CRT what's new ?

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All Main RCT's in CRT confirm what was known since 1994

Biventricular for Heart failure in LBBB wide QRS patients with low ejection fraction, symptomatic despite optimized medical treatment

And 30 to 35 % of the patients still do not respond

Since 1994, whatever the world research and companies investments : nothing really new…

What would be really new: Decrease the non-response rate unchanged since 1994?

1/ Improve the selection process of dyssynchrony

- presently based on QRS width
- only valuable in LBBB > 150 ms (historical indication)
- concerns a minority of HF patients. Majority of them have 120ms < QRS < 150ms and IVCD

2/ Improve the implant process

3/ Improve the FU and continuous adaptation of AV/VV parameters

1/ Improve the selection process: What is Dyssynchrony?

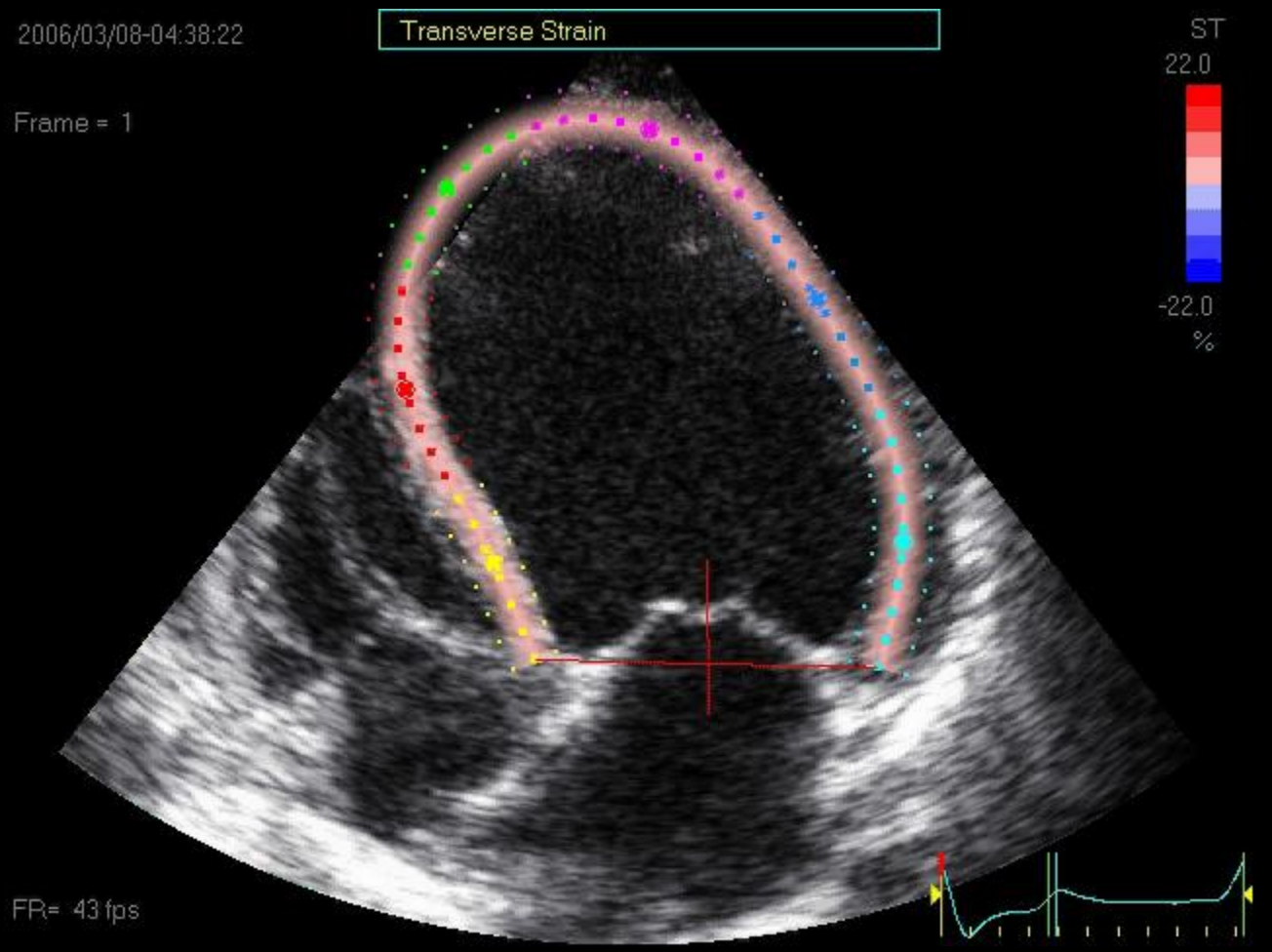
Dyssynchrony was defined in 1994 when the first CRT was implanted assessing segments not contracting simultaneously with delays

Viewed since the beginning through its surrogate QRS width (LBBB)

Although recognized by ESC as potentially more appropriate, Echo failed to produce a simple reliable and usable method to indentify dyssynchrony (Prospect study)

Probably no single parameter can describe dyssynchrony (Prospect study)

Dyssynchrony:
A 3D phenomenon very difficult to characterize



Courtesy of S. Lafitte

Improve the selection process
The Dyssynchrony model parameters

AV synchrony : LVFT reported to RR

InterV = LPEI –RPEI

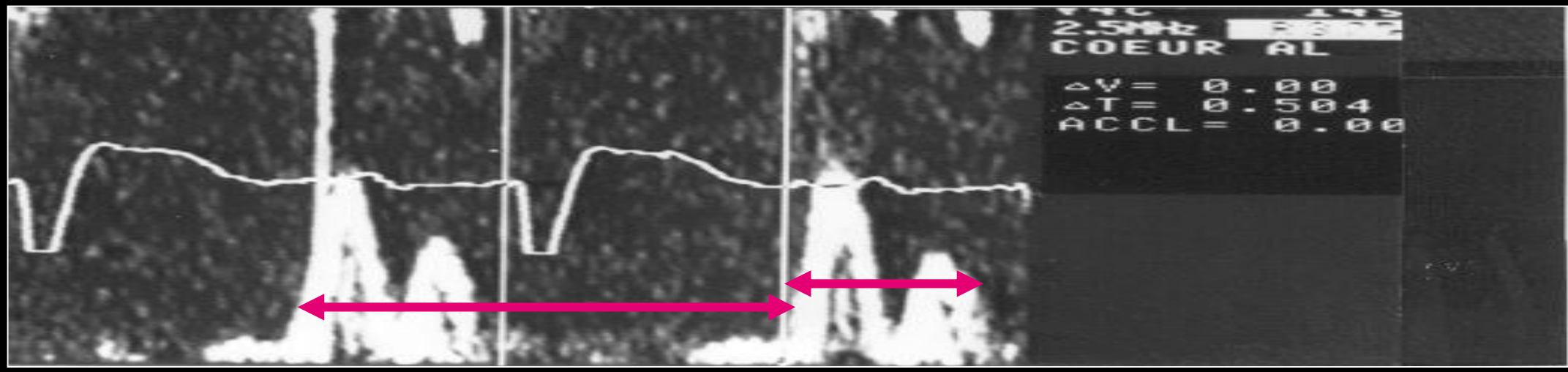
IntraV : LPEI, Diastolic contraction and overlap

