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1 **Title:** The physiological effects of cardiac resynchronization therapy on aortic and
2 pulmonary flow and dynamic and static components of systemic impedance

3

4 **Short title:** Physiological effects of CRT

5

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37 **Abstract**

38 **Background:** Patients who improve following cardiac resynchronization therapy (CRT) have
39 left ventricular (LV) remodeling and improved cardiac output (CO). Effects on the systemic
40 circulation are unknown.

41 **Objective:** To explore the effects of CRT on aortic and pulmonary blood flow and systemic
42 afterload.

43 **Methods:** At CRT implant patients underwent a non-invasive assessment of central
44 haemodynamics including wave intensity analysis (n=28). This was repeated at 6-months
45 after CRT. A sub-sample (n=11) underwent an invasive electrophysiological and
46 hemodynamic assessment immediately following CRT. CRT response was defined as
47 reduction in LV end-systolic volume $\geq 15\%$ at 6-months.

48 **Results:** In CRT responders (75% of those in the non-invasive arm), there was a significant
49 increase in CO (from 3 ± 2 L/min to 4 ± 2 L/min, $P=0.002$) and LV dP/dtmax (from $846 \pm$
50 162 mmHg/s to 958 ± 194 mmHg/s, $P=0.001$), immediately after CRT in those in the invasive
51 arm. They demonstrated a significant increase in aortic forward compression wave (FCW)
52 both acutely and at follow-up. The relative change in LV dP/dtmax strongly correlated with
53 changes in the aortic FCW ($R_s 0.733$, $P=0.025$). CRT responders displayed a significant
54 reduction in afterload; decrease in systemic vascular resistance and pulse wave velocity
55 acutely; there was a significant decrease in acute pulmonary afterload measured by the
56 pulmonary FCW and forward expansion wave.

57 **Conclusions:** Improved cardiac function following CRT is attributable to a combination of
58 changes in the cardiac and cardiovascular system. The relative importance of these two
59 mechanisms may then be important for optimizing CRT.

60

- 61 **Keywords:** Aortic flow, Cardiac resynchronization therapy, Physiology, Pressure-volume
- 62 loops, Pulmonary flow, Wave intensity analysis

63 **Introduction**

64 Cardiac resynchronization therapy (CRT) improves symptoms and reduces mortality in
65 symptomatic patients with left ventricular (LV) systolic impairment and electrical
66 dyssynchrony, who are on optimal medical therapy.(1) However, even in carefully selected
67 cases approximately 30% of patients fail to benefit.(1) In patients who improve following
68 CRT there is evidence of ventricular resynchronization, reverse LV remodeling, increased
69 cardiac output (CO) and increased external work achieved by the heart.(2) It is unknown
70 whether these physiological changes result purely from improved LV contraction thus
71 increasing CO or whether there are concomitant changes in loading conditions on the left
72 ventricle and/or changes in systemic impedance following CRT. Previous studies have shown
73 that CRT is associated with improved right ventricular function and reduced systolic
74 pulmonary pressures(3) but the mechanism through which these effects are seen are not fully
75 understood. In humans, it is understood that CRT improves coronary flow in the left anterior
76 descending artery(4) but the effect of dynamic aortic and pulmonary pressure and flow
77 changes on cardiac function requires further investigation. Wave intensity analysis enables
78 the study of cardiovascular dynamics by representing pressure and velocity waveforms as
79 successive wavefronts.(5) The forward compression wave (FCW) measures the increase in
80 pressure and flow through an artery and characterizes blood flow during early systole.(5, 6)
81 The forward expansion wave (FEW) measures the decrease in pressure and flow in late-
82 systole. The backward compression wave (BCW) measures the increase in pressure and
83 reduced flow through an artery and characterizes blood flow during mid-systole. These waves
84 are present in both the systemic and pulmonary circulation.(6, 7) Determining whether there
85 is a correlation between aortic flow and myocardial contractility helps understand how
86 improved myocardial contractility seen with CRT may influence aortic flow in CRT
87 responders and non-responders.

