Assessment of haemodynamic effects of surgical correction for severe functional tricuspid regurgitation: cardiac magnetic resonance imaging study

Hyung-Kwan Kim1,2, Yong-Jin Kim1,2, Eun-Ah Park4, Ji-Seon Bae4, Whal Lee4, Kyung-Hwan Kim1,3, Ki-Bong Kim1,3, Dae-Won Sohn1,2, Hyuk Ahn1,3, Jae-Hyung Park4, and Young-Bae Park1,2

1Cardiovascular Center, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; 2Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea; 3Department of Cardiovascular Thoracic Surgery, Cardiovascular Center, Seoul National University College of Medicine, Seoul National University Hospital, 28 Yongon-dong Chongno-gu, Seoul 110-744, Korea; and 4Department of Radiology, Seoul National University College of Medicine, Seoul, Korea

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Aims
There has been growing attention for the development of functional tricuspid regurgitation (TR) long after left-sided valve surgery. We attempted to determine the long-term haemodynamic effects of corrective surgery for severe functional TR in patients who had prior left-sided valve surgery using cardiac magnetic resonance imaging (CMR).

Methods and results
Thirty-one patients with severe functional TR (TR fraction of 46.0±16.2% by CMR) were analysed. CMR was performed within 1 month before and at a median 27.0 months after surgery. Long after TR surgery, 28 of the 31 patients had no or mild residual TR, two had mild-to-moderate TR, and one showed moderate TR. Remarkable reductions in the right ventricular (RV) end-diastolic volume index (RV-EDVI) (177.4±59.1 mL/m² vs. 118.2±31.2 mL/m², P=0.001) and end-systolic volume index (RV-ESVI) (88.5±30.1 mL/m² vs. 67.2±31.0 mL/m², P=0.002) were observed, whereas RV ejection fraction (RV-EF) showed no change (49.7±8.3% vs. 44.9±12.5%, P=0.09). Pre-operative RV-EDVI (R=-0.86, P<0.001) and RV-ESVI (R=-0.55, P=0.001) were significantly associated with their respective changes after corrective surgery. Post-surgery, a normal RV-EF was achieved in 14 patients (42.5%). Pre-operative RV-EDVI of 164 mL/m² effectively discriminated patients with normal RV-EF from those without post-surgery, with a sensitivity of 77% and a specificity of 72% (P=0.01). A significant rise in the left ventricular (LV) EDVI and cardiac index (CI) was found after surgery (from 92.9±24.4 to 123.2±31.6 mL/m² for LV-EDVI, P<0.001; from 3.8±1.3 to 4.2±0.8 L/min/m² for CI, P=0.03). Functional capacity as assessed by NYHA class showed a significant improvement from 2.7±0.6 before surgery to 2.0±0.6 long after surgery (P<0.001).

Conclusion
Successful TR surgery can remarkably reduce RV volumes and preserve RV systolic function. In addition, successful TR surgery led to a significant rise in LV preload and CI, which may significantly contribute to a significant amelioration in the functional capacity of the patients. It seems that RV volume measurement by CMR is helpful for determining optimal timing for TR surgery.

Keywords
Tricuspid regurgitation • Magnetic resonance imaging • Surgery • Right ventricle

Introduction
Tricuspid regurgitation (TR) is a common finding in patients who have previously undergone left-sided valve surgery.1–4 Although TR may decrease gradually after successful left-sided valve surgery with reduction in right ventricular (RV) pressure or volume overload, TR does not always regress after adequate repair of the underlying pathology and may even progress...
without left-sided valvular dysfunction, even after tricuspid annuloplasty.3–7

The development of late TR after left-sided valve surgery is closely linked to exercise intolerance and augurs a poor prognosis,8,9 even in the absence of LV dysfunction or pulmonary hypertension.10 To prevent adverse effects of TR, corrective surgery for TR is usually performed in the hope of preserving RV function and of improving functional capacity and long-term survival. However, the effects of corrective TR surgery on RV haemodynamics in the long term are hitherto unknown. The complex geometry of the RV is an obstacle to performing research on this issue, because it is extremely difficult using echocardiography, the technique most frequently used to assess cardiac haemodynamics, to procure accurate and reproducible information regarding RV haemodynamics in a quantitative manner.8

Cardiac magnetic resonance imaging (CMR) has emerged as the reference standard imaging modality for quantitative assessment of RV volumes, systolic function, and valve function.11–13 With this state-of-the-art technology, we here attempted to determine the effects of corrective TR surgery on RV haemodynamics and clinical symptoms in patients with severe TR in the absence of the left-sided valve dysfunction. We believe that knowledge of long-term RV changes after the surgical correction of TR would deepen our insight into the pathophysiology of TR, and thus lay the cornerstone for determining optimal surgical indication in these patients.

