Analysis of right ventricular function in healthy mice and a murine model of heart failure by in vivo MRI

FRANK WIESMANN,1 ALEX FRYDRYCHOWICZ,1 JUDITH RAUTENBERG,1 RALF ILLINGER,1 EBERHARD ROMMEL,2 AXEL HAASE,2 AND STEFAN NEUBAUER3

1Medizinische Universitätsklinik and 2Physikalisches Institut, Universität Würzburg, 97080 Würzburg, Germany; and 3Department of Cardiovascular Medicine, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, United Kingdom

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Wiesmann, Frank, Alex Frydrychowicz, Judith Rautenberg, Ralf Illinger, Eberhard Rommel, Axel Haase, and Stefan Neubauer. Analysis of right ventricular function in healthy mice and a murine model of heart failure by in vivo MRI. Am J Physiol Heart Circ Physiol 283: H1065–H1071, 2002.—Because of its complex geometry, assessment of right ventricular (RV) function is more difficult than it is for the left ventricle (LV). Because gene-targeted mouse models of cardiomyopathy may involve remodeling of the right heart, the purpose of this study was to develop high-resolution functional magnetic resonance imaging (MRI) for in vivo quantification of RV volumes and global function in mice. Thirty-three mice of various age were studied under isoflurane anesthesia by electrocardiogram-triggered cine-MRI at 7 T. MRI revealed close correlations between RV and LV stroke volume and cardiac output (r = 0.97, P < 0.0001 each). Consistent with human physiology, murine RV end-diastolic and end-systolic volumes were significantly higher compared with LV volumes (P < 0.05 each). MRI in mice with LV heart failure due to myocardial infarction revealed significant structural and functional changes of the RV, indicating RV dysfunction. Hence, MRI allows for the quantification of RV volumes and global systolic function with high accuracy and bears the potential to evaluate mechanisms of RV remodeling in mouse models of heart failure.

mouse heart; magnetic resonance imaging; ventricular remodeling; transgenic mice

WITH REGARD TO THE ROLE OF the right ventricle (RV) in the pathogenesis of chronic heart failure (4), it has been proposed that RV function may be a better guide to functional state (1) and prognosis (16, 35) than left ventricular (LV) function, particularly in patients with ischemic and valvular heart disease (12). Whereas quantification of LV volumes and function in mice by high-resolution magnetic resonance (MR) imaging (MRI) can be performed with high accuracy (21, 26, 30), assessment of RV morphology is much more difficult. This is due to the complex geometry of the RV with a wide angulation between inflow and outflow tract, its relatively coarse trabecularization, and the complexity of RV contraction as well as the unpredictability of changes in its dimensions under pathophysiological conditions (3, 14).

Unlike for the intact LV, where geometric models such as the truncated ellipsoid can be applied for volumetric calculations, a variety of assumptions has been suggested for RV shape, including the crescent, pyramidal, ellipsoidal, or prism models (7, 8). However, all of these models do not entirely apply to the asymmetric shape of the RV and are therefore unsuitable for RV volume calculations.

Attempts to evaluate RV function by echocardiography are limited by the difficulty in delineating its endocardial surfaces (10). Because of the position of the normal RV immediately beneath the sternum, the feasibility of echocardiographic assessment of the RV depends strongly on the acoustic window. Radionuclide ventriculography suffers from limitations due to restricted spatial resolution and difficulties in compartmentation due to chamber overlap (9).

MRI as an intrinsically three-dimensional imaging technique allows for volume measurements without relying on geometric assumptions (5, 6, 25). Successful quantification of RV volumes and function by MRI has been reported in both healthy volunteers (11, 15, 24, 31) and patients with hypertrophic and dilated cardiomyopathy (28, 29).

Given that the number of gene-targeted mouse models of heart failure is growing rapidly, there is currently a lack of suitable analytic tools to noninvasively assess the consequences of genetic modifications on changes of murine RV structure and function in chronic heart failure models. Hence, purpose of this study was threefold: 1) to test for the feasibility of high-resolution MRI for quantification of RV volumes and performance, 2) to evaluate the accuracy and reproducibility of RV measurements, and 3) to apply the MR technique in a model of murine heart failure for detection of RV dysfunction.

