Kussmaul Physiology in Patients With Heart Failure

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Background—A paradoxical inspiratory rise in right atrial pressure (in contrast to the normal fall during inspiration), Kussmaul sign, has been described in congestive heart failure (CHF). However, the clinical and hemodynamic characteristics and clinical outcomes of patients with CHF and Kussmaul physiology have not been studied.

Methods and Results—This is a single-center study of consecutive ambulant patients with CHF (New York Heart Association class III/IV) referred for assessment for heart transplantation between November 2011 and April 2013. Kussmaul physiology was defined as inspiratory rise in right atrial pressure during right heart catheterization. Clinical, biochemical, echocardiographic, and hemodynamic correlates were studied and outcomes assessed in patients with or without Kussmaul physiology after a mean follow-up of 379±227 days. Ninety ambulant patients (age, 53±12 years; 86% men) with CHF were studied. Kussmaul physiology was demonstrated in 39 (43%) patients, and it was associated with higher pulmonary pressures and lower cardiac index and pulmonary capacitance (all P<0.05). Patients with Kussmaul physiology were more likely to be treated with higher doses of diuretics, while higher filling pressures, N-terminal pro-B natriuretic peptide levels, and hyponatremia reflected greater neurohormonal activation. Echocardiography revealed greater left and right ventricular dimensions/volumes, restrictive transmitral filling pattern, and lower left ventricular ejection fraction and lower tricuspid annular plane systolic excursion. Peak oxygen uptake was low and comparable in both groups, but ventilation slope was higher in patients with Kussmaul physiology who also had a higher incidence of post-transplant right ventricular failure and overall mortality (P<0.05).

Conclusions—Kussmaul physiology is common in patients with CHF referred for heart transplantation and is associated with adverse cardiopulmonary hemodynamics. As a result of the latter, Kussmaul physiology is associated with poorer clinical outcomes. Kussmaul physiology may be useful during assessment of right heart function and pulmonary pressures before transplantation. (Circ Heart Fail. 2014;7:440-447.)

Key Words: heart failure ■ heart transplantation

Elevated right atrial (RA) pressure is associated with renal impairment and increased mortality in patients with heart failure. Raised jugular venous pressure, as a bedside estimate of RA pressure, has similarly been shown to be associated with adverse outcome with increased heart failure hospitalizations and death. RA pressure (and jugular venous pressure) normally falls during inspiration despite an increase in pulmonary vascular resistance and venous return, as the right ventricle (RV) normally accommodates the increase in preload and increase pulmonary arterial flow. A paradoxical increase in jugular venous pressure was described by Adolf Kussmaul in 1873, and this is now an eponymous clinical sign that bears his name. Although widely reported as a clinical sign of constrictive pericarditis, Kussmaul sign has also been described in patients with heart failure.

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Inspiratory increase in RA pressure (Kussmaul physiology) has been attributed to an inspiratory increase in venous return into a noncompliant or constricted RV. However, the clinical and cardiopulmonary correlates of Kussmaul physiology in patients with heart failure have not been studied. The association with pulmonary hemodynamics have also not been studied. Hence, this study evaluated the clinical and hemodynamic correlates of Kussmaul physiology and the association with clinical outcomes in patients with advanced heart failure referred for heart transplantation.

Methods

Study Design and Patient Population

We prospectively included consecutive ambulant patients with heart failure (New York Heart Association class III or IV) who underwent in-hospital assessment for heart transplantation between November 2011 and April 2013 to the University Hospital Birmingham NHS Foundation Trust (Birmingham, United Kingdom). Patients with congenital heart disease or severe cardiogenic shock requiring inotropic support or urgent mechanical circulatory support (including intra-aortic balloon pump) were excluded from this study. Patients were initially evaluated in the outpatient clinic and would not undergo in-hospital assessment if significant contraindications were identified or if they were too well for transplantation. These patients...
were not included. Baseline demographic data, including information on the medical history and current use of medications, were collected from all the patients at the time of heart transplant assessment. Heart failure survival score (HFSS) and Seattle Heart Failure Model (SHFM) were calculated as previously described. The investigations/procedures were performed in accordance with our institution’s protocol for assessment for heart transplantation, and approval from the NHS Research Ethics Committee was not required.