88

89 Although CRT is known to increase CO the effect on different components of afterload,
90 namely systemic vascular resistance (SVR) and arterial stiffness, is not fully understood.
91 Adjunctive medical therapy used in the treatment of heart failure alters afterload(1) and
92 identifying whether CRT has additional effects of the vascular system is important in these
93 patients. Aortic pulse wave velocity (PWV) is considered the gold standard for measuring
94 central aortic stiffness and can be used to provide important prognostic information for a
95 variety of conditions(8). A greater PWV is independently associated with incident clinical
96 heart failure.(9) Therefore understanding whether CRT alters arterial hemodynamics has
97 implications on potential therapeutic interventions.(10)

98

99 The purpose of this study was to explore the effects of CRT on aortic and pulmonary blood
100 flow and afterload by comparing intrinsic rhythm with biventricular pacing. We hypothesized
101 that response to CRT would be associated with cardiac changes, principally improved
102 myocardial contractility and stroke work and also changes in the cardiovascular system,
103 which together would facilitate an increased mean arterial blood pressure. We measured
104 wave intensity invasively and non-invasively and used pressure-volume loops to accurately
105 assess LV hemodynamics.

106

107 **Methods**

108 *Study design*

109 The study was approved by the London Research Ethics Committee (11/LO/1232), all
110 patients provided written informed consent for participation in this study and the research in
111 this study was conducted to the Helsinki Declaration guidelines on human research. The
112 inclusion criteria involved patients with a guideline directed indication for CRT(11). Patients
113 were excluded if they were under 18 years old, pregnant or unwilling to undergo non-
114 invasive assessment at 6-months and patients were also excluded from the invasive arm of
115 the study if they had significant aortic valve disease or a contraindication to heparin. A
116 quadripolar LV lead was placed at the basal lateral wall via the posterolateral or lateral
117 coronary vein, wherever possible and targeted to areas of latest electrical activation as
118 assessed by the Q-LV time. The pacing vector that produced the narrowest QRS duration was
119 chosen. Immediately following CRT, patients underwent an invasive and/or non-invasive
120 assessment of cardiac function, pulmonary and systemic hemodynamics.

121

122 *Non-invasive assessment of aortic flow and arterial stiffness*

123 This was performed on the same day following CRT and repeated at 6-months, using a
124 pacing protocol described below and using a similar protocol to previously published
125 work.(7) Brachial blood pressure was measured by a validated oscillometric method (Omron
126 705CP; Omron Healthcare, Tokyo, Japan). Radial and carotid pressure waveforms were
127 obtained using the SphygmoCor system (AtCor, West Ryde, Australia). Radial pressure was
128 calibrated from the measured values of brachial systolic and diastolic pressure because these
129 are assumed to be equal at both sites. Systolic pressure differs at the carotid and brachial sites
130 and therefore the carotid pressure was calibrated from the mean and diastolic pressure which
131 are similar at all three sites.(12) Mean pressure is derived from radial pressure integrated over

132 time. Femoral pressure waveforms were recorded by applanation tonometry using the
133 SphygmoCor system. PWV was calculated from the transit time between the carotid to
134 femoral pressure waveforms. The SphygmoCor device and transducer was used to record
135 both pressure waveforms. The difference in the time of pulse arrival between these two sites
136 was referenced to the R wave of the ECG and taken as the transit time. The path length was
137 estimated from the distance between the sternal notch and femoral artery whereby the artery
138 was applanated. PWV was then calculated as the path length divided by the transit time.
139 Aortic flow was recorded from an echocardiographic Apical 5-chamber view using
140 continuous Doppler.

141

142 *Invasive protocol*

143 Simultaneous invasive hemodynamic and electrophysiological measurements were performed
144 immediately following successful CRT. Successful CRT was defined as evidence of
145 biventricular pacing following LV lead placement and narrowing of the QRS duration. A
146 pressure-volume loop conductance catheter (CD Leycom, Netherlands) was placed within the
147 left ventricle and the tip of a 0.014-inch dual pressure-Doppler sensor wire (ComboWire
148 9500; Volcano Corp) within the ascending aorta for aortic flow and a pacing protocol
149 undertaken. The pressure-Doppler wire was then re-sited in the main pulmonary artery for
150 pulmonary flow and the pacing protocol repeated.

