analysis", by Caiani EG, Redaelli A, Parodi O, Votta E, Maffessanti F, Tripoliti E, Nucifora G, De Marchi D, Tarroni G, Lombardi M, Corsi C
Publishable summary	**Feasibility of a Novel Approach for 3D Mitral Valve Quantification from Magnetic Resonance Images** Mitral annulus (MA) assessment is of great importance for the diagnosis and treatment of mitral valve (MV) disease. Standard CMR image acquisition allows to obtain only a limited number of measurements. We propose a different way to study the MV by multiple CMR long-axis cine images, followed by 3D reconstruction and quantification. Our aim was to test the reproducibility of this approach. CMR cine imaging of 18 long-axis planes (55 frames/cardiac cycle; spatial resolution: 0.78 mm; slice thickness: 8mm), rotated every 10° along the left ventricular long-axis, was performed in 12 patients with myocardial infarction. Custom software was used for MV quantitative nalysis (Figure):

	1) in the end-diastolic (ED) and end-systolic (ES) frames, in each plane, the position of the MA annulus and papillary muscles (PM) tips were manually identified; 2) the MA geometry and PM position were automatically reconstructed in a 3D space; 3) several parameters were then computed: MA perimeter, antero-posterior and intercommissural diameters, MA height, MA 3D and projected area, the angle between PM, the distance from PM to the MA. To assess the reproducibility of the procedure, two operators repeated the analysis: the inter-operator variability was evaluated as the coefficient of variation (CV(%)=100*SD/mean). Analysis of MA was feasible in all patients, showing good inter-operator agreement for MA perimeter (CV_{ED}=1.9%; CV_{ES}=1.8%), antero-posterior (CV_{ED}=3.0%; CV_{ES}=5.8%) and intercommissural diameters (CV_{ED}=1.8%; CV_{ES}=2.0%), 3D (CV_{ED}=3.4%; CV_{ES}=4.3%) and projected areas (CV_{ED}=2.8%; CV_{ES}=3.7%), and the distance from PM and MA (CV_{ED}=4.1%; CV_{ES}=4.6%). MA height (CV_{ED}=9.9%; CV_{ES}=16.1%) and the angle between PM (CV_{ED}=6.8%; CV_{ES}=10.6%) were less reproducible, in particular at ES. Quantitative information on MA and PM morphology and function is feasible from CMR imaging n multiple long-axis planes. The proposed approach is highly reproducible and could constitute the basis for in-depth evaluation of the MV and for the planning of surgical procedures. **Development and validation of automated endocardial and epicardial contour detection for MRI volumetric and wall motion analysis** Magnetic resonance imaging (MRI) represents the gold standard for left ventricular (LV) volumes and mass analysis, as well as for the diagnosis of regional LV dysfunction. However, volumetric measurements based on multiple contour tracings are cumbersome, and visual interpretation of cine images suffers from inter-observer variability. Our aim was to develop a technique for combined automated endo and epicardial border detection from MRI images throughout the cardiac cycle, and to validate it. **Methods.** Dynamic, ECG-gated, steady-state free precession short-axis images were obtained (GE Healthcare, 1.5T) in 8–12 slices in 15 patients with previous myocardial infarction. An expert cardiologist provided the "gold standard" for: 1) LV dimensions and mass, by manually tracing endo and epicardial contours; 2) regional wall motion (WM) interpretation, by grading (normal, abnormal) three slices selected at apical, mid and basal level. Custom software based on image noise distribution (for LV endocardial detection) and level-set (for epicardial detection) was applied, from which end-diastolic (ED) and end-systolic (ES) volumes and mass were computed, as well as regional fractional area change (RFAC), from which automated classification of regional WM abnormality was defined for RFAC<50%. Comparison with "gold standard" was performed by: 1) linear regression and Bland-Altman analyses for LV volumes and mass; 2) levels of agreement between the cardiologist WM grades and the automated classification. **Results:** Optimal correlations (r^2>.97) and no bias were found for ED and ES volumes, while LV mass resulted in a good correlation (ED: r^2=.81; ES: r^2=.74) with a minimal overestimation (ED:15.2g; ES:8.7g) and narrow 95% limits of agreement (ED: ± 30 g; ES: ±

	33 g). The automated interpretation resulted in high sensitivity, specificity, and accuracy (78%, 85%, 82%, respectively) of WM abnormalities. **Conclusion**. Combined automated endo and epicardial border detection from MRI images provides reliable measurements of LV dimensions and regional WM classification.

Event n.	7
Research Direction	RD3, RD4
Title	44° Convegno Cardiologia 2010
Date	September 27th - October 1st, 2010
Location	Milan, Italy
Type	Conference
Organizer	Niguarda Hospital, "A. De Gasperis" Cardiovascular Department
Objective	Update in cardiovascular disease
Description	www.degasperis.it
Target audience	Cardiologists and cardiac surgeons (about 1.500 doctors attending)
Participating partners	IFC CNR, REGLOM, SORIN, POLIMI, NIGUARDA
Report	SYMPOSIUM. La ricerca in Europa: progetti informatici in Cardiologia. "Piattaforma virtuale per lo studio della disfunzione post-ischemica: il progetto VPH2. Dr. Luigi Martinelli, (REGLOM) Oral Presentation. Prof. Oberdan Parodi (IFC CNR) , chairman of this session.
Publishable summary	The presentation introduced the work in progress of VPH2, namely, some decision trees from data mining analysis on GISSI Prevention study, the FAT platform and the initial findings on FPT, the role of genetic SNPs in prognostic evaluation (late heart failure) of patients with recent acute myocardial infarction (GISSI project).

Event n.	8
Research Direction	RD3
Title	VPH-NoE conference
Date	September 30th – October 1st, 2010
Location	Brussel, Belgium
Type	Conference
Organizer	VPH-NoE
Objective	Bringing together key representatives from VPH groups, Industry and Clinics.
Description	The Virtual Physiological Human Network of Excellence is an umbrella project representing the Virtual Physiological Human Initiative set up by the European Commission. This meeting represented the first of a series of VPH Conferences.
Target audience	Bioengineers, Medical Doctors, ICT experts
Partners involved	Polimi
Report	The following oral presentations were given: • Alberto Redaelli: "Left ventricle modelling: a functional assessment tool

	combined with a predictive tool for the evaluation of the post-operative mechanical performance." Conti CA, Votta E, Corsi C, De Marchi D, Stevanella M, Maffessanti F, Lombardi M, Parodi O, Caiani EG, Redaelli A. • Marco Stevanella: "A framework for dynamic geometry assessment and patient-specific modeling of the mitral valve from CMR imaging." Stevanella M, Maffessanti F, Conti CA, Trunfio S, Votta E, Roghi A, Parodi O, Caiani EG, Redaelli A.
Publishable summary	"**Left ventricle modelling: a functional assessment tool combined with a predictive tool for the evaluation of the post-operative mechanical performance**." Dilated cardiomyopathy following ischemic disease increases the degree of heart failure and its surgical management remains controversial. Within EU project VPH2 we aimed at developing two software tools for the quantitatively prediction the post-operative mechanical performance of the complex left ventricle (LV): a functional assessment tool (FAT) and a functional predictive tool (FTP). In particular, the former is aimed to the automatic extraction of contours from 4D MRI images and automatic calculation of global and regional parameters (e.g. EF, synchronicity) while the latter is aimed to the prediction of postoperative LV function through mechanical modeling. A subset of 15 patients with previous myocardial infarction, manifesting regional wall motion abnormalities, was selected. All cardiac MRI studies were performed using a 1.5 Tesla scanner (Signa Hdx, GE Healthcare, Milwaukee, Wisconsin). Two segmentation strategies were included in the FAT tool: the region-based approach for endocardial detection and the edge-based level-set for epicardial detection. After the endo- and epicardial contours have been detected from base to apex, the software computes LV volume and LV mass, regional fractional area (RFA). The FAT validation was focused on the LV dimension and function indices usually computed from the cardiac MRI images, such as end-diastolic (ED) and end-systolic (ES) LV volumes, stroke volume (SV), ejection fraction (EF), LV mass computed both at ED and ES. For these measurements, the "gold standard" is represented by the result of the manual tracing of endo- and epicardial LV contours that an expert cardiologist performed on a subset of patients. FPT is a software tool for MRI modelling of post-operative mechanical performance of the complex LV. The LVis divided into 6 longitudinal sections and 3 circumferential sections, for a total of 18 segments. For each segment we applied a nearest neighbour correction algorithm to compute segmental time-variant strains both in longitudinal and circumferential direction from 4-D short-axis cardiac MRI data. The software tool allows to calculate: 1. the simulation of the restoration procedure; 2. the simulation of the resynchronization of selected regional segments; 3. the simulation of the effects of a revascularisation procedure on regions of hibernated myocardium; 4. the calculation of the myocardial contractility enhancement due to left ventricular ED volume reduction following the mitral regurgitation correction. Good correlations were found with the "gold standard" measurements of

	LV ED and ES volumes, as well as with the derived parameters of SV and EF%. Also for LV mass, correlation was acceptable. Bland-Altman analysis resulted in minimal bias and narrow limits of agreement in LV ED and ES volumes, and derived parameters. On the contrary, a significant bias and wider limits of agreement was found for LV mass. In particular, the bias expressed as error%/mean of the gold standard values resulted less than 10% in all the parameters except ED LV mass. As regards the automated detection of LV wall motion, the gold standard resulted in 135 segments interpreted as normal, and 99 as abnormal. Preliminary tests have been carried out with the FPT software concerning both synthetic data and clinical data. In this study, we present two semi-automated pieces of software for the assessment of the LV function and for the prediction of the effects of surgical treatments on LV performance, accounting for different scenarios. Although further tests to optimize and validate the algorithms are mandatory, these tools could constitute a reliable aid for the planning of surgical procedures. "**A framework for dynamic geometry assessment and patient-specific modeling of the mitral valve from CMR imaging**." Cardiac magnetic resonance (CMR) is currently recognized as the gold standard in the clinical evaluation of LV volume, function and myocardial mass. Due to its high spatial and temporal resolutions, CMR imaging could constitute the ideal technique for the quantitative analysis of the mitral valve (MV) apparatus. Thus, within the EU project VPH2, we aimed at developing a framework for the dynamic assessment of MV geometry from CMR imaging, and at integrating these data in patient-specific finite element simulations of MV closure from end-diastole to the systolic peak. CMR imaging (Signa Excite, GE Medical Systems) of 18 long-axis planes (time resolution: 55 frames/cardiac cycle; spatial resolution: 0.78 mm; slice thickness: 8mm), evenly rotated (one every 10 degrees) along the left ventricular long-axis, was performed in 12 patients with myocardial infarction using the SPSS sequence. The analysis of MV apparatus was feasible in all enrolled patients (100%), and the level of inter-operator agreement was judged adequate or good for mitral annulus (MA) perimeter, antero-posterior and intercommissural diameters, 3D and projected areas, and the distance from papillary muscles (PMs) and MA. MA height and the angle between PMs show lower level of inter-operator agreement, in particular at end systole. CMR data from a subset of 3 patients were selected for the reconstruction of the FE models. The 3-D annular profile was defined by interpolation of the points selected on the MA in the end-diastolic frame. Leaflets extent and inclination were set consistently with the CMR-derived leaflets free-edge profile. The dynamic contraction of mitral annulus and PMs was modeled via kinematic boundary conditions, i.e. imposing time-dependent nodal displacements derived from annular nodes position at each time-frame. A physiological transvalvular pressure drop, up to 120 mmHg, was applied on the ventricular side of the leaflets. The numerical simulations were performed within the finite element code ABAQUS/Explicit. In the simulated subjects, full valve closure occurred in a range of 15-20

