Halothane Restores the Altered Force-Frequency Relationship in Failing Human Myocardium

Ulrich Schmidt, M.D., Robert H. G. Schwinger, M.D., Michael Böhm, M.D.

Background: The terminally failing human myocardium exhibits a negative force-frequency relationship (FFR), whereas a positive FFR occurs in nonfailing myocardium. To study the possibility of pharmacologically influencing this defect of the failing human heart, the effect of halothane on the basal FFR and the FFR in the presence of isoproterenol and ouabain was investigated.

Methods: Experiments were performed on isolated, electrically driven (0.5–2 Hz, 37°C, Ca²⁺ 1.8 mmol/l) ventricular preparations. Myocardium from human failing and nonfailing hearts was obtained at cardiac surgery. To further characterize the studied myocardium, the positive inotropic effect of isoproterenol and the density of β-adrenoceptors were measured using the radioligand [125I]CYP.

Results: Halothane produced a negative inotropic effect. The anesthetic (0.38 mmol/l) reversed the negative FFR in failing myocardium, antagonized the effect of isoproterenol (0.1 mmol/l) on FFR, and restored the FFR in the presence of ouabain.

Conclusions: Halothane restores the FFR in human failing myocardium possibly by influencing the intracellular Ca²⁺ homeostasis. These findings provide evidence that pharmacologic interventions, e.g., during anesthesia, may influence contractility also as a result of a depressed or enhanced FFR.

(Key words: Force-frequency relationship. Heart failure. Human myocardium. Inhalational anesthetics.)

AN altered force-frequency relationship (FFR) in human failing myocardium has been reported in vivo and in vitro by several investigators. In nonfailing myocardium, an increase in the frequency of stimulation is accompanied by an increase of force of contraction, whereas in failing myocardium, the FFR becomes negative. It has been shown that compounds with a different mode of action have beneficial or detrimental effects on the FFR. Studying human failing and nonfailing myocardium, Schwinger et al. reported a detrimental effect of a high concentration of isoproterenol or an increased extracellular Ca²⁺ concentration on the FFR in human failing and nonfailing myocardium. In contrast, the Na⁺-channel activator BDF 9148 combined with ouabain has beneficial effects on the negative FFR in terminally failing myocardium, whereas no effect in the nonfailing myocardium has been reported. The authors of the latter study suggested that this is likely due to alterations of the intracellular Ca²⁺ handling in human failing myocardium. Halothane possesses Ca²⁺-antagonistic effects by interfering with the 1,4 dihydropyridine binding site of the L-type calcium channel in bovine, as well as in human myocardium. In addition, halothane has been reported to have effects on proteins responsible for the intracellular Ca²⁺ homeostasis, such as Ca²⁺-ATPase of the SR, ryanodine receptor, and proteins of the contractile apparatus. The current study addresses the question of whether the negative FFR can be influenced by pharmacologic agents. The effect of halothane on the FFR was studied in human myocardium, because its Ca²⁺-antagonistic properties make it a candidate to ameliorate FFR in failing heart muscle in which elevation of intracellular Ca²⁺ appears to induce deleterious effects. The potential effects of inhalational anesthetics on contractile parameters could possess important consequences in the peri- and intraoperative handling of patients with heart failure. To study whether the volatile anesthetic halothane interferes with the effect of myocardial β-adrenergic stimulation and of the frequently applied cardiac glycosides, the effects of isoproterenol and ouabain alone or in the presence of halothane on FFR were studied as well.