**Cardiopulmonary Exercise Test**

Each patient underwent a supervised, progressively increasing, symptom-limited cardiopulmonary exercise testing (ramp protocol) on a treadmill. The ramp protocol was personalized to achieve a peak exercise of between 8 and 12 minutes. Ventilatory expired gas analysis was obtained with a metabolic cart (Powercube, Ganshorn Medizin Electronic). The oxygen and carbon dioxide sensors were calibrated before each test with gases with known oxygen, nitrogen, and carbon dioxide concentrations. The flow sensor was also calibrated before each test with a 3-L syringe. The oxygen uptake (VO₂), carbon dioxide production (VCO₂), and minute ventilation (VE) were collected throughout the exercise test. Peak VO₂ was expressed as the highest 30-second average value obtained during the last stage of the exercise test. Peak respiratory exchange ratio was the highest 30-second averaged value during the last stage of the exercise test. Ten-second averaged VE and VCO₂ data from the initiation of exercise (after the warm-up period) to peak exercise were used to calculate the VE/VCO₂ slope.

**Transthoracic Echocardiography**

Transthoracic echocardiography was performed in accordance with standard guidelines. The left ventricular (LV) end-systolic and end-diastolic volumes and ejection fraction were obtained by Simpson method from 2-dimensional apical images. The tricuspid annular plane systolic excursion was measured by M-mode in the apical view as a measure of RV function. Mitral and tricuspid regurgitation was quantified by Doppler in accordance with current recommendations. Restrictive mitral filling pattern was defined by an E/A ratio of >2 and an E-wave deceleration time of <140 milliseconds.

**Right Heart Catheterization**

RA, RV, pulmonary artery (PA), and pulmonary artery wedge pressures (PAWP) were recorded at end expiration with a balloon-tipped catheter. Kussmaul physiology is elicited by repeated full inspiratory effort at normal respiratory rate without breath-holding, forced respiratory effort, or Valsalva. To increase specificity, we defined Kussmaul physiology as an inspiratory rise in RA pressure. Cardiac output was measured by thermodilution (using an average of 3 measurements agreed within 10%) with cold, refrigerated injectate (5% glucose). Transpulmonary gradient (TPG) was calculated as follows: mean PA−mean PAWP. Pulmonary vascular resistance (PVR) in Wood units (WU) was calculated as follows: TPG/cardiac output. PA capacitance was calculated as follows: stroke volume/PA pulse pressure. RV stroke work was calculated as follows: stroke volume×(mean PA−mean RA pressure)×0.0136. The hemodynamic data were indexed for body surface area.

**Clinical Outcome**

We evaluated a post-transplant composite outcome of post-transplant death or RV failure. Unsuitability for heart transplantation because of pulmonary hemodynamics was defined by a systolic pulmonary pressure of >60 mm Hg and TPG and PVR of >12 to 15 and 5 WU, respectively, despite vasodilators (nitropressure). In addition, we evaluated a combined composite end point of all-cause mortality, need for ventricular assist device implantation, and post-transplant RV failure (defined as the need for RV mechanical support). Data on clinical outcome were collected prospectively with a mean follow-up of 379±227 days.

**Statistical Analyses**

Continuous variables are reported as mean±SD or median (interquartile range [IQR]) and categorical variables as proportions. Characteristics of patients with or without Kussmaul physiology were compared by the χ² test, Fisher exact test, or Wilcoxon rank test for categorical variables and by the t test or Mann–Whitney U test for continuous variables as appropriate. Cox proportional hazard model was used to assess univariable association with the clinical outcomes. In 2 separate models, we adjusted for the SHFM and HFSS but not the baseline variables because they are components of these 2 risk stratification schemes and assessed association of Kussmaul physiology with clinical outcomes. We constructed 2 Kaplan–Meier curves: one for composite end point (all-cause mortality, need for bridge to transplantation with ventricular assist device, and post-transplant RV failure) and another for all-cause mortality. Event-free survival was compared between groups using the Mantel-Cox log-rank test. All statistical analyses were performed using SPSS for Windows version 20, and a 2-sided P value of <0.05 was considered statistically significant.