	mmHg transvalvular pressure drop, accordingly with in vitro observations. Leaflets maximum principal stresses at the systolic peak showed an asymmetric distribution, in which the anterior leaflet resulted more stressed than the posterior one. Peak stresses were computed next to the fibrous trigones on the mitral annulus, and their values ranged from 300 kPa to 550 kPa. PMs reaction forces ranged from 4.5 to 8.4 N. Such tensions were unevenly transmitted to chordae tendineae: the average load on a single chorda was highest in the strut chordae (up to 1.21 N) and much lower in first order chordae (0.13 N), although these, being more numerous, altogether bore the major load fraction. Quantitative information on MA and PMs morphology and function is shown to be feasible from CMR; the proposed technique provides a good reproducibility in the extracted parameters. We also introduced a novel approach for developing a FE model of the MV based on patient-specific data obtained from CMR. This approach may constitute the basis for an accurate evaluation of MV pathologic conditions and for the planning of surgical procedures.

Event n.	9
Research Direction	RD2
Title	Annual Meeting of the European Council for Cardiovascular Research (ECCR)
Date	October 8th - 10th, 2010
Location	Nice, France
Type	Conference
Organizer	European Council for Cardiovascular Research
Objective	The annual ECCR conference covers a broad range of subjects, including genetics of cardiovascular diseases, vascular biology, cardiac and renal aspects as well as modern strategies of prevention and therapy in cardiovascular disease.
Description/website	http://www.eccr.org/default.stm
Target audience	Particular emphasis is put on the participation of both basic scientists and clinicians to foster the transmission of new scientific findings into clinical practice
Participating partners	WWU
Report	**Functional analyses of Biglycan molecular promoter haplotypes** The abstract has been chosen for oral presentation.
Publishable summary	**Introduction:** The extracellular matrix protein biglycan (BGN) is involved in cardiovascular disease (CVD) pathophysiology. The aim of the current study was to identify BGN promoter haplotypes and transcription factors (TF) involved in its gene regulation. **Material and Methods:** Sequencing of the BGN gene promoter (1199 bp) in 57 CVD patients was performed to characterize its variant structure. Molecular haplotypes (MolHaps) were determined by subcloning. MolHaps and promoter deletion constructs (pGL3-basic) were transfected into endothelial (EA.hy926) and monocytic (THP-1) cells. Cells were kept under basal conditions or stimulated with 10 ng/ ml TGF-β1 (24 hours). Gel

	shift assays (EMSA) for polymorphic regions were performed with untreated and TGF-β1 stimulated nuclear extracts. **Results:** We identified three MolHaps: 1 [-578G-151G+94G; wild type (wt)], 2 [-578G-151A+94T] and 3 [-578A-151G+94G]. Under basal and stimulatory conditions, MolHap 2 and 3 were significantly less active ($p \leq 0.05$) than wt in EA.hy926 and THP-1 cells. Stimulation of wt deletion constructs with TGF-β1 increased transcriptional activity (TA) up to 3-fold in THP-1 cells. Performing co-transfection experiments, transcription factor SP1 was shown to increase TA of promoter fragments (≥ 2-fold) in EA.hy926 cells. Sequence specific binding of SP1 was demonstrated for position G-578A and G-151A in EMSA experiments and in-vivo by chromatin immunoprecipitation. Binding of hematopoietic TF PU.1 was demonstrated at position G-578A exclusively in THP-1 cells. **Conclusion:** (1) BGN promoter activity is enhanced by TGF-β1 and TF SP1 (2) transcriptional activity of BGN MolHaps 2 and 3 is significantly reduced (3) ETS-domain TF PU.1 binds position G-578A in THP-1 cells.

Event n.	10
Research Direction	RD4
Title	eChallenges e-2010 Conference
Date	October 26th -29th, 2010
Location	Warsaw, Poland
Type	Conference
Organizer	European Commission
Objective	The goal of e-2010 is to stimulate rapid take-up of Research and Technology Development (RTD) results by industry and in particular SMEs, and help open up the European Research Area (ERA) to the rest of the world.
Description/website	http://www.echallenges.org/e2010/
Target audience	Researcher from government and research organisations
Participating partners	IFC CNR
Report	Oral presentation of the abstract "A software framework for global and regional quantitative assessment of myocardial necrosis by cardiac magnetic resonance" V. Positano, M Marinelli, E Caiani, MF Santarelli, A Pingitore, A Redaelli, M Lombardi, L Landini, O Parodi.
Publishable summary	Management of heart failure is challenging for all healthcare systems, due to the need of several expensive imaging examinations and image analysis procedures to address different clinical questions. In particular, a correct identification of transmural extent of irreversible myocardial damage is cost effective, identifying subjects who will most benefit of coronary revascularization. This study show how a dedicated software tool, to be integrated within a clinical decision support system, may help to preserve the information content of medical images in the assessment of myocardial viability in management of the left ventricular dysfunction.

Event n.	11
Research Direction	all
Title	10th IEEE International Conference on Information Technology and Applications in Biomedicine (ITAB 2010)
Date	November 3rd -5th , 2010
Location	Corfu, Greece
Type	Conference
Organizer	D. I. Fotiadis (University of Ioannina); K. S. Nikita (National Technical University of Athens); M. Akay (University of Houston, USA); M. Tsiknakis (Foundation for Research and Technology – Hellas)
Objective	The overall objective of ITAB 2010 is to cover the state of the art of Information Technology Applications in Biomedicine targeting in offering patient specific health services. The theme of the conference will be: Emerging Technologies for Patient Specific Healthcare ITAB 2010 marks the continuation of the previous 9 successful conferences held in Prague in 1997, in Washington DC in 1998, in Amsterdam in 1999, in Virginia in 2000, in Birmingham in 2003, in Ioannina in 2006, in Tokyo in 2007, in Shenzhen in 2008 and in Larnaca 2009.
Description	The main topics have been: • Biomedical Signal and Image Processing and Analysis • Bioinformatics, Computational Biology • Systems Biology and Modeling Methodologies • Diagnostic and Therapeutic Systems • e-Health Systems, m-Health Systems, and Telemedicine Systems. • Personal Health Systems • Virtual Physiological Human • Economic and Managerial Aspects of e-health (special session) • Virtual Reality in Medicine and Surgery (special session) • ARTReat Workshop • Bridging Public Health Informatics with Personal Health Records: Opportunities for Wellness and Disease Prevention (special session)
Target audience	Bioengineers, clinicians, software engineers, project managers
Participating partners	CTI
Report	The participation in the meeting was fruitful and successful as more than 250 people participated in the seminar and had a chance to study our poster and get a first impression about the work we have done in data mining (datasets, methodologies, results).

Event n.	12
Research Direction	RD2
Title	Human Genome Meeting 2011
Date	March 14th – 17th, 2011
Location	Dubai, UAE
Type	Conference
Organizer	HUGO

Objective	Genomic technologies provide unheralded precision in identifying the causative genetic mutations in human disease, and uncover new mechanisms of mutagenesis. Genetic disorders represent a significant contribution to the burden of disease. Deciphering the molecular etiology of these genetic disorders is a key priority and will drive personalized healthcare into new dimensions. This HGM 2011 focused on the genomics and genetics of heritable disorders.
Description/website	http://www.hgm2011.org/
Target audience	HGM seeks to enhance the interaction of international scientists with regional investigators and clinicians and to generate new ideas in human genetics.
Participating partners	WWU, IFC-CNR
Report	**Virtual Pathological Heart of the Virtual Physiological Human (VPH2)** The abstract has been chosen for poster presentation.
Publishable summary	**Background:** VPH2 aims to develop a patient-specific platform improving the management processes of heart diseases by definition of the severity and extent of the disease in patients with post-ischemic left ventricular dysfunction (LVD). One major task is the integration of clinical, biological and genetic data, retrieved from medical records and laboratories research results. The project involves the development of tools for collecting, storing, analysing and linkage of heterogenic data. Here we present the genetic data generated for use within the VPH2 platform. We aimed to assess the prevalence of genetic variants in patients with chronic systolic heart failure and different degrees of reverse LV remodelling after cardiac resynchronization therapy (CRT) in a multicentre case-control study. **Method:** One-hundred-56 patients implanted with CRT were enrolled and DNA was prepared from mononuclear blood cells. Lack of benefit from CRT in terms of reverse remodelling was used to categorize the population as responders/non-responders. Reverse remodelling (CRT responders) was defined as a decrease from baseline at follow-up echo 6 to 12 months after CRT in LV end-systolic volume >15%. Patients DNA was subsequently genotyped for 44 genetic variants using TaqMan technology. Relative allele and genotype frequencies have been compared by chi-square test between responders and non-responders. P-values <0.05 have been considered statistically significant. Chi-square test for categorical variables and Student's t-test or Mann-Whitney test for continuous variables were used to compare the demographic characteristics in both groups. Results: Non responder (NR, n=76) and responder (R, n=80) groups were well balanced for variables known to affect outcome after CRT: age (NR 62 [56-71] vs R 65 [57-71], p=ns),symptom severity (NYHA class II NR 26% vs R 32%, p=ns) and ischemic etiology (NR 55% vs R 52%, p=ns). NR phenotypes were significantly associated with C allele of rs5443 (NR 75% vs R 60%, p=0.013) within the heterotrimeric GTP-binding protein (GNB3) and the C allele of rs3766031 (NR 93% vs R 81%, p=0.006) within the β-subunit of Na+/K+-ATPase (ATP1B1). **Conclusion:** We identified two genetic variants to be significantly associated with the CRT non-responder phenotype within our study population, which was used for data mining purposes within the VPH2

	project. Both variants reside within genes involved in signal transduction processes (GNB3 and ATP1B1), suggesting an impaired response of patients to the applied therapeutical treatment due to altered protein activity. Recently, molecular functional analysis of GNB3 have suggested C825T (rs5443) to create a novel splice variant and an in-frame deletion of 41 amino acids from the wild-type protein. The β-subunit of ATP1B1 is required for the correct cellular enzyme location and its stability and translation is proposed to be a crucial regulatory step in determining the abundance and activity of the enzyme.

