Is routine AV optimization still justified?

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My conflicts of interest

INTELLECTUAL PROPERTY

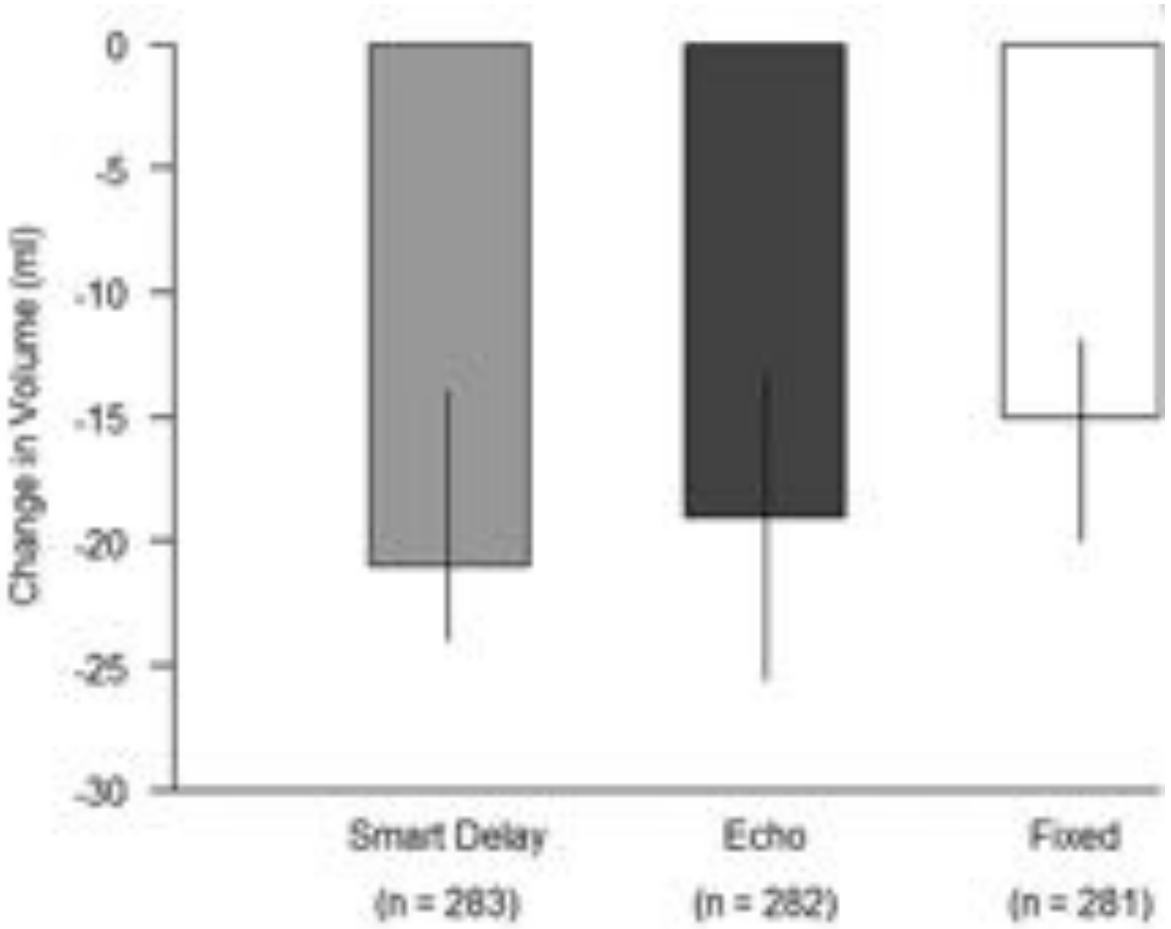
Patents for high-reproducibility methods of physiologial AV and VV optimization

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



Let's see how iterative optimization is done!

Ellenbogen, Circulation 2010

Qualitative echo optimization

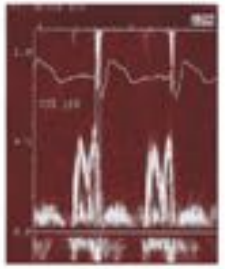
Care - HF

Protocol

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)



AV
too long

Qualitative echo optimization

Care - HF

Protocol

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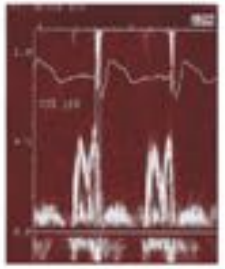
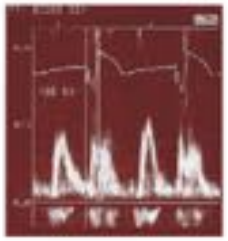
AV
too long



AV
too short



Qualitative echo optimization

Care - HF

Protocol

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AV
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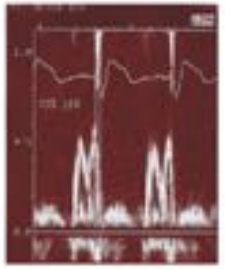
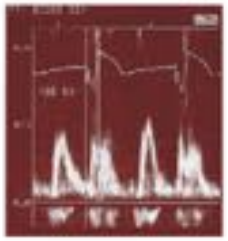
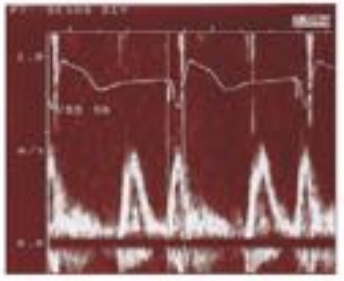


AV
too short



AV
optimal



Qualitative echo optimization

Care - HF

Cardiac resynchronization in Heart Failure

Investigational Plan

Version: 2.02.02

April 28, 2000

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AV too long

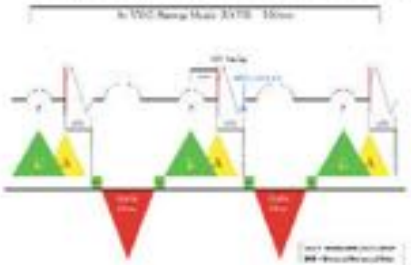
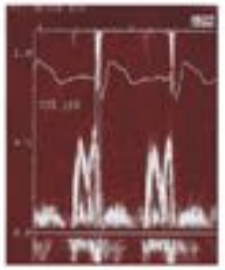


Figure 1



AV too short

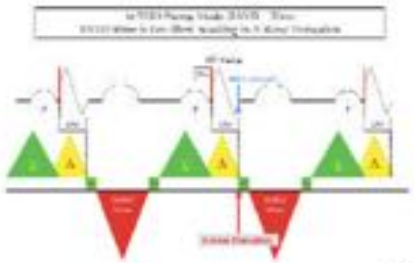
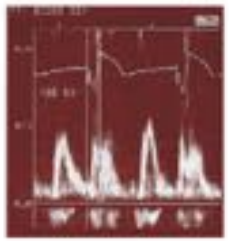
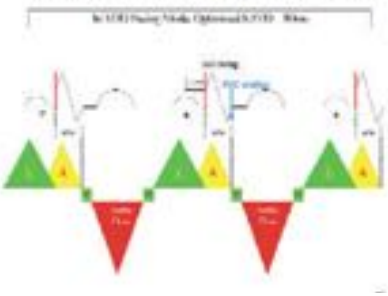
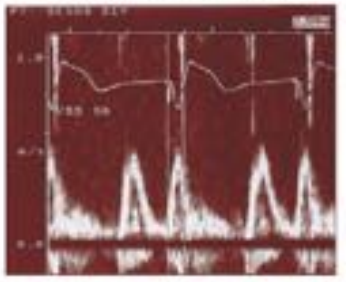


Figure 2



AV optimal





Qualitative echo optimization

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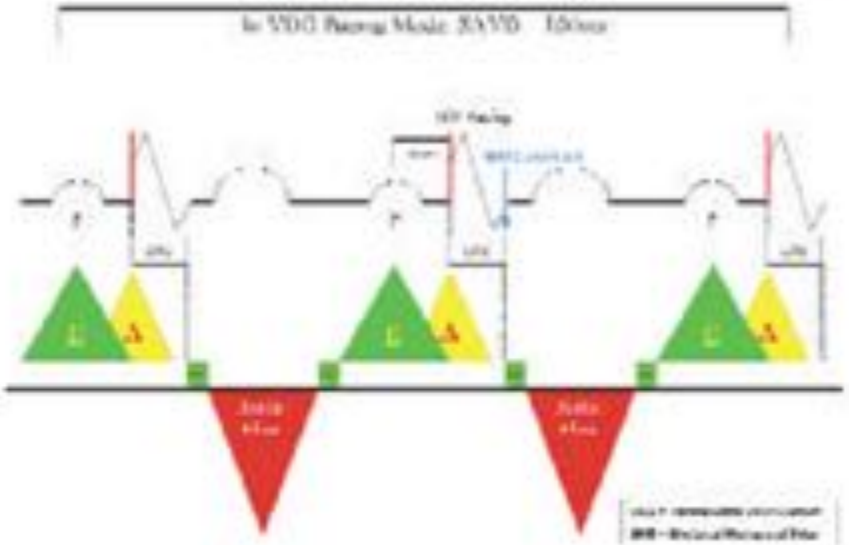
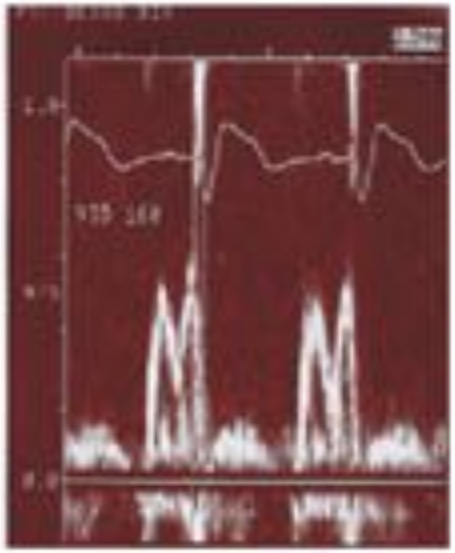
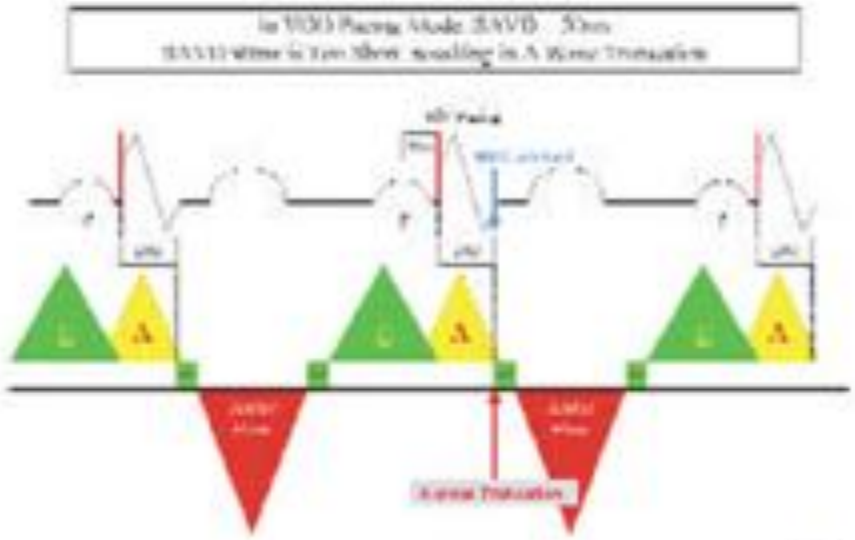


Figure 1



Qualitative echo optimization

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).



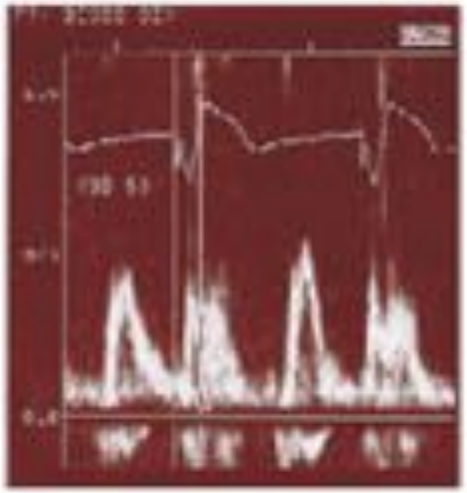
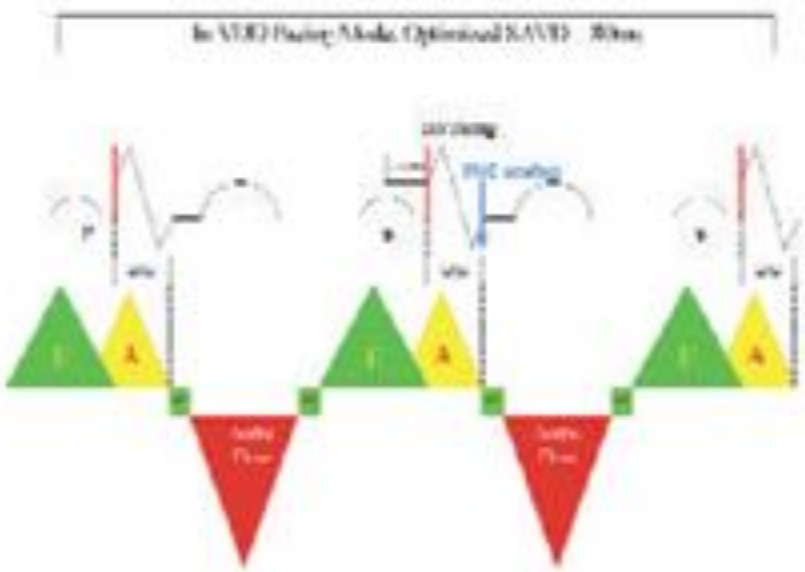


Figure 2

Qualitative echo optimization

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).



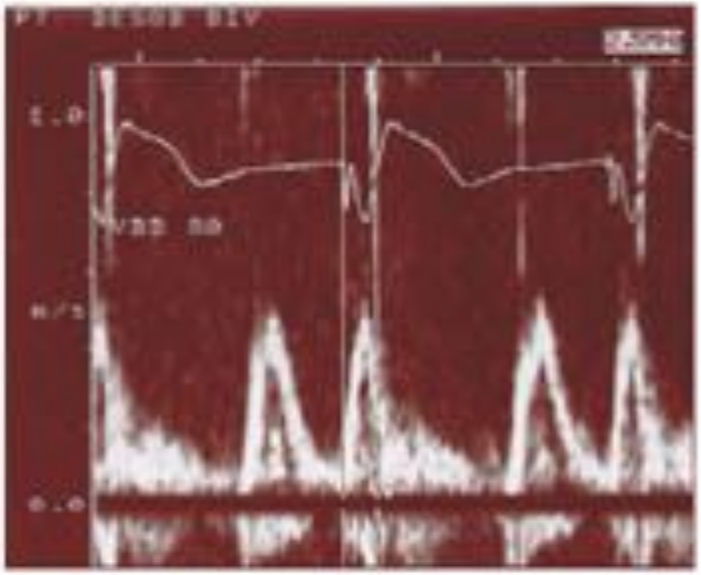


Figure 3

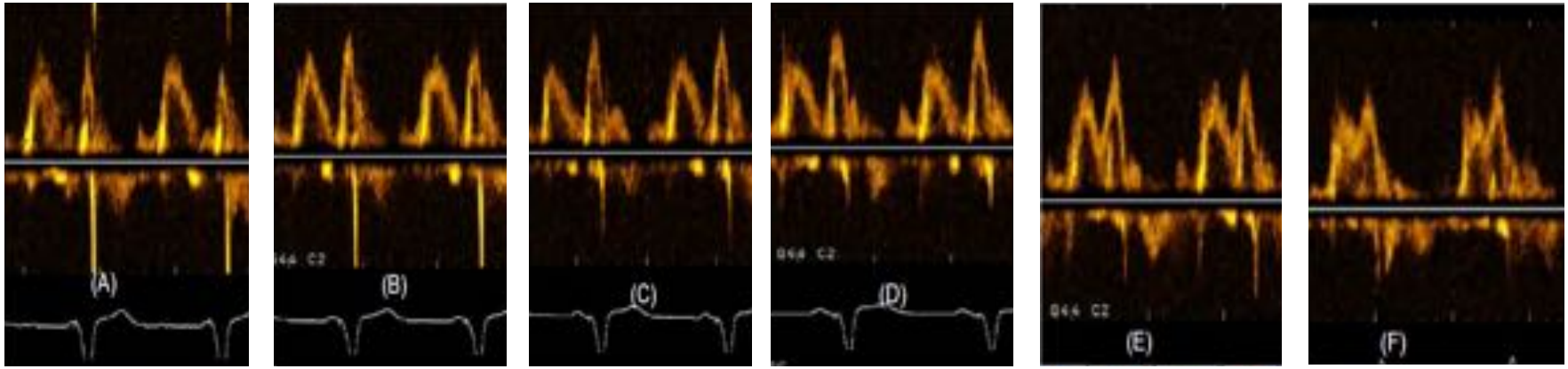
Step 5: Reprogram the device with the previous basic rate. Program adaptative AV interval On, Magnet rate On, bipolar ventricular stimulation and sensing configuration and the selected optimal AV interval.

Question:

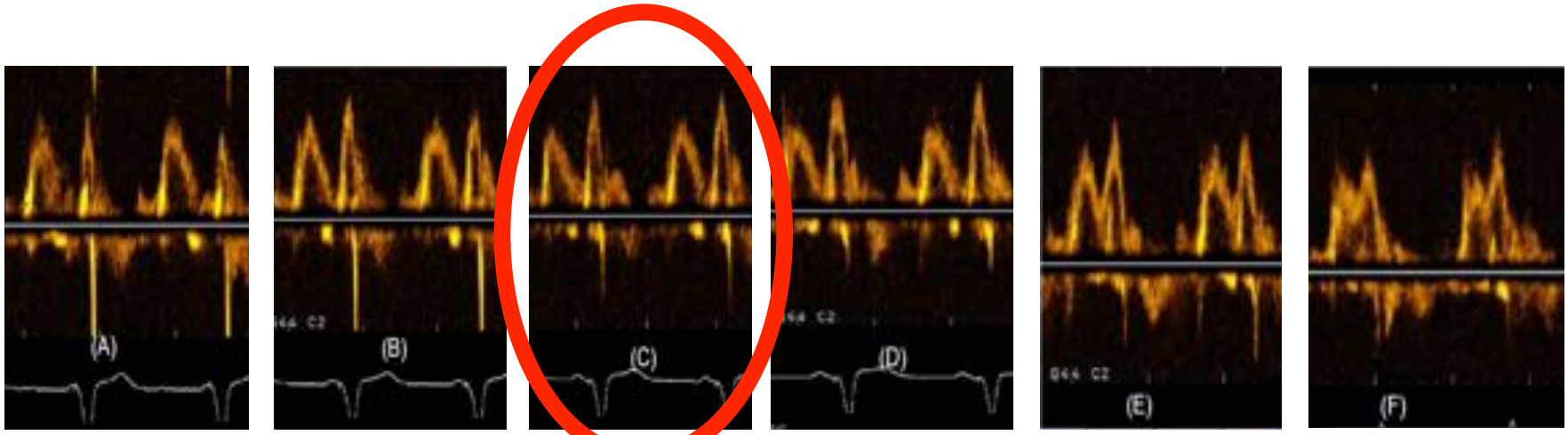
Can people really do this?

A multinational evaluation was carried out …

Patient 1



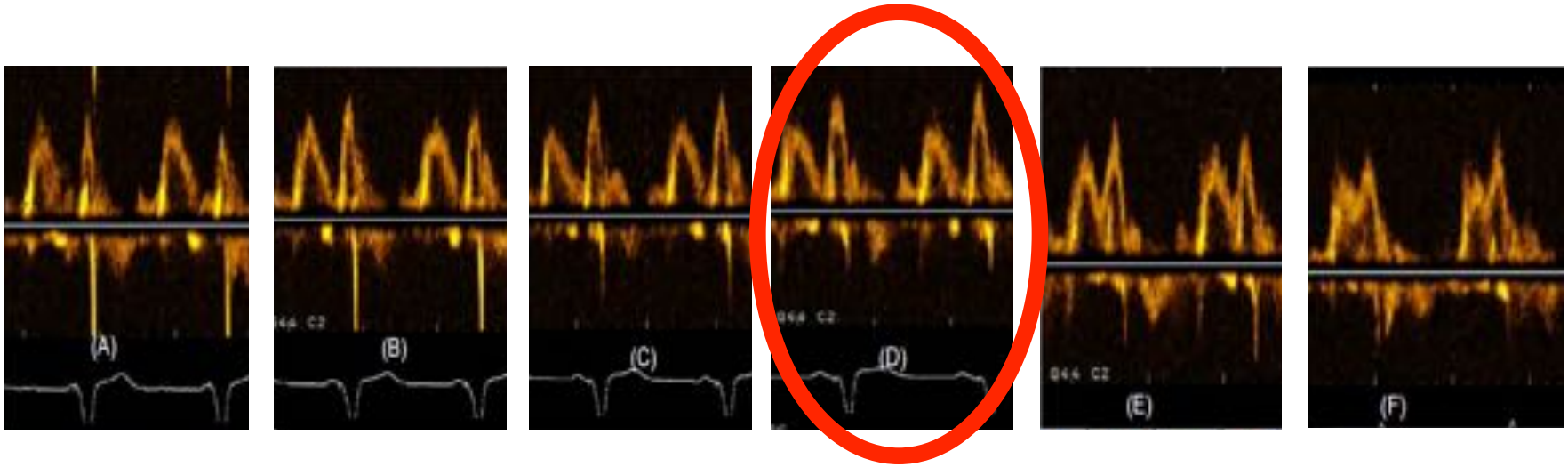
Patient 1



Observer 1 chooses option C

Raphael, *Int J Cardiol* 2013, doi: 10.1016/j.ijcard.2012.09.097

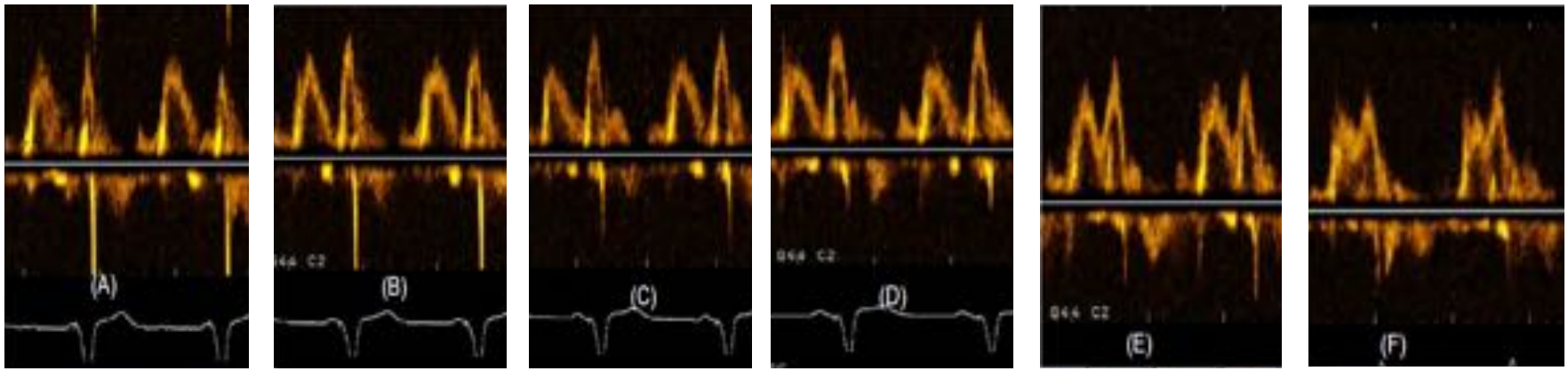
Patient 1



Observer 2 chooses option D

Raphael, *Int J Cardiol* 2013, doi: 10.1016/j.ijcard.2012.09.097

Patient 1



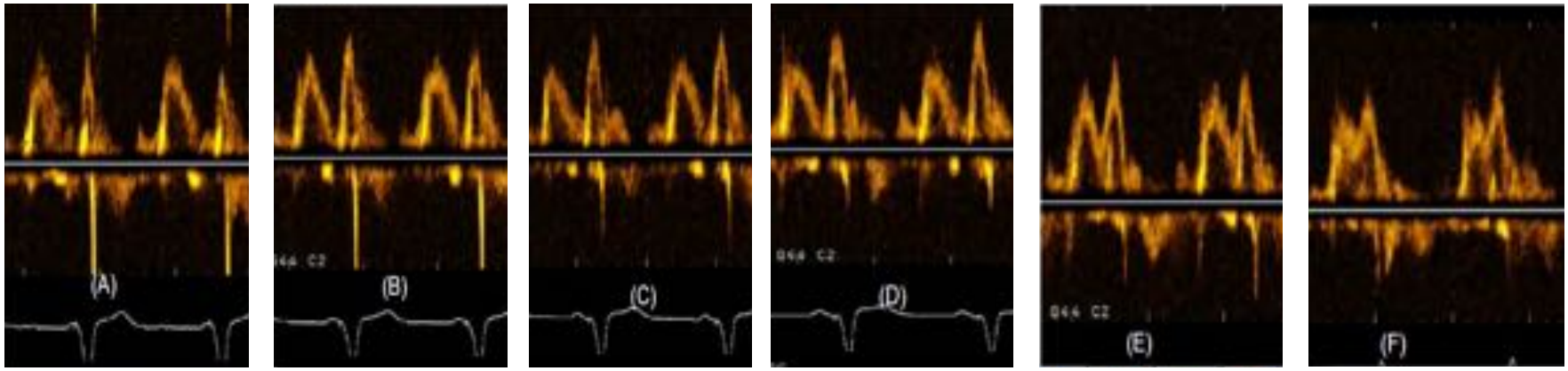
36 experts

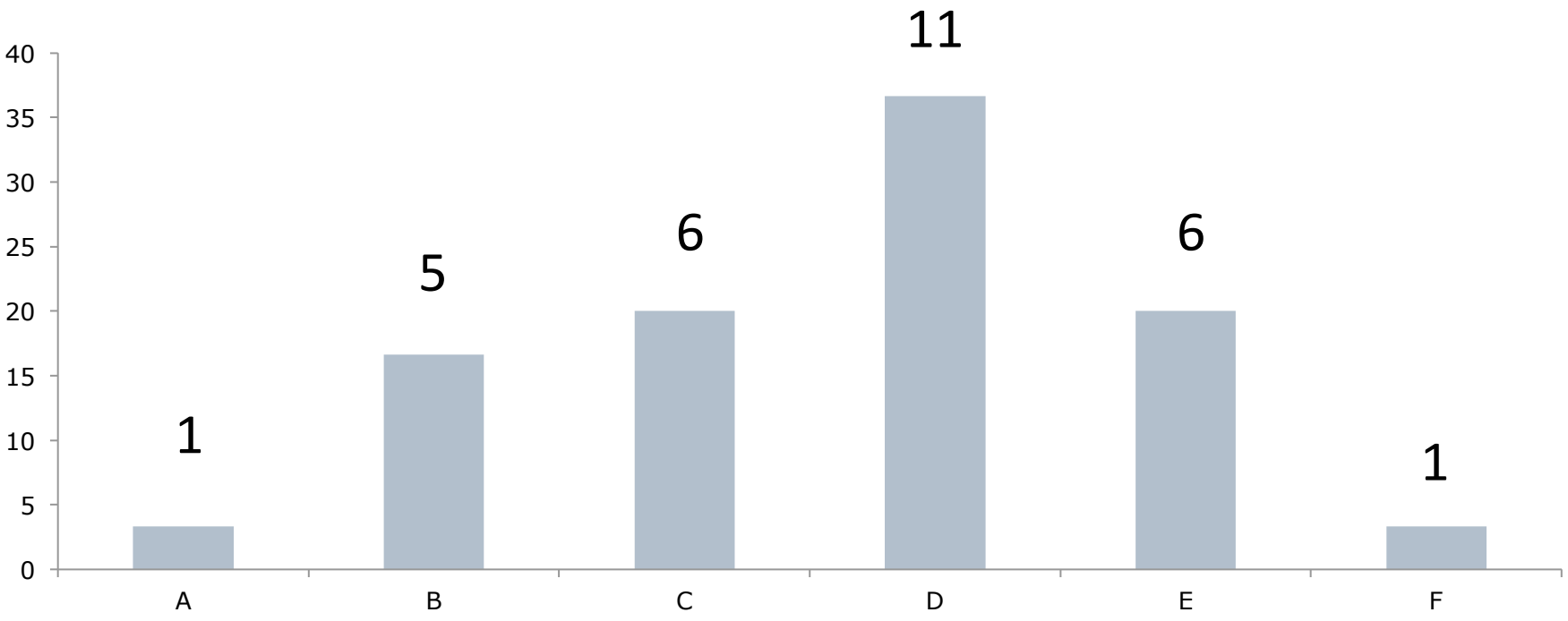
(Mainly at the ESC Congress)

