Postnatal neonatal myocardial adaptation is associated with loss of tolerance to
tachycardia: a simultaneous invasive and noninvasive assessment

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Heart Circ Physiol 310: H598–H607, 2016. First published December 30, 2015; doi:10.1152/ajpheart.00595.2015.—Doppler studies at
rest suggest left ventricular (LV) diastolic function rapidly improves from the neonate to infant. Whether this translates to its response to
hemodynamic challenges is uncertain. We sought to explore the impact of early LV maturation on its ability to tolerate atrial tachycardia. As tachycardia reduces filling time, we hypothesized that the neonatal LV would be less tolerant of atrial tachycardia. Landrace cross piglets of two age groups (1–3 days; NPs: 14–17 days, YPs; n = 7/group) were instrumented for an atrial pacing protocol (from 200 to 300 beats/min) and assessed by invasive monitoring and echocardiography. NPs maintained their LV output and blood pressure, whereas YPs did not. Although negative dP/dt in NPs at baseline was lower than that of YPs (∼1,599 ± 83 vs. −2,470 ± 226 mmHg/s, respectively, P = 0.007), with increasing tachycardia negative dP/dt converged between groups and was not different. Both groups had similar preload reduction during tachycardia; however, NPs maintained shortening fraction while YPs decreased (NPs: 35.4 ± 1.4 vs. 31.8 ± 2.2%, P = 0.35; YPs: 31.4 ± 0.8 vs. 22.9 ± 0.8%, P < 0.001). Contractility measures did not differ between groups. Peak LV twist and untwisting rate also did not differ; however, NPs tended to augment LV twist through increased apical rotation and YPs through increasing basal rotation (P = 0.009). The NPs appear more tolerant of atrial tachycardia than the YPs. They have at least similar diastolic performance, enhanced systolic performance, and different LV twist mechanics, which may contribute to improved tachycardia tolerance of NPs.

NEW & NOTEWORTHY

The neonatal left ventricles showed better tolerance to chro-
notropic stress compared with that of the young infant. This
was associated with at least similar diastolic reserve as found
in young infants, an enhanced systolic reserve, and a unique
neonatal left ventricular twist mechanics during tachycardia.

HEMODYNOmic MANAGEMENT of the critically ill term newborn is
complex. Understanding the functional nature of the neonatal
myocardium and how it evolves through the first few weeks
and months after birth is key to optimizing care. Although
many authors have provided their opinions regarding clinical
management strategies (1, 12, 32), more translational and
clinical studies are needed to provide insight into the functional
capacity of the early postnatal heart. In particular, changes in
diastolic reserve during the first few weeks and months of life in
relation to the known disproportionate left ventricular (LV)
growth (3, 27) have been poorly explored.

In human infants, most of our understanding of the evolution
of diastolic function has been derived from noninvasive Dop-
pler-based studies (16, 26, 31). These investigations have
suggested that the neonatal LV myocardium has less robust
diastolic relaxation (16) with greater dependency on atrial
contraction for filling, much like that of the diseased adult heart
with diastolic dysfunction (15). In the first few months of life,
the increasing contribution of ventricular filling during early
diastole and rapid decrease in isovolumic relaxation time is
interpreted as evidence of improving ventricular relaxation
(31). While there is a wealth of literature that documents LV
function at rest in infants and children, there is a paucity of data
that examine diastolic and systolic LV function during hemo-
dynamic stress, which would be more relevant to the critically
ill pediatric patient. This is in part due to technical difficulties
at faster heart rates with ventricular inflow and tissue Doppler
patterns frequently not interpretable due to fusion of the E
(early diastolic filling) and A (late diastolic filling during atrial
systole) waves. More recently, LV twist studied by speckle
tracking echo-based techniques has been explored in older
children during exercise (7) and might allow us to circumvent
challenges related to fast heart rates observed in infants. LV
untwisting is demonstrated to be important for the generation
of LV suction and contributes to efficient early diastolic filling
(7, 23, 35). The resting LV twising pattern in neonates differs
from the more mature heart (24) (Fig. 1A). Furthermore, the
neonatal LV has a smaller twist amplitude coupled with slower
delayed untwisting when compared with older children and
adults (23), which may reduce the contribution of LV untwist-
ing/suction to early diastolic filling.

