Impact of Inferior Venae Cava Assessment in Tetralogy of Fallot

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ABSTRACT

Background: Inferior vena cava (IVC) size and collapsibility provide a noninvasive estimate of right heart filling pressures, an important determinant of right heart hemodynamic performance that is not measured by cardiac magnetic resonance imaging (CMRI). We hypothesized that compared with CMRI risk model alone, a combined CMRI-IVC risk model will have better correlation with disease severity and peak oxygen consumption in patients with tetralogy of Fallot (TOF).

Methods: We performed a retrospective review of patients with TOF with moderate/severe pulmonary regurgitation who underwent CMRI. CMRI-IVC risk model will have better correlation with disease severity and peak oxygen consumption in patients with tetralogy of Fallot (TOF).

Results from right ventricular (RV) volume overload and dysfunction due to chronic pulmonary regurgitation. Cardiac magnetic resonance imaging (CMRI) is the gold standard for RV volumetric assessment because it provides reproducible assessment of RV volumes and systolic function. Unfortunately, CMRI does not provide an assessment of right heart filling pressure or right heart afterload, which are important components of hemodynamic performance.

Right atrial pressure is a composite metric of right heart function and reflects RV diastolic function, right atrial compliance, and volume status. Right atrial pressure can be estimated noninvasively using echocardiographic assessment of inferior vena cava (IVC) size and collapsibility (IVC hemodynamics). Although IVC hemodynamics are routinely used to guide clinical decision making in patients with right heart failure due to pulmonary arterial hypertension, the prognostic implications in patients with congenital heart disease have not been systematically studied. Because CMRI provides a good assessment of RV size and systolic function, and IVC hemodynamics reflect right heart filling pressure (not measured by CMRI), we hypothesized that a combination of CMRI indices and IVC hemodynamics will improve risk stratification in patients with TOF. The purpose of this study was to determine if the incorporation of IVC hemodynamics improved the diagnostic performance of CMRI indices in adults with repaired TOF.

Methods

Study population

We reviewed the Mayo Adult Congenital Heart Disease (MACHD) Registry and identified adults (age ≥ 18 years) with TOF and moderate/severe pulmonary regurgitation who underwent transthoracic echocardiogram and CMRI within a 2-day interval from January 1, 2000, to December 31, 2018. The diagnosis of moderate/severe pulmonary regurgitation was based on echo-Doppler assessment as previously described. Patients with inadequate echocardiographic assessment of the IVC and patients with tricuspid valve prostheses were excluded. We defined adequate IVC assessment as having 2-dimensional echocardiographic images of
and echocardiography. A CMRI risk model was constructed using right ventricular (RV) end-diastolic volume index, RV end-systolic volume index, RV ejection fraction, and left ventricular ejection fraction. We added IVC hemodynamic classification to the CMRI indices to create CMRI-IVC risk model, and IVC hemodynamics were modeled as a categorical variable: normal vs mild/moderately abnormal (dilated IVC or reduced collapsibility) vs severely abnormal IVC hemodynamics (dilated IVC and reduced collapsibility). We defined disease severity as atrial arrhythmias, ventricular arrhythmias, and heart failure hospitalization.

**Results:** Of 207 patients, 131 (63%), 72 (35%), and 4 (2%) had normal, mild/moderately abnormal, and severely abnormal IVC hemodynamics, respectively. Compared with the CMRI risk model, the CMRI-IVC risk model had a better correlation with disease severity (area under the curve, 0.62; 95% confidence interval, 0.51-0.74 vs 0.84, 95% confidence interval, 0.78-0.91, \( P = 0.006 \)) and peak oxygen consumption (\( r = 0.35, P = 0.042 \) vs \( r = 0.43, P = 0.031 \), Meng test \( P = 0.026 \)).

**Conclusions:** The combined CMRI-IVC risk model had a better correlation with disease severity compared with CMRI indices alone and can potentially improve risk stratification in the population with TOF.

**Study design**

We hypothesized that compared with CMRI risk model alone, a combined CMRI-IVC risk model will have a better correlation with disease severity and exercise capacity. The primary study objective was to compare the robustness of the correlation between the CMRI risk model and disease severity indices and the CMRI-IVC risk model and disease severity indices. The secondary study objective was to compare the robustness of the correlation between CMRI risk model and peak oxygen consumption (VO\(_2\)) and CMRI-IVC risk model and peak VO\(_2\).

