Opioids are widely used as analgesics to supplement anesthesia for tolerance of surgical procedures. In particular, fentanyl (a highly potent and fast-acting morphine-like analgesic) has been widely used in combination with the hypnotic drug propofol.

Propofol is a short-acting hypnotic that has been used in rabbits for short-term anesthesia as well as for the induction or maintenance of anesthesia, but it does not provide a substantial degree of analgesia. Propofol reduces both cardiac index and MAP. The direct effects of opioids on cardiac contractility are poorly understood and controversial. Opioids can indirectly alter cardiac function via inhibitory actions on the autonomic nervous system or CNS. Furthermore, opioids may directly alter cardiac contractility via activation of opioid receptors and by membrane interactions because of their chemical properties and structures. Fentanyl has little or no effect on myocardial contractility or exerts a negative inotropic effect. However, the cardiodepressant action may be cumulative if a combination of propofol and fentanyl is used. Therefore, the study reported here was conducted to investigate the short-term cardiovascular effects of fen-
tanyl in rabbits anesthetized by the use of TIVA with propofol.

**Materials and Methods**

**Animals**—Six healthy female New Zealand White rabbits were used in the study. Mean ± SD body weight was 3.82 ± 0.52 kg, and rabbits were between 10 and 16 weeks of age. Rabbits were obtained from a colony free of respiratory pathogens. They were housed separately in cages on dust-free wooden shavings. Animals were housed separately in cages on dust-free wooden shavings. All animals were weighed and clinically examined for behavioral, respiratory, and cardiovascular variables. Experiments were conducted between 9 AM and noon. A local anesthetic was applied topically to the skin of the left ear of each rabbit; a catheter (1.1 × 33 mm) was inserted in the median auricular artery for arterial blood pressure measurements, and another catheter (0.9 × 25 mm) was inserted in the lateral auricular vein. Anesthesia was induced by IV administration of 1% propofol (4.0 to 8.0 mg/kg). After the swallowing reflex was lost, the trachea was intubated (inner diameter of endotracheal tube, 2.5 to 3.0 mm) without direct laryngeal observation. Each rabbit was shaved in preparation for ultrasonographic measurements and placed on a heating pad to maintain body temperature at 37° to 38°C.

Anesthesia—On the day of the experiment, each rabbit was weighed and clinically examined for behavior, respiration, and cardiovascular variables. Experiments were conducted between 9 AM and noon. A local anesthetic was applied topically to the skin of the left ear of each rabbit; a catheter (1.1 × 33 mm) was inserted in the median auricular artery for arterial blood pressure measurements, and another catheter (0.9 × 25 mm) was inserted in the lateral auricular vein. Anesthesia was induced by IV administration of 1% propofol (4.0 to 8.0 mg/kg). After the swallowing reflex was lost, the trachea was intubated (inner diameter of endotracheal tube, 2.5 to 3.0 mm) without direct laryngeal observation. Each rabbit was shaved in preparation for ultrasonographic measurements and placed on a heating pad to maintain body temperature at 37° to 38°C.

Ultrasonographic measurements of the left common carotid artery and 2-dimensional guided M-mode echocardiography were conducted with the rabbits positioned in dorsal recumbency. For ultrasonography of the abdominal aorta, the rabbits were positioned in right lateral recumbency. Anesthesia was maintained with a continuous IV infusion of 2% propofol (1.2 to 1.3 mg/kg/min). With this dose, a stable and light plane of anesthesia was maintained, which was characterized by good muscle relaxation and hypnosis with stable cardiovascular variables.

Rabbits were ventilated with 100% oxygen at a rate of 29 to 32 breaths/min and peak ventilation pressure of 8 to 10 cm H2O. Monitoring of MAP, HR, PETCO2, and SpO2 was conducted by use of a patient monitor.

**Experimental protocol**—Three bolus injections of fentanyl (0.0053 mg/kg, IV) were administered to each rabbit during TIVA with propofol. No other anesthetic, analgesic, or surgical stimulation was applied during the experiment. Vascular and hemodynamic alterations induced by the first injection were recorded by ultrasonography of the left common carotid artery. After the second fentanyl injection, echocardiography of the heart was used to investigate alterations of cardiac variables. Finally, ultrasonographic indicators were measured at the abdominal aorta after the third injection. Therefore, the ultrasonographic examination was divided into 3 sections.

