# Effects of halothane, sevoflurane and desflurane on the force-frequency relation in the dog heart in vivo

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# Cardiothoracic Anesthesia, Respiration and Airway

# Effects of halothane, sevoflurane and desflurane on the force-frequency relation in the dog heart *in vivo*

## *[Les effets de l'halothane, du sévoflurane et du desflurane sur la relation force-fréquence des cœurs de chiens in vivo]*

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**Purpose**: Frequency potentiation is the increase in force of contraction induced by an increased heart rate (HR). This positive staircase phenomenon has been attributed to changes in $Ca^{2+}$ entry and loading of intracellular $Ca^{2+}$ stores. Volatile anesthetics interfere with $Ca^{2+}$ homeostasis of cardiomyocytes. We hypothesized that frequency potentiation is altered by volatile anesthetics and investigated the influence of halothane (H), sevoflurane (S) and desflurane (D) on the positive staircase phenomenon in dogs *in vivo*.

**Methods**: Dogs were chronically instrumented for measurement of left ventricular (LV) pressure and cardiac output. Heart rate was increased by atrial pacing from 120 to 220 beats·min$^{-1}$ and the LV maximal rate of pressure increase ($dP/dt_{max}$) was determined as an index of myocardial performance. Measurements were performed in conscious dogs and during anesthesia with 1.0 minimal alveolar concentrations of each of the three inhaled anesthetics.

**Results**: Increasing HR from 120 to 220 beats·min$^{-1}$ increased $dP/dt_{max}$ from 3394 ± 786 (mean ± SD) to 3798 ± 810 mmHg sec$^{-1}$ in conscious dogs. All anesthetics reduced $dP/dt_{max}$ during baseline (at 120 beats·min$^{-1}$: H, 1745 ± 340 mmHg·sec$^{-1}$; S, 1882 ± 418; D, 1928 ± 454, all $P < 0.05$ *vs* awake) but did not influence the frequency potentiation of $dP/dt_{max}$ (at 220 beats·min$^{-1}$: H, 1981 ± 587 mmHg·sec$^{-1}$; S, 2187 ± 787; D, 2307 ± 691). The slope of the regression line correlating $dP/dt_{max}$ and HR was not different between awake and anesthetized dogs. Increasing HR did not influence cardiac output in awake or anesthetized dogs.

**Conclusion**: These results indicate that volatile anesthetics do not alter the force-frequency relation in dogs *in vivo*.

***Objectif** : La potentialisation en fréquence est l'augmentation de la force de contraction musculaire induite par une élévation de la fréquence cardiaque (FC). Cet effet a été attribué à des changements dans l'entrée de $Ca^{2+}$ et dans l'accumulation du $Ca^{2+}$ intracellulaire. Les anesthésiques volatils nuisent à l'homéostase du $Ca^{2+}$ des cardiomyocytes. Nous avons supposé que la potentialisation en fréquence était modifiée par les anesthésiques volatils et nous avons vérifié l'influence de l'halothane (H), du sévoflurane (S) et du desflurane (D) sur cet effet chez des chiens in vivo.*

***Méthode** : Des chiens ont été instrumentés mesurer de façon continue la pression du ventricule gauche (VG) et le débit cardiaque. La fréquence cardiaque a été augmentée de 120 à 220 battements·min$^{-1}$ par une stimulation auriculaire et la vitesse de l'augmentation de pression maximale du VG ($dP/dt_{max}$) a été déterminée en tant qu'index de performance myocardique. Les mesures ont été réalisées chez des chiens éveillés et pendant une anesthésie avec 1.0 fois la concentration alvéolaire minimale de chacun des trois anesthésiques volatils.*

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***Résultats** : La hausse de la FC de 120 à 220 battements·min$^{-1}$ a augmenté la dP/dt$_{max}$ de 3394 ± 786 (moyenne ± écart type) à 3798 ± 810 mmHg·s$^{-1}$ chez les chiens éveillés. Tous les anesthésiques ont réduit la dP/dt$_{max}$ pendant les conditions initiales (à 120 battements·min$^{-1}$: H, 1745 ± 340 mmHg·s$^{-1}$; S, 1882 ± 418; D, 1928 ± 454, tous P < 0,05 vs éveillé) mais n'ont pas influencé la potentialisation en fréquence de dP/dt$_{max}$ (à 220 battements·min$^{-1}$: H, 1981 ± 587 mmHg·s$^{-1}$; S, 2187 ± 787; D, 2307 ± 691). La pente de la ligne de régression mettant en corrélation la dP/dt$_{max}$ et la FC n'a pas changé entre l'état d'éveil et l'état anesthésié. L'augmentation de la FC n'a pas modifié le débit cardiaque chez les chiens éveillés ou anesthésiés.*

***Conclusion** : Ces résultats indiquent que les anesthésiques volatils ne modifient pas la relation force-fréquence chez des chiens in vivo.*

THE cardiac force-frequency relation (FFR) was first identified more than a century ago, yet its mechanisms remain incompletely elucidated (for a detailed review, see reference 1).[1] In most mammalian species, changes in stimulation frequency induce an increase in contractile force. The FFR plays a major role in adaptation to exercise. Prior studies have shown that the FFR is mainly influenced by $Ca^{2+}$ handling of both the sarcoplasmic reticulum (SR) and sarcolemma, and as such can be considered a macroscopic measure of excitation-contraction coupling.[2] The FFR depends on $Ca^{2+}$-influx via L-type and SR-$Ca^{2+}$ channels[3] and the frequency-dependent force generation is accompanied by an increase in both systolic and diastolic $Ca^{2+}$ levels.

