Phase-contrast cine MRI (PC-MRI) is the current gold standard for the noninvasive measurement of vessel blood flow and is widely used in the hemodynamic assessment of children with congenital heart disease. However, the application of PC-MRI to the measurement of human fetal blood flow has only recently become possible with the development of alternatives to conventional ECG gating. Potential approaches to achieving triggered fetal cardiac imaging include self-gating and cardiotocographic gating, which have both recently been shown to be feasible in fetal lambs, with the latter used to make PC-MRI measurements. Metric-optimized gating (MOG) is a retrospective technique that acquires temporally oversampled data and then iteratively sorts the data using hypothetical ECG trigger times until artifact in the associated images is minimized. PC-MRI with MOG has been shown to be feasible in the late-gestation human fetus and validated using an in vivo simulation of fetal vessels. It has been used successfully to make preliminary observations of redistribution of the fetal circulation in human fetuses with left-sided congenital heart disease, transposition, and late-onset intrauterine growth restriction.

Clinical Perspective on p 670

However, to identify changes in regional blood flow in conditions such as congenital heart disease and placental insufficiency, it is essential first to define reference physiological ranges of fetoplacental flow using this technique. This report details PC-MRI measurements made in each of the major fetal blood vessels in 40 late-gestation human fetuses and provides preliminary means and reference ranges for the late-gestation human fetus. A wide range of variability in the way blood is streamed through the fetal circulation was found in foramen ovale shunting suggests a degree of variability in the way blood is streamed through the fetal circulation.

Methods

A single-center prospective cross-sectional study was conducted to establish normative ranges of blood flows in the late-gestation human fetus using PC-MRI with MOG.
Study Participants
The study was performed with the approval of the institutional review board, and subjects gave informed consent. Pregnant women with a family history of congenital heart disease were screened with a detailed echocardiogram at around 20 weeks’ gestation according to guidelines published by the American Society of Echocardiography. Subjects with normal studies were invited to attend for a second echocardiogram and MRI at term. Pregnancies complicated by maternal chronic illnesses, including diabetes mellitus, hypertension, and maternal autoimmune disease, as well as fetuses with any complication such as intrauterine growth restriction, multiple gestations, and known or expected aneuploidy, were excluded.

Imaging Protocol
Fetal MRI was performed according to a previously published technique using a 1.5T MRI system (Avanto; Siemens, Erlangen, Germany). Briefly, the fetal weight was calculated using segmentation of a 3-dimensional steady-state free precession acquisition of the whole fetus to measure the fetal volume (Mimics; Materialise Group, Leuven, Belgium). The weight was derived from the volume using the previously published conversion: fetal weight (g)=fetal volume (mL)×1.03+120.12. After localization of the fetus, steady-state free precession surveys were performed in 3 orthogonal planes to the fetal thorax. These were used to prescribe the PC-MRI acquisitions, which were aligned perpendicular to the long axis of the main pulmonary artery (MPA), ascending aorta (AAo), superior vena cava (SVC), ductus arteriosus (DA), descending aorta (DAO), umbilical vein (UV), right pulmonary artery (RPA), and left pulmonary artery (LPA) based on 2 orthogonal views. The UV was targeted in its mid-intrahepatic section, distal to the umbilical insertion to avoid complex flow behavior but proximal to any portal vein branches. The image parameters used for PC-MRI acquisitions were as follows: slice thickness, 5 mm; field of view, 240 mm; phase field of view, 100%+33% phase oversampling; matrix size, 192×192; voxel size, 1.25×1.25×5 mm; echo time, 2.92 ms; repetition time, 6.55 ms; flip angle, 20°; 1 average and 4 views per segment. This results in a temporal resolution of ±50 ms giving ±10 true cardiac phases, which were interpolated to 15 calculated phases. A velocity sensitivity of 150 cm/s was used for AAo, MPA, DAO, DA; 100 cm/s for SVC, RPA, and LPA; and 50 cm/s for UV. A typical scan time for each vessel was 34 seconds, with a total scan time of ±90 minutes. Using software created in our laboratory (MATLAB; MathWorks), the correct R–R intervals for each acquisition were determined retrospectively by MOG using raw data acquired at an R–R interval of 545 ms to ensure fetal heart rates down to 110 beats per minute were adequately oversampled for correct reconstruction. The details of MOG are given in previous publications. The reconstructed images were postprocessed on a commercial software package for flow quantification (Q-flow 5.2; Medis Medical Imaging Systems, Leiden, the Netherlands). The total postprocessing time for each study including fetal weight estimation was ±90 minutes.