Invasive animal studies that have explored the functional
maturation of the neonatal LV within the first weeks of life (4,
27, 30), including its response to preload (2, 19, 28), also
support the current assumption that the neonatal LV may have
relatively less diastolic reserve when faced with altered loading
conditions. The impact of atrial tachycardia on neonatal LV
function, a common finding in the critically ill neonate, and a
state that is poorly tolerated by the more mature heart with
diastolic dysfunction in part as tachycardia reduces diastolic
filling time (36), has been minimally examined. In a fetal lamb
model, rapid atrial pacing has been shown to be associated with

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some augmentation of the LV output without an increase in left atrial pressure (29), which could suggest that the immature myocardium does have diastolic reserve; however, translating these findings to the neonatal heart, which faces different loading conditions and an in-series circulation, is difficult.

In the present study, we sought to investigate the response of the neonatal and young infant myocardium to atrial tachycardia using a piglet model. We used invasive measures and noninvasive state-of-the-art echocardiography to better elucidate both LV systolic and diastolic hemodynamic and LV myocardial mechanical responses to atrial tachycardia. Given the current understanding of the evolution of diastolic function, our initial hypothesis was that rapid atrial pacing would be less tolerated by the neonatal myocardium when compared with that of the young infant.

**METHODS**

Landrace cross piglets of two different age groups were investigated. One group was studied as neonates at 1–3 days of age (NP group) and the other at 14–17 days of age (young piglet (YP group)). These developmental stages were chosen because piglets are not yet weaned at that age and they have been previously used to describe infantile cardiovascular maturation (9, 13). In addition, the heart rate of the young piglet is relatively stable within the first 2 wk after delivery (9). Seven animals were studied for each group. This study was approved by the animal research ethics board at the University of Alberta and was designed in accordance with the Canadian Council on Animal Care guidelines.

**Anesthesia and instrumentation.** General anesthesia was induced with isoflurane 2–5% in nitrous oxide (5 l/min) and oxygen (5 l/min) via face mask. Tracheotomy and external jugular venous access were performed through a neck cutdown. Piglets were then mechanically ventilated (Ohio 30/70 Proportioner Anesthesia Machine) with a peak inspiratory pressure between 20 and 25 mmHg. Along with a D10W solution through the jugular venous catheter at 5 ml·kg⁻¹·min⁻¹, a low-dose infusion of propofol (85 mcg·kg⁻¹·min⁻¹) was given and the desired level of anesthesia was adjusted with isoflurane (0.5–2%). To minimize the effects of sedatives on the hemodynamic profiles of the piglets we used the lowest concentration of isoflurane possible to achieve quiet sleep with some respiratory efforts. Although the level of isoflurane varied through the experiment within individual subjects, the level of sedation was similar between piglets.

Vascular sheaths (5 to 6.5 Fr) were introduced in both common carotids and external jugular veins and were then used to position the different catheters. Fluid filled catheters (3.5 Fr) were positioned in the superior vena cava and the common carotid artery for central venous and arterial pressure monitoring, respectively. A pacemaker lead (4 Fr) was introduced into the right atrial appendage and connected to an external pacemaker (Medtronic). A high-fidelity catheter (3.5 Fr for NPs and a 5 Fr for YPs; Millar Instruments) was positioned in the LV mid cavity. Catheter placement was done under both fluoroscopic and echocardiographic guidance. Blood gas analysis was performed before and immediately after the pacing protocol (iStat system; Abbott Point of Care). Rectal temperature and pulse oximetry were continuously monitored during the experiments. Following completion of the experiments, piglets were euthanized with an overdose of pentobarbital (100 mg/kg iv).

**Pacing protocol.** After instrumentation, a 30-min recovery period was allowed for the piglets to stabilize, defined by <10% variation in hemodynamic parameters and normal parameters in an arterial blood gas analysis. Blood gas analysis was performed before and immediately after the pacing protocol (Stat system; Abbott Point of Care). Rectal temperature and pulse oximetry were continuously monitored during the experiments. Following completion of the experiments, piglets were euthanized with an overdose of pentobarbital (100 mg/kg iv).

**Fig. 1. Left ventricle twist motion and twist rate.** Twist (A) and twist rate (C) of the piglet left ventricle. The white line represents twist of the LV as viewed from the feet. The green line is the apical rotation and the purple line is the basal rotation. By convention, a clockwise rotation is displayed as a negative value and counterclockwise rotation as a positive value. The 2 red circles on the twist rate (C) show the biphasic pattern of untwisting. The 2nd untwisting velocity peak happens just after the p wave on the elongated ECG tracing at bottom. B: human neonatal comparative with similar biphasic basal twist motion.
min was chosen as it has previously been shown that the neonatal piglet heart demonstrates signs of failure at this rate (17). The animals were allowed to stabilize for 30 s (30) before invasive recording and echocardiography Doppler cardiac output was done at each heart rate increment. Detailed echocardiography to assess LV mechanics was repeated at 200, 230, and 260 beats/min.

