EACVI project

# Prognostic indices of Right heart dysfunction in patients undergoing CABG (RH-CABG study)

## Summary of the study

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| Title | Prognostic indices of Right heart dysfunction in patients undergoing CABG (RH-CABG study) |
| Joint collaboration | EACVI HIT - HoT |
| Principal Investigator<br>Local Coordinator | Julia Grapsa MD, PhD, Erwan Donal MD, PhD, Julien Magne MD, PhD, Gilbert Habib MD, PhD |
| Participating Centers | Estimation of 30 centers X 30 patients: 900 patients |
| Aims | Right ventricular dysfunction plays a fundamental role in heart failure pathophysiology and significantly impairs patients outcome. Nonetheless, there is currently scarse knowledge on clinical correlates and predictors of right ventricular failure.<br>With the present multicenter prospective observational study we aim therefore to:<br>a) define correlates of right ventricular involvement, among several clinical variables, in an unselected large cohort of patients undergoing CABG;<br>b) identify predictors of future development of right ventricular systolic dysfunction in patients with significant coronary artery disease who are undergoing CABG operation. |
| Study design | Multicenter, prospective observational |
| Patients population | Patients who admitted for CABG from different European Countries will be enrolled in the study. |
| Inclusion criteria | - Patients will be distributed into two groups: a) patients with normal ejection fraction (EF LV > 50%) and b) patients with reduced ejection fraction (EF LV ≤ 50%) |

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| | - Patients will be also distributed in two groups: a) those who have CAD including severe RCA disease and b) those who have LAD, Cx or LMS disease<br>- Age >18 yrs;<br>- Ability to provide informed consent. |
| Exclusion criteria | - Pulmonary embolism within the previous 6 months;<br>- Known pulmonary hypertension<br>- Need for inotropic support or for ventricular assist device implantation;<br>- Congenital heart disease;<br>- Constrictive/restrictive/hypertrophic cardiomyopathy<br>- Malignancy.<br>- Patients with redo or who had to be re-operated in the same setting |
| Sample size | 900 patients (≈ 30 patients/center) |
| Study duration | Enrolment: 9 months<br>Follow-up: 1 year |
| Power analysis | The power of the study was calculated by Dr.Bernard North (Consultant in Statistical Genomics, Medical Statistics, Imperial College of Science, Technology and Medicine). There is a justification of the sample size to be employed as 200 patients for each group in order to achieve 95% power with significance $\alpha = 0.01$ to detect a difference of 15% in RV EDV with a standard deviation of the difference as 8%. |
| Statistical analysis | The value measurement will be performed with the statistical model SPSS 13.0 and mean values of groups will be compared with 2 tailed t test: standard deviations between groups will be measured with the use of test chi-square. Correlations will be examined by multiple linear regression. All data are expressed as mean ± SEM. A |

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| | value of $p<0.05$ is considered statistically significant.<br>Very important is the study of reproducibility index between the measurements of intraobserver and interobserver. An observer should measure two values and variability is defined as the mean value and the difference between the standard deviation through these groups of values. Variability between two different observers is described as the difference between pairs of values and the mean value of these.<br>The assessment of RV will include: two dimensional echocardiography, real time three dimensional echocardiography and speckle tracking of LV and RV.<br>We will also measure routine blood and biochemical tests, measurement of NT-proBNP, BNP in patients blood plasma.<br>For a better estimation of life quality, the use of Kansas City Cardiomyopathy quality of life questionnaire is suggested.<br>Blood tests for the measurement of biochemical values should be taken every 6 months.<br>Furthermore, we will monitor intra-operative parameters such as cardiopulmonary by pass time or total time of operation. |

## Workflow

| Mandatory | Baseline | Follow-up |
|---|---|---|
| Visit | √ | √ |
| ECG | √ | √ |
| Echocardiography | √ | √ |
| **Optional** | | |
| Blood sampling | √ | √ |
| Cardiopulmonary exercise test | √ | √ |
| Spirometry | √ | √ |
| Cardiac magnetic resonance | √ | √ |

## List of abbreviations

CRF, care report form

EF, ejection fracion

FA, fractional area

HF, heart failure

LV, left ventricle

NYHA, New York Heart Association

PAP, pulmonary artery pressure

PSV, peak systolic velocity

RV, right ventricle

TAPSE, tricuspid annular plane systolic excursion

TDI, tissue Doppler imaging

# *Prognostic indices of Right heart dysfunction in patients undergoing CABG (RH-CABG study)*

**Background**

Despite recent advances in pharmacological and non-pharmacological therapy, heart failure (HF) still holds a poor prognosis and represents a major global burden in terms of morbidity and mortality. Left and right ventricular functions are strictly linked in HF pathophysiology and in the development of the HF clinical syndrome. The right ventricle (RV) can be indeed primarily involved, for example as a consequence of RV infarction or following right sided valvular disease. Most commonly, RV dysfunction occurs following the increase in right side pressures due to alterations in the systolic and/or diastolic properties of left ventricle (LV).