Raphael, *Int J Cardiol* 2013, doi: 10.1016/j.ijcard.2012.09.097

Qualitative echo optimization

Patient 1





Raphael, *Int J Cardiol* 2013, doi: 10.1016/j.ijcard.2012.09.097

Qualitative echo optimization

36 experts
assessed 20 doppler sequences

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

Kappa scale
0.0 = pure guesswork
1.0 = excellent agreement

Raphael, *Int J Cardiol* 2013, doi: 10.1016/j.ijcard.2012.09.097

But we were lying

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

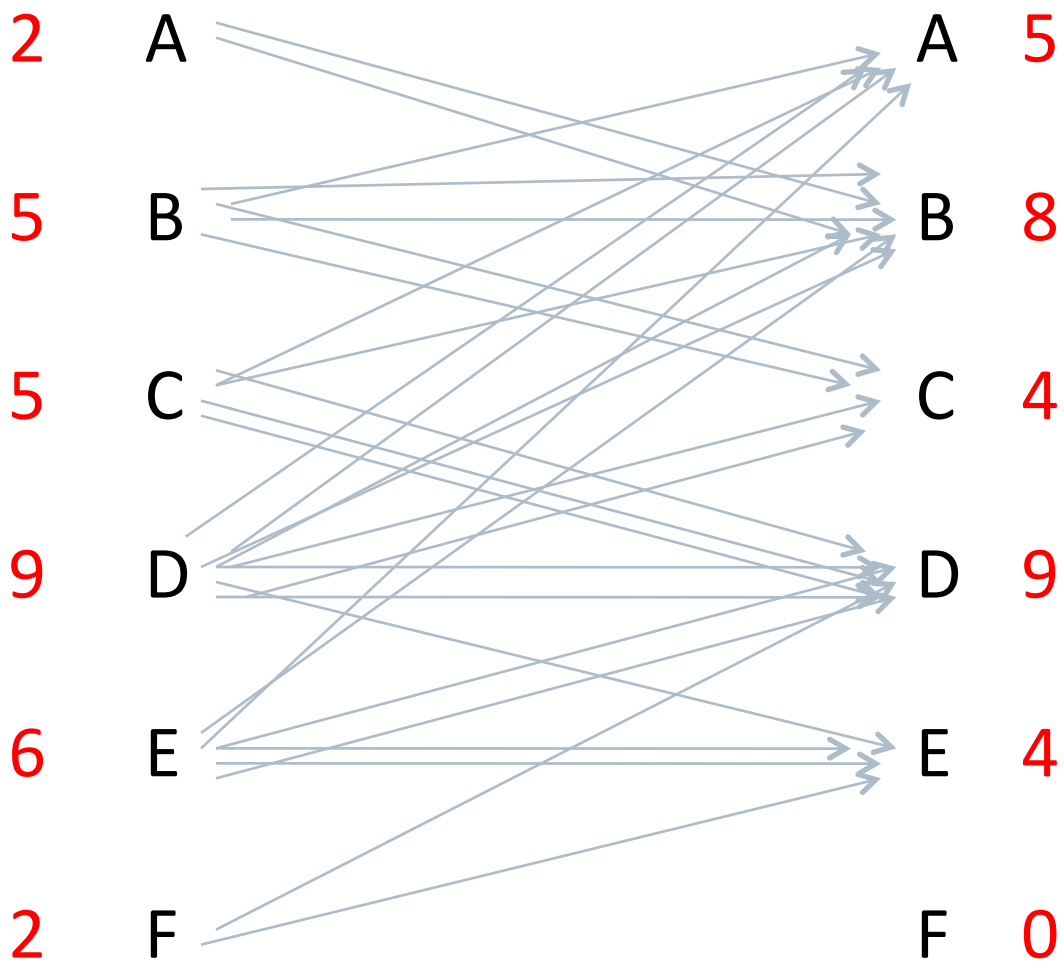
So each observer examined
10 identical sets of Dopplers, twice

Raphael, *Int J Cardiol* 2013, doi: 10.1016/j.ijcard.2012.09.097

Patient 2

"Patient 15"

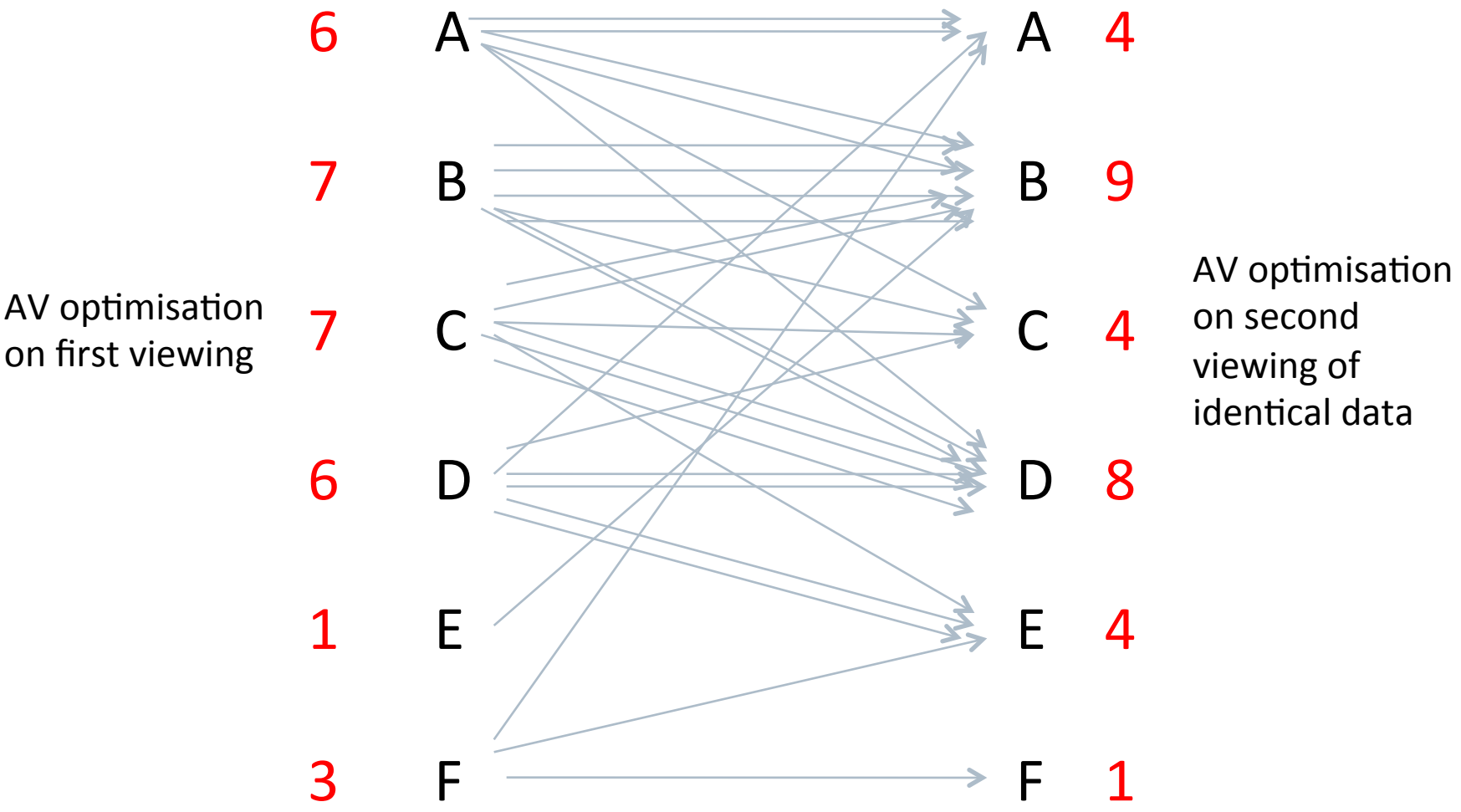
but really same Doppler as "2"



Raphael, *Int J Cardiol* 2013, doi: 10.1016/j.ijcard.2012.09.097

Patient **3**

All patients, and all observers showed the same problem



Raphael, *Int J Cardiol* 2013, doi: 10.1016/j.ijcard.2012.09.097

Qualitative echo optimization

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"

Raphael, *Int J Cardiol* 2013, doi: 10.1016/j.ijcard.2012.09.097

Qualitative echo optimization

"There are known knowns … things we know we know.

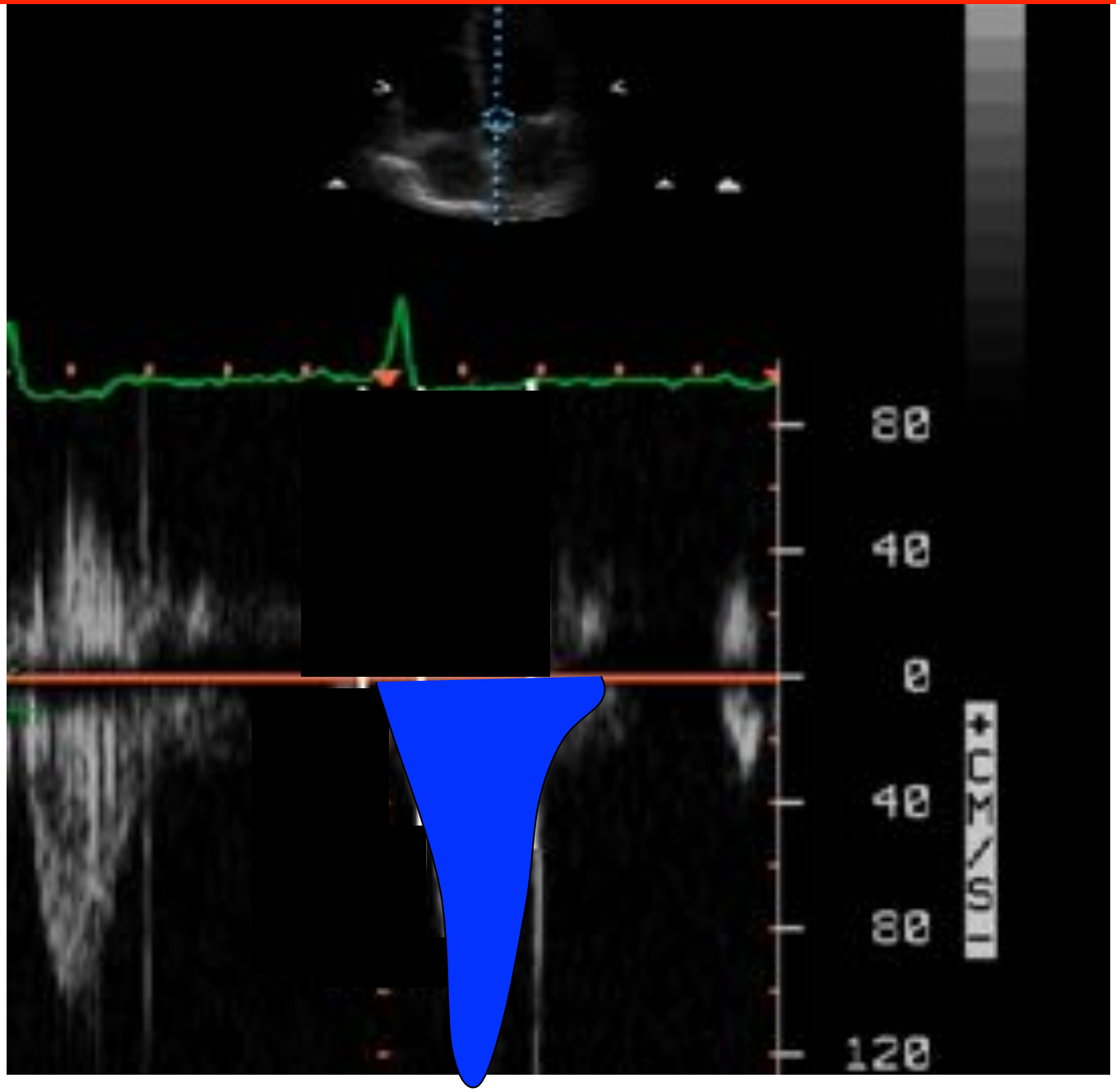
There are known unknowns; we know there are some things we do not know.

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

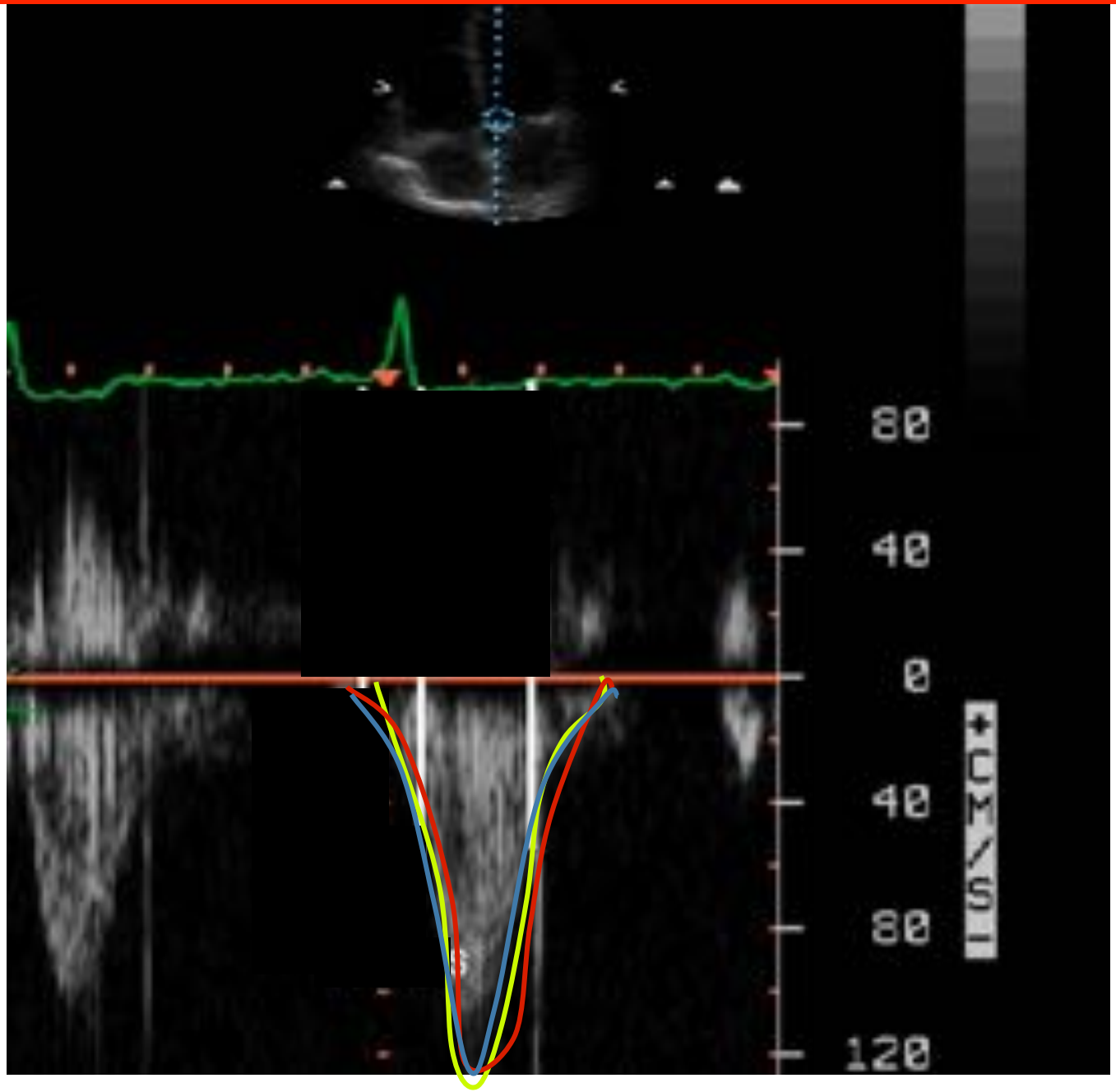
Former United States Secretary of Defense
Donald Rumsfeld

"They did not know that they did not know"

Quantitative echo optimization



Quantitative echo optimization



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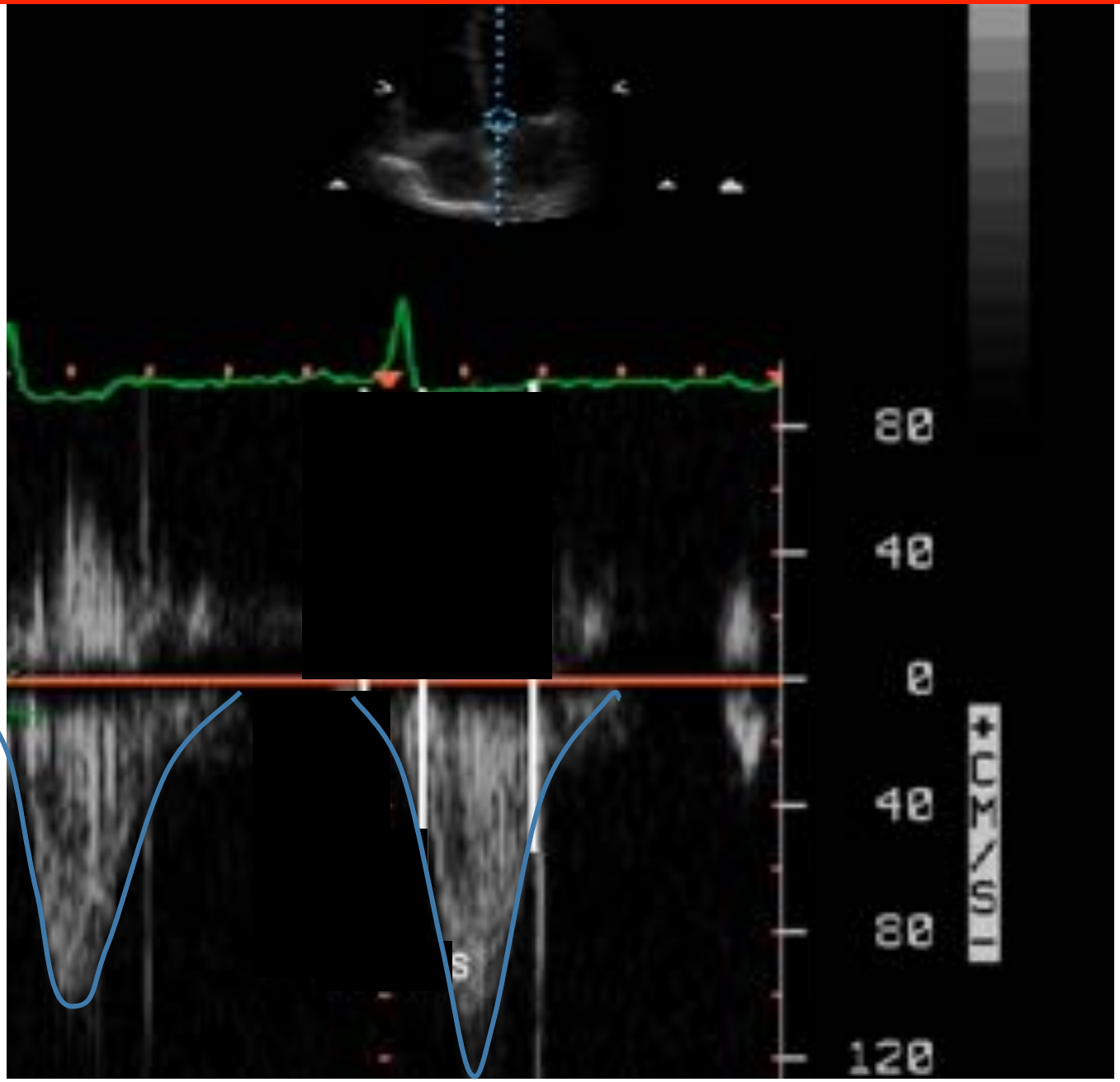