Invasive data collection. Data from invasive monitoring was analyzed using Ponemah software (Data Sciences International). Each data point for aortic blood pressure (systolic, diastolic, and mean), dP/dt, negative dP/dt, and tau was averaged from 20 to 25 heart cycles. Tau was generated by the software using the following formula:

\[ \tau = \frac{N \sum x^2 - \sum x \sum x}{N \sum \{x \cdot \ln(p)\} - \sum x \cdot \ln(p)} \]

where \( N \) is the number of points used in the calculation, \( x \) is the delta time in seconds at each sampled point (starting from the minimum dP/dt point), and \( p \) is the left ventricular pressure value at each sampled point. Left ventricular end-diastolic pressure (LVEDP) was manually averaged from 7 to 10 heart beats to avoid where possible, intrathoracic pressure variations related to mechanical ventilation. A very small number of nonconsecutive observations (5 out of 804 observations, 1 for each variable in 1 piglet) had to be generated by averaging of the values from the heart rate above and below the missing data point due to technical issues. Central venous pressure (CVP) was averaged from five cardiac cycles.

Echocardiography. Echocardiographic images were acquired with a Vivid 7 ultrasound machine (GE Healthcare) and a 5- or 7-MHz probe by one of three pediatric cardiologists specialized in echocardiography (N. S. Koo, L. Mills, and L. K. Hornberger). Arteriosus probe by one of three pediatric cardiologists specialized in echocardiography Doppler cardiac output was done at each heart rate increment. Detailed echocardiography to assess LV mechanics was repeated at 200, 230, and 260 beats/min.

RESULTS

Baseline assessment and tolerance to protocol. Both age (2.0 ± 0.2 vs. 15.0 ± 0.2 days of life, \( P < 0.001 \)) and weight (1.89 ± 0.09 vs. 5.34 ± 0.41 kg, \( P < 0.001 \)) differed between the NP and YP groups, respectively. Following the stabilization period, baseline parameters were acquired during baseline echocardiogram before the pacing protocol. Table 1 summarizes the findings between the groups, showing similar hemodynamic profiles and arterial blood gas (pH: 7.40 ± 0.03 vs. 7.37 ± 0.03; \( \text{PCO}_2; 35 ± 3 \) vs. 40 ± 2 mmHg; \( \text{PO}_2; 95 ± 11 \) vs. 121 ± 12 mmHg; \( \text{HCO}_3^-; 22 ± 1 \) vs. 23 ± 1 mmol/l of NP and YP groups, respectively; all \( P > 0.05 \)). Differences at baseline included a significantly lower blood pressure and a less negative value of the negative dP/dt in the NP group. Although basal strain and shortening fraction (SF) in the NP group were higher than those of the YP group (Table 2), the baseline LVO were also tested (sphericity, homocedasticity, and normality). If there was no interaction and no significant difference between groups and distribution within both groups was judged to be similar, data were analyzed as a single group. At baseline and at the end of the experiment, the two groups were compared using \( t \)-tests or Mann-Whitney \( U \)-tests, depending on the nature of the variable distribution.