Patients with coronary artery disease who are undergoing CABG have a significant degree of diastolic impairment. Depending on several factors – which have not been clearly documented. Few patients with a normal RV before CABG, may develop pulmonary hypertension and impaired RV post CABG. The mechanism of development of RV dysfunction is still unknown and this will be the aim of this study: to explore the mechanism of RV dysfunction development.

**Imaging of the right ventricle**

The difficult approach of right ventricle is an important factor, concerning the surveillance of pulmonary hypertensives. It is the most anteriorly situated cardiac chamber, since it is located immediately behind the sternum.[21,22] It also marks the inferior border of the cardiac silhouette. In contrast to the near conical shape of the left ventricle, the right ventricle is more triangular in shape when viewed from the front and it curves over the left ventricle. When seen from the apex, the right edge of the right ventricle is sharp, forming the acute margin of the heart. In cross section the cavity appears like a crescent. Thus, the curvature of the ventricular septum places the right ventricular outflow tract antero-cephalad to that of the left ventricle's resulting in a characteristic "cross-over" relationship between right and left ventricular outflows. Two are the anatomic

components that make right ventricle difficult to be examined in detail, especially when using two dimensional echocardiography, the irregular shape of the cavity and the heavy trabeculation which makes difficult the identification of right ventricular borders.

Nowadays, the accuracy of measuring the right heart impairment due to the disease is offered by two new methods, real time three dimensional echocardiography and cardiac magnetic resonance imaging.

## 3-dimensional echocardiography

The most recent introduction of real time 3D echocardiography (RT3DE) has revolutionized echocardiography as images may be obtained in just one beat. This has resulted in improved image resolution, higher penetration and harmonic capabilities that may be used for both grey scale and contrast imaging. The major advantage is that volumetric analysis does not rely on geometric assumptions, as has been the case with two dimensional echocardiography. Quantifications of LV volumes and mass have successfully been performed and a similar approach can be applied for RV remodeling in pulmonary hypertension.

## Cardiac magnetic resonance

With CMR, RV function can be evaluated in the short axis. This technique can also be used for measurement of flow velocity and volume by phase velocity mapping.[32,33] Phase velocity mapping is based on gradient – echo pulse sequences in combination with ECG triggering. The phase contrast allows velocity encoding and therefore flow measurements. Despite the excellent image quality and reproducibility, MRI has some disadvantages: the data acquisition and analysis is rather time consuming, and some patients groups (for example, pacemaker patients) cannot undergo MRI.

## Speckle tracking

The speckle pattern can be used to track myocardial motion due to two facts about the speckle pattern. The randomness of the speckle pattern ensures that each region of the myocardium has its own unique speckle pattern: that can differentiate a region from other regions. It resembles m-mode because the speckles follow the myocardial motion. By this, defining a region (kernel) in one frame, this kernel can be identified as region in the next frame with the same size and shape

with the most similar speckle pattern, and the motiuon of the kernel can be tracked from frame to frame. From this accumulation of regions, the search algorithm derives.

The algorithm for this seach is simple, it simply searches for the area with the smallest difference in the total sum of pixel values, the smallest sum of absolute differences (SAD). This has been shown to be as effective as cross correlation. However, the speckle pattern will not repeat perfectly. This is due to both true out of plane motion (rotation and torsion relative to apical planes and longitudinal deformation relative to short axis planes) and to small changes in the interference pattern. But the frame to frame change is small, and the approach to recognition is statistical. This means, however, that the search should be done from frame to frame, the changes over longer time intervals will be to great.

Speckle tracking has been validated by ultrasonomicrometry in the longitudinal direction as well as for rotation. One great advantage is that it is angle independent and can be used to track in two dimensions.

However, drop outs and reverberations will affect the tracking, and in the lateral direction low lateral resolution will "smear" the speckles in the lateral direction, making tracing less perfect, as can be seen above, where thacking in the inferior wall where lateral resolution is poorer, is less perfect than in the septum where the sector is narrower and lines more dense, giving a better lateral resolution.

