Is routine AV optimization still justified?

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My conflicts of interest

INTELLECTUAL PROPERTY

Patents for high-reproducibility methods of physiological AV and VV optimization

PROFESSIONAL CONFLICT OF INTEREST

Have made claims for potential benefits of physiological AV and VV optimization
Isn’t optimization dead?

SMART-AV trial of qualitative echo optimization

[Graph showing changes in volume for Smart Delay, Echo, and Fixed conditions]

Let’s see how iterative optimization is done!

Ellenbogen, Circulation 2010
Qualitative echo optimization

Protocol

AV too long
Protocol

AV too long

AV too short
Qualitative echo optimization

Protocol

AV too long

AV too short

AV optimal
Appendix 8: AV delay Optimization Via Echo

Step 1: Program the Cardiac Resynchronization device to 40 Bpm or lower to assure an intrinsic sinus rate. Program the Magnet rate Off, Rate adaptive interval Off and ventricular pacing in Unipolar mode.

Step 2: Program the AV delay after atrial sensing (SAVD) to 200 msec. With this programmed setting you will observe that the mitral valve closure occurs delayed to the end of the A-wave. (Fig 1)

Investigational Plan
Version: 2.02.02
April 28, 2000

AV too long

AV too short

AV optimal
Appendix 8: AV delay Optimization Via Echo

Step 1: Program the Cardiac Resynchronization device to 40 Bpm or lower to assure an intrinsic sinus rate. Program the Magnet rate Off, Rate adaptive interval Off and ventricular pacing in Unipolar mode.

Step 2: Program the AV delay after atrial sensing (SAVD) to 200 msec. With this programmed setting you will observe that the mitral valve closure occurs delayed to the end of the A-wave. (fig. 1).
Step 3: Decrease the SAVD by steps of 20 ms and evaluate if mitral valve closure Doppler signal is still delayed to the end of the A-wave. Stop to decrease the AV interval when mitral valve closure Doppler signal is causing A-wave truncation (fig. 2).

**Figure 2**
Step 4: When A wave is truncated, increase the AV interval in steps of 10 ms, to ensure that mitral valve closure Doppler signal coincides with or occurs shortly after the end of the A-wave. Such AV interval should not modify the A-wave morphology and assure optimal E-A duration and left ventricular filling (Fig. 3).

**Figure 3**

Step 5: Reprogram the device with the previous basic rate. Program adaptative AV Interval On, Magnet rate On, bipolar ventricular stimulation and sensing configuration and the selected optimal AV Interval.
Question:

Can people really do this?

A multinational evaluation was carried out …
Qualitative echo optimization

Patient 1
Observer 1 chooses option C

Qualitative echo optimization

Patient 1

Observer 2 chooses option D

Qualitative echo optimization

Patient 1

36 experts
(Mainly at the ESC Congress)

Patient 1

Qualitative echo optimization

36 experts
avessed 20 doppler sequences

Average kappa $0.12 +/- 0.08$
(very poor agreement)

Kappa scale
0.0 = pure guesswork
1.0 = excellent agreement

But we were lying

There were not 20 datasets
There were only 10 sets of Doppler freeze frames pictures, each shown twice

So each observer examined 10 identical sets of Dopplers, twice
Patient 2

2  A
5  B
5  C
9  D
6  E
2  F

“Patient 15”
but really same Doppler as “2”

All patients, and all observers showed the same problem.

Operators disagreed with each other
Operators disagreed with *themselves*
   kappa=0.23

Disagreed just almost as much as with others:
   = *Not* a failure of “some people”
      But a **method that is impossible** to carry out

And the participants did not realise it...

“*They did not know that they did not know*”
“There are known knowns ... things we know we know.

There are known unknowns; we know there are some things we do not know.

But there are also unknown unknowns – the ones we don't know we don't know.”

Former United States Secretary of Defense
Donald Rumsfeld

“They did not know that they did not know”
Quantitative echo optimization
Quantitative echo optimization
Optimization

AV 40

VTI

16.67
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Apparent AV optimum: 160ms, 40ms, 80ms
VTI maximisation
One single run

Can you trust this to be the optimum?
Multi-beat averages

Reduce the impact of noise.
Increase the reliability of the optimum, in proportion to \( \sqrt{n} \)

But..