151

152 *Processing waveform data and PWV*

153 Non-invasive ensemble averaged carotid pressures were used as a surrogate for ascending
154 aortic pressure and together with aortic flow velocity were processed using MATLAB
155 (MathWorks, MA) for wave intensity, pulse wave and wave decomposition analysis.(7)

156

157 Invasive waveform data was processed using a similar protocol to previously published
158 work.(2, 4) Data was imported into CardiacWaves (King's College London, UK). Wave
159 intensity analysis was performed using previously described methods.(4, 13) A polynomial
160 filter was used to refine the derivatives of aortic/ pulmonary pressure and velocity signals,
161 using a Savitzky-Golay convolution method.(13) The chosen 3-5 beats were gated to the R
162 wave on the ECG, with ensemble averaging of the aortic/ pulmonary pressure, average peak
163 velocity and heart rate.

164

165 Wave intensity (dI) was calculated from the time derivatives (dt) of ensemble-averaged
166 aortic/pulmonary pressure (dP) and flow velocity (dU) as shown: $dI = dP/dt \times dU/dt$.(5, 13)
167 Corresponding forward and backward propagating waves were separated assuming a blood
168 density of 1050 kg/m^3 and estimating aortic/ pulmonary wave speed using the sum of squares
169 method.(13) The peak energy carried by the 3 most prominent wave energies were analyzed
170 and recorded in this manuscript; the FCW, FEW and BCW (*Figure 1*).

171

172 *Processing invasive hemodynamic data*

173 Simultaneous LV pressure and volume were measured and volume calibration was performed
174 off-line post data acquisition using three dimensional echocardiography to obtain LV ejection
175 fraction, LV end-diastolic volume and LV end-systolic volume. Hemodynamic data was
176 recorded on Conduct NT (CD Leycom). Data was sampled at 250Hz and exported into
177 SimpleWires (King's College London). At least ten consecutive cycles were selected, with
178 ensemble average of at least five beats for analysis. The resulting pressure-volume loop was
179 exported to provide invasive hemodynamic data.(14)

180

181 *Pacing protocol*

182 Biventricular pacing at baseline heart rates was compared with intrinsic rhythm at baseline
183 heart rates. Measurements for patients in sinus rhythm were made in AAI mode, atrial
184 fibrillation in VVI mode and complete heart block in DDD mode. Baseline heart rates were
185 10bpm above the patient's intrinsic rate or at 70bpm in patients with complete heart block.(4)
186 The atrioventricular delay was set to 120ms and simultaneous ventricular activation.

187

188 *Definition of CRT responders*

189 Patients were defined as CRT responders if they had a reduction in LV end-systolic volume
190 $\geq 15\%$ at 6-month follow-up.(1, 15)

191

192 *Statistical Analysis*

193 Discrete data is presented as n values with corresponding percentages in parentheses and
194 continuous data as means \pm standard deviation. Responses in the same participants at different
195 pacing settings were compared using a paired 2-sided Student *t* test for normally distributed
196 data and Wilcoxon signed-rank test for non-normally distributed data. A two-sided *P*-value
197 < 0.05 was considered statistically significant. Statistical analyses were performed using
198 Prism (GraphPad Software Inc., Version 8, CA) and SPSS (IBM Switzerland, Version 25,
199 Switzerland).

200 **Results**

201 Patient recruitment is shown in *Figure 2*, a flowchart of the study in *Figure 3* and baseline
202 demographics in *Table 1*. All 28 patients underwent successful CRT with a quadripolar LV
203 lead placed in a lateral or posterolateral vein in 25 (89.3%) patients. All patients survived to
204 6-month follow-up and had >99% biventricular pacing delivery confirmed at 6 months.
205 *Appendix A* provides a sub-group analysis of patients who were in sinus rhythm only and left
206 bundle branch block at baseline.

207

208 ***Non-invasive protocol***

209 Overall, 21 (75.0%) patients were CRT responders and 7 (25.0%) CRT non-responders.

210 Patient demographics include a mean age of 72.9 ± 8.0 years, 53.6% had ischemic heart
211 disease, 85.7% had left bundle branch block, with a mean QRS duration of 158 ± 19 ms and a
212 severely reduced LV ejection fraction of $30\pm 8\%$.