Methods

Myocardial Tissue

Myocardium from terminally failing human hearts was obtained from patients after cardiectomy during cardiac transplantation. In 3.5 years, 19 patients received a heart transplant. Fifteen of these patients had been attending the Cardiac Rehabilitation Center of Medical University of Vienna for 6 months before the study. Medical history included hypertension, diabetes mellitus, hyperlipidemia, smoking, and obesity. Patients received immunosuppression with cyclosporin A, azathioprine, and prednisolone. Cardiac transplant recipients were aged 36 ± 26 years and had undergone cardiomyopathy or cardiomyopathy after transplantation. Cardiac transplant recipients were aged 36 ± 26 years and had undergone cardiomyopathy or hypertrophic cardiomyopathy after transplantation. All patients received immunosuppression with cyclosporin A, azathioprine, and prednisolone. Histology: Cardiac tissue was isolated from all hearts. Histology: Cardiac tissue was isolated from all hearts. Histology: Cardiac tissue was isolated from all hearts. Histology: Cardiac tissue was isolated from all hearts.
transplantation (n = 8, 2 women and 6 men, aged 52.4 ± 3.5 yr, ejection fraction 24 ± 2%). The tissue was received from patients who suffered from dilated cardiomyopathy and were classified as NYHA IV on the basis of clinical symptoms and signs as judged by the attending cardiologist shortly before surgery. All patients gave written informed consent before surgery. All patients were receiving diuretics, angiotensin-converting enzyme inhibitors, and cardiac glycosides. Medical treatment consisted also of nitrates. Patients receiving catecholamines, β-adrenergic receptor blockers, or Ca2⁺-antagonists were withdrawn from the study. Drugs used for general anesthesia were fentanyl and pancuronium bromide with isoflurane. No opioids were used as part of the anesthetic regimen. Cardiac surgery was performed during hypothermic cardiopulmonary bypass with cardioplegic arrest. The cardioplegic solution (modified Bretschneider solution) contained (in mmol/L): NaCl 15, KCl 10, MgCl₂ 4, histidine 180, tryptophan 2, mannitol 30, and potassium dihydrogen oxoglutarate 1. Nonfailing myocardium was obtained from five donors, who were brain dead as a result of traumatic injury. The hearts of the donors were removed after cooling with ice-cold cardioplegic solution (Bretschneider). None of these patients received catecholamines or thyrroxine before transplantation. To identify these hearts as nonfailing, the clinical situation before death was considered. The attending cardiologist gave the information that the heart was useful as a donor heart to the cardiac surgeon explaing the heart. There was no evidence for left ventricular dysfunction by echocardiography. These hearts could not be transplanted for technical reasons. Histologic examination was performed to identify myocardial diseases. Immediately after explantation, the hearts were placed in ice-cold modified Tyrode solution (composition described below). To further characterize nonfailing and failing myocardium, myocardial β-adrenoceptors were quantified, and the positive inotropic effect of isoproterenol on isolated papillary muscle strips was tested. The terminally failing myocardium exhibits a downregulation of β-adrenoceptors and a reduced increase in force of contraction after stimulation with isoproterenol. 

Isolated Cardiac Preparation and Measurement of Force of Contraction

Immediately after excision, the papillary muscle strips were placed in ice-cold pre-aerated Tyrode solution and delivered to the laboratory within 10 min. Muscle strips of uniform size were dissected under microscopic control into thin strips (<1 mm thick, and 6–9 mm long) with muscle fibers running approximately parallel to the length of the strips. There was no significant difference in muscle length or weight between groups studied. Mean length of the cardiac preparations for nonfailing myocardium were 7.6 ± 0.3 mm and NYHA class IV 7.8 ± 0.2 mm. Mean weights were 4.9 ± 0.1 mg nonfailing myocardium and NYHA class IV 5.2 ± 0.2 mg. The calculated cross-sectional areas were 0.57 ± 0.04 mm² for nonfailing myocardium and NYHA class IV 0.58 ± 0.05 mm². The basal force of contraction were 4.7 ± 0.5 and 4.8 ± 0.5 mN/mm² respectively.

The muscles were suspended in an organ bath (75 ml), maintained at 37°C, and containing a modified Tyrode solution of the following composition (in mmol/L): NaCl 119.8, KCl 5.4, MgCl₂ 1.05, CaCl₂ 1.8, NaHCO₃ 22.6, NaH₂PO₄ 0.42, glucose 5.0, ascorbic acid 0.28, and EDTA 0.05. The bathing solution was continuously aerated with 95% O₂ and 5% CO₂. The muscles were stimulated by two platinum electrodes using field stimulation from a Grass S88 (Grass, Quincy, MA) stimulator (frequency 1 Hz, impulse duration 5 ms, intensity 10–20% greater than threshold). The resting tension did not differ between failing (4.7 ± 0.1 mN) and nonfailing myocardium (4.6 ± 0.1 mN). There was no change in resting- and diastolic tension during the entire experiment. The rate force development changed in parallel with the total developed tension. This holds true for nonfailing and failing myocardium. The developed tension was measured isometrically with an inductive force transducer (W. Fleck, Mainz, Germany) attached to either a Hellige Helco Scriptor (Hellige, Freiburg, Germany) or a Gould recorder (Gould, Cleveland, Ohio). Preparations were allowed to equilibrate for at least 90 min, with the bathing solution being changed once after about 45 min. After complete mechanical stabilization, the FFR was studied starting with 0.5 Hz. The duration of stabilization was constant (5 min) until complete stabilization of force development.

