Effects of Digoxin on Systolic Time Intervals of Neonates and Infants

By Arthur M. Levy, M.D., David M. Leaman, M.D., and John S. Hanson, M.D.

SUMMARY
Systolic time intervals were measured in 27 normal newborn infants before and after administration of oral digoxin (30 \( \mu \text{g/kg} \)). Systolic intervals were also measured in 10 newborns and infants with congestive heart failure before and after this same 30 \( \mu \text{g/kg} \) dose of digoxin, but also after administration of a much larger "digitalizing dose" of 80 \( \mu \text{g/kg} \). Preejection period (PEP) shortened significantly in the normal newborns following the smaller dose. Changes in ejection time (ET) were much less striking and appeared to be transient, lasting less than 8 hours. When small doses of digoxin were given to the babies with congestive failure, PEP again shortened significantly. In general, the larger doses of digoxin produced no further changes in PEP or ET, although there were individual exceptions. The demonstration that maximal inotropic effect, as measured by PEP changes, usually occurred with small doses of digoxin may have significant clinical implications in terms of present concepts of loading doses of digitalis in the pediatric age group.

Additional Indexing Words:
Ejection time Preejection period Digitalizing regimens in infants Congestive heart failure in infants

DATA on myocardial responses of newborns and infants to positive inotropic agents is almost nonexistent in comparison with such data in normal adults and adult patients with various cardiac diseases. Extrapolation of the results of the adult data could be hazardous since no one has proven that the neonatal heart is merely a miniature of the adult heart without specific properties of its own. The cardiac literature includes a number of articles which discuss the management of infants with congestive heart failure, and the recommended digitalis regimens appear to be derived from the authors’ experiences in caring for sick babies with heart disease.\(^1\)\(^{-7}\) Gauging response to digitalis in patients of any age is notoriously difficult and this would explain the extremely wide range of recommended digitalis dosages.

The dosage problem is potentially a serious one with some authors suggesting that high-dose digitalis therapy is often necessary to control congestive heart failure in infancy,\(^1\)\(^{-4}\) and others suggesting clinical effectiveness with much lower dosage.\(^5\)\(^{-7}\) In fact, while there is no documentation, some pediatric cardiologists feel high doses may have adverse effects in the absence of overt toxicity, suggesting a descending limb of therapeutic response to digitalis. Because of recent experimental and clinical data, recommendations for digoxin dosage in adults have been standardized at a much lower level than previously suggested. Such agreement has not yet been
the case concerning treatment of congestive failure in infants.

A major reason for this lack of data related to digitalis effect in neonates may be the result of a 1962 study in which normal newborns were given digitalis to determine toxic levels of this drug. Deliberate use of high-dose digoxin has obvious potential dangers, and there was a death in that study. This resulted in a statement by Neill in 1965 that no more digitalis studies should be done on normal babies. Nonetheless, our study was designed and carried out because: (1) we were not trying to produce toxicity and in fact chose a dose we felt was completely safe, (2) consultation with other pediatric cardiologists met with a uniformly positive response as to the safety of this particular regimen, (3) the information to be gained was important if some of the problems associated with the treatment of sick infants, including those mentioned above, were to be resolved, and (4) the 1965 statement mentioned above was based on the premise that the one mortality was related to a single small dose of digitalis. (Review of this case revealed that this infant received two parenteral doses, the total amount of digoxin representing what would be considered by many to be an average dose and more than twice that used in our study.)

A noninvasive technic of measuring systolic time intervals, which has been shown to be a sensitive indicator of digitalis effect in normal adults, was chosen. These previous studies in adults, by demonstrating shortened pre-ejection periods (PEP) and left ventricular ejection time (ET), plus a few other investigations on the effects of digitalis on myocardial contractility in either nonfailing or normal hearts, appeared to have solved once and for all the old question of whether digitalis given to normal subjects results in a positive or negative inotropic response, or has

![Figure 1](image-url)

*Schematic representation of cardiac cycle demonstrating that PEP is the resultant of QS₂ minus ET. PEP (shaded area) includes QRS and isovolumetric contraction time. Comparison of the two cycles demonstrates that when PEP shortens, as with digitalis administration, the change is not in QRS length but somewhere within the period of ventricular pressure development. Presumably the slope of the upstroke of the left ventricular pressure pulse becomes steeper (i.e. LV dP/dt increases).*
no effect. All have confirmed that digitalis causes an augmentation of myocardial contractility in normal subjects, despite an absence of augmentation of cardiac output.