Speckle tracking is frame rate sensitive:

1. Too low frame rate will result in too great changes from frame to frame, resulting in poor tracking. This may also limit the use in high heart rates, as the motion and thus frame to frame change increases relative to the frame rate.
2. Too high frame rate is obtained by reduced lateral resolution, and thus resulting in poorer tracking at least in the transverse direction.

**Regarding RV dysfunction and heart failure**

The presence of RV dysfunction in HF has been associated with adverse modifications in haemodynamics and humoral response (*Spinarova L et al, 2005*). Preserved RV systolic function is a more potent predictor of event free survival in advanced HF than peak oxygen consumption (*Di Salvo TG et al, 1995; Dokainish H et al, 2007*). Several studies have demonstrated that impairment

of RV systolic function has a profound impact on patients outcome and can predict death or cardiac transplantation. Ghio and Colleagues have shown, for example, that in patients with severe LV dysfunction (LV ejection fraction, LVEF, <35%) of either ischemic and non-ischemic etiology both mean pulmonary artery pressure (PAP) and RVEF are be independent predictors of survival (*Ghio S et al, 2001*).

To date, the largest set of data on the prognostic role of RV failure has been obtained from a post-hoc analysis of the BEST trial (Beta-blocker Evaluation of Survival trial). In this study, RV systolic function was estimated in more than two thousands patients with severe HF by means of radionuclide ventriculography (*Meyer P et al, 2010*), and RVEF <20% was independently associated with the combined end-point of HF mortality and hospitalisation, after adjustment for other co-variables including LVEF. More recently, Gulati has confirmed the predictive value of RV function on all-cause mortality and cardiac transplantation in 250 patients with non ischemic dilated cardiomyopathy (*Gulati A et al, 2013*). Noteworthy, in this study assessment of RV systolic function was performed by means of cardiac magnetic resonance imaging, currently representing the gold standard for the morphological and functional evaluation of RV. Nonetheless the majority of the evidence for the prognostic role of RV failure originates from studies in which RV systolic function has been evaluated with echocardiography. Some of them have used RV fractional area (RVFA) or tricuspid annular plane systolic excursion (TAPSE) obtained with bidimensional or M-mode echocardiography, respectively, as an estimate of RV systolic function (*Di Salvo TG et al, 1995; de Groote P et al, 1998; Kjaergaard J et al, 2007; Dini FL et al , 2007; Dini FL et al, 2008*), while some others relied on echocardiographic markers of RV systolic function based on tissue Doppler imaging (TDI) (*Dokainish H et al, 2007; Meluzin J et al, 2003; Meluzin J et al, 2005; Bistola V et al, 2010*). Damy and Colleagues have compared the prognostic value of different echocardiographic indices of RV systolic function, including RVFA, TAPSE, peak systolic (PSV) and integral systolic wave velocity of tricuspid annulus, in a cohort of 136 patients with severe HF (LVEF <35%). The Authors report (after adjustment for other clinical, biohumoral and echocardiographic variables) that PSV (threshold value: 9.5 cm/sec) was the only independent predictor of the composite end-point of death, urgent heart transplantation or LV assist device implantation and acute heart failure. Currently, TAPSE represents the most widespread estimate of RV systolic function and, although it assumes that displacement of the basal RV segment is

representative of the function of the entire ventricle, it is a simple, reproducible method, less dependent on optimal image quality.

This amount of evidence-base supports a role for RV function, independently from LV systolic and diastolic impairment, in the identification of HF patients at higher risk for cardiovascular events. Despite the significant pathophysiological and clinical implications of RV involvement and its key prognostic value in patients with HF, the current clinical guidelines for HF management and recommendations for pharmacological and non pharmacological therapeutical approaches, are not substantially influenced by the coexistence of RV dysfunction, according to current guidelines on HF management (*McMurray JJ et al, 2012*). In this view, the identification of clinical correlates of RV dysfunction may help to clarify pathophysiological mechanisms undelrlying the development of RV dysfunction. This may help to delineate the profile of the patient with biventricular failure with the possibility of tailoring therapy in the future.

Although few retrospective single-center studies have investigated determinants of RV failure in selected cohorts of HF - describing associations with pulmonary capillary wedge pressure, anemia (*Guglin M et al, 2012*), LV diastolic dysfunction, tricuspid regurgitation (*Berkowitz R et al, 2010*), pulmonary artery pressure (*Grose R et al, 1983*), ventricular dyssynchrony (*Gupta S et al, 2008*) or NYHA functional class (*Ereminiene E et al, 2012*) - clear data are currently lacking.
Similarly, despite the prognostic relevance of RV involvement in HF, informations on predictors of future development of RV systolic dysfunction are limited to patients with acute myocardial infarction or those implanted with a ventricular assist device (*Azevedo PS et al, 2012; Drakos SG et al, 2010*).