Halothane was administered with a Vapor 19 vaporizer (Dräger, Lübeck, Germany) to the carbogen and bubbled into the organ baths. Concentration response curves for 0–4% halothane were determined by adding the drug cumulatively to the organ bath after equilibration of the previous effects (force of contraction stable for 5 min). Control strips were handled identically.
To study the effect of halothane on the FFR, the anesthetic (2%) was bubbled into the organ chambers. The FFR was studied after stabilization of the muscle strips, starting with a rate of 0.5 Hz. The duration of stimulation for a given frequency was constant (5 min) until complete stabilization of force of contraction. Control strips were handled identically. Inotropic interventions were performed at 1 Hz. The FFR was studied in the same way as under basal conditions. Each pharmacologic intervention was studied using a separate papillary muscle strip.

Control strips showed no change in baseline isometric contraction during that period. At the end of the experiments, maximal force development was studied using an extracellular elevation of the Ca\(^{2+}\) concentration (up to 15 mmol/l). There was no difference in force generation between nonfailing- and failing myocardium.

Membrane Preparation and Radioligand Binding
Membrane preparation and binding experiments were performed as described previously.

Determination of Halothane Concentrations
Halothane was administered with a Vapor 19 vaporizer (Dräger, Lübeck) to the carbogen (95% O\(_2\) + 5% CO\(_2\)) and bubbled into the organ baths. A concentration of 0–4% was added to the carbogen, giving a concentration of 0–0.75 mmol/l in the chamber, or approximately 60–65% of the values predicted, based on published partition coefficients for halothane. The concentration of halothane in the bathing solution was measured by gas chromatography using a head-space analysis. Separation was done on a 60-m capillary column (RTX 1701, ID 530 μm).

Materials
Halothane was from Hoechst AG (Frankfurt/Main, Germany), and isoproterenol was from Sigma Chemical Company (Deisenhofen, Germany). Ouabain was obtained from Boehringer (Mannheim, Germany). D L-Propranolol was from ICI GmbH (Heidelberg, Germany). \(^{125}\)I-CYP (specific activity 1800 Ci/mmol/l) was from Amersham-Buchler (Braunschweig, Germany). All other compounds used were the best grade commercially available. Deionized and twice-distilled water was used.

Statistical Evaluation
The data shown are mean ± SEM. Statistical significance was estimated with Student's t test for unpaired observations and analysis of variance. A P value of less than 0.05 was considered significant (SPSS PC plus).

Results
Figure 1 (top) illustrates the concentration-response curve for halothane. The anesthetic produced a concentration dependent decrease in force of contraction that was significant at each concentration of halothane, both in the nonfailing (NF) and failing myocardium. As seen in the figure, the effect of halothane was markedly greater in the failing myocardium than in the nonfailing myocardium. The concentration of halothane at which half-maximal antagonism was achieved was defined as EC\(_{50}\). Thus, halothane antagonizes both nonfailing and failing myocardium.

Under conditions of isometric contraction from 0.5 to 1.0 Hz, halothane produced a concentration-dependent decrease in force of contraction. In contrast, isoproterenol produced a concentration-dependent increase in force of contraction. In the nonfailing myocardium, the EC\(_{50}\) for halothane was 2.2 ± 0.3 mmol/l, and the EC\(_{50}\) for isoproterenol was 0.02 ± 0.001 mmol/l. In the failing myocardium, the EC\(_{50}\) for halothane was 0.7 ± 0.1 mmol/l, and the EC\(_{50}\) for isoproterenol was 0.03 ± 0.001 mmol/l. Thus, halothane antagonized both nonfailing and failing myocardium.

that was similar in nonfailing and failing myocardium with regard to potency and efficacy. The IC50 value was about 2% (0.38 mmol/l) halothane. The following experiments were performed in the presence of 2% halothane, that concentration that produced a negative inotropic effect of about 40% of predrug value. The middle and bottom panels show original recordings illustrating the effects of isoproterenol (middle) and ouabain (bottom) in the presence and absence of halothane on isometric force of contraction. Halothane (2%) produced a negative inotropic effect alone, but the positive inotropic effect of isoproterenol was enhanced in the presence of halothane (right) compared to control (left). Ouabain alone produced a small positive inotropic effect in the absence of halothane (left) that holds true in the presence of the anesthetic (right). Thus, halothane produced opposite effects on the basal and isoproterenol stimulated force of contraction.