**Results**

Ninety ambulant patients with heart failure were assessed for heart transplantation during the study period. Baseline characteristics of all patients are presented in Table 1. The cause of heart failure was dilated cardiomyopathy in 47 (52%) patients, ischemic cardiomyopathy in 27 (30%) patients, and restrictive cardiomyopathy in 8 (9%) patients. Forty-one patients (46%) had biventricular pacemakers with or without defibrillators, whereas 8 (9%) had an implantable cardiac defibrillator without biventricular pacemakers. Patients with Kussmaul physiology had higher calculated risk from the SHFM (2.177 [IQR, 0.847] versus 1.912 [IQR, 0.735]; P=0.09) and HFSS (7.478±0.872 versus 7.829±1.117; P=0.09).

**Kussmaul Physiology—Clinical and Hemodynamic Association**

Kussmaul physiology was demonstrated in 39 (43%) patients. There were no significant differences in age, sex, cause of heart failure, prevalence of diabetes mellitus and atrial fibrillation, and estimated glomerular filtration rate between patients with or without Kussmaul physiology. Patients with Kussmaul physiology were treated with higher doses of diuretics, had more severe mitral regurgitation, greater left and RV dimensions/volumes, were more likely to demonstrate restrictive mitral filling pattern on echocardiogram, had lower LV ejection fraction, and lower tricuspid annular plane systolic excursion (Table 1).

Peak VO₂ was low and comparable in both groups, but ventilation slope was higher in patients with Kussmaul physiology (46±7 versus 40±6; P<0.01). Patients with Kussmaul physiology had higher N-terminal pro–B natriuretic peptide level (3264 [IQR, 3747] versus 896 [IQR, 1922] pg/mL; P<0.01) and lower serum sodium (135±3 versus 138±3; P=0.02).

Cardiac catheter studies showed more adverse hemodynamics in patients with Kussmaul physiology, characterized by lower cardiac index and LV stroke work index, higher RA, PA, PAWP, TPG, and PVR. There were no significant differences in RV stroke work index between the 2 groups (Table 2). PA capacitance was significantly lower in patients with Kussmaul physiology (median, 1.40 [IQR, 0.57] versus 2.39 [IQR, 2.47] mL/mm Hg; P<0.01).
In a subgroup of 59 patients (29 patients with and without Kussmaul physiology) with comparable pulmonary pressures (PA systolic and diastolic pressure of 56±10 versus 53±11 and 29±5 versus 26±6, respectively), the main differences were higher RA pressure (18±5 versus 13±5 mmHg, *P*<0.01), higher RA:PAWP ratio (0.63±0.20 versus 0.53±0.12, *P*<0.01), and lower E/A ratio (2.3±0.9 versus 2.7±0.8, *P*<0.01).
0.51±0.20; \( P = 0.02 \), and lower stroke volume index (21±6 versus 24±6 mL/m\(^2\); \( P = 0.02 \)).

**Kussmaul Physiology—Heart Transplant Candidacy**

After assessment, 57 (63%) patients were deemed suitable for heart transplantation. Twenty-one patients (23%) were considered unsuitable for heart transplantation—high TPG, PA pressure, and vascular resistance were considered to be the reason for unsuitability for transplantation in 15 of the 21 cases. Patients who did not demonstrate Kussmaul physiology were more likely to be unsuitable for transplantation for reasons other than pulmonary hemodynamics (4/6 patients). Reasons included severe concomitant airways disease (n=1), diabetes mellitus with severe end-organ involvement (n=2), and extensive vascular disease (n=3).