Table 1. Baseline assessment of the 2 piglet groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neonatal Piglets</th>
<th>Young Infant Piglets</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>66 ± 2</td>
<td>84 ± 3</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>28 ± 3</td>
<td>44 ± 2</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>45 ± 2</td>
<td>59 ± 4</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>142 ± 8</td>
<td>159 ± 3</td>
<td>0.1</td>
</tr>
<tr>
<td>Cardiac output, ml/kg·min⁻¹</td>
<td>245 ± 16</td>
<td>257 ± 13</td>
<td>0.5</td>
</tr>
<tr>
<td>Stroke volume, ml/kg</td>
<td>1.74 ± 0.12</td>
<td>1.62 ± 0.08</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Invasive parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dP/dt, mmHg/s</td>
<td>1.574 ± 0.18</td>
<td>1.737 ± 0.14</td>
<td>0.5</td>
</tr>
<tr>
<td>Negative dP/dt, mmHg/s</td>
<td>−1.599 ± 0.83</td>
<td>−2.470 ± 0.22</td>
<td>0.007</td>
</tr>
<tr>
<td>MinLVP, mmHg</td>
<td>3.3 ± 1.9</td>
<td>3.1 ± 1.5</td>
<td>0.9</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>8.4 ± 2.2</td>
<td>9.0 ± 0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Tau, ms</td>
<td>24 ± 2</td>
<td>22 ± 2</td>
<td>0.6</td>
</tr>
<tr>
<td>CVP, cmH₂O</td>
<td>2.8 ± 0.8</td>
<td>3.6 ± 0.8</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Echocardiography: m-mode</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>1.59 ± 0.07</td>
<td>2.23 ± 0.12</td>
<td>0.001</td>
</tr>
<tr>
<td>Shortening fraction, %</td>
<td>35.4 ± 1.4</td>
<td>31.4 ± 0.77</td>
<td>0.03</td>
</tr>
<tr>
<td>VcFe</td>
<td>3.1 ± 0.2</td>
<td>3.4 ± 0.17</td>
<td>0.3</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>2.9 ± 0.1</td>
<td>3.9 ± 0.2</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Echocardiography: mitral inflow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.81 ± 0.04</td>
<td>0.81 ± 0.04</td>
<td>0.98</td>
</tr>
<tr>
<td>Deceleration time, ms</td>
<td>71 ± 4</td>
<td>78 ± 8</td>
<td>0.5</td>
</tr>
<tr>
<td>A filling fraction, %</td>
<td>52 ± 2</td>
<td>50 ± 2</td>
<td>0.5</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>57 ± 2</td>
<td>55 ± 3</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Tissue Doppler imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E/e'</td>
<td>9.3 ± 0.4</td>
<td>10.0 ± 1.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Lateral wall isovolumic acceleration, cm/s</td>
<td>3.27 ± 0.26</td>
<td>4.31 ± 0.61</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Twist and twist rates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak twist, °/s</td>
<td>18.3 ± 2.0</td>
<td>14.7 ± 1.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Peak twist rate, °/s</td>
<td>181 ± 29</td>
<td>234 ± 24</td>
<td>0.2</td>
</tr>
<tr>
<td>Peak untwisting rate, °/s</td>
<td>−243 ± 31</td>
<td>−267 ± 33</td>
<td>0.7</td>
</tr>
<tr>
<td>Peak untwisting rate before MVO</td>
<td>−152 ± 29</td>
<td>−170 ± 47</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Values are means ± SE. MinLVP, minimum left ventricular pressure reached during diastole; LVEDP, left ventricular end-diastolic pressure; CVP, central venous pressure; LVEDD, left ventricular end-diastolic dimension; VcFe, velocity of circumferential fiber shortening corrected for heart rate; E/A, early and late diastolic mitral filling velocity ratio measured by Doppler; IVRT, isovolumic relaxation time; MVO, mitral valve opening. *e′ was averaged from the left ventricular free wall and the interventricular septum values. e′ could only be measured for 6 neonatal and 5 piglets, whereas all other parameters could be measured in 7 piglets for each group.
Table 2. Baseline strain and rotation parameters

