Effects of phenylephrine on cardiac output and venous return depend on the position of the heart on the Frank-Starling relationship

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Introduction: phenylephrine is used daily during anesthesia for treating hypotension. However, the effects of phenylephrine on cardiac output (CO) are not clear. We hypothesized that the impact of phenylephrine on cardiac output is related to preload dependency.

Methods: eight pigs were studied at a preload independent stage (after a 21 ml/kg hemorrhage). At each stage, phenylephrine boluses (0.5, 1.0, 2.0, and 4.0 μg/kg) were given randomly while mean arterial pressure (MAP), CO, inferior vena cava flow (IVCf) (both measured using ultrasonic flow probes), and pulse pressure variation were measured. Results: at the preload independent stage, phenylephrine boluses induced significant increases in MAP (from 72 ± 6 to 100 ± 6 mmHg; P < 0.05) and decreases in CO and IVCf (from 7.0 ± 0.8 to 6.0 ± 1.1 l/min and from 4.6 ± 0.5 to 3.8 ± 0.6 l/min, respectively). At the preload-dependent stage, phenylephrine boluses induced significant increases in MAP (from 40 ± 7 to 65 ± 9 mmHg), CO (from 4.1 ± 0.6 to 4.9 ± 0.7 l/min), and IVCf (from 3.0 ± 0.4 to 3.5 ± 0.6 l/min; all data presented are for 4 μg/kg). Incremental doses of phenylephrine induced incremental changes in cardiac output. A pulse pressure variation >16.4% before phenylephrine predicted an increase in stroke volume with a 93% sensitivity and a 100% specificity. Conclusion: impact of phenylephrine on cardiac output is related to preload dependency. When the heart is preload independent, phenylephrine boluses induce on average a decrease in cardiac output. When the heart is preload dependent, phenylephrine boluses induce on average an increase in cardiac output.

There are two main mechanisms by which phenylephrine could alter cardiac output: the first is that phenylephrine raises ventricular afterload and thereby decreases stroke volume (SV) and thus cardiac output as outlined above. The second is that phenylephrine causes a release of blood volume from peripheral to central veins, thereby raising central venous pressure, SV, and thus cardiac output (10, 29, 30). This second mechanism would be based on the assumption that a significant portion of venous blood is stored in the splanchnic organs and that phenylephrine induces an unloading of this reservoir (6, 7). Clearly, as recently suggested by Magder (12), the two mechanisms are not mutually exclusive and likely compete against one another. In this light we propose that the discrepancy as to the effects of phenylephrine on cardiac output may relate to where on its ventricular function curve the heart is operating at the time of phenylephrine administration. Were the heart operating on the flat portion of its ventricular function curve (i.e., was preload independent), any rise in preload would have little or no influence on stroke volume and thus only the afterload effect would be manifest. Conversely, were the heart operating on the steep portion of its ventricular function curve (i.e., was preload dependent), any rise in preload should raise SV and this effect could overwhelm any rise in afterload such that cardiac output would rise. In addition, it has been suggested that the effects of phenylephrine are dose dependent because different tissues have different thresholds for α1-receptor activation (6).

In this animal study, we tested the hypothesis that the impact of phenylephrine on cardiac output is related to the position of the heart on the Frank-Starling relationship and, consequently, on its preload dependency. Our approach was to alter the heart’s operating point on its ventricular function curve via volume loading and hemorrhage in anesthetized pigs.

METHODS

The study was approved for the use of Yorkshire cross swine by the Institutional Animal Care and Use Committee at the Edwards Life-sciences Biological Resource Center, and all experimentation was done in accordance with the Guide for the Care and Use of Laboratory Animals (ILAR, NAP, Washington, DC, 2011).

Eight anesthetized and mechanically ventilated pigs (80–100 kg) were studied. Animals were premedicated with intramuscular midazolam (0.5 mg/kg) and atropine (0.5 mg) and anesthetized with an injection of propofol (2 to 4 mg/kg) and fentanyl (1 to 2 μg/kg) followed by continuous infusion of propofol (15 to 25 mg·kg⁻¹·h⁻¹) and fentanyl (1.5 μg·kg⁻¹·h⁻¹). After tracheal intubation, pigs were mechanically ventilated in a volume-controlled mode with a FIO₂ of 0.5. Respiratory rate was set at 13/min and tidal volume at 10 ml/kg. Baseline crystalloid (standard lactated Ringer solution) infusion was 5 ml·kg⁻¹·h⁻¹.
All animals were monitored with a radial arterial catheter (28) that was placed after induction of general anesthesia. After sternotomy and pericardectomy, an ultrasonic flow probe was placed with an acoustic coupling agent on the ascending aorta and another ultrasonic flow probe was placed on the inferior vena cava (IVC), at the junction with the right atrium (T402 model, Transonic System, Ithaca, NY). The pericardium was then carefully opposed with stay sutures and the sternum was closed. A 9- Fr. Intro-Flex Percutaneous Sheath Introductor Kit (Edwards Lifesciences, Irvine, CA) was placed in the left femoral vein to induce hemorrhage and a central line was placed in the right internal jugular vein. A Swan-Ganz pulmonary artery catheter was inserted through the internal jugular vein to the pulmonary artery (Edwards Lifesciences).