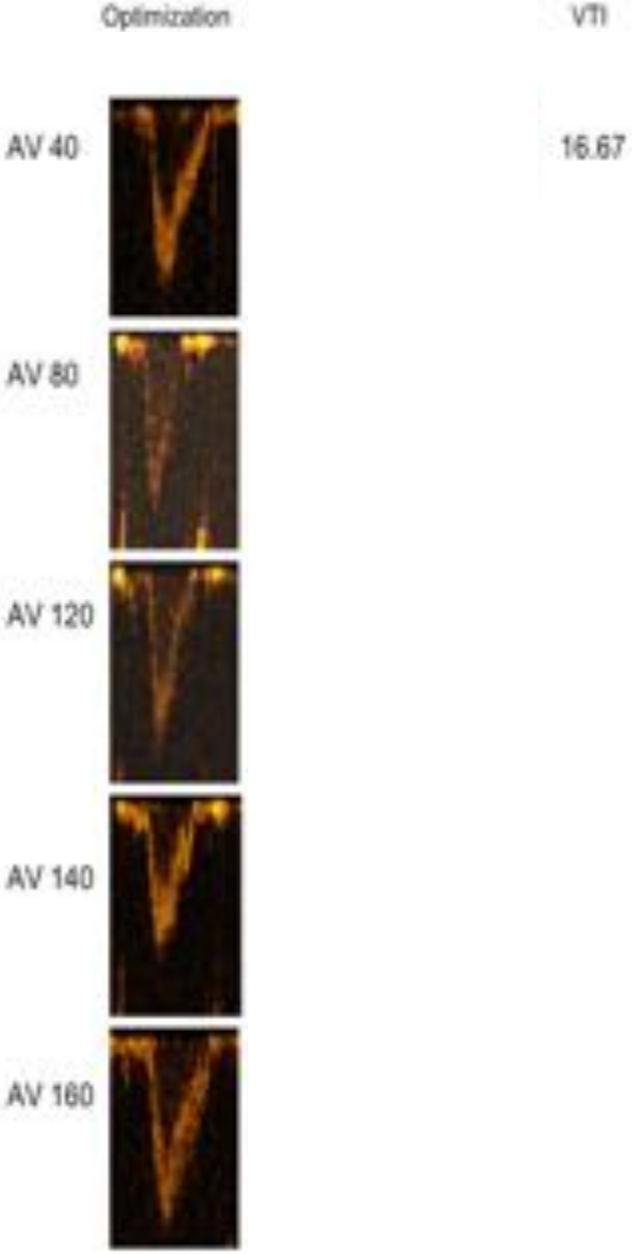
AV 40

16.67

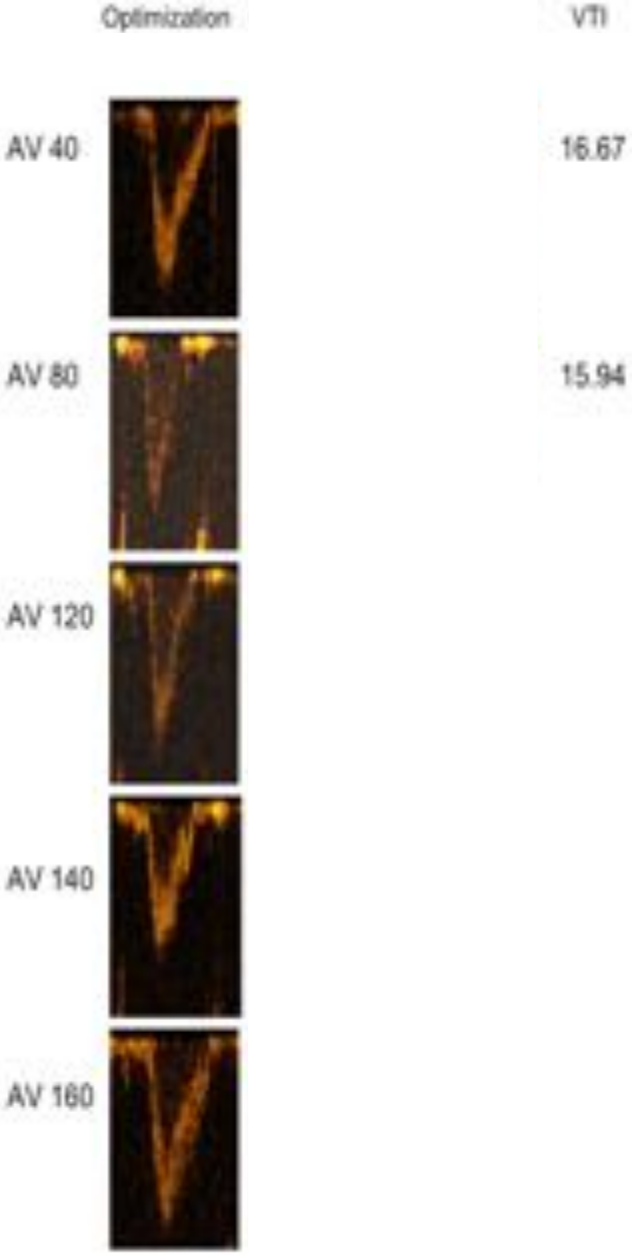
Pabari, Francis *Heart Failure Reviews* 2011

Optimization		VTI
AV 40		16.67

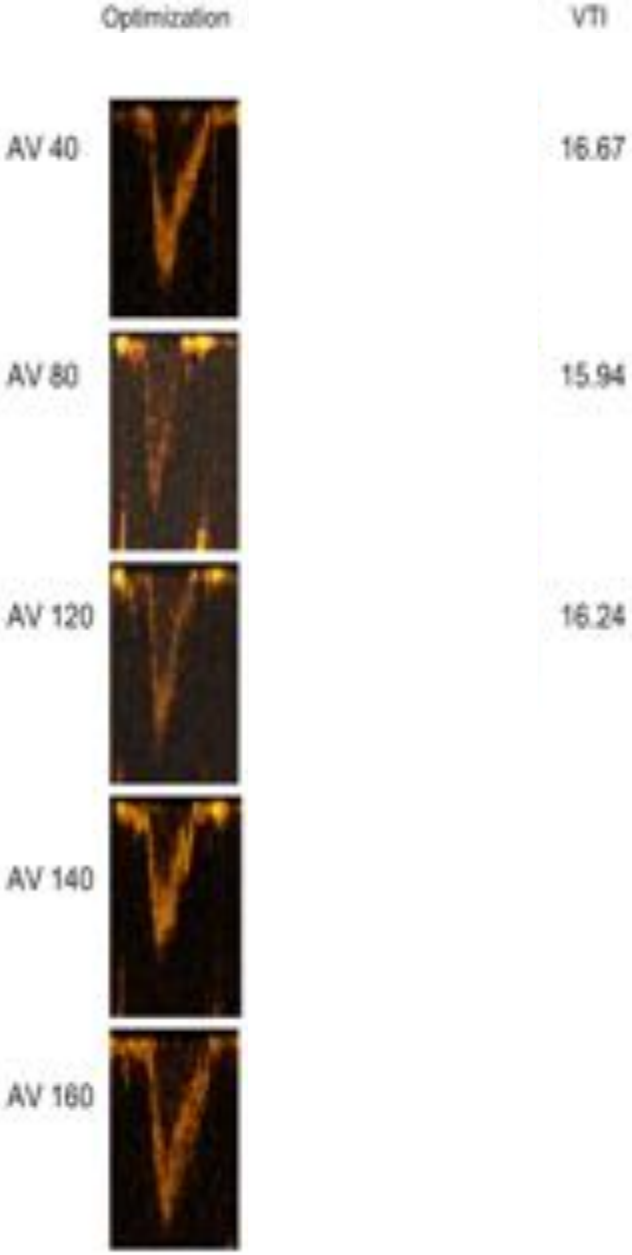
Pabari, Francis *Heart Failure Reviews* 2011



Pabari, Francis *Heart Failure Reviews* 2011



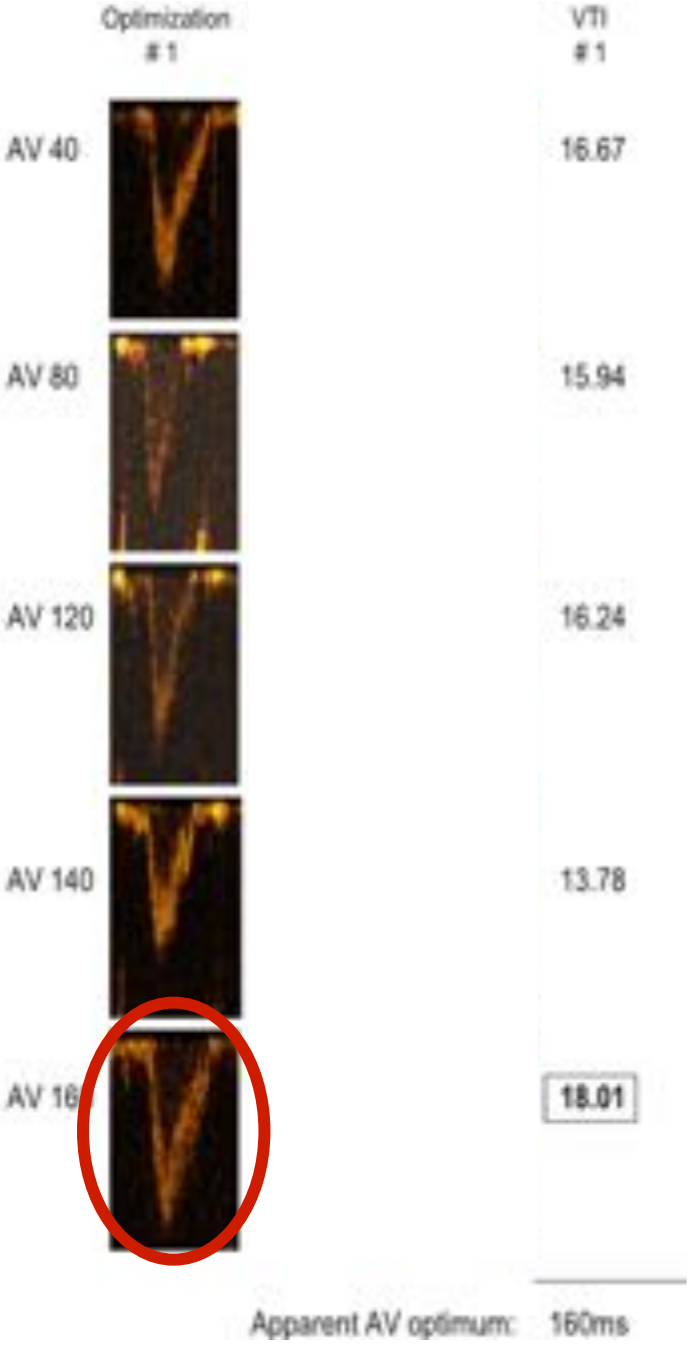
Pabari, Francis *Heart Failure Reviews* 2011

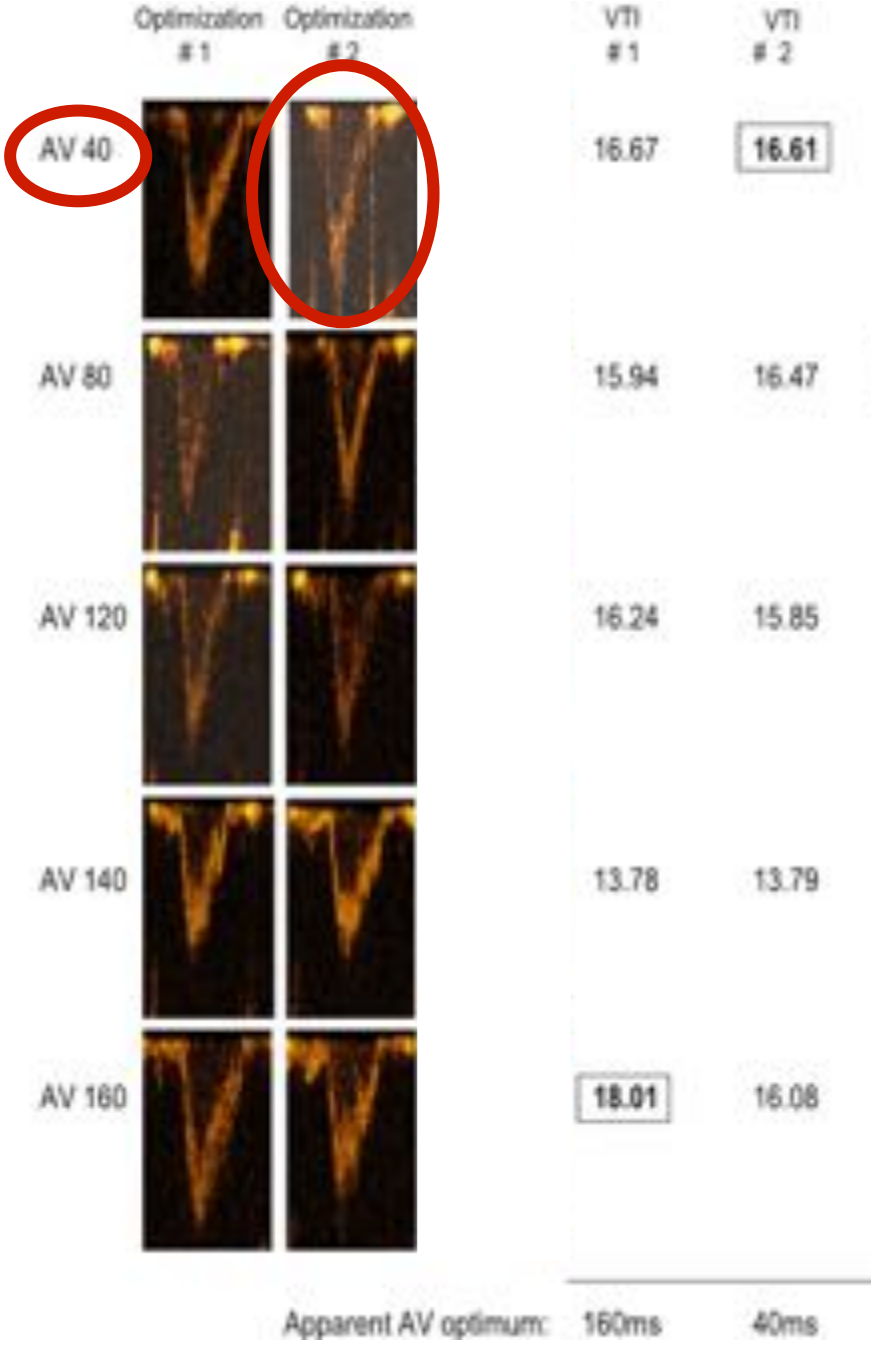


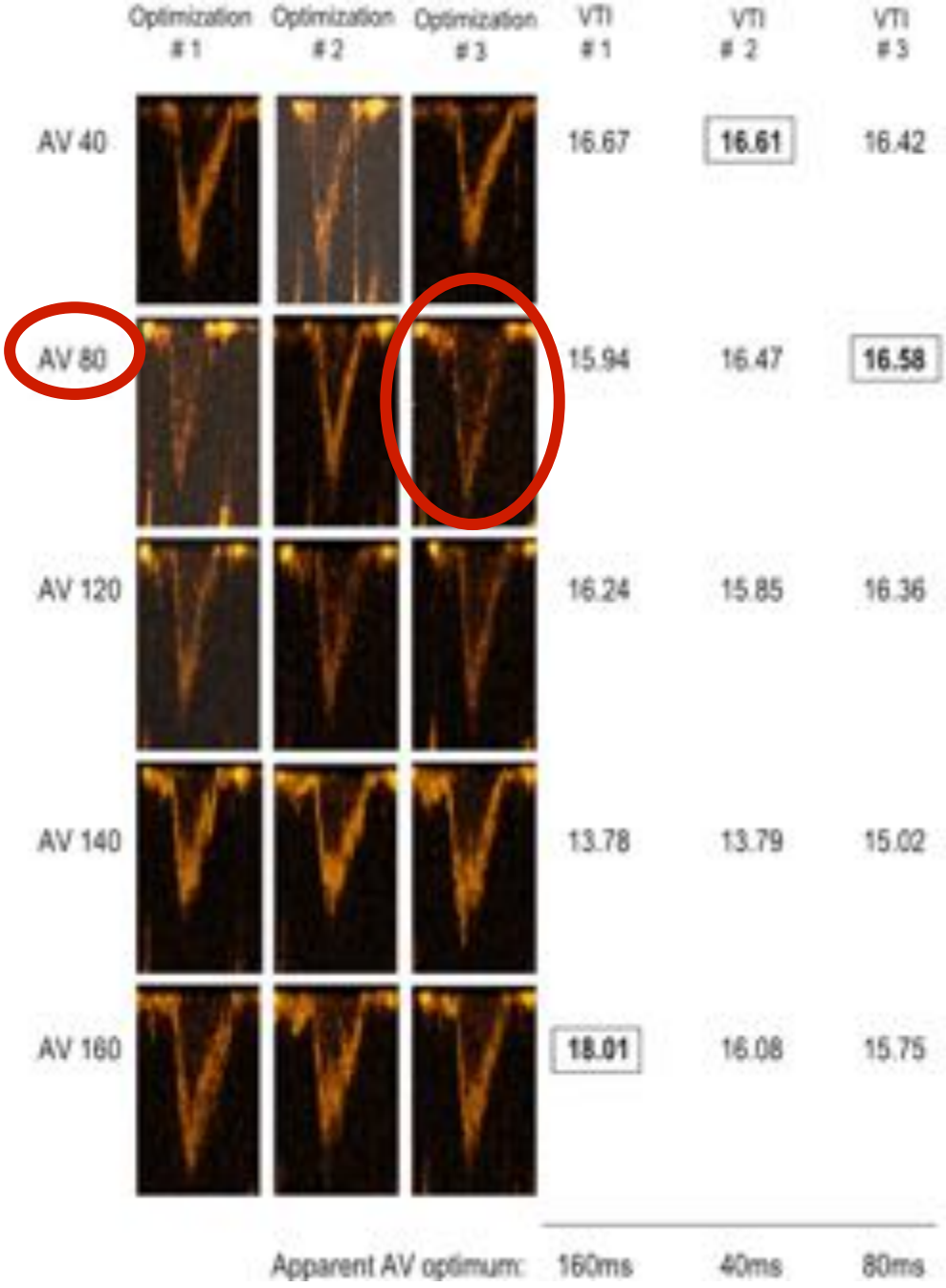
Pabari, Francis *Heart Failure Reviews* 2011

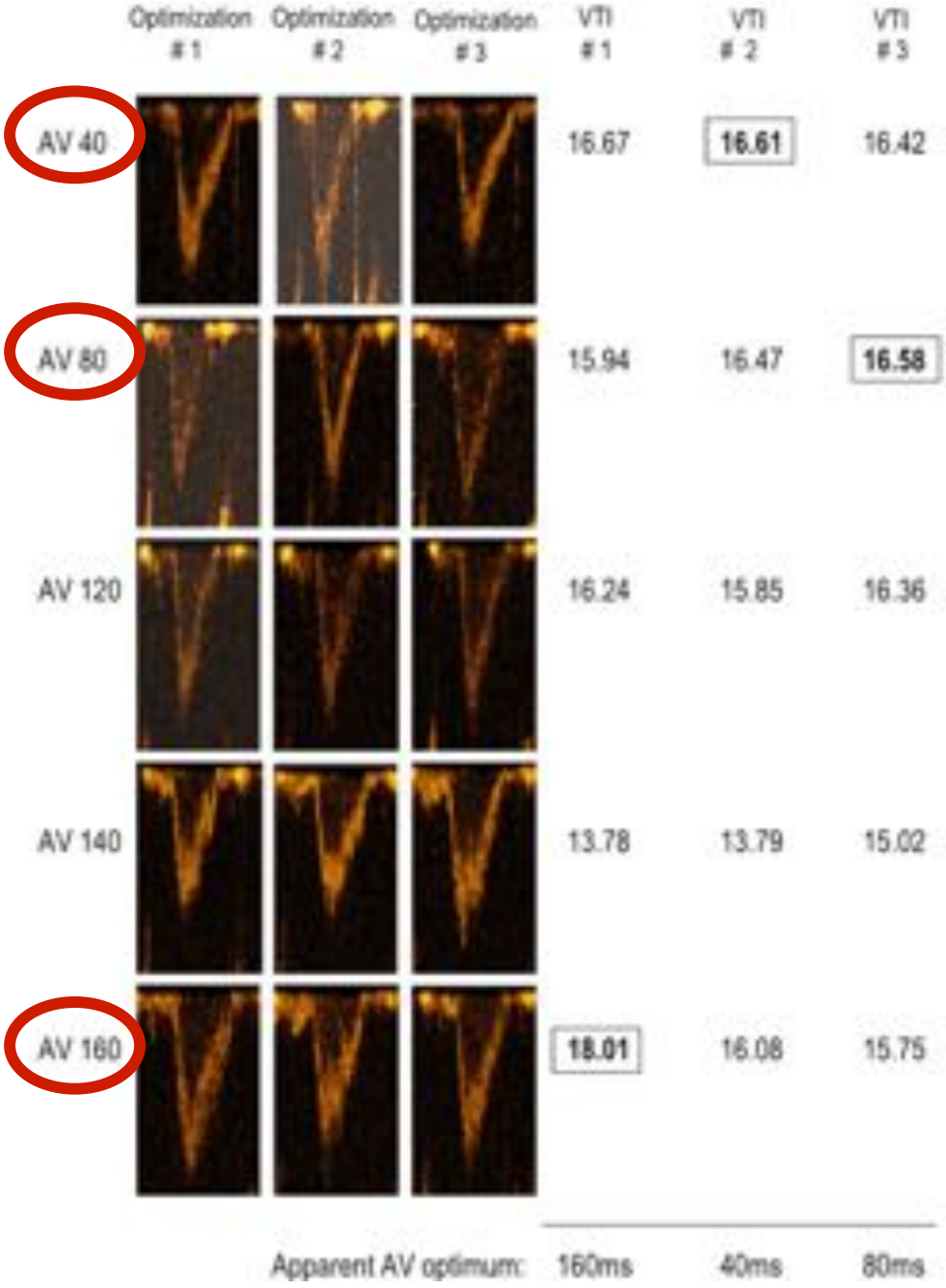
Optimization		VTI
AV 40		16.67
AV 80		15.94
AV 120		16.24
AV 140		13.78
AV 160		

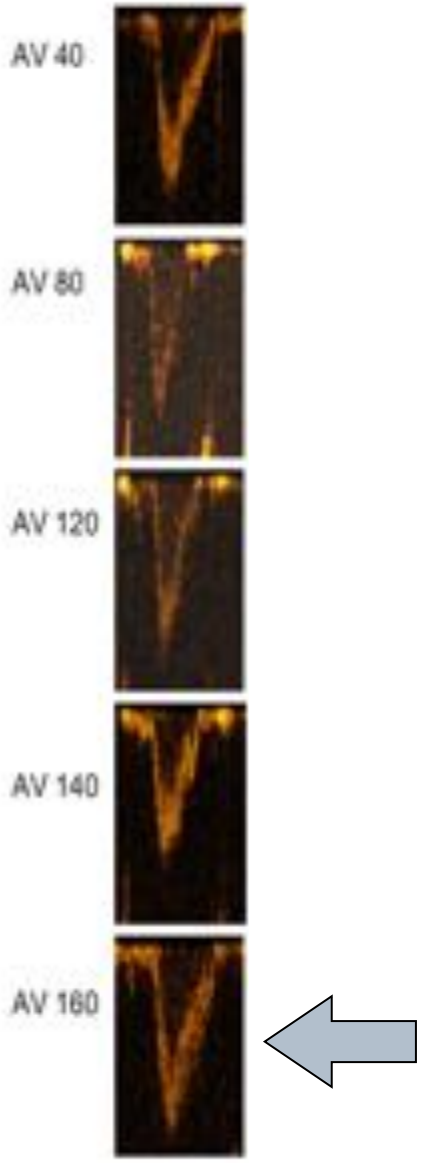
Pabari, Francis *Heart Failure Reviews* 2011


Optimization
1
VTI
1
AV 40
16.67
AV 80
15.94
AV 120
16.24
AV 140
13.78
AV 16
18.01
Apparent AV optimum:
160ms


Optimization # 1
Optimization # 2
VTI # 1
VTI # 2
AV 40
16.67
16.61
AV 80
15.94
16.47
AV 120
16.24
15.85
AV 140
13.78
13.79
AV 160
18.01
16.08
Apparent AV optimum:
160ms
40ms


Optimization #1
Optimization #2
Optimization #3
VTI #1
VTI #2
VTI #3
AV 40
16.67
16.61
16.42
AV 80
15.94
16.47
16.58
AV 120
16.24
15.85
16.36
AV 140
13.78
13.79
15.02
AV 160
18.01
16.08
15.75
Apparent AV optimum:
160ms
40ms
80ms


Optimization #1
Optimization #2
Optimization #3
VTI #1
VTI #2
VTI #3
AV 40
AV 80
AV 120
AV 140
AV 160
16.67
16.61
16.42
15.94
16.47
16.58
16.24
15.85
16.36
13.78
13.79
15.02
18.01
16.08
15.75
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