Different volatile anesthetics have unique effects on the $Ca^{2+}$-homeostasis of cardiomyocytes. Halothane inhibits $Na^+/Ca^{2+}$ exchange,[4,5] directly blocks the $Ca^{2+}$ dependent $Ca^{2+}$ release channel (ryanodine receptor),[6,7] and might increase $Ca^{2+}$ uptake of the SR.[8] Sevoflurane blocks transmembrane $Ca^{2+}$ influx,[9,10] stimulates $Ca^{2+}$ uptake into the SR[11] and reduces fractional $Ca^{2+}$ release from the SR,[12] leading finally to a reduction of cytoplasmic $Ca^{2+}$ concentration. Influences of desflurane on cardiac $Ca^{2+}$ homeostasis have not been established.

With regards to general anesthesia all variables influencing FFR are influenced by volatile anesthetics: heart rate and contractile force of the myocardium are reduced and $Ca^{2+}$ homeostasis is altered. These changes are similar to alterations in the failing myocardium, in which a positive FFR may be reversed to a negative FFR.[13] Importantly, the FFR has been investigated predominantly in isolated muscle preparations, with very few comparable data available in the intact state of *in vivo* experiments. Limited data are available as to whether volatile anesthetics may alter the FFR. In isolated human ventricular myocardium in non-failing hearts, halothane, sevoflurane and isoflurane did not affect FFR.[14] In contrast, halothane restored the positive relation of the FFR in failing myocardium,[14] while similar findings for isoflurane or sevoflurane have not been demonstrated.

The present study was designed, first, to confirm the FFR in the intact animal, and to corroborate findings from isolated muscle studies. Secondly, because volatile anesthetics alter $Ca^{2+}$ handling of cardiomyocytes, we hypothesized that the FFR is altered during general anesthesia with inhaled anesthetics. Therefore, the effects of halothane on FFR were compared with equipotent concentrations of the two newer anesthetics desflurane and sevoflurane.

## Materials and methods

The present study conforms to the Guiding Principles in the Care and Use of Animals, as approved by the Council of the American Physiologic Society, and was approved by the local Bioethical Committee of the District of Düsseldorf.

Mongrel dogs weighing 25–32 kg were trained daily for three weeks to become familiar with the laboratory environment and the investigators. Under general anesthesia, nine dogs were surgically instrumented for long-term physiological monitoring as previously described.[15] The instrumentation included an aortic catheter (Tygon R3603; Norton, Akron, OH, USA) to determine aortic pressure (AOP), a Koenigsberg transducer (LP 200, Koenigsberg, Pasadena, CA, USA) for measurement of left ventricular pressure (LVP) and its first derivative, rate of pressure change (dP/dt), and an ultrasonic flow-probe (T 208; Transonic Systems Inc., Ithaca, NY, USA) around the pulmonary artery for measurement of cardiac output (CO). A pair of ultrasonic crystals (Triton Technology Inc., San Diego, CA, USA) was implanted in the subendocardium of the LV antero-apical wall. For cardiac pacing, two electrodes were fixed epicardially at the left atrium. The dogs were allowed to recover for a minimum of two weeks prior to experimentation.

### *Experimental protocol*

Data were collected during steady-state conditions in awake dogs and, in a cross-over design, each animal was anesthetized with 1.0 minimal alveolar concentration (MAC) of the respective anesthetic on different days. The order in which the anesthetics were

TABLE I Hemodynamic response to increasing heart rates in awake dogs

| | *120 beats·min$^{-1}$* | *140 beats·min$^{-1}$* | *160 beats·min$^{-1}$* | *180 beats·min$^{-1}$* | *200 beats·min$^{-1}$* | *220 beats·min$^{-1}$* |
|---|---|---|---|---|---|---|
| LVP (mmHg) | 143 ± 28 | 139 ± 30 | 143 ± 26 | 140 ± 29 | 134 ± 21 | 137 ± 23 |
| LVPed (mmHg) | 14 ± 6 | 13 ± 5 | 11 ± 5 | 10 ± 6 | 13 ± 7 | 17 ± 10 |
| $dP/dt_{min}$ (mmHg·sec$^{-1}$) | -2992 ± 692 | -3012 ± 725 | -3186 ± 694 | -3128 ± 702 | -3163 ± 703 | -3124 ± 728 |
| $dP/dt_{max}$ (mmHg·sec$^{-1}$) | 3394 ± 786 * | 3357 ± 751 * | 3563 ± 707 * | 3572 ± 698 * | 3577 ± 676*† | 3798 ± 810*† |
| RPP (mmHg·min$^{-1}$·10$^3$) | 15.0 ± 3.3 | 17.9 ± 4.1 † | 21.0 ± 3.6 † | 22.7 ± 4.7 † | 25.8 ± 5.5 † | 28.2 ± 6.2 † |
| MAP (mmHg) | 105 ± 17 | 111 ± 20 | 113 ± 20 | 112 ± 18 | 115 ± 18 | 115 ± 17 |
| CO (L·min$^{-1}$) | 2.62 ± 0.56 | 2.69 ± 0.63 | 2.82 ± 0.64 | 2.88 ± 0.64 | 2.69 ± 0.53 | 2.66 ± 0.61 |
| SVR (mmHg·min$^{-1}$·L$^{-1}$) | 39.7 ± 10.4 | 40.9 ± 10.4 | 41.0 ± 9.6 | 39.0 ± 10.8 | 42.0 ± 10.1 | 43.4 ± 12.4 |
| SLed (mm) | 10.8 ± 3.8 | 10.7 ± 4.0 | 10.3 ± 3.6 | 10.3 ± 3.7 | 10.1 ± 3.5 | 10.0 ± 3.7 |
| SLes (mm) | 8.7 ± 2.8 | 8.7 ± 3.1 | 8.5 ± 2.9 | 8.5 ± 2.9 | 8.3 ± 2.9 | 8.4 ± 3.1 |
| SLes% (%) | 20.4 ± 7.3 | 19.3 ± 7.2 | 19.0 ± 6.5 | 18.0 ± 7.0 | 17.4 ± 6.7 | 16.8 ± 6.9 |
| SLmv (mm·sec$^{-1}$) | 12.3 ± 6.4 | 11.8 ± 6.3 | 11.7 ± 5.0 | 11.0 ± 5.4 | 11.1 ± 5.3 | 11.8 ± 5.6 |

