Guytonian approach in controlling cardiac output

2013.3.5

慈恵ICU勉強会
藤井 智子
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• Observations on the Circulation
  – Mean systemic filling pressure
  – Guyton’s venous return curve

• Clinical Utility of the model
  – VR curve at bedsides
  – Norepinephrine on CO in septic shock
  – Norepinephrine on CO in cardiac surgery
“People who wish to analyze nature without using mathematics must settle for a reduced understanding.”

- RICHARD FEYNMAN
Starling’s observation on the Heart

Commonly used explanation on cardiac output

Another observation by Starling

**Pms ‘mean systemic pressure’**

Cardiac arrest by sympathectomy and vagal stimulation

All vascular pressures rapidly equilibrated

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Bayliss WM, Starling EH. Observations on venous pressures and their relationship to capillary pressures. J Physiol 1894; 16: 159-318
Pms ‘mean systemic pressure’

When Heart beats…

- The arterial pressure rises above and the venous pressure sinks below Pms
- Does not diminish Pms, cause a variation in the distribution of Pms

Bayliss WM, Starling EH. Observations on venous pressures and their relationship to capillary pressures. J Physiol 1894; 16: 159-318
## Function of the Venous system

<table>
<thead>
<tr>
<th>Structure</th>
<th>Percentage of Total Blood Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic venous system</td>
<td>64</td>
</tr>
<tr>
<td>Systemic arterial system</td>
<td>13</td>
</tr>
<tr>
<td>Capillaries</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary circuit</td>
<td>9</td>
</tr>
<tr>
<td>Heart</td>
<td>7</td>
</tr>
</tbody>
</table>

What determines cardiac output?

The Heart?

The Circulation?

The Heart?

Venous Return

- the quantity of blood which returns to the heart from the peripheral circulatory system

The Circulation?
Hagen-Poiseuille’s law
(=Ohm’s law of electrical current flow)

\[ Q = \frac{P_1 - P_2}{R} \]

Q: fluid flow  
P1: upstream pressure  
P2: downstream pressure  
R: resistance to flow

\[ CO = \frac{MAP - P_{RA}}{SVR} \]

Commonly used explanation on left ventricular function
Venous Return

Guyton’s explanation on CO

\[ VR = \frac{P_{ms} - P_{RA}}{R_v} \]

At steady state, CO=VR

Bayliss WM, Starling EH. Observations on venous pressures and their relationship to capillary pressures. J Physiol 1894; 16: 159-318
Hagen-Poiseuille’s law
(=Ohm’s law of electrical current flow)

\[ \dot{Q} = \frac{P_1 - P_2}{R} \]

Q: fluid flow  P1: upstream pressure  P2: downstream pressure  R: resistance to flow

\[ CO = \frac{MAP - P_{RA}}{SVR} \]

\[ VR = \frac{P_{ms} - P_{RA}}{R_v} \]

VR: Venous Return  Pms: mean systemic pressure  Rv: resistance to VR
What makes up $P_{ms}$?

(1) Change in the total volume in the reservoir

Adding or removing volume: fluid resuscitation

(2) Change in the proportion of \( V_0 \) and \( V_s \)

Alteration of autonomic tone, catecholamine stress response, infusion of exogenous vasoactive substances
Compliance and Resistance

Poiseuille’s law for resistance

\[ R = \frac{8 \eta l}{\pi r^4} \]

\( \eta \)  Viscosity

Blood, crystalloid infusion…
Venous Return Curve

\[ VR = \frac{P_{ms} - P_{RA}}{R_v} \]
Guyton’s Observation

- Recently dead dog
  - A pump replacing the heart
  - RA → pump → Aorta
- MCFP changed by increasing or decreasing the total quantity of blood

AC Guyton. Determination of Cardiac Output By Equating Venous Return Curves With Cardiac Response Curves Physiol Rev 1955; 35: 123-139
Guyton’s Observation

Determinants of Venous Return

- Right Atrial Pressure ($P_{RA}$)
- Mean circulatory filling pressure ($P_{mcf}$)

AC Guyton. Determination of Cardiac Output By Equating Venous Return Curves With Cardiac Response Curves Physiol Rev 1955; 35: 123-139
Guyton’s Observation

\[ P_{RA} < 0 \]

Major veins entering the thorax collapsed
NOT continue to increase the venous return

AC Guyton. Determination of Cardiac Output By Equating Venous Return Curves With Cardiac Response Curves Physiol Rev 1955; 35: 123-139
AC Guyton. Determination of Cardiac Output By Equating Venous Return Curves With Cardiac Response Curves Physiol Rev 1955; 35: 123-139
Guyton’s Observation

$P_{RA}$ is not one of the primary determinants of cardiac output but is itself determined along with cardiac output.