In the subgroup of patients who underwent pulmonary valve replacement within 12 months from the time of CMRI, we performed an exploratory analysis to compare the strength of association for cardiovascular adverse events for IVC hemodynamics vs CMRI indices (RV ejection fraction [RVEF] < 30% and left ventricular ejection fraction [LVEF] < 45%) alone. These CMRI indices were chosen because of known association with adverse outcomes in the population with TOF.2

**Assessment of IVC hemodynamics**

IVC hemodynamics (size and collapsibility) were assessed using respirophasic changes in IVC diameter as stipulated in the American Society of Echocardiography guidelines for the assessment of right heart function.3 Normal IVC hemodynamics were defined as IVC diameter \( \leq 21 \) mm with \( \geq 50\% \) collapsibility during inspiration. On the basis of these criteria, we categorized all patients into 3 groups: (1) normal IVC hemodynamics; (2) mild/moderately abnormal IVC hemodynamics defined as IVC size > 21 mm or < 50% collapsibility during inspiration; (3) severely abnormal IVC hemodynamics defined as IVC size > 21 mm and < 50% collapsibility during inspiration. Offline image analyses and measurements were performed by an experienced sonographer (RP). To determine interobserver variability, a random sample of 100 images was reviewed by a second sonographer (JW) who was blinded to the assessment of the first sonographer.

**Cardiac magnetic resonance imaging**

For the purpose of this study, we created the CMRI risk model using the 4 CMRI volumetric indices that have been shown to have prognostic significance based on previous studies.2,3,14 The indices were RV end-diastolic volume index (RVEDVi), RV end-systolic volume index (RVESVi), RVEF, and LVEF. The protocol for volumetric assessment using CMRI at this institution has been described.12 All CMRI studies were performed on a 1.5-T system (Signa; GE Healthcare, Waukesha, WI) using an 8-element phased-array cardiac coil. Initial scout images were obtained, and this was followed by short-axis cine balanced steady-state free precession images obtained from the atrioventricular...
ring to the apex and then axial steady-state free precession images. RV and LV volumes and ejection fraction were obtained by manual tracing of endocardial borders from axial images at end-diastole and end-systole. RV stroke volume and ejection fraction were calculated from end-diastolic and end-systolic volumes. All volumetric data were abstracted from CMRI report and indexed to the body surface area.

**Outcomes assessment**

We assessed disease severity on the basis of a current or a history of any of the following: atrial arrhythmias, ventricular arrhythmias, or heart failure hospitalization at the time of CMRI assessment. Atrial arrhythmia was defined as sustained or nonsustained atrial fibrillation, atrial tachycardia, or atrial flutter recorded on electrocardiogram or Holter monitor. Atrial flutter and atrial tachycardia were considered as the same arrhythmia in this study because of the difficulty differentiating between both arrhythmias on surface electrocardiogram. Clinically, this macro-reentrant atrial arrhythmia is characterized by sudden onset and termination. Atrial fibrillation was defined by a lack of a constant atrial activity/p-wave with irregular ventricular activation.15

Ventricular arrhythmia was defined as sustained or nonsustained ventricular tachycardia recorded on electrocardiogram or Holter monitor. Nonsustained ventricular tachycardia was defined as greater than 3 consecutive ventricular beats, and sustained ventricular tachycardia was defined as greater than 30 consecutive ventricular beats.

Heart failure hospitalization was defined as hospitalization for volume overload requiring intravenous diuretics. Disease severity indices were ascertained by review of the medical records. Peak VO$_2$ was assessed using symptom-limited maximum effort cardiopulmonary exercise test with upright treadmill ergometer and respiratory exchange ratio $> 1.1.$16 Only exercise tests performed within 6 months from the time of CMRI were analyzed for this study.

Cardiovascular adverse event was defined as a combined end point of incident sustained ventricular tachycardia, aborted sudden cardiac death, heart transplant, or death occurring after pulmonary valve replacement. Sustained ventricular tachycardia was ascertained by review of electrocardiogram, Holter, and device interrogation reports. Heart transplant and death (all-cause mortality) were ascertained from the medical records and Accurint database in 100% of the patients as of December 31, 2018.