<table>
<thead>
<tr>
<th>Strain: basal</th>
<th>Neotnal Piglets</th>
<th>Young Infant Piglets</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak strain, %</td>
<td>$-18.4 \pm 1.7$</td>
<td>$-9.7 \pm 0.74$</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic SR, 1/s</td>
<td>$-1.73 \pm 0.21$</td>
<td>$-1.32 \pm 0.10$</td>
<td>0.1</td>
</tr>
<tr>
<td>Diastolic E SR, 1/s</td>
<td>$2.25 \pm 0.27$</td>
<td>$1.53 \pm 0.11$</td>
<td>0.029</td>
</tr>
<tr>
<td>Diastolic A SR, 1/s</td>
<td>$2.04 \pm 0.33$</td>
<td>$0.74 \pm 0.12$</td>
<td>0.006</td>
</tr>
<tr>
<td>Strain: apical</td>
<td>Peak strain, %</td>
<td>$-22.21 \pm 1.89$</td>
<td>$-20.43 \pm 2.43$</td>
</tr>
<tr>
<td>Systolic SR, 1/s</td>
<td>$-2.72 \pm 0.34$</td>
<td>$-2.86 \pm 0.41$</td>
<td>0.80</td>
</tr>
<tr>
<td>Diastolic E SR, 1/s</td>
<td>$4.65 \pm 0.64$</td>
<td>$3.84 \pm 0.51$</td>
<td>0.34</td>
</tr>
<tr>
<td>Diastolic A SR, 1/s</td>
<td>$3.24 \pm 0.47$</td>
<td>$2.48 \pm 0.42$</td>
<td>0.24</td>
</tr>
<tr>
<td>Rotation: basal</td>
<td>Early positive, °</td>
<td>$5.3 \pm 2.0$</td>
<td>$4.8 \pm 1.0$</td>
</tr>
<tr>
<td>Negative, °</td>
<td>$-2.7 \pm 1.1$</td>
<td>$-5.1 \pm 1.2$</td>
<td>0.15</td>
</tr>
<tr>
<td>Rotation: apical</td>
<td>Positive, °</td>
<td>$19.3 \pm 2.7$</td>
<td>$13.02 \pm 1.6$</td>
</tr>
<tr>
<td>Twist</td>
<td>Peak twist, °</td>
<td>$18.3 \pm 2.0$</td>
<td>$14.7 \pm 1.8$</td>
</tr>
<tr>
<td>%Untwist before MVO</td>
<td>$33 \pm 8$</td>
<td>$32 \pm 13$</td>
<td>0.93</td>
</tr>
<tr>
<td>Rotation rate: basal</td>
<td>Peak positive, °/s</td>
<td>$166 \pm 54$</td>
<td>$137 \pm 14$</td>
</tr>
<tr>
<td>Negative, °/s</td>
<td>$-85 \pm 14$</td>
<td>$-123 \pm 19$</td>
<td>0.17</td>
</tr>
<tr>
<td>Rotation rate: apical</td>
<td>Peak positive, °/s</td>
<td>$223 \pm 57$</td>
<td>$213 \pm 37$</td>
</tr>
<tr>
<td>Negative, °/s</td>
<td>$-261 \pm 57$</td>
<td>$-227 \pm 30$</td>
<td>0.46</td>
</tr>
<tr>
<td>Twist rate</td>
<td>Peak twist rate, °/s</td>
<td>$181 \pm 29$</td>
<td>$234 \pm 24$</td>
</tr>
<tr>
<td>Peak untwist rate, °/s</td>
<td>$-243 \pm 31$</td>
<td>$-267 \pm 33$</td>
<td>0.71</td>
</tr>
<tr>
<td>Peak twist rate before MVO, °/s</td>
<td>$-152 \pm 29$</td>
<td>$-170 \pm 47$</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Values are means ± SE. SR, strain rate. *One piglet in each group had no positive component to basal rotation at baseline heart rate. The positive rotation rate for these piglets was analyzed as a missing value.
Invasive measures of LV contractility showed increasing positive dP/dt with pacing in both NPs and YPs, with no significant difference between groups (Fig. 3). Noninvasive assessment of contractility showed progressive increase of velocity of circumferential fiber shortening corrected for heart rate (VcFc) from baseline to 260 beats/min pacing (3.22 ± 0.15 to 5.28 ± 0.37 cm/s, P = 0.001), with a similar degree of enhancement between groups. Both basal and apical circumferential systolic strain rates were also similar between groups, demonstrating an increase with increasing heart rate (basal circumferential strain rate: −1.53 ± 0.13 to −2.42 ± 0.27 /s, P = 0.004; apical circumferential strain rate: −2.79 ± 0.26 to −4.42 ± 0.49 /s, P = 0.002).

**LV systolic rotation and twist during pacing.** Changes in peak systolic twist with pacing were similar between the NP and YP groups. LV twist increased at atrial rates of 200 and 230 beats/min with a return to baseline values thereafter (P = 0.014, quadratic effect P = 0.015; Fig. 4). The most striking difference between the groups was in how twist was augmented and then maintained during atrial pacing. NPs tended to increase their LV twist by increasing apical rotation (P = 0.1) with significant difference between groups at 260 beats/min (18.4 ± 0.93 vs. 12.4 ± 0.98 ms, P = 0.04; Fig. 4). In contrast, YPs augmented and maintained their LV twist by enhancing basal rotation. The early counterclockwise basal rotation was not different between groups and did not vary significantly during atrial pacing; however, the YPs increased the basal clockwise rotation in response to pacing more than the NPs (interaction, P = 0.014; Fig. 4). Significant differences between groups were observed at 200 and 230 beats/min (P = 0.002 for both), but this response was not linear (quadratic effect, P = 0.003) as the YPs could not maintain the increased clockwise rotation amplitude at the highest heart rates. The difference in time between peak apical and peak basal rotation (synchrony of basal and apical rotation) was similar between groups and narrowed with increasing heart rate (baseline: 108 ± 25 vs. at 260 beats/min 41 ± 11 ms, P = 0.013), a mechanism by which LV twist may be potentially augmented with pacing. The interobserver variability was good for both the assessment of peak clockwise basal and peak counter clockwise apical rotation (intraclass correlation coefficient of 0.93 and 0.98 respectively, P < 0.05 for both) when analyzing the exact same heart beat (Fig. 6).