Of the remaining 12 patients, 8 patients were thought to be too well (all without Kussmaul physiology) for transplantation, 2 patients required (and awaiting) further investigations, 1 patient underwent conventional surgery (low-flow, low-gradient aortic stenosis), and 1 declined transplantation. By virtue of its association with adverse pulmonary hemodynamics, patients with Kussmaul physiology were more likely to be unsuitable for heart transplantation and undergo implantation of ventricular assist device, initially as a bridge to candidacy (to improve pulmonary hemodynamics) and subsequently as a bridge to transplantation after improvement in pulmonary hemodynamics (Table 3).

**Kussmaul Physiology—Heart Transplantation and Mortality**

During follow-up, 32 patients (36%) underwent orthotopic heart transplantation: 10 in patients with and 22 in patients without Kussmaul physiology (Table 3). All 10 patients with Kussmaul physiology and 10 of the 22 patients were upgraded to the urgent list for heart transplantation because of progressive clinical deterioration (see Data Supplement for criteria for urgent listing). Post-transplant RV failure requiring mechanical circulatory support (5 RV assist device and 3 extracorporeal membrane oxygenation [ECMO]) occurred by guest on December 18, 2017 http://circheartfailure.ahajournals.org/Downloaded from
Table 3. Clinical Outcomes in Patients With and Without Kussmaul Physiology

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Kussmaul Positive (n=39)</th>
<th>Kussmaul Negative (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsuitable for transplant</td>
<td>14/39 (36%)</td>
<td>7/51 (14%)</td>
</tr>
<tr>
<td>Too well for heart transplantation</td>
<td>0 (0%)</td>
<td>8/51 (16%)</td>
</tr>
<tr>
<td>Heartmate II LVAD</td>
<td>5/39 (13%)</td>
<td>2/51 (4%)</td>
</tr>
<tr>
<td>Alive on waiting list without LVAD*</td>
<td>2/39 (5%)</td>
<td>6/51 (12%)</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplanted</td>
<td>10/39 (25%)</td>
<td>22/51 (43%)</td>
</tr>
<tr>
<td>Right ventricular failure</td>
<td>8/10 (80%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>post-transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death in patients</td>
<td>3/14 (21%)</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>unsuitable for transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-transplant death</td>
<td>4/10 (40%)</td>
<td>2/22 (9%)</td>
</tr>
<tr>
<td>Post-LVAD death</td>
<td>1/5 (20%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>Death on waiting list</td>
<td>8/25 (32%)</td>
<td>2/44 (4%)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>16/39 (41%)</td>
<td>6/51 (12%)</td>
</tr>
</tbody>
</table>

LVAD indicates left ventricular assist device.

*Excluding 4 patients without Kussmaul physiology (2 undergoing further investigations, 1 underwent conventional surgery, and 1 declined transplantation).

Discussion

Kussmaul physiology (as a bedside sign) has been reported in patients with heart failure, but there are no reports on the prevalence and clinical significance in patients with heart failure. This study has shown that Kussmaul physiology is common (when measured invasively) in patients with heart failure referred for heart transplantation, associated with adverse cardiopulmonary hemodynamics, and consequently also associated with poor clinical outcomes including RV failure after transplantation and higher overall mortality.

Cardiopulmonary Interaction in Kussmaul Physiology

This study did not specifically address the pathophysiologic mechanism of Kussmaul physiology. Previous studies in dogs suggest that hypervolemia and increased venous return via the inferior vena cava because of increase in intra-abdominal pressure (diaphragmatic descent) with inspiration is requisite for Kussmaul physiology. Animal studies suggest that resistance in PA increases during inspiration such that inspiratory RA pressure increase exceeds RV outflow. A compliant RV with normal contractile function normally accommodates the excess volume without an increase (indeed a fall) in RA pressure. However, RV afterload may prevent this accommodation. On the basis of our results, we speculate that reduced RA and RV compliance as a result of diastolic ventricular interaction and simply a function of operating at a steeper segment of the pressure–volume relation of the cardiac chambers (inferred from the association with elevated RA pressure, restrictive transmural Doppler filling pattern, and greater LV and RV dimensions) are central to Kussmaul physiology. An inspiratory increase in pulmonary resistance in the context of greater PVR and lower PA capacitance may exacerbate adverse RV afterload, reduce RV outflow, and contribute to further rise in RV filling pressure with increased venous return during inspiration.