The determinants of CO and $P_{RA}$ are the shape of the cardiac response curve and the peripheral circulatory factors which affect venous return ($P_{mcf}$, viscosity of the blood…)

AC Guyton. Determination of Cardiac Output By Equating Venous Return Curves With Cardiac Response Curves Physiol Rev 1955; 35: 123-139
Effects on VR curve

Venous Return

- Pms
- Rv
- Normal
- Pms

Right Atrial Pressure
Fluid infusion

Cardiac Output or Venous Return

Right Atrial Pressure
Inotropic vasopressors

Cardiac Output or Venous Return

Right Atrial Pressure

↑Rv + ↑Pms (↑Vs)

↑contractility (dop, NE)

normal

A

B

C

D
Some assumptions in the Guyton model

- DOG
- Steady State: Pressure and flow variables represent mean values averaged over many cardiac cycles
- Closed System: blood volume in the systemic circulation remaining constant
- Intrathoracic Pressure: ignored
"It doesn't matter how beautiful your theory is, it doesn't matter how smart you are. If it doesn't agree with experiment, it's wrong."

- RICHARD FEYNMAN
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  – Mean systemic filling pressure
  – Guyton’s venous return curve

• Clinical Utility of the model
  – VR curve at bedsides
  – Norepinephrine on CO in septic shock
  – Norepinephrine on CO in cardiac surgery
VR curves at bedsides

• Hypothesis: using inspiratory hold maneuver enables to measure vascular parameters and generate VR curves at the bedside

• Methods: 12 post-CABG/AVR patients
  – Pa: 20G, 3.8cm long radial arterial catheter
  – Pcv: right internal jugular vein
  – Reference: anterior axillary line and the fifth intercostal space
  – Pvent: entrance of endotracheal tube

Protocol

• Mechanical Ventilation: SIMV→APRV adapted to have the same gas exchange
• No spontaneous breathing movements
• Measurements: Pa, Pcv, CO
• Pvent plateau: 5, 15, 25, 35cmH2O
• Three volumetric conditions:
  – supine (baseline)
  – 30 degree head-up (hypo)
  – 500mL HES130/0.4 (hyper)
Measurements during inspiratory hold maneuver

- \( P_{cv} \) increases concomitantly

- \( P_{vent} \) increases...
Pa decreases with three-four beats delay

Pvent increases...

CO decreases with three-four beats delay
Data plotted…VR curves!

- **Baseline**
- **Hypovolemia**
- **Hypervolemia**

Values:
- a: 18.76 (4.53)
- b: 14.54 (2.99)
- c: 29.07 (5.23)

P-values:
- p = 0.005
- p = 0.001
a: baseline
↓ +500mL HES

c: hypervolemia

Vs can be determined!

\[
P_{ms} = \frac{V_t - V_o}{C}
\]

The graph shows the relationship between CO\textsubscript{mf} (L/min) and Pcv (mmHg) for baseline, hypovolemia, and hypervolemia conditions. The slopes for each condition are as follows:

- Slope a: \(-0.465 \pm 0.151\) with p=0.388
- Slope b: \(-0.429 \pm 0.160\) with p=0.388
- Slope c: \(-0.389 \pm 0.135\) with p=0.134
hypovolemia
baseline
hypervolemia

Rv: did not change with fluid status
Guyton’s original VR curve

Inspiratory hold manoeuvre

AC Guyton. Determination of Cardiac Output By Equating Venous Return Curves With Cardiac Response Curves Physiol Rev 1955; 35: 123-139
Effects of norepinephrine and VR curve

