Pozitivně inotropní léky

Jiří Vítovec,

LF MU a FN u sv. Anny v Brně
Excitace-kontrakce
AN ACCOUNT OF THE FOXGLOVE,
AND
Some of its Medical Uses:
with
PRACTICAL REMARKS ON DROPSY,
AND OTHER DISEASES.

By
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Physician to the General Hospital at Birmingham.

nonumque prematur in annum.
Horace.

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Birmingham, England: M. Swinney, 1785: X, V.
HEART FAILURE IN OUTPATIENTS

A Randomized Trial of Digoxin versus Placebo

Daniel Chia-Sen Lee, M.D., Robert Arnold Johnson, M.D., John B. Bingham, M.D.,
Marianne Leahy, R.N., Robert E. Dinsmore, M.D., Allan H. Goroll, M.D.,
John B. Newell, B.A., H. William Strauss, M.D., and Edgar Haber, M.D.

Abstract The view that digitalis clinically benefits patients with heart failure and sinus rhythm lacks support from a well-controlled study. Using a randomized, double-blind, crossover protocol, we compared the effects of oral digoxin and placebo on the clinical courses of 25 outpatients without atrial fibrillation. According to a clinicoradiographic scoring system, the severity of heart failure was reduced by digoxin in 14 patients; in nine of these 14, improvement was confirmed by repeated trials (five patients) or right-heart catheterization (four patients). The other 11 patients had no detectable improvement from digoxin. Patients who responded to digoxin had more chronic and more severe heart failure, greater left ventricular dilation and ejection-fraction depression, and a third heart sound. Multivariate analysis showed that the third heart sound was the strongest correlate of the response to digoxin (P<0.0001). These data suggest that long-term digoxin therapy is clinically beneficial in patients with heart failure unaccompanied by atrial fibrillation whose failure persists despite diuretic treatment and who have a third heart sound. (N Engl J Med. 1982; 306:699-705.)
Dvojitě slepé studie (s vysazením digoxinu)

RADIANCE
Packer (NEJM 1993)
178 pts, s.r., NYHA II-III, EF< 35%, Rx ACEI, diuretika
Závěr: Po vysazení digoxinu zhoršení stavu srd. selhání.

PROVED
Uretsky (JACC 1993)
88 pts, s.r., NYHA II-III, EF< 35%, Rx pouze, diuretika
Závěr: Po vysazení digoxinu zhoršení stavu srd. selhání.
Cíl: Určit vliv digoxinu na úmrtnost a hospitalisaci u nemocných se srdečním selháním a sinusovým rytmem

Pts: Digoxin 3397, Placebo 3403, EF < 0,45
Rx: ACE-I 94%, diuretika 82%, nitráty 43%
Dg: ICHS 71%, DKM 29%
NYHA: I 14%, II 53%, III 31%, IV 2%

N Engl J Med 1997;336:525-33
DIG

Celková mortalita

Mortalita a hospitalisace pro zhoršení srdečního selhání

N Engl J Med 1997;336:525-33
All-Cause Mortality Rates by Serum Digoxin Concentration Groups

- Digoxin group
  - Crude mortality rate
  - Risk adjusted mortality rate
- Placebo group
- -- Mortality rate

Serum Digoxin Concentration, ng/mL

Mortality, Rate %

J Am Coll Cardiol 2005;46:497-504
Fakta o digoxinu

Jaký?
vyřešeno - digoxin

Dávka?
tak aby plazm. \[0,55 - 0,9 \text{ ng/ml} = 0,6 - 1,1 \text{ nmol/L}\]

Kdy?
lék 3. volby
po ACEi/ARB, BB ev. diu

Myslet na předávkování!!
AFFIRM

**Whitbeck et al.**
- Study design: Non-randomized, observational analysis using data from randomized AFFIRM trial
- Time point digoxin used assessed: Time-varying covariate, throughout study
- Cohort: Full cohort (n = 4058)
- Propensity method: Adjustment
- Primary HR for digoxin and all-cause mortality association: HR 1.41, 95% CI 1.19–1.67; P < 0.001
- Main conclusion from authors: Digoxin associated with significant increase in all-cause mortality in patients with AF

**Gheorghiade et al.**
- Study design: Non-randomized, observational analysis using data from randomized AFFIRM trial
- Time point digoxin used assessed: Fixed, at baseline only
- Cohort: Selected cohort (n = 1756)
- Propensity method: Matching
- Primary HR for digoxin and all-cause mortality association: HR 1.06, 95% CI 0.83–1.37; P = 0.640
- Main conclusion from authors: No evidence of increased mortality associated with digoxin use as baseline initial therapy in patients with AF

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European Heart Journal (2013) 34, 1481–1488 a 1489–1497
Freeman et al looked at 2891 digoxin-naive adults with recently diagnosed systolic heart failure from 2006 to 2008, 18% of whom were started on digoxin; they were followed for a median of 2.5 years. Hazard ratio* (95% CI) for Outcomes, Digoxin (n=529) vs No Digoxin (n=2362) for Recent-Onset Systolic HF

![](image)

**Conclusions**—Digoxin use in patients with incident systolic HF was independently associated with a higher risk of death but no difference in HF hospitalization