All data were digitized and captured using a laptop computer, through a data acquisition card (DAQCard 6036e, National Instruments, Austin, TX). The sampling rate was 500 Hz. Data analysis was conducted on MatLab (Mathworks, Natick, MA). All the data shown in the tables are averaged over a 20-s period of time.

Study protocol. The protocol was started after the preparation of the animals. Animals were studied at two distinct stages. The first stage was a preload-independent stage where the heart was brought to the plateau of the Frank-Starling relationship. This was achieved by increasing cardiac output by successive volume expansion using 6% hydroxyethyl starches (HES) (Voluven, Fresenius Kabi, Germany). For this stage, cardiac output was first measured at baseline using the aortic ultrasonic flow probe. We then performed a volume expansion consisting of 500 ml of HES over a 15-min period of time. If cardiac output increased by less than 15%, we stopped volume expansion. If it increased by more than 15%, we performed further volume expansion consisting in 250 ml of HES until cardiac output increased by less than 10%. At this stage, we considered that cardiac output had reached the plateau of the Frank-Starling relationship and this constituted a preload-independent stage. The second stage was a preload-dependent stage where we brought the heart to the steep portion of the Frank-Starling relationship. This was achieved by a volume expansion consisting of 500 ml of HES over a 60-min period of time.

At each stage of the protocol, phenylephrine boluses were given intravenously at four different doses: 0.5, 1.0, 2.0, and 4.0 mg/kg. The order of these doses was randomly selected. All hemodynamic data were measured: systolic (SAP), diastolic arterial pressure (DAP) and MAP, central venous pressure (CVP), heart rate, respiratory variations in pulse pressure (PPV) from the arterial pressure waveform, stroke volume variation (SVV) from the aortic flow probe, cardiac output from the aortic flow probe (COfp) and the pulmonary artery catheter (COpac), left ventricular SV (with the aortic ultrasonic flow probe), and venous flow in the IVC with the ultrasonic IVC flow probe (IVCf).

COpac was measured by thermodilution, using the average of five successive measurements obtained by injection of 10 ml of dextrose at room temperature randomly during respiratory cycle.

Pulse pressure (PP) was defined as the difference between systolic and diastolic arterial pressure obtained from the arterial pressure waveform.

Maximal (PPmax) and minimal (PPmin) values were determined over the same respiratory cycle. PPV was then calculated as (15): PPV = (PPmax — PPmin)/[PPmax + PPmin]/2. The measurements were repeated on three consecutive respiratory cycles and averaged for statistical analysis.

Maximal (SVmax) and minimal (SVmin) values were determined over the same respiratory cycle from the aortic flow probe signal. SVV was then calculated as SVV = (SVmax — SVmin)/[(SVmax + SVmin)/2]. The measurements were repeated on three consecutive respiratory cycles and averaged for statistical analysis.

Statistical analysis. All data are presented as mean ± SD. Changes in hemodynamic variables induced by volume expansion were assessed using a nonparametric Mann-Whitney U test for unpaired data (such as comparison between responders and nonresponders to volume expansion) or Wilcoxon rank sum test for paired data (such as comparison between before and after volume expansion or between each steps of the protocol). Changes in cardiac output (COfp) induced by successive phenylephrine boluses were assessed using a one-way repeated measures ANOVA followed by a post hoc Tukey’s honestly significant test.

The effects of phenylephrine boluses on SV were divided into two groups according to the change in SV induced by phenylephrine bolus (increase in SV vs. decrease in SV). Receiver operating characteristic (ROC) curve was generated for PPV varying the discriminating threshold of this parameter, and area under the ROC curve was reoptimized preload using the protocol described above but we started with a 250 ml bolus of HES.

After the phenylephrine boluses were given, a phenylephrine drip was started at 0.5 μg·kg⁻¹·min⁻¹. This dose was maintained for 5 min and then doubled every 5 min until MAP increased by more than 20%.