213

214 In CRT responders at 6-months, biventricular pacing resulted in a significant increase in the
215 systolic blood pressure (106.8 ± 18.4 vs. 97.9 ± 18.3 mmHg; $P=0.015$), mean arterial pressure
216 (84.2 ± 12.3 vs. 77.7 ± 13.7 mmHg; $P=0.046$) and central pulse pressure (38.8 ± 15.2 vs.
217 35.1 ± 14.9 ; $P=0.031$) but not the diastolic blood pressure (68.0 ± 10.7 vs.
218 62.8 ± 13.0 mmHg; $P=0.083$). There was no significant difference in CRT non-responders at 6-
219 months in the systolic blood pressure, mean arterial pressure or central pulse pressure.

220

221 ***Non-invasive aortic wave intensity at baseline heart rates***

222 In CRT responders, biventricular pacing compared with intrinsic rhythm resulted in an
223 immediate increase in the FCW ($2.1[1.3-2.8]$ vs. $1.4[1.1-2.0]$ W/m²/s² $\times 10^6$; $P=0.006$) but not
224 the FEW and BCW (*Figure 4 and Table 2*). There was no significant difference in the timing

225 of the FCW wave (35.7 vs. 37.9ms; $P=0.255$). These findings were maintained at 6-months,
226 with a significant increase in the FCW ($P=0.025$). These effects were not seen in CRT non-
227 responders.

228

229 *PWV*

230 In CRT responders, biventricular pacing resulted in a significant reduction in the PWV
231 acutely ($0.5\pm 1.2\text{m/s};P=0.021$) and a non-significant reduction at follow-up
232 ($0.7\pm 1.6\text{m/s};P=0.086$) when compared with intrinsic rhythm. There were no significant
233 differences in changes from baseline in PWV in CRT non-responders.

234

235 ***Invasive protocol***

236 The invasive study was used to validate the major findings of the non-invasive study. 11
237 patients underwent an invasive protocol with 11 aortic and 7 pulmonary electrophysiology
238 recordings. Acquisition of pressure-volume loop data was attempted in all cases but
239 successful in 9 patients since there was significant interference during data collection in 2
240 patients preventing reliable recordings. There were no acute complications arising from this
241 study.

242

243 Overall, 7 (63.6%) patients met the study definition for CRT response. Patients demographics
244 include a mean age of 68.1 ± 9.1 years, QRS duration of 151 ± 18 ms and severely impaired LV
245 ejection fraction of $27\pm 9\%$ (*Table 1*). In CRT responders, biventricular pacing resulted in a
246 significant increase in the CO (4 ± 2 vs. $3\pm 2\text{L/min};P=0.002$) and reduction in SVR (26 ± 10 vs.
247 $44\pm 26\text{mmHg min/L};P=0.040$) (*Table 3*). There was no significant difference in CO nor SVR
248 in CRT non-responders. All CRT responders showed an acute hemodynamic improvement in
249 LV $\text{dP/dt}_{\text{max}} > 10\%$ which was not seen in any of the non-responders.

250

251 *Invasive aortic wave intensity and correlation between aortic flow and myocardial*

252 *contractility*

253 In CRT responders, biventricular pacing compared with intrinsic rhythm resulted in a

254 significant increase in the FCW acutely (8.3[4.4-8.4] vs. 4.8[3.0-7.0]W/m²/s²×10⁵;P=0.023)

255 (*Appendix B*) and shorter time to peak FCW (50.0 vs. 55.0ms;P=0.020). These effects were

256 not seen in CRT non-responders. The relative change in LV dP/dt_{max} strongly correlated with

257 the change in aortic FCW (*R*_s 0.733;P=0.025).

258

259 *Invasive pulmonary wave intensity following CRT*

260 There were 4 (57.1%) CRT responders and 3 (42.9%) CRT non-responders who underwent

261 pulmonary flow assessment (*Appendix B*). In CRT responders, biventricular pacing resulted

262 in a significant reduction in the FCW (0.8[0.4-1.2] vs. 1.2[0.8-1.6]W/m²/s²×10⁵; P=0.004)

263 and FEW (P=0.030) (*Appendix B*). Biventricular pacing resulted in a significantly longer time

264 to the peak FCW (72.5 vs. 47.5ms;P=0.009) and FEW (268.8 vs. 212.5ms;P=0.014). These

265 changes were not seen in CRT non-responders.