Event n.	13
Research Direction	RD3
Title	Blood-flow numerical simulation - 16th International Conference on Finite Elements in Flow Problems (FEF2011)
Date	March 23rd-25th, 2011
Location	Munich, Germany
Type	Conference
Organizer	W. A. Wall, TUM, V. Gravemeier, TUM
Objective	The Finite Elements in Flow Problems (FEF) Conference is the principal forum for the exchange of research results in all aspects of flow modeling via the finite element method. This conference has an extensive history that closely parallels the development and maturation of finite element methods as applied to computational fluid dynamics. The purpose of this 16th conference in the series continues to be the gathering of mathematicians, engineers, computer scientists and students for the exchange of the latest information on all aspects of flow modeling and simulation of finite elements and other computation approaches. The scope of the conference is very broad with coverage of theory, implementation, assessment and application in all of the major and emerging areas of fluid dynamics and flow-related phenomena.
Description/website	Minisymposium "*Cardiovascular FSI modelling".* This symposium has focused on numerical techniques targeting cardiovascular Fluid-Structure Interaction (FSI) modeling and applications of such techniques. Special techniques, such as how to extract data from medical images, how to model the arterial wall, how to generate high-quality meshes, and how to process the computed data, have been covered. The presentations have emphasized the advances made in cardiovascular modeling and brought out the challenges that are still to be addressed. This symposium organization has been coordinated with the organization of its more general version: " Fluid-Structure Interaction".
Target audience	Numerical and Computational scientists
Participating partners	EPFL
Report	This conference has been very useful to both dissemination and monitoring. It was the occasion to present recent advances of our group in methods and algorithms for FSI in hemodynamic simulations.
Publishable summary	The numerical tools to simulate blood flow in the cardiovascular system are constantly developing due to the great clinical interest and to scientific

	advances in mathematical models and computational power. The present work aims to address and validate new algorithms to effi- ciently predict the hemodynamics in large arteries. These algorithms rely on finite elements simulation of the fluid-structure interaction between blood flow and arterial wall deformation. Different sets of boundary conditions are devised and tested. The mean velocity and pressure time evolution is plotted on different sections of the aorta and the wall shear stress distribution is computed. The results are compared with those obtained with a rigid wall simulation. Pulse wave velocity is computed and compared with the values available from the literature. The flow boundary conditions used for the outlets are obtained using the solution of a one dimensional model. The results of the simulations are in agreement with the physiological data in terms of wall shear stress, wall displacement, pressure waveforms and velocities. The efficient solution of optimal control and/or shape optimization problems is an open problem in cardiovascular modelling. Since the recursive evaluation of the flow solution is required for many possible cardiovascular configurations, strategies able to reduce the dimensionality of the problem and the associated computational complexity need to be devised. Moreover, the possi- bility to develop predictive surgery stems from numerical blood flow simulations performed in a rapid and reliable way, often on patient-dependent geometries. Efficient numerical schemes for many-query (e.g. optimization, control) and real-time (e.g. rapid simulation, parameter identification) problems dealing with flows across domains of complex and/or variable shape are proposed. They combine a suitable low-dimensional parametrization of the cardiovas- cular geometry (yielding a geometrical complexity reduction) with numerical approximation schemes based on reduced basis methods (allowing a reduction of computational complexity). Among existing model order reduction strategies, the reduced basis method represents a very efficient tool for simulating flows in parametrized geometries, as well as for solving shape optimization and more general inverse problems. An implementation of the reduced ba- sis method for viscous flows modelled by (Navier)-Stokes equations will be presented, by con- sidering some flexible shape parametrization techniques (such as free-form deformations, radial basis functions, transfinite mappings) in order to deal efficiently with complex shapes. Our analysis will focus on haemodynamics applications – such as the shape optimization of aorto-coronaric bypass grafts and the blood flow simulations in carotid artery bifurcations – and highlight suitability and effectiveness of these model reduction techniques.

Event n.	14
Research Direction	RD2
Title	41° Congresso nazionale di Cardiologia dell'ANMCO
Date	May 11th – 14th, 2011
Location	Florence - Italy
Type	National Congress

Organizer	Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)
Objective	ANMCO promotes good clinical practice, prevention and rehabilitation in cardiovascular disease through education, research programs and development of appropriate guidelines.
Description/website	The ANMCO National Congress is an important meeting place to create general awareness at the national level in the professional field. www.anmco.it
Target audience	Medical and research communities
Participating partners	IFC CNR, WWU
Report	Varianti genetiche associate al rimodellamento inverso dopo terapia di resincronizzazione cardiaca. Dr. R. De Maria (IFC CNR). Oral Presentation
Publishable summary	Three genetic variants are significantly associated to a non-responder phenotype after cardiac resynchronization therapy (CRT). These polymorphisms lie on *GNB3* gene, encoding for a protein involved in signal transduction at the extracellular/intracellular interface, on *ATP1B1*, encoding the β-subunit of Na^+/K^+-ATPase and on *NR3C2*, encoding the mineralcorticoid receptor. Lack of reverse remodelling after CRT is due to an altered protein activity or cellular receptor structures. These findings have potential implications for optimized drug treatment after CRT.

Event n.	15
Research Direction	RD2
Title	Heart Failure Congress 2011
Date	May 21st – 24th, 2011
Location	Gothenburg - Sweden
Type	Conference
Organizer	Heart Failure Association of the ESC
Objective	To improve quality of life and longevity, through better prevention, diagnosis and treatment of heart failure, including the establishment of networks for its management, education and research.
Description/website	http://www.escardio.org/congresses/HF2011.
Target audience	World cardiologists and cardiac basic researchers.
Participating partners	IFC CNR, WWU
Report	The abstract has been chosen for its outstanding quality and will be presented in the JUDGES CHOICE Oral Abstract Session of "Treatment Research".
Publishable summary	Genetic variants associated to reverse remodelling after cardiac resynchronization therapy. De Maria R, Lunati M, Landolina M, Gasparini M, Schmitz B, Campolo J, Parolini M, Brand SM, Parodi O. **Background**: Reverse remodelling (RR) may occur as a beneficial effect of cardiac resynchronization therapy (CRT). RR, defined in most studies as a decrease > 15% in left ventricular end systolic volume (LVESV) with respect to pre-procedural values, is associated to clinical outcome in

	heart failure (HF) patients. There are currently no data on the association of genetic factors with RR after CRT. We aimed to assess genetic variants in patients with chronic systolic HF and different degrees of RR **Method**: We sampled blood from 156 patients implanted with CRT since at least 12 months. Lack of RR after CRT (RR-) was defined as a LVESV decrease at follow-up echo 6 to 12 months after CRT from baseline <15%. RR- patients were compared to RR+ controls matched by age, gender, NYHA class and etiology. DNA, prepared from mononuclear blood cells, was genotyped for 44 genetic variants using TaqMan technology. Relative allelic frequencies were compared by chi-square test between RR- patients and RR+ controls. **Results**: RR- (n=76) and RR+ (n=80) subjects were well matched for variables known to impact on CRT outcomes such as age (RR- 61 [56-70] vs RR+ 64 [57-71], p=ns),symptom severity (NYHA class III-IV RR- 72% vs RR+ 71%, p=ns) and ischemic etiology (RR- 53% vs RR+ 49%, p=ns). Lack of RR was significantly associated with C allele of rs5443 within the heterotrimeric GTP-binding protein (GNB3) (RR- 74% vs RR+ 58%, p=0.004), C allele of rs3766031 within the β-subunit of Na+/K+-ATPase (ATP1B1) (RR- 92% vs RR+ 82%, p=0.011), and the C allele of rs5522 that encodes for the mineralocorticoid receptor (NR3C2) (RR- 16% vs RR+ 6%, p=0.006). **Conclusion**: We identified three genetic variants significantly associated with the CRT non-responder phenotype. These variants reside either within genes involved in signal transduction processes (GNB3 and ATP1B1), suggesting reduced benefit from CRT due to altered protein activity, or in cellular receptor structures (NR3C2). These findings have potential implications for optimized drug treatment after CRT.

Event n.	16
Research Direction	RD4
Title	European Congress ESC 2011
Date	August 27th – 31th, 2011
Location	Paris, France
Type	Congress
Organizer	European Society of Cardiology
Objective	Learn about the most recent developments in the management of Cardiovascular Disease, and on the role of MRI on diagnostic assessment in cardiopathic patients.
Description	www.escardio.org
Target audience	World Cardiologist and cardiac basis researchers
Participating partners	IFC CNR, WWU, PoliMI
Report	"Genetic variants associated to reverse remodelling after cardiac resynchronization therapy". De Maria R, Schmitz B, Gasparini M, Landolina M, Lunati M, Galimberti P, Sanzo A, Campolo J, Brand SM, Parodi O. R. De Maria, Oral presentation in the Session of Cardiac resynchronisation

	therapy in heart failure. Dr. Caiani was invited to co-chair the session "How to integrate computers into practice", and gave an oral presentation of the abstract: Stevanella M, C.A. Conti, E. Votta, F. Maffessanti, Sotaquira M., A. Roghi, O. Parodi, E.G. Caiani, A. Redaelli. A patient-specific computational analysis from CMR imaging for annuloplasty ring assessment for the treatment of ischemic mitral regurgitation. (http://spo.escardio.org/eslides/view.aspx?eevtid=48&fp=2142)
Publishable summary	**Genetic variants associated to reverse remodelling after cardiac resynchronization therapy** **Background**: Reverse remodelling (RR) may occur as a beneficial effect of cardiac resynchronization therapy (CRT). RR, defined in most studies as a decrease >15% in left ventricular end systolic volume (LVESV) with respect to pre-procedural values, is associated to clinical outcome in heart failure (HF) patients. There are currently no data on the association of genetic factors with RR after CRT. We aimed to assess whether genetic variants within systems known to be involved in ventricular remodelling was associated to different degrees of RR in patients with chronic systolic HF. **Method**: We sampled blood from 156 patients implanted with CRT since at least 12 months. Lack of RR after CRT (RR-) was defined as a LVESV decrease at follow-up echo 6 to 12 months after CRT from baseline <15%. RR- patients were compared to RR+ controls matched by age, gender, NYHA class and etiology. DNA, prepared from mononuclear blood cells, was genotyped using TaqMan technology. The association of clinical factors and genetic variants within the renin-angiotensin and adrenergic systems with the RR- phenotype was assessed by multivariable logistic regression analysis and expressed by odds ratios (OR) and their 95% confidence interval (CI). **Results**: RR- (n=76) and RR+ (n=80) patients were well matched for age (RR- 61 [56-70] vs RR+ 64 [57-71], years, p=ns), symptom severity (NYHA class III-IV RR- 72% vs RR+ 71%, p=ns) and ischemic etiology (RR- 53% vs RR+ 49%, p=ns). LVESV decreased by -1 [-6, 5] % in RR- and -32 [-46, -23] % in RR+, while left ventricular ejection fraction (LVEF) increased by 2.5 [-2, 5] units in RR- and 11 [6, 16] units in RR+ (p<0.001). By multivariable logistic regression analysis, after adjustment for age, gender, LVEF and previous myocardial infarction, the RR- phenotype was independently associated with diabetes (OR 3.29, 95% CI 1.20-9.02), the CC genotype of rs5443 within the heterotrimeric GTP-binding protein (GNB3, OR 3.0, 95% CI 1.43-6.28) and the CC genotype of rs3766031, within the β-subunit of Na+/K+-ATPase (ATP1B1, OR 2.67, 95% CI 1.14-6.26). The combined presence of the CC genotype in both rs 5443 and rs3766031 gave an OR of 8.07 (95% CI 2.60-25) for lack of RR. **Conclusion:** Genetic variants residing within genes involved in signal transduction processes (GNB3 and ATP1B1) were significantly associated with the CRT non-responder phenotype. These findings suggest altered protein activity as a contributory factor to reduced benefit from CRT.