**Aims**

With the present study we aim therefore:

1) to define prognostic indices of RV dysfunction in a large cohort of CABG patients;
2) to associate echocardiographic predictors with clinical/hemodynamic data.

**Study design**

Patients admitted for CABG from 30 centers between December 2015 and August 2016 will be enrolled in this multicenter prospective observational study, according to the following criteria.

*Inclusion criteria*

- Patients will be distributed into two groups: a) patients with normal ejection fraction (EF LV > 50%) and b) patients with reduced ejection fraction (EF LV ≤ 50%)
- Patients will be also distributed in two groups: a) those who have CAD including severe RCA disease and b) those who have LAD, Cx or LMS disease
- Age >18 yrs;
- Ability to provide informed consent.

*Exclusion criteria*

Pulmonary embolism within the previous 6 months;

- Known pulmonary hypertension
- Need for inotropic support or for ventricular assist device implantation;
- Congenital heart disease;
- Constrictive/restrictive/hypertrophic cardiomyopathy
- Malignancy.
- Patients with redo or who had to be re-operated in the same setting

Patients will receive an extensive clinical examination, including history, anthropometric characteristics, symptoms, pharmacological and non-pharmacological therapy. All subjects will also be submitted to transthoracic echocardiography, with assessment of RV systolic function by means of a multiscoring system. Patients data will be used for the purpose of the study only if obtained within 30 days. Anonymisation of data will be obtained.

Clinical and echocardiographic characteristics of patients with impaired RV function will be then compared to those of patients with preserved RV systolic function. Clinical correlates of RV dysfunction will be identified among all mandatory variables assessed at baseline evaluation.

A follow-up clinical, electrocardiographic and echocardiographic evaluation will be performed at 6 and 12 months after CABG operation in order to verify changes in RV systolic function. Predictors of future development of RV failure will then be identified among variables considered at baseline evaluation.

*Data acquisistion*

Patients clinical, biohumoral and istrumental data will be collected through CRF.

Accuracy of data will be verified and CRF will be filled by investigators in each center.

*Exit criteria*

At any time during the protocol patients may choose to leave the study without any penalty or loss of benefits to which they are otherwise entitled and will continue to receive standard of medical care.

*Sample size estimation and statistical analysis*

Assuming 30 participating Centers all over Europe and 30 patients recruited by each center in the 9-months enrolment period, the estimated size of the study population is ≈900.

Variable distribution will be reported as mean and standard deviation (normally distributed variables), median and interquartile range (non-normally distributed variables) or as percentage (cathegorical variables). Comparison between groups will be performed with Student T test for unpaired data or with analysis of variance and Bonferroni correction. Categorical variables will be compared with Chi-square test (with Yates correction) or with Fisher test.

Correlates and predictors of right ventricular dysfunction will be identified by means on logistic univariate analysis. Univariate correlates/predictors will then enter a multivariable model. All statistical tests will be 2-tailed. A p value of <0.05 will be considered as statistically significant.

**Expected value of results**

The study will have a great input in predicting the patients who will develop RV dysfunction post CABG. Therefore, it may have a great impact on their management (percutaneous intervention or CABG consideration beforehand) or even pharmacological management afterwards (for example initiation of ACE inhibitors).

**Confidentiality**

Patients data will be collected in a central electronic database under the responsibility of EACVI. All data will be anonymized and access to the database will be protected by a personal password provided to principal investigators.

**Centers participating to the study**

The following Centers will participate to the study by recruiting patients:

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2.
3.
4.
5.

**Steering committee**

**Intellectual property**

The property of study data will be shared among participating centers. Data will be published (in form of presentation in nationa/international meetings or as full paper) after anonymization, statistical analysis, and independently from results.

## References


Berkowitz R, Alhaj E, Manchikalapudi RB, Satya K, Dadfarmay S, Zakir R. Determinants of right ventricular failure in patients admitted with acute left heart failure. *Congest Heart Fail.* 2010;16:243-8.