Cazeau et al Heart 2000

Global response : LPEI, LPEI/LVET, ratio diastole/systole

The Dyssynchrony model parameters

AV synchrony : LVFT reported to RR < 40%

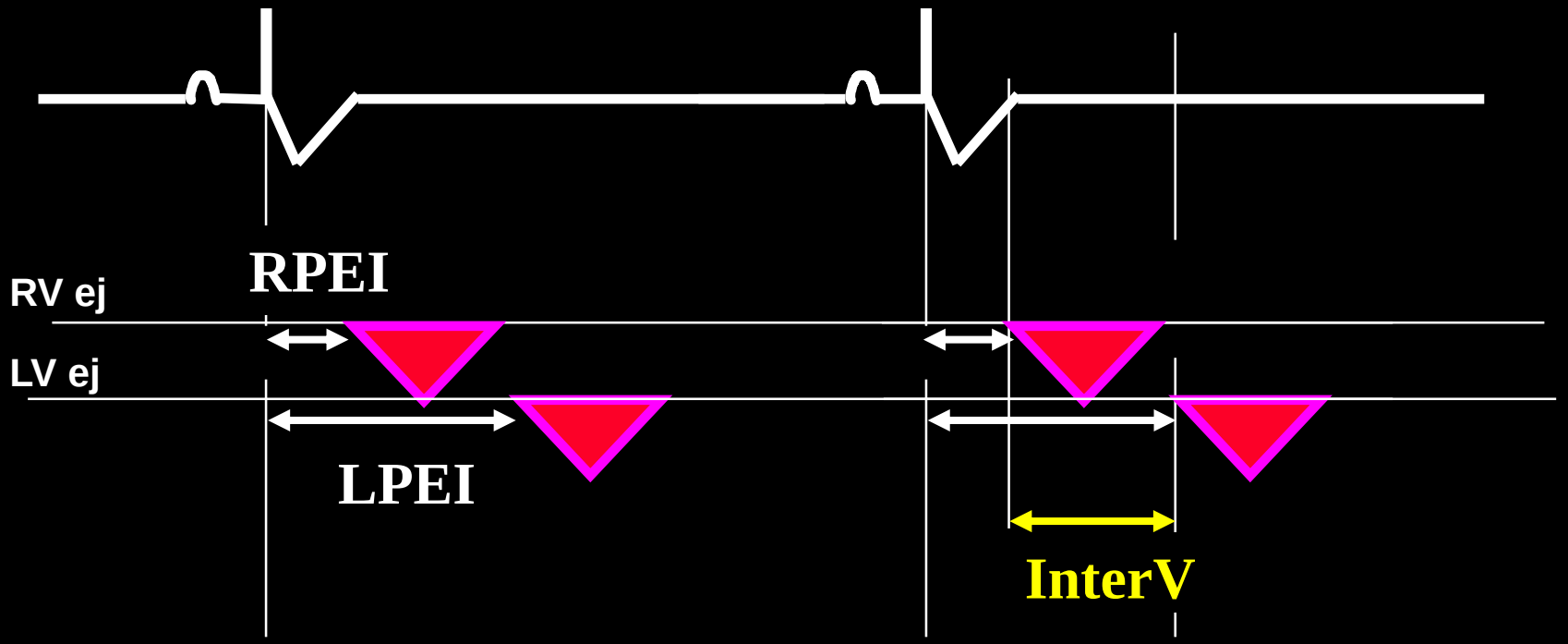


Cazeau et al Heart 2000

The Dyssynchrony model parameters

AV synchrony : LVFT reported to RR > 50%

InterV = LPEI –RPEI < 40 ms



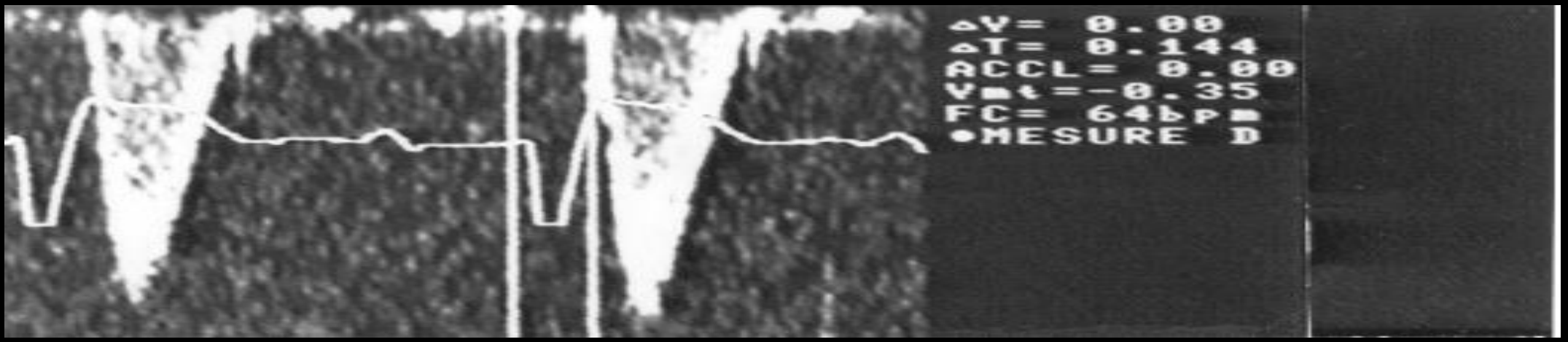
Cazeau et al Heart 2000

The dyssynchrony model parameters

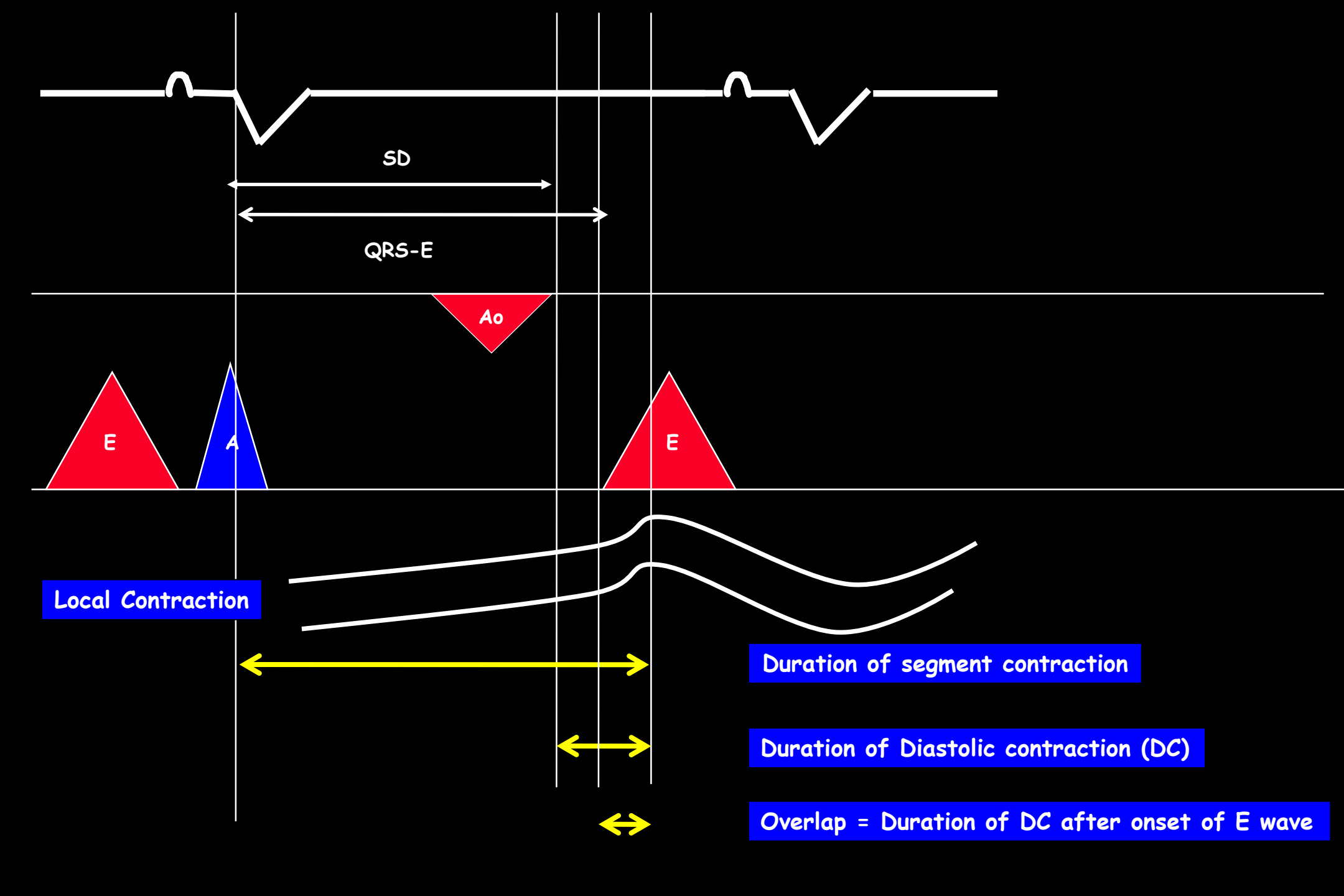
AV synchrony : LVFT reported to RR < 40%

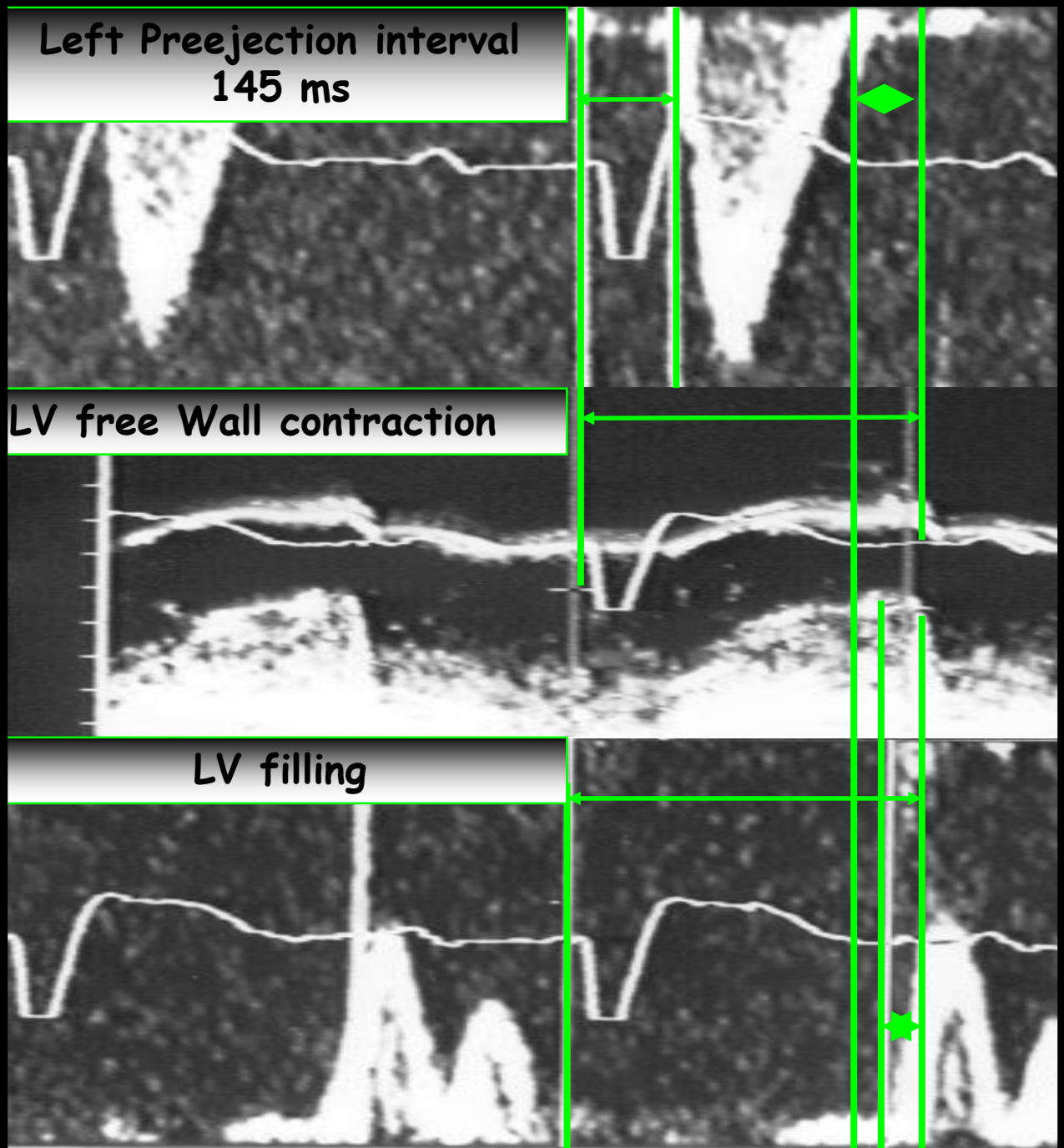
InterV = LPEI –RPEI > 40 ms

IntraV : LPEI > 120 ms



Cazeau et al Heart 2000


SD
QRS-E
Ao
E
A
E
Local Contraction
Duration of segment contraction
Duration of Diastolic contraction (DC)
Overlap = Duration of DC after onset of E wave



Diastolic Contraction
100 ms

QRS - LLW
524 ms

LV filling

Overlap contraction-filling
20 ms

Improve the selection process : wide QRS pts

Monocentric open prospective study not controlled in wide QRS patients
From the 2001 referred population for CRT in Bizet and Val d'Or
n = 66, QRS 182±33 ms, NYHA III,IV presented at least one type of dyssynchrony

LV filling duration/HR 38±12 %, Inter V delay 63 ± 30 ms, LPEI = 186 ± 31 ms, Diastolic Contraction of the Left Lateral Wall = 111±117 ms, and Overlap = 20 ± 68 ms

85% clinical success rate instead of 65% rate in the same experienced center vs previous years

Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation : a prospective evaluation in wide QRS pts
(PACE 2003)

Improve the selection process : narrow QRS pts

The Desire study (EJHF 2008)
Multicentric prospective study : 60 narrow QRS120 ms patients

Separated into 2 groups according the presence or not of mechanical dyssynchrony

Evaluated at one year (Milton Packer: alive and not hosp and functionally improved)

70% success rate in narrow QRS dyssynchronized patients
33% only in “not” dyssynchronized group $p < 0.04$

Independently from QRS width and pattern

The Dyssynchrony model: 18 parameters

Cazeau et al Heart 2000

The nightmare needs simplification

Using 455 sets of 18 parameters coming from the 92 patients of the Meteor study*

Optimizing ventricular leads position and numbers
Per operatively using trans-thoracic echo
Led to significant changes in synchrony configuration
3 to 8 pacing configuration per patient

* Moubarak, Ritter, Daubert, Cazeau, Arch Mal Coeur 2014

Statistical analysis
1. Parameters correlations
2. Related to Ideal Sense of variation
3. Variance-based selection of variables for global dyssynchrony evaluation
(Column Subset Selection of machine learning)

Cazeau ,Toulemont , Ritter *et al*. *Statistical ranking* of electromechanical dyssynchrony parameters for CRT. *Open Heart 2019:e000933.* doi:10.1136/openhrt-2018-000933