Methods

Eighty-two normal newborns, aged 1–3 days, had systolic intervals recorded and measured for control data. Twenty-seven of these received an oral dose of digoxin, and these measurements were repeated 4 hours later. Of these 27 newborns, 17 had measurements repeated a third time, 8 hours after the digoxin administration. Another group of 10 newborns and infants with severe congenital heart disease and congestive failure, or suspected congestive failure, was studied before digoxin therapy, 4 hours after a "partial digitalizing dose" and again after a so-called "full digitalizing dose."

Pediatric digoxin (Lanoxin Elixir) was used in the normal infants in a single dose of 30 μg/kg (15 μg/lb). This amount was derived as follows: The usual digitalizing dose in newborns at this institution is a commonly used 80 μg/kg. However, in infants exhibiting only borderline failure, a dose of 60 μg/kg is used. This has been found to be a safe dose in newborns with heart disease. Therefore, one half of the smaller total dose, or 30 μg/kg, was chosen for this normal study. In other terms, three-eighths of our usual total digitalizing dose was used.

The 10 babies with signs of decompensation were studied after the same 30 μg/kg and then again after the total 80 μg/kg dose had been given. However, in most instances, the first dose was given intramuscularly. In these cases, this initial dose was reduced to 20 μg/kg, since it has been a common pediatric practice to adjust parenteral digoxin by giving two-thirds the calculated oral dose.

A phonocardiogram, an external axillary artery pulse tracing, and an ECG were recorded simultaneously at a paper speed of 100 mm/sec for each infant. The ejection time (ET) was measured from the onset of upstroke of the axillary pulse to the incisura of the dicrotic notch. The pre-ejection period (PEP) was determined by subtracting the ejection time (ET) from the QS2, defined as the interval from the onset of the QRS complex to the first high-frequency component of the second heart sound (fig. 1). The phonocardiograph was recorded with a small, lightweight instrument made especially for infants* and was taped to the upper sternum. A small funnel connected by rubber tubing to a Cambridge pulse transducer was placed over the axillary artery. A six-channel Cambridge (English) photographic recorder was used. Measurements of time intervals were made to the nearest 5 msec.

Data were subjected to standard statistical analyses employing a PDP-12 digital computer. These included calculation of standard deviation and standard error of the mean, least-squares linear regression and correlation, and the Student t test for differences in paired samples.

*Manufactured by Elecath Electro-Catheter Corporation, Rahway, New Jersey.

Figure 2

Relationships of ET, QS4, and PEP to HR in 82 normal newborns.

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Results

Systolic Time Intervals in Normal Newborns

Regression equations relating heart rate and systolic time intervals in 82 normal newborns were calculated (fig. 2) and are listed as follows (expressed in msec):

\[
\begin{align*}
QS_2 & = 372 - 0.88 \text{ HR} \pm 15 \text{ msec} \\
ET & = 281 - 0.69 \text{ HR} \pm 13 \text{ msec} \\
PEP & = 91 - 0.18 \text{ HR} \pm 8 \text{ msec}
\end{align*}
\]

Indices were derived by transposition of the above equation in order to express the relationship between each of these intervals and heart rate, and are as follows:

\[
\begin{align*}
QS_2I & = Q_2 + 0.88 \text{ HR} \\
ETI & = ET + 0.69 \text{ HR} \\
PEPI & = PEP + 0.18 \text{ HR}
\end{align*}
\]

No significant differences in these intervals were noted between male and female neonates.

AM–PM Controls

Ten normal newborns had systolic time intervals measured in the morning and afternoon, with approximately 4 hours between measurements. This schedule duplicated that of the newborns receiving digitalis, but no medication was given. No significant differences were found by paired \( t \) test (all \( P \) values > 0.3) in PEP, QS2, ET, and PEP/ET when comparing the AM and PM data.

Systolic Time Intervals in Normal Newborns before and 4 Hours after Receiving Digoxin

Twenty-seven newborns received digoxin 30 \( \mu \text{g/kg} \) orally, and systolic time intervals done before and 4 hours after receiving the digoxin were compared. Statistically significant changes at the 0.001 probability level were seen for QS2, QS2I, PEP, and PEP/ET (table 1), all group mean values for these variables decreasing. Shortening of ET between control and postdigoxin measurements was significant only at the \( P < 0.05 \) level, while reduction in ETI was significant at \( P < 0.01 \). There was no significant change in heart rate (\( P > 0.40 \)).