	A patient-specific computational analysis from CMR imaging for annuloplasty ring assessment for the treatment of ischemic mitral regurgitation. Purpose. Ischemic mitral regurgitation (IMR) is usually treated through restrictive annuloplasty via rigid rings, which constrain the annular shape, or flexible rings, which preserve annular dynamics. The choice between these two options is still debated and several methodologies have been adopted to identify the best solution. Among those, finite element (FE) models have provided useful insight, but past models suffered of simplifications that could have limited and biased the conclusions. We aimed at analyzing the effects of ring's flexibility in restrictive annuloplasty through mitral valve (MV) patient-specific realistic FE models based on cardiac magnetic resonance (CMR) imaging, thus overcoming previous limitations. Methods. CMR imaging of 18 evenly rotated long-axis planes (one every 10°) along the left ventricular long-axis was performed in 7 ischemic patients (55 time-frames/cardiac cycle). In each plane and for each systolic frame, MV annulus, leaflets, and papillary muscles were manually identified using custom software. These structures were then automatically reconstructed in the 3-D space, and used as input to the MV FE models. MV tissue response was modeled as non-linear elastic and anisotropic. A physiological transvalvular pressure load was applied to the leaflets to simulate valve closure up to peak systole. For each patient, three conditions were simulated: (i) pre-operative, (ii) after insertion of a ring with closed profile and regionally varying bending stiffness (CV ring), and (iii) after implanting a rigid ring with partially open profile at saddle-horn (RO ring). Results. The RO ring restored MV competence in 7/7 patients resulting in higher coaptation length, while CV ring succeeded only in 5/7. Conversely, annular dynamics was lost with the RO ring, while CV ring partially preserved it. Both rings significantly reduced leaflets stresses and tensions on chordae tendineae and papillary muscles. Conclusions. While RO rings seem resulting in a good performance, flexible CV rings could not always guarantee to counterbalance the effect of leaflets tethering associated to IMR. Moreover, despite their flexibility, annular dynamics was not completely preserved. Our patient-specific FE approach could provide new insight in optimizing tuning of local stiffness, thus potentially improving the performance of new ring design, as well as help in surgery planning.

Event n.	17
Research Direction	RD3
Title	SIMBIO 2011
Date	September 2011
Location	Brussels
Type	Conference
Organizer	ECCOMAS
Objective	In recent years there is a growing interest in the simulation and modeling of flows in living organisms. The main applications are related to blood flow in the vessels and airflow in the respiratory tract. But also other

	applications such as e.g. fluid and solute transport in bones, artificial blood pumps, phonation and speech production fall into the category of biological flows. The aim of the present thematic conference is to bring together scientists and researchers working in this field and providing them a forum for discussion and technical exchanges in this rapidly growing field. This is the first thematic ECCOMAS conference on this topic. It will be held at the Vrije Universiteit Brussel (VUB), Brussels, Belgium and is organized by VUB and Von Karman Institute, from 21st to 23th September 2011.
Description/website	https://www.vki.ac.be/simbio2011/
Target audience	Numerical and Computational scientists
Participating partners	EPFL
Publishable summary	We present some preliminary numerical simulations obtained in the framework of the FP7 project VPH2 (Virtual Pathological Heart of a Virtual Physiological Human). A simplified 3D fluid-structure inter- action model for blood flow through the left ventricle is constructed. The goal of the project is to reconstruct the three-dimensional geometry of the ventricle and its movement from MRI images, and then to simulate the post-surgical effects of ventricular remodelling to the global circulation. To ac-comodate reconstruction errors and large time steps between the images, we propose to surround the ventricle with a fictitious compressible structure, and to impose the reconstructed movements on the latter. A monolithic fluid-structure interaction solver based on the LifeV finite-element library is used to simulate blood flow inside the idealized left ventricle. To account for the interaction between the heart and the circulatory system the flow is coupled through an ideal valve with a 1D model of the arterial tree with viscoelastic effects. We apply a multiscale coupling strategy based on the integrated quantitites of flow rate and/or normal stress. The peripheral circulation is modelled by 0D Windkessel models. We demonstrate that the multiscale model is (i) highly modular in that component models can be easily replaced with higher-fidelity ones whenever the user has a specific interest in modelling a particular part of the system, (ii) passive in that it reaches a stable limit cycle of flow rate and pressure in a few heartbeat cycles when driven by a periodic inflow at the mitral valve, and (iii) capable of operating at or near physiological regimes. Future work involves assimilation of patient-specific data obtained from MRI images using interpolation in both time and space, and simulating a pathological heart and the circulation pre- and post-surgery.

Event n.	18
Research Direction	RD2
Title	Wissenschaftlichen Kongress der Deutschen Hochdruckliga e. V. DHL

Date	December 9th – 11th, 2011
Location	Berlin, Germany
Type	Conference
Organizer	German Hypertension League (Deutsche Hochdruckliga)
Objective	The DHL congress puts an emphais on the transfer between basic science and medicine.
Description/website	http://www.hypertonie-2011.de/
Target audience	Scientists and clinicians
Participating partners	WWU
Report	**Profiling of Biglycan Molecular Promoter Haplotypes** The abstract has been chosen for poster presentation.
Publishable summary	**Background and aims:** The extracellular matrix proteoglycan biglycan (BGN) is involved in cardiovascular disease (CVD) pathophysiology. It mediates binding of low-density lipoproteins to the artery wall in atherogenesis, exerts pro-inflammatory effects and mediates remodelling after myocardial infarction. This project aimed at the specification of BGN gene expression and the impact of molecular promoter haplotypes. Material and methods: We screened 1199 bp of the BGN promoter region in 57 high-risk CVD patients (MolProMD Study) to characterize its variant structure. Molecular haplotypes (MolHaps) were identified by subcloning and resequencing of patients DNA. MolHaps and promoter deletion constructs were generated and transfected into EA.hy926 endothelial cells and THP-1 monocytes. Cells were kept under basal conditions or stimulated with TGF-β1 (10ng/ml) for 24 hrs. Transcriptional start sites were determined by 5'RACE. DNA/protein interactions were analysed by EMSA, competition assays, and ChIP. **Results:** We identified three common MolHaps: 1 [G-578-G-151-G+94; wild type (wt)], 2 [G-578-A-151-T+94] and 3 [A-578 -G-151-G+94]. Transcriptional activity of MolHaps 2 and 3 was significantly reduced (all p values <0.05) in EA.hy926 and THP-1 cells. Co-expression with SP1 revealed a significant promoter activation over mock control (P<0.01) and physical interaction of SP1 was demonstrated by ChIP. EMSA experiments revealed binding of c-FOS to the 5'-UTR site G+94T. TGF-β1 stimulation enhanced SP1 interaction with the G-578A site. In THP-1 cells, ETS family member PU.1 bound G-578 with higher affinity (4-fold) compared to -578A. **Conclusion:** BGN gene expression is under the control of activating transcription factor (TF) SP1. TGF-β1 reinforces SP1 binding and thus enhances transcriptional activity of the BGN promoter. The polymorphic position G+94T reside within a cis-active promoter element were AP-1 complex formation was observed. Monocyte-specific regulation of BGN expression is also controlled by ETS TF PU.1.

4.3.2. Workshops, seminars

IFC-CNR organized a workshop on VPH2 during which the preliminary platform has been shown to cardiologist experts. The venue was Milan, Fiera Rho, during the 44° Congress of Cardiologia (Cardiologia 2010) of the Niguarda Hospital. Five distinguished experts in cardiac imaging, heart failure, cardiac surgery and myocardial remodelling were invited and asked for evaluating the prototype, giving advices, suggestions on the project and judgment on operability and usability of the platform. Sorin, Polimi, Niguarda and SCS collaborated in the preparation and management of the workshop.

Event n.	1
Research Direction	RD3, RD4
Title	44° Convegno Cardiologia 2010
Date	September 27th -October 1st, 2010
Location	Milan, Italy
Type	Workshop
Organizer	Niguarda Hospital, "A. De Gasperis" Cardiovascular Department
Objective	Update in cardiovascular disease
Description	www.degasperis.it
Target audience	Cardiologists and cardiac surgeons
Participating partners	IFC CNR, REGLOM, SORIN, POLIMI, NIGUARDA
Report	IFC CNR organized the workshop (WORKSHOP VPH2) with seven extramural experts to test the software for MV analysis. IFC CNR prepared the clinical questionnaire that was filled by the participants. IFC CNR participated with the other partners involved in the task for definition of the measurable indicators.
Useful for Exploitation	Yes

Event n.	2
Nature	Dissemination and knowledge
Research Direction	RD3, RD4
Title	L'Imaging in Cardiologia e Cardiochirurgia: Il ruolo delle metodiche di imaging nell'inquadramento diagnostico e nel follow-up del paziente cardiopatico
Date	February 25th -26th, 2011
Location	Milano, Italy
Type	Workshop
Organizer	Niguarda Hospital, Cardiovascular Department A.De Gasperis, Milan
Objective	The role of imaging techniques on diagnostic assessment, surgical management and follow-up of patients in cardiac surgery.
Description/website	ww.degasperis.it
Target audience	Cardiologists and Cardiac Surgeons (about 200 doctors attending)

Participating partners	NIGUARDA, IFC CNR
Report	Title: Sistemi integrati di valutazione e guida al trattamento della cardiopatia ischemica: la piattaforma VPH2. Aim of the presentation is to introduce the work in progress of VPH2, namely, some decision trees from data mining analysis on GISSI Prevention study, the FAT platform and the initial findings on FPT, the role of genetic SNPs in prognostic evaluation (late heart failure) of patients with recent acute myocardial infarction (GISSI project). Movies on mitral valve repair simulation, myocardial cut and patch positioning for virtual ventricular restoration, quantification of transmural necrosis by late gadolinium imaging (MRI) will be presented. Prof. Oberdan Parodi, IFC CNR Milano. Oral Presentation in the "Heart Failure" Session.