Correlations between the 18 parameters

LPEI : correlated to 13 out of 17

									ept	DClat	IsovolRT	Overlap Sept	Overlap LLW	Sept-LLW	MVR/LA	IsovolCT	LVET	LPEI/LVET
DFT%	1	X	X	-0.23	X	X	X	X	X	X	X	X	X	X	X	-0.48	0.37	-0.38
QRS-E	X	1	0.29	0.38	X	0.68	0.35	0.39	X	X	0.8	-0.17	-0.29	X	X	X	0.41	X
RPEI	X	0.29	1	0.63	-0.4	0.24	X	X	X	X	X	X	X	X	X	X	X	0.45
LPEI	-0.23	0.38	0.63	1	0.47	0.45	0.32	0.28	0.15	X	X	0.17	X	X	0.35	0.34	-0.34	0.85
IVD	X	X	-0.4	0.47	1	X	X	X	X	X	X	X	X	X	X	0.28	X	0.33
SD	0.17	0.88	0.24	0.45	X	1	0.4	0.32	X	-0.22	-0.14	X	-0.17	0.13	X	X	0.89	X
Sept	X	0.35	X	0.32	X	0.4	1	0.29	0.91	X	X	0.32	X	0.71	0.18		0.15	0.18
LLW	X	0.39	X	0.28	X	0.32	0.29	1	0.18	0.85	0.24	X	0.7	-0.48	0.15	X	X	0.14
DCsept	X	X	X	0.15	X	X	0.91	0.18	1	0.18	X	0.88	0.15	0.71	X	X	-0.15	0.2
DCLLW	X	X	X	X	X	-0.22	X	0.85	0.18	1	0.32	X	0.81	-0.55	X	X	-0.28	0.17
IsovolRT	X	0.80	X	X	X	-0.14	X	0.24	X	0.32	1	-0.34	-0.25	-0.14	X	-0.23	-0.18	X
Overlap Sept	X	-0.17	X	0.17	X	X	0.82	X	0.88	X	-0.34	1	0.28	0.71	0.15	0.24	X	0.18
OverlapLat	X	-0.29	X	X	X	-0.17	X	0.7	0.15	0.81	-0.25	0.28	1	0.45	X	-0.21	X	X
Sept-LLW	X	X	X	X	X	0.13	0.71	-0.48	0.71	-0.55	-0.14	0.71	0.45	1	X	X	X	X
MVR/LA	X	X	X	0.35	X	X	0.18	0.15	X	X	X	0.15	X	X	1	0.17	-0.15	0.33
IsovolCT	-0.48	X	X	0.34	0.28	X	X	X	X	X	-0.23	0.24	X	X	0.17	1	-0.31	0.38
LVET	0.37	0.41	X	-0.34	X	0.89	0.16	X	-0.15	-0.28	-0.18	X	-0.21	X	-0.15	-0.31	1	-0.74
LPEI/LVET	-0.38	X	0.45	0.85	0.33	X	0.18	0.14	0.2	0.17	X	0.18	X	X	0.33	0.38	-0.74	1

Cazeau ,*et al. Statistical ranking* of electromechanical dyssynchrony parameters for CRT *Open Heart 2019:e000933*. doi:10.1136/openhrt-2018-000933

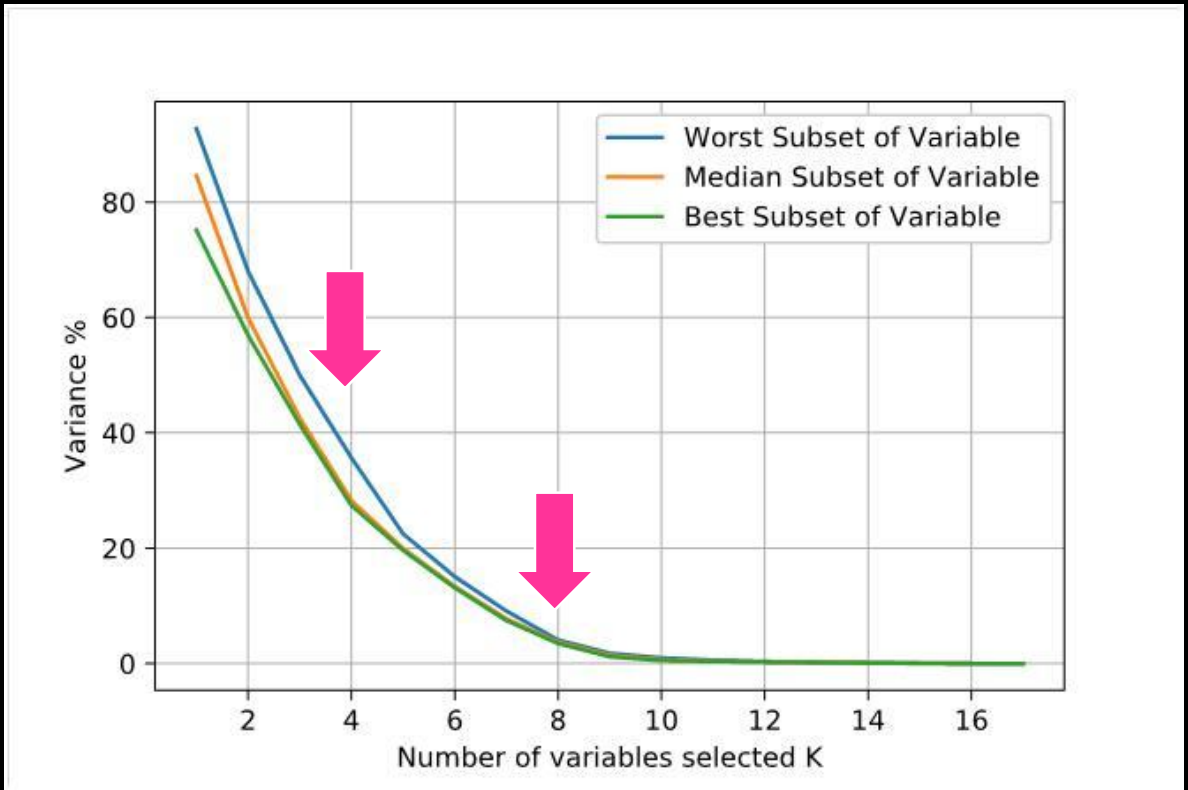
The nightmare needs simplification
Individual variable(s) ranking

None of any variable alone
is able to capture dyssynchrony

Cazeau ,Toulemont , Ritter *et al. Statistical ranking* of electromechanical dyssynchrony parameters for CRT. *Open Heart 2019:e000933.* doi:10.1136/openhrt-2018-000933

Determination of the best variable(s)

The model can be reduced to 8 variables for 95% of DyS description
3 to 4 variables carefully selected can reasonably describe 65% of DyS



Cazeau ,Toulemont , Ritter *et al. Statistical ranking* of electromechanical dyssynchrony parameters for CRT. *Open Heart 2019:e000933.* doi:10.1136/openhrt-2018-000933

Determination of the best variable(s)

Possible to obtain similar performance from totally different sets of variables because captured variance is similar.

K=	Variables	Captured
3	Sept, Sept-LLW, QRS-E	59
	SD, DCSept, DCLLW	58
	LPEI, Sept, QRS-E	57
	LPEI, IVD, DFT%	34
4	Sept, Sept-LLW, QRS-E, LPEI/LVET	73
	Overlap Sept, Overlap LLW, QRS-E, LPEI/LVET	72
	Sept, Sept-LLW, QRS-E, LPEI	72
	SD, DCSept, DCLLW, LPEI/LVET	72
	LPEI, IVD, DFT%, Overlap LLW	49
6	SD, DCSept, DCLLW, LPEI/LVET, RPEI, IsovolRT	87
	LPEI, Sept, QRS-E, Sept-LLW, RPEI, SD	87
	QRS-E, Sept-LLW, Sept, LVEI/LVET, IVD, SD	87

Cazeau ,Toulemont , Ritter *et al. Statistical ranking* of electromechanical dyssynchrony parameters for CRT. *Open Heart 2019:e000933.* doi:10.1136/openhrt-2018-000933

What would be really new: Decrease the non-response rate unchanged since 1994?

1/ Improve the selection process of dyssynchrony

The electromechanical model, taking specific parameters according to the number you select

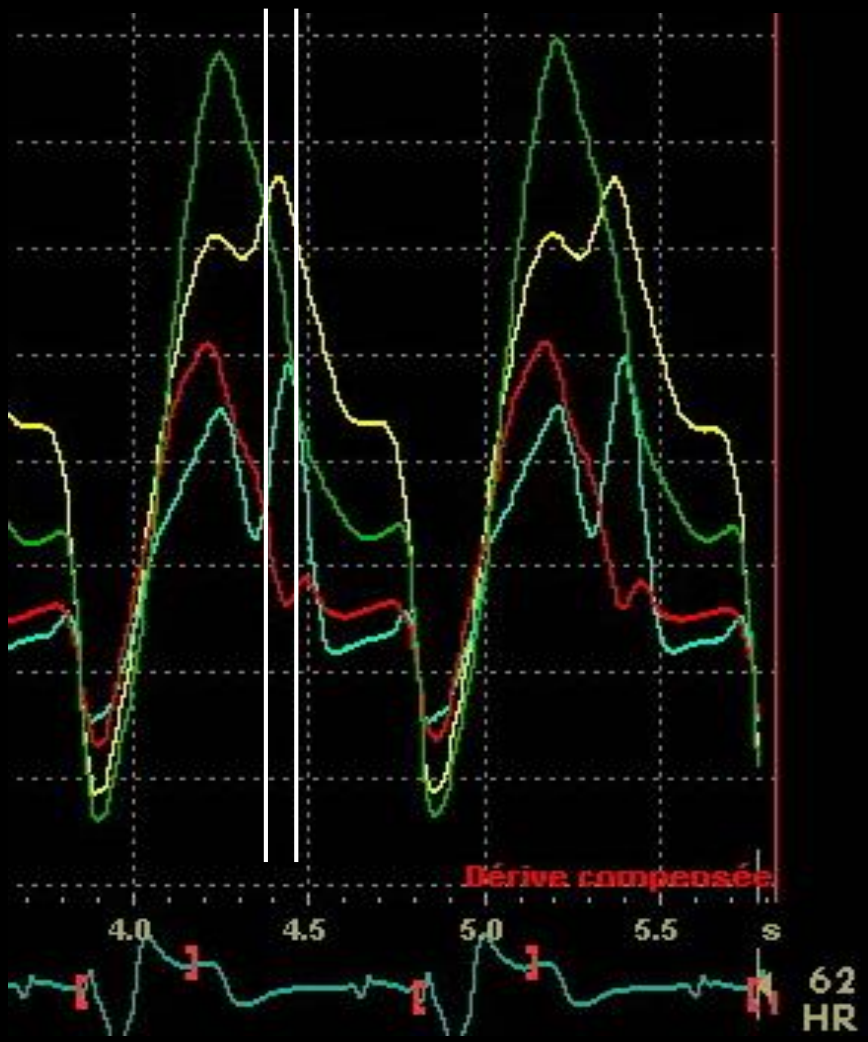
How to decrease the non-response rate unchanged since 1994?

1/ Improve the selection process of dyssynchrony

The electromechanical model, taking specific parameters according to the number you select

2/ Improve the implant process

2/ Improve the Implant Process



Non-delivered therapy
DEATH 15 days later

S. Cazeau 2020

2/ Improve the Implant Process

Meteor 1 : Pacing configurations comparison
AV and InterVentricular resynchronization