Under basal conditions, after an increase in stimulation frequency (from 0.5 to 2 Hz), force of contraction increased in human nonfailing myocardium. In contrast, in terminally failing myocardium, the FFR became negative (fig. 2). Myocardial β-adrenoceptors were quantified using 125I-CYP-binding to demonstrate that the samples exhibit a biochemical alteration well characterized in the failing human heart, namely a down-regulation of β-adrenoceptors. The maximal binding of 125I-CYP was significantly reduced in terminally failing myocardium (Bmax, 50 ± 3 fmol/mg protein) compared to nonfailing myocardium (Bmax, 72 ± 4 fmol/mg protein). In addition, the maximal positive inotropic effect of isoproterenol on isolated electrically driven papillary muscles strips was also significantly reduced in terminally failing myocardium (3.7 ± 0.2 mN) compared with nonfailing myocardium (8.8 ± 0.4 mN).

Figure 3 illustrates the effect of halothane on the FFR in failing human myocardium. In the presence of the anesthetic the former negative FFR became positive (P < 0.05). In human nonfailing myocardium, the positive FFR was not affected by the anesthetic.

To investigate the effect of the anesthetic on the FFR after β-adrenergic stimulation, the FFR was studied after pretreatment with isoproterenol (0.1 µmol/l) alone and with isoproterenol in the presence of halothane. The efficacy of isoproterenol was enhanced in the presence of halothane (P < 0.05, table 1). Isoproterenol alone worsened the FFR (fig. 4A). In the presence of halothane the FFR became restored.

Figure 4B summarizes the effect of halothane on FFR in ouabain (0.02 µmol/l)-treated human papillary muscle strips. Ouabain alone had no positive inotropic effect, whereas in the presence of the anesthetic, a

---

Anesthesiology, V 82, No 6, Jun 1995
Table 1. Absolute Values of Contractile Parameters Studied

<table>
<thead>
<tr>
<th></th>
<th>FOC 0.5 Hz (mN)</th>
<th>FOC 2 Hz (mN)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal force of contraction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfailing</td>
<td>2.7 ± 0.2</td>
<td>4.1 ± 0.4</td>
</tr>
<tr>
<td>Failing</td>
<td>2.8 ± 0.3</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td><strong>Inotropic stimulation in</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Basal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halothane</td>
<td>2.8 ± 0.3</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>+Halothane</td>
<td>2.1 ± 0.3</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td><strong>Isoproterenol (0.1 μM)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−Halothane</td>
<td>3.7 ± 0.6</td>
<td>2.7 ± 0.4</td>
</tr>
<tr>
<td>+Halothane</td>
<td>8.7 ± 0.9</td>
<td>10.1 ± 0.9</td>
</tr>
<tr>
<td><strong>Ouabain (0.02 μM)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−Halothane</td>
<td>3.1 ± 0.8</td>
<td>3.1 ± 0.7</td>
</tr>
<tr>
<td>+Halothane</td>
<td>4.5 ± 0.8</td>
<td>5.3 ± 0.3</td>
</tr>
</tbody>
</table>

Values for force of contraction (FOC) are given as mean ± SEM.

slightly positive inotropic effect was observed. Halothane was able to augment force of contraction after an increase in stimulation frequency (P < 0.05).

**Discussion**

The current study provides evidence that the FFR in failing myocardium can be influenced by pharmacologic interventions. Halothane restored the negative FFR in terminally failing heart and was able to prevent the detrimental effect of an intracellular enhancement of CAMP by isoproterenol. Furthermore, the anesthetic augmented the force of contraction after an increase in frequency of stimulation in the presence of ouabain.

