Influence of opioids on the vascular tone of isolated porcine coronary artery segments

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Background: It was the aim of this study to elucidate the influence of opioids on coronary vascular tone using the model of isolated porcine coronary artery segments.

Methods: We studied the effects of fentanyl (0.01, 0.1, 1.0 μg ml⁻¹), alfentanil (0.1, 1.0, 10 μg ml⁻¹), and sufentanil (0.01, 0.1, 1.0 μg ml⁻¹) on the contractile response to three vasoconstrictors, acetylcholine, histamine and serotonin.

Results: Fentanyl (0.1, 1.0 μg ml⁻¹) dose-dependently attenuated the contractile response to acetylcholine, but not to histamine and serotonin. There were no differences in fentanyl’s vasorelaxing potency between rings with intact and denuded endothelium. Alfentanil and sufentanil did not exert any significant influence on any of the vasoconstrictors tested.

Conclusion: It is concluded that, in isolated porcine coronary artery rings, fentanyl at high concentrations has an attenuating effect on acetylcholine-induced contractions, which is independent of endothelial function, whereas alfentanil and sufentanil do not influence coronary vascular tone.

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Opioids are widely used in clinical anaesthesia as analgesics during inhalational anaesthesia or as part of a total intravenous anaesthesia. Substances most commonly used are fentanyl, alfentanil, sufentanil, and the short-acting compound remifentanil. Haemodynamic stability is maintained during opioid analgesia even if high doses are administered (1). However, the direct effects of opioids on the vascular tone of coronary arteries are poorly understood. Especially in patients with coronary artery disease the influence of opioids on coronary blood flow is of great importance. In healthy individuals there is a balance of vasodilating (endothelium-derived relaxing factor, EDRF (2), endothelium-derived hyperpolarizing factor, EDHF (3), prostacyclin, PGI₂ (4)) and constricting factors regulating the tone of the vessels. In patients with endothelial dysfunction this balance is likely to be compromised and may promote acute coronary syndromes (5). There is no doubt that patients with coronary artery disease are at risk of myocardial infarction when undergoing non-cardiac surgery (6). It is a matter of debate whether substances administered during anaesthesia may aggravate or alleviate the dysbalance of vasoconstricting and dilating factors. It was the aim of this study to elucidate the effects of three opioids (fentanyl, alfentanil, sufentanil) on isolated coronary arteries. Endothelial intact and denuded segments were studied to clarify whether possible effects are dependent on endothelial function or not.

Methods

Material and vessel preparation
This study was performed in porcine coronary artery segments. Hearts of adult pigs were obtained immediately post mortem at a nearby slaughterhouse and stored in ice-cold Krebs-Ringer solution. Left anterior descending coronary arteries were dissected from the hearts, flushed with Krebs-Ringer solution, cleaned of surrounding fat and cut into 3 mm wide rings (n=4–12 per vessel). In half of the segments, the endothelium was deliberately removed by gently rubbing the vessel intima. Artery rings were placed in organ chambers filled with 10 ml of Krebs-Ringer solution at 37°C and bubbled with an O₂ (95%)/CO₂ (5%) gas mixture. The vessel segments were suspended between two stainless steel hooks, one of which was anchored in the organ chamber and the other connected to a high fidelity force transducer (Hugo Sachs Elektronik, March, Germany), allowing continuous measurement of vessel tension and display on a printer.

The following compounds were used: fentanyl (Fentanyl, Janssen), alfentanil (Rapifen, Janssen), and
sufentanil (Sufenta, Janssen). All drugs were dissolved in distilled water. The Krebs-Ringer solution contained (mmol l\(^{-1}\)): NaHCO\(_3\) 25.0, indomethacin 0.03, glucose 11.1, titriplex III 0.026, MgSO\(_4\)·7H\(_2\)O 1.2, KH\(_2\)PO\(_4\) 1.2, KCl 4.7, CaCl\(_2\) 1.9, and NaCl 118.2. These drugs were purchased from Sigma.

Experimental protocol
Having stretched the artery rings until an optimum level had been reached, they were allowed to equilibrate for 45 min. A standard contractile response to 8×10\(^{-2}\) mol l\(^{-1}\) KCl was obtained first. Having flushed the segments, a long-lasting contraction was obtained with 3.5×10\(^{-5}\) mol l\(^{-1}\) PGF\(_2\alpha\). The effectiveness of the endothelial denudation was assessed by exposing the rings to 10\(^{-6}\) mol l\(^{-1}\) bradykinin. In rings with a dilation of more than 60% of the PGF\(_2\alpha\) contraction an intact endothelial function was supposed, while those with a dilation of less than 10% were regarded as segments with poor endothelial function. Preparations meeting neither of the two criteria were excluded. We studied the influence of fentanyl (0.01, 0.1, 1.0 μg ml\(^{-1}\)), alfentanil (0.1, 1.0, 10 μg ml\(^{-1}\)), and sufentanil (0.01, 0.1, 1.0 μg ml\(^{-1}\)) on the effects of three vasoconstricting mediators, acetylcholine (3.5×10\(^{-5}\) mol l\(^{-1}\)), histamine (2×10\(^{-5}\) mol l\(^{-1}\)), and serotonin (3×10\(^{-5}\) mol l\(^{-1}\)). First, the contractile response to each mediator was obtained. Having allowed the rings to rest for 60 min, they were contracted again, having added the anaesthetic drug two minutes before. Sixty minutes later, the contractile response to the mediator was repeated without the anaesthetic.