Event n.	3
Nature	Dissemination and knowledge
Research Direction	RD3, RD4
Title	Integrative Hybrid modeling of the heart
Date	September 13th -15th, 2011
Location	Luebeck,Germany
Type	Seminar
Organizer	Institute fur Mathematik, University of Luenbeck
Objective	New trends in patient specific therapies
Description/website	http://www.math.uni-luebeck.de/
Target audience	Expert mathematicians (about 10 people)
Participating partners	Polimi
Report	The seminar has been dedicated to describe the new virtual reality approaches which can support the surgeon in the decision process. Indeed, computational biomechanics has undergone a tremendous evolution in the last ten years. Thanks to increasing computational resources and novel and sophisticated software tools, biomechanical problems, which could be hardly undertaken ten years ago, are now easily addressed. As happens in these cases, borders are then moved farther and researchers explore new applications. In the last years a growing interest has been focused on patient specific modeling thanks to the concomitant great progress in imaging which is providing diagnostic possibilities that have not been available before. Indeed, personalized healthcare can greatly benefit from imaging; the phenomenology of complex biological behaviors can be, at a large extent, caught through imaging; although currently limited by inadequate spatial and temporal resolutions, indeed, imaging can represent an important source of information thus integrating and complementing simulation capabilities. In the talk a number of examples of possible applications have been provided where patient specific modeling can be successfully approached by combining simulations and imaging, in a heterogeneous framework, what we define as integrative or hybrid modeling.

IFC CNR and **NIGUARDA** organized two focus groups during the development and integration of the different modules of the platform.
Niguarda Hospital has provided six clinicians (4 cardiologists and 2 cardiac surgeons) of different seniority to be involved in the two focus groups in order to collect their feedbacks about platform usability, efficiency and clinical applicability. Physicians were asked to give their opinion as VPH2 users and to fill in the proper questionnaires to collect information in a structural way.

Event n.	4
Research Direction	RD3, RD4
Title	Focus Group on VPH2
Date	July 6th and September 20th, 2011
Location	Niguarda Cà Granda Hospital Milan, Italy
Type	Workshop
Organizer	NIGUARDA and IFC CNR
Objective	Validation of the VPH2 platform
Description	Presentation/demo of the system functionalities (explaining the context and the main functionalities), presentation of four cases with clinical relevance and their discussion, submission of the questionnaires.
Target audience	Clinicians (4 cardiologists and 2 cardiac surgeons)
Participating partners	Niguarda, IFC-CNR, REGLOM, NoemaLife, Polimi, SCS, Patmos, CTI
Report	The **first focus group** was organized in July 2011 at Niguarda Hospital to provide a complete overview of the functionalities of the platform with demo sections and to collect a first set of feedbacks and recommendations from potential end-users of the VPH2 platform. During the **second focus group** specific use case scenarios have been prepared and distributed to the clinicians involved in the previous focus group. They evaluated the diagnosis results with respect to the standard practice. At the end, they were asked to fill in a questionnaire through which utility, and efficacy etc of the tool have been measured. The feedback from these questionnaires will be used in order to refine the tool (approach and interfaces). Questionnaires have been prepared by clinical and technical partners formulating specific question for each module and trying to design for them a list of possible answers (i.e. level from 1 to 6, yes/no) in order to avoid open questions, which could be difficult to post-process and interpret.
Useful for Exploitation	NO

4.4. Press releases and Publications

Articles on peer reviewed journals and abstracts proceedings.

Publication n.	1
Research Direction	RD4
Title	Feasibility of a novel approach for 3D mitral valve quantification from cardiac magnetic resonance images. Maffessanti F, Stevanella M, Votta E, Lombardi M, Parodi O, De Marchi D, Conti CA, Redaelli A, Caiani EG.
Date	July 2010
Journal/URL	Atti II Congresso Nazionale di Bioingegneria (Patron), pag. 513-514
Field/sector	Biomedical engineering
Type	scientific
Objective	RD4
Description	These proceedings present all the contributions presented at the conference, underlining the current research paths in the field of the biomedical engineering.
Target audience	Biomedical Engineers
Partners involved	POLIMI, IFC CNR
Publishable summary	See poster in the relevant session above

Publication n.	2
Research Direction	RD3, RD4
Title	Patient-specific CMR-based finite element model of the mitral valve. Stevanella M, Maffessanti F, Conti CA, De Marchi D, Votta E, Lombardi M, Parodi O, Caiani EG, Redaelli A.
Date	July 2010
Journal/URL	Atti II Congresso Nazionale di Bioingegneria (Patron), pag. 281-282
Field/sector	Biomedical engineering
Type	scientific
Objective	RD3, RD4
Description	These proceedings present all the contributions presented at the conference, underlining the current research paths in the field of the biomedical engineering.
Target audience	Biomedical Engineers
Partners involved	POLIMI, IFC CNR
Publishable summary	See poster in the relevant session above

Publication n.	3
Research Direction	RD3, RD4
Title	Feasibility of the evaluation of the mitral valve by patient-specific computational model based on cardiac MRI. Stevanella M, Redaelli A, Maffessanti F, Votta E, Lombardi M, Parodi O, Caiani EG.

Date	September 2010
Journal/URL	Eur H Journal 2010;31(Suppl 1):288
Field/sector	Cardiology
Type	scientific
Objective	RD3, RD4
Description	Abstract accepted for presentation as poster at European Society of Caridiology meeting
Target audience	Biomedical Engineers, Cardiologists, Industry
Partners involved	POLIMI, IFC CNR
Publishable summary	See poster in the relevant session above

Publication n.	4
Research Direction	RD3, RD4
Title	"Piattaforma virtuale per lo studio della disfunzione post-ischemica: il progetto VPH2. Luigi Martinelli, Salvatore Trunfio
Date	September 2010
Field/sector	Cardiology
Type	Book: ATTI DEL 44° CONVEGNO INTERNAZIONALE "Cardiologia 2010" (contribution in conference proceeding).
Objective	Update on VPH2 project and NIGUARDA activity
Description	www.degasperis.it
Target audience	Cardiologists and cardiac surgeons
Partner(s) involved	NIGUARDA, IFC CNR
Publishable summary	Post-ischemic Left Ventricle Dysfunction (LVD) is the leading cause of heart failure, a clinical syndrome that accounts for almost a quarter of all admission to hospital for cardiovascular events, has a high mortality (median survival around 18 months), and places a great burden on all healthcare systems. The aim of the VPH2 project is the development of a high powered framework platform aiming at improving the ischemic heart disease management. VPH2 clinical objectives are: – Prediction of post-ischemic LVD progression – Choice of therapy (medical, device, surgical) – Surgical plan-training by simulation of different clinical scenarios. We report the work in progress of VPH2 project and the activity of Niguarda.

Publication n.	5
Research Direction	RD2
Title	EUROASPIRE III. Management of cardiovascular risk factors in asymptomatic high-risk patients in general practice: cross-sectional survey in 12 European countries. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Reiner Z, Keil U; EUROASPIRE Study Group.

Date	October 2010
Journal/URL	Eur J Cardiovasc Prev Rehabil
Field/sector	Cardiovascular research
Type	Scientific Journal
Objective	Journal publishing original articles.
Description	The publication investigated whether the 2003 Joint European Societies' guidelines on cardiovascular disease prevention in people at high cardiovascular risk have been followed in general practice.
Target audience	Medical and research communities
Partner(s) involved	WWU
Publishable summary	**Design:** Cross-sectional survey. **Methods:** The EUROASPIRE survey was carried out in 2006-2007 in 66 general practices in 12 European countries. Patients without a history of coronary or other atherosclerotic disease either started on antihypertensive and/or lipid-lowering and/or antidiabetes treatments were identified retrospectively, interviewed and examined at least 6 months after the start of medication. RESULTS: Four thousand, three hundred and sixty-six high-risk individuals (57.7% females) were interviewed (participation rate 76.7%). Overall, 16.9% smoked cigarettes, 43.5% had body mass index ≥30 kg/m, 70.8% had blood pressure ≥140/90 mmHg (≥130/80 in people with diabetes mellitus), 66.4% had total cholesterol ≥5.0 mmol/l (≥4.5 mmol/l in people with diabetes) and 30.2% reported a history of diabetes. The risk factor control was very poor, with only 26.3% of patients using antihypertensive medication achieving the blood pressure goal, 30.6% of patients on lipid-lowering medication achieving the total cholesterol goal and 39.9% of patients with self-reported diabetes having haemoglobin A1c ≤6.1%. The use of blood pressure-lowering medication in people with hypertension was: β-blockers 34.1%, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers 60.8%, calcium channel blockers 26.3%, diuretics 36.9%. Statins were prescribed in 47.0% of people with hypercholesterolemia. About 22.0% of all patients were on aspirin or other antiplatelet medication. **Conclusion:** The EUROASPIRE III survey in general practice shows that the lifestyle of people being treated as high cardiovascular risk is a major cause of concern with persistent smoking and high prevalence of both obesity and central obesity. Blood pressure, lipid and glucose control are completely inadequate with most patients not achieving the targets defined in the prevention guidelines. Primary prevention needs a systematic, comprehensive, multidisciplinary approach, which addresses lifestyle and risk factor management by general practitioners, nurses and other allied health professionals, and a health care system which invests in prevention.

Publication n.	6
Research Direction	RD2
Title	A Software Framework for Global and Regional Quantitative Assessment

	of Myocardial Necrosis by Cardiac Magnetic Resonance. V Positano, M Marinelli, E Caiani, MF Santarelli, A Pingitore, A Redaelli, M Lombardi, L Landini, O Parodi.
Date	October 27th – 29th, 2010, Warsaw, Poland.
Journal/URL	Proceedings of the International Conference eChallenges e-2010 (P Cunningham and M Cunningham, Eds)
Field/sector	Biomedical technologies
Type	eChallenges e-2010
Objective	The goal of e-2010 is to stimulate rapid take-up of Research and Technology Development (RTD) results by industry and in particular SMEs, and help open up the European Research Area (ERA) to the rest of the world.
Description	This study show how a dedicated software tool, to be integrated within a clinical decision support system, may help to preserve the information content of medical images in the assessment of myocardial viability in management of the left ventricular dysfunction.
Target audience	Biomedical Engineers, Cardiologist, Bioinformatics
Partner(s) involved	IFC CNR, POLIMI
Publishable summary	Management of heart failure is challenging for all healthcare systems, due to the need of several expensive imaging examinations and image analysis procedures to address different clinical questions. In particular, a correct identification of transmural extent of irreversible myocardial damage is cost effective, identifying subjects who will most benefit of coronary revascularization. This study show how a dedicated software tool, to be integrated within a clinical decision support system, may help to preserve the information content of medical images in the assessment of myocardial viability in management of the left ventricular dysfunction.