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METHODS

Mouse preparations. Thirteen healthy C57bl/6 mice (both genders) of varying ages (20 ± 12 wk, range 14–57 wk) and weights (34 ± 2 g, range 22–50 g) were anesthetized by applying 1.5 vol% isoflurane via a nose cone at 1.5 l/min oxygen flow as previously described (21). For electrocardiogram (ECG) triggering, two copper ECG electrodes were attached to the front paws. The ECG signal was detected by a home-built ECG unit equipped with multiple filters and a trigger module to accurately detect R-waves as well as to enable respiratory gating (20). The mean heart rate was 461 ± 14 beats/min (range 375–550 beats/min). Throughout the experiment, all mice were positioned supine on a non-magnetic warming pad to maintain a constant body temperature within the scanner. In a separate study, 12 C57BL/6 mice (7 male and 5 female, range 22–28 g body wt) were investigated by MRI for validation of in vivo MR-determined RV myocardial mass against ex vivo RV wet weight at autopsy. In addition to inter- and intraobserver variability assessment in all mice investigated, three mice were studied by MRI on consecutive days for evaluation of interstudy reproducibility of MR measurements of RV volumes. For detection of RV structural and functional changes with MRI, five male C57bl/6 mice with global heart failure due to LV myocardial infarction (MI) after left anterior descending (LAD) coronary artery ligation were also examined [surgical procedure described in detail previously (32)]. MR-determined measurements in this MI group were compared with results from age- and weight-matched healthy mice. All experimental procedures were accomplished according to institutional guidelines and were approved by local authorities.

NMR imaging. In vivo NMR studies were performed on a 7.05-T horizontal-bore MR scanner (BRUKER), which was equipped with a 60-mm microscopy gradient system capable of 870 mT/m gradient strength and a rise time of 280 μs at complete gradient switching. For transmission and reception of signal, a birdcage probe head with an inner diameter of 35 mm was used.

MRI experiments were conducted by applying an ECG-triggered fast gradient echo cine sequence (FLASH) with the following imaging parameters: echo time, 1.6 ms; repetition time, 4.3 ms; field of view, 3.0 cm²; acquisition matrix, 256 × 256; maximal in-plane resolution, 117 μm²; and slice thickness, 1.0 mm.

The temporal resolution per acquired cine frame performing FLASH MRI was 8.6 ms. Hence, data acquisition was done with a sampling rate of ~115 Hz. At a heart rate of 550 beats/min, the corresponding cardiac cycle length was 109 ms, allowing for acquisition of 12 cine frames within each cardiac cycle with the given temporal resolution of 8.6 ms.

For correct image plane localization, scout images in a transverse and coronal plane and subsequently in the vertical and horizontal LV long-axis orientation were acquired. On the basis of the horizontal long-axis plane, multiple contiguous short-axis slices without an interslice gap were acquired positioned orthogonal to the interventricular septum to depict both the LV and RV as accurately as possible and to minimize partial volume effects. Typically, 11 ± 1 slices with 10–14 frames depending on the length of the R-R interval were acquired for a complete coverage of both the right and left heart.

Data analysis. For all slices, both end-diastolic and end-systolic frames were visually determined by taking into account the filling size of all chambers as well as the wall thickening patterns. In almost all experiments, the first cine frame after triggering on the QRS was the frame with maximal ventricular cavity area and, hence, referred to as end diastole. However, in two mice studied, the last cine frame acquired within the cardiac cycle exhibited the largest ventricular slice volume and was therefore chosen as end diastole. This was due to a reduced R amplitude in these mice, so that the trigger point was on the peak of the R-wave instead on the ascending R-wave limm, resulting in a delayed initiation of data acquisition. End systole was referred to as the cine frame with minimal ventricular cavity volume and maximal myocardial thickness in each single slice. RV and LV cavity measurements in diastole and systole were performed for each slice by delineating the endocardial borders, distinguishable by the strong MRI-derived intrinsic contrast between blood and myocardium.