Each section of the experiment began with measurement of baseline values. Baseline measurements at the various locations were determined only after a stable anesthetic plane was evident, which was defined as mean HR, MAP, PETCO2, and ultrasonographic variables with no obvious fluctuation (ie, ± 5% of initial values) for 5 minutes. Baseline ultrasonographic data were measured at the carotid artery before the first injection, at the heart before the second injection, and at the abdominal aorta before the third injection.

After each fentanyl injection, vascular and echocardiographic images were recorded at 30 seconds, at 1 minute, and at 1-minute intervals for up to 10 minutes. The injection volume was adjusted with saline (0.9% NaCl) solution to achieve 0.6 mL/bolus, and each injection was administered during a period of 20 seconds. Time 0 was defined as the end of each fentanyl injection. During ultrasonographic examinations of the left common carotid artery and abdominal aorta, vessel images and velocity spectra were recorded for subsequent determination of vessel diameter, psBFV, minimum diastolic blood flow velocity, edBFV, and time-average blood flow velocity.

The RI of the vessels, which was derived from psBFV and edBFV, is an important index that reflects the vascular resistance distal to the point of Doppler imaging. The RI was calculated by use of the following equation**: RI = (psBFV – edBFV)/psBFV. The PI was also used to characterize peripheral vascular resistance in accordance with the following equation**: PI = (psBFV – mdBFV)/Vave, where mdBFV is minimum diastolic blood flow velocity and Vave is time-average blood flow velocity. Mean volumetric flow in the abdominal aorta and left common carotid artery was calculated as Vave × π × r², where r is the vessel radius.

**Echocardiographic investigation** in the second section of the study measured fractional shortening, which was calculated by use of the following equation**: (LVEDD – LVESD)/(LVEDD) × 100, where LVEDD is left ventricular end-diastolic diameter and LVESD is left ventricular end-systolic diameter.

![Figure 1](image-url) —Doppler ultrasonographic image of the left carotid artery of a representative rabbit. Blood velocity spectrum of the left carotid artery, psBFV, and edBFV are evident. The scale for the y-axis indicates blood flow velocity in meters per second, and the scale for the x-axis indicates time in seconds.
For the ECG, a recording speed of 25 mm/s was used. Tracings were evaluated for rhythm disturbances and changes in the general configuration of complexes. Measurement of interval durations (eg, R–R and Q–T intervals) was completed from lead II data. From ECG recordings, which were derived from measurements at the left common carotid artery and heart, the QTc was calculated from the Q–T and R–R intervals by use of the following correction equation: QTc = QT × (RR−0.3), where QT is the sum of the durations of venous depolarization (QRS complex) and repolarization (ST–T interval), and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex. Hemodynamic data, including HR, MAP, SpO2, PETCO2, body temperature, and the plethysmographic amplitude, were recorded concurrently during each section of the ultrasonographic examination.

Ultrasonography of the vessels and heart—Vascular imaging was conducted by use of a 10-MHz linear transducer. For echocardiography, a 10-MHz sector transducer was used. The transducers were used in conjunction with an ultrasonographic system. Vascular variables of the left common carotid artery and abdominal aorta were measured in accordance with a method described elsewhere. Doppler evaluations were conducted in pulse-wave mode. Recorded velocity spectra were assessed for quality on the basis of clarity of the visual and audible signal and then stored for subsequent measurement of psBFV, minimum diastolic blood flow velocity, edBFV, and time-average blood flow velocity (Figure 1). From these variables, the RI, PI, and mean volumetric flow were derived. Furthermore, 2-dimensional images of the vessel wall were assessed and stored for subsequent measurement of the luminal diameter between the leading edge of the innermost echogenic layer by cursor adjustment. For the echocardiographic assessment, a right parasternal view was used. Two-dimensional M-mode short-axis views at the level of the chorda tendinae were recorded for measurement of ventricular dimensions (left ventricular end-systolic and end-diastolic diameters). From these variables, fractional shortening of the left ventricle was derived.

Statistical evaluation—Mean ± SD values were reported for all data. Statistical comparisons were for an exploratory data analysis; thus, no correction of α error rate was considered. A value of α = 0.05 was used to determine significant differences for each statistical comparison.