This set of continuous phenylephrine administration was performed at the preload-independent stage and at the preload-dependent stage.

At each step of the protocol the following hemodynamic variables were measured: systolic (SAP), diastolic arterial pressure (DAP) and MAP, central venous pressure (CVP), heart rate, respiratory variations in pulse pressure (PPV) from the arterial pressure waveform, stroke volume variation (SVV) from the aortic flow probe, cardiac output from the aortic flow probe (COfp) and the pulmonary artery catheter (COpac), left ventricular SV (with the aortic ultrasonic flow probe), and venous flow in the IVC with the ultrasonic IVC flow probe (IVCf).

Table 1. Impact of phenylephrine boluses on hemodynamic variables during the preload-independent stage

<table>
<thead>
<tr>
<th>Phenylephrine</th>
<th>Cardiac output</th>
<th>Stroke volume</th>
<th>IVC f low</th>
<th>Heart rate</th>
<th>SAP</th>
<th>DAP</th>
<th>MAP</th>
<th>CVP</th>
<th>SVR</th>
<th>PPV</th>
<th>SVV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 μg/kg</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6.6 ± 0.8</td>
<td>6.5 ± 1.0</td>
<td>7.1 ± 0.8</td>
<td>6.7 ± 0.9*</td>
<td>6.9 ± 1.0</td>
<td>6.4 ± 1.1*</td>
<td>7.0 ± 0.8</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6.8 ± 0.8</td>
<td>6.2 ± 1.1*</td>
<td>7.2 ± 0.7</td>
<td>6.1 ± 0.9*</td>
<td>7.1 ± 0.4</td>
<td>5.9 ± 0.8*</td>
<td>6.9 ± 0.4</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
| 105 ± 6       | 112 ± 6*       | 104 ± 6       | 116 ± 5*  | 104 ± 9    | 119 ± 8* | 104 ± 7
| 59 ± 4        | 67 ± 5*        | 57 ± 5        | 72 ± 4*   | 59 ± 5     | 77 ± 7*  | 58 ± 6
| 73 ± 5        | 81 ± 4*        | 72 ± 5        | 87 ± 4*   | 72 ± 6     | 91 ± 7*  | 72 ± 6
| 800 ± 109     | 923 ± 160*     | 754 ± 110     | 968 ± 184*| 745 ± 105  | 1,045 ± 217*| 738 ± 80
| 11 ± 3        | 9 ± 2*         | 9 ± 2         | 7 ± 2*    | 10 ± 3     | 7 ± 1*   | 10 ± 3
| 12 ± 3        | 10 ± 2*        | 10 ± 2        | 8 ± 1*    | 10 ± 2     | 8 ± 2*   | 11 ± 3

Data are presented as mean ± SD. FP, flow probe; PAC, pulmonary artery catheter; IVC, inferior vena cava; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CVP, central venous pressure; SVR, systemic vascular resistances; PPV, pulse pressure variation; SVV, stroke volume variation. *P < 0.05.

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calculated (MedCalc 8.0.2.0, MedCalc Software, Mariakerke, Belgium). A P value < 0.05 was considered as statistically significant. All statistical analyses were performed using SPSS 13.0 for Windows, SPSS, Chicago, IL.

RESULTS

Effects of preload augmentation on hemodynamic variables. At baseline, after experimental preparation, COfp was 4.93 ± 0.99 l/min; IVCf was 3.35 ± 0.47 l/min; heart rate was 79 ± 7 beats/min; systolic, diastolic, and MAP were 82 ± 9 mmHg, 47 ± 2 mmHg, and 59 ± 4 mmHg, respectively; PPV was 17 ± 6%; SVV was 22 ± 5%; and central venous pressure was 6 ± 1 mmHg. On average 1,250 ± 216 ml of HES was given to reach the preload-independent stage (plateau of the Frank-Starling relationship) where CO was 7.04 ± 1.24 l/min (P < 0.01 compared with baseline); IVC flow was 4.94 ± 0.89 l/min (P < 0.01); heart rate was 73 ± 6 beats/min (P < 0.01); systolic, diastolic, and MAP were 100 ± 7 mmHg, 55 ± 5 mmHg, and 70 ± 5 mmHg (P < 0.01); respectively; PPV was 9 ± 3% (P < 0.01); SVV was 8 ± 2% (P < 0.01); and central venous pressure was 10 ± 1 mmHg (P < 0.01).