Doporučení digoxinu

Jaký?
digoxin
Dávka?
tak aby plazm.
[0,55 - 0,9 ng/ml = 0,6-1,1 nmol/L] !!
Kdy?
lék 3-4.volby
po ACEi/ARB,BB ev.diu
Myslet na předávkování a používat klinický náhled!!
Were such data presented in an article submitted to any modern journal, they would no doubt be immediately rejected. What did Withering know about a randomized, prospective, double blind study to determine therapeutic efficacy? Fortunately for millions of patients over the last 200 years, this was no impediment to his wonderful contribution.
<table>
<thead>
<tr>
<th>Inotropic mechanism</th>
<th>Drugs</th>
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</thead>
<tbody>
<tr>
<td>Sodium-potassium-ATPase inhibition</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Beta-1-adrenoceptor stimulation</td>
<td>Dobutamine, dopamine</td>
</tr>
<tr>
<td>Phosphodiesterase III inhibition</td>
<td>Enoximone, milrinone</td>
</tr>
<tr>
<td>Calcium sensitization</td>
<td>Levosimendan</td>
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<tr>
<td>Sodium-potassium-ATPase inhibition plus SERCA activation</td>
<td>Istaroxime</td>
</tr>
<tr>
<td>Acto-myosin cross-bridge activation</td>
<td>Omecamtiv mecarbil</td>
</tr>
<tr>
<td>SERCA activation</td>
<td>Gene transfer</td>
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<tr>
<td>SERCA activation plus vasodilation</td>
<td>Nitroxylo donor; CXL-1020</td>
</tr>
<tr>
<td>Ryanodine receptor stabilization</td>
<td>Ryanodine receptor stabilizer; S44121</td>
</tr>
<tr>
<td>Energetic modulation</td>
<td>Etomoxir, pyruvate</td>
</tr>
</tbody>
</table>
Conclusions Six-month intermittent low-dose dobutamine administration was well tolerated by patients with severe CHF; it did not improve the functional status and did not significantly increase the mortality rate as found with higher dobutamine doses in other studies. Hospitalizations for all causes and for worsening of CHF tended to be fewer in the dobutamine group. (Am Heart J 1999;138:247-53.)
<table>
<thead>
<tr>
<th>Stav</th>
<th>Beta mimetika</th>
<th>Dávka</th>
<th>Poznámka</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligourie</td>
<td>Dopamin</td>
<td>2-5 ug/kg/min</td>
<td>DA, VD, ren??</td>
</tr>
<tr>
<td>Hypotenzí</td>
<td></td>
<td>5-20 ug/kg/min</td>
<td>β i α st., inotropní</td>
</tr>
<tr>
<td>Hypotenzí + ↓ CI, ESHF bridging před OTS,</td>
<td>Dobutamin</td>
<td>1-20 ug/kg/min</td>
<td>β st., inotrop</td>
</tr>
</tbody>
</table>
OPTIME CHF
951 pts s TKs > 80 mmHg a TF < 110/min
diuretika ACE-I, betabli., digitalis povoleny

Mortalita 60 dní
Mortalita FiSi
Slehání léčby
Milrinon 72 hod vs placebo

JAMA 2002;287:1541–7
Mortality Comparison - 31 Days

**Study**

**LIDO** (N = 203)

**CASINO** (N = 200)

**SURVIVE** (N = 1327)

**SURVIVE, LIDO, CASINO** (N = 1730)

Relative Risk (95% CI)

- **Favors Levosimendan**
- **Favors Dobutamine**

P = 0.032
Istaroxim inhibuje aktivitu Na-K ATPasy a současně stimuluje SR Ca ATPase (SERCA) isoform 2a (SERCA2a).
Omecamtiv mecarbil

A•M•ADP

Power stroke

Cardiac myosin activators

A•M•ADP•Pi

ATP binding

A•M

ADP release

Actin release

M•ATP

ATP hydrolysis

M•ADP•Pi

Pi

Actin

Actin

Myosin head
Primary Outcome Measures:
The primary objective of the study is to evaluate the effect of 48 hours of intravenous (IV) omecamtiv mecarbil compared with placebo on dyspnea in subjects with left ventricular systolic dysfunction hospitalized for acute heart failure.
New inotropes

[Diagram showing various calcium handling pathways and modulators including Ca2+, RyR2, SERCA2a, ATP, HNO, 2K, 3Na+, NCX, and energetic modulators represented by TNT, TNC, and TNI.]
Mýty o inotropicích

1. Hledání zlatého grálu tzn. perorálního inotropika, který by nahradil digoxin

2. Zlepšení hemodynamiky sníží úmrtnost

3. Kvalita života je méně významný cíl léčby než statisticky vyčíslitelná mortalita!
Fakta o inotropících

1. Hemodynamické zhoršení s nízkým MO (př. CI pod 2 l/min/m2) a zvýšení plnícího tlaku LK či PK (př. PCWP nad 18–20 mmHg a RAP nad 10–12 mmHg)

2. Optimalní farmakologická léčba, včetně inhibitorů RAA, diuretik event. s nitráty
3. Kriticky nemocný na podkladě abnormalní hemodynamiky a:
   a. Závažná limitace zátěže
   b. Převodnění s rezistencí na diuretika
   c. Renální či hepatální postižení (zvýšení krea, urea, JT, bili apod.)
4. Tam, kde nelze použít LVAD – jako „bridging“ před OTS
Using IV inotropes is still controversial among doctors because they increase your risk of death. However, if a CHFer suffers severe symptoms that standard drugs don't help, he might want inotropes anyway. Keep in mind that using IV inotropes will probably shorten your life. On the other hand, they may greatly improve your quality of life, even if only for a short while. It's your body, your life, and your call.