Data are mean ± SD, 21 experiments in seven dogs. LVP = left ventricular (LV) peak systolic pressure; LVPed = LV end-diastolic pressure; $dP/dt_{min}$ = minimal velocity of LV pressure change; $dP/dt_{max}$ = maximal velocity of LV pressure change; RPP = rate pressure product; MAP = mean aortic pressure; CO = cardiac output; SVR = systemic vascular resistance; SLed = end-diastolic segment length; SLes = end-systolic segment length; SLes% = percent systolic segment length shortening; SLmv = mean systolic segment length shortening velocity. †$P$ < 0.05 *vs* 120 beats·min$^{-1}$.

sequentially administered was randomized. Following insertion of an endotracheal tube (after induction of anesthesia with propofol 3 mg·kg$^{-1}$ *iv*), the animals' lungs were ventilated with 30% $O_2$ in air (tidal volume 10 mL·kg$^{-1}$, respiratory frequency 14 min$^{-1}$ to maintain normocarbia) and anesthesia was maintained with 1.0 MAC halothane (end-tidal concentration, Datex Capnomac Ultima, Division of Instrumentarium Corp., Helsinki, Finland), sevoflurane or desflurane (Vapor 19.3, Devapor, Drägerwerke AG, Lübeck, Germany); MAC values in dogs: halothane, 0.9 vol.%, sevoflurane 2.4 vol.%; desflurane 7.2 vol.%.[16,17] To measure the FFR, data were collected at increasing heart rates of 120, 140, 160, 180, 200, and 220 beats·min$^{-1}$ using atrial pacing. After each measurement, heart rate was increased and at least ten minutes were allowed to reach steady state conditions before the next data were collected. To exclude variations of dP/dt caused by mechanical ventilation, measurements were performed during transient periods of applied apnea.

*Data recording*

Left ventricular pressure, dP/dt, CO, AOP and myocardial segment length (SL) in the anteroapical wall were continuously recorded on an ink-recorder (Recorder 2800; Gould Inc., Cleveland, OH, USA) during all experiments. The data were digitized using an analogue-to-digital converter (Data Translation, Marlboro, MA, USA) at a sampling rate of 500 Hz and later processed on a personal computer.

Global systolic function was measured in terms of LVP and the maximal rate of pressure increase ($dP/dt_{max}$). Left ventricular $dP/dt_{min}$ was used as an index

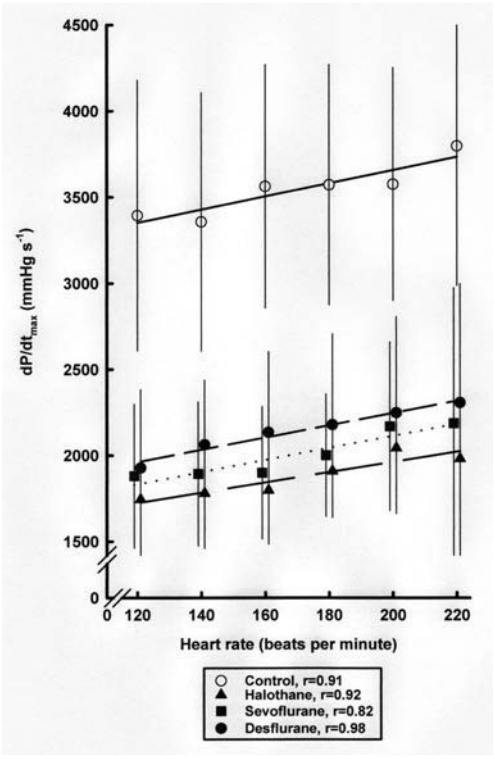


FIGURE Force-frequency relation in conscious dogs and during anesthesia with 1-minimal alveolar concentrations of halothane, sevoflurane or desflurane. The slope of the regression lines were different from zero but were not altered during anesthesia. Equations of regression lines: Awake: y = 3.8 ± 0.9 × + 2891 ± 150; Halothane: y = 3.0 ± 0.6 × + 1371 ± 107; Sevoflurane: y = 2.8 ± 1.0 × + 1540 ± 170; Desflurane: y = 3.6 ± 0.3 × + 1536 ± 56. All values during anesthesia are significantly different from the respective values in awake dogs ($P$ < 0.05).

TABLE II Hemodynamic response to increasing heart rate in halothane anesthetized dogs

| | *120 beats·min$^{-1}$* | *140 beats·min$^{-1}$* | *160 eats·min$^{-1}$* | *180 beats·min$^{-1}$* | *200 beats·min$^{-1}$* | *220 beats·min$^{-1}$* |
|---|---|---|---|---|---|---|
| LVP (mmHg) | 98 ± 17 * | 91 ± 11 * | 93 ± 11 * | 93 ± 9 * | 94 ± 9 * | 91 ± 12 * |
| LVPed (mmHg) | 12 ± 5 | 12 ± 3 | 14 ± 3 | 12 ± 3 | 12 ± 2 | 12 ± 4 |
| $dP/dt_{min}$ (mmHg·sec$^{-1}$) | -1823 ± 532 * | -1930 ± 494 * | -1951 ± 476 * | -1996 ± 504 * | -1916 ± 496 * | -1701 ± 439 * |
| $dP/dt_{max}$ (mmHg·sec$^{-1}$) | 1745 ± 341 * | 1780 ± 320 * | 1797 ± 313 * | 1909 ± 270 * | 2043 ± 382*† | 1981 ± 587*† |
| RPP (mmHg·min$^{-1}$·10$^3$) | 12.1 ± 2.1 † | 13.5 ± 1.8 *† | 15.5 ± 1.5 *† | 17.9 ± 1.7 *† | 18.9 ± 2.6 *† | 19.5 ± 3.0 *† |
| MAP (mmHg) | 79 ± 13 * | 76 ± 11 * | 79 ± 10 * | 82 ± 10 * | 80 ± 12 * | 78 ± 11 * |
| CO (L·min$^{-1}$) | 2.47 ± 0.99 | 2.49 ± 0.92 | 2.51 ± 0.93 | 2.46 ± 0.88 | 2.47 ± 0.91 | 2.32 ± 1.35 |
| SVR (mmHg·min$^{-1}$·L$^{-1}$) | 32.0 ± 8.3 | 31.3 ± 7.2 | 32.9 ± 9.1 | 34.8 ± 8.9 | 33.9 ± 9.7 | 37.3 ± 14.2 |
| SLed (mm) | 10.6 ± 4.7 | 10.3 ± 3.8 | 10.1 ± 3.8 | 10.0 ± 3.8 | 9.9 ± 3.6 | 7.9 ± 2.2 |
| SLes (mm) | 8.9 ± 3.8 | 8.9 ± 3.3 | 8.8 ± 3.3 | 8.8 ± 3.2 | 8.7 ± 3.2 | 7.1 ± 1.9 |
| SLes% (%) | 16.0 ± 3.8 | 13.9 ± 3.9 | 13.0 ± 3.6 | 12.1 ± 4.3 | 12.1 ± 4.4 | 9.5 ± 5.2 † |
| SLmv (mm·sec$^{-1}$) | 8.6 ± 4.5 | 7.2 ± 3.1 | 7.2 ± 3.1 | 6.9 ± 3.2 | 6.8 ± 3.0 | 5.8 ± 3.0 |