Methods: 16 septic shock patients
- Respiratory hold maneuver (Insp. & Exp.)
- CO: PiCCO2
- Pcv: right internal jugular vein
- Reference: anterior axillary line and 5cm below the sternal angle
- Pvent: proximal of endotracheal tube
Methods to determine $P_{msf}$

- Mechanical Ventilation: A/C VCV
- Baseline Measurements: mAP, CVP, CI, GEDV,
- Continuous Measurements: mAP, CVP, Paw, SV, CI
- $P_{vent}$ plateau: 5, 30cmH$_2$O (Insp & Exp)

BEFORE and AFTER norepinephrine decreases
Example of the estimation of the venous return curves in a patient. Norepinephrine was decreased from 1.5 to 0.7 ug/kg/min.
<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of norepinephrine (µg/kg/min)</td>
<td>0.30 [0.10–1.40]</td>
<td>0.19 [0.08–1.15]</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>90 ± 21</td>
<td>89 ± 18</td>
<td>.352</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>9 ± 5</td>
<td>8 ± 5</td>
<td>.023</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>91 ± 9</td>
<td>77 ± 7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.47 ± 0.86</td>
<td>3.28 ± 0.76</td>
<td>.045</td>
</tr>
<tr>
<td>Cardiac index variation during a passive leg raising test (%)</td>
<td>1 ± 4</td>
<td>8 ± 4</td>
<td>.001</td>
</tr>
<tr>
<td>Mean systemic pressure (mm Hg)</td>
<td>33 ± 12</td>
<td>26 ± 10</td>
<td>.0003</td>
</tr>
<tr>
<td>Inverse of the slope of the venous return curve (mm Hg·min·m²/L)</td>
<td>6.2 [4.4–8.0]</td>
<td>5.0 [3.6–6.5]</td>
<td>.01</td>
</tr>
<tr>
<td>Resistance to venous return (mm Hg·min·m²/L)</td>
<td>6.5 [4.4–8.2]</td>
<td>5.2 [3.7–7.1]</td>
<td>.01</td>
</tr>
<tr>
<td>Arterial resistance (mm Hg·min·m²/L)</td>
<td>18.3 [14.9–22.2]</td>
<td>16.4 [12.1–19.7]</td>
<td>.048</td>
</tr>
<tr>
<td>Systemic resistance (mm Hg·min·m²/L)</td>
<td>25.3 [17.8–27.4]</td>
<td>21.0 [19.4–24.5]</td>
<td>.001</td>
</tr>
<tr>
<td>Global end-diastolic volume index (mL/m²)</td>
<td>819 ± 204</td>
<td>774 ± 171</td>
<td>.032</td>
</tr>
<tr>
<td>Cardiac function index (/min)</td>
<td>4.7 ± 1.6</td>
<td>4.7 ± 1.6</td>
<td>.481</td>
</tr>
</tbody>
</table>
1/Slope = Rv

High dose NE: 6.2 (4.4-8.0)
Low dose NE: 5.0 (3.6-6.5)

p = 0.01

Crit Care Med 2012 Vol. 40, No. 12
CVP/GEDV, Pmsf, Rv $\propto$ NE doses

- Decreasing NE in septic shock patients
  - Decreases Pmsf and Rv
  - Decreases cardiac preload (CVP/ GEDV)

- NE=$\alpha_1$-adrenergic stimulation increases the stress against the vessel walls
  - Increases intravascular pressure
  - Increases stressed blood volume and decreases unstressed blood volume
CVP/GEDV, Pmsf, Rv $\propto$ NE doses

- Decreasing NE in septic shock patients
  - Decreases Pmsf and Rv
  - Decreases cardiac preload (CVP/ GEDV)

- NE=$\alpha_1$-adrenergic stimulation increases the stress against the vessel walls
  - Increases intravascular pressure
  - Increases stressed blood volume and decreases unstressed blood volume

\[ P_{ms} = \frac{V_t - V_o}{C} \]
CO response to NE?

- Preload (Pmsf, Vs)
- Afterload (mAP)
- Resistance to Venous Return
CO response to NE?