Effects of phenylephrine bolus at the preload-independent stage. At the preload-independent stage, phenylephrine boluses, irrespective of the dose, induced significant increases in mean arterial pressure, cardiac output, and inferior vena cava flow. Phenylephrine induced significant increases in MAP and significant decreases in CO and IVCf. These effects are larger when the phenylephrine dose is increased. Red lines show the average changes, blue lines show the individual changes.

Table 2. Time for mean arterial pressure, cardiac output, and inferior vena cava flow to reach maximum and minimum values after phenylephrine boluses at preload-independent stage

<table>
<thead>
<tr>
<th>Phenylephrine 4 µg/kg</th>
<th>Phenylephrine 2 µg/kg</th>
<th>Phenylephrine 1 µg/kg</th>
<th>Phenylephrine 0.5 µg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time for MAP to reach its maximum value</td>
<td>16.1 ± 3.7</td>
<td>15.5 ± 4.0</td>
<td>14.0 ± 4.3</td>
</tr>
<tr>
<td>Time for CO to reach its minimum value</td>
<td>16.5 ± 6.1</td>
<td>15.7 ± 4.5</td>
<td>14.5 ± 4.2</td>
</tr>
<tr>
<td>Time for IVCf to reach its minimum value</td>
<td>28.0 ± 10.*</td>
<td>26.7 ± 8.4*</td>
<td>28.4 ± 9.7*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. CO, cardiac output; IVCf: inferior vena cava flow. *P < 0.05 compared with CO.

Fig. 1. Impact of phenylephrine bolus on cardiac output and inferior vena cava flow measured with flow probe and mean arterial pressure during the preload-independent stage. Changes in cardiac output (CO) in the inferior vena cava flow (IVCf) (both measured with ultrasonic flow probe) and in the mean arterial pressure induced by different phenylephrine boluses. Phenylephrine induced significant increases in MAP and significant decreases in CO and IVCf. These effects are larger when the phenylephrine dose is increased. Red lines show the average changes, blue lines show the individual changes.
arterial pressure and central venous pressure as well as significant decreases in CO and in IVCf (Table 1). At the same time, we observed no statistically significant changes in heart rate. Time for MAP, COFP, and IVCf to reach maximum and minimum values after phenylephrine boluses are shown in Table 2.

The impact of phenylephrine on MAP and COFP was greater at a higher phenylephrine doses, suggesting that the effects of

Table 3. Impact of phenylephrine bolus on cardiac output and inferior vena cava flow measured with flow probe, and mean arterial pressure during the preload-dependent stage

<table>
<thead>
<tr>
<th></th>
<th>Phenylephrine 0.5 µg·kg⁻¹</th>
<th>Phenylephrine 1 µg·kg⁻¹</th>
<th>Phenylephrine 2 µg·kg⁻¹</th>
<th>Phenylephrine 4 µg·kg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output FP, l/min</td>
<td>Before: 4.3 ± 0.8</td>
<td>After: 4.6 ± 0.8*</td>
<td>Before: 4.3 ± 1.1</td>
<td>After: 4.9 ± 1.1*</td>
</tr>
<tr>
<td>Cardiac output PAC, l/min</td>
<td>Before: 4.2 ± 0.8</td>
<td>After: 4.6 ± 0.8*</td>
<td>Before: 4.0 ± 1.0</td>
<td>After: 4.6 ± 1.0*</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>Before: 47 ± 7</td>
<td>After: 50 ± 7*</td>
<td>Before: 48 ± 9</td>
<td>After: 55 ± 9*</td>
</tr>
<tr>
<td>IVC flow, l/min</td>
<td>Before: 3.3 ± 0.4</td>
<td>After: 3.4 ± 0.5*</td>
<td>Before: 3.1 ± 0.7</td>
<td>After: 3.6 ± 0.8*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>Before: 91 ± 17</td>
<td>After: 89 ± 13</td>
<td>Before: 88 ± 9</td>
<td>After: 93 ± 8*</td>
</tr>
<tr>
<td>SAP, mmHg</td>
<td>Before: 60 ± 13</td>
<td>After: 69 ± 15*</td>
<td>Before: 59 ± 10</td>
<td>After: 70 ± 12*</td>
</tr>
<tr>
<td>DAP, mmHg</td>
<td>Before: 34 ± 7</td>
<td>After: 39 ± 8*</td>
<td>Before: 34 ± 5</td>
<td>After: 40 ± 6*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>Before: 43 ± 9</td>
<td>After: 49 ± 11*</td>
<td>Before: 42 ± 6</td>
<td>After: 50 ± 8*</td>
</tr>
<tr>
<td>CVP, mmHg</td>
<td>Before: 5 ± 2</td>
<td>After: 5 ± 2</td>
<td>Before: 5 ± 2</td>
<td>After: 6 ± 2*</td>
</tr>
<tr>
<td>SVR, dyn·s/cm⁵</td>
<td>Before: 713 ± 173</td>
<td>After: 840 ± 209*</td>
<td>Before: 721 ± 187</td>
<td>After: 879 ± 243*</td>
</tr>
<tr>
<td>PPV, %</td>
<td>Before: 44 ± 9</td>
<td>After: 35 ± 8*</td>
<td>Before: 44 ± 14</td>
<td>After: 34 ± 8*</td>
</tr>
<tr>
<td>SVV, %</td>
<td>Before: 45 ± 9</td>
<td>After: 39 ± 8*</td>
<td>Before: 48 ± 11</td>
<td>After: 38 ± 10*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. *P < 0.05.
phenylephrine on CO and MAP are dose dependent (Fig. 1). Figure 2 shows the raw MAP, CO, and IVC flow data after phenylephrine bolus in an illustrative animal at the preload-independent stage.