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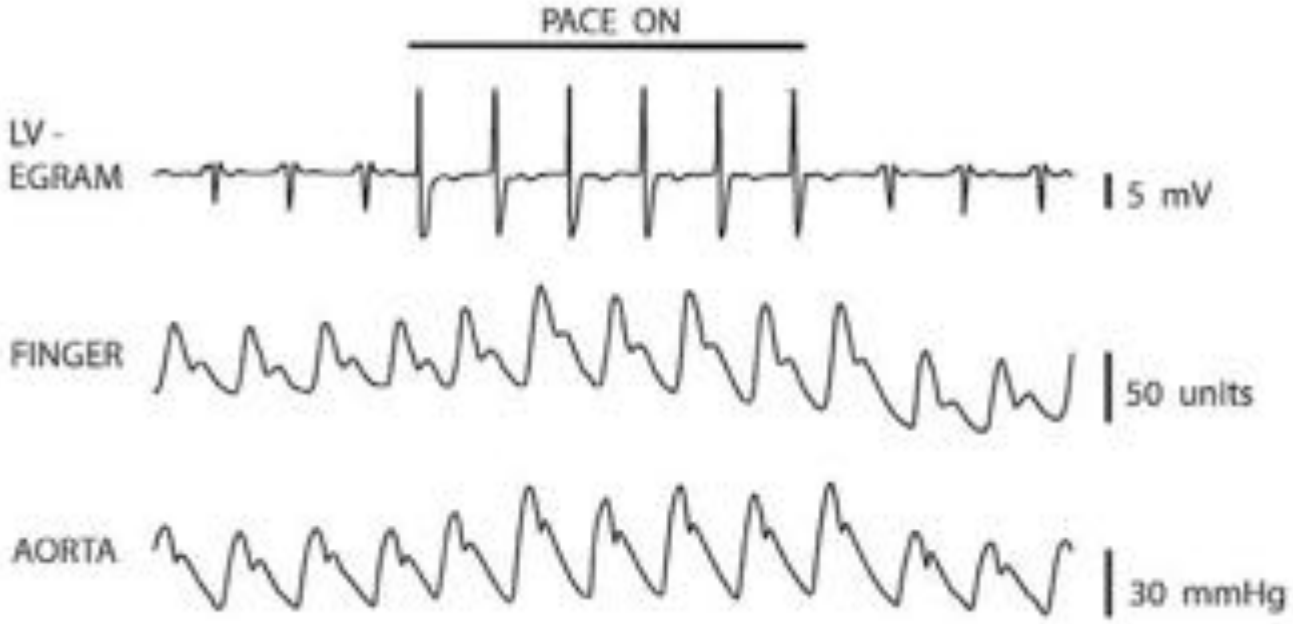
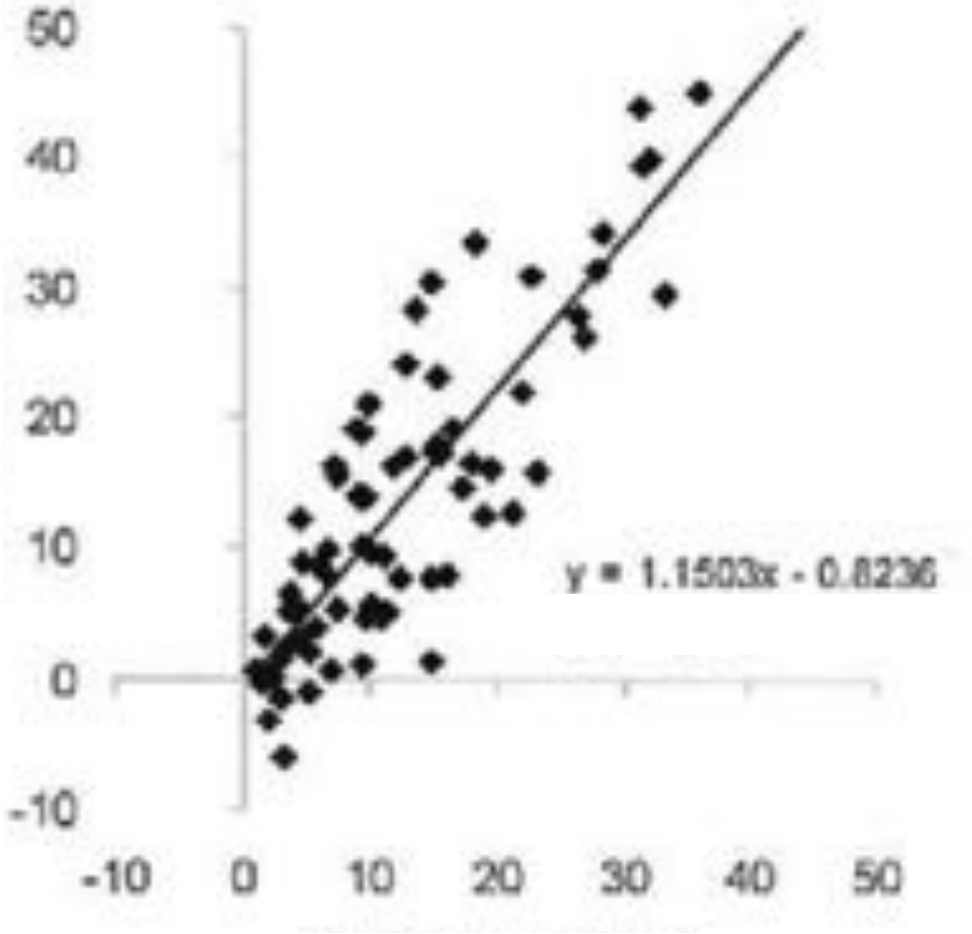
[c]*Guidant CRM Research, St. Paul, Minnesota, and*
[d]*Guidant CRM Research, Brussels, Belgium.*



Heart Rhythm 2004;1:568–575

Quantitative optimization

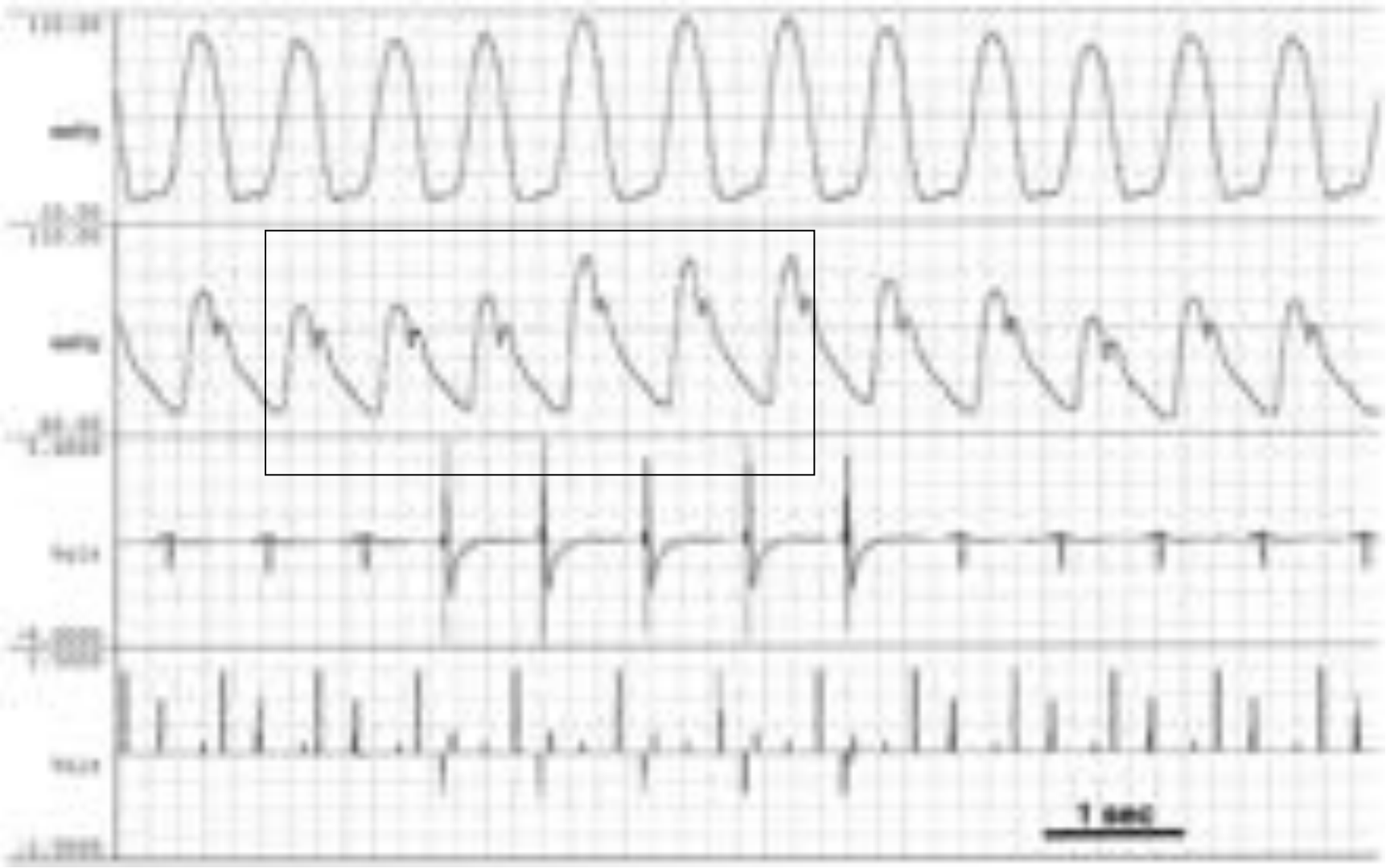


% change in aortic pressure

% change in finger signal

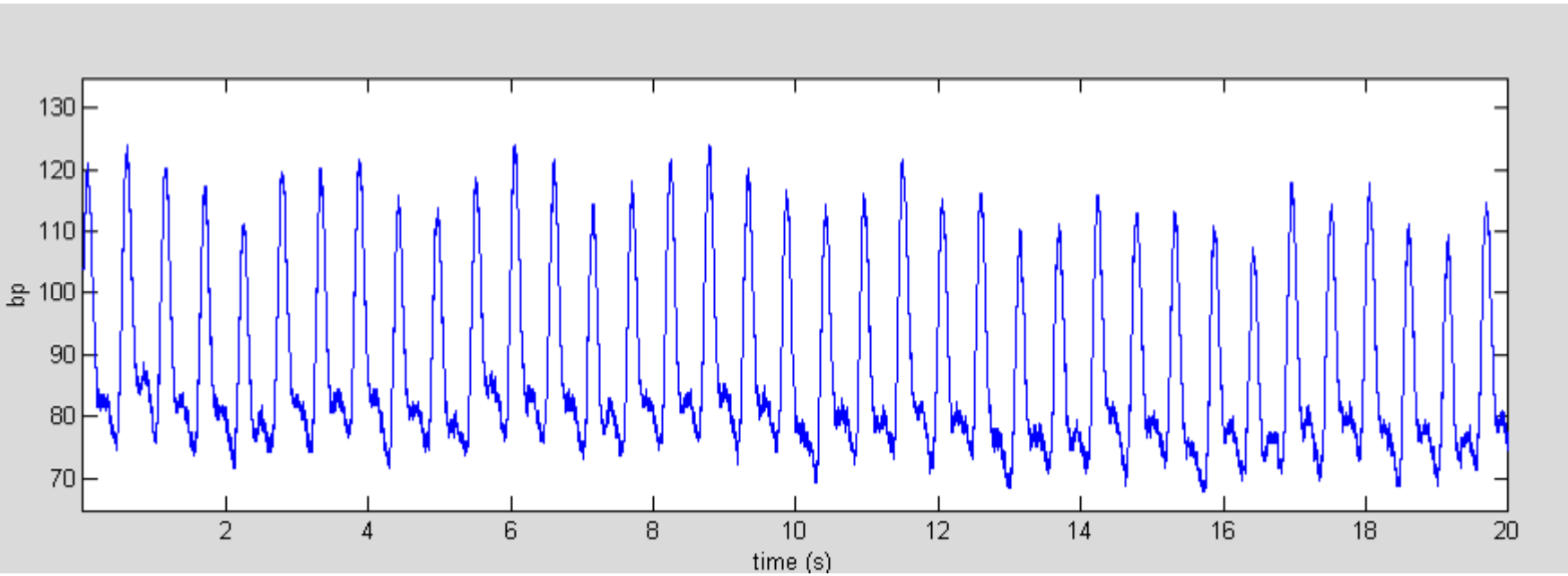
Butter et al, Heart Rhythm 2004;1:568–575

Quantitative optimization

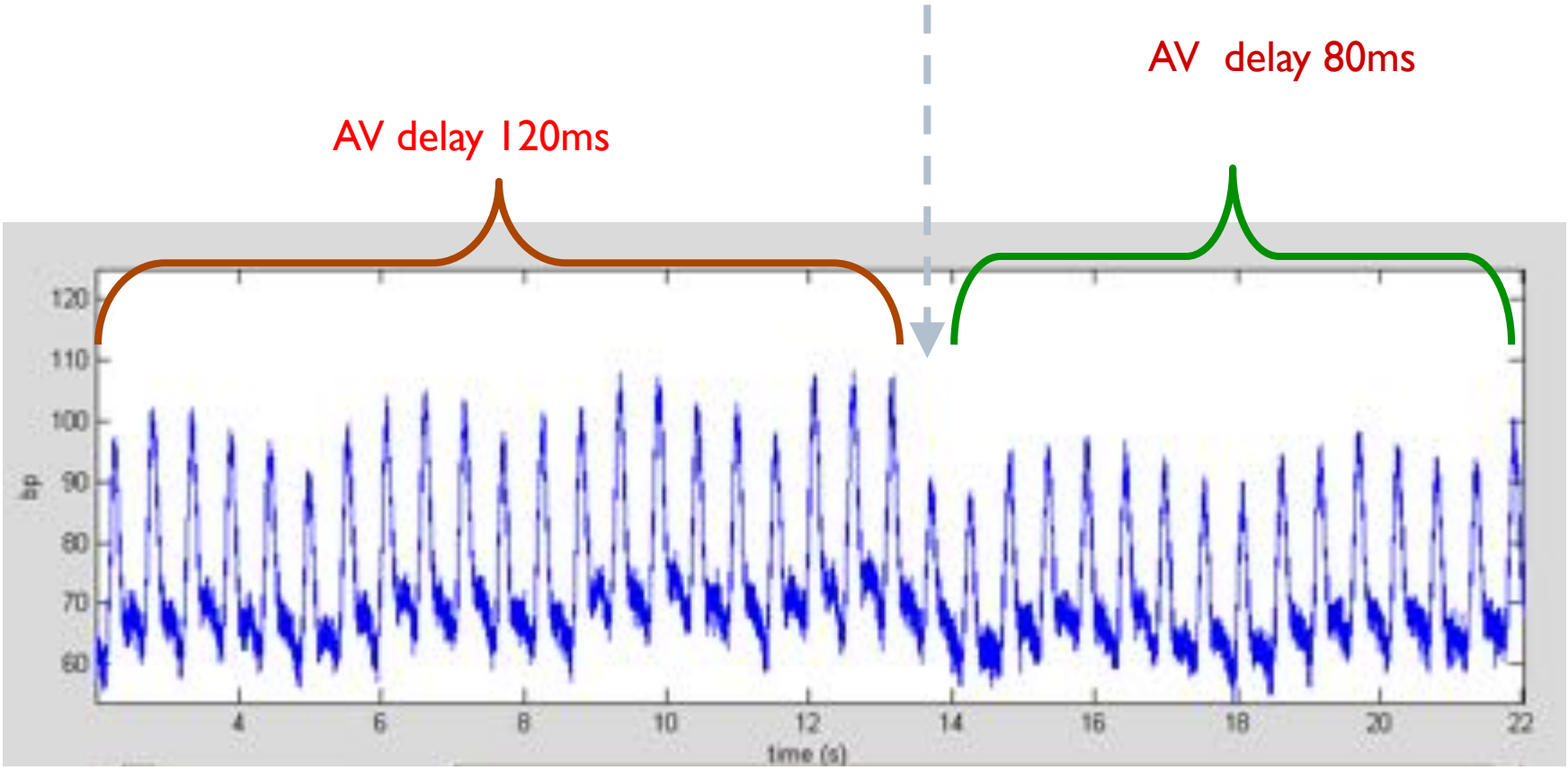


Auricchio A. *Circulation* 1999;99:2993-3001.

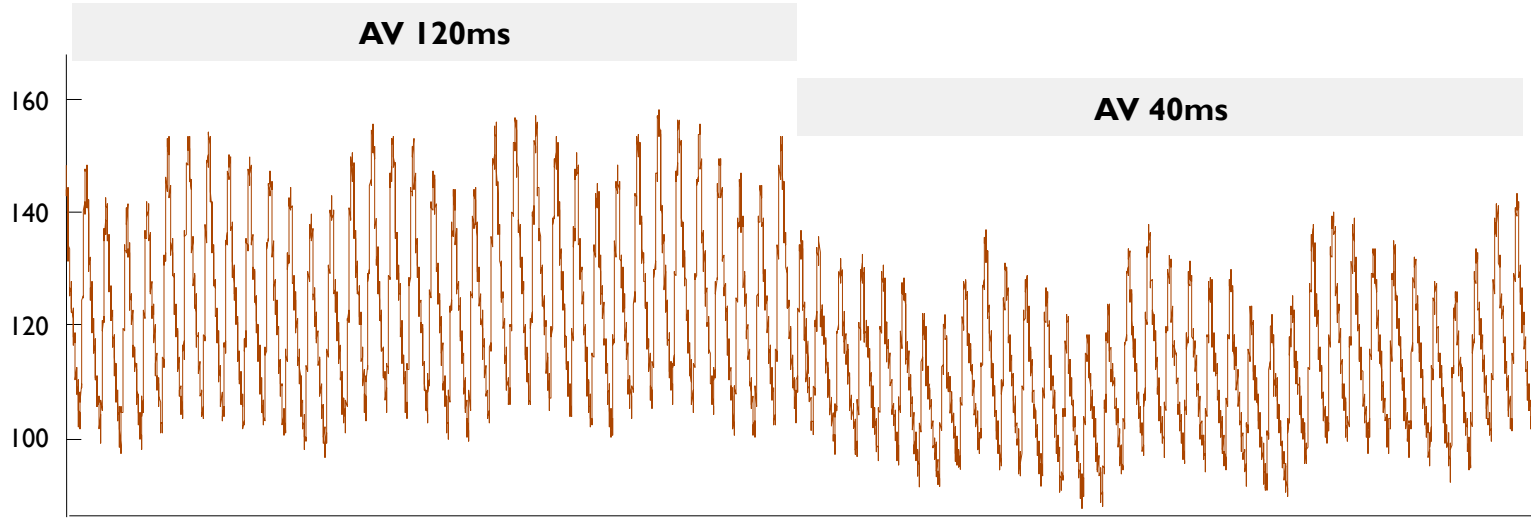
Blood pressure trace



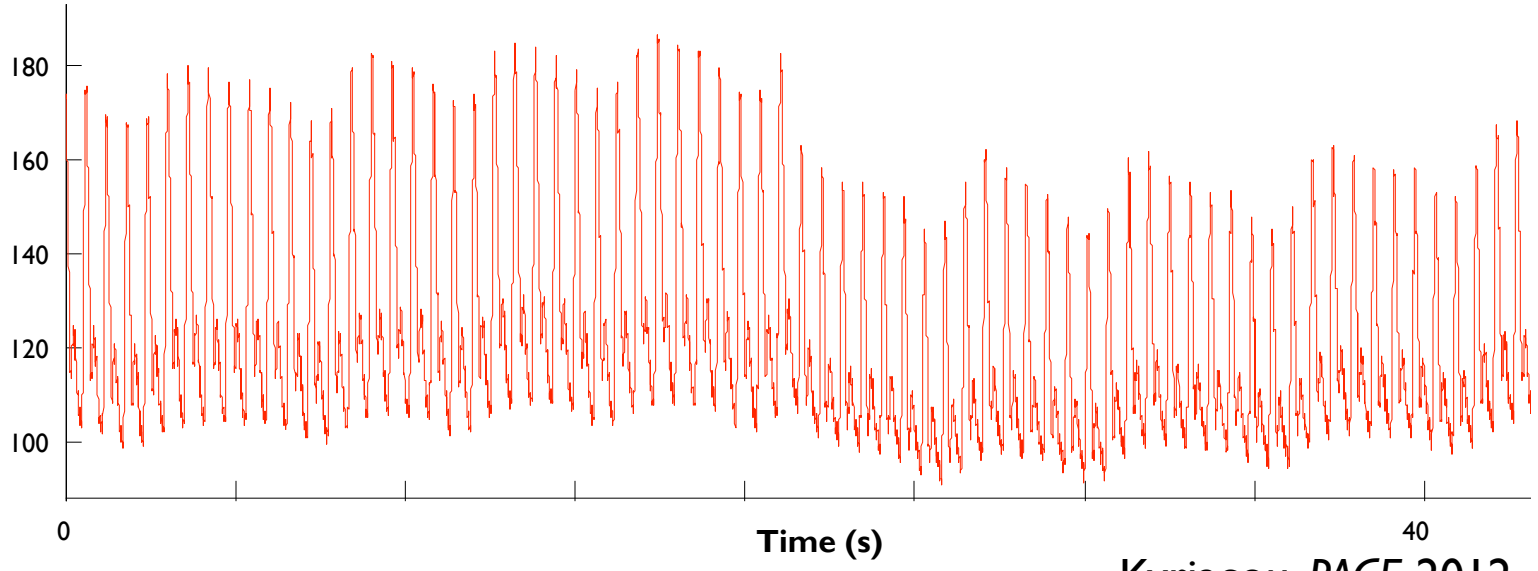
Quantitative optimization



Invasive aortic root

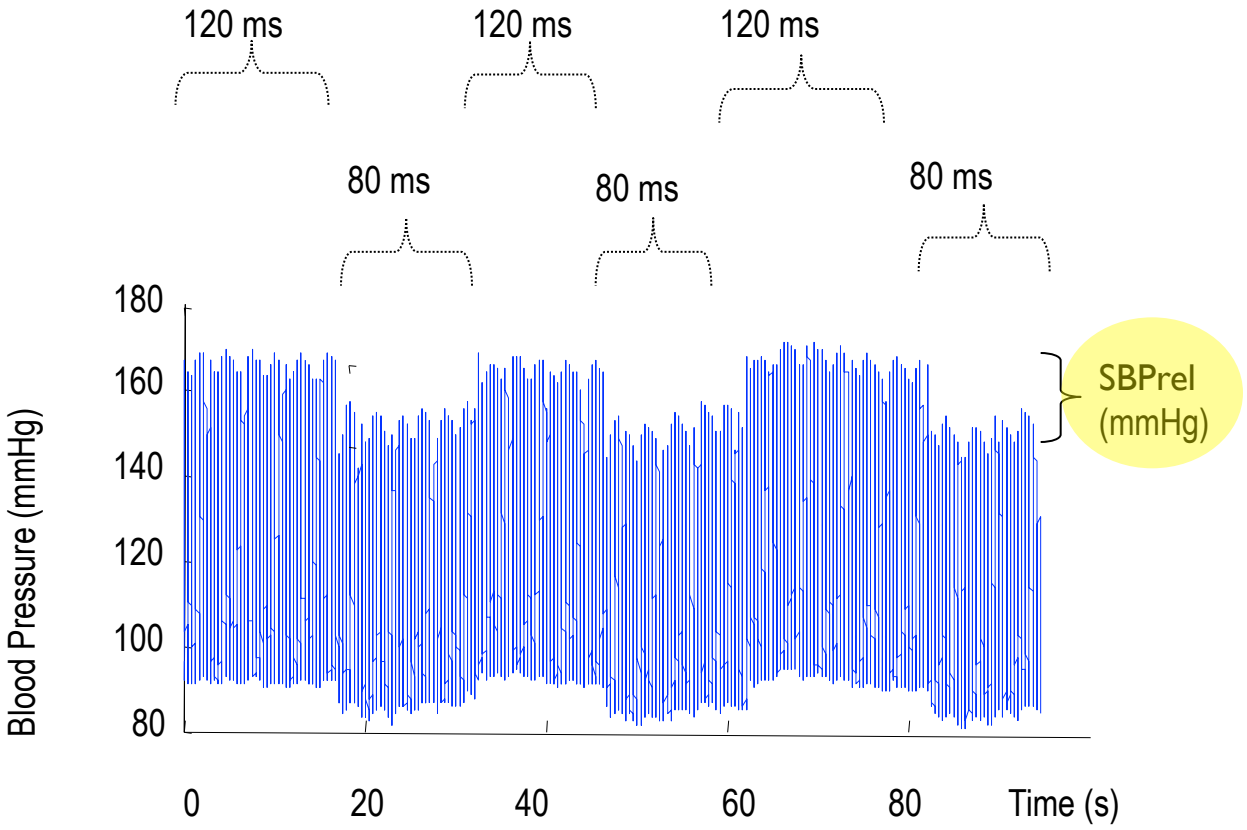


Non Invasive Finger



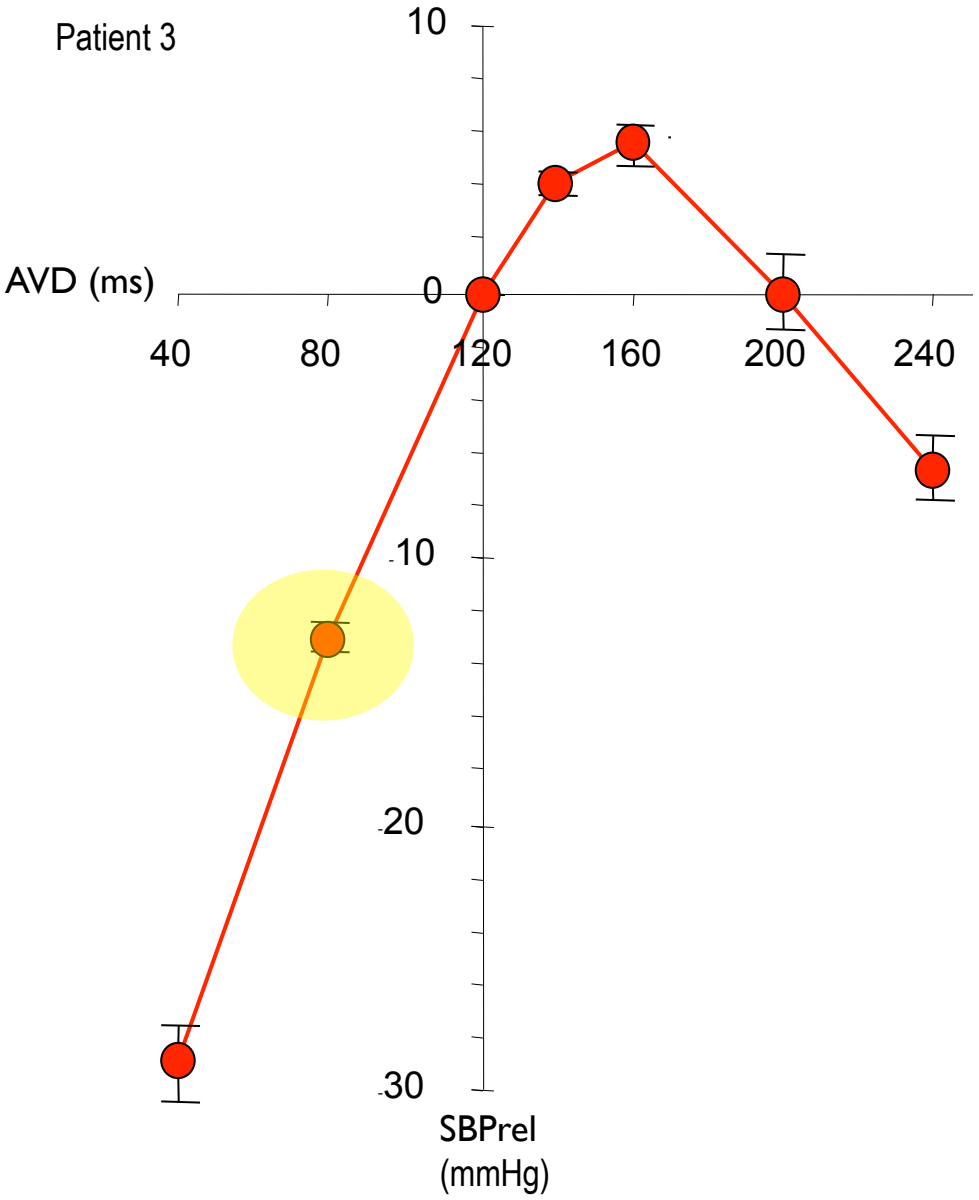
Kyriacou, *PACE* 2012

Quantitative optimization



Whinnett *EuroPACE*. 2006; 8(5): 358–366.