Many beats = a lot of effort to analyse
Cardiac resynchronization therapy optimization by finger plethysmography

Christian Butter, MD, a Christoph Stellbrink, MD, b Andres Belalcazar, MS, c Don Villalta, MS, c Michael Schlegl, MD, a Anil Sinha, MD, b Francisca Cuesta, PhD, d Craig Reister, MS c

aFrom the Department of Cardiology, German Heart Institute Berlin, Berlin, Germany,
bDepartment of Cardiology, RWTH University Hospital, Aachen, Germany,
cGuidant CRM Research, St. Paul, Minnesota, and
dGuidant CRM Research, Brussels, Belgium.

Pace on

LV - EGRAM

15 mV

FINGER

50 units

AORTA

30 mmHg
Quantitative optimization

% change in aortic pressure

% change in finger signal

Butter et al, Heart Rhythm 2004;1:568–575
Quantitative optimization

Blood pressure trace
AV delay 120ms

AV delay 80ms

Quantitative optimization
Kyriacou, PACE 2012

Invasive aortic root

Invasive proximal aortic pressure (mmHg)

AV 120ms

AV 40ms

Non Invasive Finger

Finometer derived finger pressure (mmHg)
Quantitative optimization

Patient 3

AVD (ms)

SBPrel (mmHg)

Unfortunately

Clinical Endpoint Evidence will require an implausibly large study

Half the effect size of CRT itself

4 × the effect size of CRT itself
How else to choose?

The 3 features to look out for in any optimization scheme
One single peak

AV Delay

Singularity
Two optimizations a few minutes apart should be same

Reproducibility
Multiple independent methods should agree
Multiple independent methods should agree
A gold standard for testing quick new optimization methods?

Agreement with a *cluster* of reference physiological methods, that show:

1. Singularity
2. Reproducibility
3. Clustering
This is now available

Kyriacou, PACE 2012
Quick shortcut formulae for the optimum?
Quick shortcut formulae
Quick shortcut formulae

• Rarely make sense
• Are sometimes secret
• Have often been “validated against echo”
  i.e. “agree” with something
  that doesn’t agree with itself!

• Disagree between companies!

If $N-1$ can be wrong,
all $N$ can be wrong.
Inflection points?
Inflection points?

E wave area

A wave area

QRS duration

First heart sound loudness

Short AV Delay

Long AV Delay

Contradictory “find the inflection” optima

Optimum
Quick shortcut formulae and inflection points

• Rarely make sense
• Are sometimes secret
• Have often been “validated against echo”
  i.e. “agree” with something that doesn’t agree with itself!

• Disagree between companies!

If $N-1$ can be wrong, all $N$ can be wrong.
Why study optimization, knowing the effect size is small?
Left Ventricular Versus Simultaneous Biventricular Pacing in Patients With Heart Failure and a QRS Complex ≥120 Milliseconds

Background—Left ventricular (LV) pacing alone may theoretically avoid deleterious effects of right ventricular pacing. Methods and Results—In a multicenter, double-blind, crossover trial, we compared the effects of LV and biventricular (BiV) pacing on exercise tolerance and LV remodeling in patients with an LV ejection fraction ≤35%, QRS ≥120 milliseconds, and symptoms of heart failure. A total of 211 patients were recruited from 11 centers. After a run-in period of 2 to 8 weeks, 121 qualifying patients were randomized to LV followed by BiV pacing or vice versa for consecutive 6-month periods. The greatest improvement in New York Heart Association class and 6-minute walk test occurred during the run-in phase before randomization. Exercise duration at 75% of peak VO₂ (primary outcome) increased from 9.3±6.4 to 14.0±11.9 and 14.3±12.5 minutes with LV and BiV pacing, respectively, with no difference between groups (P=0.4327). LV ejection fraction improved from 24.4±6.3% to 31.9±10.8% and 30.9±9.8% with LV and BiV pacing, respectively, with no difference between groups (P=0.4530). Reductions in LV end-systolic volume were likewise similar (P=0.6788). The proportion of clinical responders (≥20% increase in exercise duration) to LV and BiV pacing was 48.0% and 55.1% (P=0.1615). Positive remodeling responses (≥15% reduction in LV end-systolic volume) were observed in 46.7% and 55.4% (P=0.0881). Overall, 30.6% of LV nonresponders improved with BiV and 17.1% of BiV nonresponders improved with LV pacing. Conclusion—LV pacing is not superior to BiV pacing. However, nonresponders to BiV pacing may respond favorably to LV pacing, suggesting a potential role as tiered therapy. Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00901212.