**Effects of hemorrhage on hemodynamic variables.** After hemorrhage, at the preload-dependent stage, we observed a decrease in CO (from 6.85 ± 1.05 to 4.08 ± 1.07 l/min; \( P < 0.01 \)); IVC flow (from 4.81 ± 0.44 to 3.03 ± 0.85 l/min; \( P < 0.01 \)); systolic, diastolic, and MAP (from 102 ± 9 to 52 ± 4, from 55 ± 7 to 30 ± 2, and from 70 ± 7 to 37 ± 2 mmHg, respectively; \( P < 0.01 \) for all); and CVP (from 8 ± 2 to 5 ± 2 mmHg; \( P < 0.01 \)). At the same time, we observed an increase in PPV (from 12 ± 3 to 48 ± 14%; \( P < 0.01 \)).

**Effects of phenylephrine bolus at the preload-dependent stage.** At the preload-dependent stage, the phenylephrine boluses, irrespective of the dose, induced significant increases in arterial pressure, central venous pressure, CO, and IVC flow (Table 3). At the same time, we observed no changes in heart rate. Time for MAP, CO, and IVC to reach maximum and minimum values after phenylephrine boluses are shown in Table 4.

Moreover, the impact of phenylephrine on MAP and CO was also greater at a higher phenylephrine doses (Fig. 3) Figure 4 shows

**Table 4. Time for mean arterial pressure, cardiac output, and inferior vena cava flow to reach maximum and minimum values after phenylephrine boluses at preload-dependent stage**

<table>
<thead>
<tr>
<th>Phenylephrine 4 ( \mu )g/kg</th>
<th>Phenylephrine 2 ( \mu )g/kg</th>
<th>Phenylephrine 1 ( \mu )g/kg</th>
<th>Phenylephrine 0.5 ( \mu )g/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time for MAP to reach its maximum value</td>
<td>17.8 ± 3.5</td>
<td>17.3 ± 1.9</td>
<td>14.5 ± 2.9</td>
</tr>
<tr>
<td>Time for CO to reach its maximum value</td>
<td>52.3 ± 26.9†</td>
<td>52.2 ± 23.0†</td>
<td>49.3 ± 18.2†</td>
</tr>
<tr>
<td>Time for IVC to reach its maximum value</td>
<td>42.5 ± 28.8*</td>
<td>40.4 ± 19.4*</td>
<td>37.1 ± 20.0*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. *\( P < 0.05 \) compared with CO, †\( P < 0.05 \) compared with MAP.

![Image](http://jap.physiology.org/)

**Fig. 3. Impact of phenylephrine bolus on CO and IVC flow measured with flow probe and mean arterial pressure during the preload-dependent stage.** Changes in CO in the IVC flow (both measured with ultrasonic flow probe) and in the MAP induced by different phenylephrine boluses. Phenylephrine induced significant increases in MAP and increases in CO and IVC flow. These effects are more important when the phenylephrine dose is increased. Red lines show the average changes, blue lines show the individual changes.
the raw MAP, COfp, and IVCf data after phenylephrine bolus in an illustrative animal at the preload-dependent stage.