To evaluate overall patterns for variables of interest, LMMs with monotonous (linear) or transient (quadratic) time effects were calculated. The LMM approach properly reflects the structure of repeated data and accounts for correlation between measurements within the same subjects. An autoregressive correlation structure (first order) as well as random effects for each rabbit was considered in the regression analysis. Effects of time were specified first by graphic assessment and verified by stepwise model derivation. When a significant effect of time was detected during LMM analysis, a post hoc Student t test for paired samples was used to assess differences between each time point during the 10-minute examination period and the baseline value. Furthermore, the Friedman test followed by Student t tests for paired samples was used to separately compare

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vessel diameter (mm)</th>
<th>psBFV (cm/s)</th>
<th>edBFV (cm/s)</th>
<th>RI</th>
<th>VFmean (mL/s)</th>
<th>PI</th>
<th>QTC (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMM†</td>
<td>Intercept</td>
<td>1.86†</td>
<td>69.61†</td>
<td>0.15†</td>
<td>0.079†</td>
<td>0.83†</td>
<td>2.89†</td>
</tr>
<tr>
<td></td>
<td>Time × coef</td>
<td>−0.0298</td>
<td>3.0690†</td>
<td>−0.9120†</td>
<td>0.0195†</td>
<td>0.0045</td>
<td>0.1450</td>
</tr>
<tr>
<td></td>
<td>Time2 × coef</td>
<td>0.0028</td>
<td>−0.2500†</td>
<td>0.0021†</td>
<td>−0.0004</td>
<td>−0.0190</td>
<td>0.1170</td>
</tr>
</tbody>
</table>

Table 1—The LMM variables and mean ± SD values for ultrasonographic evaluation of the left common carotid artery in anesthetized rabbits after injection of the first bolus of fentanyl (0.0053 mg/kg, IV), which was administered 16 minutes after onset of a continuous infusion of propofol (1.2 to 1.3 mg/kg/min).

Time (min)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Baseline</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.92 ± 0.11</td>
<td>1.84 ± 0.10</td>
<td>1.76 ± 0.08</td>
<td>1.74 ± 0.09</td>
<td>1.78 ± 0.10</td>
<td>1.77 ± 0.08</td>
<td>1.79 ± 0.06</td>
<td>1.82 ± 0.10</td>
<td>1.82 ± 0.10</td>
<td>1.85 ± 0.11</td>
<td>1.87 ± 0.11</td>
<td>1.82 ± 0.10</td>
</tr>
<tr>
<td>Vessel diameter (mm)</td>
<td>75.02 ± 22.08*</td>
<td>81.56 ± 21.08*</td>
<td>84.12 ± 25.86*</td>
<td>88.23 ± 27.21*</td>
<td>87.53 ± 22.59*</td>
<td>89.08 ± 25.39*</td>
<td>82.77 ± 28.05*</td>
<td>82.86 ± 19.02*</td>
<td>73.97 ± 8.50</td>
<td>74.00 ± 8.20</td>
<td>75.94 ± 8.94</td>
<td>75.94 ± 8.94</td>
</tr>
<tr>
<td>edBFV (cm/s)</td>
<td>0.79 ± 0.06*</td>
<td>0.82 ± 0.03</td>
<td>0.83 ± 0.05*</td>
<td>0.82 ± 0.04</td>
<td>0.84 ± 0.08a</td>
<td>0.83 ± 0.06a</td>
<td>0.83 ± 0.06a</td>
<td>0.83 ± 0.06a</td>
<td>0.80 ± 0.07</td>
<td>0.76 ± 0.08</td>
<td>0.77 ± 0.10</td>
<td>0.77 ± 0.10</td>
</tr>
<tr>
<td>RI</td>
<td>0.079†</td>
<td>0.0195†</td>
<td>0.0021†</td>
<td>0.0004</td>
<td>0.0021†</td>
<td>0.0004</td>
<td>0.0004</td>
<td>0.0004</td>
<td>0.0004</td>
<td>0.0004</td>
<td>0.0004</td>
<td>0.0004</td>
</tr>
<tr>
<td>VFmean (mL/s)</td>
<td>2.89†</td>
<td>0.1450</td>
<td>−0.0190</td>
<td>0.1170</td>
<td>0.1170</td>
<td>0.1170</td>
<td>0.1170</td>
<td>0.1170</td>
<td>0.1170</td>
<td>0.1170</td>
<td>0.1170</td>
<td>0.1170</td>
</tr>
<tr>
<td>PI</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
<td>296 ± 8</td>
</tr>
<tr>
<td>QTC (ms)</td>
<td>2.62 ± 1.47</td>
<td>2.96 ± 1.41</td>
<td>3.29 ± 1.35</td>
<td>3.45 ± 1.91</td>
<td>3.45 ± 1.91</td>
<td>3.45 ± 1.91</td>
<td>3.45 ± 1.91</td>
<td>3.45 ± 1.91</td>
<td>3.45 ± 1.91</td>
<td>3.45 ± 1.91</td>
<td>3.45 ± 1.91</td>
<td>3.45 ± 1.91</td>
</tr>
</tbody>
</table>