Data are mean ± SD, $n = 7$. LVP = left ventricular (LV) peak systolic pressure; LVPed = LV end-diastolic pressure; $dP/dt_{min}$ = minimal velocity of LV pressure change; $dP/dt_{max}$ = maximal velocity of LV pressure change; RPP = rate pressure product; MAP = mean aortic pressure; CO = cardiac output; SVR = systemic vascular resistance; SLed = end-diastolic segment length; SLes = end-systolic segment length; SLes% = percent systolic segment length shortening; SLmv = mean systolic segment length shortening velocity.* $P < 0.05$ *vs* same heart rate in awake dogs (see Table I); † $P < 0.05$ *vs* 120 beats·min$^{-1}$.

TABLE III Hemodynamic response to increasing heart rate in sevoflurane anesthetized dogs

| | *120 beats·min$^{-1}$* | *140 beats·min$^{-1}$* | *160 beats·min$^{-1}$* | *180 beats·min$^{-1}$* | *200 beats·min$^{-1}$* | *220 beats·min$^{-1}$* |
|---|---|---|---|---|---|---|
| LVP (mmHg) | 104 ± 36 * | 107 ± 36 * | 109 ± 36 * | 109 ± 33 * | 105 ± 28 * | 91 ± 16 * |
| LVPed (mmHg) | 10 ± 6 | 9 ± 7 | 8 ± 7 | 8 ± 7 | 6 ± 6 | 5 ± 5 |
| $dP/dt_{min}$ (mmHg·sec$^{-1}$) | -1587 ± 372 * | -1721 ± 334 * | -1805 ± 418 * | -1857 ± 411 * | -1728 ± 426 * | -1481 ± 514 * |
| $dP/dt_{max}$ (mmHg·sec$^{-1}$) | 1880 ± 418 * | 1893 ± 419 * | 1899 ± 385 * | 2001 ± 356 * | 2169 ± 490*† | 2187 ± 787*† |
| RPP (mmHg·min$^{-1}$·10$^3$) | 10.7 ± 2.4 * | 11.6 ± 2.2 *† | 14.1 ± 2.9 *† | 15.9 ± 3.6 *† | 17.1 ± 4.7 *† | 19.4 ± 4.9 *† |
| MAP (mmHg) | 64 ± 18 * | 68 ± 15 * | 73 ± 19 * | 76 ± 20 * | 72 ± 23 * | 75 ± 19 * |
| CO (L·min$^{-1}$) | 2.29 ± 1.07 | 2.35 ± 1.17 | 2.27 ± 1.19 | 2.26 ± 1.22 | 2.28 ± 1.25 | 2.26 ± 1.49 |
| SVR (mmHg·min$^{-1}$) | 32.1 ± 13.1 | 35.0 ± 16.8 | 38.7 ± 17.7 | 40.3 ± 19.2 | 37.7 ± 16.7 | 40.8 ± 15.7 |
| SLed (mm) | 10.7 ± 4.4 | 10.6 ± 4.2 | 10.5 ± 4.4 | 10.3 ± 4.1 | 10.1 ± 4.2 | 9.5 ± 4.3 |
| SLes (mm) | 8.7 ± 3.5 | 8.7 ± 3.5 | 8.7 ± 3.7 | 8.7 ± 3.5 | 8.8 ± 3.7 | 8.6 ± 4.4 |
| SLes% (%) | 18.0 ± 6.8 | 17.7 ± 4.4 | 16.4 ± 5.6 | 15.3 ± 6.0 | 13.3 ± 6.5 | 11.1 ± 6.0 |
| SLmv (mm·sec$^{-1}$) | 11.7 ± 4.7 | 10.8 ± 3.8 | 10.4 ± 3.8 | 10.1 ± 3.1 | 9.0 ± 3.1 | 7.5 ± 2.6 |

Data are mean ± SD, $n = 7$. LVP = left ventricular (LV) peak systolic pressure; LVPed = LV end-diastolic pressure; $dP/dt_{min}$ = minimal velocity of LV pressure change; $dP/dt_{max}$ = maximal velocity of LV pressure change; RPP = rate pressure product; MAP = mean aortic pressure; CO = cardiac output; SVR = systemic vascular resistance; SLed = end-diastolic segment length; SLes = end-systolic segment length; SLes% = percent systolic segment length shortening; SLmv = mean systolic segment length shortening velocity.* $P < 0.05$ *vs* same heart rate in awake dogs (see Table I). † $P < 0.05$ *vs* 120 beats·min$^{-1}$.

of global LV diastolic function. The rate pressure product was calculated from the product of systolic pressure and heart rate. Regional myocardial systolic function was assessed in the anteroapical wall and was evaluated as mean systolic SL shortening velocity as well as percent systolic SL shortening (SLes%), calculated as:

SLes% = (SLed-SLes/SLed) × 100, where SLed represents end-diastolic SL and SLes represents end-systolic SL.