Montreal, Canada

Multicentre RCT, 121 pts, EF≤35, QRS≥120 ms
Tried different pacing modes…
Is this mode LV or BiV?
CRT off

P<0.0001

NYHA III-IV
NYHA I-II
P<0.0001

CRT off

LV

BiV

n.s.

n.s.

NYHA III-IV

NYHA I-II
What is the symptomatic response rate caused by CRT pacing?

0 – 30%
31–50%
51–60%
61–70%
71–80%
81–90%
91–100%
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Weighted Mean

Open Contak CD

Weighted Mean

Companion (CRT-P)

Weighted Mean

Weighted Mean of All Studies

CRT minus control -23
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**Blinded**

MIRACLE
MIRACLE ICD

**Weighted Mean**

Open Contak CD

**Weighted Mean**

Companion (CRT-P)

**Weighted Mean of All Studies**

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**But** these were controlled trials

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**Weighted Mean of All Studies**

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But these were controlled trials. Was their Response Rate zero?
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**Weighted Mean of All Studies**

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- CRT: 51
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Participants with improved NYHA Class Response with CRT truly attributable to CRT pacing.
Participants with improved NYHA Class Response with CRT: 51%

Response without CRT: 35%
51% Participants with improved NYHA Class

51% Response with CRT

16% Response truly attributable to CRT pacing

35% Response without CRT

Participants with improved NYHA Class Response with CRT is 51%. Response without CRT is 35%. Is this 35% a placebo effect?
<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>CRT</th>
<th>CRT minus Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blinded</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIRACLE</td>
<td>9</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>MIRACLE ICD</td>
<td>11</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>MIRACLE ICD II</td>
<td>10.7</td>
<td>13.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Mustic</td>
<td>3.8</td>
<td>17.4</td>
<td>13.6</td>
</tr>
<tr>
<td><strong>Weighted Mean</strong></td>
<td>9.5</td>
<td>16.9</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>Open</strong></td>
<td></td>
<td></td>
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<tr>
<td>CARE HF</td>
<td>4.8</td>
<td>14.5</td>
<td>9.7</td>
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<td>Companion</td>
<td>12</td>
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<td>Contak CD</td>
<td>-5</td>
<td>7</td>
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<tr>
<td><strong>Weighted Mean</strong></td>
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<td>17.3</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Weighted Mean of All Studies</strong></td>
<td>6.0</td>
<td>17.2</td>
<td>11.2</td>
</tr>
</tbody>
</table>
Mean Improvement in Minnesota Living With Heart Failure Score

- **Blinded studies**:
  - + CRT
  - Control

- **Partly placebo**

- **Open studies**
Blinded Studies

Open Studies

Response

truly

attributable
to CRT

pacing

Placebo

Effect

attributable
to device

implantation

Spontaneous

Improvement

+ CRT

Control

Control

Mean Improvement in Minnesota Living With Heart Failure Score

Open studies

No placebo

Open Studies

- **Blinded Studies**
  - + CRT
  - Control
  - Response truly attributable to CRT pacing
  - Placebo Effect attributable to device implantation
  - Spontaneous Improvement

- **Open Studies**
  - + CRT
  - Control

Mean Improvement in Minnesota Living With Heart Failure Score
Percentage of patients whose symptoms improved:

- **ACEi:** 23%
- **CRT:** 16%

35% improvement for CRT.
How to justify “2/3” response

Quoted Response to CRT

- 66%
- 15%
- 20%
- 16%
- 15%

Response attributable to CRT pacing

- 15%

Placebo effect

- 20%

Spontaneous improvement

- 15%

Inflation

- 15%

Rationale for routine optimization
1. Small increment in function in the average LBBB patient

2. Difference between positive and negative response in the grey zone patient

3. Valid comparison between leads and pacing configurations

4. Reproducible marker of response, not confounded by other disease events

Bogaard, Europace (2010) 12, 1262–1269