Time 0 was defined as the end of each fentanyl injection. Baseline measurements were obtained only after a stable anesthetic plane was evident, which was defined as mean HR, MAP, SpO2, PETCO2, and ultrasonographic variables with no obvious fluctuation (ie, ± 5% of initial values) for 5 minutes.

* The LMM with individual random effects and autoregressive correlation structure, which yielded the following equation: predicted value = intercept + (time × coef.) + (time × coef.), where coef. is the slope of the predicted value/1-minute increment and coef. is the additive change of predicted value in dependence on time squared (ie, minute2). †Value differs significantly (P < 0.05) from baseline value.

† Not determined.

a,b Within a column, values with different superscript letters differ significantly (P < 0.05).
related samples for equivalent time points after the first, second, and third bolus for the variables HR, MAP, SpO₂, PetCO₂, and body temperature. All statistical analyses were conducted with commercially available software.

**Results**

**Ultrasonography of the carotid artery**—Data for vascular ultrasonographic measurements of the left common carotid artery after injection of the first fentanyl bolus were determined (Table 1). The psBFV and RI had a significant increase immediately after injection; they remained significantly increased for 7 minutes. Additionally, edBFV significantly decreased, with a maximum decrease at 4 minutes after fentanyl injection. Changes were transient, but because results of the post hoc tests did not reveal significant values, effects were considered to be only minor. On the basis of results for the LMM, vessel diameter, time-average volumetric blood flow, and PI of the left common carotid artery were not significantly changed after injection of the first fentanyl bolus.

**Ultrasonography of the abdominal aorta**—Data for vascular ultrasonographic measurements of the abdominal aorta after the third injection of fentanyl were determined (Table 2).

Luminal diameter of the abdominal aorta was significantly decreased after injection of the fentanyl bolus. The psBFV and PI were significantly increased, with a maximum at 1 minute and 5 minutes after fentanyl injection, respectively. In particular, changes of PI were only minor because results of post hoc tests did not reveal significant values. Mean volumetric flow significantly decreased from baseline immediately after injection of the fentanyl bolus and again 3 to 6 minutes and 10 minutes after injection. On the basis of results of the mixed-model regression, edBFV and RI of the abdominal aorta were not significantly changed after injection of the fentanyl bolus.

**Echocardiographic assessment**—Selected echocardiographic variables measured after injection of the second bolus of fentanyl were determined (Table 3). Fractional shortening decreased for 2 minutes, and left ventricular end-systolic diameter increased after 2 minutes. However, on the basis of the results of the mixed-model regression, no significant changes of echocardiographic variables were detected.

**ECG recordings for QTc interval**—The QTc values were determined for measurements at the left common carotid artery after injection of the first fentanyl bolus and for measurements of the heart after injection of the second fentanyl bolus (Tables 1 and 2).

---

Table 2—The LMM variables and mean ± SD values for ultrasonographic evaluation of the abdominal aorta in anesthetized rabbits after injection of the third bolus of fentanyl, which was administered 65 minutes after onset of a continuous infusion of propofol.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vessel diameter (mm)</th>
<th>psBFV (cm/s)</th>
<th>edBFV (cm/s)</th>
<th>RI</th>
<th>Vmean (mL/s)</th>
<th>PI (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LMM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>3.071</td>
<td>86.861</td>
<td>2.206</td>
<td>0.211</td>
<td>0.841</td>
<td>3.351</td>
</tr>
<tr>
<td>Time × coef₁</td>
<td>≈0.042₁</td>
<td>2.076</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Time² × coef₂</td>
<td>≈0.005₁</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 3—The LMM variables and mean ± SD values for echocardiographic variables in anesthetized rabbits after injection of the second bolus of fentanyl, which was administered 40 minutes after onset of a continuous infusion of propofol.