**Statistical analysis**

Data were presented as mean ± standard deviation, median (interquartile range), or number (%). The interobserver agreement between observer number 1 (RP) and observer number 2 (JW) was assessed using kappa coefficient (κ). Multivariable logistic regression analysis was used to assess the correlation between CMRI indices and disease severity indices, and between CMRI-IVC indices and disease severity indices. The CMRI risk model was created using the following predefined CMRI indices: RVEDVi, RVESVi, RVEF, and LVEF. The combined CMRI-IVC risk model was created using these 4 CMRI indices and IVC hemodynamics. IVC hemodynamics was modeled as a categorical variable (normal, mild/moderately abnormal, and severely abnormal IVC hemodynamics), and the normal IVC hemodynamic category was used as the reference.

Likewise, multivariable linear regression analysis was used to assess the correlation between CMRI indices and peak VO$_2$, and between CMRI-IVC indices and VO$_2$. Model comparisons were performed using area under the curve (AUC) for logistic regression models and Meng test for linear regression models. All models were adjusted for age, sex, age at the time of TOF repair, type of TOF repair (transannular patch repair vs others), tricuspid regurgitation severity (moderate or greater vs others), QRS duration, and TOF-pulmonary atresia diagnosis. We used manual backwards stepwise model selection based on likelihood ratio $P$ value, with $P < 0.25$ required for entry and $P < 0.1$ required to remain in the model.

Cox regression analysis was used to assess the correlation among predefined RVEF, LVEF, IVC hemodynamic indices, and cardiovascular adverse events occurring after pulmonary valve replacement in the subset of patients who underwent pulmonary valve replacement. These variables were modeled as binary variables: RVEF ($<30\%$ vs $\geq30\%$), LVEF ($<45\%$ vs $\geq45\%$), and IVC hemodynamics (normal vs abnormal [dilated IVC or reduced collapsibility]). The cutoff points for RVEF and LVEF were chosen on the basis of data from previous studies.2 The strength of association was assessed using hazard ratio (HR) and 95% confidence interval (CI). All statistical analyses were performed with JMP software (version 14.1.0; SAS Institute Inc., Cary, NC). A $P$ value $< 0.05$ was considered statistically significant.

**Results**

**Baseline characteristics**

A total of 207 patients met the study inclusion criteria. The median age was 27 (19-39) years, age at the time of TOF repair was 1.6 (0.8-4.5) years, and 54 patients (26%) had transannular patch repair (Table 1).

Of the 207 patients, 131 (63%) had normal IVC hemodynamics, 72 (35%) had mild/moderately abnormal IVC hemodynamics, and 4 (2%) had severely abnormal IVC hemodynamics. There was excellent interobserver agreement for IVC categories (κ 0.94, 0.86-0.98). The RVEDVi was 140 ± 44 mL/m$^2$, RVESVi was 78 ± 32 mL/m$^2$, RVEF was 45% ± 7%, and LVEF was 59% ± 9% (Table 1).

**Disease severity indices**

Of the 207 patients, 44 (21%) had a history of atrial arrhythmias, including 26 with atrial fibrillation, 45 (22%) had a history of ventricular arrhythmias, including 9 with sustained ventricular tachycardia, and 9 (4%) had prior heart failure hospitalizations. Altogether, 50 patients (24%) had at least 1 disease severity metric.

Tables 2 and 3 show the univariable and multivariable logistic regression models, respectively. The CMRI indices risk model had a modest correlation with disease severity (AUC, 0.68; 95% CI, 0.59-0.75). Compared with the CMRI risk model, the combined CMRI-IVC risk model had a better correlation with disease severity (AUC, 0.68; 95% CI, 0.59-0.74 vs AUC, 0.84; 95% CI, 0.78-0.91; $P = 0.006$). This suggests that the
Discussion