**DISCUSSION**

Our study suggests the neonatal LV may have better cardiac reserve in response to atrial tachycardia than that of the young infant as demonstrated by the NPs’ ability to maintain LVO, which did not occur in YPs. With respect to diastolic function, despite a lower baseline negative dP/dt, we found NPs to have similar enhancement of LV relaxation during tachycardia compared with YPs. We observed similar acceleration of relaxation through shortening of both IVRT and tau in both groups. In the NPs, negative dP/dt increased from baseline to levels similar to those of YPs soon after initiation of atrial tachycardia. The LVO in NPs was maintained from baseline, and this was associated with preserved FS and enhancement of its ejection phase through a progressive reduction of LV end systolic dimension (Fig. 5) compared with YPs. Differences in LVO did not appear to be a function of differences in LV contractility given similar invasive LV dP/dt and noninvasive echo markers of contractility, VcFc, and LV strain rate (38) between groups. There was, however, an intriguing finding of significant differences in LV twist mechanics in response to tachy-
cardia, which potentially may contribute to NPs’ tolerance of tachycardia.

Diastolic function of the neonatal heart. Contrary to our initial hypothesis that NPs would have impaired diastolic reserve during chronotropic stress, our study showed that NPs have similar acceleration of relaxation compared with YPs. This is demonstrated by comparable shortening of IVRT and decreasing tau and appropriate enhancement of baseline negative dP/dt to levels similar to YPs during tachycardia. Given the observed response to tachycardia, despite worse baseline values, we conclude that the NP myocardium must have at least comparable diastolic reserve compared with YPs. We speculate that the observed early enhancement of negative dP/dt likely contributed to NPs’ maintenance of LVO. This is supported by the findings of an in vitro study of human ventricular muscle strips from neonates with congenital heart disease, which suggests preserved acceleration of relaxation (39) in neonatal hearts.

Early filling ventricular mechanics are affected by ventricular active relaxation through efficient sequestration of calcium into the sarcoplasmic reticulum by energy-dependent calcium exchangers. They are also impacted by mechanical restoring forces through “spring-like” myocardial proteins such as titin, when the LV is compressed beyond its “equilibrium volume” during LV chamber compression and twisting in systole (25, 35). Although not reaching statistical significance, the NP untwisting velocity, a measure intimately linked to restoring forces (23), tended to further accelerate during increasing tachycardia compared with YPs (Fig. 4). This was consistent with the finding of a smaller LV end-systolic dimension in NPs, which may represent greater stored potential energy for LV relaxation. Interestingly, based on previous investigations, the titin isoform transitions to the stiffer adult variant would have already begun at 2 wk of age in piglets (20), which should theoretically have favored potential energy storage in the YPs. One would have expected this evolution of titin expression to result in increased untwisting velocity in the YPs compared with the NPs; however, the lack of this enhancement in our findings suggests perhaps at this early age titin may play less of a role in diastolic function and ventricular untwisting. At a cellular level, the relative overexpression of NCX (sarcoplasmal gradient-driven calcium exchanger) in the neonatal heart.

Fig. 3. Evolution of invasive variables through the pacing protocol (continued). A: systolic blood pressure. B: diastolic blood pressure. C: tau. D: central venous pressure (CVP). E: dP/dt.

*Difference between the groups at that heart rate (P < 0.05). †Neonatal group within group difference compared with baseline (P < 0.05). ‡Young infant group within group difference compared with baseline (P < 0.05). §Piglets were analyzed as a single group. ||As 1 group of 14 piglets, within group difference compared with baseline.
has been shown to decrease with maturation (37, 39). A larger number of NCX in the very young may allow for more efficient clearing of cytosolic calcium, and may favor NP LV relaxation performance during chronotropic stress, when compared with YPs.