*Statistical analysis*

Measured values are presented as means ± SD. For comparison of the FFR between experimental groups, a Tukey-Kramer test was calculated for the hemodynamic variables at each individual heart rate. Control measurements of three experiments in each dog were summarized and used as one data point. To assess the FFR within experimental groups (awake, respective anesthetics), regression analysis was performed for $dP/dt_{max}$. Differences between regression lines were analyzed by an F-test. Other hemodynamic variables were analyzed within each group using Dunnett's test with 120 beats·min$^{-1}$ as reference value. Changes were considered statistically significant when $P < 0.05$.

## Results

Nine dogs were instrumented and studied on different days. In two dogs, atrial pacing was not always pos-

TABLE IV Hemodynamic response to increasing heart rate in desflurane anesthetized dogs

| | *120 beats·min$^{-1}$* | *140 beats·min$^{-1}$* | *160 beats·min$^{-1}$* | *180 beats·min$^{-1}$* | *200 beats·min$^{-1}$* | *220 beats·min$^{-1}$* |
|---|---|---|---|---|---|---|
| LVP (mmHg) | 92 ± 4 * | 98 ± 6 * | 97 ± 9 * | 94 ± 10 * | 90 ± 13 * | 87 ± 13 * |
| LVPed (mmHg) | 12 ± 5 | 13 ± 6 | 12 ± 5 | 11 ± 6 | 13 ± 9 | 14 ± 9 |
| $dP/dt_{min}$ (mmHg·sec$^{-1}$) | -1535 ± 409 * | -1781 ± 496 * | -1977 ± 495 * | -2037 ± 533 * | -1993 ± 524 * | -1920 ± 642 * |
| $dP/dt_{max}$ (mmHg·sec$^{-1}$) | 1928 ± 454 * | 2062 ± 376 * | 2135 ± 469 * | 2179 ± 528 * | 2249 ± 558* | 2307 ± 691*† |
| RPP (mmHg·min$^{-1}$·10$^3$) | 12.0 ± 3.6 | 13.6 ± 2.7 *† | 16.2 ± 3.1 *† | 18.3 ± 4.1 † | 19.5 ± 4.7 *† | 20.0 ± 5.8 *† |
| MAP (mmHg) | 68 ± 28 * | 73 ± 20 * | 79 ± 19 * | 81 ± 23 * | 81 ± 22 * | 78 ± 24 * |
| CO (L·min$^{-1}$) | 2.35 ± 1.08 | 2.45 ± 0.98 | 2.49 ± 0.89 | 2.47 ± 0.91 | 2.45 ± 0.87 | 2.44 ± 0.98 |
| SVR (mmHg·min$^{-1}$·L$^{-1}$) | 31.9 ± 11.0 | 32.1 ± 9.7 | 33.7 ± 8.8 | 35.6 ± 11.0 | 35.4 ± 10.8 | 34.1 ± 13.0 |
| SLed (mm) | 10.5 ± 4.9 | 10.3 ± 4.0 | 9.7 ± 3.9 | 9.6 ± 3.9 | 9.5 ± 3.6 | 9.1 ± 3.2 |
| SLes (mm) | 8.5 ± 3.8 | 8.5 ± 3.3 | 8.2 ± 3.2 | 8.2 ± 3.3 | 8.1 ± 3.3 | 8.2 ± 3.3 |
| SLes% (%) | 18.7 ± 7.4 | 17.1 ± 6.2 | 15.2 ± 5.9 | 14.1 ± 6.8 | 15.0 ± 5.7 | 13.2 ± 7.0 |
| SLmv (mm·sec$^{-1}$) | 10.1 ± 6.5 | 9.2 ± 4.6 | 8.3 ± 4.4 | 8.9 ± 4.4 | 8.3 ± 3.8 | 7.3 ± 4.2 |

Data are mean ± SD, $n = 7$. LVP = left ventricular (LV) peak systolic pressure; LVPed = LV end-diastolic pressure; $dP/dt_{min}$ = minimal velocity of LV pressure change; $dP/dt_{max}$ = maximal velocity of LV pressure change; RPP = rate pressure product; MAP = mean aortic pressure; CO = cardiac output; SVR = systemic vascular resistance; SLed = end-diastolic segment length; SLes = end-systolic segment length; SLes% = percent systolic segment length shortening; SLmv = mean systolic segment length shortening velocity.*$P < 0.05$ *vs* same heart rate in awake dogs (see Table I); †$P < 0.05$ *vs* 120 beats·min$^{-1}$.

sible. Therefore, data are presented from seven experiments with each anesthetic and the respective control recordings in seven dogs.

The hemodynamic data of experiments in awake dogs are summarized in Table I. In chronically instrumented awake dogs, increasing heart rate from 120 to 220 augmented $dP/dt_{max}$ from 3394 ± 786 to 3798 ± 810 mmHg sec$^{-1}$ (Figure), confirming the existence of FFR *in vivo*. The slope of the regression line was 3.8 ± 0.9 mmHg sec$^{-1}$·beats$^{-1}$ and significantly different from zero ($P < 0.05$, r = 0.91).