The morphology of the fetal hearts was assessed at the initial echocardiogram using a segmental sequential analysis of the anatomy. At follow-up echocardiography, we measured the mitral, tricuspid, aortic, and pulmonary valve dimensions and the end-diastolic diameters of the right ventricles (RVs) and left ventricles (LVs) according to previously published techniques. Z scores were calculated for each of these structures. The morphology of the interatrial septum was assessed and size of the foramen ovale (FO) measured. Each subject underwent Doppler assessment of the umbilical artery, UV, middle cerebral artery, and ductus venosus. As newborns, the study subjects were examined by a pediatrician, who checked the oxygen saturations using a pulse oximeter.

In a subset of subjects, we attempted to assess the reproducibility of the MRI measurements by repeating them in each vessel. We also compared the MRI flows with ultrasound measurements made in the AAo and MPA. Ultrasound flows were measured using pulsed Doppler tracings from a sample volume at the fetal aortic and pulmonary valves. The mean velocity time integral of these traces was multiplied by the fetal heart rate and vessel area (calculated from vessel diameter measured by 2-dimensional ultrasound) to calculate flow. The MRI flows were also assessed for internal validation by comparing pulmonary blood flow (PBF) measured directly (sum of RPA and LPA flows) and indirectly (difference between MPA and DA flow). Interobserver variation was assessed for the MRI flow measurements, with the second reader blinded to the first reader’s results.

Statistical Analysis
The collected flows for each vessel were confirmed to be normally distributed using the Kolmogorov–Smirnov test, and means, SDs, and references ranges were calculated using 2 SDs either side of the mean for the reference range. Pearson correlation was used to investigate the relationships between the different measurements of flow, and Bland Altman plots were used to assess bias in comparisons of flows measured by different techniques or observers. Significant relationships between all measured parameters were sought using multiple regression analysis. Statistical analysis was performed using MATLAB and Graphpad Prism. P values <0.05 were considered statistically significant.

The combined ventricular output (CVO) was calculated as the sum of the MPA and AAo flows plus 3% to allow for coronary blood flow, based on previous fetal lamb data. PBF was calculated as the sum of the RPA and LPA flows. The FO shunt could not be directly measured using PC-MRI. However, because PBF and FO shunt are the 2 exclusive sources of LV filling, FO flow can be calculated as the difference between the LV output, which comprises the AAo plus coronary blood flow and PBF. Although the calculated mean percentages of the distribution of the CVO required minimal adjustment to conform to a principle of conservation of flow across the fetal circulation, a model was extrapolated from measured flows using constrained nonlinear optimization, where the active set algorithm attempts to find a constrained minimum of the scalar function MPA+AAo−SVC−PBF−DAO, starting at an initial estimate based on measured values, subject to MPA−PBF≥0, MPA+AAo−SVC−PBF−DAO=0, and MPA+AAo+97.18−20.16 Once MPA, AAo, SVC, PBF, and DAO are established, the remaining flows are calculated as DAO=DAO+AAo−SVC−PBF−DAO, and FO=AAo+CA−PBF.

Results
Fifty subjects with normal second-trimester fetal echocardiograms who met the inclusion criteria were enrolled between 2012 and 2014. Ten fetuses were excluded from the analysis: 3 for fetal weights below the tenth percentile by MRI, 3 because of incomplete MRI data sets resulting from vigorous fetal motion, 1 for an abnormally high middle cerebral artery peak velocity, and 1 for an abnormally low middle cerebral artery pulsatility index by Doppler. Two further subjects were excluded based on follow-up echocardiography: 1 for an apical ventricular septal defect and 1 because no Dopplers were recorded. Complete echocardiograms and a complete set of MRI flow measurements were obtained in all of the remaining 40 subjects. All 40 of these fetuses were subsequently born at term with normal birth weights, and there were no significant perinatal complications or postnatal medical problems identified. MRI was performed at a mean gestational age of 37 (SD=1.1) weeks with a mean fetal weight of 3.0 (SD=0.5) kg.