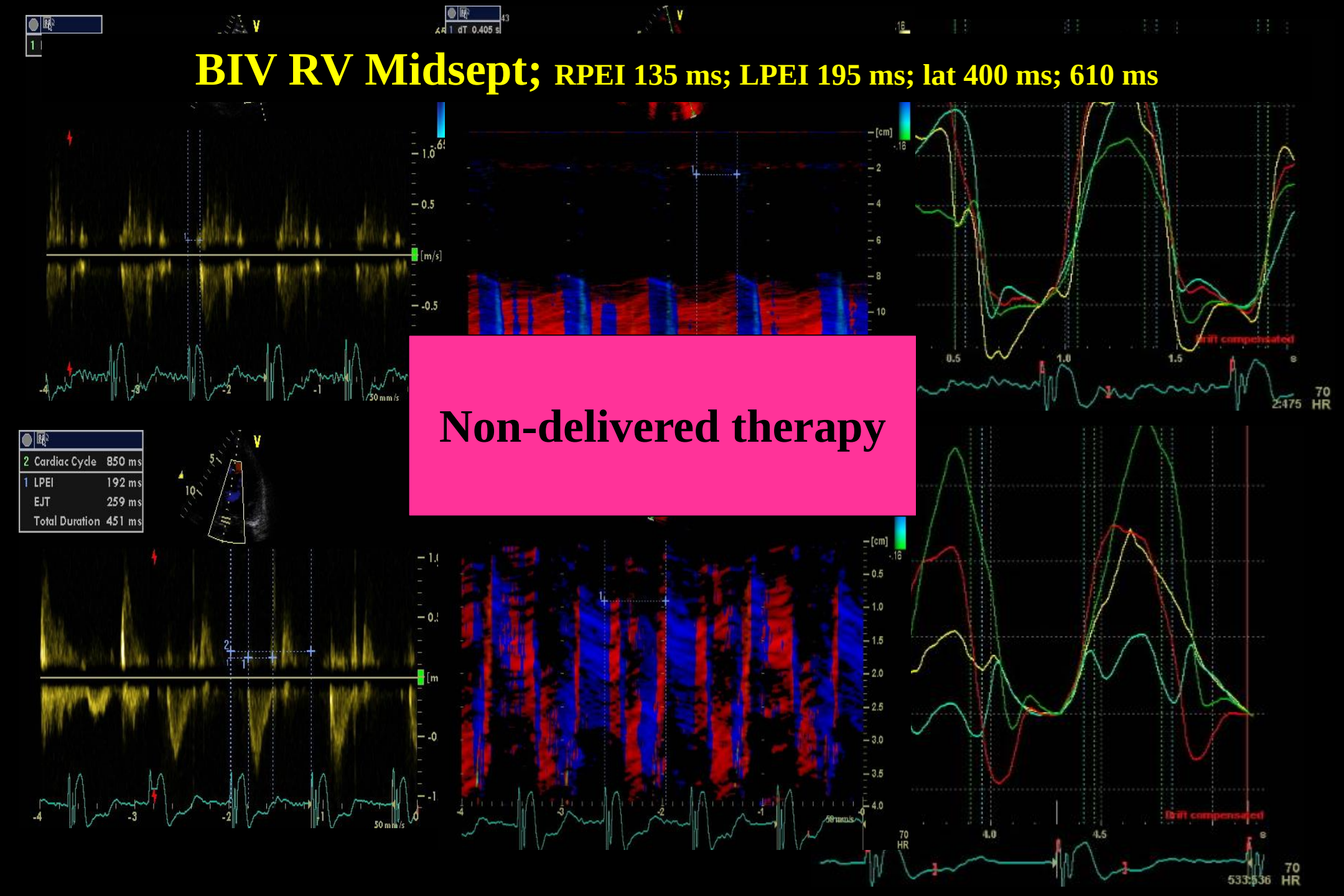
	LPEI	DFT%	IVD
Baseline	154±40	43±8	43±32
RV pacing	184±33*****	42±8*	42±31
LV pacing	180±36*****	43±7	-40±48**
BiV initial	158±36	44±8	34±38
Final config	134±29*****	47±7****	10±29*

All values compared to baseline

* p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001

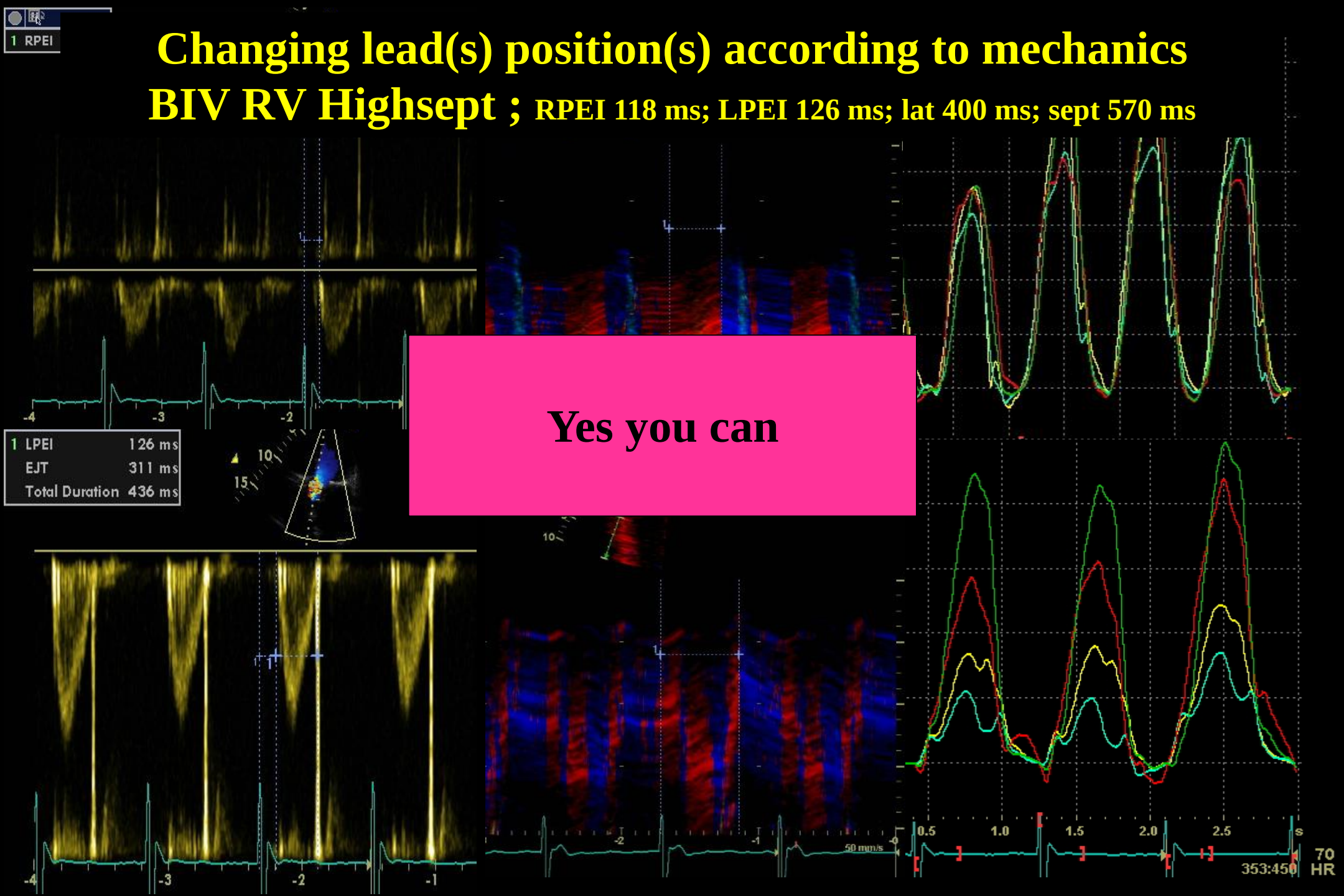
Moubarak, Ritter, Daubert, Cazeau, Arch Mal Coeur 2014

BIV RV Midsept; RPEI 135 ms; LPEI 195 ms; lat 400 ms; 610 ms

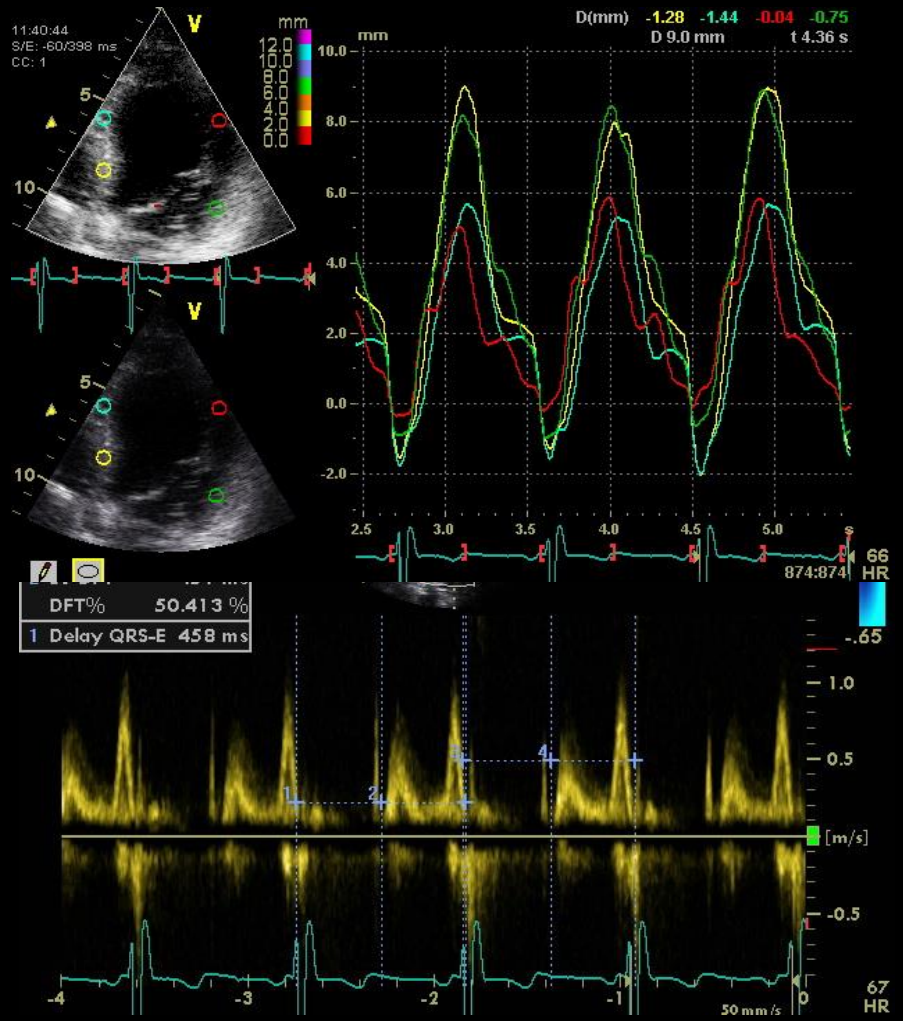


Changing lead(s) position(s) according to mechanics

BIV RV Highsept ; RPEI 118 ms; LPEI 126 ms; lat 400 ms; sept 570 ms



Correction of IntraV dyssynchrony improves AV synchrony



Correcting dyssynchrony parameters
Ideal Sense of variation

	Favorable when Increase	Favorable when Decrease
	DFT%, IsovolRT, LVET	LPEI, IVD, QRS-E, RPEI, SD, IsovolCT, LPEI/LVET, Sept, LLW, DCSept, DCLLW, Overlap Sept, Overlap LLW, Sept-LLW, MVR/LA,

Cazeau ,Toulemont , Ritter *et al. Statistical ranking* of electromechanical dyssynchrony parameters for CRT. *Open Heart 2019:e000933.* doi:10.1136/openhrt-2018-000933

LPEI is the Best parameter to describe resynchrony

LPEI is correlated with 13 out of 17 other variables
Sept and LLW contractions, DCSept, Overlap Sept, IVD, IsovolCT, RPEI, LPEI/LVET, and mitral valve regurgitation

When LPEI decreases (improves), all other correlated parameters decrease (improve) except for LVET and DFT%, which increase (improve)