Total ventricular volumes were calculated applying Simpson’s rule. The parameters to be analyzed were calculated as follows: stroke volume (SV), equal to end-diastolic volume (EDV) minus end-systolic volume (ESV); ejection fraction, equal to SV divided by EDV; and cardiac output, equal to SV multiplied by heart rate. RV free wall thickness and ventricular diameters were measured in a midventricular (equatorial) slice. RV diameters are given as endocardial diameters and were evaluated in a septolateral direction, crossing the interventricular septum orthogonally. RV myocardial mass was calculated from the multiplication of total RV myocardial volume with the specific gravity of myocardium (1.05 g/cm³).

Statistical analysis and evaluation of reproducibility. LV evaluation was performed by one observer (F. Wiesmann); RV measurements were accomplished by two independent examiners (F. Wiesmann and A. Frydrychowicz) and repeated twice by one observer (A. Frydrychowicz). There was a 6-wk time interval between evaluation rounds to avoid memory effects. Statistical analysis was performed using StatView (Abacus). A paired Student’s t-test was used for direct comparison of LV and RV parameters. Regression analysis was used to test for correlation of LV and RV volume measurements. Values of P < 0.05 were considered significant. Bland-Altman analysis for intra- and interobserver variability was carried out by comparing differences in assessed RV and LV volumes with the mean of RV and LV volume comparisons. All results are given as means ± SE.

RESULTS

Average study duration including the experimental setup and mouse preparation was between 60 and 90 min. The heart rate was kept constant during the experiment at a mean of 461 ± 14 beats/min. All mice survived the experiment and recovered quickly after cessation of anesthesia.

Scout images of coronal and long-axis planes afforded a detailed and comprehensive overview over the murine cardiovascular anatomy (Fig. 1). In all 33 mice studied, there was good image quality with clear delineation of endocardial and epicardial borders. Hence, cine MRI allowed for a detailed visualization of systolic RV wall motion and contraction not only in apical and midventricular but also in basal slice orientation (Fig. 2).

LV-RV comparison. Table 1 reveals the results of MRI-determined measurements of RV and LV volumes. Comparison of LV and RV stroke volumes and of cardiac output showed nearly identical values [P = not significant (NS) each], as expected under physiological conditions.
conditions, where LV SV equals RV SV as long as all valves are competent. Furthermore, we found a close correlation in comparing LV and RV SV ($r = 0.97$, $P < 0.0001$; Fig. 3A). Bland-Altman analysis for testing the degree of measurement agreement between RV and LV SV revealed a mean difference of 0.4 μl between RV and LV SV with close limits of agreement (±4.2 μl, representing ±2 SD; Fig. 3B). Consistent with human physiology, RV EDV and ESV were significantly higher compared with LV volumes ($P < 0.05$ each). In parallel, the RV ejection fraction tended to be lower than the LV ejection fraction ($P < 0.06$). LV endocardial diameter (measured in the septolateral direction) was 3.7 ± 0.1 mm at end diastole and 2.0 ± 0.2 mm at end systole. MRI revealed a mean LV wall thickness of 0.81 ± 0.05 mm in end diastole and 1.39 ± 0.14 mm at end systole. Hence, the relative systolic wall thickening of the LV myocardium was 71 ± 12%.

Fig. 1. A: end-diastolic magnetic resonance (MR) image in coronal plane orientation as a scout for MR data acquisition in multiple contiguous slices orthogonal to the interventricular septum. B and C: end-diastolic short-axis slices at the midventricular level (B) and basal slice position (C) with detailed visualization of the cardiac compartments. The small circular structures at the bottom of B and C are the tubes of the circulating water warming pad, visualized as cross sections. RV, right ventricle; LV, left ventricle; PM, papillary muscles; RVOT, RV outflow tract; TV, tricuspid valve; AO, aorta; LA, left atrium; RA, right atrium.