The first 5 fetuses had repeat PC-MRI measurements made in each of the vessels. The comparison reveals good reproducibility with no significant bias (r=0.96; P<0.0001; bias≈−10.8; SD of bias=71.3 mL/min) as shown in Figure 1. Measurements made in the last 10 fetuses were examined...
for interobserver correlation and showed good agreement with no significant bias ($r=0.97$; $P=0.0001$; bias=$-21.2$; SD of bias=$48.3$ mL/min; Figure 2). In this same group of 10 fetuses, the MRI measurements correlated reasonably well with ultrasound measurements of flow in the MPA and AAo ($r=0.77$; $P=0.0001$), with a small bias of $26$ mL/min for higher flows by ultrasound (SD of bias=$98.6$ mL/min; Figure 3). The assessment of internal validation between MRI flow measurements through comparison of direct and indirect measurements of PBF for the whole study group also revealed reasonable agreement with no significant bias ($r=0.43$; $P=0.004$; bias=$-10.5$; SD of bias=$56.0$ mL/min per kilogram) as shown in Figure 4.

The results of the flow measurements are shown in Table 1 and Figures 5 and 6, with a full table of individual flows and cardiac morphology included in the Data Supplement. The mitral, tricuspid, aortic, and pulmonary valves and RV and LV diameters were all with 2 SDs of the mean. A significant inverse correlation was found between FO flow and PBF ($r=-0.64$; $P<0.0001$) as shown in Figure 7. We found a moderate correlation between the ratio of MPA to AAo flow by MRI and the ratio of RV to LV end-diastolic diameter ($r=0.54$; $P=0.0003$; Figure 8), with a weaker correlation between MPA to AAo flow and tricuspid valve to mitral valve ratio ($r=0.31$; $P=0.05$). There was no relationship between the ratio of the pulmonary and aortic valve diameters to MPA/AAo flow, and there was no correlation between FO size and magnitude of FO shunt. There was no correlation between the fetal weight and any of the vessel flows or cardiac output by MRI. We could not demonstrate a significant relationship between the flow in any vessel by MRI and the pulsatility index in the middle cerebral artery or umbilical artery by Doppler, although there were trends toward inverse correlations between umbilical artery pulsatility index and PBF ($r=-0.24$; $P=0.38$) and UV flow ($r=-0.20$; $P=0.47$). We found no other significant correlation between measured parameters.

**Discussion**

**Accuracy of PC-MRI and Comparison With Previous Measurements**

PC-MRI flow measurements made in adult blood vessels are more accurate than flow measurements made using ultrasound, with PC-MRI flows in the AAo and MPA agreeing to <3% in normal volunteers. Flow turbulence and small vessel size affect the fidelity of the technique, although turbulence was not a particular concern in our study, and even the smallest vessels we interrogated had >8 voxels across the vessel area, which has been shown to be the lower limit of spatial resolution for accurate flow measurement. We previously attempted to establish the accuracy of PC-MRI for fetal MRI using an in vivo fetal vessel simulation and demonstrated good agreement between conventionally gated and MOG measurements. The reproducibility, internal validation, and comparison with ultrasound obtained in the current study suggest the technique is at least reasonably reliable. However, inspection of the individual flows reveals some discrepancies between our results and the expected distribution of flow. These include 3 fetuses with higher LV outputs than that of RV despite having larger RV than LV by echocardiography; a fetus with higher SVC flow than AAo flow, which would imply the presence of retrograde flow across the aortic isthmus; and some variation in the proportion of DAo flow reaching the UV. These findings raise concerns about the accuracy of the technique and, therefore, its utility for clinical decision making. However, the dramatic redistribution of flow we have demonstrated in some fetuses with congenital heart disease and placental insufficiency is unlikely to be attributable to errors in phase-contrast measurement. Furthermore, our study suggests that when PC-MRI measurements are collected from several fetuses, the averaged results are similar to experimental animal data. The most comprehensive studies of the distribution of the fetal circulation were performed in fetal lambs using a radioactive microsphere technique. Based on their lamb measurements,
these investigators made estimations of the absolute and relative proportions of the CVO directed to the various parts of the human fetal circulation. A comparison of these estimations with the mean flows we obtained by MRI is shown in Table 2. There is generally good agreement between these 2 sets of results. The most striking difference between their estimates and our findings is the mean UV flow, estimated at 180 mL/min per kilogram by Rudolph and measured at 129 mL/min per kilogram by MRI. However, in the more recent edition of Rudolph’s textbook, the estimate of UV flow has been modified to be more in line with human ultrasound data to 115 mL/min per kilogram. Our own measurements of UV flow are most in keeping with the ultrasound measurements of Van Lierde et al., with a mean UV flow of 117 and 140 mL/min per kilogram. Our results indicate a ratio of 1.27, slightly higher than the MRI measurements, which may be because of the fact that our ultrasound technique assumed a constant flow velocity across the vessel lumen, where in reality flow was likely slower around the vessel periphery than in the middle of the vessel where it was sampled. In addition to intrinsic inaccuracies in our ultrasound and MRI measurements, we are also aware of the possibility that although the 2 techniques were performed on the same day, changes in the physiological state of the fetus during and between the MRI and ultrasound could have affected their agreement.