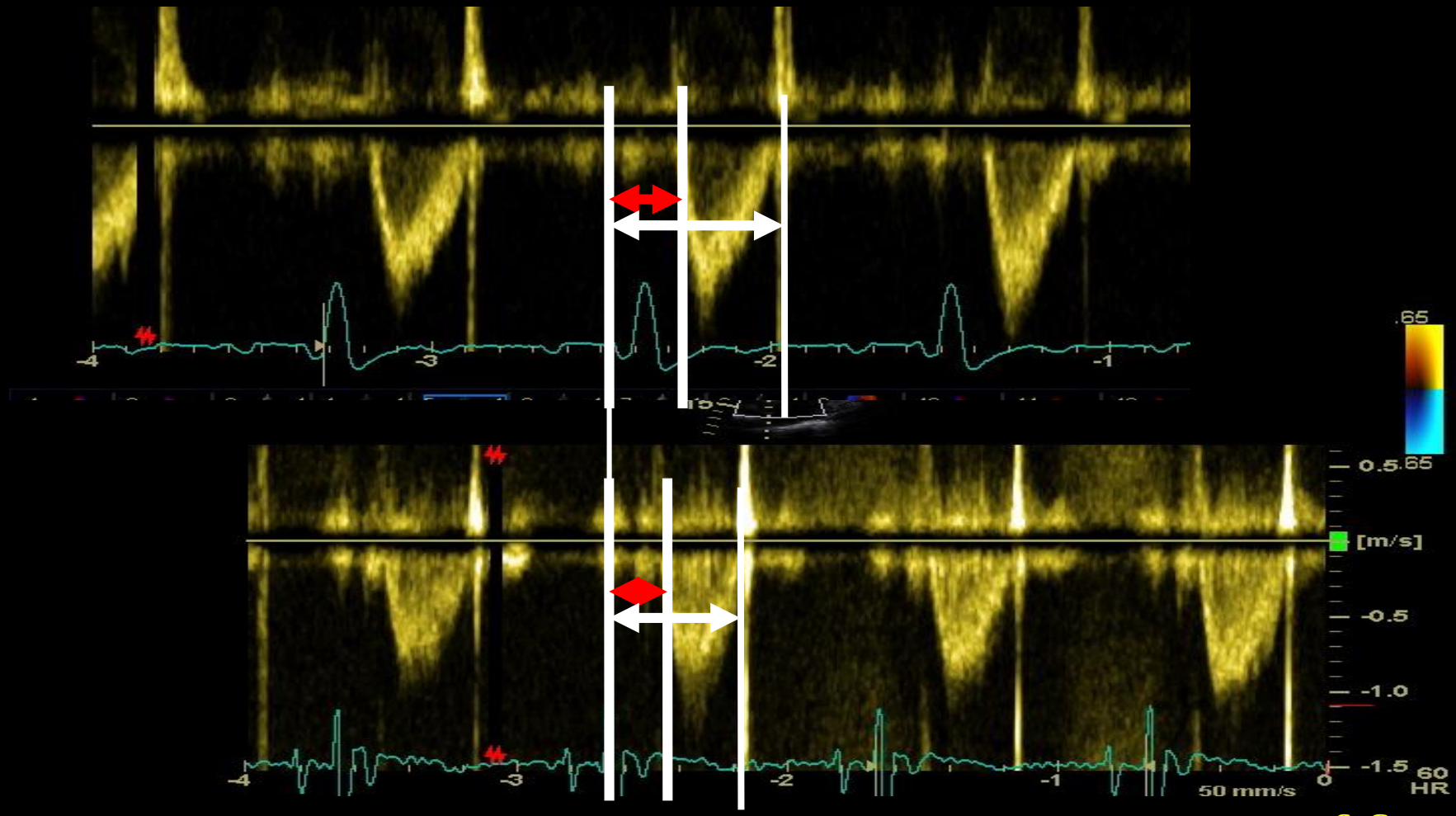
IVD et DFT% only correlated with 4 other parameters

Sept-LLW difference only with 5
Furthermore negatively with LLW indices +++++

Cazeau ,Toulemont , Ritter *et al. Statistical ranking* of electromechanical dyssynchrony parameters for CRT. *Open Heart 2019:e000933.* doi:10.1136/openhrt-2018-000933

2/ Improving the Implant process

Efficient delivery of CRT = LPEP Reduction



S. Cazeau 2020

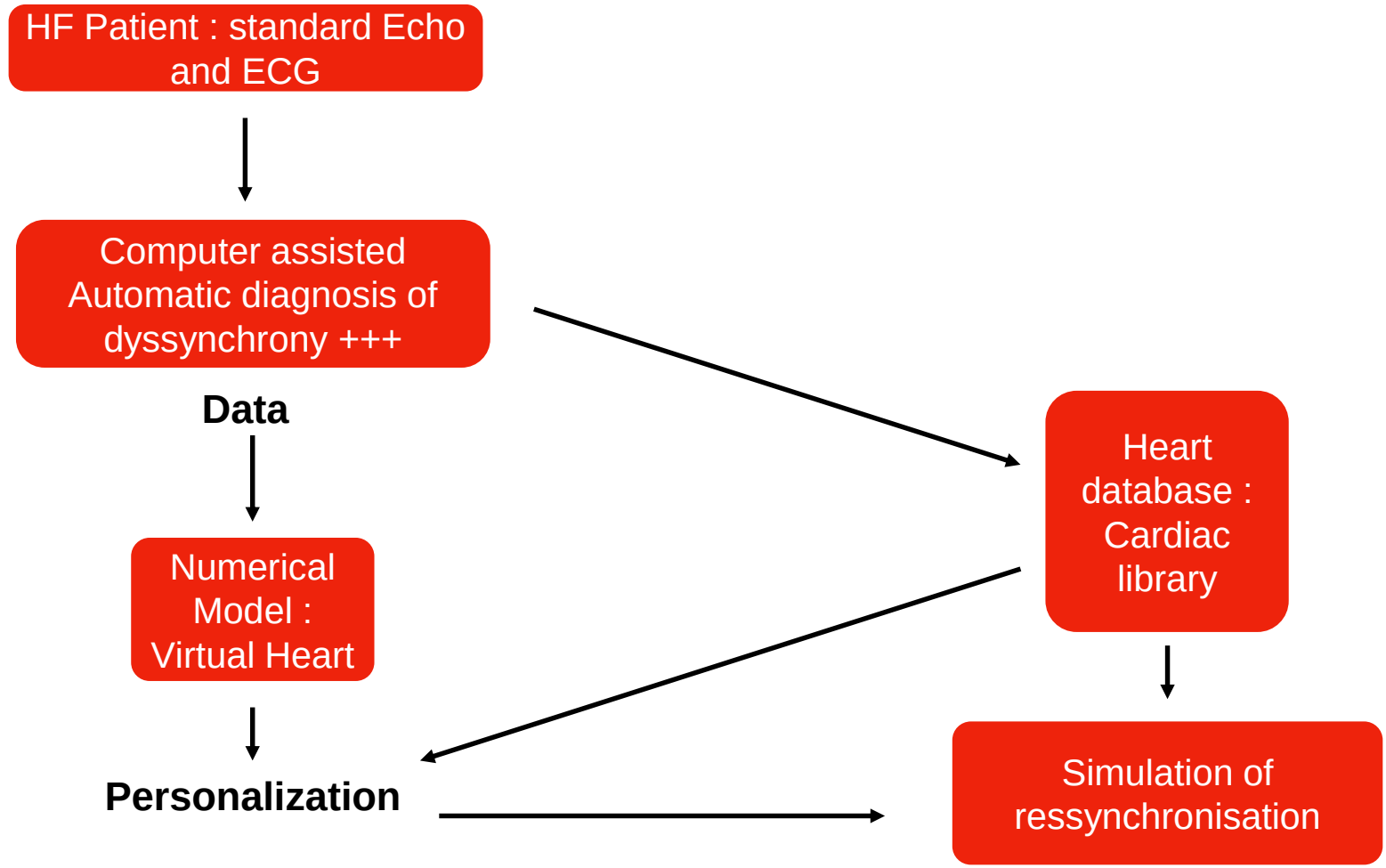
How to decrease the non-response rate unchanged since 1994?

1/ Improve the selection process of dyssynchrony
The electromechanical model, taking specific parameters according to the number you select

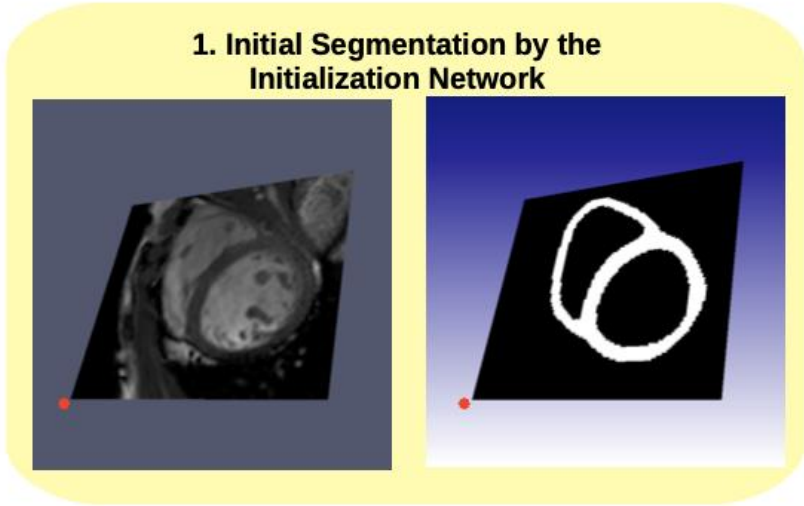
2/ Improve the implant process

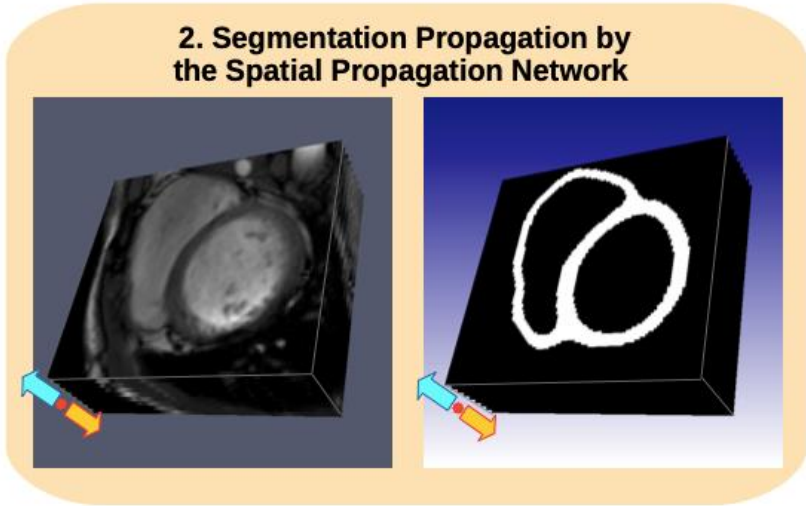
3/ Improve the Global process
(including FU and parameters setting)