Methods

Study population

From May 2004 to April 2008, 50 patients who had prior left-sided valve surgery were operated on due to isolated severe TR without any evidence of the presence of left-sided valve dysfunction. Of these 50 patients, 47 underwent CMR before surgery and were considered initial candidates in the present study. The decision to perform pre-operative CMR was totally at the discretion of the attending surgeon. Of these 47 patients, four rejected follow-up performance of CMR, six passed away, two had a suboptimal quality of pre-operative CMR data for analysis, three could not undergo follow-up CMR due to implanted pacemaker, and one was lost to follow-up. Consequently, the follow-up CMR was performed in the remaining 31 patients, who are the subject of this report. To be included in the current study, the following three criteria for severe TR should be satisfied based on the pre-operative echocardiography: (i) a TR jet area $>$30% of the right atrial (RA) area, (ii) coaptation failure of tricuspid leaflets, and (iii) systolic flow reversal in the hepatic vein. Patients with documented organic disease in the tricuspid valve were excluded based on echocardiographic, surgical, and pathological findings. Cardiac magnetic resonance was performed within 1 month before surgery and 10–52 months postoperatively during follow-up. The study protocol was approved by the Institutional Review Board of our hospital, and all patients gave written informed consent to participate in the study.

Cardiac magnetic resonance imaging

All 31 patients underwent CMR before and after surgical procedure. Postoperative CMR was repeated using the same protocol and the same machine in all patients. Cardiac magnetic resonance examinations were performed on a 1.5 T system (Sonata Magnetom, Siemens, Erlangen, Germany). All images were acquired by a phased-array body surface coil during breath holds and were electrocardiogram triggered.

After localizer imaging, cine true fast imaging with steady-state precollision imaging (TrueFISP, repetition time/echo time 45/1.3 ms, flip angle 80°, matrix 256 × 169, field of view 330 × 330 mm, slice thickness 8 mm) was performed in several long-axis planes (two-, three-, and four-chamber views) of the heart. Parallel short-axis sections from the valve plane to the apex were acquired for volumetric analysis. Right ventricular and LV end-diastolic (EDV) and end-systolic volumes (ESV), stroke volumes, cardiac output, and ejection fractions (EF) were measured using dedicated software (QMASS MR; Medis, Leiden, The Netherlands). Left (LA) and RA volumes were measured using biplane area–length method.14 Left atrial length was measured from the LA posterior wall to the mitral annular plane, both in the two- and four-chamber orientations at maximal atrial diastole that is defined as the image immediately before the opening of the mitral and tricuspid valves. Right atrial length was similarly measured from the RA posterior wall to the tricuspid annular plane in the four-chamber orientation. Left atrial areas in the apical two- and four-chamber orientations were planimetered by tracing the endocardial border at maximal atrial diastole. Care was exercised to exclude the confluence of the pulmonary veins and LA appendage. Right atrial area was planimetered in a similar fashion in the apical four-chamber orientation with exclusion of the confluence of the vena cava and the RA appendage. Atrial and ventricular volumes, stroke volume, and cardiac output were corrected for body surface area.

Velocity-encoding cine CMR with free breathing and prospective ECG gating (repetition time/echo time 45/3.2 ms, flip angle 30°, matrix 256 × 238, field of view 330 × 330 mm, slice thickness 5 mm) was performed in a plane orthogonal to the right (RPA) and left (LPA) pulmonary arteries to allow net forward volume of the RV to be calculated. Flow profiles of the RPA and LPA were analysed on velocity-encoding cine CMR images using specialized software (Argus; Siemens Medical Solutions). The contours of each pulmonary artery were automatically traced, with manual correction if necessary, on magnitude and velocity-map images of all 20 reconstructed phases. All measurements were performed by one independent observer.