Differences in sampling techniques may explain the wide variation in results obtained in different human ultrasound studies. For example, Rasanen found an RV/LV output ratio of 1.5 in late-gestation fetuses, compared with a ratio of 1.08 at term in De Smedt’s study. Our results indicate a ratio of 1.27, in keeping with the 1.28 found by Kenny. Estimates of mean CVO range from 425 to 553 mL/min per kilogram, although most estimates are ≈450 mL/min per kilogram, which is in keeping with the MRI result of 465 mL/min per kilogram. The good correlation we found between the ratio of MPA by AAO flow by MRI with echocardiographic measurements of the ratio of the RV and LV end-diastolic dimensions was a reassuring demonstration of congruent physiological and morphological parameters of the relative dominance of each ventricle with respect to the CVO by 2 different imaging modalities.

Previous ultrasound measurements of mean fetal PBF range from 47 mL/min per kilogram or 11% of CVO in Mielke’s large cohort to 25% of CVO in third-trimester fetuses in Rasanen’s study. One reason for the wide range of PBF found by different authors might be the different measurement techniques used, because in the majority of studies, the PBF is calculated by subtraction of the DA flow from the MPA. Rasanen used direct ultrasound measurements of PBF and found that PBF increased from 13% at 20 weeks to ≈25% of CVO at 30 weeks and then dropped again to ≈20% of CVO by 38 weeks. Rasanen’s results indicate that the increase in PBF seen in the third trimester was associated with a reduction in FO shunt but no change in AAo flow. This inverse relationship between PBF and FO shunt was also seen in our study, although in our case the variation in PBF and FO flow was seen in fetuses of the same gestational age. In Rasanen’s study,
there was a 2- to 3-fold range in PBF at 37 weeks, whereas in our own study, the range of PBF was higher with at least a 10-fold difference between the subject with the lowest PBF of 13 mL/min per kilogram or 2% of CVO and the highest PBF of 187 mL/min per kilogram or 30% of CVO. The reason for this discrepancy is not clear. Rasanen's study reports a higher level of agreement between direct and indirect measurements of PBF using ultrasound than we obtained using MRI, raising the possibility that inaccuracy of the MRI measurements could have resulted in the discrepancy. The pulmonary arteries are certainly the smallest vessels we measured by MRI and are at the lower limit of size for established criteria for PC-MRI accuracy. However, it is also possible that the sample size had an influence, because although Rasanen's study included 63 patients, these were evenly distributed across a gestational age range of 18 to 40 weeks, whereas our own 40 subjects were concentrated around the same gestational age of 37 weeks. The wider range of PBF found by our study might, therefore, be expected based on the larger number of patients studied at this gestation. This conclusion is supported by the similar range in right and left cardiac outputs and CVO at term found at this gestation. This conclusion is supported by the similar range of 18 to 40 weeks, whereas our own 40 subjects were evenly distributed across a gestational age range of 18 to 40 weeks, whereas our own 40 subjects were concentrated around the same gestational age of 37 weeks.