• Hypothesis: Stroke volume variation (SVV) as a predictor of the NE induced change in CO

• Patients and Monitoring:
  16 post-CABG/MVP patients
  – Pa: radial arterial catheter
  – Pcv: right internal jugular vein
  – Reference: anterior axillary line and the fifth intercostal space
  – Pvent: proximal end of endotracheal tube

Clinical Utility of the VR curve (3)
Protocol

Measurements: mAP, PCV, CO, $P_{msf}$

Baseline-1

↑ 20mmHg in mAP

NE

↓ 20mmHg in mAP

Baseline-2

CCM 2013; 41:143-150
VR curve for one patient

- ▲ baseline
- ○ after NE dosage increase

CCM 2013; 41:143-150
<table>
<thead>
<tr>
<th></th>
<th>Baseline-1</th>
<th>NE</th>
<th>Baseline-2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients ($n=16$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>81.60±10.16</td>
<td>101.85±9.81</td>
<td>82.80±13.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>74.4±14.0</td>
<td>70.1±13.8</td>
<td>75.7±14.1</td>
<td>0.003</td>
</tr>
<tr>
<td>CO (L·min⁻¹)</td>
<td>4.30±0.78</td>
<td>4.09±0.67</td>
<td>4.44±0.80</td>
<td>0.043</td>
</tr>
<tr>
<td>SV (mL)</td>
<td>59.4±13.3</td>
<td>60.4±15.2</td>
<td>60.7±15.6</td>
<td>0.825</td>
</tr>
<tr>
<td>PCV (mm Hg)</td>
<td>7.61±2.07</td>
<td>8.55±2.35</td>
<td>7.58±2.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PMSF (mm Hg)</td>
<td>21.44±6.12</td>
<td>27.57±7.39</td>
<td>21.98±5.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR (mm Hg)</td>
<td>13.60±5.66</td>
<td>19.02±6.20</td>
<td>14.26±5.16</td>
<td>0.001</td>
</tr>
<tr>
<td>RVR (mm Hg·min⁻¹·L⁻¹)</td>
<td>3.14±0.94</td>
<td>4.72±1.64</td>
<td>3.22±0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RSYS (mm Hg·min⁻¹·L⁻¹)</td>
<td>17.42±3.88</td>
<td>23.31±4.09</td>
<td>17.35±4.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVR/RSYS (%)</td>
<td>19.0±7.9</td>
<td>20.4±6.6</td>
<td>19.2±6.9</td>
<td>0.305</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>11.1±4.0</td>
<td>7.9±4.3</td>
<td>11.0±4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Baseline-1</td>
<td>NE</td>
<td>Baseline-2</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------</td>
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<td>------------</td>
<td></td>
</tr>
<tr>
<td><strong>Patients with CO increase after NE Group A</strong> (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>81.65 ± 13.67</td>
<td>98.41 ± 10.68</td>
<td>85.14 ± 19.27</td>
<td></td>
</tr>
<tr>
<td>HR (min⁻¹)</td>
<td>73.2 ± 17.0</td>
<td>72.7 ± 16.1</td>
<td>73.0 ± 16.1</td>
<td></td>
</tr>
<tr>
<td>CO (L·min⁻¹)</td>
<td>4.06 ± 0.93</td>
<td>4.31 ± 0.86</td>
<td>4.16 ± 0.80</td>
<td></td>
</tr>
<tr>
<td>SV (mL)</td>
<td>57.5 ± 16.9</td>
<td>61.4 ± 16.8</td>
<td>59.2 ± 17.1</td>
<td></td>
</tr>
<tr>
<td>PCV (mm Hg)</td>
<td>7.57 ± 2.30</td>
<td>8.03 ± 2.68*</td>
<td>7.37 ± 2.25</td>
<td></td>
</tr>
<tr>
<td>PMSF (mm Hg)</td>
<td>19.80 ± 5.27</td>
<td>23.57 ± 4.62</td>
<td>19.22 ± 4.40</td>
<td></td>
</tr>
<tr>
<td>PVR (mm Hg)</td>
<td>12.23 ± 4.36</td>
<td>15.55 ± 4.34</td>
<td>11.85 ± 4.02</td>
<td></td>
</tr>
<tr>
<td>RVR (mm Hg·min⁻¹)</td>
<td>2.97 ± 0.57</td>
<td>3.58 ± 0.64*</td>
<td>2.82 ± 0.73</td>
<td></td>
</tr>
<tr>
<td>RSYS (mm Hg·min⁻¹)</td>
<td>18.83 ± 5.01</td>
<td>21.54 ± 4.36*</td>
<td>18.97 ± 5.07</td>
<td></td>
</tr>
<tr>
<td>RVR/RSYS (%)</td>
<td>16.7 ± 6.0</td>
<td>17.1 ± 4.3</td>
<td>15.2 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>SVV (%)</td>
<td>14.4 ± 4.2*</td>
<td>11.9 ± 2.7b</td>
<td>14.9 ± 3.7a</td>
<td></td>
</tr>
</tbody>
</table>