Fig. 2. Midventricular short-axis cine MR frames at end diastole (a) and end systole (b) and diastolic and systolic cine MR images at the level of the RVOT (c and d). Dotted lines demonstrate the cropped areas for RV volume evaluation.
Analysis of intraobserver reproducibility of MRI-determined RV volumes revealed a variability of 4.71 µl or 5.7% for RV EDV, 2.94 µl or 9.1% for RV ESV, and 3.72 µl or 7.9% for RV SV, respectively. Evaluation of interobserver variability showed a difference of 6.10 µl or 7.0% for RV EDV, 4.76 µl or 14.8% for RV ESV, and 3.99 µl or 7.7% for RV SV, respectively. Interstudy variability assessed in three mice investigated by MRI on consecutive days was 2.95 µl or 4.8% for RV EDV, 1.38 µl or 5.0% for RV ESV, and 1.57 µl or 5.5% for RV SV, respectively.

Comparison of in vivo MR-determined RV myocardial mass with ex vivo RV wet weight assessed at autopsy showed no significant differences (26.8 ± 1.8 vs. 23.1 ± 1.4 mg after autopsy, \( P = \text{NS} \)). Furthermore, regression analysis revealed a close correlation between MR-determined and autopsy RV mass (\( y = 1.53 + 1.22x, r = 0.96, P < 0.0001 \)). However, there was a slight but systematic overestimation of RV mass by MRI with a mean absolute difference of 3.7 µl and a mean relative difference of 12.9% compared with the ex vivo RV mass.

RV changes in a murine model of heart failure. In mice with chronic LV myocardial infarction due to LAD coronary artery ligation, there was gross dilatation of the LV with the formation of a large anterior-apical aneurysm. LV EDV (157.4 ± 9.3 vs. 68.0 ± 3.5 µl, \( P < 0.0001 \)) and ESV (122.8 ± 10.8 vs. 23.3 ± 3.6 µl, \( P < 0.0001 \)) were significantly increased compared with healthy mice. LV SV (34.6 ± 3.3 vs. 44.7 ± 2.7 µl, \( P < 0.05 \)) as well as LV ejection fraction in mice with MI (22.6 ± 2.9% vs. 66.4 ± 3.9%, \( P < 0.0001 \)) were significantly reduced compared with healthy controls, indicating global LV dysfunction. Mean LV infarct size was 54 ± 3%. Concomitant with these LV changes, MRI also showed significant alterations in RV geometry and function (Fig. 4). There was a significant reduction of RV SV (26.1 ± 4.0 vs. 46.7 ± 2.3 µl, \( P < 0.01 \)) and cardiac output (10.3 ± 1.3 vs. 21.9 ± 1.2 ml/min, \( P < 0.001 \)) in the MI group compared with healthy mice. In contrast to LV dilatation due to MI, there was no significant difference for comparison of RV EDV in mice with MI compared with healthy controls (69.8 ± 4.6 vs. 81.5 ± 3.9 µl, \( P = \text{NS} \)). However, there was a trend toward higher RV ESV in infarcted hearts compared with normals, but without reaching statistical significance (43.7 ± 2.8 vs. 34.7 ± 2.6 µl, \( P = 0.16 \)). MR imaging showed a >100% increase in RV diastolic wall thickness (\( P < 0.0001 \)) in mice with MI, representing RV myocardial hypertrophy (Table 2). Furthermore, there was a massive reduction in RV systolic wall thickening in mice with MI (\( P < 0.0001 \)), indicating...
impaired RV contractility. This finding was supported by a significant decrease of the RV ejection fraction ($P < 0.001$). Similar to increased RV ESV, MR measurements of RV endocardial dimensions revealed a significant increase of RV systolic diameter ($P < 0.05$), reflecting geometric alterations of the RV in response to LV dysfunction (Table 2). Furthermore, there was a significant reduction in RV systolic diameter shortening in mice with MI ($P < 0.0001$), indicating involvement of the RV after the LV remodelling process.

**DISCUSSION**

Despite a large body of research in the field of heart failure, the role of the right heart for the failing cardiovascular system remains to be fully defined. Experimental studies in the early 1940s showed an absence of any functional impairment in canine hearts after electrocauter damage of the free RV wall (27). Approximately 20 years later, Sade and Castaneda (22) concluded from the success of RV bypass procedures for tricuspid atresia that the RV is “dispensable.” However, it rapidly became clear, e.g., from negative long-term results of the Fontan operation, that this may have been an oversimplification. In the past 10 years, it has become increasingly apparent that RV dysfunction is a significant prognostic factor. For example, Zehender et al. (35) reported a significantly poorer prognosis in patients with infarct involvement of the RV independent from LV function.