Quantitative optimization



Whinnett *EuroPACE*. 2006; 8(5): 358–366.

Unfortunately

Clinical Endpoint Evidence
will require an
implausibly large study

Half the
effect size of
CRT itself

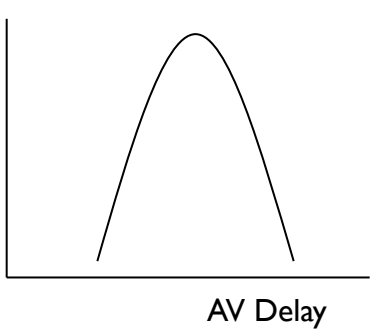
4 × the
effect size of
CRT itself

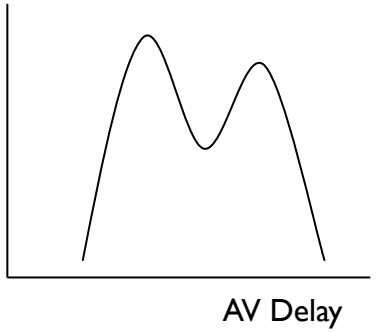
How else to choose?

The 3 features to look out for in any optimization scheme

One single peak

1

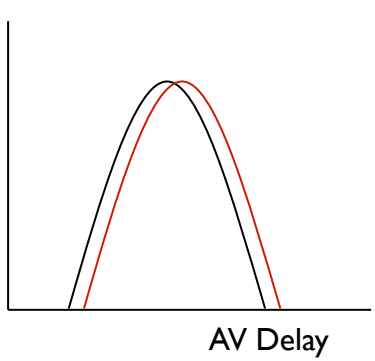


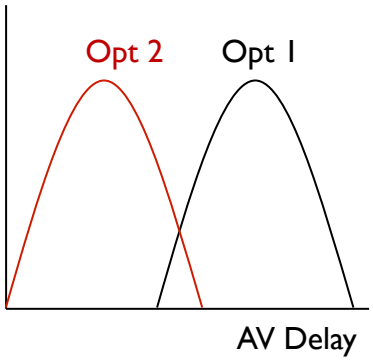


X

2

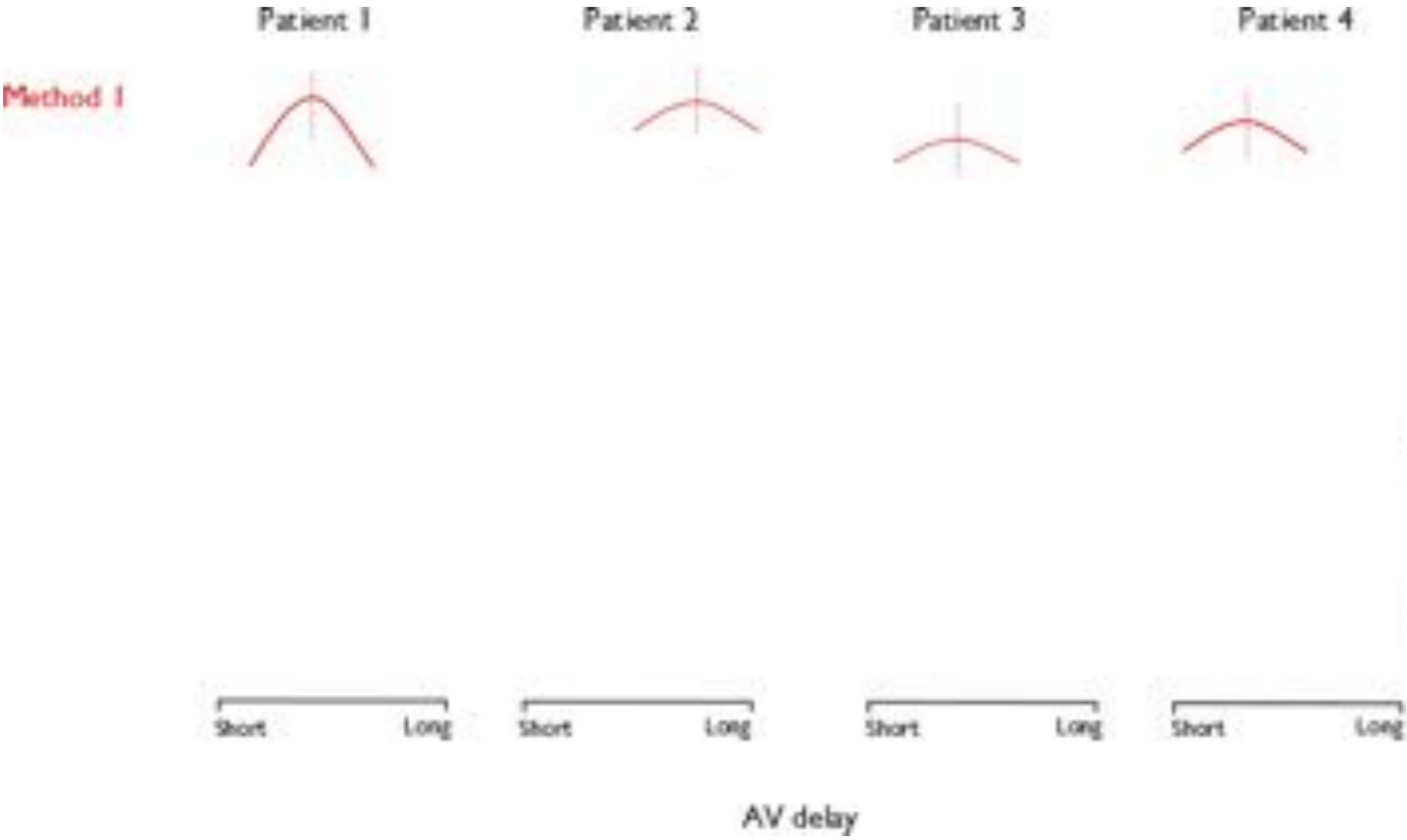
Two optimizations a few minutes apart should be same

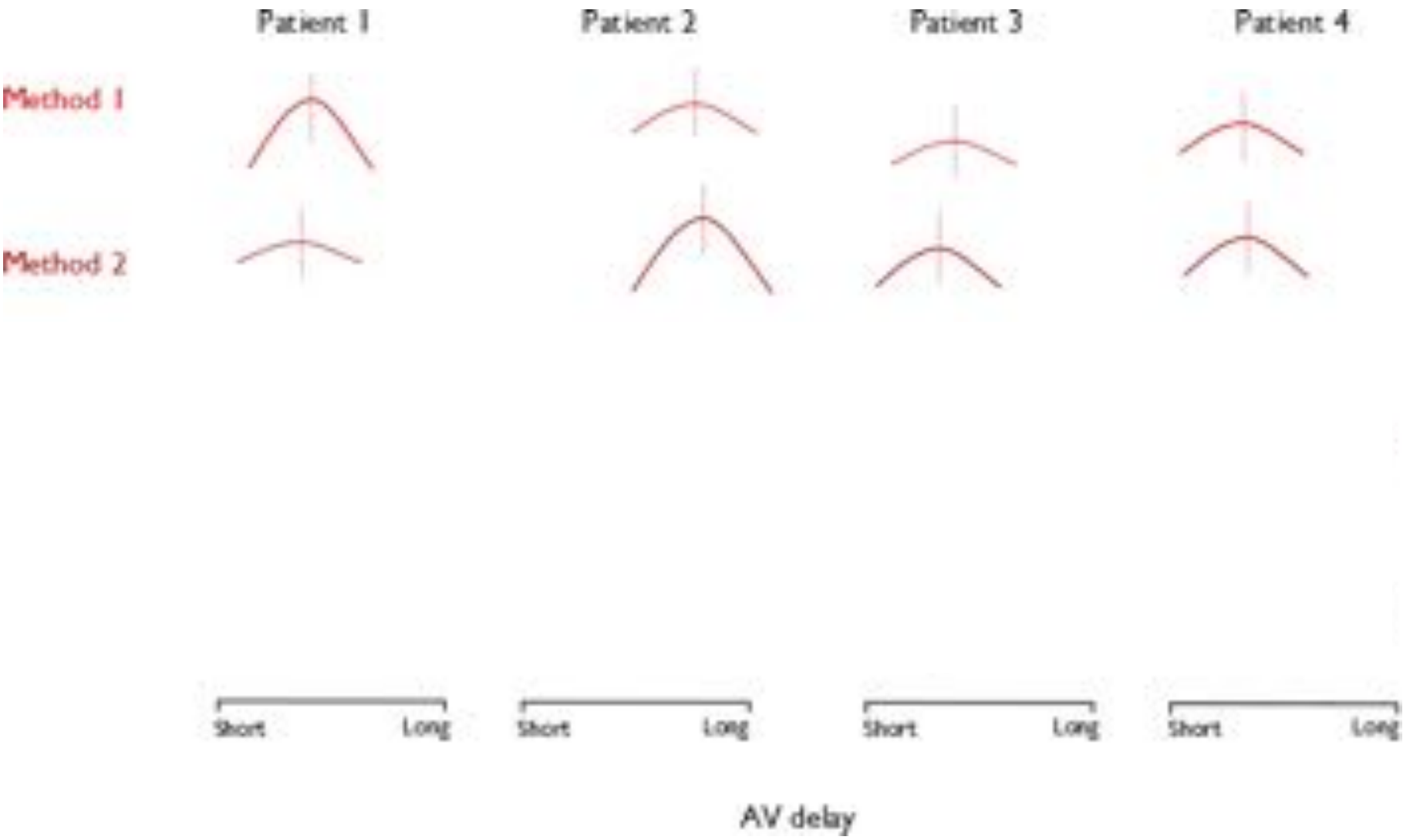


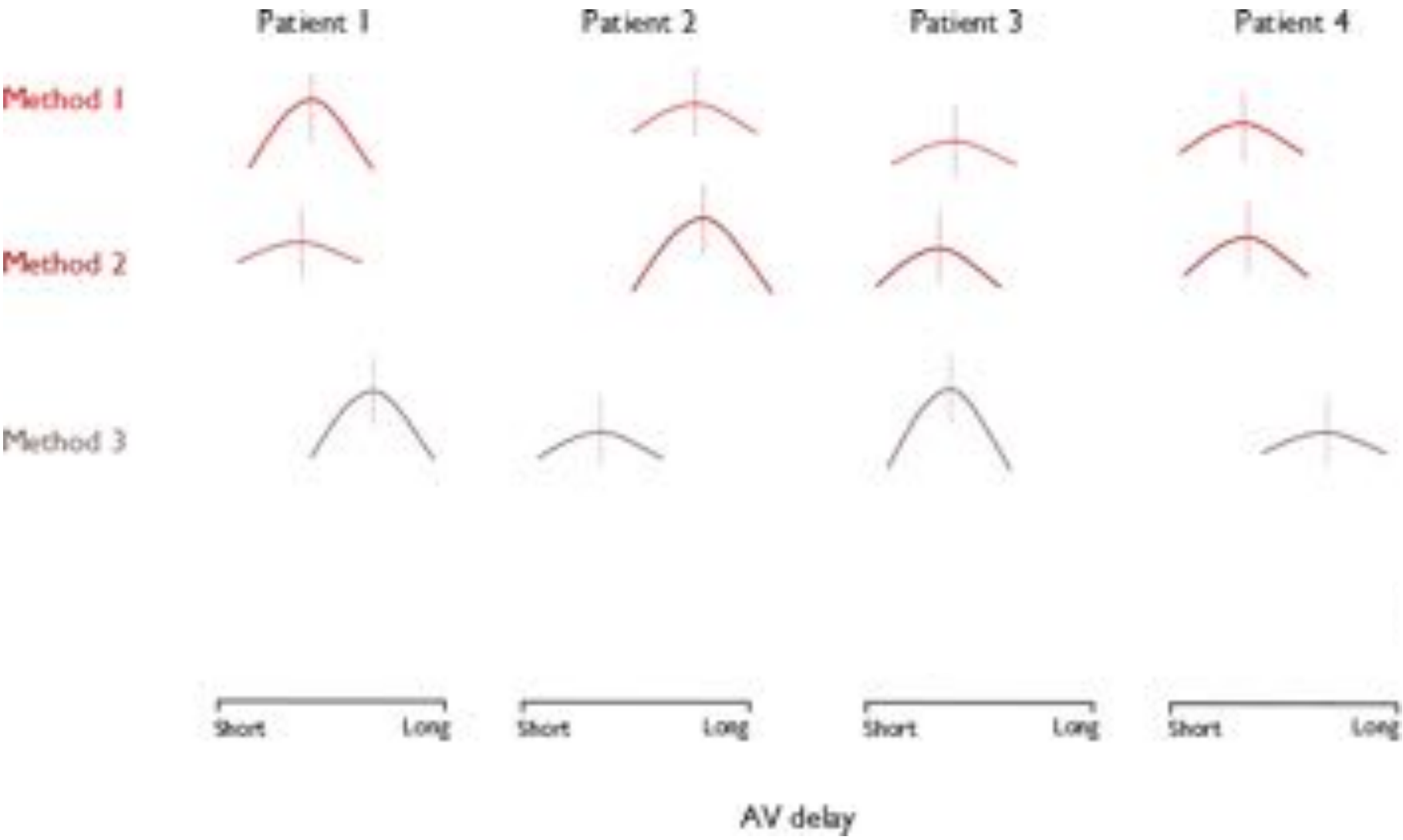


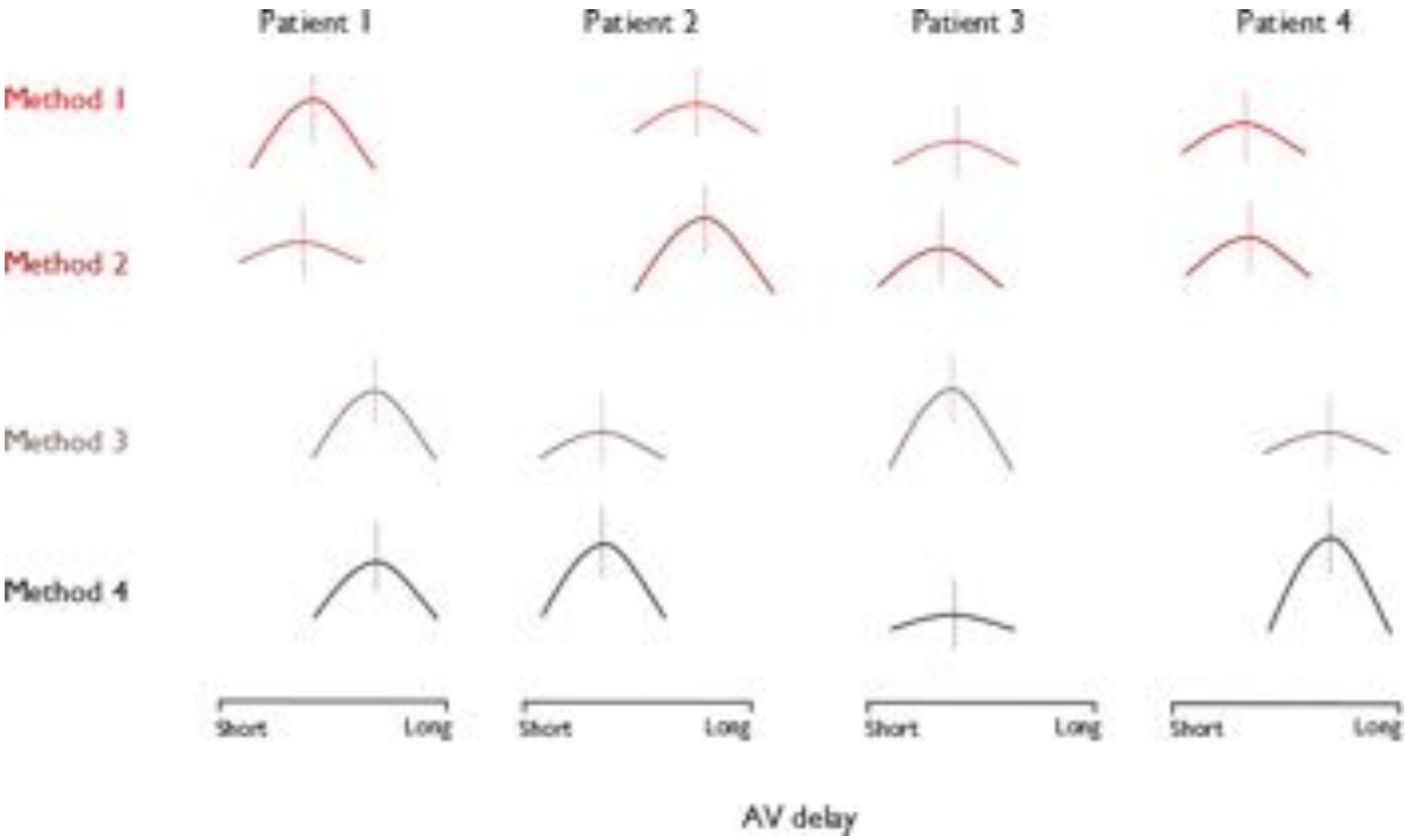
Multiple independent methods should agree

3


Patient 1
Patient 2
Patient 3
Patient 4
Method 1
Short
Long
Short
Long
Short
Long
Short
Long
AV delay

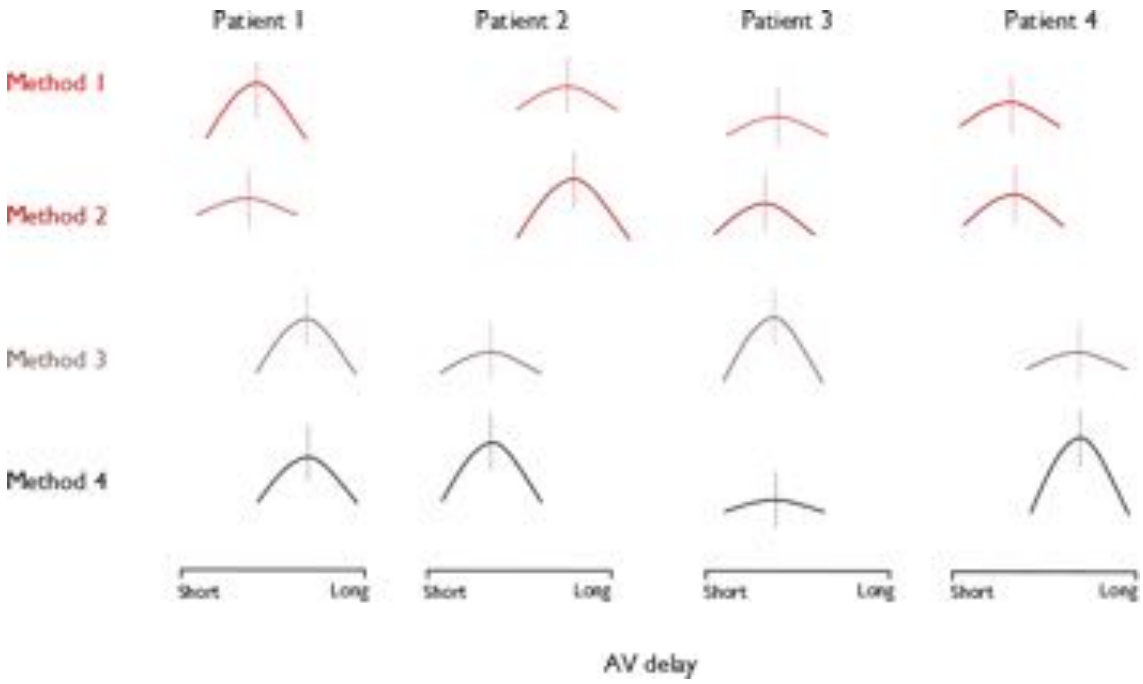

Patient 1
Patient 2
Patient 3
Patient 4
Method 1
Method 2
Short
Long
Short
Long
Short
Long
Short
Long
AV delay


Patient 1
Patient 2
Patient 3
Patient 4
Method 1
Method 2
Method 3
Short
Long
Short
Long
Short
Long
Short
Long
AV delay


Patient 1
Patient 2
Patient 3
Patient 4
Method 1
Method 2
Method 3
Method 4
Short
Long
Short
Long
Short
Long
Short
Long
AV delay

3

Multiple independent methods should agree



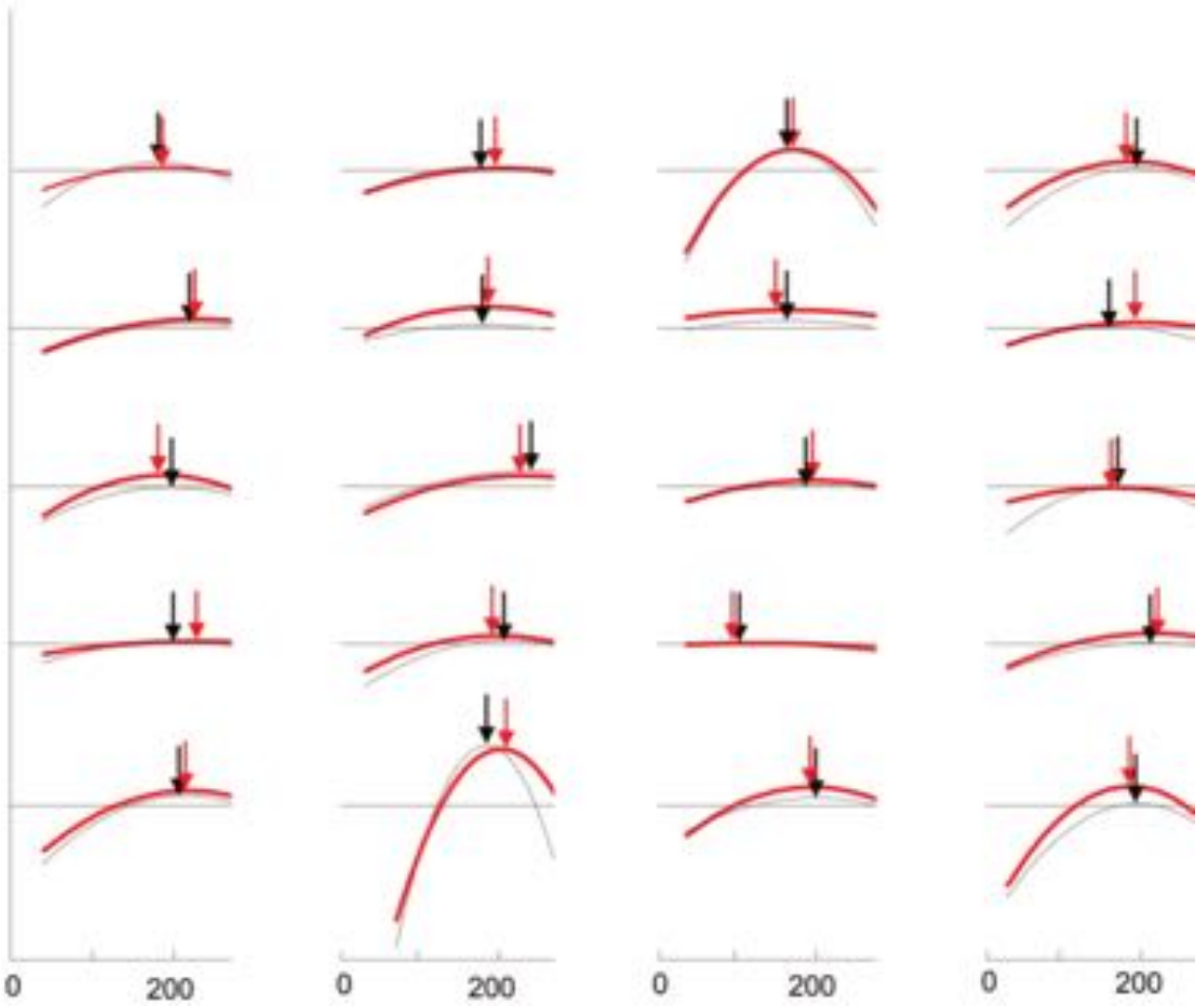
A gold standard for testing quick new optimization methods?