Bistola V, Parissis JT, Paraskevaidis I, Panou F, Nikolaou M, Ikonomidis I, Flessas N, Filippatos G, Iliodromitis E, Kremastinos DT. Prognostic value of tissue Doppler right ventricular systolic and diastolic function indexes combined with plasma B-type natriuretic Peptide in patients with advanced heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 2010;105:249-54.

de Groote P, Millaire A, Foucher-Hossein C, Nugue O, Marchandise X, Ducloux G, Lablanche JM. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. *J Am Coll Cardiol.* 1998;32:948–54.

Dini FL, Conti U, Fontanive P, Andreini D, Banti S, Braccini L, De Tommasi SM. Right ventricular dysfunction is a major predictor of outcome in patients with moderate to severe mitral regurgitation and left ventricular dysfunction. *Am Heart J.* 2007;154:172–9.

Dini FL, Fontanive P, Panicucci E, Andreini D, Chella P, De Tommasi SM. Prognostic significance of tricuspid annular motion and plasma NT-proBNP in patients with heart failure and moderate-to-severe functional mitral regurgitation. *Eur J Heart Fail.* 2008;10:573–80.

Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. *J Am Coll Cardiol.* 1995;25:1143-53.

Dokainish H, Sengupta R, Patel R, Lakkis N. Usefulness of right ventricular tissue Doppler imaging to predict outcome in left ventricular heart failure independent of left ventricular diastolic function. *Am J Cardiol.* 2007;99:961–5.

Drakos SG, Janicki L, Horne BD, Kfoury AG, Reid BB, Clayson S, Horton K, Haddad F, Li DY, Renlund DG, Fisher PW. Risk factors predictive of right ventricular failure after left ventricular assist device implantation. *Am J Cardiol.* 2010;105:1030-5.

Ereminiene E, Vaskelyte JJ, Stoskute N, Kavoliuniene A, Bieseviciene M, Ordiene R, Nedzelskiene I. Determinants of reduced tricuspid annular plane systolic excursion in patients with severe systolic left ventricular dysfunction. A*cta Cardiol.* 2012;67:657-63.

Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol.* 2001;37:183–8.

Grose R, Strain J, Yipintosoi T. Right ventricular function in valvular heart disease: relation to pulmonary artery pressure. *J Am Coll Cardiol.* 1983;2:225-32.

Guglin M, Win CM, Darbinyan N, Wu Y. Predictors of right ventricular systolic dysfunction in compensated and decompensated heart failure. *Congest Heart Fail.* 2012;18:278-83.

Gulati A, Ismail TF, Jabbour A, Alpendurada F, Guha K, Ismail NA, Raza S, Khwaja J, Brown TD, Morarji K, Liodakis E, Roughton M, Wage R, Pakrashi TC, Sharma R, Carpenter JP, Cook SA, Cowie MR, Assomull RG, Pennell DJ, Prasad SK. The prevalence and prognostic significance of right ventricular systolic dysfunction in nonischemic dilated cardiomyopathy. *Circulation*. 2013;128:1623-33.

Gupta S, Khan F, Shapiro M, Weeks SG, Litwin SE, Michaels AD. The associations between tricuspid annular plane systolic excursion (TAPSE), ventricular dyssynchrony, and ventricular interaction in heart failure patients. E*ur J Echocardiogr*. 2008;9:766-71.

Kjaergaard J, Akkan D, Iversen KK, Kober L, Torp-Pedersen C, Hassager C. Right ventricular dysfunction as an independent predictor of short- and long-term mortality in patients with heart failure. *Eur J Heart Fail.* 2007;9:610–6.

Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2015;16:233-70.

McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33:1787-847.

Meluzin J, Spinarova L, Dusek L, Toman J, Hude P, Krejci J. Prognostic importance of the right ventricular function assessed by Doppler tissue imaging. *Eur J Echocardiogr.* 2003;4:262–71.

Meluzin J, Spinarova L, Hude P, Krejci J, Kincl V, Panovsky R, Dusek L. Prognostic importance of various echocardiographic right ventricular functional parameters in patients with symptomatic heart failure. *J Am Soc Echocardiogr*. 2005;18:435– 44.

Meyer P, Filippatos GS, Ahmed MI, Iskandrian AE, Bittner V, Perry GJ, White M, Aban IB, Mujib M, Dell'Italia LJ, Ahmed A. Effects of right ventricular ejection fraction on outcomes in chronic systolic heart failure. *Circulation.* 2010;121:252–8.

Spinarova L, Meluzin J, Toman J, Hude P, Krejci J, Vitovec J. Right ventricular dysfunction in chronic heart failure patients. *Eur J Heart Fail.* 2005;7:485–9.