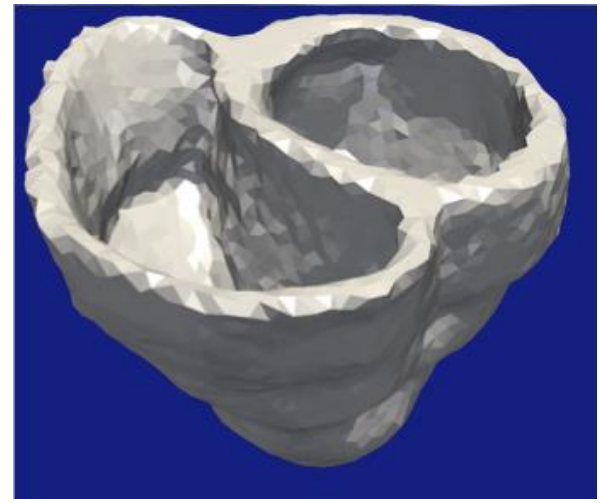
Improving the global process

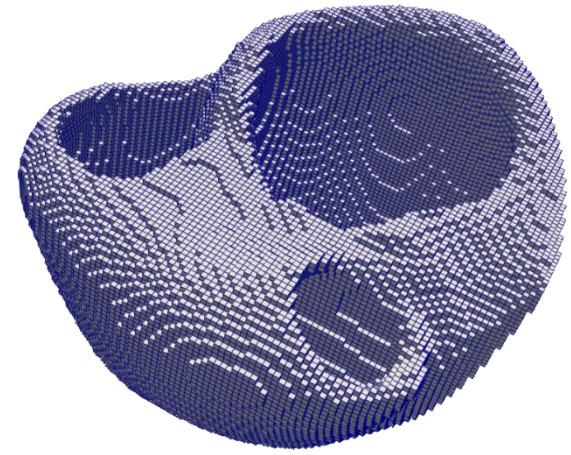


Basic geometry



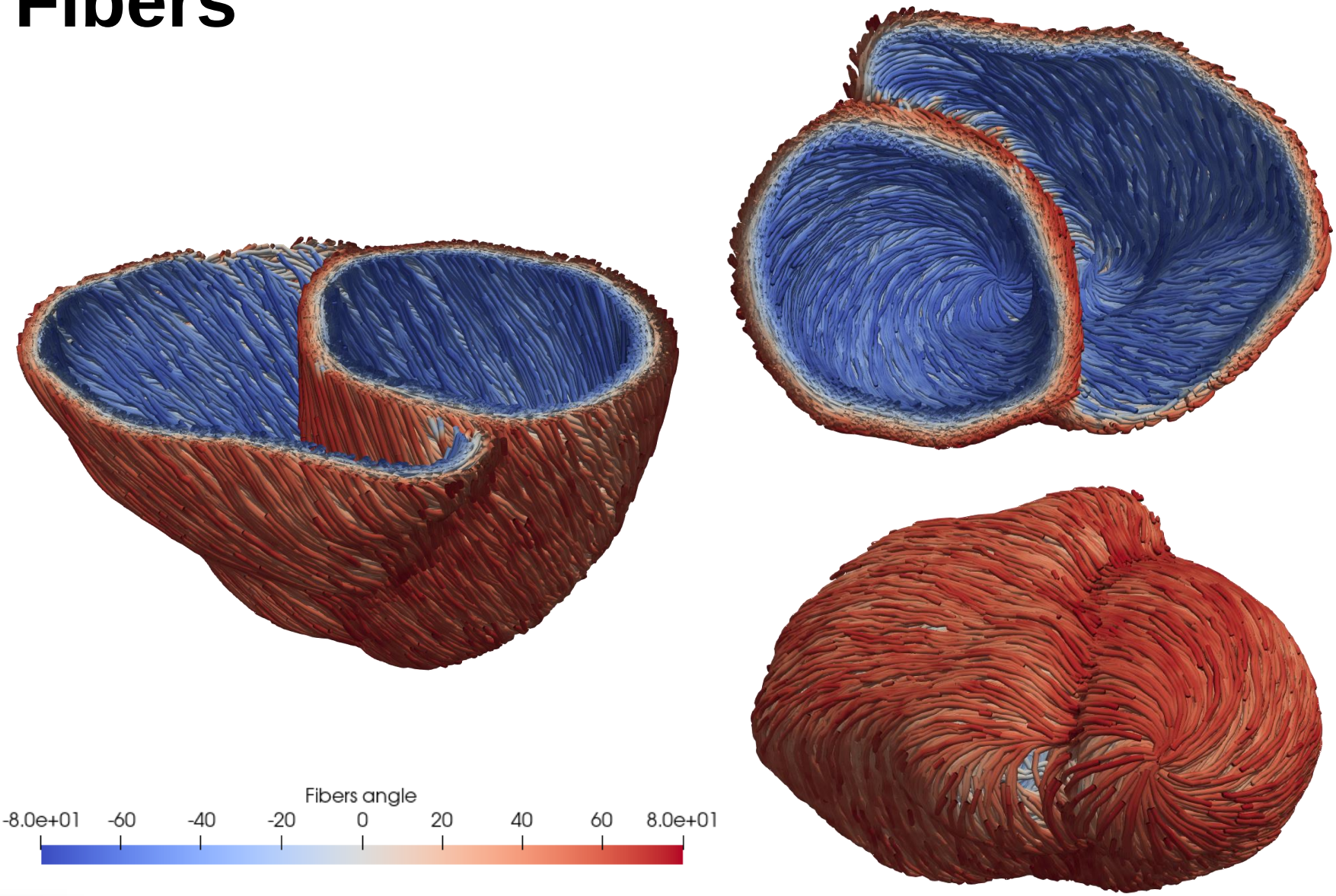






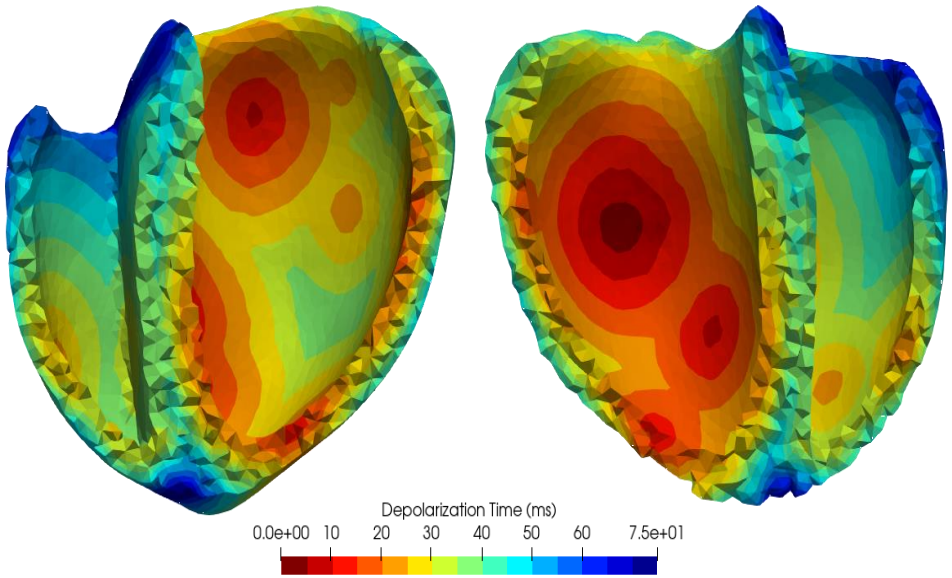
~ 1M voxels

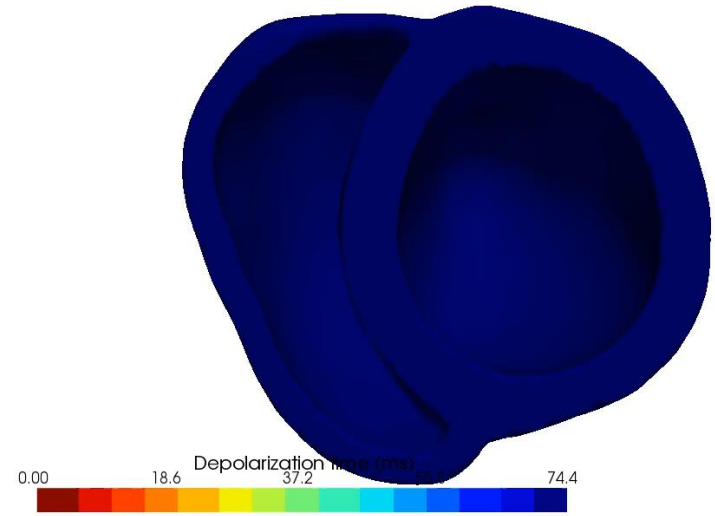
Fibers

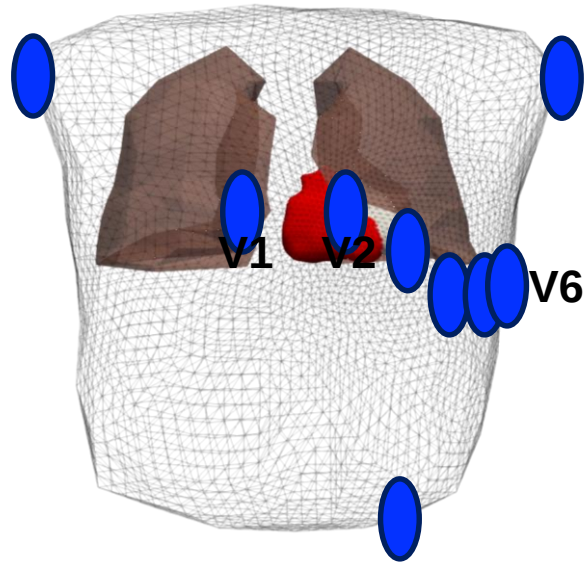


Activation map

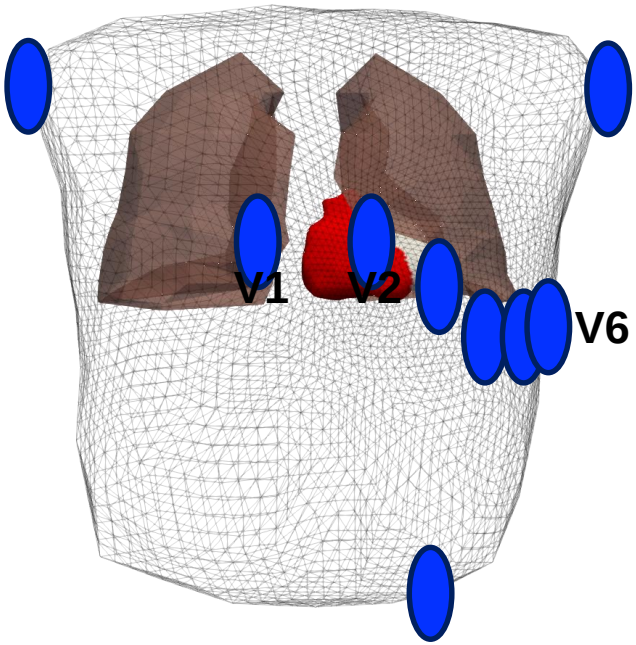
t = 0 ms

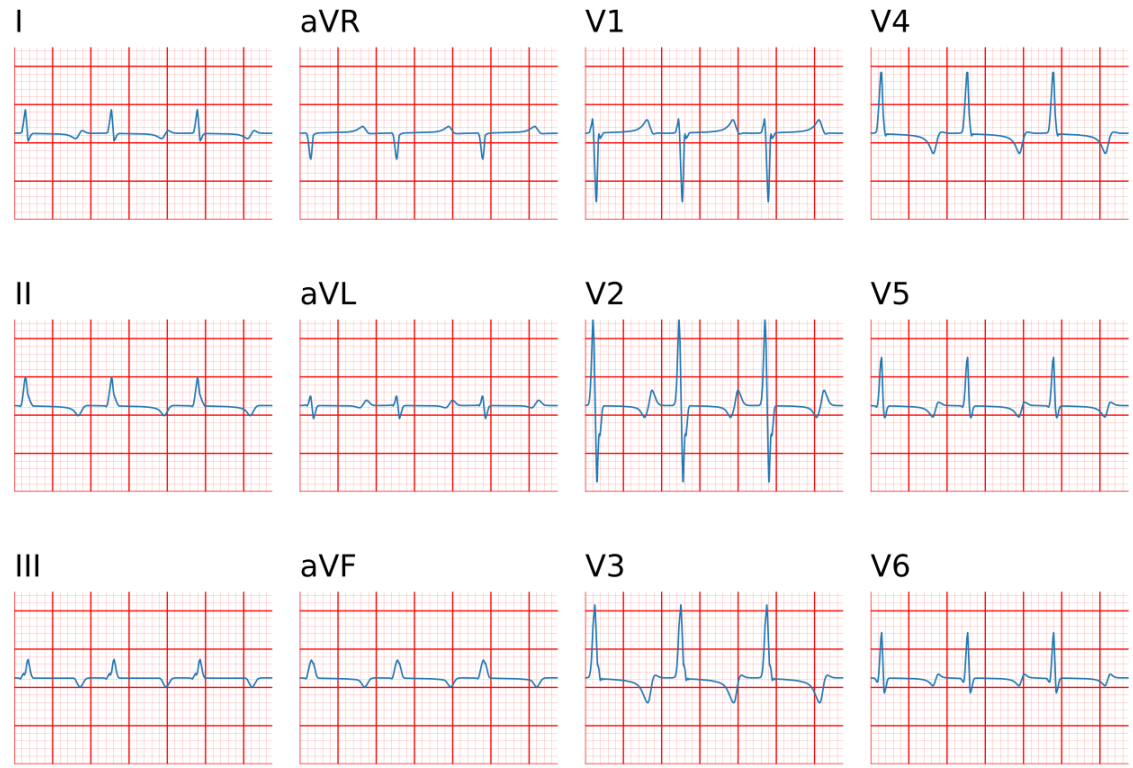




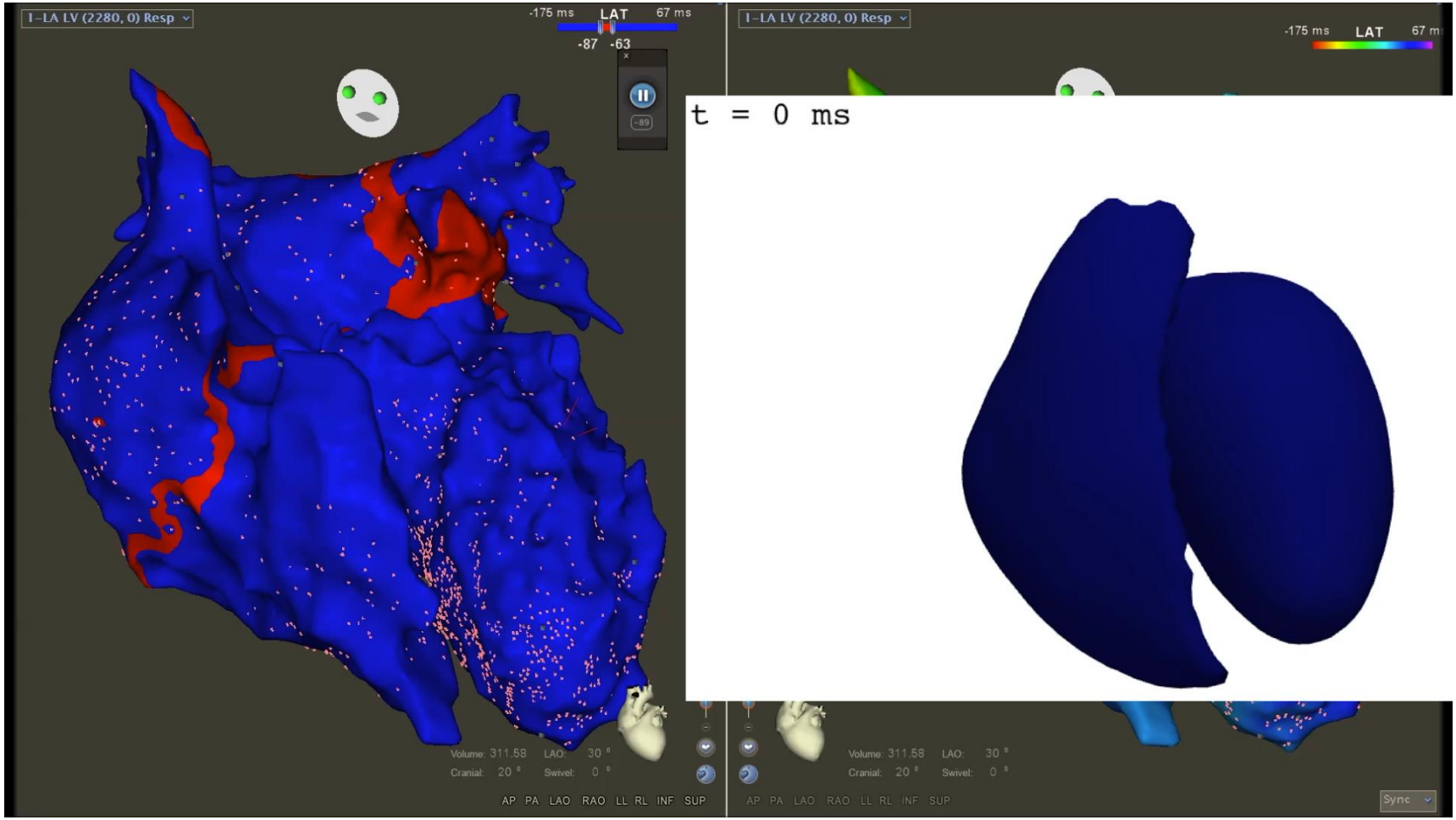


Creating a virtual ECG

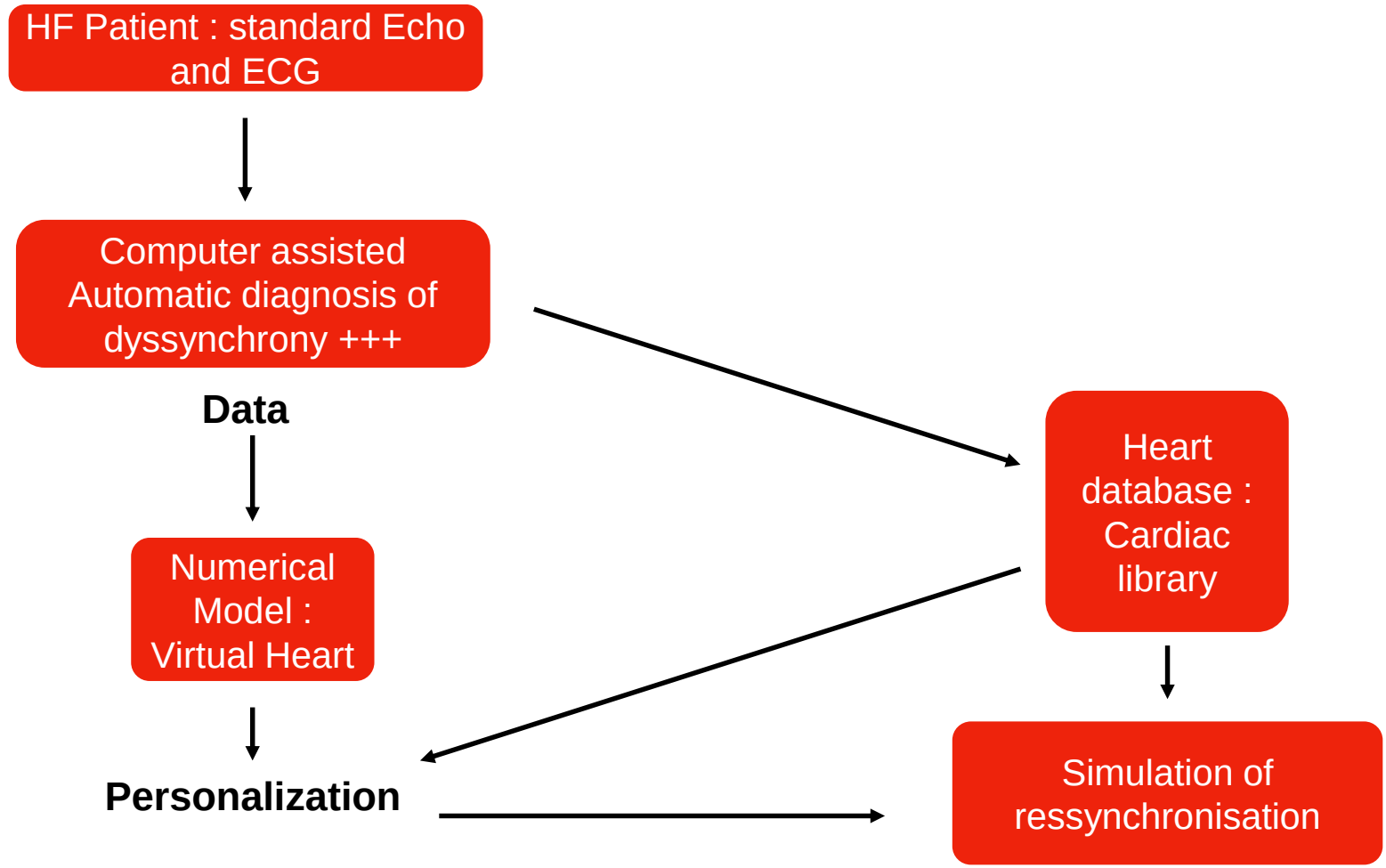




Activation potential propagation



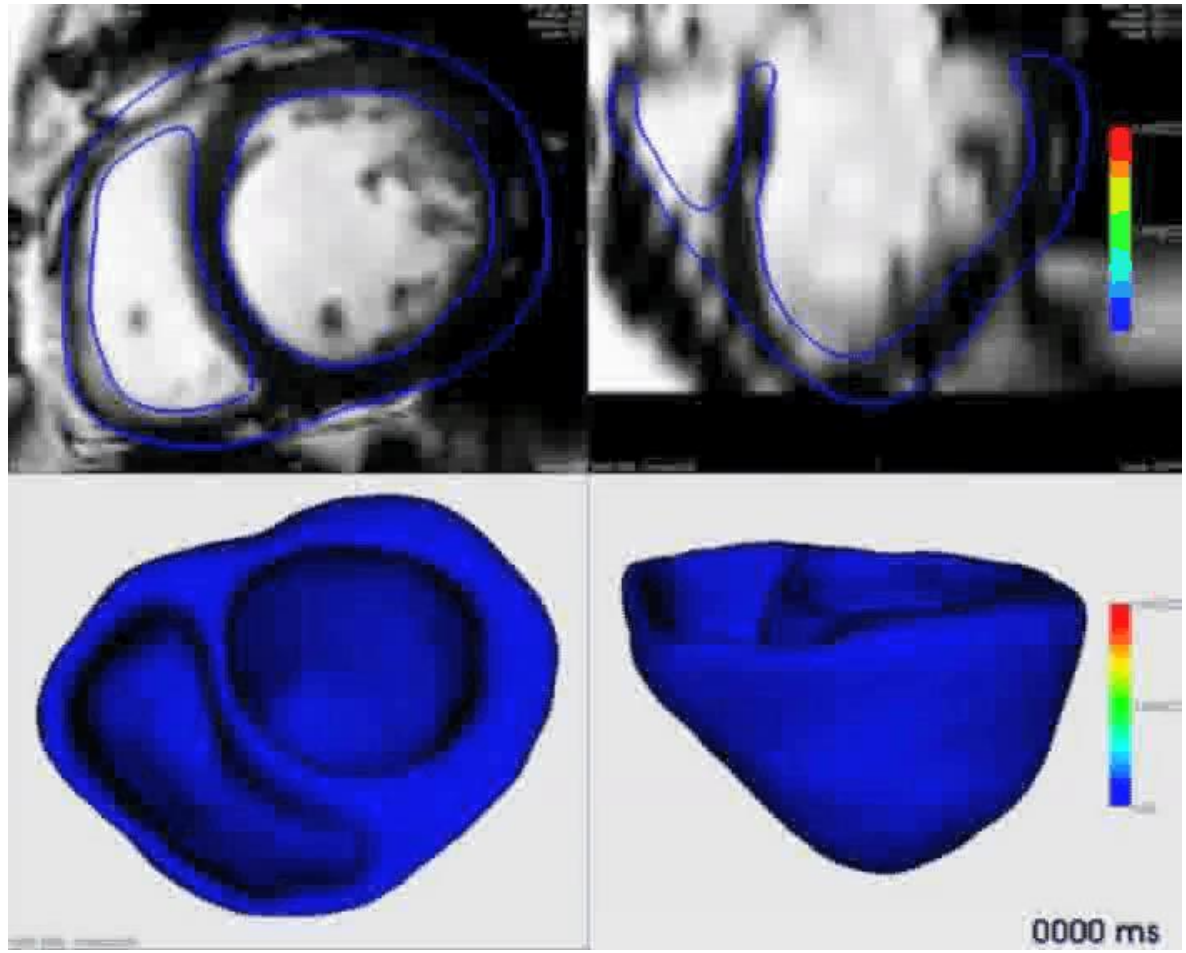
Improving the global process



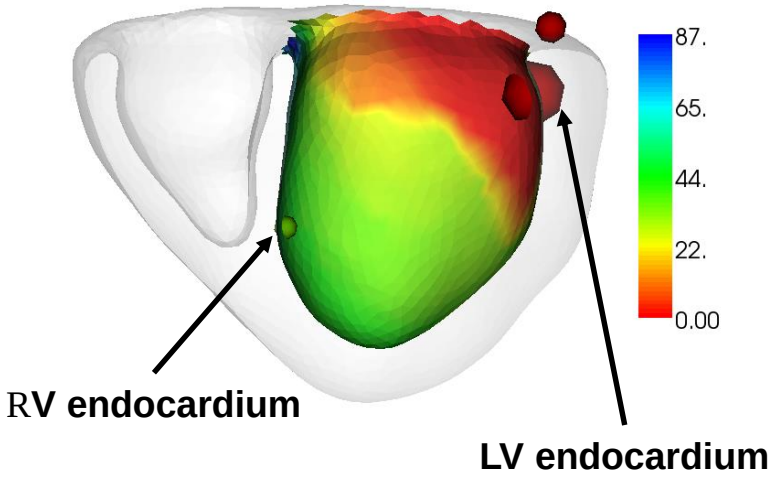
2012: proof of concept

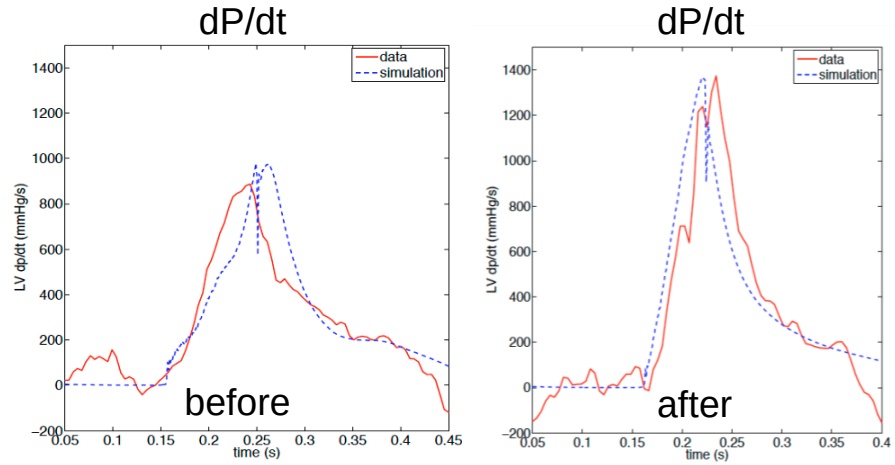
Desynchronized heart

LBBB

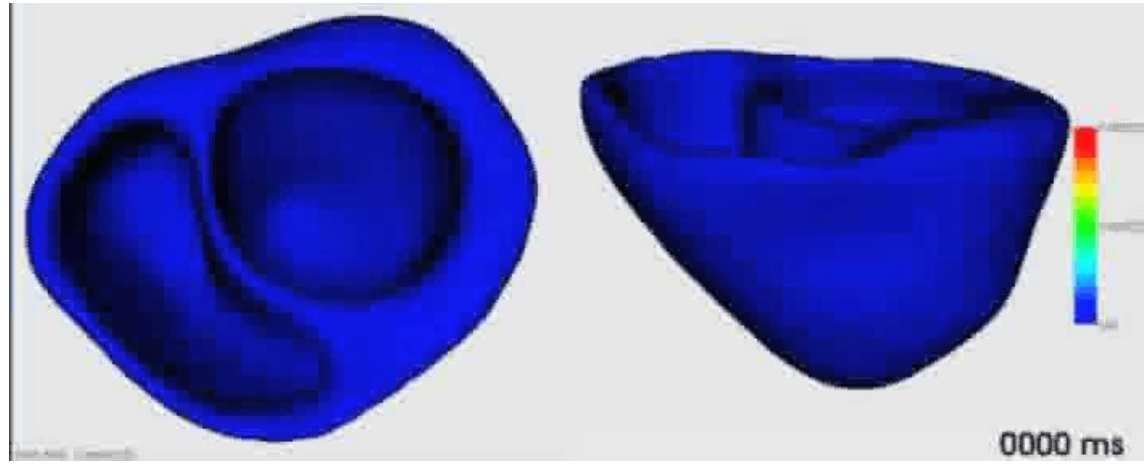


2012: proof of concept





Simulated CRT



3/ Improving the Global process
Natural History of resynchrony

75 pts, 15F, 20 ICM, 55 LBBB (QRS 166 ms), 20 nonLBBB (QRS 151 ms)

Indicated for CRT

- **NYHA II-IV, EF < 35%**

Evaluated at baseline, predischarge, FU (1-3M), FU2 (> 6M)

- **« Synchrony » parameters**
- **Global LV function parameters**

Results : Clinical and Reverse remodelling

75 pts, 15F, 20 ICM

QRS from 162 ± 25 to 150 ± 29 (p < 0,01)

75 alive at one year, 1 rehospitalized for HF with AF and loss of CRT (then ablated)