Publication n.	7
Research Direction	RD2
Title	Knowledge extraction in a population suffering from heart failure. Dimitris Gatsios, John Garofalakis, Theodora Chrysanthakopoulou, Evanthia Tripoliti, Renata De Maria, Maria Grazia Franzosi, Boris Schmitz, Stefan-Martin Brand and Oberdan Parodi.
Date	November 2nd – 5th, 2010, Corfù Greece
Journal/URL	In Proceedings of the 10th IEEE International Conference on Information Technology and Applications in Biomedicine (ITAB 2010), 2010. Book of Abstracts.
Field/sector	Biomedical technologies
Type	Online Paper
Objective	The overall objective of ITAB 2010 is to cover the state of the art of Information Technology Applications in Biomedicine targeting in offering patient specific health services.
Description	The aim of the study was to apply data mining methodologies in order to classify the patients in those who developed late onset heart failure against those that did not develop the trait. Data derived from a multiple genetic variant analysis added predictive value to this study.

	The methodology followed, the results and the clinically important findings are presented in this work
Target audience	Biomedical Engineers, Cardiologist, Biologists, Bioinformatics
Partner(s) involved	CTI, IFC CNR, WWU
Publishable summary	The prevalence of heart failure is 2-3% of the general population and affects millions of people. In recent years, considerable progress has been made decoding the pathophysiology of this multi-factorial trait. Still the search for new variables with significant impact on the development of heart failure is an ongoing process. As part of the VPH2 project, a data mining study was conducted aiming specifically at extracting new knowledge from a population suffering from heart failure In particular, the population consists of patients suffering from post-mitral infarction development of myocardial remodelling. The aim of the study was to apply data mining methodologies in order to classify the patients in those who developed late onset heart failure against those that did not develop the trait. Data derived from a multiple genetic variant analysis added predictive value to this study. The methodology followed, the results and the clinically important findings are presented in this work.

Publication n.	8
Research Direction	RD3, RD4
Title	Conti CA, Stevanella M, Maffessanti F, Trunfio F, Votta E, Roghi A, Parodi O, Caiani EG, Redaelli A. Mitral valve modelling in ischemic patients: finite element analysis from cardiac magnetic resonance imaging.
Date	December 2010
Journal/URL	Comput Cardiol 2010; 1059-62 (www.cinc.org)
Field/sector	Biomedical engineering
Type	scientific
Objective	RD3, RD4
Description	This book contains the proceedings of the conference Computing in Cardiology.
Target audience	Biomedical Engineers, Cardiologists, Industry
Partners involved	POLIMI, IFC CNR
Publishable summary	See poster in the relevant session above

Publication n.	9
Research Direction	RD4
Title	Feasibility of a novel approach for 3D mitral valve quantification from magnetic resonance images. Maffessanti F, Stevanella M, Votta E, Lombardi M, Parodi O, De Marchi D, Conti CA, Redaelli A, Caiani EG.
Date	December 2010
Journal/URL	Comput Cardiol 2010; 157-60 (www.cinc.org)
Field/sector	Biomedical engineering
Type	scientific
Objective	RD3, RD4

Description	This book contains the proceedings of the conference Computing in Cardiology.
Target audience	Biomedical Engineers, Cardiologists, Industry
Partners involved	POLIMI, IFC CNR
Publishable summary	See oral presentation in the relevant session above

Publication n.	10
Research Direction	RD4
Title	Development and validation of automated endocardial and epicardial contour detection for MRI volumetric and wall motion analysis. Caiani EG, Redaelli A, Parodi O, Votta E, Maffessanti F, Tripoliti E, Nucifora G, De Marchi D, Tarroni G, Lombardi M, Corsi C.
Date	December 2010
Journal/URL	Comput Cardiol 2010; 1083-6 (www.cinc.org)
Field/sector	Biomedical engineering
Type	scientific
Objective	RD3, RD4
Description	This book contains the proceedings of the conference Computing in Cardiology.
Target audience	Biomedical Engineers, Cardiologists, Industry
Partners involved	POLIMI, IFC CNR
Publishable summary	See oral presentation in the relevant session above

Publication n.	11
Research Direction	RD4
Title	Visualisation and Simulated Surgery of the Left Ventricle in VPH2
Date	2011: Vol 1, No 3, pp 374-383
Journal/URL	Interface Focus, Royal Society
Field/sector	Computation in the natural Sciences
Type	Journal paper
Objective	A publication in a special issue of the journal devoted to VPH
Description	A journal paper elaborating visualisation aspects of the surgical planning system developed in VPH2
Target audience	Biomedical Engineers, Cardiologist, Biologists, Bioinformatics
Partner(s) involved	BED, POLIMI, SCS, IFC CNR
Publishable summary	Ischaemic heart failure remains a significant health and economic problem worldwide. This paper presented a user-friendly software system that forms a part of the Virtual Pathological Heart of the Virtual Physiological Human (VPH2) project, currently being developed under the European Commission Virtual Physiological Human (VPH) programme. VPH2 is an integrated medicine project, which will create a suite of modelling, simulation and visualisation tools for patient-specific prediction and planning in cases of post-ischaemic left ventricular dysfunction. The paper described a three-dimensional interactive visualisation for

	simulating left ventricle restoration surgery, comprising the operations of cutting, stitching and patching, and for simulating the elastic deformation of the ventricle to its post-operative shape. This will supply the quantitative measurements required for the post-operative prediction tools being developed in parallel in other parts of VPH2

Publication n.	12
Research Direction	RD3
Title	Virtual Pathological Heart of the Virtual Physiological Human (VPH2) Oberdan Parodi, M.D., Alberto Redaelli PhD, Luigi Martinelli, M.D., Debora Testi, Dr, Michele Carenini, Dr
Date	January 2011
Journal/URL	Newsletter No. 5
Field/sector	VPH – NOE (Network of Excellence)
Type	Article
Objective	Aim of the project, list of the partners, focus of the research and research techniques description
Description	The aim of the article is to promote and disseminate VPH2 objectives inside the VPH Network of Excellence
Target audience	VPH involved organizations
Partner(s) involved	NOEMALIFE, IFC-CNR, POLIMI, SCS, NIGUARDA
Publishable summary	VPH2 is the development of a high powered framework platform aiming at improving the heart diseases management processes in defining the severity and extent of disease in patients with post-ischemic left ventricular dysfunction, and in particular at: • Integrating clinical, biological and genetic data retrieved from medical records and laboratories research results in order to offer an innovative therapeutic tool for the surgical and medical decision making in patients with heart failure. • Supporting cardiac surgeons with advanced simulation and modelling tools to be applied to obtain better selection and simulation of specific surgical procedures. • Providing a new framework and multimodal approach that will be then useful in other clinical scenarios of cardiology and cardiac-surgery involving for example hybrid imaging PET-CT, molecular and functional imaging, etc.

Publication n.	13
Research Direction	RD3
Title	Mitral Valve Patient-Specific Finite Element Modeling from Cardiac MRI: Application to an Annuloplasty Procedure Stevanella M, Maffessanti F, Conti CA, Votta E, Arnoldi A, Lombardi M,

	Parodi O, Caiani EG, Redaelli A
Date	February 2011
Journal/URL	Cardiovascular Engineering and Technology 2011;2:66-76
Field/sector	Biomedical engineering
Type	Peer-reviewed journal
Target audience	Biomedical Engineering, cardiologists, cardiac surgeons, manufacturers
Partner(s) involved	POLIMI, CNR
Publishable summary	**Abstract—**We aim at testing the possibility to build patientspecific structural finite element models (FEMs) of the mitral valve (MV) from cardiac magnetic resonance (CMR) imaging and to use them to predict the outcome of mitral annuloplasty procedures. MV FEMs were built for one healthy subject and for one patient with ischemic mitral regurgitation. On both subjects, CMR imaging of 18 longaxis planes was performed with a temporal resolution of 55 time-frames per cardiac cycle. Three-dimensional MV annulus geometry, leaflets surface and PM position were manually obtained using custom software. Hyperelastic anisotropic mechanical properties were assigned to MV tissues. A physiological pressure load was applied to the leaflets to simulate valve closure until peak systole. For the pathological model only, a further simulation was run, simulating undersized rigid annuloplasty before valve closure. Closure dynamics, leaflets stresses and tensions in the subvalvular apparatus in the healthy MV were consistent with previous computational and experimental data. The regurgitant valve model captured with good approximation the real size and position of regurgitant areas at peak systole, and highlighted abnormal tensions in the annular region and sub-valvular apparatus. The simulation of undersized rigid annuloplasty showed the restoration of MV continence and normal tensions in the subvalvular apparatus and at the annulus. Our method seems suitable for implementing detailed patient-specific MV FEMs to simulate different scenarios of clinical interest. Further work is mandatory to test the method more deeply, to reduce its computational time and to expand the range of modeled surgical procedures.

Publication n.	14
Research Direction	RD3, RD4
Title	Left ventricular modelling: a quantitative functional assessment tool based on cardiac magnetic resonance imaging. Conti CA, Votta E, Corsi C, De Marchi D, Tarroni G, Stevanella M, Lombardi M, Parodi O, Caiani EG, Redaelli A.
Date	Approved, February 2011
Journal/URL	Journal of the Royal Society Interface *Interface focus* 2011; 1:384-395
Field/sector	Biomedical engineering
Type	Online Paper
Objective	Society's cross-disciplinary publication promoting research at the interface between the physical and life sciences.
Description	This article presents the development and testing of a semi-automated tool to support the diagnosis of left ventricle (LV) dysfunctions from

	cardiac magnetic resonance (CMR).
Target audience	Biomedical Engineers, Cardiologist, Biologists, Bioinformatics
Partner(s) involved	POLIMI, IFC CNR
Publishable summary	CMR short-axis images of the LVs were obtained in 15 patients and processed to detect endocardial and epicardial contours and compute volume, mass and regional wall motion (WM). Results were compared with those obtained from manual tracing by an expert cardiologist. Nearest neighbour tracking and finite-element theory were merged to calculate local myocardial strains and torsion. The method was tested on a virtual phantom, on a healthy LV and on two ischaemic LVs with different severity of the pathology. Automated analysis of CMR data was feasible in 13/15 patients: computed LV volumes and wall mass correlated well with manually extracted data. The detection of regional WM abnormalities showed good sensitivity (77.8%), specificity (85.1%) and accuracy (82%). On the virtual phantom, computed local strains differed by less than 14 per cent from the results of commercial finite-element solver. Strains calculation on the healthy LV showed uniform and synchronized circumferential strains, with peak shortening of about 20 per cent at end systole, progressively higher systolic wall thickening going from base to apex, and a 108 torsion. In the two pathological LVs, synchronicity and homogeneity were partially lost, anomalies being more evident for the more severely injured LV. Moreover, LV torsion was dramatically reduced. Preliminary testing confirmed the validity of our approach, which allowed for the fast analysis of LV function, even though future improvements are possible.