All anesthetics produced a marked negative inotropic effect, reducing LVP, mean aortic pressure, systemic vascular resistance, and dP/dt in comparison to the awake state (Tables II–IV, Figure). The variable of contractile function, $dP/dt_{max}$, was reduced during baseline from 3394 ± 786 mmHg·sec$^{-1}$ in awake dogs to 1745 ± 340 mmHg·sec$^{-1}$ (halothane), 1882 ± 418 mmHg·sec$^{-1}$ (sevoflurane) and 1928 ± 454 mmHg·sec$^{-1}$ (desflurane) at 120 beats·min$^{-1}$, respectively (all $P < 0.05$ *vs* awake). However, the FFR was not influenced by volatile anesthetics, and $dP/dt_{max}$ increased to 1981 ± 587 mmHg·sec$^{-1}$ (halothane), 2187 ± 787 mmHg·sec$^{-1}$ (sevoflurane) and 2307 ± 691 mmHg·sec$^{-1}$ (desflurane) at 220 beats·min$^{-1}$, respectively (in each group, $P < 0.05$ *vs* 120 beats·min$^{-1}$). Although reduction of $dP/dt_{max}$ was numerically greater during halothane anesthesia, no significant differences were observed between the three inhalational agents. The slopes of the regression lines (halothane: 3.0 ± 0.6 mmHg·sec$^{-1}$·beats$^{-1}$; sevoflurane: 2.8 ± 1.0 mmHg·sec$^{-1}$·beats$^{-1}$; desflurane: 3.6 ± 0.3 mmHg·sec$^{-1}$·beats$^{-1}$) were significantly different from zero but not significantly different from the experiments in awake dogs (3.8 ± 0.9 mmHg·sec$^{-1}$·beats$^{-1}$). Increasing heart rate had no significant effect on mean aortic pressure, CO or systemic vascular resistance during general anesthesia. However, regional myocardial function assessed as systolic SL shortening was slightly impaired at least at higher heart rates.

## Discussion

The results of the present study confirm the positive FFR in awake dogs *in vivo*. In addition, we demonstrated that the FFR is not altered during general anesthesia with 1 MAC concentrations of halothane, sevoflurane or desflurane.

In most mammalian species, changes in stimulation frequency induce an increase in contractile force. This phenomenon (the "treppe" or positive staircase) was described more than a century ago by Bowditch. In certain species including rats, the staircase is negative.[1,18,19] This difference may be caused by different origins of calcium available for contraction (i.e., transsarcolemmic movements, SR release, or both).[20] On a molecular level, the FFR is related to a net gain of circulation of $Ca^{2+}$ in the cell and increased calcium-induced calcium release, by either increased $Ca^{2+}$-influx via L-type and SR-$Ca^{2+}$ channels,[3] or a reduction in $Na^+$/ $Ca^{2+}$ exchanger activity during diastole. The frequency-dependent force generation is accompanied by an increase in both systolic and diastolic $Ca^{2+}$ levels.[3] In the intact animal, $Ca^{2+}$ handling by the SR is a primary determinant of mechanical

performance.[21] Ryanodine induced augmentation of the force-frequency response indicates a central role for $Ca^{2+}$ influx in producing frequency potentiation.[21] Endogenous nitric oxide might also influence the FFR, showing an enhancement or a reduction of FFR depending on the experimental setup.[22]

Mostly previous investigations examining the FFR have been conducted in isolated heart preparations, where experimental conditions might have a substantial influence, and might even change a positive to a negative FFR.[23] Very few studies have shown a positive staircase *in situ*,[22,24–26] and from most of these investigations it is apparent that the relevance of FFR is overestimated *in vitro*, since changes in contraction are smaller *in vivo* than *in vitro*.[24] The smaller changes *in vivo* might be attributable to changes in loading conditions during the controlled increase in heart rate.[26] Our data confirm previous findings, showing an increase of $dP/dt_{max}$ by 17 ± 7% over a nearly twofold increase in heart rate from 120 to 220 beats·min$^{-1}$. The frequency-dependent force generation is accompanied by an increase in both systolic and diastolic $Ca^{2+}$ levels. Thus, especially at high stimulation frequencies, the $Ca^{2+}$ lowering mechanism may become crucial and may be responsible for the blunted force-frequency relation in failing human myocardium.[3] In contrast to force potentiation, when the interval between successive beats is too short, the force of the following contraction may be attenuated due to an incomplete recovery process. In accordance with previous studies,[24,26] a reversal of the positive into a negative staircase was not observed in the frequency range between 120 and 220 beats·min$^{-1}$.

The sarcoplasmic reticulum plays a central role in cardiac contraction and relaxation by regulating intracellular $Ca^{2+}$ concentration. $Ca^{2+}$ uptake by the SR is mediated by an adenosine triphosphate (ATP)-dependent $Ca^{2+}$ pump, the sarco(endo)plasmic reticulum $Ca^{2+}$-ATPase (SERCA).[27] An increase in SERCA expression increases the ability of the SR to store $Ca^{2+}$. Thus, more calcium is available to be released during each heartbeat at higher stimulation rates.[28] The interaction of the SERCA2a with its inhibitory protein phospholamban might be involved in the control of the FFR.[1,29] The ratio of phospholamban to SERCA2a is an important component in the control of the FFR[30] and the level of phospholamban is a critical negative determinant of myocardial contractility *in vivo*.[31]

Different volatile anesthetics have different effects on the $Ca^{2+}$ homeostasis of cardiomyocytes. Halothane reduces intracellular $Ca^{2+}$ concentration by inhibiting $Na^+/Ca^{2+}$ exchange [4,5] and blocking the $Ca^{2+}$ dependent $Ca^{2+}$ release channel (ryanodine receptor).[6,7] By the latter mechanism, halothane reduces $Ca^{2+}$ oscillations during reoxygenation of previous anoxic cardiomyocytes.[32] In addition, halothane might increase $Ca^{2+}$ uptake of the SR.[8] Sevoflurane blocks transmembrane $Ca^{2+}$ influx,[9,10] stimulates $Ca^{2+}$ uptake into the SR[11] and reduces fractional $Ca^{2+}$ release from the SR,[12] leading finally to a reduction of cytoplasmic $Ca^{2+}$ concentration. Influences of desflurane on cardiac $Ca^{2+}$ homeostasis have yet to be investigated. Most studies on the effects of volatile anesthetics on myocardial $Ca^{2+}$ handling were performed under artificial experimental conditions in isolated hearts or isolated cardiomyocytes. Studying the effect of the anesthetics in the dog heart *in vivo* shows that the FFR is maintained, suggesting that besides changes in $Ca^{2+}$ handling, other mechanisms may be involved in the staircase phenomenon.