**Effects of continuous administration of phenylephrine.** At the preload-independent stage, the phenylephrine dose required to achieve a 20% increase in MAP was $0.69 \pm 0.26 \mu g \cdot kg^{-1} \cdot min^{-1}$. At this dose, MAP increased (from $74 \pm 13$ to $88 \pm 13$ mmHg; $P < 0.001$). We also observed small but statistically significant increases in COfp (from $6.3 \pm 1.2$ to $6.6 \pm 1.1$ l/min; $P = 0.027$) and CVP (from $8 \pm 1$ to $9 \pm 1$ mmHg; $P = 0.0001$), whereas we observed no changes in IVCf (from $4.4 \pm 0.6$ to $4.5 \pm 0.6$ l/min; $P = 0.19$). However, PPV and SVV were decreased (from $13 \pm 5$ to $10 \pm 2$% and from $14 \pm 5$ to $11 \pm 3$% respectively; $P < 0.05$ for both). It is worth noting that PPV and SVV before phenylephrine drip were higher than before phenylephrine bolus, which may explain the little increase in COfp.

At the preload-dependent stage, the phenylephrine dose required to achieve a 20% increase in MAP was $0.88 \pm 0.23 \mu g \cdot kg^{-1} \cdot min^{-1}$. At this dose, MAP increased (from $54 \pm 10$ to $67 \pm 12$ mmHg; $P < 0.001$) and PPV and SVV decreased (from $38 \pm 6$ to $24 \pm 5$% and from $42 \pm 6$ to $33 \pm 5$% respectively; $P < 0.05$ for both). We also observed an increase in COfp (from $4.4 \pm 0.8$ to $4.7 \pm 0.9$ l/min; $P = 0.0004$), IVCf (from $3.4 \pm 0.5$ to $3.5 \pm 0.5$ l/min; $P = 0.004$), and in CVP (from $6 \pm 1$ to $7 \pm 2$ mmHg; $P = 0.0001$).

**Ability of PPV and SVV to predict the effects of phenylephrine bolus on SV.** Overall, 64 phenylephrine boluses were given. Thirty-five boluses (55.2%) induced an increase in SV. The range of increases was from 0.2% to 27.2%. Twenty-nine boluses (47.8%) induced a decrease in SV. The range of decreases was from −30.3% to −0.6%. In situations where SV increased after phenylephrine administration, we observed a higher PPV at baseline compared with situation where SV decreases (36 ± 11% vs. 8 ± 2%; $P < 0.001$; Fig. 5). A threshold PPV value of 16.4% allowed discrimination between phenylephrine-induced increase in SV and phenylephrine-induced decrease in SV with a 94% sensitivity and a 100% specificity. The area under the curve for the accuracy of PPV to predict an increase in SV was 0.97 ± 0.04. A threshold SVV value of 17.2% allowed discrimination between phenylephrine-induced increase in SV and phenylephrine-induced decrease in SV with a 97% sensitivity and a 100% specificity. The area under the curve for the accuracy of SVV to predict an increase in SV was 0.98 ± 0.04.

Fig. 4. Raw data showing arterial pressure, CO, and IVCf in 1 pig after a 2 μg/kg phenylephrine bolus at the preload-dependent stage. As shown in this figure, phenylephrine bolus induced an increase in arterial pressure followed by an increase in IVC and an increase in CO.
observed that at the preload-independent stage, phenylephrine left ventricular afterload. When analyzing timing of events, we suggesting that the effect of phenylephrine was primarily on over, this effect was related to a decrease in IVC flow, cardiac output when the heart is preload independent. More-

present study because phenylephrine administration decreased output would be revealed. That is what we observed in the relationship (where the heart is said to be preload independent), phenylephrine boluses induced significant increases in IVC flow and, subsequently, in cardiac output. In this situation, the amount of blood mobilized by the venaconstrictive effect of phenylephrine was able to increase cardiac output (6, 7). It is worth emphasizing that most of the increase in COpac (which reflects the total right ventricular cardiac output) was related to the increase in IVCf, suggesting that the increase in preload induced by phenylephrine at this stage is mostly mediated by an unloading of the splanchnic reservoir. When analyzing timing of events, we observed that at the preload-dependent stage, phenylephrine boluses induced first an increase in arterial pressure (∼18 s after phenylephrine bolus; Table 4 and Fig. 4), followed by an increase in IVC flow (∼40 s later) and then by an increase in cardiac output (∼50 s later; Table 4 and Fig. 4). Interestingly, these effects were all dose dependent, and in each situation the arterial pressure was increased. These effects were related to changes in SV and not to changes in heart rate. In fact, phenylephrine boluses induced no statistically significant changes in heart rate despite a trend toward reduction. This may be related to an anesthetic effect which may counteract the expected decrease in heart rate following the increase in blood pressure induced by phenylephrine or simply related to the limited statistical power of this study to detect small changes in heart rate. Finally, the effects of phenylephrine on cardiac output disappear when phenylephrine is given continuously. This suggests that the bolus effect is mediated by an unloading of the splanchnic reservoir. One may also postulate that this may be related to tachyphylaxis to the drug but this cannot be demonstrated here.