In terminally failing myocardium, an increase in frequency of stimulation is accompanied by a reduction of force of contraction in vitro. In these studies, as well as in the current study, the tension generation per cross-sectional area did not differ between failing and nonfailing myocardium when stimulated at basal stimulation, but it became evident when increased stimulation rates were employed. The negative treppe phenomenon also was observed in patients suffering from severe heart failure. Rapid atrial pacing (1.3–2 Hz) produced no increase in peak rate of left ventricular pressure rise (dp/dtmax) in patients with heart failure due to dilated cardiomyopathy, whereas in healthy volunteers, this procedure is accompanied by an increase in dp/dtmax of 30%. The negative FFR in human failing myocardium could be due to an altered Ca2⁺ homeostasis. Using the Ca2⁺-indicator aequorin, Gwathmey et al. reported in myocardial hearts an additional signal L2 indicating an elevation of the diastolic Ca2⁺ concentration. In addition, Beuckelmann et al. reported in isolated cardiomyocytes from terminally failing hearts an increase of the diastolic Ca2⁺ concentration. The hypothesis that the negative FFR is due to an altered Ca2⁺ homeostasis is supported by the findings of Schwinger et al. They reported a negative effect of an elevation of the extracellular Ca2⁺ concentration on FFR in human failing and nonfailing myocardium. Furthermore, magnesium ions, which possess Ca2⁺-antagonistic effects, have been reported to prevent the detrimental effect of an increase of the FFR in failing myocardium.

It has been proposed that the increase in venous return with low cardiac output in the failing heart may result from an increased adrenergic tone and the inhibition of the activation of phosphoinositides. This action of the venoconstrictor effect of noradrenaline is accompanied by a decrease in FFR. The influence of adrenergic tone on FFR has been reported to be important in the pathophysiology of failing myocardium. The negative FFR in failing myocardium is associated with an increase in venous return and a decrease in cardiac output. The negative FFR in failing myocardium is associated with an increase in venous return and a decrease in cardiac output. The negative FFR in failing myocardium is associated with an increase in venous return and a decrease in cardiac output.

**Fig. 4.** Force-frequency relationship (0.5–2 Hz) after inotropic stimulation with (A) isoproterenol (0.1 μmol/l) and (B) ouabain (0.02 μmol/l) alone and in the presence of halothane in electrically driven papillary muscle strips from human failing myocardium. Asterisks denote significance versus 0.5 Hz (P < 0.05). Seventeen to nine preparations of six hearts were studied in each group. Abscissa = frequency of stimulation (Hz); ordinate = change in force of contraction (mN).

Anesthesiology, V 82, No 6, Jun 1995
rimental effect of an elevated Ca\(^{2+}\) concentration on the FFR in isolated human myocardium.\(^8\)\(^-\)\(^10\)

It has been observed that high concentrations of isoproterenol worsened the FFR (five, this study), whereas low concentrations possess a positive effect on the FFR in failing myocardium.\(^5\) Stimulation of myocardial β-adrenoceptors increased intracellular cAMP levels and the activity of the protein kinase A. This leads to a phosphorylation of the sarcolemmal L-type Ca\(^{2+}\) channels, followed by an increased influx of Ca\(^{2+}\) ions,\(^17\) and to a phosphorylation of phospholamban, accompanied by an increased uptake of Ca\(^{2+}\) ions into the SR.\(^18\) Phospholamban phosphorylation occurs at lower cAMP levels than Ca\(^{2+}\)-channel phosphorylation.\(^19\) Diastolic Ca\(^{2+}\) levels are increased in myopathic cells,\(^13\) and high concentrations of isoproterenol lead to a further increase of the diastolic Ca\(^{2+}\) concentration. Such an increase will have adverse effects on the FFR in failing myocardium. In contrast, low concentrations of isoproterenol induce only phosphorylation of phospholamban and augmentation of the Ca\(^{2+}\) uptake in the SR. This effect will enhance the FFR. Cardiac glycosides act by inhibiting the membrane bound Na\(^+\)/K\(^+\)-ATPase, thereby increasing the intracellular Na\(^+\) concentration. This activates the intracellular Na\(^+\)/Ca\(^{2+}\) exchanger to enhance the intracellular Ca\(^{2+}\) concentration.\(^20\) It has been reported that a concentration of ouabain (0.4 μmol/l) that increased the intracellular Ca\(^{2+}\) concentration worsened the FFR in human failing myocardium.\(^21\) In contrast, ouabain in a concentration that exerts only a slight positive inotropic effect partially restored the FFR.\(^2\) This may be due in larger part to the action of ouabain on the Na\(^+\) influx than to an alteration of the intracellular Ca\(^{2+}\) homeostasis, because it has been reported that Na\(^+\) ions exert a positive effect on FFR in rat myocytes.\(^20\) Accordingly, the Na\(^+\) activator BDF 9148, with a low concentration of digitalis, has been reported to restore the FFR in failing human myocardium.\(^3\) The general anesthetic octanol has been shown to inhibit the Na\(^+\)/Ca\(^{2+}\) exchanger in adult rat myocytes.\(^22\) However, it is unknown whether halothane inhibits Na\(^+\)/Ca\(^{2+}\) exchanger in human myocardium.