Amount of TR was calculated by subtracting net pulmonary blood volume of the RPA and LPA from RV stroke volume. Tricuspid regurgitation fraction was calculated by dividing TR amount by RV stroke volume and was expressed as percentage. After RV-EF calculation, RV-EF was corrected for TR flow by dividing pulmonary forward flow (the sum of the flows in RPA and LPA) by RV-EDV, i.e. effective RV-EF (eRV-EF) = net pulmonary forward flow/RV-EDV.13

The interventricular septal curvature was measured in the short-axis image that included papillary muscles. Great care was taken to select the same level of short-axis CMR image pre- and post-operatively. With the selected image, the cine image with the most evident deviation of the septum was used for quantification (Figure 1).
Statistical analysis

Data are expressed as means ± SDs or median with interquartile ranges for continuous variables and as numbers (%) for categorical variables, as appropriate. After evaluating normality distribution for each continuous variable with Shapiro–Wilk test, two-sided Wilcoxon signed rank test or paired t-test was used for statistical comparison, as appropriate. For comparison of categorical variables before and after surgery, Fisher’s exact test was used. Pearson’s correlation coefficient was calculated to quantify correlations between continuous variables. Multiple logistic regression analysis using the forward conditional selection process, including all significant pre-operative CMR variables by univariate analysis, age, and gender, was undertaken to determine which pre-surgical CMR variables were independently associated with post-operative RV-EF preservation within normal range, receiver-operating characteristic curve analysis was used. The cut-off value was defined as one with maximal sum of sensitivity and specificity. SPSS version 13.0 was used for statistical analyses. A P-value of <0.05 was taken as a cut-off value for statistical significance.

Results

The baseline characteristics of the 31 patients are summarized in Table 1. Twenty-six patients were on atrial fibrillation and 27 patients were female. Median follow-up time for CMR after TR surgery was 27.0 (range, 10 – 52) months. At the time of the previous valve surgery, tricuspid valvuloplasty was performed in three patients and tricuspid annuloplasty in four patients, due to significant TR and/or tricuspid annular dilation. Median time interval between the previous left-sided valve surgery and the current TR surgery is 18 years (range 2 – 29 years). Concomitant maze procedure at the previous left-sided valve surgery was conducted only in one of 31 patients.

Changes in cardiac magnetic resonance variables and clinical data after corrective surgery

Haemodynamic changes after TR surgery are described in Table 2. As expected, TR fraction was significantly decreased from 46.0 ± 16.2% pre-surgery to 3.8 ± 11.7% post-surgery (P < 0.001). Twenty-eight patients had no residual TR. Mild to moderate residual TR was present in two patients and moderate residual TR in one.

There was no change in heart rate and RV-EF after TR surgery, whereas eRV-EF increased remarkably by approximately 103% (26.9 ± 8.5% pre-operatively vs. 50.9 ± 12.7% during follow-up, P < 0.001). A significant reduction in RV volumes, including RV end-diastolic volume index (RV-EDVI) (from 177.4 ± 59.1 to 118.2 ± 31.2 mL/m², P < 0.001) and RV end-systolic volume index (RV-ESVI) (from 88.5 ± 30.1 to 67.2 ± 30.1 mL/m², P = 0.002) was observed (Figure 1A and B). With a cut-off change of 10% vs. pre-operative value, no decrement in RV-EDVI was observed in seven patients (22.5%). Of note, two of three patients who had more than mild degree of residual TR showed reductions in RV volumes after TR surgery. Right ventricular-EDVI returned to the normal range (defined as <108 mL/m²) in 13 patients (41.9%), whereas RV-ESVI (defined as <47 mL/m²) was normalized in eight patients (25.8%).

In terms of LV volumes, a significant rise in LV-EDVI and LV-ESVI was demonstrated (for LV-EDVI, 92.9 ± 24.4 vs. 123.2 ± 31.6 mL/m² and for LV-ESVI, 39.8 ± 14.9 vs. 63.5 ± 26.1 mL/m², both P < 0.001) (Figures 1 and 2). Besides, CI showed a significant rise post-operatively (3.8 ± 1.3 vs. 4.2 ± 0.8 L/min/m², P = 0.03) (Table 2 and Figure 1B). A percent change in CI displayed a positive correlation with a percent change in pulmonary artery flow (R = 0.38, P = 0.03).