Our results have several physiological and clinical implications. First, they help to better understand the effects of a pure vasoconstrictor on global hemodynamics. In an experiment conducted in dogs, Nouira et al. (20) were able to show that norepinephrine induces a significant increase in cardiac output during severe hypovolemia. In their study, the authors suggested that the increase was related to the shift of blood from unstressed to stressed volume. However, their experiment did not test the effects of norepinephrine on cardiac output when the heart is preload independent (20) and IVC flow was not measured. Our study specifically focused on a pure α1-agonist and we were able to demonstrate that these effects are mainly dependent on the vasoconstrictive effect and on the position on the Frank-Starling relationship. Second, our results may help to better understand the relationship between global and regional hemodynamics (13). Most clinicians still rely on arterial pressure alone during intraoperative hemodynamic management in patients undergoing high-risk surgery (3). However, several studies have clearly showed that cardiac output optimization can improve outcome in this setting and it is now well understood that arterial pressure optimization does not guarantee that oxygen delivery is optimal (8, 21, 25, 26). Our study underlines the complexity of this relationship by demonstrating that the effect of phenylephrine on cardiac output can vary depending on the volume status. This again emphasizes the importance of cardiac output monitoring and/or of end organ perfusion for

Fig. 5. Pulse pressure variation (PPV) values at baseline according to situations where stroke volume increases or decreases after phenylephrine bolus. In situations where stroke volume increased after phenylephrine administration, we observed a significantly higher respiratory variations in pulse pressure at baseline compared with situation where stroke volume decreases. A threshold PPV value of 16.4% (horizontal dashed line) allowed discrimination between phenylephrine-induced increase in stroke volume and phenylephrine-induced decrease in stroke volume with a 94% sensitivity and a 100% specificity.

DISCUSSION

The results from this animal study demonstrate that the impact of phenylephrine on cardiac output is related to the position of the heart on the Frank-Starling relationship (preload dependence) and is dose dependent. When the heart is preload independent, phenylephrine boluses induce a decrease in cardiac output. When the heart is preload dependent, phenylephrine boluses induce an increase in cardiac output. These changes in cardiac output are closely related to changes in venous flow induced by phenylephrine administration. Interestingly, these effects disappear when phenylephrine is given continuously, suggesting that the bolus effect is mediated by an unloading of the splanchnic reservoir. Finally, the effects of a phenylephrine bolus on SV can be predicted by pulse pressure variation and stroke volume variation.

Phenylephrine is widely used during anesthesia management (29, 30). However, its effects on global and regional hemodynamics are not clearly understood and its impact on cardiac output has been extensively discussed (13). In the present study, we postulated that the effects of phenylephrine on cardiac output may depend on the volume status and on where the heart is functioning on the Frank-Starling relationship (preload dependent or independent). On the plateau of this relationship (where the heart is said to be preload independent), an increase in preload will not induce any change in cardiac output because the heart is already preload optimized. Then, only the afterload effect responsible for a decrease in cardiac output would be revealed. That is what we observed in the present study because phenylephrine administration decreased cardiac output when the heart is preload independent. Moreover, this effect was related to a decrease in IVC flow, suggesting that the effect of phenylephrine was primarily on left ventricular afterload. When analyzing timing of events, we observed that at the preload-independent stage, phenylephrine boluses induced simultaneous increase in arterial pressure and decrease in cardiac output (occurring ∼16 s after phenylephrine bolus; Table 2 and Fig. 2), whereas it induced a decrease in IVC flow ∼28 s after the bolus. During hypovolemia, when the heart is working on the steep portion of the Frank-Starling relationship (preload dependent), phenylephrine boluses induced significant increases in IVC flow and, subsequently, in cardiac output. In this situation, the amount of blood mobilized by the venaconstrictive effect of phenylephrine was able to increase cardiac output (6, 7). It is worth emphasizing that most of the increase in COpac (which reflects the total right ventricular cardiac output) was related to the increase in IVCf, suggesting that the increase in preload induced by phenylephrine at this stage is mostly mediated by an unloading of the splanchnic reservoir. When analyzing timing of events, we observed that at the preload-dependent stage, phenylephrine boluses induced first an increase in arterial pressure (∼18 s after phenylephrine bolus; Table 4 and Fig. 4), followed by an increase in IVC flow (∼40 s later) and then by an increase in cardiac output (∼50 s later; Table 4 and Fig. 4). Interestingly, these effects were all dose dependent, and in each situation the arterial pressure was increased. These effects were related to changes in SV and not to changes in heart rate. In fact, phenylephrine boluses induced no statistically significant changes in heart rate despite a trend toward reduction. This may be related to an anesthetic effect which may counteract the expected decrease in heart rate following the increase in blood pressure induced by phenylephrine or simply related to the limited statistical power of this study to detect small changes in heart rate. Finally, the effects of phenylephrine on cardiac output disappear when phenylephrine is given continuously. This suggests that the bolus effect is mediated by an unloading of the splanchnic reservoir. One may also postulate that this may be related to tachyphylaxis to the drug but this cannot be demonstrated here.