<table>
<thead>
<tr>
<th>Variable</th>
<th>LVEDD (mm)</th>
<th>LVESD (mm)</th>
<th>FS (mm)</th>
<th>QTc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LMM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>8.801</td>
<td>13.901</td>
<td>4.125</td>
<td>2.252</td>
</tr>
<tr>
<td>Time × coef₁</td>
<td>0.067</td>
<td>0.042</td>
<td>0.0308</td>
<td>0.0280</td>
</tr>
<tr>
<td>Time² × coef₂</td>
<td>—0.0060</td>
<td>0.0002</td>
<td>—0.0002</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

See Table 1 for key.
and 3). After the second bolus injection, the values increased significantly after 4 and 10 minutes, compared with baseline values.

**Clinical hemodynamic variables**—Values for HR, MAP, SpO₂, PetCO₂, and body temperature were determined after each of the 3 injections of fentanyl (Tables 4–6). The MAP significantly decreased 3 minutes after injection of the first fentanyl bolus and had a further significant decrease after the second and third injections. In particular, HR, MAP, and body temperature were significantly decreased after the first fentanyl injection, compared with values after the second and third bolus injections.

Recorded plethysmographic amplitude revealed a slight flattening, especially immediately after injection of the third fentanyl bolus. Thereafter, plethysmographic amplitude clearly was increased, with a maximum at 5 minutes after injection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>SpO₂ (%)</th>
<th>PetCO₂ (kPa)</th>
<th>Body temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMM*</td>
<td>215.37†</td>
<td>70.81†</td>
<td>5.16†</td>
<td>38.13†</td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time × coef</td>
<td>−2.267</td>
<td>−3.449†</td>
<td>−0.005</td>
<td>−0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Time² × coef</td>
<td>0.153</td>
<td>0.395†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time-adjusted differences†</td>
<td>Bolus 1 vs bolus 3</td>
<td>21.21†</td>
<td>9.54†</td>
<td>0.60</td>
<td>−0.10†</td>
</tr>
<tr>
<td></td>
<td>Bolus 2 vs bolus 3</td>
<td>16.22†</td>
<td>5.38†</td>
<td>−0.58</td>
<td>0.10†</td>
</tr>
<tr>
<td>Time (min)‡</td>
<td>Baseline</td>
<td>216 ± 5</td>
<td>71 ± 15§</td>
<td>100 ± 1</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>216 ± 12</td>
<td>71 ± 15§</td>
<td>100 ± 0</td>
<td>5.2 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>213 ± 12</td>
<td>66 ± 12</td>
<td>100 ± 1</td>
<td>5.2 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>206 ± 28</td>
<td>64 ± 10</td>
<td>100 ± 1</td>
<td>5.2 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>211 ± 17</td>
<td>63 ± 9§</td>
<td>100 ± 1</td>
<td>5.2 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>210 ± 17</td>
<td>63 ± 9§</td>
<td>100 ± 0</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>208 ± 18</td>
<td>62 ± 10</td>
<td>100 ± 0</td>
<td>5.2 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>209 ± 10</td>
<td>62 ± 9§</td>
<td>100 ± 0</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>208 ± 15</td>
<td>65 ± 10</td>
<td>100 ± 0</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>207 ± 20</td>
<td>66 ± 9§</td>
<td>100 ± 0</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>206 ± 23</td>
<td>69 ± 11</td>
<td>100 ± 0</td>
<td>5.1 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>203 ± 27</td>
<td>72 ± 15</td>
<td>100 ± 0</td>
<td>5.2 ± 0.25</td>
</tr>
</tbody>
</table>

†Time-adjusted differences between boluses; bolus 1 was considered the reference value. §Value differs significantly (P < 0.05) from corresponding value after the second bolus injection. ‡Value differs significantly (P < 0.05) from corresponding value after the third bolus injection.

*See Table 1 for remainder of key.