Halothane reduces myocardial contractility in a dose-dependent manner.[33] Sevoflurane and desflurane also have negative inotropic properties,[33–35] although desflurane might exert positive inotropic actions by direct catecholamine release from cardiac nerve endings.[36] The negative inotropic effects were also observed in the present investigation, with no significant differences between anesthetics. However, the negative inotropy did not alter FFR *in vivo*.

Halothane inhibited the SERCA2a, an effect that was reduced by phospholamban.[37] However, this anesthetic had no effect on FFR in dogs *in vivo*. Effects of sevoflurane or desflurane on SERCA or phospholamban are not known. Hydroxyl radicals induce an impairment of contraction and relaxation and an attenuation of the FFR in human myocardium accompanied by an inhibition of SERCA.[38] Inhalational anesthetics inhibited generation and cytotoxic effects of free hydroxyl radicals[39] and might thereby change SERCA activity and maintain FFR.

There are several potential limitations with the experimental model used in this study. First, a pacing induced tachycardia was used to investigate the FFR in dogs *in vivo*. Whether this effect mirrors the hemodynamic response to sinus tachycardia is not known. Importantly, however, atrial pacing avoids the ventricular wall motion abnormalities and changes in ventricular preload associated with ventricular pacing. In addition, mechanical respiration might have introduced a subtle confounding influence on the measured hemodynamic variables. To take this possibility into consideration, we sampled the data over ten to 12 successive heart beats to minimize influences of intrathoracic pressure changes, and recorded measurements during apnea. The normal resting heart rate of this canine species averages 82 beats·min$^{-1}$,[40]

and a maximal heart rate of 220 beats·min$^{-1}$ was chosen because higher pacing rates frequently result in severe arrhythmias. Therefore, a decline in the FFR at heart rates above 220 beats·min$^{-1}$ might have been anticipated. Heart rates were increased in a stepwise manner during each experiment, while allowing sufficient time for hemodynamic variables to equilibrate after each step increase. However, possible carry-over effects from one step change in heart rate to the next cannot be excluded. Furthermore, the changes in contractile force were relatively small, and might therefore not lead to alterations of a well regulated hemodynamic variable - CO. Higher heart rates led to a reduced SLes%, showing reduced regional myocardial function. This might be explained by reduced left ventricular filling at higher heart rates, as evidenced by a reduced diastolic SL and a reduction in stroke work per cardiac cycle. Finally, we examined the cardiac response at only one concentration of each anesthetic, and conclusions about higher or lower concentrations cannot be drawn. Because only a single injection of propofol was used and sufficient time was allowed to reach steady state conditions, an effect of propofol on dP/dtmax is unlikely.

In conclusion, the present study confirms the existence of a positive FFR *in vivo* and demonstrates for the first time that general anesthesia with 1-MAC concentrations of halothane, sevoflurane or desflurane does not alter FFR.

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**References**

1 *Endoh M.* Force-frequency relationship in intact mammalian ventricular myocardium: physiological and pathophysiological relevance. Eur J Pharmacol 2004; 500: 73–86.

2 *Bers DM.* Excitation-Contraction Coupling and Cardiac Contractile Force. Dordrecht: Kluwer Academic Publisher; 1991: 155–70.

3 *Reuter H, Zobel C, Brixius K, Bolck B, Schwinger RH.* The force-frequency relationship is dependent on Ca2+-influx via L-type and SR-Ca2+-channels in human heart. Basic Res Cardiol 1999; 94: 159–70.

4 *Haworth RA, Goknur AB.* Inhibition of sodium/calcium exchange and calcium channels of heart cells by volatile anesthetics. Anesthesiology 1995; 82: 1255–65.

5 *Eskinder H, Rusch NJ, Supan FD, Kampine JP, Bosnjak ZJ.* The effects of volatile anesthetics on L- and T-type calcium channel currents in canine cardiac Purkinje cells. Anesthesiology 1991; 74: 919–26.

6 *Komai H, Rusy BF.* Direct effect of halothane and isoflurane on the function of the sarcoplasmic reticulum in intact rabbit atria. Anesthesiology 1990; 72: 694–8.

7 *Lynch C III, Frazer MJ.* Anesthetic alteration of ryanodine binding by cardiac calcium release channels. Biochim Biophys Acta 1994; 1194: 109–17.

8 *Blanck TJ, Thompson M.* Calcium transport by cardiac sarcoplasmic reticulum: modulation of halothane action by substrate concentration and pH. Anesth Analg 1981; 60: 390–4.

9 *Azuma M, Matsumura C, Kemmotsu O.* The effects of sevoflurane on contractile and electrophysiologic properties in isolated guinea pig papillary muscles. Anesth Analg 1996; 82: 486–91.

10 *Hatakeyama N, Ito Y, Momose Y.* Effects of sevoflurane, isoflurane, and halothane on mechanical and electrophysiologic properties of canine myocardium. Anesth Analg 1993; 76: 1327–32.

11 *Bartunek AE, Housmans PR.* Effects of sevoflurane on the intracellular Ca2+ transient in ferret cardiac muscle. Anesthesiology 2000; 93: 1500–8.

12 *Davies LA, Gibson CN, Boyett MR, Hopkins PM, Harrison SM.* Effects of isoflurane, sevoflurane, and halothane on myofilament Ca2+ sensitivity and sarcoplasmic reticulum Ca2+ release in rat ventricular myocytes. Anesthesiology 2000; 93: 1034–44.

13 *Sipido KR, Stankovicova T, Flameng W, Vanhaecke J, Verdonck F.* Frequency dependence of Ca2+ release from the sarcoplasmic reticulum in human ventricular myocytes from end-stage heart failure. Cardiovasc Res 1998; 37: 478–88.