We did not directly measure caval venous blood flow, but Kussmaul physiology did not seem to be mediated by greater absolute venous return. Venous return approximates cardiac output under steady-state conditions, which was lower in patients with Kussmaul physiology in this study. A plot of stroke volume index to RA pressure simulates the venous return curve described by Guyton. Although the interpretation of this curve has been debated, the relationship between cardiac output and RA pressure is unequivocal. The position of the x-intercept of this curve is determined by mean systemic filling pressure (ie, RA pressure in the absence of cardiac output), which is dependent of the circulating volume and vascular tone. The slope (steepness) of the curve is dependent on the resistance to venous return. The higher filling pressures, N-terminal pro-B natriuretic peptide levels, and hyponatremia reflect greater neurohormonal activation and
congestion, reduced RV compliance and contractile function, and increased afterload all of which would result in the shallower venous return slope and higher x-intercept in patients with Kussmaul physiology (2-sided $P=0.07$; Figure 2). Indeed, significant increase in right-sided filling pressures with reduced venous return would be consistent with the low operating RA and RV compliance.

**Cardiopulmonary Hemodynamics and Prognosis in Advanced Heart Failure**

The use of risk stratification tools, such as SHFM and HFSS, is routine in the selection of patients for heart transplantation. The SHFM and the HFSS contain several established risk factors for adverse outcome (eg, serum sodium and LV ejection fraction), but the discriminatory value of these risk stratification schemes seems to be modest particularly in patients with advanced heart failure. Crucially, these risk stratification schemes do not incorporate direct or indirect evaluation of right heart–pulmonary hemodynamics (eg, restrictive transmural filling pattern, higher VE/V$\text{CO}_2$ slope, and poorer RV function), which are established indices of adverse prognosis in heart failure. Using presence of Kussmaul physiology as a surrogate marker of adverse pulmonary hemodynamics, our data suggest that invasive assessment of cardiopulmonary hemodynamics may have additional clinical predictive value in patients with advanced heart failure, independent of both SHFM and HFSS. Of note, the adverse prognosis associated with Kussmaul physiology is not a result of undertreatment, as evidenced by significantly greater use of aldosterone antagonists and implantable defibrillators/biventricular pacemakers.
The use of respiratory maneuvers has a well-established precedence for diagnostic and therapeutic purposes. Similarly, Kussmaul physiology represents an unmasking of an underlying abnormal diastolic ventricular interaction and adverse right heart–pulmonary vascular interaction, which may not be evident on static measurement of cardiac filling pressures alone. The prognostic significance of abnormal right heart–pulmonary vascular interactions could be inferred from prior studies. Ghiotto et al. reported poorer outcomes in patients with heart failure referred for transplantation who had pulmonary hypertension, and the risk of adverse outcomes was greater in the presence of RV dysfunction. Similarly, therapy aimed at improving cardiopulmonary hemodynamics with reduction in RA pressure, PAWP, and pulmonary pressure (hemodynamic correlates of Kussmaul physiology) and increase in cardiac output with vasodilators can improve clinical outcomes.

Hence, our results confirm the clinical significance of invasive assessment of pulmonary hemodynamics, and the finding of Kussmaul physiology may offer complementary prognostic information in patients with advanced heart failure. Crucially, it is not possible to disentangle the prognostic implication of Kussmaul physiology from other invasive measures of pulmonary hemodynamics because Kussmaul sign is itself a product of adverse cardiopulmonary hemodynamic interaction.