Table 5—The LMM variables and mean ± SD values for clinical hemodynamic variables in anesthetized rabbits after injection of the second bolus of fentanyl, which was administered 40 minutes after onset of a continuous infusion of propofol.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>SpO₂ (%)</th>
<th>PetCO₂ (kPa)</th>
<th>Body temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMM*</td>
<td>209.94†</td>
<td>65.67†</td>
<td>99.19†</td>
<td>5.27†</td>
<td>37.62†</td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time × coef</td>
<td>−1.573</td>
<td>−1.705</td>
<td>0.0080</td>
<td>−0.0002</td>
<td>0.0010</td>
</tr>
<tr>
<td>Time² × coef</td>
<td>0.0648</td>
<td>0.141</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time (min)‡</td>
<td>Baseline</td>
<td>210 ± 20</td>
<td>66 ± 24</td>
<td>99 ± 1</td>
<td>5.3 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>210 ± 20</td>
<td>70 ± 23</td>
<td>99 ± 2</td>
<td>5.3 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>209 ± 10</td>
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§Value differs significantly (P < 0.05) from corresponding value after the third bolus injection.

*See Table 1 for remainder of key.
Fentanyl injection is accompanied by a delayed decrease in blood pressure, which is attributable to a reduction in total peripheral resistance and a decrease in cardiac output.\(^{31}\) The decrease in cardiac output is believed to be the result of bradycardia. The mechanism of opioid-induced bradycardia is not fully understood, but a centrally mediated increase in parasympathetic tone, direct negative chronotropic action at the sinus node, potentiation of vagally released acetylcholine at the sinus node, and reduction in sympathetic activity have all been implicated.\(^{22-26}\) Our study revealed that fentanyl decreased HR after single bolus injections. Hence, the effect was most pronounced after the third bolus injection, which indicated a cumulative effect of the drug. These findings are in accordance with those of another study\(^{27}\); investigators in that study suggested that multiple or prolonged respiratory depression, which suggests that the duration of action is limited by redistribution within the body rather than removal from the body. In another
In our study, a significant decrease of MAP was detected after each bolus injection, which may have been caused by a decrease in cardiac output after fentanyl injection. Results of studies conducted to investigate the direct effects of fentanyl on myocardial contractility are controversial; fentanyl increases calcium influx and leads to increased calcium transit and decreased intracellular pH, which reduces myofilibril responsiveness to calcium. However, it is difficult to distinguish whether hypotension or a decrease in stroke volume results from changes in myocardial loading conditions, bradycardia, or direct negative inotropic effects of the drug because fentanyl can also cause changes in the release of norepinephrine at neuroeffector junctions in the coronary circulation.

A decrease in blood pressure is typically accompanied by a compensatory increase in HR, but it has been reported in studies conducted in rabbits that propofol reduces sympathetic tone, which further reduces sensitivity of arterial baroreceptors to changes in blood pressure. Because of the propofol-related depression of baroreceptor reflexes on HR, which may be potentiated by additional fentanyl, no compensatory increase in HR was detected in the study reported here, even though MAP was significantly reduced (especially after injection of the third bolus of fentanyl).

Furthermore, it has been reported that high concentrations of fentanyl cause significant prolongation of the action potential duration in vitro in canine Purkinje fibers. Because alterations in the action potential duration can be arrhythmogenic or arrhythmicogenic, depending on concomitant changes in the effective refractory period, the ECG was recorded before and at defined time points after the bolus injections in the study reported here. Accordingly, a significant increase of QTc was detected 4 and 10 minutes after injection of the second bolus of fentanyl. The QT–T interval is the sum of the durations of ventricular depolarization (QRS) and repolarization (ST–T interval). Prolongation of the QTc interval has been proposed as a risk factor for ventricular arrhythmias, which may be induced by electrolyte imbalances, antiarrhythmic drugs, myocardial ischemia or infarction, hypothermia, or myocarditis. The QT–T interval increases as the RR interval increases (ie, as HR decreases). Because of this, the QT–T interval was corrected for HR by use of an equation to yield the QTc. However, all rabbits in our study maintained a sinus rhythm, and no arrhythmias developed during the measurements. Therefore, additional studies are needed to investigate the predictive power of prolongation of the QTc for adverse cardiac effects in rabbits anesthetized with fentanyl and propofol.

The respiratory rate and tidal volume were held constant during fentanyl injection. Analysis of data collected after injection of the third bolus revealed a significant decrease in PETCO₂. This was probably caused by a decrease in ventilatory function related to changes in loading conditions and bradycardia. The alterations were evident only after the third bolus injection, which confirms a cumulative effect of the analgesic.