Right heart failure is a leading cause of mortality in adults with repaired TOF, and it usually results from chronic volume or pressure overload due to residual or recurrent RV outflow tract lesion.\(^2,3,8,14,17\) Pulmonary valve replacement is an effective therapy in this population, and the best outcome is achieved when it is performed at the onset of RV dysfunction to prevent progressive RV dysfunction and cardiovascular death.\(^2,3,8,14,17\) RV systolic function is routinely assessed using CMRI, and it is a central metric in determining the timing of intervention.\(^6,18\) A limitation of CMRI is that it does not provide an assessment of right heart filling pressures, which is an equally important component of right heart performance. In this study, we showed that compared with CMRI risk models, the combination of CMRI-IVC hemodynamics had better correlation with disease severity indices and exercise capacity. The assessment of IVC hemodynamics was reproducible as shown by excellent interobserver agreement, and IVC hemodynamics were associated with cardiovascular events similar to RVEF.

The prognostic role of CMRI has been demonstrated in several studies.\(^2,3,8,14,19-21\) RVESVI and RVEF inversely

combined CMRI-IVC risk model had more robust diagnostic performance to detect high-risk patients (patients with more severe disease) than the CMRI risk model alone.

Exercise test data were available in 142 patients (69%), and the mean peak VO\(_2\) was 25 ± 7 mL/kg/min (64% ± 9% predicted). In a multivariable model based on CMRI indices alone, the addition of IVC assessment had a better correlation with VO\(_2\) (r = 0.35, P = 0.042 vs r = 0.43, P = 0.031, Meng test P = 0.026) (Table 4).

An exploratory analysis was performed in the subgroup of 166 patients (80%) who underwent pulmonary valve replacement within 12 months from the time of CMRI to determine the predictors of cardiovascular adverse events. These 166 patients had a median follow-up of 98 (56-128) months. During this period, 5% had incident sustained ventricular tachycardia, of whom 1 patient presented as a case of aborted sudden cardiac death, 1 patient (0.6%) underwent heart transplant, and 6 patients died. The causes of death were sepsis and multiorgan failure (n = 1), sudden cardiac death (n = 1), heart failure–related death (n = 3), and endocarditis (n = 1). Altogether, cardiovascular adverse event end points occurred in 16 patients (10%). RVEF < 30% (hazard ratio, 1.12; 95% CI, 1.02-1.31; P = 0.039) and abnormal IVC hemodynamics (dilated IVC or reduced collapsibility (hazard ratio, 1.19; 95% CI, 1.06-1.46; P = 0.027) were associated with cardiovascular events. This suggests that the association between RVEF and cardiovascular adverse events was not significantly different from that of IVC hemodynamics and cardiovascular adverse events because of the overlap of the 95% CI of both estimates. There was no association between LVEF < 45% and cardiovascular adverse events (hazard ratio, 1.07; 95% CI, 0.88-1.35; P = 0.2). However, it is important to note that these estimates were based on univariate analyses, because we were unable to adjust for potential confounding because of the low event rate.

**Table 1.** Baseline characteristics (n = 207)

| Characteristic                        | Value       |
|--------------------------------------|-------------|
| Age, y                               | 27 (19-39)  |
| Male                                 | 103 (50%)   |
| Body mass index, kg/m\(^2\)          | 25 ± 5      |
| Body surface area, m\(^2\)           | 1.8 ± 0.4   |
| Age at TOF repair, y                 | 1.6 (0.8-4.5) |
| Prior pulmonary valve replacement    | 48 (23%)    |
| Comorbidities                        |             |
| Diabetes mellitus                    | 16 (8%)     |
| Hypertension                         | 32 (16%)    |
| Coronary artery disease              | 11 (5%)     |
| Chronic kidney disease               | 2 (1%)      |
| Medications                          |             |
| Loop diuretics                       | 17 (8%)     |
| RAAS antagonist                      | 33 (16%)    |
| Beta-blocker                         | 27 (13%)    |

