Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 34, No. 1, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00147-3

Effect of Acetylsalicylate on Cardiac and Muscular Pain Induced by Intracoronary and Intra-Arterial Infusion of Bradykinin in Humans

Achille Gaspardone, MD, MPHIL, FACC, Filippo Crea, MD, FACC, Fabrizio Tomai, MD, FACC, Francesco Versaci, MD, FACC, Antonio Pellegrino, MD, Luigi Chiariello, MD, FACC, Pier A. Gioffré, MD

Rome, Italy

OBJECTIVES This study assessed the algesic activity of bradykinin (BK) in humans and the effects of acetylsalicylate on muscular and cardiac BK-induced pain.

BACKGROUND Bradykinin is released by the ischemic myocardium and may be involved in the genesis of ischemic pain.

METHODS Increasing doses of BK (from 30 to 960 ng/min) were randomly infused, for periods of 2 min each, into the iliac artery of 10 patients. The same protocol was repeated 30 min after the IV administration of 1 g of acetylsalicylate. In eight other patients with coronary artery disease, the same increasing doses of BK, for periods of 2 min each, were infused into the left coronary artery. The same protocol was repeated 30 min after the IV administration of 1 g of acetylsalicylate. Time to pain onset and maximal pain severity were obtained.

RESULTS Before acetylsalicylate administration, all patients experienced pain during intra-iliac infusion of BK. After acetylsalicylate, eight patients did not experience any pain during BK infusion ($p = 0.0014$), and in the two remaining patients, time to pain onset and maximal pain severity were similar to those recorded before acetylsalicylate. Before acetylsalicylate administration, all patients experienced pain similar to their habitual angina during intracoronary BK infusion. After acetylsalicylate, six patients did not experience any pain during BK infusion ($p = 0.0098$), whereas in the two remaining patients time to pain onset and maximal pain severity were similar to those recorded before acetylsalicylate.

CONCLUSIONS Intra-iliac infusion of BK causes muscular pain, and its intracoronary infusion in patients with coronary artery disease causes cardiac pain, which is similar to their habitual angina. The BK-induced pain is abolished or reduced by acetylsalicylate, thus suggesting that acetylsalicylate-sensitive mediators, such as prostaglandins, are involved in its pathogenesis. (J Am Coll Cardiol 1999;34:216–22) © 1999 by the American College of Cardiology

Bradykinin (BK), a polypeptide with potent vasodilator and algesic properties, is released in large amounts by ischemic myocardium (1) and is believed to be a mediator of cardiac ischemic pain (2–5). Applied directly to the exposed epicardium, BK stimulates afferent nerve endings (6), and autoradiographic studies have demonstrated BK receptors in myocardial-sensory neurons (7). Furthermore, a number of experimental studies have shown the antinociceptive effects of BK antagonists (7–9). Although BK has been used for more than 20 years as a pain-causing substance, and although there is convincing experimental evidence that BK causes activation of cardiac afferent nerves, its precise role in the genesis of cardiac pain in humans remains uncertain.

To establish the role played by BK in the genesis of cardiac pain and to explore the mechanisms of its algesic properties, we carried out a systematic study in humans of intra-arterial BK infusion before and after administration of acetylsalicylate.

METHODS

The study protocols were approved by the institutional Ethics Committee, and all patients gave informed signed consent.

Bradykinin and adenosine preparation. The BK (50 μg in ampules of 1 ml of physiologic saline solvent) was provided by Clinalfa AG (Laufelfingen, Switzerland). Adenosine (2.7 mg/ml in ampules of 2 ml) was provided by Sigma Tau Pharmaceutics (Pomezia, Italy). Both substances

From the Divisione di Cardiochirurgia, Università di Roma Tor Vergata, Rome, Italy. This study was supported by a grant from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST 60%, AF 1997).

Manuscript received October 13, 1998; revised manuscript received February 2, 1999, accepted March 15, 1999.