Systolic Time Intervals in Normal Newborns
8 Hours after Receiving Digoxin

Repeat measurements were made in 17 of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>4-hr Postdigoxin</th>
<th>Predigoxin</th>
<th>P*</th>
<th>8-hr Postdigoxin</th>
<th>Predigoxin</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>119 ± 10.1</td>
<td>121 ± 12.5</td>
<td>NS</td>
<td>120 ± 14.9</td>
<td>121 ± 13.9</td>
<td>NS</td>
</tr>
<tr>
<td>QS2</td>
<td>269 ± 14.3</td>
<td>256 ± 13.9</td>
<td>&lt;0.01</td>
<td>253 ± 17.8</td>
<td>256 ± 13.9</td>
<td>NS</td>
</tr>
<tr>
<td>QS2I</td>
<td>271 ± 14.3</td>
<td>199 ± 12.7</td>
<td>&lt;0.001</td>
<td>198 ± 12.5</td>
<td>199 ± 12.5</td>
<td>NS</td>
</tr>
<tr>
<td>ET</td>
<td>198 ± 12.5</td>
<td>160 ± 10.3</td>
<td>&lt;0.001</td>
<td>169 ± 12.2</td>
<td>160 ± 10.3</td>
<td>NS</td>
</tr>
<tr>
<td>ETI</td>
<td>275 ± 12.4</td>
<td>372 ± 23.3</td>
<td>&lt;0.001</td>
<td>382 ± 12.2</td>
<td>375 ± 3.3</td>
<td>NS</td>
</tr>
<tr>
<td>PEP</td>
<td>32 ± 6.1</td>
<td>28 ± 6.5</td>
<td>&lt;0.001</td>
<td>28 ± 6.4</td>
<td>28 ± 6.5</td>
<td>NS</td>
</tr>
<tr>
<td>PEP/ETI</td>
<td>0.77 ± 0.05</td>
<td>0.77 ± 0.05</td>
<td>&lt;0.001</td>
<td>0.77 ± 0.05</td>
<td>0.77 ± 0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Testing for statistical significance of differences in pre- and postdigoxin values was performed by paired \( t \) test on individual subject data.

Table 1

**Group Mean Values and their Standard Deviations for Systolic Time Intervals (Msec) and Indices Pre- and Postdigoxin Administration in Normal Newborns**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>4-hr Postdigoxin</th>
<th>Predigoxin</th>
<th>P*</th>
<th>8-hr Postdigoxin</th>
<th>Predigoxin</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
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<td>256 ± 13.9</td>
<td>NS</td>
</tr>
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<td>199 ± 12.7</td>
<td>&lt;0.001</td>
<td>198 ± 12.5</td>
<td>199 ± 12.5</td>
<td>NS</td>
</tr>
<tr>
<td>ET</td>
<td>198 ± 12.5</td>
<td>160 ± 10.3</td>
<td>&lt;0.001</td>
<td>169 ± 12.2</td>
<td>160 ± 10.3</td>
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<tr>
<td>ETI</td>
<td>275 ± 12.4</td>
<td>372 ± 23.3</td>
<td>&lt;0.001</td>
<td>382 ± 12.2</td>
<td>375 ± 3.3</td>
<td>NS</td>
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<td>PEP</td>
<td>32 ± 6.1</td>
<td>28 ± 6.5</td>
<td>&lt;0.001</td>
<td>28 ± 6.4</td>
<td>28 ± 6.5</td>
<td>NS</td>
</tr>
<tr>
<td>PEP/ETI</td>
<td>0.77 ± 0.05</td>
<td>0.77 ± 0.05</td>
<td>&lt;0.001</td>
<td>0.77 ± 0.05</td>
<td>0.77 ± 0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviation: NS = not significant (\( P > 0.05 \)); see text for other abbreviations.
There was no significant further change in the heart rate interval (table 2). These babies were studied again approximately 4 hours after receiving digoxin 80 μg/kg (our standard digitalizing dose). The changes were basically similar to the larger group of normal subjects, the major effect being a decrease in PEP and PEP/ET, which were no longer seen by 8 hours postdigoxin. These babies were studied before and 4 hours after receiving the same 80 μg/kg dose given to the normal infants (table 2). These were basically the same babies that had severe congenital heart disease and were judged to be in congestive heart failure. The changes seen were not significant. Table 2 shows that the changes were not significant.

Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Predigoxin 1/2 Dose</th>
<th>Predigoxin Full dose</th>
<th>Predigoxin Full dose</th>
<th>Predigoxin Full dose</th>
<th>Predigoxin Full dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>QRS</td>
<td>255 ± 26.7</td>
<td>258 ± 25.7</td>
<td>258 ± 25.7</td>
<td>258 ± 25.7</td>
<td>258 ± 25.7</td>
</tr>
<tr>
<td>ET</td>
<td>192 ± 26.0</td>
<td>197 ± 24.7</td>
<td>197 ± 24.7</td>
<td>197 ± 24.7</td>
<td>197 ± 24.7</td>
</tr>
<tr>
<td>PEP</td>
<td>73 ± 14.8</td>
<td>61 ± 16.4</td>
<td>&lt;0.001</td>
<td>61 ± 16.4</td>
<td>61 ± 16.4</td>
</tr>
<tr>
<td>QiI</td>
<td>393 ± 18.5</td>
<td>386 ± 18.1</td>
<td>&lt;0.01</td>
<td>386 ± 18.1</td>
<td>386 ± 18.1</td>
</tr>
<tr>
<td>ETT</td>
<td>293 ± 23.3</td>
<td>298 ± 23.8</td>
<td>&lt;0.01</td>
<td>298 ± 23.8</td>
<td>298 ± 23.8</td>
</tr>
<tr>
<td>PEP/ET</td>
<td>0.39 ± 0.10</td>
<td>0.32 ± 0.10</td>
<td>&lt;0.001</td>
<td>0.32 ± 0.10</td>
<td>0.32 ± 0.10</td>
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</tbody>
</table>

Testing for statistical significance of differences in pre- and postdigoxin values was performed by paired t test on individual subject data. Abbreviation: ns = not significant (P > 0.05); see text for other abbreviations.
group mean preejection phase data (PEP and PEP/ET) compared to the values after the smaller dose (fig. 4). The change in ETI was again transient and was no longer noted after full digitalization. There were, however, three of 10 who showed a further decrease in PEP and PEP/ET with the additional 50 \( \mu \)g/kg of digoxin. The patient mentioned in the first paragraph above, who showed no decrease in PEP or PEP/ET with the smaller dose, was one of these exhibiting significant shortening of PEP and decrease in PEP/ET following additional digoxin dosage.

**Discussion**

While digoxin produced a definite change in systolic time intervals in the normal neonates, this response was not totally identical to that reported in normal adults. Specifically, in the adults both ET and PEP shortened with digitalis administration, and this effect persisted for days. In the newborns, PEP shortened significantly but the ET effect was less prominent and was transient (figs. 3, 4). ET has been demonstrated to have a direct relationship to stroke volume and ejection fraction. It was felt by Weissler et al. that the digitalis-induced shortening of ET in adults represented a true effect on myocardial contractility since stroke volume actually increased rather than decreased and, therefore, stroke volume could not be the cause for more rapid left ventricular emptying. In other words, the mean rate of left ventricular ejection (MRLVE) increased as the result of digitalis administration. The shortened PEP was felt to be further evidence of positive inotropy. Although the PEP includes the subintervals of electromechanical delay and isovolumetric contraction time (ICT), Weissler et al. have demonstrated the majority of this shortening occurs during ICT. This change is secondary to a steeper upstroke of the left ventricular pressure pulse (fig. 1), i.e. an increased left ventricular dP/dt. Another way to explain this is that a decreased PEP signifies an increased rate of myocardial force development and thus a decrease in the time required for intraventricular pressure to reach the aortic diastolic pressure. Recent investigation has further demonstrated the relationship between an altered inotropic state and PEP. It has been shown that a number of positive inotropic agents (including isoproterenol, epinephrine, norepinephrine, and digitalis) shorten PEP, and conversely the negative inotropic agent propranolol lengthens PEP.

The disappearance of the early (4 hours) small but significant shortening of ET and ETI by 8 hours is difficult to explain. Other studies on adults have shown persistence of the ET changes for days after an initial loading dose of digitalis. For some unknown reason, in newborns, the changes in pre-ejection (increased LV dP/dt) do not produce a measurable change in actual ejection except transiently. It may be that the infant's left ventricle is already emptying as efficiently as possible with a fairly fixed MRLVE. It is also possible, however, that in the neonate receiving digitalis, stroke volume increases even more than in the adult, thus counterbalancing the inotropic effect of a tendency to shorten systole. That is, MRLVE is increasing, but increased stroke volume results in minimal ET changes.