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hemodynamic monitoring and management (19). Third, our results also help to better understand how a cardiac output monitor should behave in the setting of vasopressors administration (4, 22, 27). Several authors recently suggested that the accuracy of pulse contour analysis devices, which are frequently used during anesthesia (3), are negatively impacted by vasopressor administration (5, 9, 11, 14, 18). In our study, we used the gold standard for cardiac output measurement (ultrasonic flow probe). Studies using technologies such as esophageal Doppler or pulse contour analysis (calibrated or uncalibrated) may actually be impacted by the device itself when it comes to accurate measurement of cardiac output (14).

Finally, our data suggest that PPV and SVV could potentially help to predict the increase in SV induced by phenylephrine bolus. In the present study, when PPV was more than 16.4%, SV was more likely to increase after a phenylephrine bolus, whereas it was more likely to decrease when PPV was less than 16.4%. Interestingly, high PPV values also predict fluid responsiveness (2). It then raises the question of whether vasoconstrictors or volume expansion should be used in this setting (24). This may depend on arterial pressure or on more sophisticated variables such as the ratio between SVV and PPV, which can provide information on arterial compliance (17, 23). For note, PPV and SVV measured in this study are manually calculated. Whether the same prediction could be obtained using a specific algorithm for PPV or SVV measurement still has to be proven.

Study limitations. Our study comes with some limitations. First, we did not measure the flow in the superior vena cava. This is because the IVC flow represents the vast majority of the venous return and is more likely to reflect the potential impact of phenylephrine on the splanchnic venous reservoir. Moreover, we also present the pulmonary artery flow obtained using a specific algorithm for PPV or SVV measurement still has to be proven.

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First, we did not measure the flow in the superior vena cava. This is because the IVC flow represents the vast majority of the venous return and is more likely to reflect the potential impact of phenylephrine on the splanchnic venous reservoir. Moreover, we also present the pulmonary artery flow obtained using the Swan Ganz catheter, showing that most of the increase in venous return is induced by the increase in the IVC flow. Second, we did not control cardiac contractility during the study. It is possible that changes in cardiac contractility during the preload-dependent stage had an impact. However, this would not invalidate our findings because this would reflect what happens in the clinical setting. Finally, we did not measure regional circulations. It is possible that phenylephrine induces different hemodynamic effects depending on the organ. Furthermore, phenylephrine increasing MAP and CO at the preload-dependent stage does not guarantee that tissue oxygenation is actually increased. Our study does not answer this specific question and further studies are required to investigate this hypothesis.

As a conclusion, our study demonstrates that the impact of phenylephrine bolus on cardiac output is related to the position of the heart on the Frank-Starling relationship (preload dependence) and is dose dependent. When the heart is working on the plateau of the Frank-Starling relationship, phenylephrine bolus induces a decrease in cardiac output. When the heart is working on the steep portion of the Frank-Starling relationship, phenylephrine bolus induces an increase in cardiac output.

DISCLOSURES

Edwards Lifesciences provided the software, hardware, and animals for the study. All salaries of Maxime Cannesson, Trung Vu, and Guo Chen were paid solely by the Department of Anesthesiology and Perioperative Care. All data were analyzed at the Department of Anesthesiology and Perioperative Care.

AUTHOR CONTRIBUTIONS

Author contributions: M.C. and F.H. conception and design of research; M.C., Z.J., G.C., and F.H. performed experiments; M.C., Z.J., T.Q.V., and F.H. analyzed data; M.C., G.C., T.Q.V., and F.H. interpreted results of experiments; M.C. and Z.J. prepared figures; M.C., Z.J., and F.H. drafted manuscript; M.C., Z.J., G.C., T.Q.V., and F.H. edited and revised manuscript; M.C., Z.J., G.C., T.Q.V., and F.H. approved final version of manuscript.

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