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

1. Singularity
2. Reproducibility
3. Clustering

1
2
3

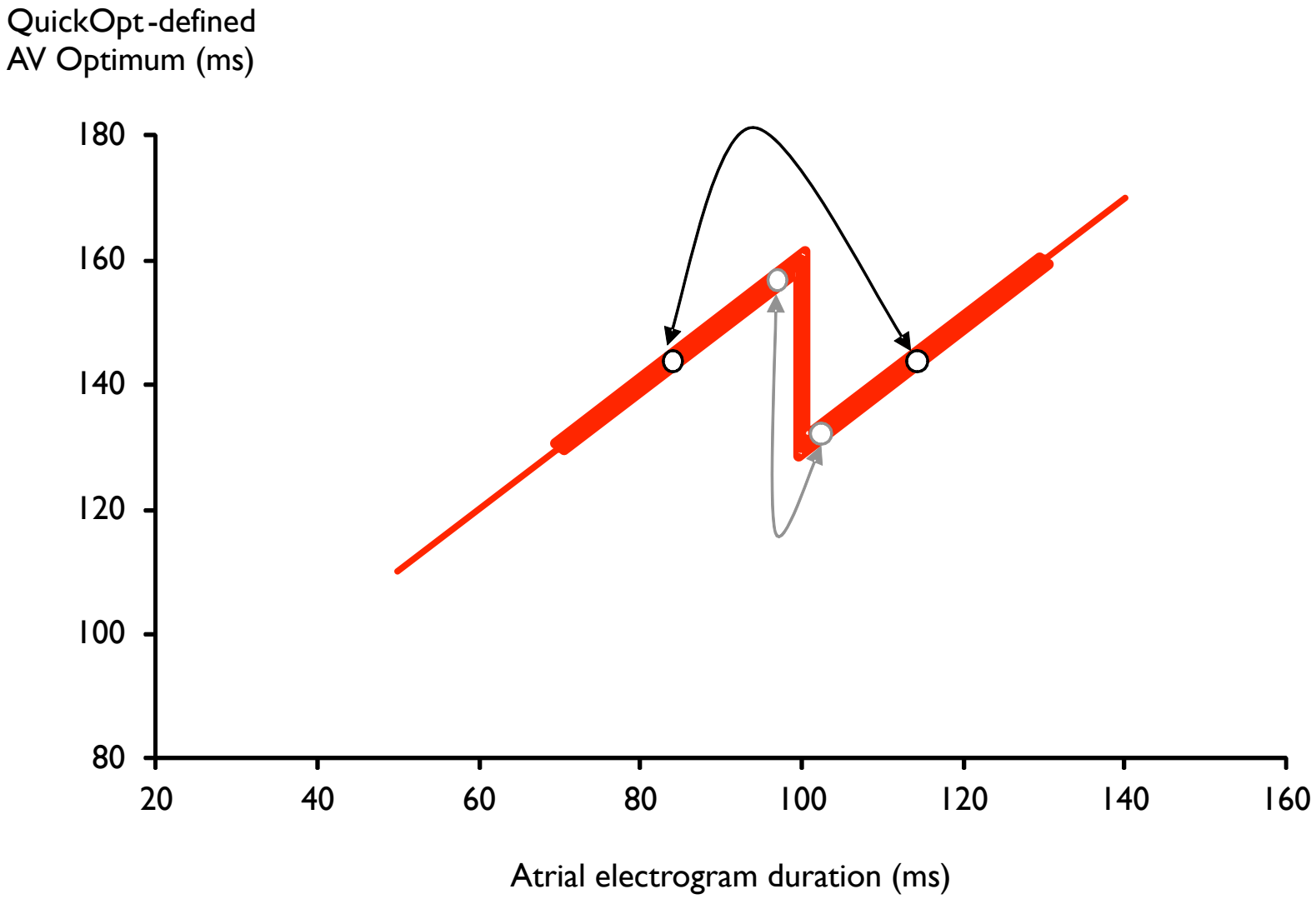
This is now available



Kyriacou, *PACE* 2012

Quick shortcut formulae for the optimum?

Quick shortcut formulae



Quick shortcut formulae

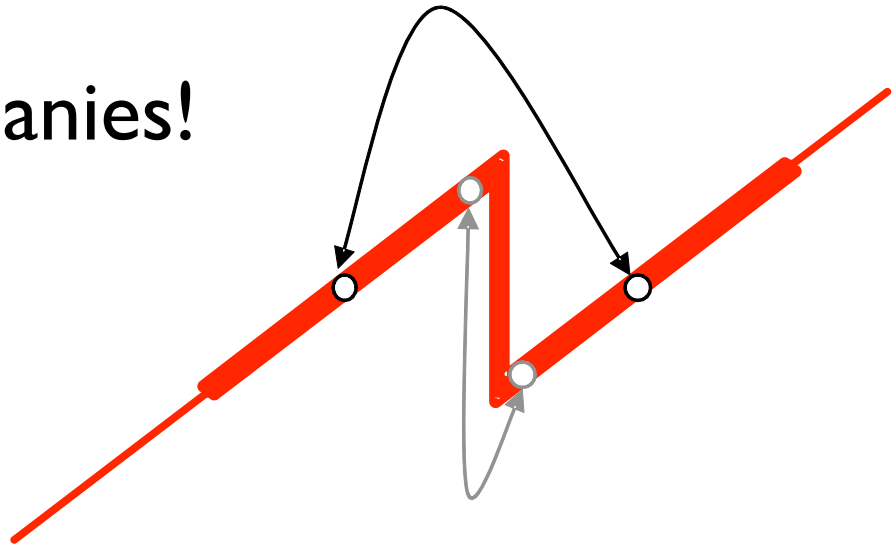
- Rarely make sense
- Are sometimes *secret*
- Have often been "validated against echo"

  i.e. "agree" with something

  that doesn't agree with itself!

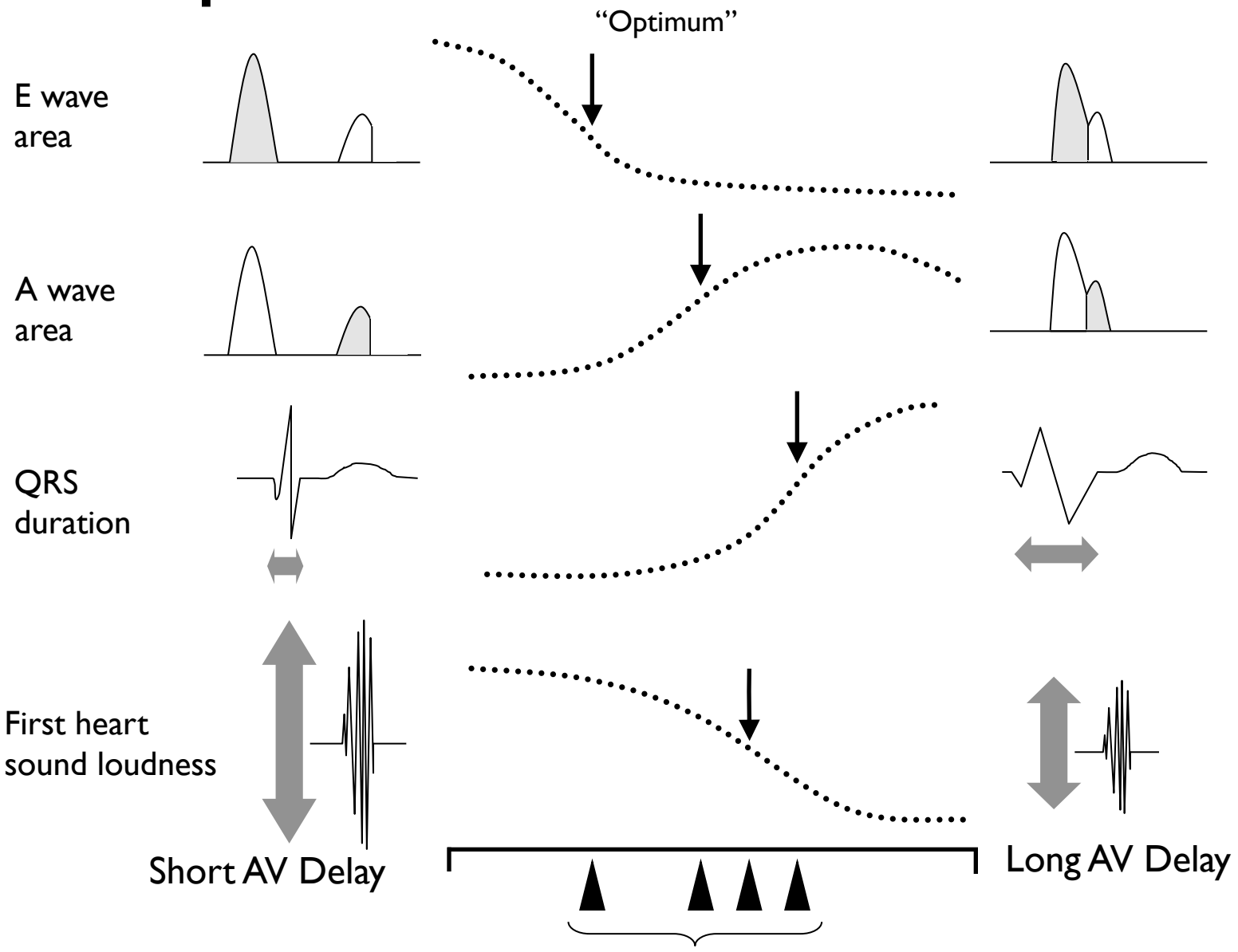
- Disagree between companies!

If *N*-1 can be wrong,
all *N* can be wrong.



Inflection points?

Inflection points?

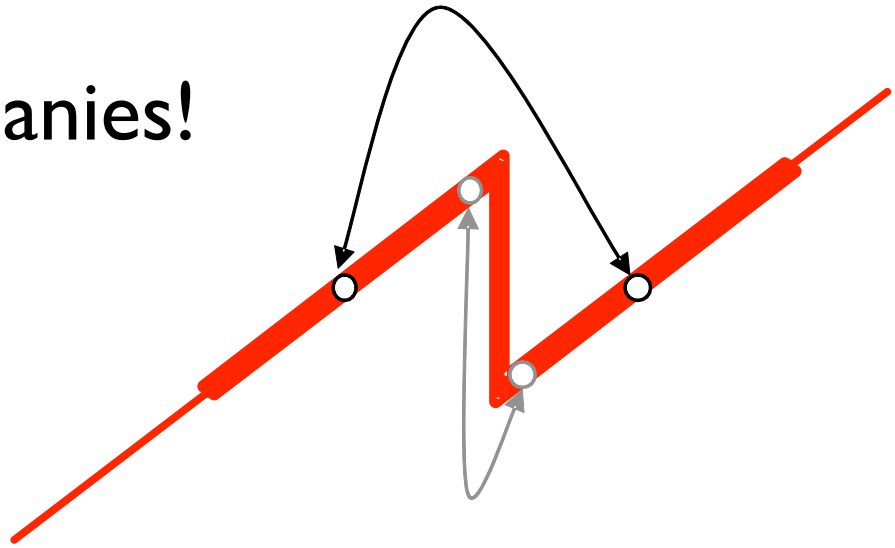


Quick shortcut formulae and inflection points

- 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

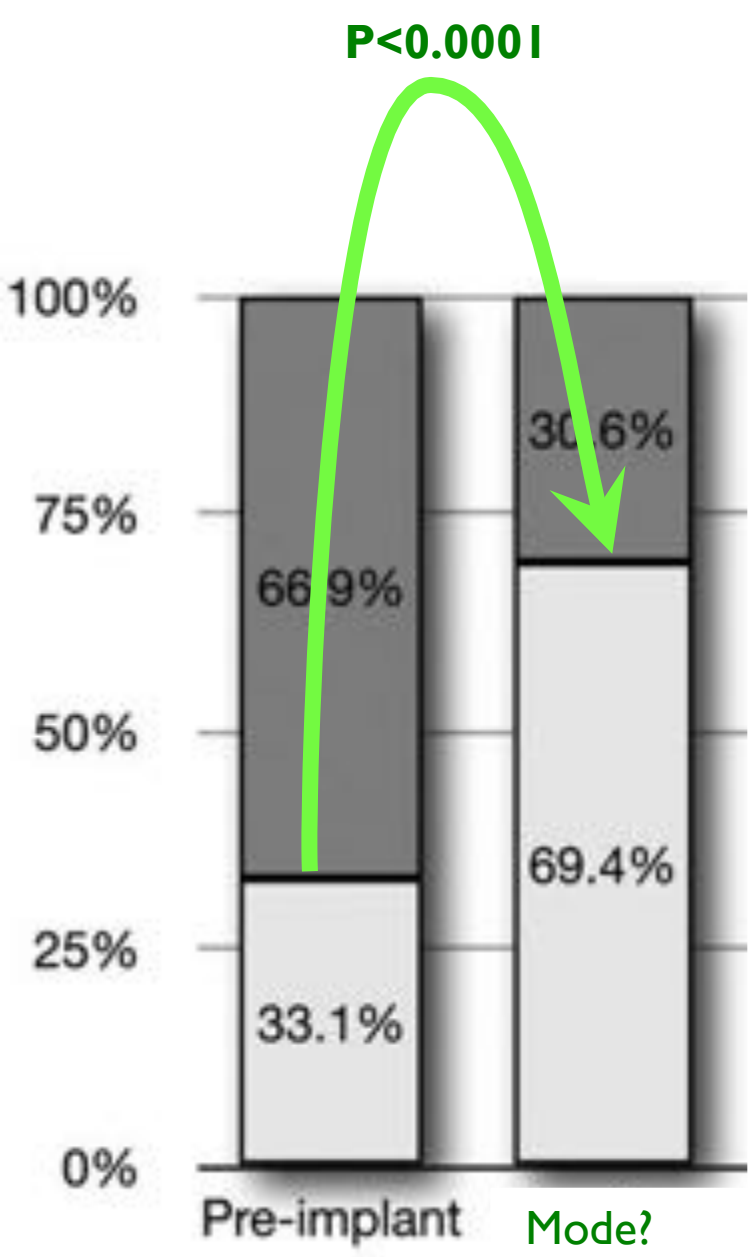
Bernard Thibault, MD; Anique Ducharme, MD, MSc; François Harel, MD, PhD; Michel White, MD; Eileen O'Meara, MD; Marie-Claude Guertin, PhD; Joel Lavoie, PhD; Nancy Frasure-Smith, PhD; Marc Dubuc, MD; Peter Guerra, MD; Laurent Macle, MD; Léna Rivard, MD; Denis Roy, MD; Mario Talajic, MD; Paul Khairy, MD, PhD; for the Evaluation of Resynchronization Therapy for Heart Failure (GREATER-EARTH) Investigators

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 Vo_2 (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.
(*Circulation*. 2011;124:2874-2881.)

Montreal, Canada

Multicentre RCT, 121 pts, EF≤35, QRS≥120 ms

Tried different pacing modes…

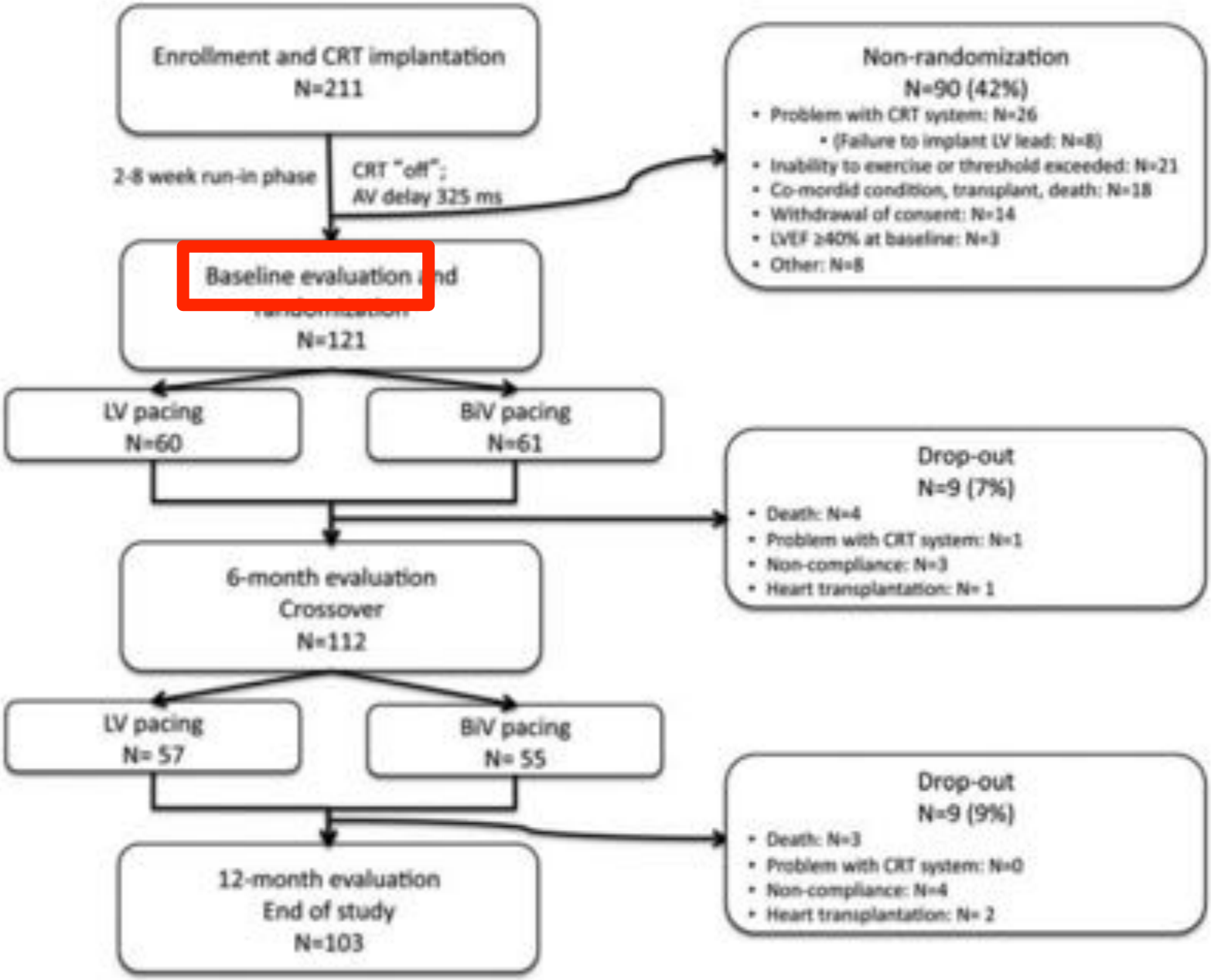


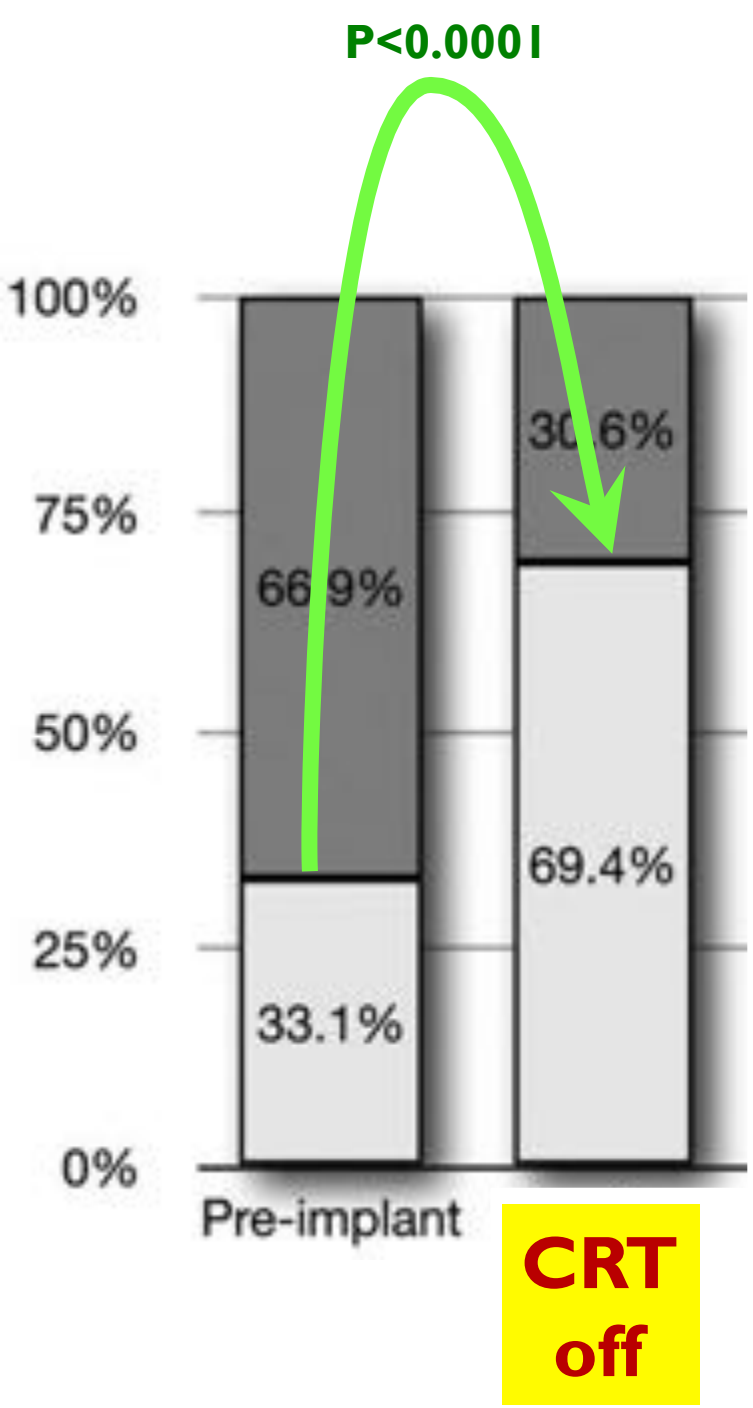
NYHA III-IV
NYHA I-II

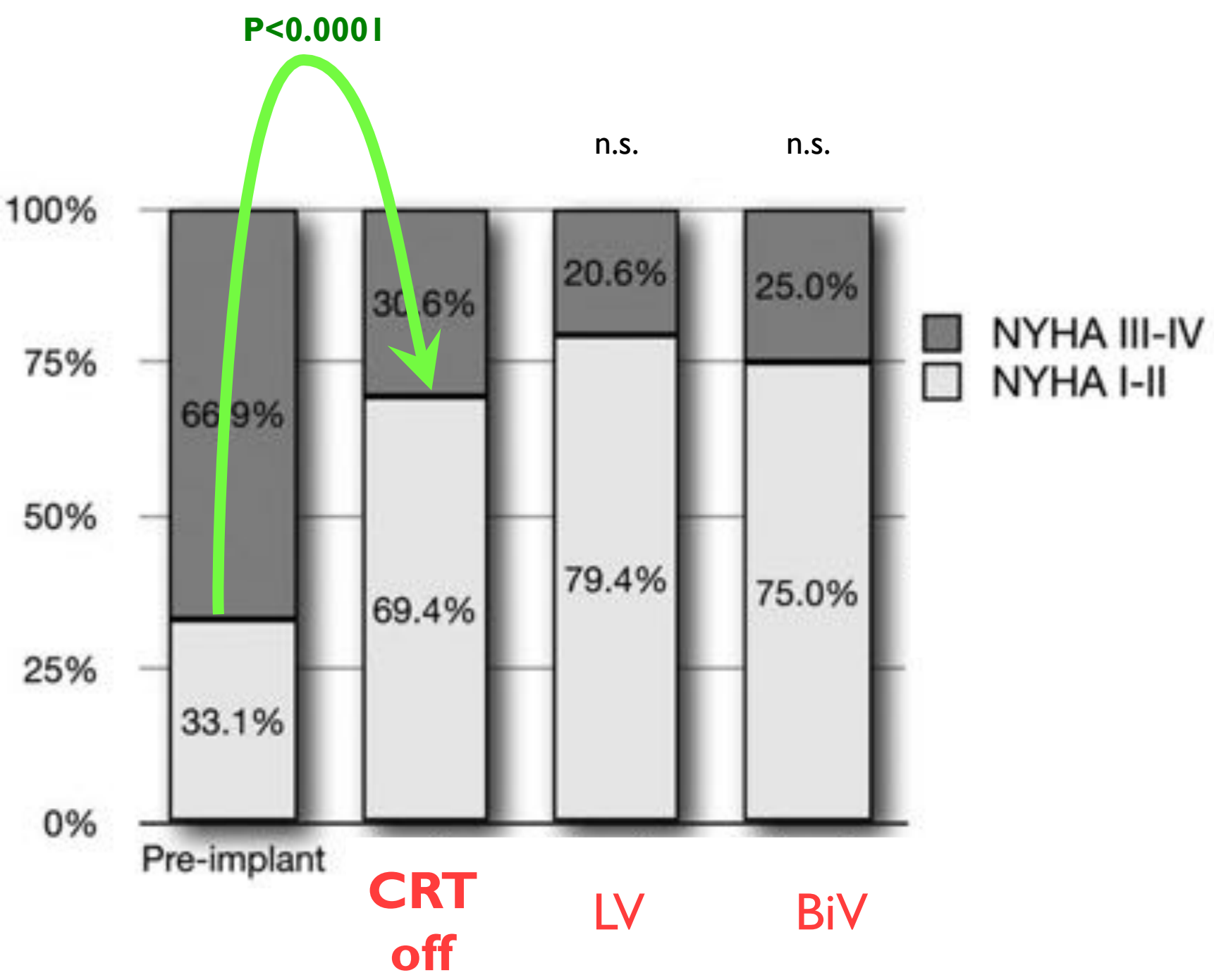
LV

BiV

Is this mode LV or BiV?