**Systolic function of the neonatal heart.** We found the neonatal heart to be more tolerant to tachycardia, contrary to our initial hypothesis where worse tolerance to tachycardia was expected as a consequence of presumed less robust diastolic function given the observations at rest in NPs and in human infants (16, 26, 31). Our findings are in keeping with those of Schmidt et al. (30) who elegantly demonstrated the unique ability of the immature heart (9 ± 4 days of age) to adapt to tachycardia by optimizing its force-frequency relationship following sustained tachycardia, something that the adult heart could not manage. Our work suggests that even compared with that of the YPs, the neonatal heart has better tolerance to atrial tachycardia despite apparently reduced diastolic function at rest. The difference in LVO between groups is not explained by differences in preload as both LVED dimension decreased similarly during atrial tachycardia. Stroke volume, however, was better maintained in our NP relative to YP groups, likely a function of better maintenance of FS, consistent with the finding of a lower relative LV end-systolic dimension during tachycardia in NPs. Given that we observed no difference in both invasive (positive dP/dt) and noninvasive (strain rate and VcFc) measures of contractility between the two groups, this response to atrial tachycardia in NPs may not be related to differences in LV contractility. What we did observe were differences in LV deformation and twist mechanics in response to tachycardia, suggesting a potential role of differing LV mechanics that may have contributed to the observed better NP systolic performance and maintenance of LVO during atrial tachycardia.

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Fig. 4. Rotation studies. A: twist. B: peak untwist rate. C: apical rotation. D: basal negative rotation. *Difference between the groups at that heart rate (P < 0.05). ‡Young infant group within group difference compared with baseline (P < 0.05). §Piglets were analyzed as a single group. ||As 1 group of 14 piglets, within group difference compared with baseline (P < 0.05).

Fig. 5. M-mode assessment of left ventricular dimensions and shortening fraction (SF). M-mode assessment (A) of LVED dimension (solid line) and end systolic dimension (dashed line) expressed as a fraction of baseline LVED dimension. LVED dimension and end-systolic dimension decrease with pacing (no interaction). However, end-systolic dimension was significantly lower in the YP group at baseline and 260 beats/min. SF evolution through pacing (B). *Difference between the groups at that heart rate (P < 0.05). ‡Young infant group within group difference compared with baseline (P < 0.05).
The LV twisting and wringing motion was first described in 1669, and vigorous LV twisting during cardiac surgery has long been recognized in the operating room as a sign of good intraoperative LV health (34). LV rotation by convention is described as being viewed from the apex of the heart. During LV systole, the base of the LV has an early counterclockwise motion followed by a more dominant clockwise rotation and the apex has a counterclockwise motion. This is followed by a rapid untwisting during the isovolumic relaxation period, a recoil motion from stored potential energy generated by LV systolic twist, contributing to early LV reformation and generation of LV suction during early diastolic filling. Hence, LV twisting provides a coupled link between LV systole and diastole. In addition, LV twist helps redistribute transmural stress and tension from the endocardial to the epicardial myofibers and may reduce overall myocardial oxygen consumption (6, 35). LV twist has also been postulated to have a role in aiding the development of efficient endocardial myofiber sheet rearrangement, a feature that is important during LV endocardial thickening (LV radial deformation) (34). Maturational studies that examine LV twist have shown that infants have different twist mechanics at rest compared with older children and adults (24). Infants have a more prominent basal early counterclockwise rotation and a delayed clockwise rotation component relative to the apical peak counterclockwise rotation. This results in a smaller at rest total LV twist compared with older children and adult hearts (24). We found baseline LV twist patterns in both NPs and YPs to be similar to those of human infants (Fig. 1, A and B) with a prominent basal early counterclockwise rotation and delayed clockwise rotation. However, during atrial tachycardia, the LV twist response between the two groups differed despite generating similar peak LV twist. NPs increased peak LV twist by enhancing peak LV apical rotation while the YPs achieved it through enhanced basal rotation. We now understand that the ventricular rotation and LV twist are the final outcomes of opposing forces generated by subendocardial (right hand helix oriented) and subepicardial (left hand helix oriented) myofibers. In addition to the balance of endocardial and epicardial forces, rotation patterns are influenced by the electric activation sequence, with an earlier electrical depolarization of the subendocardial fibers (33). LV geometry also likely plays a role in LV twist through relative change in LV fiber orientation secondary to LV remodeling as has been shown in adults with myocardial disease (8, 18). Given the observations of the current study, we postulate that the differences in LV twist mechanics between NPs and YPs would suggest fundamental differences in LV myocardial architecture, which may contribute to the enhanced response of the NP LV to tachycardia. Whether this reflects differences in endocardial to epicardial fiber orientation angles, LV geometry, and/or differences in LV electromechanical efficiency, is not certain and warrants further investigation.