266 **Discussion**

267 To our knowledge, this is the first study to comprehensively examine the effects of
268 biventricular pacing on aortic and pulmonary flow and determine its effects on SVR and
269 PWV. Although wave intensity analysis has traditionally been measured invasively, we
270 sought to determine the effects of CRT both acutely and chronically, requiring us to use a
271 combination of invasive and non-invasive measurements. We found in CRT responders there
272 was a:

- 273 1. Significant increase in CO and decrease in SVR. There was a significant reduction in
274 the PWV acutely and a non-significant reduction chronically.
- 275 2. Significant increase in the aortic FCW both acutely and chronically.
- 276 3. Strong positive correlation between maximal rise in LV pressure and aortic FCW
- 277 4. Significant reduction in the pulmonary FCW and FEW.

278

279 This study demonstrates that in CRT responders there are significant changes to both the
280 cardiac and vascular system. Principally, there is an increase in myocardial contractility and
281 LV dP/dt_{max} , and vascular changes with a resulting decrease in afterload. These combined
282 changes lead to an increased CO, stroke work and mean arterial blood pressure.

283

284 *Effect of CRT on aortic pressure/flow waves*

285 The heart is part of an integrated system. Changes in cardiac contractility and perfusion are
286 affected by preload and afterload, both of which dynamically respond to changes in cardiac
287 function. The effects of CRT on coronary flow has previously been investigated,(2, 4) and
288 demonstrate that biventricular pacing increases coronary flow in the left anterior descending
289 artery by increasing the backward expansion wave and homogenizing wave timings that
290 determine flow in the left anterior descending and circumflex arteries. The effects of CRT on

291 aortic flow are not well described. Fok et al. showed in hypertensive patients that dobutamine
292 increased the FCW by a greater proportion than in normotensive patients.(7) Dobutamine
293 partly exerts its effects through improving myocardial contractility and this improved
294 contractility is evident in CRT responders. The current study demonstrates that in CRT
295 responders there is a significant increase in the FCW both acutely and chronically. The
296 relative change in acute LV pressure strongly correlated with the FCW at baseline heart rates
297 suggesting that as LV pressure increases, from improved myocardial contractility, so does
298 aortic forward flow in early systole. The aortic forward flow can only increase if systemic
299 impedance does not rise in parallel with the rise in LV pressure. When measured invasively,
300 the timing to the peak FCW occurred significantly earlier in the cardiac cycle which may
301 enable longer diastolic filling and improved cardiac function.

302

303 *Effect of CRT on pulmonary pressure/ flow waves*

304 The effect of CRT on pulmonary wave intensity, to our knowledge, has not been previously
305 described. In an invasive study of 31 patients investigating pulmonary flow, patients with
306 pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension were
307 shown to have a significantly higher FCW and FEW compared with control subjects.(6)
308 Severe LV systolic impairment is a common cause of post-capillary pulmonary hypertension.
309 We demonstrated that in patients with severe LV systolic impairment who respond with
310 CRT, biventricular pacing resulted in a significant reduction in the FCW and FEW. The time
311 to the peak FCW and FEW was also significantly longer, in keeping with biventricular pacing
312 allowing for more effective LV relaxation and filling, thereby increasing preload which in
313 turn increases CO evidenced by a significant increase in the LV dp/dt_{min} .

314

315 *Effect of CRT on afterload*

316 The effect of CRT on afterload has not been comprehensively investigated to our knowledge.
317 The two major components of afterload or impedance are PWV and SVR.(16) PWV
318 determines the characteristic impedance which is afterload when pressure and flow are
319 rapidly changing at the beginning of systole. However, SVR is the steady state afterload.
320 Importantly, a greater aortic FCW can only generate greater flow if impedance remains
321 constant or falls. In the current manuscript, we have shown that CRT responders have a
322 significant increase in FCW with a concomitant reduction in SVR and PWV acutely and non-
323 significant reduction in PWV at follow-up. Several studies have shown that increased arterial
324 blood pressure is associated with an increase in PWV.(16) Our findings are in stark contrast
325 to these studies where we have shown that CRT responders demonstrate a rise in mean
326 arterial blood pressure, however this was not associated with a rise in PWV. Faconti et al.
327 found a significant reduction in mean arterial pressure despite an increase in PWV after using
328 lower-limb venous occlusion devices.(10) They postulated that these findings were explained
329 by sympathetic activation leading to increased vascular smooth muscle. Our findings could
330 be explained by the increased FCW seen with biventricular leading to greater pulsatility and
331 CO which resulted in decreased baroreceptor activation of the sympathetic nervous system
332 due to a higher pulse pressure and decreased activation of the renin-angiotensin-aldosterone
333 system.