NYHA from 3,17 ± 0,66 to 1,27 ± 0,52

EF%	EDD mm	ESD mm	EDVol ml	ESVol ml	PR ms	Axe °	QRS ms
26 ± 8	63 ± 9	54 ± 10	196 ± 70	145 ± 57	210 ± 57	-11 ± 57	162 ± 24
33 ± 9	61 ± 9	51 ± 10	189 ± 74	131 ± 64		-3 ± 98	150 ± 29
40 ± 10	58 ± 9	46 ± 11	167 ± 64	104 ± 50			
44 ± 10	54 ± 9	42 ± 10	146 ± 65	86 ± 53			
< 0,001	< 0,01	< 0,0001	< 0,01	< 0,0001		NS	0,01
< 0,001	< 0,0001	< 0,0001	< 0,01	< 0,0001			
< 0,001	< 0,0001	< 0,0001	< 0,05	< 0,0001			
< 0,001	< 0,0001	< 0,0001	< 0,0001	< 0,0001			
< 0,05	< 0,0001	< 0,0001	< 0,0001	< 0,0001			

Standard Electromechanical parameters

	RR	LPEI	interV	LVFT%	LVET	Sept-LLW
Baseline	**872**	**154**	**55**	**0,42**	**283**	**59**
	133	32	30	0,08	35	158
PreD	**872**	**139**	**28**	**0,49**	**281**	**37**
	126	30	31	0,08	35	114
FU1	**914**	**136**	**26**	**0,53**	**301**	**40**
	119	34	30	0,07	30	115
FU2	**887**	**136**	**25**	**0,51**	**301**	**21**
	109	34	26	0,07	27	86

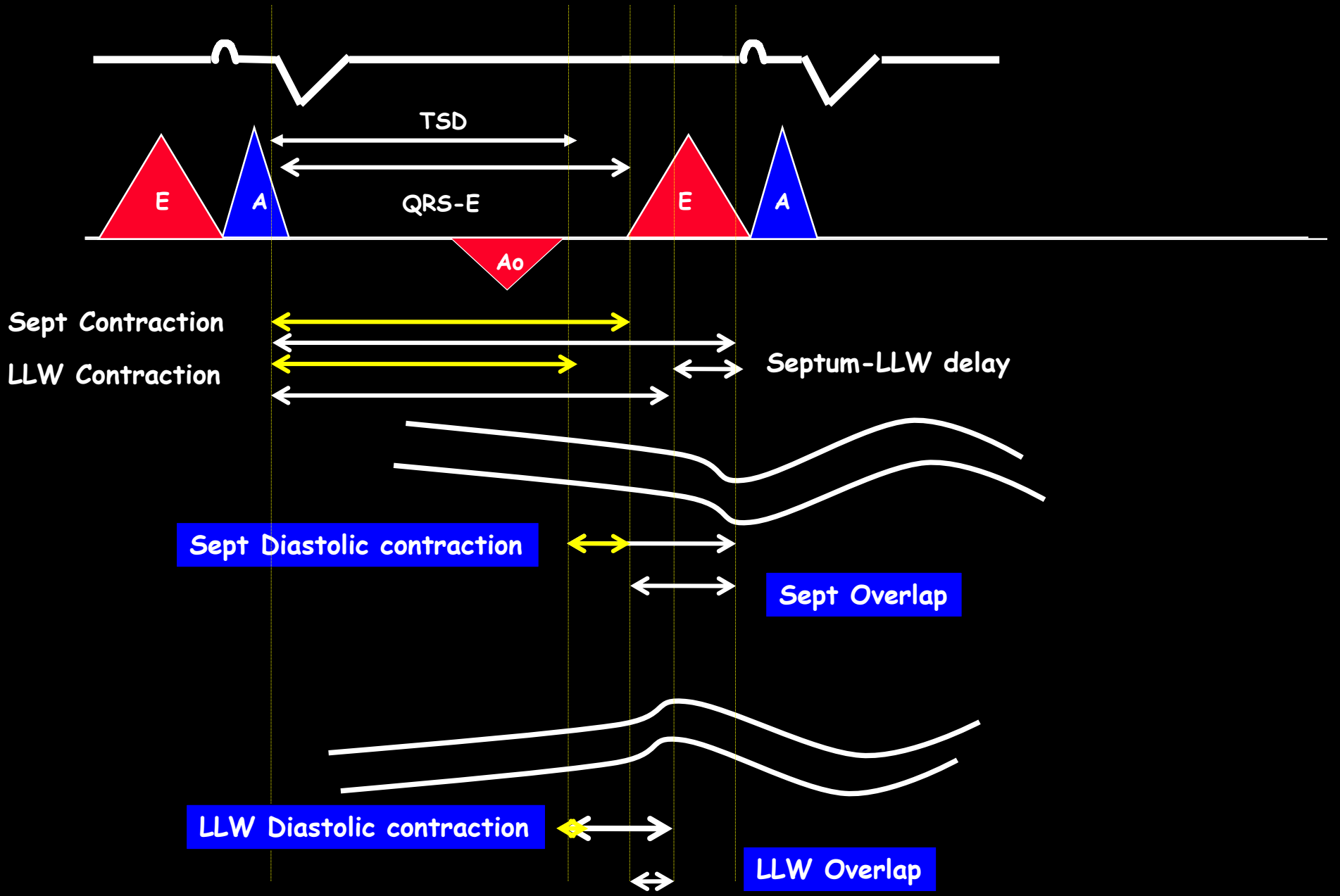
	RR	LPEI	interV	LVFT%	LVET	Sept-LLW
Baseline/PreD	0,8900	**0,0015**	**0,0000**	**0,0000**	0,8254	0,2499
Baseline/FU1	**0,0185**	**0,0002**	**0,0000**	**0,0000**	**0,0001**	0,5706
Baseline/FU2	0,4739	**0,0007**	**0,0000**	**0,0000**	**0,0003**	0,0678
PreD/FU1	**0,0124**	0,4240	0,7497	**0,0001**	**0,0000**	0,6752
FU1/FU2	0,1414	0,9388	0,7980	0,0877	0,9562	0,3398

IntraV dyssynchrony parameters

	S Diast C	LLW Diast C	SeptOverlap	LLWOverlap	Sept-LLW