Enrollment and CRT implantation
N=211
2-8 week run-in phase
CRT "off";
AV delay 325 ms
Non-randomization
N=90 (42%)
• Problem with CRT system: N=26
• (Failure to implant LV lead: N=8)
• Inability to exercise or threshold exceeded: N=21
• Co-mordid condition, transplant, death: N=18
• Withdrawal of consent: N=14
• LVEF ≥40% at baseline: N=3
• Other: N=8
Baseline evaluation
N=121
LV pacing
N=60
BiV pacing
N=61
Drop-out
N=9 (7%)
• Death: N=4
• Problem with CRT system: N=1
• Non-compliance: N=3
• Heart transplantation: N= 1
6-month evaluation
Crossover
N=112
LV pacing
N= 57
BiV pacing
N= 55
Drop-out
N=9 (9%)
• Death: N=3
• Problem with CRT system: N=0
• Non-compliance: N=4
• Heart transplantation: N= 2
12-month evaluation
End of study
N=103


P<0.0001
100%
75%
50%
25%
0%
66.9%
33.1%
30.6%
69.4%
Pre-implant
CRT off
NYHA III-IV
NYHA I-II


P<0.0001
n.s.
n.s.
100%
75%
50%
25%
0%
66.9%
33.1%
30.6%
69.4%
20.6%
79.4%
25.0%
75.0%
NYHA III-IV
NYHA I-II
Pre-implant
CRT off
LV
BiV

What is the symptomatic response rate caused by CRT pacing?

0 – 30%

31–50%

51–60%

61–70%

71–80%

81–90%

91–100%

Trial	Patients Blinded?	Total Participants		Follow up (months)	Baseline NYHA Class
		CRT	Control		
MIRACLE	Yes	225	228	6	III/IV
MIRACLE ICD	Yes	182	187	6	III/IV
MIRACLE ICD II	Yes	101	85	6	II
REVERSE	Yes	419	191	6	I/II
Mustic	Yes	29	29	3	III
Contak CD	No	245	245	6	II/III/IV
Companion	No	617	308	6	III/IV
CARE HF	No	409	404	3	III/IV

	CRT		
Blinded	Worse	Same	Better
MIRACLE	2	30	68

	CRT		
Blinded	Worse	Same	Better
MIRACLE	2	30	68
MIRACLE ICD	3	30	67

	CRT		
Blinded	Worse	Same	Better
MIRACLE	2	30	68
MIRACLE ICD	3	30	67
REVERSE	10	59	31

	CRT		
Blinded	Worse	Same	Better
MIRACLE	2	30	68
MIRACLE ICD	3	30	67
REVERSE	10	59	31
Weighted Mean			48

	CRT		
Blinded	Worse	Same	Better
MIRACLE	2	30	68
MIRACLE ICD	3	30	67
REVERSE	10	59	31
Weighted Mean			48
Open			
Contak CD	13	51	36
Companion (CRT-P)	39		61
Weighted Mean			56
Weighted Mean of All Studies			51

But these were controlled trials

	Control	CRT		
Blinded		Worse	Same	Better
MIRACLE		2	30	68
MIRACLE ICD		3	30	67
REVERSE		10	59	31
Weighted Mean				48
Open				
Contak CD		13	51	36
Companion (CRT-P)		39		61
Weighted Mean				56
Weighted Mean of All Studies				51

But these were controlled trials

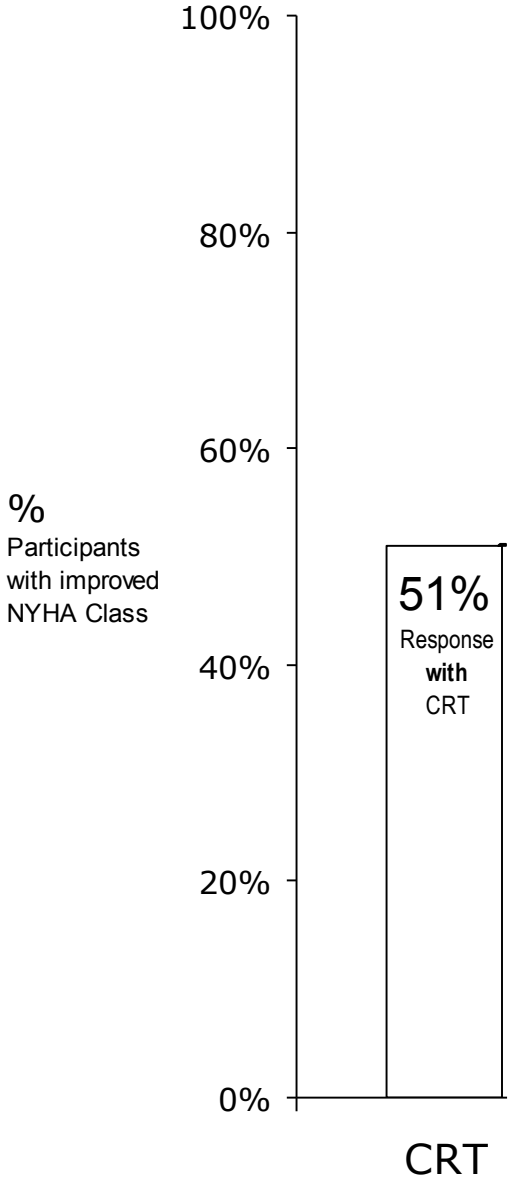
	Control	CRT		
Blinded		Worse	Same	Better
MIRACLE		2	30	68
MIRACLE ICD		3	30	67
REVERSE		10	59	31
Weighted Mean				48
Open				
Contak CD		13	51	36
Companion (CRT-P)		39		61
Weighted Mean				56
Weighted Mean of All Studies				51

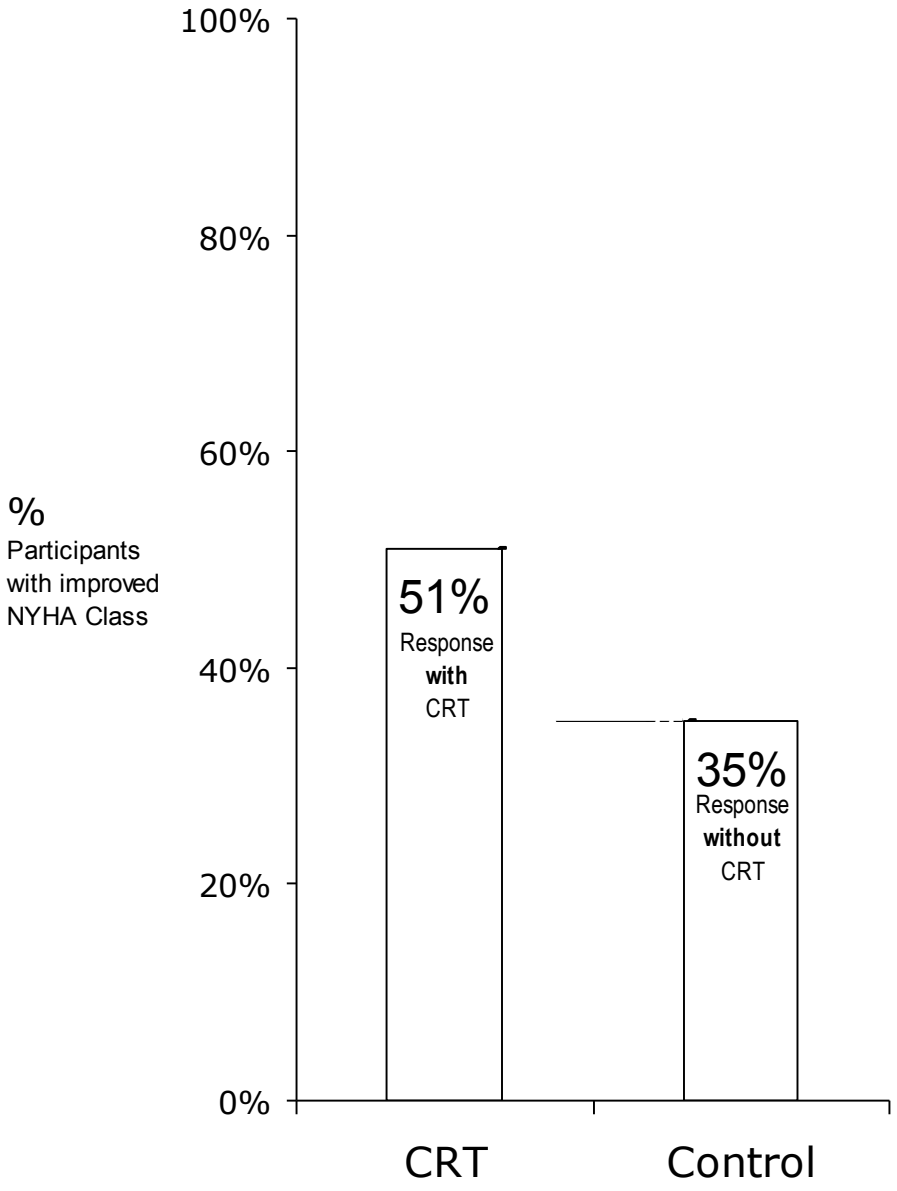
Was their Response Rate zero?

	Control			CRT		
Blinded	Worse	Same	Better	Worse	Same	Better
MIRACLE	4	59	38	2	30	68
MIRACLE ICD	5	45	50	3	30	67
REVERSE	9	70	20	10	59	31
Weighted Mean			34			48
Open						
Contak CD	17	51	32	13	51	36
Companion (CRT-P)	62		38	39		61
Weighted Mean			36			56
Weighted Mean of All Studies			35			51

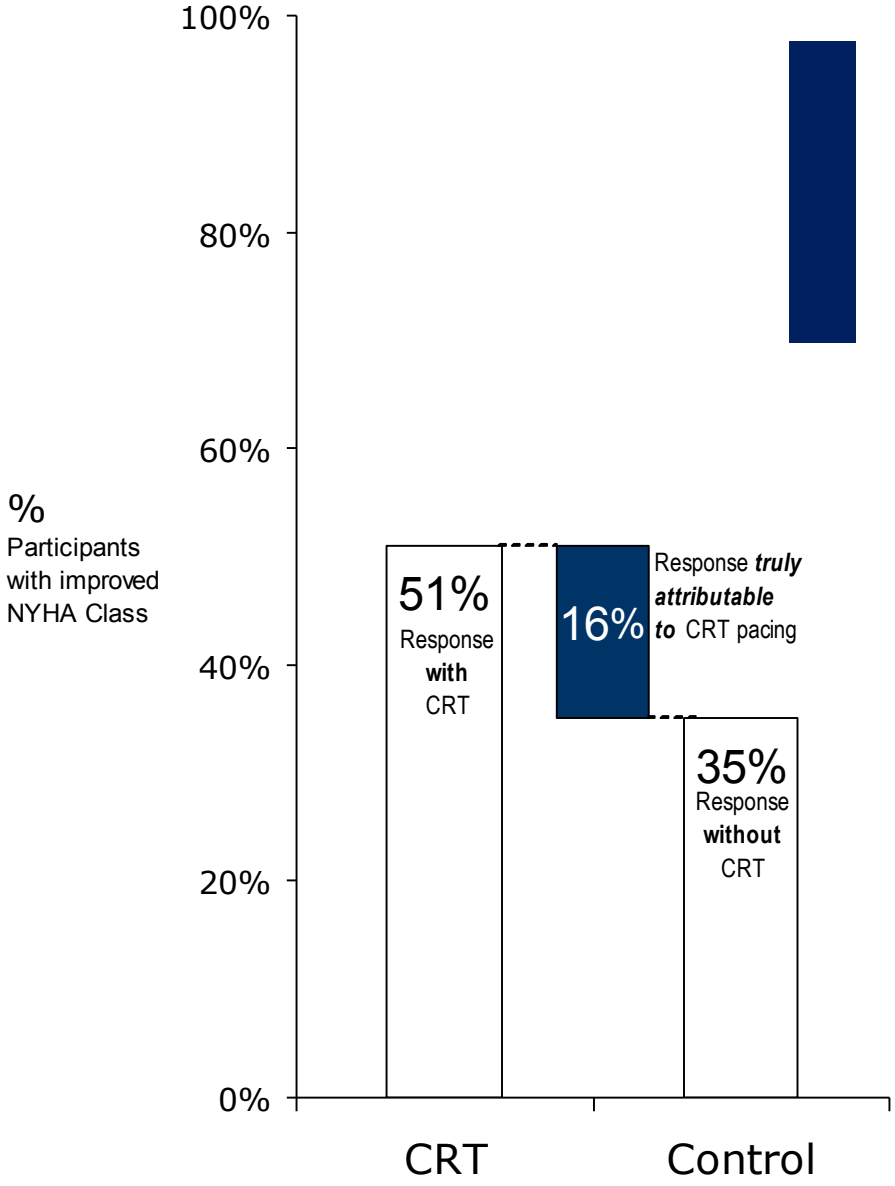
	Control			CRT			CRT minus control		
Blinded	Worse	Same	Better	Worse	Same	Better	Worse	Same	Better
MIRACLE	4	59	38	2	30	68	-2	-29	30
MIRACLE ICD	5	45	50	3	30	67	-2	-15	17
REVERSE	9	70	20	10	59	31	1	-11	10
Weighted Mean			34			48			13
Open									
Contak CD	17	51	32	13	51	36	-4	0	4
Companion (CRT-P)	62		38	39		61	-23		23
Weighted Mean			36			56			20
Weighted Mean of All Studies			35			51			16

Sohaib, *Eur J Heart Fail* 2013;15(12):1419-1428.


100%
80%
60%
40%
20%
0%
%
Participants
with improved
NYHA Class
51%
Response
with
CRT
CRT

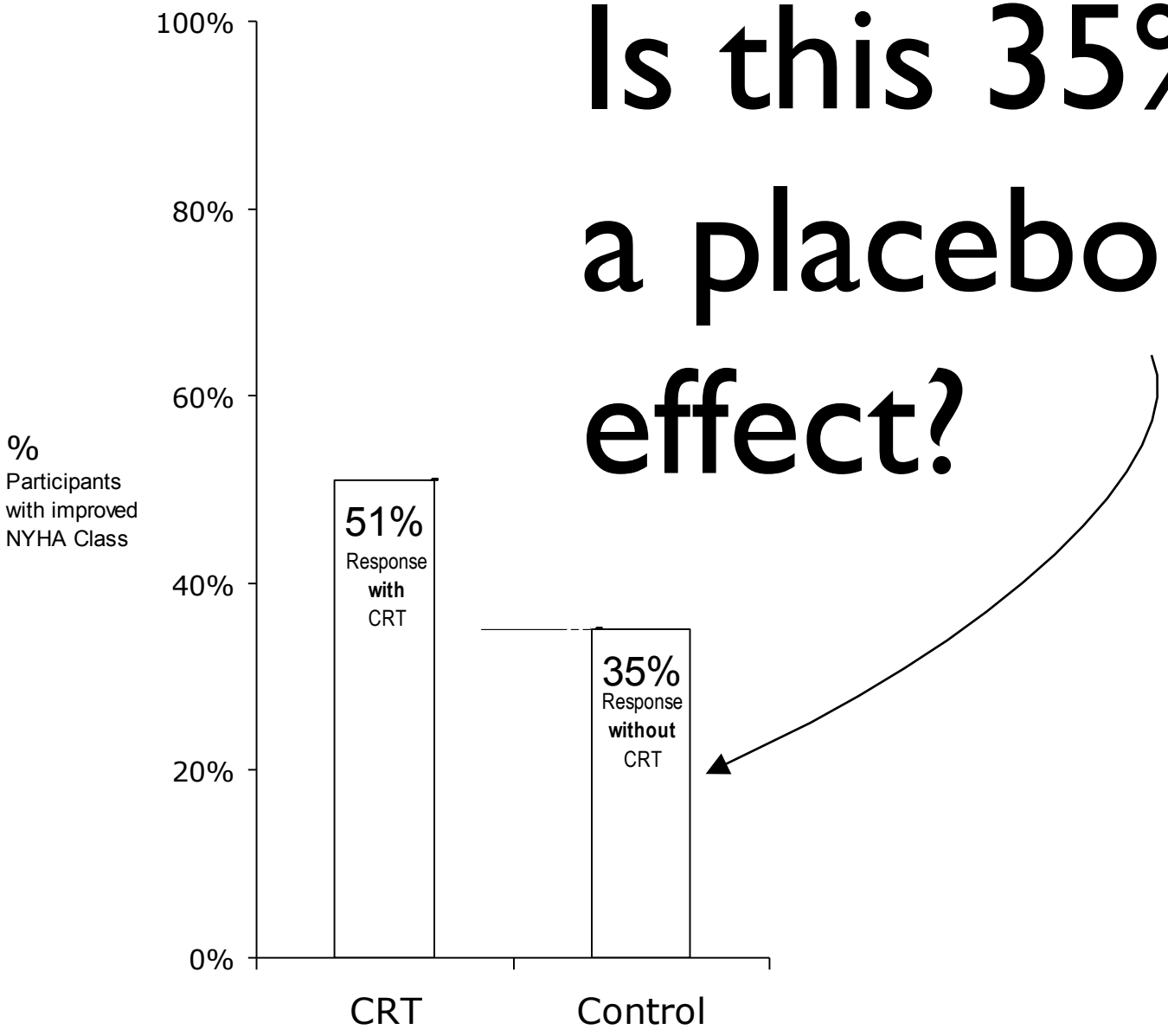

100%
80%
60%
40%
20%
0%
%
Participants
with improved
NYHA Class
51%
Response
with
CRT
35%
Response
without
CRT
CRT
Control

16%

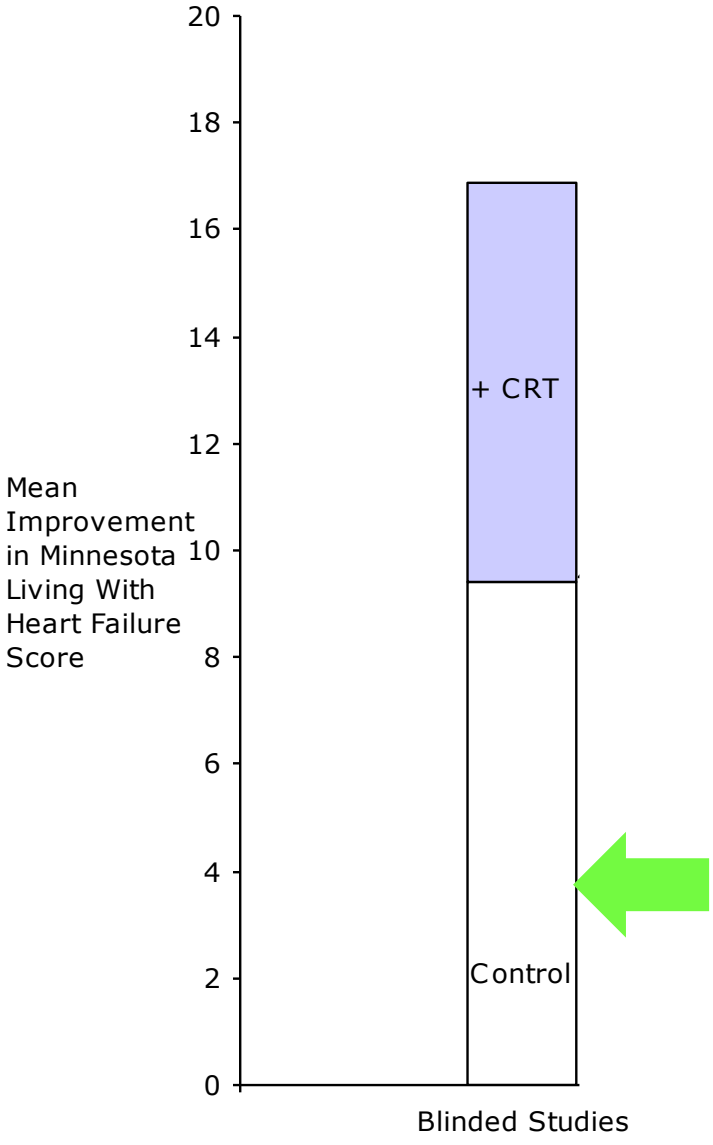


Sohaib, *Eur J Heart Fail* 2013;15(12):1419-1428.

Is this 35% a placebo effect?

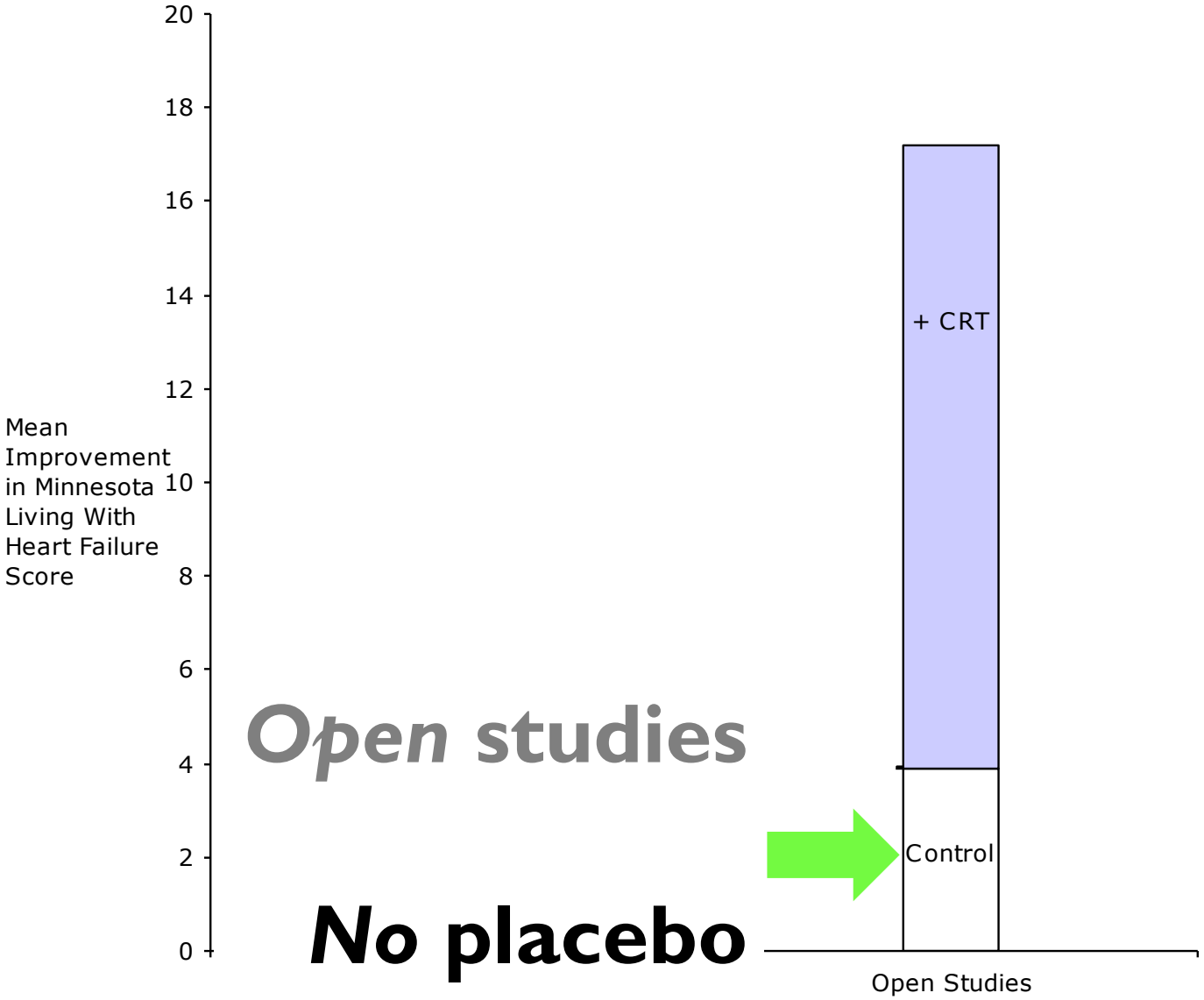


	Minnesota Living with Heart Failure Score (Improvement from baseline)		
	Control	**CRT**	**CRT minus Control**
Blinded			
MIRACLE	9	18	9
MIRACLE ICD	11	17	6
MIRACLE ICD II	10.7	13.3	2.6
Mustic	3.8	17.4	13.6
Weighted Mean	9.5	16.9	7.4
Open			
CARE HF	4.8	14.5	9.7
Companion	12	25	13
Contak CD	-5	7	12
Weighted Mean	3.9	17.3	13.3
Weighted Mean of All Studies	6.0	17.2	11.2