334

335 *Clinical perspective*

336 This study offers new explanations as to how CRT may exert its benefits in heart failure
337 patients. Understanding the role of the cardiovascular system on CRT response supports
338 considering the cardiovascular system as a whole in CRT patient selection. Therefore, it's
339 important to examine both the cardiac and systemic haemodynamics to understand who will
340 respond best to CRT and how to optimise response. It's possible, for example, that those who

341 show benefit in cardiac mechanics but not in systemic vascular responses could benefit from
342 additional vasodilator therapy.

343 **Limitations**

344 The study size was small because patients were asked to undergo a rigorous and lengthy
345 invasive and non-invasive protocol, therefore the results may not be generalizable to the
346 whole CRT population. However, our sample size is in keeping with other published studies
347 relating to invasive wave intensity analysis.(2, 4) The invasive protocol carried additional
348 procedural risks and therefore is unlikely to be used in routine clinical practice, although the
349 non-invasive protocol could be adopted. Both groups were matched in terms of sex,
350 aetiology, presence of left bundle branch block, QRS duration and LV ejection fraction. The
351 confidence intervals for hemodynamic and electrophysiology data in CRT non-responders
352 was wide due to a small cohort and consequently we are unable to speculate why they have
353 failed to improve. During the pacing protocol we fixed the patient's heart rate to control for
354 the effect of changes in chronotropy can cause to inotropy, but it should be noted that this
355 will prevent reflex heart rate regulation to alterations in inotropy. No variation in
356 atrioventricular delay was assessed in the current study due to the complexity of the protocol
357 and therefore we could not study the changes in acute hemodynamics which may have
358 occurred with atrioventricular or ventricular optimization. Defining CRT response is
359 heterogenous and can be based on hard and/or soft end-points.(1) The aim of this study was
360 to further investigate the physiological effects of CRT on the cardiac and cardiovascular
361 system and therefore we used patients who displayed evidence of LV remodeling to define
362 CRT response. Although the present study suggests increased FCW in CRT responders, we
363 are unable to provide a cut-off value for predicting response. Further studies with a larger
364 sample size will be needed to determine whether this is possible. Furthermore, the study was
365 underpowered to determine whether changes in FCW were different in patients with non-left
366 bundle branch block and in CRT non-responders whether the FCW worsens or remains static
367 with biventricular pacing. The sample size was too small to draw reliable conclusions from

368 the effect of rhythm (i.e. sinus rhythm versus atrial fibrillation) alone and optimal pre-load
369 was not possible for patients in atrial fibrillation.

370 **Conclusion**

371 This study demonstrates that response to CRT is characterised by an increased FCW, due to
372 increased cardiac contractility, with a reduction in both dynamic (PWV) and steady state
373 components (SVR) of afterload that results in an increased CO. Therefore, both cardiac and
374 systemic vascular responses determine response to CRT which may be particularly important
375 in optimizing therapy and informing patient selection.

376

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436 **Figure legends**

437 **Figure 1.** The predominant waves seen in aortic and pulmonary flow are displayed. The
438 forward travelling waves consist of the forward compression wave and forward expansion
439 wave. The backward compression wave is the predominant backward travelling wave. Key:
440 BCW=backward compression wave, FCW=forward compression wave and FEW=forward
441 expansion wave

442 **Figure 2.** Patient recruitment into non-invasive and invasive studies

443 **Figure 3.** Flowchart of invasive and non-invasive arms of the study

444 **Figure 4.** Box and whisker plot showing the non-invasive aortic wave intensity at baseline
445 rhythm before cardiac resynchronization therapy and at 6-months with biventricular pacing in
446 different patient groups. Tukey whiskers have been used to represent the data by displaying the
447 box consisting of the median, upper and lower quartiles and the whiskers consisting of the
448 maximum and minimum value followed by any outlining patient data represented by a dot.