Clinical implications. This study provides evidence of “normal” diastolic reserve in the neonate despite worse baseline diastolic measures. This finding is important to the clinician decision-making process when providing care for neonates. One has to consider the relative risk and benefits of inotropy vs. the side effects of extreme tachycardia (heart rate >180 beats/min) when using pharmacological means to support the patient’s cardiovascular circulation. Based on traditional concepts of LV maturation where neonates are viewed as having impaired diastolic performance compared with older infants, the clinician may choose to decrease a medication or even change the treatment because of the perceived risk of causing further ventricular inefficiency in an unstable patient when iatrogenically induced tachycardia is present. Our findings are novel and provide new insights to neonatal cardiac reserve during tachycardia. This not only alerts the research community to the limitations of extrapolating a patient’s diastolic reserve from at rest invasive and noninvasive assessment of diastolic function, it has the potential to influence future randomized controlled trial protocols on early hemodynamic management in neonates.
**Limitations.** The main limitation for translation of the findings in this animal model is the use of atrial pacing to induce atrial tachycardia, which is physiologically different from sinus tachycardia secondary to endogenous or exogenous adrenergic stimulation from neonatal disease states such as sepsis or low cardiac output from cardiac dysfunction. However, the use of pacemaker-induced tachycardia with relative absence of exogenous adrenergic stimulation serves to precisely control heart rate and limit the confounding properties of stress hormones on the observed acceleration of relaxation and diastolic function, such as its potentiating properties on myocyte calcium handling capacities (5), as well as on the vascular system that may have impacted loading conditions. The use of an animal model is essential as it allows for invasive measurements as well as more extreme hemodynamic challenges that are not feasible in the human neonate. Comparison of noninvasive echocardiographic markers of cardiac function to invasive markers provides invaluable information that can facilitate translation of our findings to the clinical setting for further investigation of the critically ill neonate and the development of better management strategies. The piglet cardiac anatomy is very close to that of the human’s (21), and it is a well-established model for neonatal cardiovascular studies (3, 17, 30).

The effects of sedation on hemodynamics are always a concern as both isoflurane (14) and propofol (10) have been shown to negatively affect the myocardium. As this was a closed chest model, we were able to minimize the use of anesthetic to produce shallow anesthesia once instrumentation was completed. Levels of isoflurane fluctuated during the experiments, in order for the animal to be comfortable with pacing and echocardiography, a situation that more likely approximates the clinical setting with variable levels of sedation. However, such fluctuations would have been difficult to reproduce in a sham animal with only peripherally inserted catheters and without pacing or echocardiography as both of the latter would have required isoflurane to maintain quiet sleep. Performing the experiment under deep sedation to have a fixed amount of sedation for all animals would have, in our opinion, greatly affected tolerance to tachycardia and made this study less informative. As we used low doses of sedatives through the protocol, the animals presented normal hemodynamic profiles after stabilization, and each animal was its own control, we are confident that our results represent tolerance to tachycardia.

We were not able to accurately assess LVED compliance given a relative decrease in LV preload induced with our model (i.e., pacing tachycardia) as indirectly evidenced by a reduction in LV end-diastolic dimension. As for any animal model, it is difficult to fully translate our findings to human neonates and infants. Furthermore, the cellular processes that contribute to the transition of diastolic function in piglets are incompletely described. More in-depth examination of calcium handling and evolution of titin and other myocardial elements during this period in the model to better establish their role in the evolution of systolic and diastolic reserve would be valuable.

**Conclusions.** Despite the observed worse diastolic measures at rest, the neonatal LV may have better tolerance to chronotropic stress compared with that of the young infant. The neonatal LV demonstrated better maintenance of cardiac output at extreme tachycardia, which is supported by having at least comparable diastolic reserve and an enhanced LV ejection performance. The differences in observed LV ejection could relate to the unique patterns of LV twist, which suggest the presence of fundamental differences in neonatal vs. young infant myocardial architecture. Whether this reflects differences in endocardial to epicardial fiber orientation angles, LV geometry, and/or other LV electromechanical efficiency or in unique cellular and molecular mechanisms is uncertain but warrants further study to further improve our understanding of its role in developmental changes in myocardial reserve. This study further highlights the necessary caution in the translation of findings from infants, children, or adult literature to the neonate.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


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