Echocardiography

| Characteristic                        | Value       |
|--------------------------------------|-------------|
| Moderate or greater tricuspid regurgitation\(^a\) | 36 (17%)   |
| Moderate or greater RV enlargement\(^a\)    | 158 (76%)   |
| Moderate or greater RV systolic dysfunction\(^a\) | 38 (18%)  |
| Moderate or greater RA enlargement\(^a\)    | 99 (48%)    |
| RA volume index, mL/m\(^2\)              | 42 ± 14     |
| FAC, %                                 | 38 ± 9      |
| RV s', cm/s                            | 10 ± 2      |
| TAPSE, mm                              | 18 ± 4      |
| RV systolic dysfunction\(^1\) (n = 195) | 73 (37%)   |
| Tricuspid regurgitation velocity, m/s   | 3.0 ± 0.6   |
| Pulmonary valve peak velocity, ms       | 2.4 ± 0.8   |
| LVEF, %                                | 59 ± 8      |

Magnetic resonance imaging

| Characteristic                        | Value       |
|--------------------------------------|-------------|
| RVEDVi, mL/m\(^2\)                   | 140 ± 44    |
| RVESVi, mL/m\(^2\)                   | 78 ± 32     |
| RVSVi, mL/m\(^2\)                    | 62 ± 21     |
| RVEF, %                               | 45 ± 7      |
| LVSVi, mL/m\(^2\)                    | 42 ± 8      |
| LVEF, %                               | 59 ± 9      |

Data presented as mean ± standard deviation, median (interquartile range) or number (%). Chronic kidney disease was defined as stage ≥ III (creatinine clearance < 60 mL/min).

FAC, fractional area change; LVEF, left ventricular ejection fraction; LSVi, left ventricle stroke volume index; RA, right atrium; RAAS, renin angiotensin aldosterone system; RV, right ventricle; RVEDVi, right ventricle end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricle end-systolic volume index; RVSVi, right ventricle stroke volume index; s', tissue Doppler systolic velocity; TAPSE, tricuspid annular plane systolic excursion; TOF, tetralogy of Fallot.

\(^a\) Qualitative echocardiographic assessment.

\(^1\) RV systolic dysfunction based on quantitative assessment defined as FAC < 35% or s' < 10 cm/s or TAPSE < 16 mm.

**Table 2.** Univariable predictors of disease severity

| Predictor                                  | OR (95% CI) | P value |
|--------------------------------------------|-------------|---------|
| RVEDVi (per 10 mL/m\(^2\))                 | 1.01 (0.43-2.77) | 0.3     |
| RVESVi (per 10 mL/m\(^2\))                 | 1.05 (0.91-1.09) | 0.089   |
| RVEF (per 5% decrease)                     | 1.03 (1.01-1.06) | 0.032   |
| LVEF (per 5% decrease)                     | 1.05 (1.00-1.12) | 0.053   |
| Dilated IVC or reduced collapse            | 1.68 (1.12-2.23) | 0.027   |
| Dilated IVC and reduced collapse           | 2.17 (1.02-9.04) | 0.041   |
| Age (per 5 y)                              | 1.28 (1.27-1.47) | < 0.001 |
| Age of TOF repair (per 1 y)                | 1.06 (1.01-1.11) | 0.014   |
| Trans annular patch repair                 | 1.24 (0.66-2.35) | 0.7     |
| TOF pulmonary atresia diagnosis            | 0.92 (0.49-1.85) | 0.9     |
| QRS duration (per 10 ms)                   | 1.08 (0.86-1.91) | 0.3     |
| Moderate or greater tricuspid regurgitation| 5.03 (2.31-10.97) | < 0.001 |
| Male sex                                   | 0.91 (0.48-1.72) | 0.8     |

CI, confidence interval; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; OR, odds ratio; RVEDVi, right ventricle end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricle end-systolic volume index; TOF, tetralogy of Fallot.
correlate with the risk of cardiovascular adverse events, such as sustained ventricular arrhythmias and all-cause mortality. On the basis of these studies, CMRI indices are used to determine the optimal timing for pulmonary valve replacement and to identify high-risk patients who may benefit from other advanced heart failure therapies. In the current study, a combined CMRI-IVC risk model had more robust correlation with disease severity and exercise capacity compared with CMRI risk model alone, suggesting that right heart filling pressures provide complementary hemodynamic data beyond what is routinely measured by CMRI. We speculate that a combination of CMRI volumetric indices and noninvasive assessment of right heart filling pressures using IV C hemodynamics provides a more comprehensive hemodynamic assessment.