Far more has been published on the role of LV dysfunction than on RV dysfunction in both acquired and congenital heart disease. However, awareness of the functional relevance of the RV in maintaining the circulation is increasing (14), aided by recent improvements in imaging techniques allowing us to study the right heart more accurately.

Although advances in three-dimensional echocardiography are beginning to show promising results in quantitative imaging, the current gold standard for cardiac volumetry clearly is the MRI. As a tomographic imaging technique, it offers free choice of the imaging plane without restrictions and allows for three-dimensional data acquisition with high temporal and spatial resolution.

This is the first report on the feasibility of high-resolution MRI for quantification of RV volumes and performance in the living mouse. Comparison of MR-determined measurement of RV SV revealed close agreement with the internal standard of LV SV. Because of the adaptation of both MR hardware as well as pulse sequences to the requirements of the mouse heart, resulting in high temporal and spatial resolution, we obtained an accuracy of RV volume quantification similar to that reported in human MRI studies (5, 19, 31). A recently published murine transoesophageal echocardiographic study using an intravascular ultrasound catheter reported close correlation between two-dimensional echo-derived and flow-probe cardiac output and high accuracy in the quantification of RV cast volume (23). However, RV volume measurements by transesophageal echocardiography have revealed a significantly higher intra- and interobserver variability (difference in SV of 10.3 ± 13.6% and 13.5 ± 20.0%, respectively) than what was found in this study for

**Table 2. MRI measurements of RV dimensions and wall thickness in control mice and mice with MI**

<table>
<thead>
<tr>
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<th>Control (n = 10)</th>
<th>MI (n = 5)</th>
<th>P Values</th>
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<tbody>
<tr>
<td>Body mass, g</td>
<td>29.9 ± 6.5</td>
<td>28.8 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>RV diastolic wall thickness, mm</td>
<td>0.34 ± 0.87</td>
<td>0.76 ± 0.21</td>
<td>&lt;0.0001</td>
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<tr>
<td>RV systolic wall thickness, mm</td>
<td>0.81 ± 0.12</td>
<td>0.82 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>RV systolic wall thickening, %</td>
<td>142 ± 45</td>
<td>16 ± 36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV diastolic diameter, mm</td>
<td>2.03 ± 0.24</td>
<td>1.76 ± 0.68</td>
<td>NS</td>
</tr>
<tr>
<td>RV systolic diameter, mm</td>
<td>1.09 ± 0.15</td>
<td>1.53 ± 0.61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RV systolic diameter, reduction, %</td>
<td>46.4 ± 4.7</td>
<td>13.1 ± 11.9</td>
<td>&lt;0.0001</td>
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Values are means ± SE; n = no. of mice. RV diameters were measured in the septolateral direction. MRI, magnetic resonance imaging; MI, myocardial infarction; NS, not significant.
MRI. The reproducibility of RV volume quantification in the present study is slightly lower than that of MR-derived LV volume measurements reported earlier (21), but this is not surprising given the complex geometry of the right heart. Whereas delineation of endocardial borders in the RV can be easily done in midventricular imaging planes, assessment of the cardiac structures is much more complex in basal slices. This is mainly due to the significant through-plane motion of the heart with the appearance of the right atrial compartment within the imaging plane. In parallel to LV volumetry, detailed observation of motion components in the MR images by cine-mode display is crucial for the decision making. Furthermore, delineation of the RV outflow tract from the proximal pulmonary artery can often only be done by careful analysis of the basal cine slice. Nevertheless, the complex shape of the RV still makes volumetric analysis more difficult than that for the left heart. This can also be seen from the validation of in vivo MR-determined RV mass against RV wet weight at autopsy. Our comparison revealed a continuous overestimation of RV mass by MRI. This systematic error is most likely due to partial volume effects in the basal slices, where the RV wall runs oblique to the imaging plane. Additionally, correct separation of the RV from the right atrium in these basal slices is often difficult due to significant through-plane motion of the atrium during systole. Comparison of LV and RV SV also showed slight variations in mice with MI. One potential source for these differences might be the choice of end systole in this study being defined as the minimal ventricular cavity volume in each single slice acquired. This approach was chosen to correct for any potential variations of the cardiac cycle length during the data acquisition in multiple contiguous short-axis slice covering the entire heart from apex to base. Nevertheless, this might explain some of the variations between RV and LV SV in the infarcted animals.