Variation in PBF and FO Shunting
As in Rasanen's study, there was no correlation between PBF and AAo flow measured by MRI, with AAo remaining fairly constant between patients. Because PBF and FO shunt are the 2 sources of LV filling, a wide range of FO shunt and inverse relationship with PBF should, therefore, be anticipated. In our study, the lowest FO shunt was just 29 mL/min per kilogram or 5% of the CVO, with a 10-fold increase to the largest FO shunt of 283 mL/min per kilogram or 54% of the CVO. We found a strong inverse correlation between FO shunt and PBF. The physiological mechanism behind this finding is not yet clear. Our results would not support anatomic restriction at the FO as a likely cause, although accurate measurements of the FO orifice are difficult to obtain. One potential explanation is normal variation in fetal pulmonary vascular resistance. Evidence for this is provided by the wide range of pulmonary arterial wall thickness in Naeve's histological studies of perinatal subjects and ultrasound studies showing variation in shunting at the DA in newborns at birth. Variation in PVR, and therefore PBF, could be the driver behind the inverse variation we found in FO flow. Konduri et al showed that an increase in pulmonary arterial PaO₂ of 7 mmHg resulted in a 3-fold increase in PBF and increase in left atrial pressure from 4 to 8 mmHg. It seems feasible, therefore, that PVR is an important determinant of the relative contributions to LV filling from the pulmonary circulation and FO shunt. The inverse relationship between fetal PVR and oxygen content of the blood in the pulmonary arteries was initially shown by Rudolph using flow probes around the pulmonary arteries of fetal lambs during variation of the concentration of inspired oxygen of the ewes. Rasanen has since demonstrated human fetal pulmonary vasodilation in response to maternal hyperoxegenation using Doppler. Normal variation in the pulmonary arterial oxygen content in the human fetus is perhaps to be expected when the normal variation in umbilical venous blood oxygen content is taken into account. Blood gas analysis of

### Table 1. Means, SDs, and Reference Ranges (mean±2SD) of Flows in 40 Normal Late-Gestation Human Fetuses Measured by Phase-Contrast MRI (mL/min per kilogram) and as Percentages and as Modeled Mean Percentages of the Combined Ventricular Output

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Mean±2 SD CVO</th>
<th>Mean±2 SD MPA</th>
<th>Mean±2 SD AAo</th>
<th>Mean±2 SD SVC</th>
<th>Mean±2 SD DA</th>
<th>Mean±2 SD PBF</th>
<th>Mean±2 SD DAo</th>
<th>Mean±2 SD UV</th>
<th>Mean±2 SD FO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, mL/min per kg</td>
<td>465, 579</td>
<td>261, 353</td>
<td>191, 216</td>
<td>137, 177</td>
<td>187, 197</td>
<td>74, 139</td>
<td>252, 134</td>
<td>134, 135</td>
<td>49, 49</td>
</tr>
<tr>
<td>Mean, % CVO</td>
<td>56, 60</td>
<td>41, 45</td>
<td>29, 33</td>
<td>20, 25</td>
<td>40, 44</td>
<td>16, 19</td>
<td>55, 58</td>
<td>29, 29</td>
<td>29, 29</td>
</tr>
<tr>
<td>Modeled mean, % CVO</td>
<td>56, 56</td>
<td>41, 45</td>
<td>28, 32</td>
<td>20, 25</td>
<td>41, 44</td>
<td>15, 19</td>
<td>54, 58</td>
<td>29, 29</td>
<td>29, 29</td>
</tr>
</tbody>
</table>