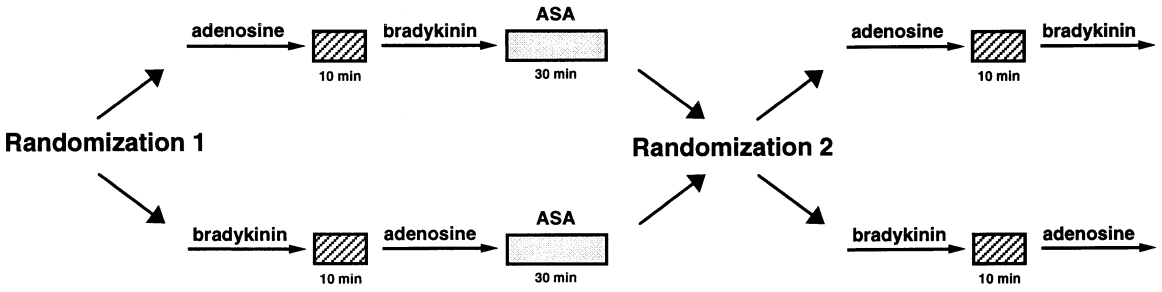


Figure 1. Diagrammatic representation of the infusion protocol for intra-iliac study. After randomization, BK or adenosine was infused at increasing doses for periods of 2 min each. At the onset of pain, either BK or adenosine infusion was continued to complete the infusion protocol and was then stopped. Ten minutes after the disappearance of BK or adenosine-induced pain, the cross-over infusion with adenosine or BK was carried out. At the end of the first phase of the infusion protocol, acetylsalicylate was infused intravenously. Thirty minutes after the end of acetylsalicylate infusion a second randomization was performed, and the same infusion protocol with BK or adenosine was repeated.

were stored at −60°C and were dissolved in normal saline to the final concentrations on the day of the study.

Intra-iliac study. A total of 10 consecutive patients with coronary artery disease (8 men; mean age 61 ± 9 years; range 48 to 71 years) who did not show any evidence of peripheral vascular disease (ankle-brachial index >1 assessed by vascular Doppler) participated in this study. Calcium channel-blocking and beta-adrenergic blocking agents were withdrawn two days before the study. Patients were also requested to abstain from xanthine-containing drugs, food, and drinks for at least 48 h before the study. At the end of routine cardiac catheterization, patients underwent a randomized cross-over study of the algogenic effects of the infusion of BK and adenosine (Fig. 1). After heparinization (5,000 IU IV), a 5F catheter was inserted through a 7F femoral sheath and advanced into the right external iliac artery. Either BK (at increasing doubling doses from 30 to 960 ng/min for periods of 2 min each) or adenosine (at increasing doubling doses from 108 to 3,456 μg/min for periods of 2 min each) was then infused. Either BK or adenosine infusion was continued also after pain onset to complete the infusion protocol. The time to pain onset (in seconds from the beginning of the infusion) and maximal pain severity were recorded. Six patients received BK, and four patients received adenosine as first infusion. Arterial blood pressure, obtained via the side port of the femoral sheath, and the standard 12 electrocardiographic (ECG) leads were recorded continuously throughout the study. The same infusion protocols were repeated, after a second randomization, 30 min after IV infusion of 1 g of lysine acetylsalicylate (Sanofi Winthrop, Milan, Italy). Five patients received BK and five patients received adenosine as first infusion.

ASSESSMENT OF BLOOD FLOW VELOCITY. Right iliac artery blood flow velocity was measured at baseline and after every step of infusion of BK or adenosine by using an intravascular 0.014-in. Doppler guide wire (FloWire and FloMap, Cardiometrics, Inc.). A Doppler guide wire was advanced through the 5F femoral sheath into the right external iliac artery and positioned until an optimal and stable Doppler signal, not in the proximity of a side branch, was obtained. Blood flow velocity was calculated from the Doppler frequency shift of a reflected 15-MHz signal by fast Fourier transformation and displayed in a spectral format, as previously described (10). Flow velocity signals were continuously displayed throughout the study. Average peak velocity (cm/s) was derived automatically by the integrated signal-analyzing computer. Satisfactory velocity data were obtained for all 10 patients. A derived resistance-related index (mean blood pressure/average blood flow velocity) was calculated at the end of each infusion dose.