The angle of the interventricular septal bowing was significantly changed from 78.6 ± 6.1° pre-operatively to 83.7 ± 3.8° post-operatively (P = 0.005). Right atrial volume index showed a significant decline from 191.5 ± 113.6 mL/m² pre-surgery to 92.3 ± 37.9 mL/m² post-surgery (P < 0.001), whereas LA volume index displayed no change pre- (227.6 ± 159.7 mL/m²) vs. post-surgery (208.4 ± 136.1 mL/m²) (P = 0.41) (Figure 3).
When functional capacity was assessed according to NYHA class, a significant improvement was demonstrated from 2.7 ± 0.6 before surgery to 2.0 ± 0.6 after surgery (P < 0.001). In eight patients (25.8%), no change in NYHA class was observed, whereas one patient (3.2%) showed symptomatic aggravation. Thus, 22 patients (71.0%) achieved a symptomatic improvement whereas one patient (3.2%) showed symptomatic aggravation.

Changes in right ventricular volumes and right ventricular ejection fraction in relation to pre-operative variables

Successful surgical correction of TR resulted in a decrease in RV-EDVI by 27.2% (P < 0.001) and a decrease in RV-ESVI by 19.9% (P = 0.002) (Table 2). A significant relation was found between RV-EDVI and RV-ESVI reductions and their respective pre-operative values (for RV-EDVI, R = −0.86, P < 0.001 and for RV-ESVI, R = −0.55, P = 0.001) (Figure 5A and B). Of note, we could not find any upper limit, above which RV did not decrease in size after TR surgery. This was also true for RV-EF and eRV-EF (Figure 5C and D). Furthermore, relationship between pre-operative RV parameters and their surgically induced changes were independent of pre-operative exercise capacity, as assessed by NYHA functional class (Figure 5A–D). When a normal RV-EF was defined as ≥48% for male and ≥50% for female,16 RV-EF values were within normal ranges in 14 patients (45.2%) after TR surgery.

Pre-surgical CMR variables discriminating patients with a normal RV-EF from those without successful TR surgery were RV-EDVI, RV-EDVI, RV-ESVI, and LV-EDVI (Table 3). To identify independent pre-operative CMR variables for normal RV-EF after corrective TR surgery, we performed multivariate logistic regression analysis. As a result, only pre-operative RV-EDVI emerged as an independent determinant of post-operative normal RV-EF [P = 0.025, R² = 0.3, exponential β = 1.023 (95% CI, 1.003 – 1.044)]. Sensitivity and specificity for normal RV-EF post-surgery were 77 and 72%, with a pre-operative RV-EDVI of 164 mL/m² as the cutoff value (P = 0.01) (Figure 6).

Measurement reproducibility

Inter- and intra-observer variabilities for measurement of LV-EDV, RV-EDV, and flow profiles of the RPA and LPA were determined in 10 randomly selected patients. Inter-observer variabilities were as follows: R = 0.99, standard error of the estimate (SEE) = 13.7, P < 0.001 for RV-EDV; R = 0.98, SEE = 11.7, P < 0.001 for LV-EDV; R = 0.99, SEE = 2.1, P < 0.001 for RPA; and R = 0.99,
See $\frac{\text{SE}}{\text{P}} = 0.9$, for LPA. Intra-observer variabilities were as follows: $R = 0.99$, $\text{SEE} = 8.4$, $P < 0.001$ for RV-EDV; $R = 0.98$, $\text{SEE} = 6.5$, $P < 0.001$ for LV-EDV; $R = 0.99$, $\text{SEE} = 1.1$, $P < 0.001$ for RPA; and $R = 0.99$, $\text{SEE} = 1.3$, $P < 0.001$ for LPA.