High TPG and PVR, by imposing excessive afterload on an unaccustomed donor RV, are established risk factors for post-transplant RV failure. The risk of adverse outcomes rises with increasing PVR is a positive continuum. This would explain the higher incidence of post-transplant RV failure in patients with Kussmaul physiology. In addition, we postulate that abnormal heart–lung interaction may reflect the presence of greater pulmonary vascular disease that may modulate (increase) this relationship between TPG/PVR and post-transplant outcomes. In contrast to heart transplantation, LVAD has been used successfully in patients with severe, disproportionate, and apparently fixed pulmonary hypertension. Based on the aforementioned pathophysiological mechanism, the reduction in LV filling pressure by LVAD would be expected to reduce diastolic ventricular interaction and improve operant RV compliance. The reduction in PVR would also improve RV function. In this regard, our finding that patients with Kussmaul physiology have poor outcome from heart transplantation but not with LVAD offers the intriguing possibility that the underlying cardiopulmonary hemodynamic correlates of Kussmaul physiology may guide LVAD therapy. This would need to be confirmed on further investigations.

**Study Limitations**

This study has the inherent limitations of a relatively small, single-center observational study of patients referred for heart transplantation. However, potential biases should be minimized by the inclusion of consecutive patients prospectively. In addition, we defined Kussmaul physiology as an inspiratory rise in RA pressure. This definition may have increased specificity for more advanced pathophysiology at the expense of excluding milder forms of Kussmaul physiology (absence of inspiratory change in RA pressure), which may partly explain the results of our study. Specific measurement of the magnitude of pressure changes with respiration may provide additional insight into the cardiopulmonary interaction and deserve further investigations. Also, we assessed Kussmaul physiology by direct invasive measurement in contrast to bedside assessment of venous pressure. Bedside assessment of Kussmaul sign in patients with heart failure should afford similar results, but further investigation is necessary to confirm this. Finally, Kussmaul physiology is intimately and inextricably linked to pulmonary hemodynamics and as such should not replace the need for invasive assessment of the latter in the decision making regarding transplantation or ventricular assist device therapy.

**Conclusions**

Kussmaul physiology is common in patients with advanced heart failure referred for heart transplantation and associated with several unfavorable clinical, echocardiographic, biochemical, and cardiopulmonary hemodynamic parameters. As a result of these adverse cardiopulmonary hemodynamics, Kussmaul physiology is associated with higher risk of post-transplant RV failure and mortality but not after LVAD implantation. The latter finding deserves further study. Kussmaul physiology may be useful during assessment of right heart function and pulmonary pressures before transplantation.

**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

A paradoxical increase in jugular venous pressure was described by Adolf Kussmaul in 1873, and this is now an eponymous clinical sign that bears his name. Although widely recognized as a clinical sign of constrictive pericarditis, Kussmaul sign has also been described in patients with heart failure. Kussmaul physiology has been attributed to an inspiratory increase in venous return into a noncompliant or constricted right ventricle. In this study of patients with advanced heart failure undergoing transplant assessment, Kussmaul physiology (defined as inspiratory rise in right atrial pressure during right heart catheterization) was demonstrated in 43% of patients and associated with higher pulmonary pressures, lower cardiac index, and pulmonary capacitance. Patients with Kussmaul physiology were more likely to have been treated with higher doses of diuretics and have more evidence of neurohormonal activation such as higher N-terminal pro-B natriuretic peptide levels and hypotension. Kussmaul physiology was also associated with higher incidence of post-transplant right ventricular failure and overall mortality. This study has shown that Kussmaul physiology is common (when measured invasively) in patients with heart failure referred for heart transplantation, associated with adverse cardiopulmonary hemodynamics and poor clinical outcomes including right ventricular failure after transplantation and higher overall mortality.
Supplemental Material

UK Cardiothoracic Advisory Group of NHS Blood and Transplant criteria for Urgent Listing for Heart Transplantation

Need for continuous inotropic treatment at high dose or in combination

Intraaortic balloon pump with or without inotropic support

Mechanical circulatory support with a short-term device including venoarterial extracorporeal membrane oxygenation

Long-term LVAD support with device-related complications

Exceptional cases out with these criteria may be listed with permission from the chair of the advisory group