A potential application of the results of the study is in the risk stratification of symptomatic patients with RV volume overload. Although RV volume overload due to chronic pulmonary regurgitation is the most common pathophysiologic pathway for RV systolic dysfunction and symptomatic deterioration, there is significant variation in how well patients tolerate RV volume overload. Some patients with severe right heart enlargement remained asymptomatic for several years, whereas some become very symptomatic (exertional symptoms and arrhythmias) even in the setting of relatively modest RV dilation and preserved RV systolic function. We speculate that assessment of right heart filling pressure using IV C hemodynamics can help guide management in these patients because they provide complementary data beyond what is measured by CMRI (RV size and ejection fraction). In this subset of patients with symptoms out of proportion with the degree of RV dilation and systolic dysfunction, the presence of abnormal IV C hemodynamics should perhaps prompt an early referral for intervention if they have a target lesion or intensification of medical therapy in the absence of a target lesion.

### Study limitations

A limitation of the current study is the small sample size, which may limit the ability to detect significant differences in outcomes and limit our ability to perform important subgroup analyses. Another limitation of the study is that although it provides data for risk stratification, it is unknown if interventions based on the proposed risk models will result in better outcomes. Additionally, this is a retrospective single-centre study conducted on an older population with TOF, whose demographic characteristics may not reflect that of patients with TOF seen at other centres.

### Conclusion

The assessment of IV C hemodynamics is reproducible and complements CMRI volumetric indices. A combined CMRI-IVC risk model provides assessment of both systolic and diastolic function, and thus is a better reflection of disease severity status. Although the differences between the predictive values of the different models are modest, the central message is that the addition of IV C hemodynamics (which is a simple echocardiographic metric that is obtained as part of routine imaging) can improve the current risk-stratification models that are based on RV volumetric indices alone. Further studies are required to determine if interventions based on this combined risk model will lead to improvement in survival in this population.

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Table 3. Multivariable predictors of disease severity

| Model without IVC hemodynamics (AUC 0.68 [0.59-0.75]) | OR (95% CI) | P value |
|------------------------------------------------------|-------------|---------|
| RVESVi (per 10 mL/m²)                                |             |         |
| RVEF (per 5% decrease)                               | 1.03 (1.01-1.06) | 0.032 |
| LVEF (per 5% decrease)                               | 1.03 (0.93-1.18) | 0.094 |
| Age (per 1 y)                                        | 1.11 (1.03-1.26) | 0.018 |
| Age of TOF repair (per 1 y)                          |             |         |
| Moderate or greater tricuspid regurgitation           | 6.38 (2.53-9.03) | < 0.001 |

Table 4. Multivariable predictors of peak oxygen consumption

| Model without IVC hemodynamics [r = 0.35, P = 0.042] | β ± SE | P value |
|-----------------------------------------------------|--------|---------|
| RVESVi (per 10 mL/m²)                               | −0.18 ± 0.16 | 0.041 |
| RVEF (per 5% decrease)                              |         |         |
| LVEF (per 5% decrease)                              |         |         |
| Age (per 1 y)                                       | −0.12 ± 0.06 | 0.030 |
| Age of TOF repair (per 1 y)                         | −0.33 ± 0.19 | < 0.001 |

| Model with IVC hemodynamics [r = 0.43, P = 0.031] | β ± SE | P value |
|--------------------------------------------------|--------|---------|
| RVESVi (per 10 mL/m²)                             | −0.15 ± 0.21 | 0.074 |
| RVEF (per 5% decrease)                            |         |         |
| LVEF (per 5% decrease)                            |         |         |
| Dilated IVC or reduced collapse                   | −0.29 ± 0.17 | 0.041 |
| Dilated IVC and reduced collapse                  | −0.26 ± 0.29 | 0.1 |
| Age (per 1 y)                                      | −0.11 ± 0.07 | 0.032 |
| Age of TOF repair (per 1 y)                        |         |         |
| Moderate or greater tricuspid regurgitation        | −0.31 ± 0.28 | 0.001 |

beta coefficient; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; RVESVi, right ventricle end-systolic volume index; SE, standard error; TOF, tetralogy of Fallot.
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**Disclosures**

The authors have no conflicts of interest to disclose.

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