Intracoronary study. Eight patients (6 men; mean age 59 ± 11 years, range 44 to 65 years) with stable angina pectoris and significant left coronary artery atherosclerosis participated in this study. No patient had suffered a previous myocardial infarction. All patients had an exercise test positive for myocardial ischemia and angina. All patients had at least one significant coronary artery stenosis (internal diameter reduction >70% by visual assessment): 3 patients had significant stenosis in the left anterior descending coronary, 2 patients in the proximal circumflex, and 3 patients in both arteries. All patients were normotensive, in sinus rhythm and without evidence of heart failure, cardiomyopathy or valvular disease. Patients with history of glucose intolerance were excluded from the study. No patient had evidence of left ventricular hypertrophy or conduction defects that could interfere with the interpretation of ST-segment changes, and no patient was taking digitalis. Calcium channel-blocking and beta-blocking agents were withdrawn two days before the study. Patients were also requested to abstain from xanthine-containing drugs, food and drinks for at least 48 h before the study.

On completion of the diagnostic angiograms of both coronary arteries and after further heparinization (5,000 IU IV), the left coronary artery was recannulated with a 5F catheter. Increasing doubling doses of BK (from 30 to

JACC Vol. 34, No. 1, 1999
July 1999:216–22

960 ng/min for periods of 2 min each) were then infused into the left coronary artery. At the onset of pain the infusion of BK was continued to complete all the infusion protocol and was then stopped. Both the time to the onset of pain (in seconds from the beginning of the infusion) and maximal pain severity were recorded. The same infusion protocol was repeated 30 min after the IV infusion of 1 g of lysine acetylsalicylate. Arterial blood pressure, obtained via the side port of the 7F femoral sheath, and the standard 12 ECG leads were continuously recorded throughout the study.

Assessment of pain. At the beginning of each BK or adenosine infusion, patients were informed that they might develop pain because of the procedure; this request was not repeated during the infusion of BK or adenosine to avoid any potential bias. Patients were also instructed to report promptly the onset of pain and to record the maximal severity of the pain. Immediately after the infusions, patients were asked to report the maximal severity of pain using a visual analog scale (11). To this end the 100-mm scale was marked from no symptoms to severe symptoms. The scale was measured from 0 to the subject's mark in millimeters (mm). All subjects were blinded to the nature of the infused materials. Testing personnel were aware of the nature of the infused materials.

Statistical analysis. Continuous normally distributed data are expressed as mean ±1 SD and were analyzed by two-tailed paired Student *t* test. Data on pain severity, which are not normally distributed, are expressed as median and interquartile range and analyzed using the Wilcoxon rank-sum test. Repeated measures analysis of variance (ANOVA) was used to compare the effects of BK and adenosine over time regarding heart rate, mean systemic blood pressure and resistance index; for a p value <0.05, parities comparisons were performed by using the Scheffé F test. Proportions were compared by using the chi-square test. Differences were considered to be statistically significant at a p value <0.05.

RESULTS

Intra-Iliac Study

Infusion of BK and adenosine before acetylsalicylate administration. All patients experienced pain localized to the right leg during infusion of both BK and adenosine. During the BK infusion, seven patients described the pain as a feeling of heaviness associated with burning involving the entire limb below the site of injection, and three patients as severe cramp. Of note, three patients lamented to feeling a sensation of burning at the sole of the right foot and in the fingertips. During the infusion of adenosine, eight patients described the pain as a feeling of heaviness localized at the right leg with some burning sensations, and two patients as a severe cramp. In all patients, pain severity and time to the onset of pain were similar during the infusion of BK and adenosine (50 mm, interquartile range 30 to 65 vs. 54 mm, interquartile range 50 to 75, p = 0.135 and 477 ± 156 vs. 449 ± 139 s, p = 0.288) (Fig. 2). The pain disappeared spontaneously within 60 s of the end of the infusions in all patients.