The current study provides evidence that halothane is able to restore the positive FFR in failing myocardium. It antagonized the deleterious effect of a high concentration of isoproterenol and increased the FFR in the presence of ouabain. This may be caused by actions of halothane on the intracellular Ca\(^{2+}\) homeosta-sis, e.g., on the sarcolemmal Ca\(^{2+}\) influx and on the SR function. An antagonistic effect of halothane on L-type Ca\(^{2+}\) channels has been observed in functional studies on electrically driven left ventricular multicellular preparations\(^4\) as well as radioligand binding studies on membrane preparations obtained from human left ventricular myocardium.\(^7\) Beside these effects on the L-type Ca\(^{2+}\) channel, the anesthetic has been reported to have effects on proteins responsible for the intracellular Ca\(^{2+}\) homeostasis. The anesthetic increased the Ca\(^{2+}\)-ATPase activity of SR vesicles isolated from the fast twitch skeletal muscle of rabbits.\(^8\) In experiments investigating the Ca\(^{2+}\)-release from the bovine cardiac sarcoplasmic reticulum, halothane increased the duration of the “open state” of the Ca\(^{2+}\)-release channel.\(^9\) Recently, halothane has been reported to decrease the Ca\(^{2+}\)-sensitivity of skinned fiber preparations obtained from human myocardium indicating effects on the contractile apparatus.\(^11\)

In addition to these effects of halothane on the intracellular Ca\(^{2+}\) homeostasis of the cell, halothane increased the positive inotropic effect of isoproterenol in isolated human papillary muscle strips obtained from terminally failing myocardium.\(^35\)\(^\)\(^-\)\(^36\) In addition, halothane has been shown to increase the adenylate-cyclase activity in human membrane preparations as well as in S49 lymphoma cells due to an impairment of G\(\alpha\) function.\(^37\) These mechanisms play a crucial role in the observed increase of the positive inotropic effect of isoproterenol in the presence of halothane.\(^33\) The enhancement of adenylate-cyclase activity leads to an increase of PKA activity accompanied by an increase of cAMP accompanied by an increase of PKA activity. Because the Ca\(^{2+}\) influx through L-type Ca\(^{2+}\) channels is antagonized by halothane, one can suggest that, in the presence of halothane, the Ca\(^{2+}\) uptake into the SR is enhanced via phosphorylation of the phospholamban rather than the Ca\(^{2+}\) influx via phosphorylation of the L-type Ca\(^{2+}\) channel. Furthermore, the anesthetic has been reported to stimulate the Ca\(^{2+}\)-ATPase of sarcoplasmic vesicles in striated muscles obtained from rabbits.\(^8\) If this holds true in human myocardium, the direct effect of halothane on the Ca\(^{2+}\) uptake into the SR would be a potential explanation for the beneficial effects of the anesthetic on the FFR in isolated human failing myocardium.

The results of this study provide evidence that halothane possesses beneficial effects on the FFR in human failing myocardium. The described effects may be due to the effect of halothane on the Ca\(^{2+}\) homeostasis of the failing myocardium by preventing a diastolic “Ca\(^{2+}\) overload” of the failing myocardium. Whether this phenomenon could be beneficial for the force gener-
ation in clinical situations with enhanced stimulation frequencies in patients with compromised left ventricular function is uncertain.

References

Anesthesiology. V 82, No 6, Jun 1995