AAo indicates ascending aorta; CVO, combined ventricular output; DA, ductus arteriosus; DAo, descending aorta; FO, foramen ovale; MPA, main pulmonary artery; PBF, pulmonary blood flow; SVC, superior vena cava; and UV, umbilical vein. FO flow was calculated as the difference between the left ventricular output and PBF.
cordocentesis samples has revealed a normal range of oxygen saturation from 60% to 80% in term fetuses. This hypothesis is supported by the fact that although we were not able to demonstrate any statistically significant relationships between Doppler parameters of placental function, we did observe trends suggesting that umbilical artery pulsatility index was inversely proportional to PBF and UV flow. This result would be in keeping with the concept that higher placental resistance might result in a reduction in UV flow and PBF because of reduced fetal oxygen delivery. However, contrary to this conclusion, we found no relationship between UV flow and PBF. We were also unable to demonstrate any evidence of a relationship between cerebral vascular resistance and pulmonary or placental blood flow by Doppler or MRI in the fetuses in this study. This would suggest that none of the fetuses in the current group were approaching the brain-sparing physiology we have seen in fetuses with established intrauterine growth restriction in which we have demonstrated SVC flows >300 mL/min per kilogram and >50% of the CVO. In future, new techniques for MR oximetry may be helpful for investigating the relationship between oxygen transport and the distribution of blood flow in the fetal circulation and provide a technique to measure fetal oxygen delivery and consumption. A combination of PC-MRI and MR oximetry may also provide useful information regarding the streaming of the umbilical venous return, which by convention is preferentially directed through the ductus venosus and left lobe of the liver to form a high-velocity stream in the leftward posterior aspect of the IVC, which is directed toward the FO. In fetal lambs, this mechanism maintains a higher oxygen content of the blood in the left heart than the right, although the wide variation in the FO shunt seen in our study suggests this mechanism may be subject to some variation.

Strengths and Limitations
Although this study establishes provisional reference ranges for MRI flows, the sample size of 40 is too small to establish normal ranges. However, one strength of our study compared with previous ultrasound studies is that flow was measured in each of the large vessels. This allows for characterization of distribution of the whole fetal circulation, which has been a conceptually helpful aspect of the fetal lamb research and permits internal validation of the measurements. Our reference ranges are indexed by fetal weight rather than gestational age. This allows for comparison with the lamb measurements and is made possible by the high accuracy of fetal weight measurement by MR segmentation at term. Our study differs from the majority of ultrasound studies, because all of the subjects...
were studied during a short-gestational age window. Although this might be regarded as a limitation, we would argue that it results in a more homogeneous study group, focusing on a period of pregnancy when PC-MRI is less prone to movement artifact but when sonographic windows are more limited. However, we wish to emphasize that our results can only be applied to the late-gestation human fetus. Furthermore, our technique is not currently suitable for studying fetuses at younger gestational ages because of the inherent difficulties encountered with imaging small moving structures using MRI. The vulnerability of MRI to movement artifact resulting from fetal motion represents a significant drawback of the technique compared with ultrasound.

Conclusions

This study provides a comprehensive set of measurements of blood flow in the major vessels of the late-gestation human fetal circulation. The results are consistent with a previous estimate of human fetal flows based on detailed measurements made in fetal lambs using radioactive microspheres and provide a preliminary set of reference data for future MRI and ultrasound measurements of the fetal circulation. A new observation was the wide range and inverse relationship of PBF and FO shunt among fetuses of the same gestational age. We propose that the mechanism and implications of this finding deserve further investigation.

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

This paper establishes a preliminary set of reference ranges for blood flow in the major vessels of the normal human fetal circulation at term by phase-contrast MRI. The results are in keeping with previous estimates based on invasive measurements made in fetal lambs and noninvasive measurements made in humans using ultrasound. The results also reveal that a wider range of pulmonary blood flow and foramen ovale shunt may be present in normal late-gestation fetuses than was previously appreciated. These reference ranges should be useful to researchers interested in investigating the use of MRI to examine the distribution of blood flow in the setting of fetal cardiovascular diseases such as congenital heart disease or placental insufficiency. Although there are currently no established clinical indications for performing fetal cardiovascular MRI, preliminary experience indicates that the technique may provide new insights into fetal cardiovascular physiology. Furthermore, preliminary work using new MRI techniques for performing oximetry in fetal vessels suggests that a combination of phase-contrast MRI and MR oximetry may be used to measure such basic parameters of fetal cardiovascular physiology as fetal oxygen delivery and consumption. We wish to emphasize that the results are only applicable to late-gestation fetuses and that this technique is currently only feasible close to term.
Reference Ranges of Blood Flow in the Major Vessels of the Normal Human Fetal Circulation at Term by Phase-Contrast Magnetic Resonance Imaging
Milan Prsa, Liqun Sun, Joshua van Amerom, Shi-Joon Yoo, Lars Grosse-Wortmann, Edgar Jaeggi, Christopher Macgowan and Mike Seed

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