14 *Schotten U, Greiser M, Braun V, Karlein C, Schoendube F, Hanrath P.* Effect of volatile anesthetics on the force-frequency relation in human ventricular myocardium: the role of the sarcoplasmic reticulum calcium-release channel. Anesthesiology 2001; 95: 1160–8.

15 *Mullenheim J, Preckel B, Obal D, et al.* Left stellate ganglion block has only small effects on left ventricular function in awake dogs before and after induction of heart failure. Anesth Analg 2000; 91: 787–92.

16 *Kazama T, Ikeda K.* Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. Anesthesiology 1988; 68: 435–7.

17 *Doorley BM, Waters SJ, Terrell RC, Robinson JL.* MAC of I-653 in beagle dogs and New Zealand white rabbits. Anesthesiology 1988; 69: 89–91.

18 *Shattock MJ, Bers DM.* Rat vs. rabbit ventricle: Ca flux and intracellular Na assessed by ion-selective microelectrodes. Am J Physiol 1989; 256(4 Pt 1): C813–22.

19 *Palomeque J, Vila Petroff MG, Mattiazzi A.* Pacing

staircase phenomenon in the heart: from Bodwitch to the XXI century. Heart Lung Circ 2004; 13: 410–20.
20 *Fabiato A, Fabiato F.* Calcium-induced release of calcium from the sarcoplasmic reticulum of skinned cells from adult human, dog, cat, rabbit, rat and frog hearts and from fetal and new-born rat ventricles. Ann N Y Acad Sci 1978; 307: 491–522.
21 *Prabhu SD.* Ryanodine and the left ventricular force-interval and relaxation-interval relations in closed-chest dogs: insights on calcium handling. Cardiovasc Res 1998; 40: 483–91.
22 *Cotton JM, Kearney MT, MacCarthy PA, et al.* Effects of nitric oxide synthase inhibition on basal function and the force-frequency relationship in the normal and failing human heart in vivo. Circulation 2001; 104: 2318–23.
23 *Marin RM, Franchini KG.* Reduced oxygen supply explains the negative force-frequency relation and the positive inotropic effect of adenosine in buffer-perfused hearts. Am J Physiol Heart Circ Physiol 2005; 289: H131–6.
24 *Kalthof B, Sato N, Iwase M, et al.* Effects of ryanodine on cardiac contraction, excitation-contraction coupling and "Treppe" in the conscious dog. J Mol Cell Cardiol 1995; 27: 2111–21.
25 *Arentzen CE, Rankin JS, Anderson PA, Feezor MD, Anderson RW.* Force-frequency characteristics of the left ventricle in the conscious dog. Circ Res 1978; 42: 64–71.
26 *Richmond DR, Angus JA, Goodman AH, Cobbin LB.* The effect of heart rate on indices of myocardial contractility in the dog. Clin Exp Pharmacol Physiol 1975; 2: 469–79.
27 *Frank KF, Bolck B, Erdmann E, Schwinger RH.* Sarcoplasmic reticulum Ca2+-ATPase modulates cardiac contraction and relaxation. Cardiovasc Res 2003; 57: 20–7.
28 *Hashimoto K, Perez NG, Kusuoka H, Baker DL, Periasamy M, Marban E.* Frequency-dependent changes in calcium cycling and contratile activation in SERCA2a transgenic mice. Basic Res Cardiol 2000; 95: 144–51.
29 *Huke S, Liu LH, Biniakiewicz D, Abraham WT, Periasamy M.* Altered force-frequency response in non-failing hearts with decreased SERCA pump-level. Cardiovasc Res 2003; 59: 668–77.
30 *Meyer M, Bluhm WF, He H, et al.* Phospholamban-to-SERCA2 ratio controls the force-frequency relationship. Am J Physiol 1999; 276(3 Pt 2): H779–85.
31 *Bluhm WF, Kranias EG, Dillmann WH, Meyer M.* Phospholamban: a major determinant of the cardiac force-frequency relationship. Am J Physiol Heart Circ Physiol 2000; 278: H249–55.
32 *Siegmund B, Schlack W, Ladilov YV, Balser C, Piper HM.* Halothane protects cardiomyocytes against reoxygenation-induced hypercontracture. Circulation 1997; 96: 4372–9.
33 *Kazama T, Ikeda K.* The comparative cardiovascular effects of sevoflurane with halothane and isoflurane. J Anesth 1988; 2: 63–8.
34 *Bernard JM, Wouters PF, Doursout MF, Forence B, Chelly JE, Merin RG.* Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Anesthesiology 1990; 72: 659–62.
35 *Grundmann U, Muller M, Kleinschmidt S, Larsen B, Larsen R.* Cardiovascular effects of desflurane and isoflurane in patients with coronary artery disease. Acta Anaesthesiol Scand 1996; 40: 1101–7.
36 *Hanouz JL, Massetti M, Guesne G, et al.* In vitro effects of desflurane, sevoflurane, isoflurane, and halothane in isolated human right atria. Anesthesiology 2000; 92: 116–24.
37 *Karon BS, Geddis LM, Kutchai H, Thomas DD.* Anesthetics alter the physical and functional properties of the Ca-ATPase in cardiac sarcoplasmic reticulum. Biophys J 1995; 68: 936–45.
38 *Flesch M, Maack C, Cremers B, Baumer AT, Sudkamp M, Bohn M.* Effect of beta-blockers on free radical-induced cardiac contractile dysfunction. Circulation 1999; 100: 346–53.
39 *Tanguay M, Blaise G, Dumont L, Beique G, Hollmann C.* Beneficial effects of volatile anesthetics on decrease in coronary flow and myocardial contractility induced by oxygen-derived free radicals in isolated rabbit hearts. J Cardiovasc Pharmacol 1991; 18: 863–70.
40 *Picker O, Schindler AW, Schwarte LA, et al.* Xenon increases total body oxygen consumption during isoflurane anaesthesia in dogs. Br J Anaesth 2002; 88: 546–54.