Statistics
The contractile response to each vasoconstrictor in the presence of the anaesthetic (k\(_1\)) was compared with the contractile response in the absence of the anaesthetic (k\(_2\)), where k\(_2\) is the mean of contractions before and after the contraction in the presence of the opioid. Dilation was defined as D [%]=100−k\(_1\)/(k\(_2\)/100) and expressed as mean±SEM. Student’s t-test was used for the comparison of mean values of rings contracted in the presence and absence of the anaesthetic. A P-value <0.05 was regarded as statistically significant.

Results
For each opioid 34–36 rings obtained from 12 vessels from 12 animals were studied. The contractile response to acetylcholine, histamine, and serotonin in the absence of an opioid (control values) are given in Table 1.

Histamine- and serotonin-mediated contractions were not influenced by pretreatment of the rings with

Table 1
| Contractile response to vasoconstrictors in tension (g). |
|-----------------|-----------------|
| Tension (g)     | Tension (g)     |
| denuded rings (n=149) | intact rings (n=151) |
| KCl | 7.2±0.5 | 8.0±0.2 |
| Acetylcholine | 6.4±1.7 | 6.1±1.6 |
| Histamine | 8.8±1.6 | 8.8±1.6 |
| Serotonin | 2.9±0.9 | 2.7±0.4 |

The values are means±SD. There were no significant differences between intact and denuded rings.
fentanyl, alfentanil, or sufentanil even when administered in high concentrations (Figs. 1 and 2).

Acetylcholine-induced contractions, however, were attenuated after pretreatment with medium (0.1 µg ml\(^{-1}\), \(-14\%\), \(P<0.05\)) and high (1.0 µg ml\(^{-1}\), \(-22\%\), \(P<0.05\)) concentrations of fentanyl, whereas alfentanil and sufentanil did not exert a significant effect on acetylcholine-mediated contractions (Fig. 3). There were no differences in the vasorelaxing potency of fentanyl in intact and denuded preparations (data not shown in detail).

Discussion

Opioids are a class of substances with a high receptor affinity. Consequently, low concentrations are needed for sufficient analgesia. For fentanyl, serum concentration is reported to be about 50 ng ml\(^{-1}\) (7, 8). Taking into consideration a protein bound fraction of 79–84% (9), the unbound part equals about 10 ng ml\(^{-1}\).

For alfentanil, total and free serum concentrations are 10-fold higher (100 and 1000 ng ml\(^{-1}\)) (9, 10). The serum concentration of sufentanil needed for analgesia is 7–12 ng ml\(^{-1}\) (11). On the basis of these pharmacokinetic data the concentrations studied in organ chambers in our experiments were chosen.

With a few exceptions (12–14), data concerning the influence of opioids on coronary arteries have not been presented yet. There is, however, a number of studies in rat or rabbit aorta (15–17). These results suggest that fentanyl acts as an alpha-blocking substance. It was demonstrated that fentanyl attenuates norepinephrine-(15) and phenylephrine-mediated contractions (16, 17), and that this effect is independent of endothelial function and of opioid receptors (18). It seems to be mediated by an attenuation of the norepinephrine-induced phosphatidylinositol response (19).

Blaise et al. (12), studying isolated canine coronary arteries, intact pig and isolated rat hearts, found no relevant influence of fentanyl on vascular reactivity or myocardial metabolism. However, acetylcholine contractions were not tested. It was Yamanoue et al. (13) who demonstrated that fentanyl attenuates the contractile response to acetylcholine independently of endothelial function or opioid receptors. This effect, which was not seen with morphine or sufentanil, is obviously due to a specific blockade of the M\(_3\) subtype of muscarinic receptors in vascular smooth muscle (14), but is not mediated by sigma receptor activation (20).

This finding explains why fentanyl has no positive chronotropic properties, as this effect is mediated by the M\(_3\) subtype of muscarinic receptors. In the vessel wall, however, where M\(_3\) subtype receptors predominate, fentanyl’s antimuscarinic effect mediates vasodilatory action.

Our results are in accordance with these data, indicating that fentanyl dose-dependently attenuates the contractile response to acetylcholine, but not to histamine and serotonin. Our work is the first to show that neither alfentanil nor sufentanil share this effect. These opioids did not exert any significant influence on the contractile responses to any of the constrictors tested. This indicates that the anti-muscarinic effect of fentanyl is a specific feature of this substance, and is not shared by other opioids. To answer the question whether this probably desirable effect seen in \textit{in vitro} experiments is really relevant in clinical anaesthesia, further studies including \textit{in vivo} measurements are warranted. Further experimental data are needed to elucidate the exact mechanisms whereby fentanyl attenuates the contractile response in coronary arteries.

In summary, our study had three principal results:

1. In isolated coronary arteries, alfentanil and sufentanil do not alter the contractile responses to different vasoconstrictors.
2. In this model, fentanyl is devoid of significant effects on histamine- or serotonin-mediated contractions, but has an antimuscarinic potency.
3. This effect is independent of endothelial function.

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