No patient exhibited ECG changes during infusion of BK or of adenosine. Compared with baseline values, heart rate showed a mild but significant increase at the highest dose of BK and adenosine (68 ± 8 vs. 64 ± 9 beats/min, p = 0.048 and 69 ± 9 vs. 63 ± 8 beats/min, p = 0.043); mean arterial blood pressure was similar (100 ± 15 vs. 105 ± 12 mm Hg, p = NS and 101 ± 10 vs. 104 ± 8 mm Hg, p = NS). The resistance index decreased similarly during the infusion of both BK (p < 0.001 baseline vs. peak) and adenosine (p < 0.001 baseline vs. peak) (Fig. 3A).

Infusion of BK and adenosine after acetylsalicylate administration. After the administration of acetylsalicylate, eight patients did not experience any pain, even during the infusion of the highest dose of BK (p = 0.0014 vs. prevalence of pain before acetylsalicylate administration). In the two remaining patients, pain severity and the time to pain onset were similar to that recorded before acetylsalicylate administration (Fig. 2). Conversely, the infusion of adenosine caused pain in all patients, and pain severity and the time to pain onset did not change compared with those recorded before acetylsalicylate administration (60 mm, interquartile range 54 to 70 mm vs. 54 mm, interquartile range 50 to 75 mm, p = NS and 402 ± 160 vs. 449 ± 139 s, p = NS). Eight patients described the pain as a feeling of heaviness localized at the right leg, and two patients described a severe cramp. The character of the pain during the infusion of adenosine was similar to that reported before acetylsalicylate administration. The pain disappeared spontaneously within 60 s of the end of the infusions in all patients. Compared with baseline values, heart rate showed a mild but significant increase at the highest dose of BK and adenosine (69 ± 9 vs. 61 ± 9 beats/min, p = 0.035 and 70 ± 9 vs. 60 ± 8 beats/min, p = 0.031); mean arterial blood pressure was similar (102 ± 13 vs. 107 ± 11 mm Hg, p = NS and 102 ± 10 vs. 107 ± 9 mm Hg, p = NS). The resistance index decreased similarly during the infusion of both BK (p < 0.001 peak vs. baseline) and adenosine (p < 0.001 peak vs. baseline) (Fig. 3B).

Intracoronary Study

Infusion of BK before acetylsalicylate administration. All patients experienced chest pain during BK infusion. Median pain severity was 55 mm, interquartile range 32 to 70 mm and mean time to pain onset 536 ± 167 s (Fig. 4). In seven patients the severity, localization, and radiation of BK-induced pain were similar to those experienced during daily life. In particular, in six patients both BK-induced pain and spontaneous pain were localized in the retrosternal region without any radiation. In one patient, both BK-induced pain and spontaneous pain were localized in the retrosternal region with radiation to the left shoulder. In the