The PEP/ET ratio has been found to be an excellent index of function by virtue of its very good correlation with ejection fraction.
and its inherent characteristics of partially nullifying heart rate variability. With respect to the possibility of basic differences in contractility or response to inotropic agents between adult and infant myocardium, one of the more interesting findings in this study was that of a mean PEP/ET ratio in normal newborns of 0.350, almost identical to the ratio of 0.345 found by Garrard et al.\textsuperscript{16} in adults. This occurred despite markedly different absolute values in PEP and ET in the two groups.

The infants with congestive heart failure received much larger doses of digoxin than the normal subjects. These babies were studied before and after receiving the same doses of digoxin as the normal infants (30 μg/kg) and then restudied after receiving our standard “total digitalizing dose” of 80 μg/kg. The majority showed the same shortening of PEP after the first dose as did the normal subjects, and there was no further change after the much larger dose (table 2, fig. 4). In this group there were again only transient changes in ETI.

It is certainly of interest to speculate about the implications of the fact that small doses of digoxin in general produced the same effects on systolic time intervals as the much larger dose. The relative effectiveness of low-dose digitalis was also noted by Weissler et al.\textsuperscript{18} using i.v. lanatoside C (Cedilanid) in adults and measuring systolic intervals. Our data suggest that the group of pediatric cardiologists who utilize the smaller doses is, in general choosing an effective regimen which probably is less hazardous than one chosen by cardiologists (our group included) who routinely utilize the larger dose of 80 μg/kg.

Obviously, clinical response to inotropic agents is the effect in which we are interested, and these indirect measurements of inotropic effect may or may not be related to clinical effect. However, determining clinical effects of digitalis as a therapeutic guideline has always been a major problem in digitalis therapy, whether with adults or babies. Since the widely varying opinions regarding the best digitalizing doses for babies are based on clinical evidence, and perhaps “evidence” is an incorrect choice of words, it would seem that the use of objective measurements, such as PEP shortening described in this paper, should be considered even though we would all admit that clinical improvement is a more desirable index. Attempting to tailor the dose to each patient is admittedly the correct approach when possible, but this is easier said than done. While the usual response to the suggestion that low-dose digitalis is as effective as high-dose digitalis is skepticism, and the recall of large numbers of cases who have shown marked improvement after pushing the drug, clinical improvement in babies with congestive heart failure is often associated with therapeutic maneuvers other than just increasing dosage of digoxin. For instance, the use of ethacrynic acid in newborns with large shunts, with or without transposition, can be extremely effective, but when administered with digitalis the picture of what caused the improvement becomes cloudy.

Cardiologists practicing over the last decade or two have watched the rather marked change that has occurred in recommended doses of digitalis (particularly digoxin) for adults. Suggested digitalizing doses in many texts were 2.5–3.5 mg of digoxin, but it now appears to be more common practice to use approximately one half to two thirds of this amount. During this same time, there has been no similar wave of enthusiasm to reduce digitalizing doses for babies even though there is evidence that these doses in babies are truly high. One recent study\textsuperscript{19} showed serum digoxin levels in a group of digitalized infants were 65% higher than in a group of digitalized adults. Most of the infants in fact were in the so-called toxic range of digoxin levels established in adults. Another study\textsuperscript{20} found absorption, tissue concentration, and excretion of digoxin the same in infants as in adults, suggesting there is no good reason to perpetuate digitalizing schedules that produce such high digoxin levels in infants.

We are not yet suggesting that these systolic time intervals should be measured in all babies who are being digitalized and the
total dose determined by changes in PEP. However, since quantitative assessment of the inotropic effect of digitalis in babies with congestive heart failure is difficult, if not impossible, on a clinical basis, these indirect measurements should be studied closely as a possible aid with pharmacologic manipulation. One approach with sick babies would be to measure systolic time intervals before and after modest loading doses of digoxin. If there is significant shortening of PEP and serum levels are normal or high normal, other therapeutic measures would then be instituted if the baby does not show the expected amount of improvement. We are in the process of evaluating this approach even though this study was not designed to test this.

This noninvasive approach to studying myocardial function in the pediatric age group would appear to have some promise. The pattern of response to digitalis in normal infants has now been demonstrated. Dose-response characteristics in sick babies need further delineation, but this study suggests that, as with adults, the first relatively small dose of digitalis may be the best dose each patient receives in terms or resultant increase in myocardial contractility. With further studies on babies with all varieties of cardiac lesions, this relatively simple noninvasive tool may afford us the opportunity to make the treatment of congestive failure in infancy more scientific than it has been up to now.

References
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