Publication n.	15
Research Direction	RD2
Title	Relationship Between Myocardial Redox State and Matrix Metalloproteinase Activity in Patients on Left Ventricular Assist Device Support. Caruso R, Caselli C, Boroni C, Campolo J, Milazzo F, Cabiani M, Russo C, Parolini M, Giannessi D, Frigerio M, Parodi O.
Date	Submission: April 2011
Journal/URL	Circulation Journal
Field/sector	Cardiology
Type	Scientific Journal
Objective	Journal publishing original articles and reviews on either clinical or experimental investigation of the cardiovascular and related systems.
Description	This article investigates the effects of myocardial redox state on the activities of metalloproteinases (MMP)-2 and -9, implicated in cardiac remodeling in end-stage heart failure patient supported by left ventricular assist device.
Target audience	Medical and research communities
Partner(s) involved	IFC CNR, NIGUARDA
Publishable summary	**Background:** Redox aminothiols have been reported to modulate the activity of recombinant MMPs. Aim of this study was to investigate the effects of myocardial redox state on the activities of metalloproteinases

	(MMP)-2 and -9 implicated in cardiac remodeling in ESHF-patients supported by left ventricular assist device (LVAD). **Methods:** During heart transplant (HT)-surgery, myocardial specimens (MS) from right and LV walls were obtained from 7 LVAD-recipients (LVAD-group, MS n=35) and from 7 stable HT candidates on medical therapy (MT-group, MS n=35). Myocardial MMP-2/-9 activities and expression, tissue inhibitor of MMP (TIMP)-1 and -4, transforming growth factor (TGF)-β1 and aminothiol levels were measured. MMP-2/-9 activity was evaluated also incubating MS with different amounts of reduced and oxidized glutathione (GSH). **Results:** MMP-2/-9 activity and expression were lower in LVAD-group, while myocardial TIMP-1 and -4 were comparable to those of MT-patients. Higher GSH and TGF-β1 levels were found in LVAD-recipients. Only GSH levels were inversely related to MMP-2/-9 activity. In vitro, GSH had an inhibitory effect on MMP-2/-9 activity. **Conclusions:** LVAD-recipients show reduced myocardial MMP-2/-9 activities and expression when compared to medically treated patients. Changes of myocardial redox state, predominantly GSH-dependent, appear to modulate MMP-2/-9 activity by an inhibitory effect dependent on thiol content. These data support a role of GSH cycle in modulating the extracellular matrix in ESHF-patients supported by LVAD.

Publication n.	16
Research Direction	RD3
Title	Parallel Algorithms for Fluid-Structure Interaction Problems in Haemodynamics.
Date	April 21st,2011
Journal/URL	SIAM journal of Scientific Computing
Field/sector	numerical methods and techniques for scientific computation
Type	scientific
Objective	Includes some part of the research carried out in RD3 and RD4
Description	The SIAM Journal on Scientific Computing contains research articles on numerical methods and techniques for scientific computation. Papers address computational issues relevant to the solution of scientific or engineering problems and include computational results demonstrating the effectiveness of the proposed techniques.
Target audience	Numerical and Computational scientists
Partners involved	EPFL
Publishable summary	The increasing computational load required by most applications and the limits in hardware performances affecting scientific computing contributed in the last decades to the development of parallel software and architectures. In Fluid-Structure Interaction (FSI, in short) for haemodynamic applications, parallelization and scalability are key issues (see~\cite{formaggia09:_cardiov_mathem}). In this work we introduce a class of parallel preconditioners for the FSI problem obtained by exploiting the block-structure of the linear system. We stress the possibility of extending the approach to a general linear system with a block-structure, then we provide a bound in the condition number of the

	preconditioned system in terms of the conditioning of the preconditioned diagonal blocks, finally we show that the construction and evaluation of the devised preconditioner is modular. The preconditioners are tested on a benchmark 3D geometry discretized in both a coarse and a fine mesh, as well as on two physiological aorta geometries. The simulations that we have performed show an advantage in using the block preconditioners introduced and confirm our theoretical results. Keyword(s): Fluid-Structure Interaction, blood-flow models, Finite Elements, Preconditioners, Parallel algorithms

Publication n.	17
Research Direction	RD3, RD4
Title	A patient-specific computational analysis from CMR imaging for annuloplasty ring assessment for the treatment of ischemic mitral regurgitation. Stevanella M, C.A. Conti, E. Votta, F. Maffessanti, Sotaquira M., A. Roghi, O. Parodi, E.G. Caiani, A. Redaelli.
Date	September 2011
Journal/URL	Eur H Journal 2011
Field/sector	Cardiology
Type	scientific
Objective	RD3, RD4
Description	Abstract accepted for oral presentationat European Society of Caridiology meeting
Target audience	Biomedical Engineers, Cardiologists, Industry
Partners involved	POLIMI, IFC CNR
Publishable summary	See poster in the relevant session above

4.5. Web site and promotional materials

Material n.	1
Research Direction	All
Type	VPH2 – Project Website
Description	Project Website. The Project website has been constantly updated, both in the private and the public areas, in order to allow the maximum visibility of the project.
Date	Monthly update
Partners involved	Sorin - all

Material n.	2
Research Direction	All
Type	VPH2 – Project promotional materials
Description	Leaflets and project posters have been produced to disseminate VPH2 results and tailored to reach specific targets or event types.
Date	When possible during conferences, meetings and workshops
Partners involved	Sorin - all

5. Scientific Dissemination Board and Dissemination Responsible.

The Scientific Dissemination Board has had the aim to promote, assess and validate communication towards the User Community for gathering needs, validating research outcomes and disseminating scientific and technical knowledge beyond the consortium.

During the third year of the project the Board held 2 meetings in concomitance of the General Meetings in order to reduce the travel expenses.

5.1. Scientific Dissemination Board

Appointed members of the Scientific Dissemination Board are listed in the table below.

Partner	name	email	role	phone
SORIN	Eric Manasse	eric.manasse@sorin.com	Chair	+39 0161 487442
REGLOM	Armando Beffani	armando.beffani@cefriel.it	Member	+39 02 23954303
IFC CNR	Oberdan Parodi	oberpar@tin.it	Member	+39 02 64442605
POLIMi	Alberto Redaelli	alberto.redaelli@PoliMi.it	Member	+39 02 23993375
EPFL	Simone Deparis	simone.deparis@epfl.ch	Member	+41 21 6932547
WWU	Stefan Martin Brand-Herrmann	StefanMartin.BrandHerrmann @ukmuenster.de	Member	+49-251-8352996
CTI	John Garofalakis	garofala@cti.gr	Member	+30 2610 960317
NOEMALIFE	Michele Carenini	mcarenini@noemalife.com	Representative for technological partners	+39 051 7098271

5.2. Responsible for Dissemination

A responsible for Dissemination has been identified for each Partner in order to facilitate the communication and the effective circulation of information relevant to Dissemination activities.

Partner	Name	e-mail/phone
NOEMALIFE	Gianpiero Camilli	gcamilli@noemalife.com
WWU	Stefan Martin	StefanMartin.BrandHerrmann@ukmuenster.de
REGLOM	Armando Beffani	armando.beffani@cefriel.it +39 02 23954303
CNR	Jonica Campolo	jonica.campolo@ospedaleniguarda.it +39 02 64442605
POLIMI	Alberto Redaelli	alberto.redaelli@PoliMi.it +39 02 23993375
SCS	Debora Testi	d.testi@scsitaly.com +39 051 593543
EPFL	Simone Deparis	simone.deparis@epfl.ch +41 21 693 2547
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SORIN	Silvia Pascale	Silvia.pascale@sorin.com +39 0161 487335
CTI	Dimitris Gatsios	dgatsios@westgate.gr +30 2610 960430
INTERCON	Rafal Grzybowski	rafal.grzybowski@intercon.pl +48 42 630 50 29
PATMOS	Ivano Biacchi	vph2@patmos.it
NIGUARDA	Luigi Martinelli	luigi.martinelli@ospedaleniguarda.it +39 02 64 442 565

6. Individual Dissemination

6.1. NOEMALIFE

In the last year of the project, NL did not focus on particular dissemination activities. This is due to the fact that, as a private company, NL is generally more interested in defining market and exploitation strategies rather than disseminating results (an activity more apt to scientific/academic partners). Possible spreading of (technical) intermediate results can be thought of as a first, preparatory step towards a thorough exploitation phase that will take place after the completion of the project.

Anyway NoemaLife supports and promotes all the activities in the VPH - NOE context, contributing in publishing articles on newsletter, participating in specific VPH conferences or providing data and support to other partners in such a context.

6.2. WWU

In the last year of the project, WWU did focus on the national and international dissemination of knowledge connected with VPH2 with special respect to the communication between basic researchers and health professionals. Thus, conferences chosen for data presentation targeted participants from both groups. In detail WWU disseminated at the following events:

- DGPT [Pharmacology congress, Germany]
- DGK [German Cardiology congress, Germany]
- ECCR [European Council for Cardiovascular Research, France]
- DHL [Hypertension congress, Germany]
- HGM [Human Genome Conference, UAE]

6.3. REGLOM

In the last year of the project, REGLOM has not focused on specific dissemination activities, as primary contributor. We have rather supported dissemination activities run by the Niguarda Hospital.

6.4. SCS

Being SCS role mainly in integration and in presenting via the visualisation module other WPs and partners' results, few actions have been undertaken as primary contributor to disseminate VPH2 results. However, whenever possibile SCS contributed to other partners dissemination activities.

6.5. EPFL

The paper *Parallel Algorithms for Fluid-Structure Interaction Problems in Haemodynamics*, P. Crosetto, S. Deparis, G. Fourestey and A. Quarteroni, has been accepted for publication in SIAM Journal of Scientific Computing. One other paper is in preparation on the multiscale coupling of the 1D tree model and a 3D FSI simulation of the left ventricle.