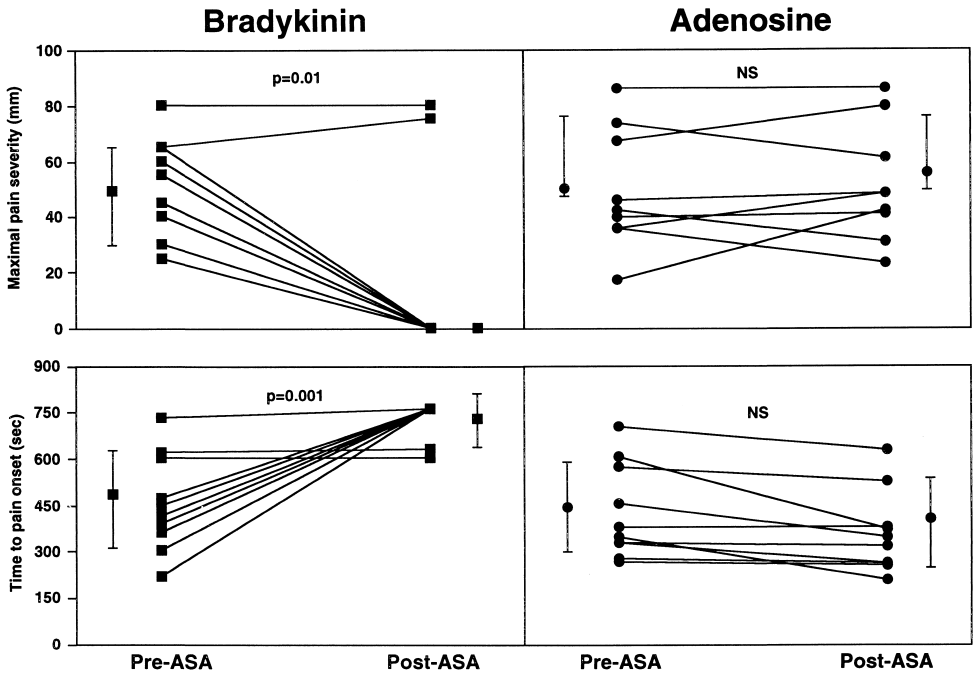


Figure 2. Maximal pain severity (median values and interquartile ranges) and time to pain onset (mean values ± SD) during the intra-iliac infusion of BK **(squares)** and adenosine **(circles)**, before and after acetylsalicylate administration. The maximal duration of the infusion was 750 s.

remaining patient, BK infusion caused retrosternal pain with radiation to the neck, both arms, and the epigastric region, whereas spontaneous pain was limited to the chest. The pain disappeared spontaneously within 60 s of the end of the infusions in all patients. No patient exhibited ECG changes during the BK infusion. Compared with baseline values, heart rate showed a mild but significant increase at the highest dose of BK (68 ± 11 vs. 63 ± 7 beats/min, $p = 0.02$); mean arterial blood pressure was similar (109 ± 10 vs. 112 ± 10 mm Hg, p = NS).

Infusion of BK after acetylsalicylate administration. After the administration of lysine acetylsalicylate, six patients did not experience any pain at all, even during the infusion of the highest dose of BK ($p = 0.0098$ vs. prevalence of pain before lysine acetylsalicylate administration). In the two remaining patients maximal pain severity and time to pain onset were similar to those experienced before acetylsalicylate administration (Fig. 4). The pain disappeared spontaneously within 60 s of the end of the infusions. Compared with baseline values, heart rate showed a mild but significant increase at the highest dose of BK (66 ± 10 vs. 62 ± 8 beats/min, $p = 0.04$); mean arterial blood pressure was similar (112 ± 10 vs. 112 ± 11 mm Hg, p = NS).

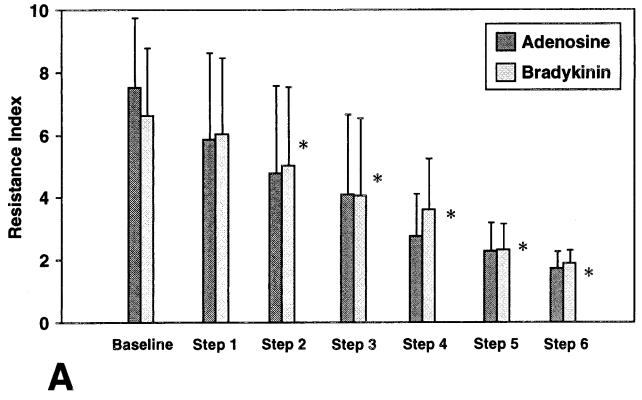
DISCUSSION

Bradykinin has been generally regarded as one of the most likely chemical mediators of ischemic pain (2–5,12). Indeed, BK is formed and released from the ischemic tissue within minutes of the onset of hypoxia or ischemia (13,14), and its algesic properties have been demonstrated in a variety of animal models (15). Furthermore, BK receptors have been localized over myocardial and coronary visceral nociceptive afferents, and several BK antagonists have been shown to block BK-induced acute vascular pain in animal models (7,8). However, despite this strong experimental evidence, in other studies the algogenic effects of BK have been disputed (16–18).

Results of the present study consistently show that, in humans, the intra-iliac infusion of BK causes pain similar to that provoked by adenosine, a known mediator of ischemic pain in man (19–21); furthermore, intracoronary infusion of BK in patients with symptomatic coronary artery disease caused cardiac pain that was similar to their habitual angina. Finally, in most individuals, acetylsalicylate abolished or reduced both muscular and cardiac pain induced by intra-arterial and intracoronary BK infusion and yet, it did not affect BK-induced vasodilation. These results indicate that BK is a potential mediator of ischemic pain in man and that its algesic effects are mainly mediated by acetylsalicylate-sensitive mediators.