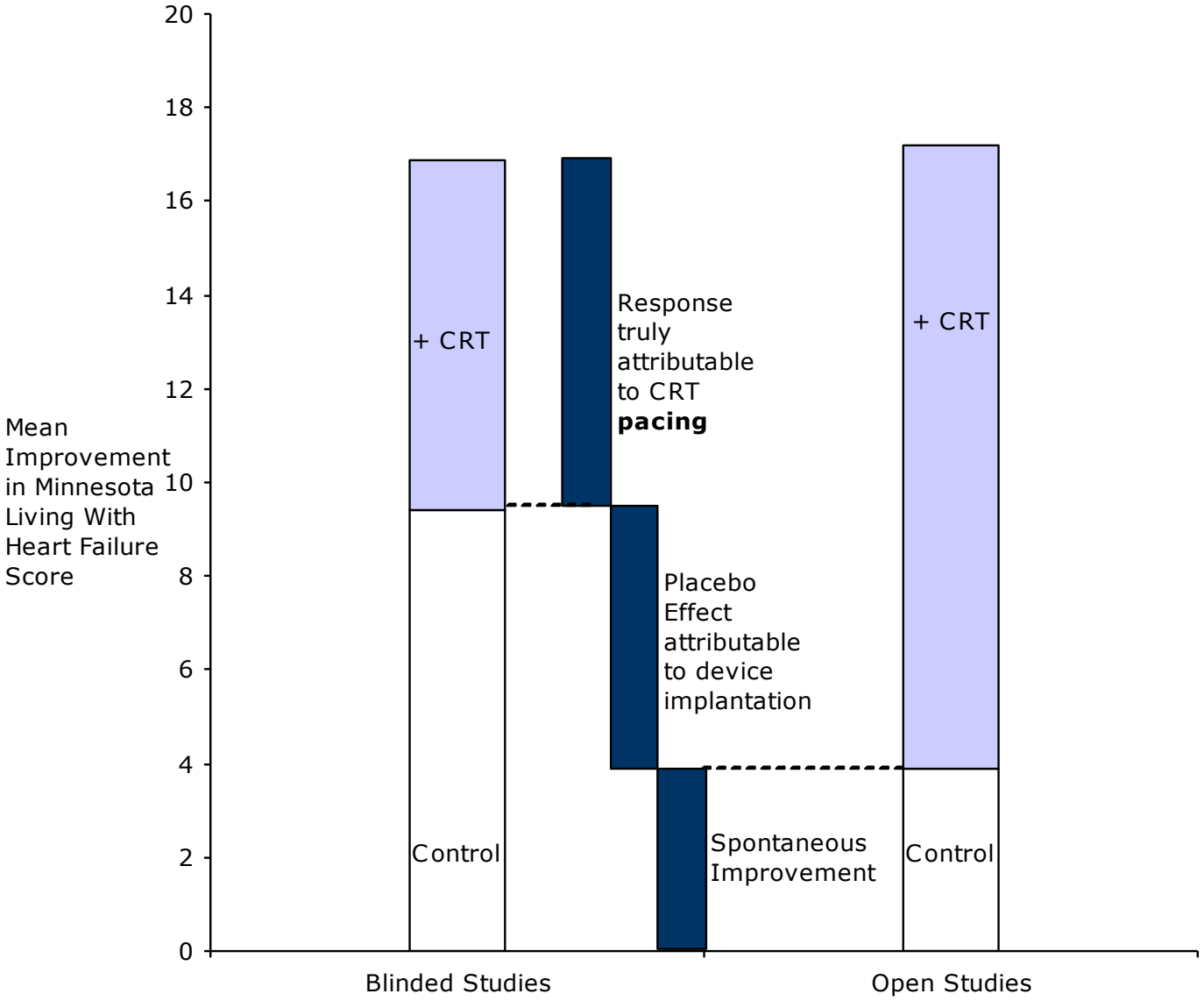
Blinded studies

Partly placebo



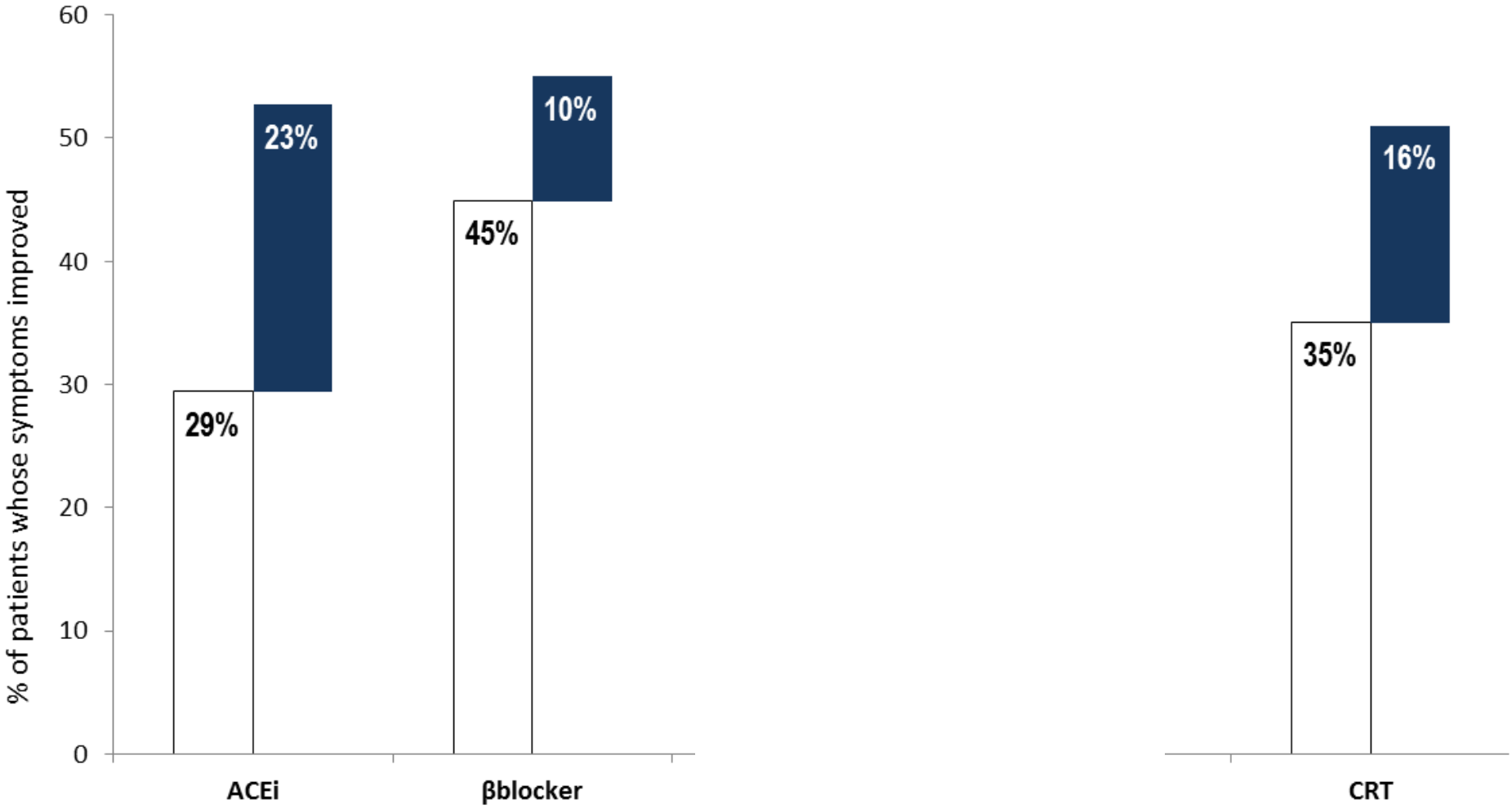
Open studies

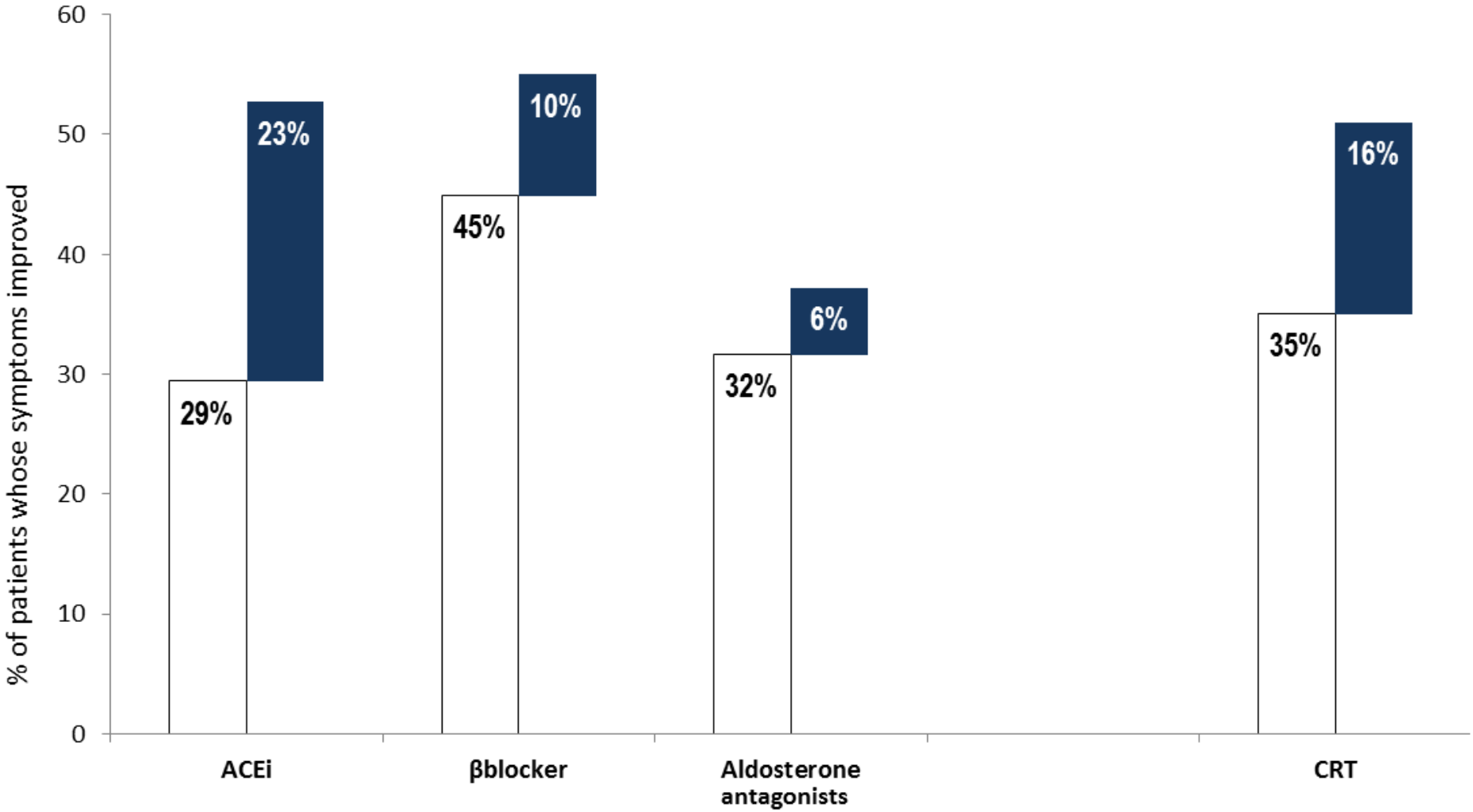
No placebo



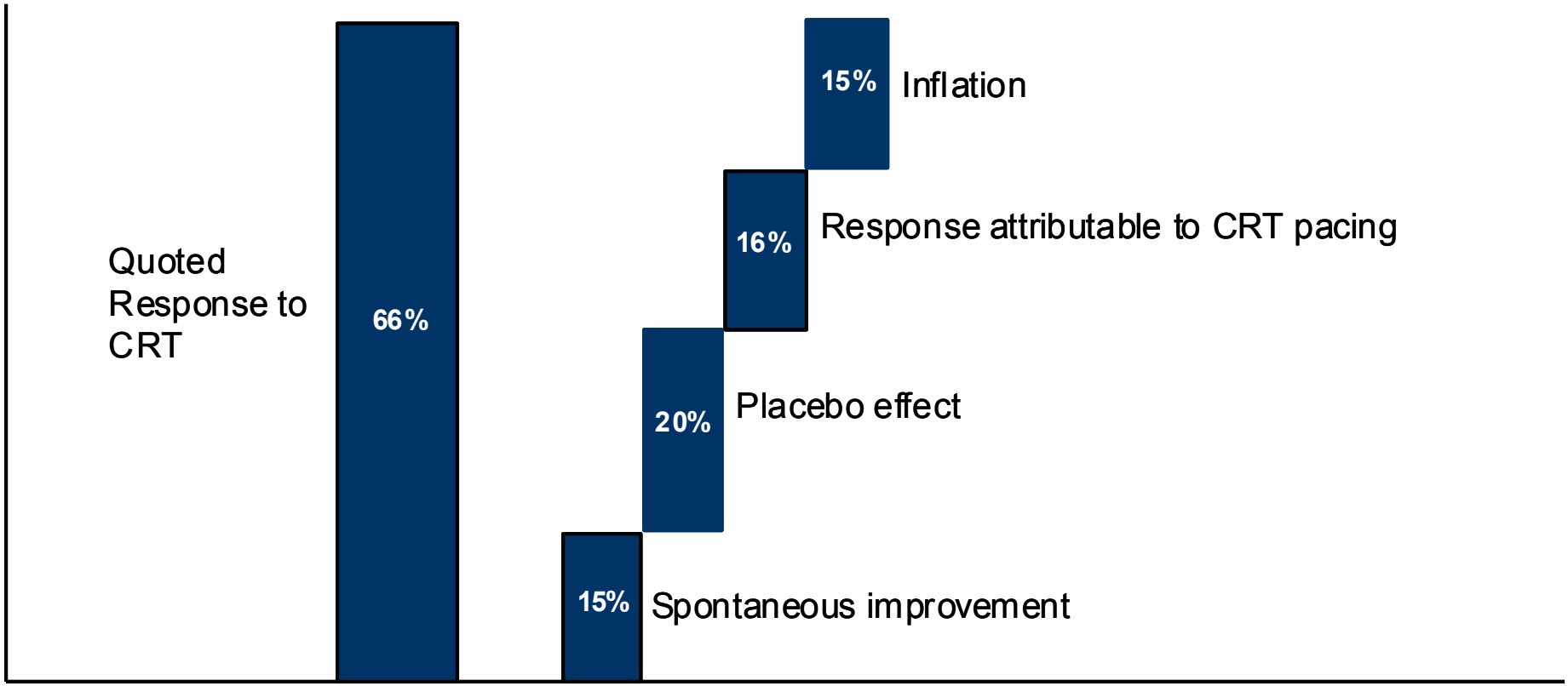
Sohaib, *Eur J Heart Fail* 2013;15(12):1419-1428.


60
50
40
30
20
10
0
% of patients whose symptoms improved
23%
29%
16%
35%
ACEi
CRT

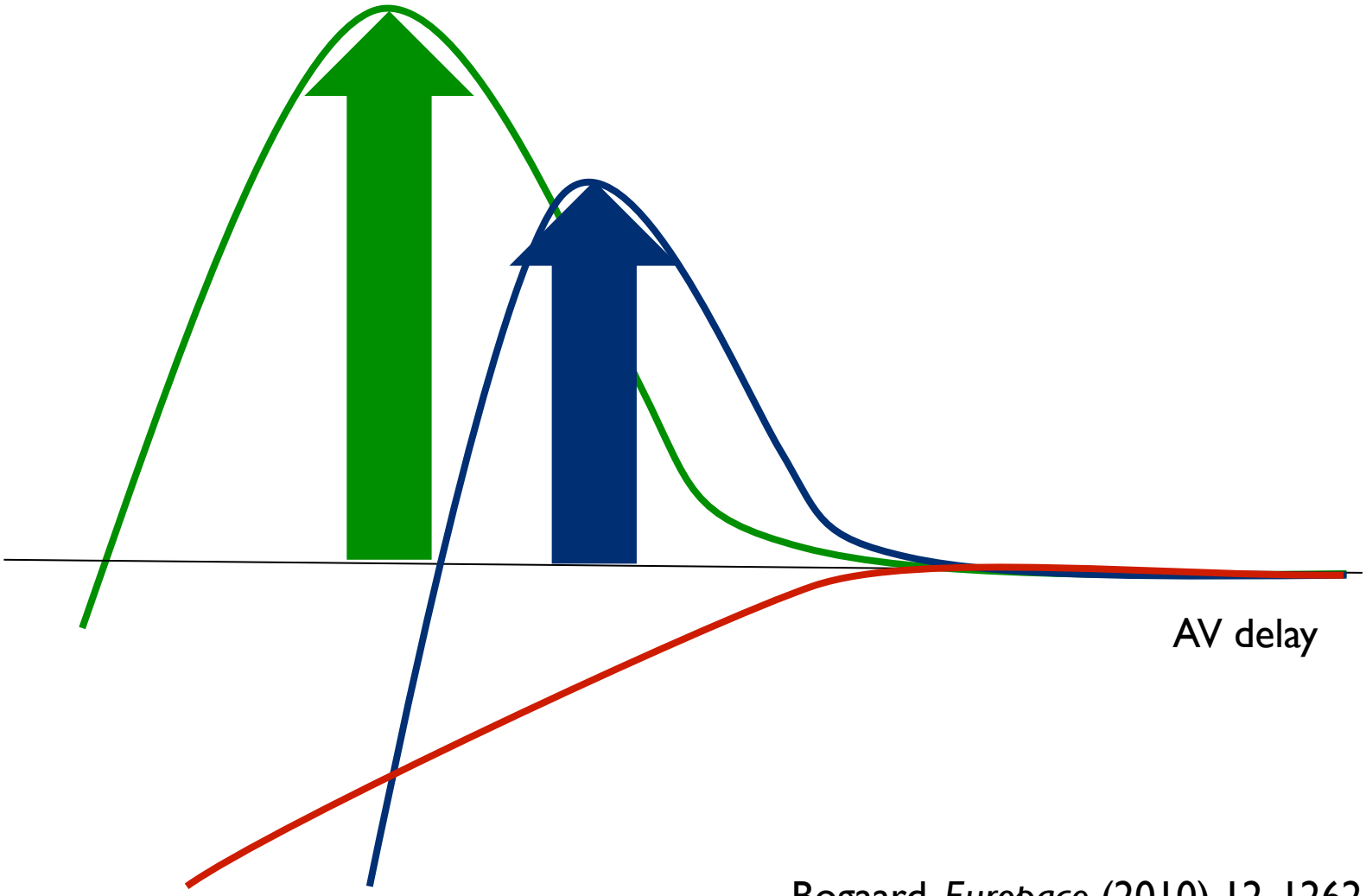

60
50
40
30
20
10
0
% of patients whose symptoms improved
23%
10%
16%
29%
45%
35%
ACEi
βblocker
CRT


% of patients whose symptoms improved
60
50
40
30
20
10
0
23%
29%
10%
45%
6%
32%
16%
35%
ACEi
βblocker
Aldosterone antagonists
CRT

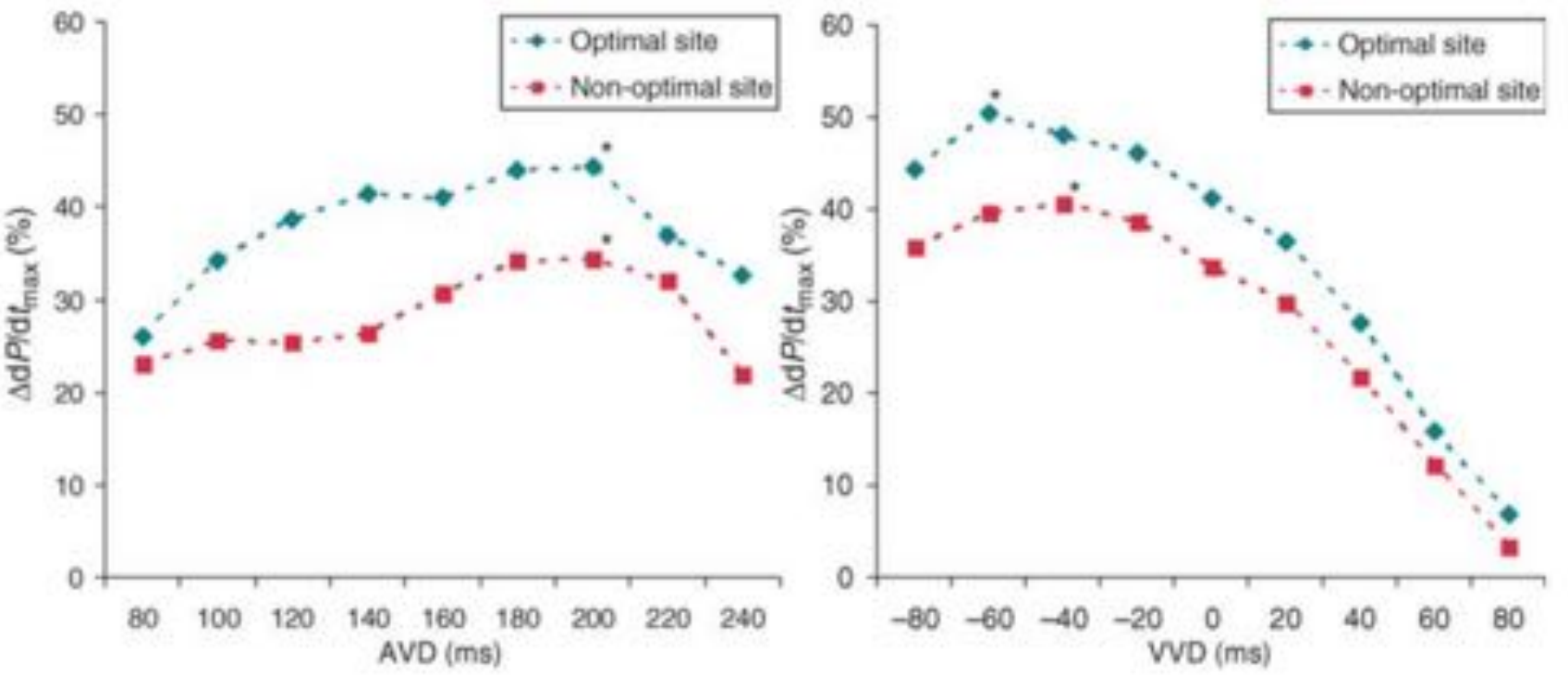
How to justify "2/3" response



Sohaib, *Eur J Heart Fail* 2013;15(12):1419-1428.



Bogaard, *Europace* (2010) 12, 1262–1269



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Rationale for routine optimization

1

Small increment in function in the average LBBB patient

2

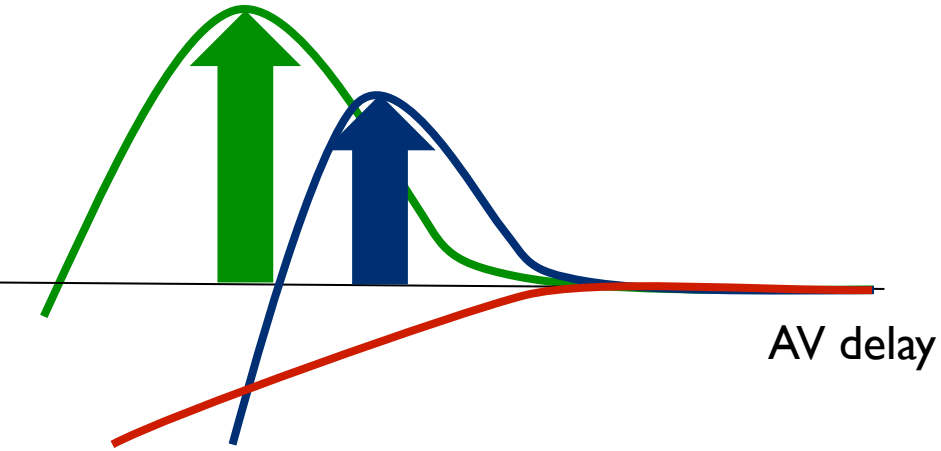
Difference between positive and negative response in the *grey zone* patient

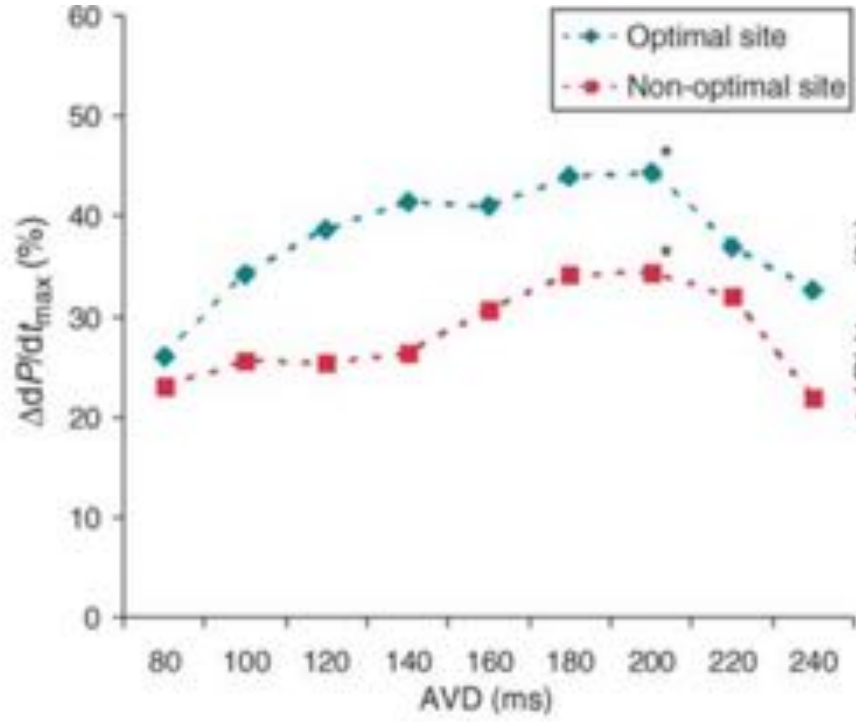
3

Valid comparison between leads and pacing configurations

4

Reproducible marker of response, not confounded by other disease events





Bogaard, *Europace* (2010) 12, 1262–1269