Changes in plethysmographic amplitude were recorded during the measurements. Plethysmography has been used to measure changes in tissue blood volume. During the cardiac cycle, perfused tissue initially expands as the blood flow into the arterioles exceeds capillary bed flow. Later during the cardiac cycle, accumulated blood drains into the venous vasculature, which allows the tissue to return to its presystolic blood volume. Specific changes of the plethysmographic amplitude and specific features of the waveform can be used to identify normal and abnormal peripheral perfusion patterns. Hypotension and peripheral vasoconstriction are associated with flattening of the plethysmographic amplitude. In the study reported here, a decrease of plethysmographic amplitude was evident only immediately after (ie, 30 seconds after) the third injection of fentanyl. This was followed by an increase of the plethysmographic amplitude, which presumably corresponded to reexpansion of the blood vessels and a decrease in the RI.

Noncardiovascular reflexes were not measured during anesthesia because it was important to maintain probe position, a task complicated by reflex movement. In a preliminary study, the effects on vascular volume resulting from injection of 1 to 2 mL of saline solution were examined by ultrasonography of the carotid and abdominal arteries, and conspicuous changes were not detected. Therefore, we have excluded this possible effect from the analysis of our findings.

The principal limitation of our study stemmed from the fact that ultrasonographic measurements were not obtained simultaneously at the various locations. Therefore, cumulative effects have to be assumed when comparing the data. However, hemodynamic variables were simultaneously recorded throughout the various parts of the study, and comparing changes in variables (such as HR, MAP, SPO₂, PETCO₂, and body temperature) after the second and third injection with results after the first bolus injection revealed a significant decrease in HR, MAP, and body temperature, which confirmed an accumulation of the drug and a potentiation of hemodynamic effects.

Regarding the statistical analysis, the Student t test for paired samples was used to assess differences between each time point during the 10-minute examination period and the baseline value (eg, baseline, 30 seconds, and 1 minute). Because the probability of detecting significant differences by chance alone directly increases with the number of tests conducted, correction of the error rate would be needed to ensure confidence in all considerations. Nevertheless, because of the large number of comparisons performed, any correction method would lead to strong conservative results, and a more substantial sample size would be necessary to maintain acceptable power within this detailed analysis. Therefore, we decided to use nonadjusted P values as a statistical measure of importance, which then have
to be interpreted as explorative results. Thus, the de-
tailed changes between time points must be confirmed
in additional studies.

The study reported here indicated that clinically use-
ful doses of fentanyl (0.0053 mg/kg) induced a signifi-
cant, transient decrease in the diameter of the abdominal
aorta and a short-lasting significant increase in vascular
resistance, particularly in the distal distribution area of
the left common carotid artery. Because MAP, HR, and
VFmean in the abdominal aorta significantly decreased,
the change in diameter was most likely attributable to a
lower transmural pressure (which reduced vessel disten-
tion), rather than a direct vascular effect. The decrease
of transmural pressure may have been the result of a
change in cardiac output, most likely caused by a sub-
stantial negative chronotropic effect. However, because
the flow and loading conditions of the heart were not
directly measured in this study, additional experiments
are needed to directly investigate the effects of fentanyl
on cardiac output.

Furthermore, recording of clinical variables indicated
that for tolerance of surgical procedures, repeated
doses of fentanyl induce a significant decrease in MAP,
bradycardia, and body temperature. As suggested in the
literature, cardiovascular stability achieved with fen-
tanyl is an indication for its use in hemodynamically
compromised patients. However, in the study reported
here, fentanyl injection was followed by a transient re-
duction in vascular diameters, which indicated a lower
transmural pressure (particularly in the abdominal aor-
a). Accordingly, results revealed decreases in MAP, HR,
and body temperature with an increasing effect after
the third bolus injection, which indicated a cumulative
effect of the drug. Therefore, fentanyl should be used
carefully in rabbits during TIVA with propofol.

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**Correction:** In vivo effects of intra-articular injection of gelatin hydrogen microspheres containing basic fibroblast growth factor on experimentally induced defects in third metacarpal bones of horses

The title of the report “In vivo effects of intra-articular injection of gelatin hydrogen microspheres containing basic fibroblast growth factor on experimentally induced defects in third metacarpal bones of horses” (Am J Vet Res 2008;69:1555–1559) is incorrect. The correct title is “In vivo effects of intra-articular injection of gelatin hydrogel microspheres containing basic fibroblast growth factor on experimentally induced defects in third metacarpal bones of horses.”