**Discussion**

The principal findings of the current study include: (i) corrective TR surgery significantly reduced RV volumes by approximately 27%, and increased LV volumes by 39%, and CI by 18%, when compared with pre-operative values; (ii) postoperative decreases in RV volumes were found to be significantly associated with pre-operative RV volumes. Similar relationship was also detected in terms of RV-EF; (iii) 42.5% of patients (14 of the 31 patients) achieved a normal RV-EF after successful TR surgery, which is not a low proportion given the large RV-EDVI pre-surgery; (iv) pre-operative RV-EDVI of 164 mL/m² emerged as a potential cut-off value that was significantly associated with a normal RV-EF after corrective TR surgery; and finally (v) functional capacity (as expressed by NYHA classification) improved by at least one NYHA class in 65.5% of the patients.

**Changes in the right ventricular haemodynamics after successful tricuspid regurgitation surgery**

Severe TR induces a chronic volume overload of the RV, which leads to progressive RV dilatation, dysfunction, and finally RV failure. In the present study, we found that surgical correction of TR reduced RV-EDVI and RV-ESVI without reducing RV-EF, highlighting that timely performed surgery for severe functional TR can preserve RV function.

Evaluation of ventricular function is a difficult problem in the presence of mitral or tricuspid valve regurgitation. Ejection phase indexes such as EF tend to overestimate ventricular contractile function because of favourable loading condition stemming from an increase in preload. In contrast, end-systolic volume is relatively independent of preload and varies linearly with ventricular
In this context, the 19% decrement of RV-ESVI clearly demonstrates the beneficial effects of TR surgery. In addition, RV-EF was not changed significantly and remained in a normal range post-operatively in 14 of the 31 patients (45.2%), when an RV-EF of 48% for male or 50% for female was considered the lower limit of reference value. Given that postoperative RV-EF is an important predictor of progressive RV remodelling, these results are somewhat encouraging because successful functional TR correction, although performed in the setting of advanced status of disease (e.g. severe RV dilation), can lead to a normal RV-EF in not a few percentage of patients in the long-term. In addition, a cut-off value of 164 mL/m² for pre-operative RV-EDVI was found to be an effective predictor for post-operative preservation of RV-EF, suggesting that this cut-off value for RV-EDVI assessed by pre-operative CMR can be helpful for determining optimal timing for corrective TR surgery. Moreover, when we adopted eRV-EF by using net pulmonary flow, rather than RV-EF, eRV-EF was found to have increased significantly from 27.1 ± 8.7 to 51.4 ± 12.9% (P < 0.001).

Of note, pre-operative RV volumes (both RV-EDVI and RV-ESVI) were found to be in close association with the extent of RV remodelling, that is, larger RV volumes pre-surgery showed greater reductions in RV volumes after surgery. Furthermore, no ceiling effect was evident. This was also true for RV-EF, independently of pre-operative functional capacity. Similar findings were reported in patients with corrected Tetralogy of Fallot. Oosterhof et al. observed that pulmonary valve replacement in patients with corrected Tetralogy of Fallot substantially reduced RV-EDVI and RV-ESVI without a definite threshold, above which a decrease in RV size could not be achieved. Despite the inclusion of a wide range of RV volumes and RV-EF in the present study, this finding requires confirmation in the future study.

Changes occurring in the left ventricular and functional capacity of patients

Another interesting observation is that there was a significant rise in LV-EDVI (a representative of LV preload) and CI after successful TR surgery. This is likely to have occurred due to a ventricular interaction mediated through the interventricular septum, as was previously described in the setting of an RV pressure-overload such as that caused by chronic thromboembolic pulmonary hypertension or idiopathic pulmonary arterial hypertension. We believe that this is the first demonstration of the possible impact of RV-ESVI on LV-EDVI and CI.

Figure 3 Cardiac magnetic resonance imaging demonstrating changes in right (RV) and left ventricular (LV) volumes before and after surgery for tricuspid regurgitation. Pre-operative images of horizontal long-axis (four-chamber) (A) and short-axis views (B) at end-diastole show a markedly enlarged RV with interventricular septal shifting toward the LV. After surgery, a remarkable reduction in RV size is obvious in horizontal long-axis (C) and short-axis view images (D). More importantly, a significant increase in LV volume is also noted. Movie files are available as Supplementary material online.
of RV volume overload and its correction on maintenance of LV preload and cardiac output. When TR is severe, progressive dilation of the RV and right atrium takes place with time, and eventually, pericardial compliance may become exhausted. Simultaneously, RV holds a dominant position in occupying space, and in turn the reduction of LV size and the impairment of preserving LV preload ensue through ventricular interaction. Post-surgery, the disappearance of regurgitant flow through tricuspid valve and a reduction in RV size increase LV preload (as evidenced by a significant increase in LVEDVI) and CI. This is further advocated by a statistically significant positive correlation between the percent change in CI and the percent change in pulmonary artery flow as well as a progressive increase in NYHA functional capacity in relation to the percent increase in CI (Figure 4B).