<p>| <strong>Patients with CO decrease after NE Group B</strong> (n = 10) |            |          |            |
| MAP (mm Hg)             | 82.52 ± 8.10 | 103.91 ± 9.19 | 82.22 ± 9.21 |
| HR (min⁻¹)              | 75.1 ± 12.8  | 68.6 ± 12.9*  | 77.3 ± 13.4  |
| CO (L·min⁻¹)            | 4.46 ± 0.64  | 3.96 ± 0.52*  | 4.61 ± 0.74  |
| SV (mL)                 | 60.5 ± 11.6  | 59.8 ± 15.1  | 61.6 ± 15.5  |
| PCV (mm Hg)             | 7.57 ± 1.93  | 8.86 ± 2.22*  | 7.65 ± 2.06  |
| PMSF (mm Hg)            | 22.40 ± 6.11 | 29.97 ± 7.88  | 23.51 ± 4.94  |
| PVR (mm Hg)             | 14.77 ± 5.52 | 21.10 ± 6.38  | 15.86 ± 4.54  |
| RVR (mm Hg·min⁻¹)       | 3.29 ± 1.00  | 5.41 ± 1.68*  | 3.48 ± 0.93  |
| RSYS (mm Hg·min⁻¹)      | 16.67 ± 2.34 | 24.37 ± 3.74* | 16.49 ± 2.96  |
| RVR/RSYS (%)            | 20.3 ± 7.8   | 22.3 ± 7.2   | 21.5 ± 6.4   |
| SVV (%)                 | 9.1 ± 2.4*   | 5.3 ± 2.9b   | 8.7 ± 3.5a   |</p>
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<td>RSYS (mm Hg·min⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVR/RSYS (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVV (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutoff value:</td>
<td>8.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity:</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity:</td>
<td>70%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Predicting CO response to NE Based on SVV
AUROC 0.900 (95%CI 0.647-0.987 p=0.0001)

CO↑

CO↓
a→b: increase in $V_S$ (increase resistance to the circulation of unstressed volume)
b→c: increase in $R_V$ (diminish the cross sectional area of the venous vessels)

Patients who increased CO on NE
NE recruited intravascular volume
→ increase in Pmsf
stronger effect than ↑$R_V$, mAP

SVV (%) 14.4 → 11.9
d→e: increase in $V_S$ (increase resistance to the circulation of unstressed volume)

e→f: increase in $R_V$ (deminish the cross sectional area of the venous vessels)

f→g: ! ! 

PCV(mmHg) 7.57→8.56

Patients who decreased CO on NE

NE increased left ventricular afterload
→decrement in the cardiac function curve

stronger effect than ↑Pmsf

Hypotensive
SVV<8.7%
→NE+Dobutamine …!? 

CCM 2013; 41:143-150
A Leader...

Michael Pinsky

The European Society of Intensive Care Medicine proudly awards this citation of Honorary Membership to Professor Michael Pinsky for his major contributions to Intensive Care Medicine around the world.

Michael Pinsky received his MD from McGill University much in the right place and I am honoured to count him among my friends.

Michael has established himself as a leader in his field, an inspired proponent of translation from basic physiology to patient care. When someone mentions
“We can imagine that this complicated array of moving things which constitutes "the world" is something like a great chess game being played by the gods, and we are observers of the game. We do not know what the rules of the game are; all we are allowed to do is to watch the playing. Of course, if we watch long enough, we may eventually catch on to a few of the rules.”

- RICHARD FEYNMAN