Baseline	**117,74**	**58,59**	**25,15**	**-34,24**	**59,39**
	130,49	140,95	93,26	107,63	157,81
PreD	**89,93**	**53,13**	**-2,41**	**-39,00**	**36,81**
	71,60	95,62	77,21	94,77	114,30
FU1	**75,10**	**34,79**	**-6,12**	**-46,43**	**39,78**
	96,23	91,11	98,63	99,55	115,18
FU2	**26,82**	**6,22**	**-47,89**	**-68,50**	**20,61**
	69,46	70,39	80,50	75,03	85,72

	S Diast C	LLW Diast C	SeptOverlap	LLWOverlap	Sept-LLW
Baseline/PreD	0,1	0,7	**0,05**	0,4	0,2
Baseline/FU1	0,04	0,1	0,09	0,3	0,6
Baseline/FU2	**0,000**	**0,003**	**0,000**	**0,01**	0,07
PreD/FU1	0,4	0,3	0,9	0,7	0,7
FU1/FU2	**0,001**	**0,005**	**0,005**	**0,03**	0,3

Long term Effects of CRT on segments contraction



What could be new:
Changing physicians approach

- Before Implant: Select patients using the **Electromechanical model** with at least 4 dyssynchrony parameters

- At implant, a lot of questions for targeting the Latest activated segment.
Because:
  - Septum-LLW difference is a not a prerequisite
  - Its reduction is not an acute objective
  - Sept-LLW reduction will come with reverse remodelling
  - **If possible use LPEI during implant …. It drives the others**

- After implant during PM settings focus on **Systolic parameters (LPEI).**
Diastolic parameters will improve further and intraV dyssynchrony will improve in the longterm in parallel with reverse remodelling

S. Cazeau 2020