Although statistical significance was not reached, LV-EF decreased from 57.3 ± 11.4% pre-operatively to 49.7 ± 11.6 post-operatively (P = 0.07). Considering the chronic effect of TR on the RV and then LV by means of shared interventricular septum and continuity between the muscle fibres of the LV and RV,25 this phenomenon might be regarded as post-operative manifestation of pre-operative latent LV systolic dysfunction. Nevertheless, this slight decline of LV-EF appears to be clinically insignificant, given the postoperative increment in CI and improvement of functional capacity. In particular, LV-EF failed to prove its usefulness as a prognosticator in the setting of LV compression caused by pressure or volume overload of the RV.19,26 Therefore, we believe that a slight,
non-significant decline in LV-EF postoperatively observed is clinically irrelevant.

In addition to the beneficial effects of TR surgery in terms of CMR-derived RV and LV haemodynamics, we also found clinical improvements in patients’ symptoms, as assessed by NYHA class, though not in all patients. Because low cardiac output is believed to contribute to low functional capacity, a significant increase in cardiac output may contribute to a significant improvement in functional capacity after successful TR correction.

Taken together, corrective TR surgery can be considered clinically relevant despite not insignificant operative morbidity and mortality, given a significant improvement in functional capacity and cardiac haemodynamics occurring in both ventricles. Cardiac magnetic resonance indexes that can aid in choosing appropriate timing for corrective TR surgery should be further evaluated in the future studies.

Study limitations

Several limitations of the present study need to be acknowledged. First, the decision to perform TR surgery was at the discretion of the attending physicians and was not guided by specific criteria, resulting in CMR not being performed in three patients. Second, because the number of patients enrolled was relatively small, definitive conclusions cannot be drawn. However, in an attempt to minimize bias caused by including heterogeneous group of patients with severe TR, we recruited only patients with isolated severe TR and without left-sided valve dysfunction, which we believe strengthens our conclusions. Third, follow-up CMR could not be performed in one-third of patients. Therefore, our findings are prone to selection bias and may not be directly applied in all patients undergoing surgery for isolated TR. However, we made every effort to have follow-up examination in all patients and not to be biased by the selection. Furthermore, our study population had wide range of pre-operative RV systolic and diastolic volumes and showed no significant differences in pre-operative RV volumes compared with those in whom follow-up CMR data were not available (data not shown). Fourth, postoperative CMR was not performed at the same time period. Fifth, metal-induced magnetic field inhomogeneity may induce signal loss of adjacent structures and cause image degradation on CMR in patients with mechanical prosthetic valves. However, in our patients, image degradation by mechanical valves was not so great that we could easily delineate LV and RV endocardium in volume measurement. Likewise, in terms of phase contrast CMR, metal-induced artefact might cause underestimation of pulmonary flow measurement. However, the errors caused by metallic valves would be negligible, because there was no patient who had previously undergone pulmonary valve replacement and both RPA and LPA are somewhat apart from the position where mechanical mitral or tricuspid valve was placed. Finally, this study was not designed to analyse clinical outcomes after corrective TR surgery. A larger study with a longer follow-up is required to resolve this issue.

Conclusions

CMR imaging demonstrated that remarkable reduction in RV volumes as well as preservation of RV-EF within a normal range can be achieved after successful corrective TR surgery. Pre-operative RV-EDVI assessed by CMR has a potential for determining optimal timing of TR surgery, although requiring confirmation in a large-scale study. In addition, successful TR surgery led to a significant rise in LV preload and CI, which may significantly
contribute to a significant amelioration in functional capacity of the patients.

**Supplementary material**

Supplementary material is available at *European Heart Journal* online.

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