With the given temporal resolution of the FLASH cine sequence used, the average cine image sampling rate was 12 cine frames per cardiac cycle. Because we aimed for maintenance of physiological heart rates by the use of isoflurane anesthesia, we were limited in the number of image samplings per cardiac contraction and relaxation. However, the down side of this imaging strategy is at time missing true end diastole and end systole. This again might result in some degree of measurement error during volumetric quantification of cardiac compartments.

One possible solution to overcome this restriction could be the use of advanced imaging sequences allowing for ultrafast data sampling. However, in this study, we were limited in our choice of fast MRI sequences. As the 300-MHz scanner used in this study is equipped with unshielded gradients, our efforts to establish rapid imaging using a fast steady state of free precession sequence were hampered by severe image artefacts. Because of these hardware limitations, we had to choose a conventional gradient echo sequence, which, however, allowed for reliable data acquisition with sufficient temporal and spatial resolution.

Because we were interested in the feasibility of quantification of RV volumes and mass by MRI, we performed MR imaging in a group of mice with a wide range of ages and body weights (between 22 and 50 g). MRI allowed for high image quality with clear definition of the anatomic structures in all mice studied. Furthermore, there was high accuracy and reproducibility of RV volumetric measurements. In a previous study, we were able to demonstrate that by adapting imaging parameters, such as in-plane image resolution, slice thickness, and number of signal averages, to the size of the studied mouse, sufficient image quality can be achieved not only in adult but also in juvenile and even newborn mice (33). Hence, in vivo MR volumetry in the murine heart is not limited to a certain age or size but is feasible even in very young and small mice, provided that MR imaging parameters are adapted to the small size of the cardiac structures.

To assess potential interspecies differences of right heart morphology and function between men and mice, we compared the structural and functional findings of this study with the human physiology data published for the right heart. MRI revealed significantly higher EDV and ESV in the studied mice compared with LV volumes, which is in agreement with human studies (24, 34). Hence, the RV ejection fraction also tended to be lower than the LV ejection fraction, without reaching statistical significance (P = 0.06). The fact that human and mouse RV physiology are similar suggests that mouse models of RV dysfunction are relevant for understanding human RV pathophysiology. Presently, the mechanisms of RV remodeling are poorly understood, and therapeutic options for treatment of chronic RV failure are sparse. Potential therapeutic strategies such as endothelin-A blockade showed promising reductions of pulmonary hypertension in rats (13, 17), whereas effects on RV remodeling have not yet been studied, due to the lack of suitable analytic tools.

Here, MRI as a noninvasive tomographic imaging method allowing for free choice of Imaging plane may play a pivotal role in future studies. Applying high-resolution MR cine imaging in a murine model of LV heart failure due to MI in this study, we were able to demonstrate the feasibility of MRI to evaluate structural and functional changes of the right heart. The high temporal and spatial resolution in this study allowed for clear visualization of the cardiac anatomy and for quantification of the changes in RV volumes, wall thickness, and contraction. As expected and in accordance to human MI studies (2, 18), we found changes in murine RV volumes and wall thickness, reflecting the remodeling process of the RV concomitant to LV dilatation. Furthermore, there was significant impairment of RV contraction with reduced ejection fraction and overt wall motion abnormality of the RV myocardium, providing additional evidence of marked involvement of the right heart in the postinfarction remodeling process. These findings underline
the potential of MRI for in vivo evaluation of both RV and LV pathophysiology in the mouse.

Hence, our present study demonstrates for the first time the capability of high-resolution MRI for in vivo quantitative assessment of RV morphology and function in normal mice and in mice with biventricular remodeling after MI. The future application of the described method in transgenic or gene-targeted mouse models in combination with murine models of RV dysfunction should contribute new insights into the determinants of RV remodeling and failure.

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