The work done in collaboration with VPH2 has been cited and thanked in several occasions:

Simone Deparis, Parallel Algorithms for Fluid-Structure Interaction and Application to Cardiovascular Flows, FEF2011, 16th International Conference on Finite Elements in Flow Problems, Munich March 2011

Later this year, Toni Lassila has submitted an abstract to SIMBIO 2011, Simulation and Modeling of Biological Flows, Brussel September 2011. He will present several results coming from the research carried out by EPFL in the VPH2 project.

6.6. BED

The work of BED within VPH2 has related mainly to providing visualisation and modelling tools for use in the final system. This has involved close work with other partners, particularly SCS and Polimi, and the dissemination materials produced reflect this.

The involvement of BED was scheduled at a low level in the early months of the project while users prepared specifications and discussed the project needs.

A paper describing the surgical planning tool in its entirety was presented, in July 2010, at MediVis 2010, the proceedings of which are published by the IEEE Computer Society and are thus widely available. The audience at MediVis is fairly specialised being primarily interested in visualisation within the biomedical context. This paper covered the new methods that had to be implemented to create reasonable surface models from the data.

A paper that focused more closely on the interaction within the surgical planner was presented at the VPH2010 conference in September 2010. This conference is organised by the VPH Network of Excellence; it takes place every two years and is the major concertation event for the VPH community as a whole. As a result, submission was invited for an extended version of the paper to be included in the Royal Society journal Interface Focus which was producing a special issue on the VPH; this paper appeared in early 2011.

While this paper was well received by the reviewers, their comments led us to believe that evidence of utility within the clinical context would be essential for the acceptance of papers planned on more recent aspects of the work. Thus, further papers will be submitted once the outcomes of the testing of the final system by the medical partners have been assimilated.

6.7. SORIN

During the third year of project activities, the Website has been continuously updated and maintained, in order to improve its performance and rationalize its appearance. A periodic control has been done, so to assure the correct and timely passage of information.

Sorin participated to the workshop held during the 44th Cardiology Congress in Milan, September 30th, and helped in the preparation and management of the workshop (minutes included).

Sorin participated also at the General Meetings held in Brussels (October 13th, 2010) and in Milan-Niguarda (March 30th and 31st, 2011), during which updates on Dissemination were presented.

Sorin, as Dissemination Manager, monitored the dissemination activities done by the other partners, but didn't submit articles to peer-reviewed journals nor gave lectures during conferences, since they are activities more suitable to technical/scientific partners.

6.8. CTI

During this last year of the project CTI has participated in ITAB 2010, in November, where a poster was presented and the respective paper was published in the Conference proceedings. Moreover, CTI was invited in the special session "Computational biomechanics and tissue engineering" of the 7GRACM (Greek Association of Computational Mechanics) International Congress on Computational Mechanics. Since the Congress was organised on 30 June - 2 July 2011 CTI could only participate if the project was extended, and due to the relevant delay we missed that event at the end. Finally, CTI has worked in an article to be submitted in the "International Journal of Medical Informatics". The Journal provides an international medium for dissemination of original results and interpretative reviewsconcerning the field of medical informatics. In order to include all data mining results and the validation activities that recently took place this is ongoing work and the plan is to submit it by the end of 2011.

6.9. INTERCON

During this period, Intercon according to the plan approached Medical University of Lodz in order to organize the promotional event for medical & scientific staff. Due to objective reasons event was postponed.

6.10. PATMOS

During the third year of the project, the dissemination activity of PATMOS has been oriented to promote VPH2 to Local Health Agencies, hospitals and health institutions in general. Particularly, the objectives and preliminary results of VPH2 were presented to Modena AUSL (the local health agency) on March 14 2011 at the Baggiovara hospital. Next June PATMOS will introduce the VPH2 project to the Cardiac-Vascular Department of IRCCS Casa Sollievo della Sofferenza hospital in San Giovanni Rotondo (Foggia).

6.11. CNR

For this year, our activity was oriented again towards the participation of conferences and meetings in order to disseminate the knowledge about VPH2 project but also towards the VPH2 platform training and validation, by the organization of a specific workshop. Presentation of the first prototype of VPH2 platform, discussion with potential stakeholders, advises by invited experts in HF and cardiac imaging have been some of the important point of IFC CNR dissemination. Publications on the results of the scientific activity of VPH2 are also foreseen.

6.12. POLIMI

The dissemination actions of PoliMi consisted mainly in general scientific and teaching activities including meetings and workshops with bioengineers and medical doctors within the framework of the ongoing national and international collaborations, as well as conference presentations with formal presentations (papers, posters, abstracts) and lecturers within and outside the Politecnico di Milano University. PoliMi has mentioned and quoted VPH2, as far as the opportunity occurred.

6.13. NIGUARDA

In the last year dissemination activity of NIGUARDA included:

- participation and organization of conferences, meetings and workshops, within and outside the Niguarda Hospital in Milan (the 44th Cardiology Congress in Milan – 2010; the VPH2 global meeting of March 30th and 31st in Niguarda Hospital - 2011, etc.) in order to disseminate the knowledge about VPH2 project and talk about the work in progress;
- publication of a paper in international journal (ASAIO Journal 2010; 56:313-318) with VPH2 project mentioning;
- organization of focus groups to present and validate VPH2 platform.

7. Conclusion

The Consortium has delivered 3 Deliverables containing the Dissemination Plan (D1.5.1) and its Updates (D1.5.2 and D1.5.3), as written in the DoW.

The Consortium has gone beyond the expectations by involving a significant number of Key Opinion Leaders in cardiology and cardio surgery, both in the academic and in the clinical field, thus confirming the need of an instrument like VPH2 platform.

In order to disseminate VPH2 contents, the partners participated to high-level conferences, workshops, congresses, with lectures, posters or articles, as reported in this deliverable and in the previous ones; moreover, a huge number of publications on peer-reviewed journals have been published. This all demonstrates the validity of the scientific work done during the VPH2 project.

The project also joined the VPH Network of Excellence, and produced a paper describing the results obtained.

7.1. Dissemination objectives

The objectives of the Dissemination were:

1. Raise the interest of the cardiologic and cardio surgery communities.
2. Obtain the confirmation that the Consortium was on the right track, specifically, that it was developing a tool really useful for on-the-field cardiologists and cardiac surgeons.
3. Reach a wide scientific public.
4. Involve European experts, in order to obtain their opinion on the platform.

7.2. Dissemination Major achievements

The project will impact mainly on the cardiologist/cardiac surgeon's ability to accurately plan the intervention on the patient. A number of focus groups have been organised in order to assess the impact of the project and the acceptance of the platform in the community.

During the workshops, organized at different stages of the platform development, questionnaires were submitted to the participants in order to understand what was ameliorable, and if such an instrument could be of true help for operative cardiologists and cardiac surgeons.

Here is presented a summary about main results of VPH2 external focus group held in Milan during the 44° Convention "Cardiologia 2010" on September 30th, 2010, and on September 20th, 2011.

The external focus group for SW evaluation took place in Milan during **44° Convention *"Cardiologia 2010"*** on **September 30th 2010**. The Organization of the workshop was mainly managed by IFC-CNR.

The aim of the event was receiving clinical inputs from clinicians on the usefulness of the **VPH2 FAT** module in the characterization of patients with post-ischemic heart failure. Seven expert cardiologists/cardiac surgeons have been invited to attend a brief presentation/demo of the FAT module functionalities, then they were asked to fill a questionnaire in order to express their opinion and suggestions about tool usefulness.

The main objective of the workshop was to capture the users' feedback about VPH2 platform functional aspects: usability, efficacy, efficiency and clinical applicability.

Through the use of specific case scenarios the clinicians were asked to test the tool by working remotely on the platform and to measure their degree of appreciation filling some questionnaires. The questionnaire made it possible to collect in a structural way the clinicians' opinions about tool's ease of use, completeness of the achievable information and visualization facilities implemented.

The indications contained in the usability reports give to the software developers important information in order to improve and refine platform characteristics (approach and interfaces) and adjust them accomplishing final users' requirements.

Finally, giving clinicians an overview of tool's functionality, it was possible to focus on the VPH2 potentiality, so its possibility to give a support and save time in everyday clinical practice.

The interviewee was asked to evaluate VPH2 platform by scoring each indication as follows:

- **Score 7 to 9:** Appropriate for specific indication (system is generally acceptable and is a reasonable approach for the indication).
- **Score 4 to 6:** Uncertain for specific indication (system may be generally acceptable and may be a reasonable approach for the indication. Uncertainty also implies that more research and/or patient information is needed to classify the indication definitively).
- **Score 1 to 3:** Inappropriate for that indication (system is not generally acceptable and is not a reasonable approach for the indication).

Main outcomes:

- 6/7 clinicians have evaluated the DSS very useful in giving information about **prediction of ventricular remodelling progression** (7,6 average "appropriateness" score)
- 5/7 clinicians gave a positive response about FAT capability to **simulate the effects of revascularisation of hibernating myocardium** (7,3 average "appropriateness" score)
- 5/7 clinicians have positively evaluated the IDSS in providing support to the **operations of ventricular restoration** (7,1 average "appropriateness" score)
- Only 29% gave a positive response concerning the capability of information provided by VPH2 **DSS in reducing pharmaceutical costs**

- The 71% assessed that information provided by DSS could **reduce the proportion of patients who may not benefit ending up in surgery**
- The 57% assessed that DSS may have effects of reduction in morbidity and mortality rates
- In general the 86% asserted that the use of VPH2 platform will have possible effects on patients' final clinical outcome**.**

More details are included in the validation deliverable D7.2.

Comments were received on some aspects of the software during the **first focus group** in Niguarda Hospital on July 6th, 2011: it was suggested to improve the importer DICOM so that the data naming conventions so to be meaningful to a clinical user and to facilitate the navigation of the medical images; comments were also received on the use of some functionalities by non technical persons, few concerns were also expressed on the performances of some algorithms; regarding DSS the main problem was that sometimes the classifiers were either too generic and couldn't be applied to specific cases or they didn't have useful clinical interpretation.
During the **second internal focus group** in Niguarda Hospital on September 20th, 2011 the system was perceived in general as effective, in particular providing good quality of the results, clear classification and standardization of variables, and a useful system to objectively quantify prognosis. As limitation, it was reported that the system was not easy to use. This might be related both to the fact that the prototype is not yet an industrial product and that none of the users had familiarity with software tools for identification of severity and extent of disease in patients with post-ischemic LVD and with MRI data processing and visualisation software tools.

After the end of the project, the Consortium will probably constitute itself in a Business Consortium as described in the Exploitation Plan (D8.1.3) and will continue to disseminate the results it will obtain by the improvements of the platform.

Surely, since the VPH2 will be close on the commercialization, the sensitive information will not be disseminated, and non-disclosure agreements will be signed by the KOL participating in the workshops, so to be able to patent and protect the intellectual rights.