Previous studies in humans. Bradykinin has been shown to cause pain by intradermal injection (22), on a blister base preparation (2,23,24) and intra-arterially (3,25,26). In 1963, Burch and Depasquale reported that injection of 1 to 10 μg of synthetic BK into the brachial artery produced pain in all the subjects studied (3). Interestingly, there was no tachy-

JACC Vol. 34, No. 1, 1999
July 1999:216–22



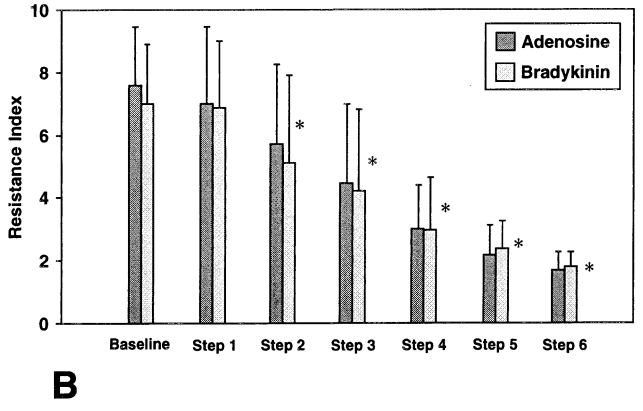
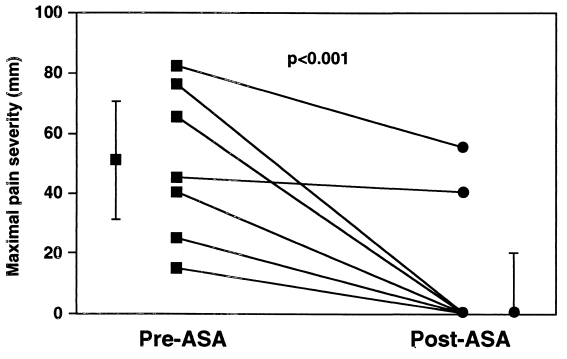


Figure 3. Effect of increasing doses of BK or adenosine on the resistance index before **(Panel A)** and after acetylsalicylate administration **(Panel B)**. Data are mean ± SD. Differences between groups (BK and adenosine) before and after acetylsalicylate administration at the different steps were not significant. *$p < 0.001$ compared with baseline values.



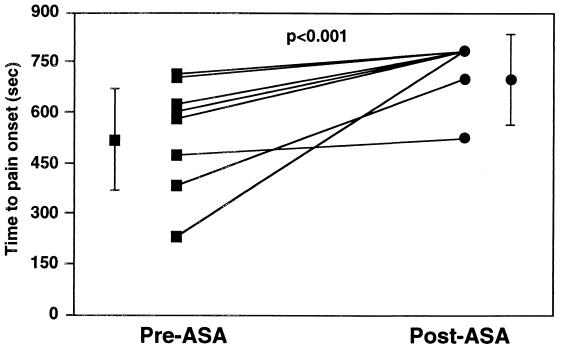


Figure 4. Maximal pain severity (median values and interquartile ranges) and time to pain onset (mean values ± SD) during intracoronary infusion of BK, before and after acetylsalicylate administration. The maximal duration of the infusion was 750 s.

phylaxis of the pain to repeated intra-arterial injections. The absence of tachyphylaxis was later confirmed by Coffman (26), who showed that the latency of pain response and pain severity remained essentially unchanged with BK injections given at 15-min intervals for 2 h. Furthermore, in this latter study, pain induced by the intra-arterial injection of BK was not related to its vasodilatory effect and was reduced or abolished after the oral administration of buffered sodium or calcium acetylsalicylic acid. More recently, the intracoronary administration of BK in individuals with and without coronary artery disease was shown to elicit a painful sensation, which, however, in patients with ischemic heart disease appeared to be different from their habitual angina (17). Finally, in contrast to effects observed in dogs (1), Eldar et al. (18) reported that ischemic pain induced by the occlusion of left anterior descending coronary artery during balloon angioplasty was not associated with an increase in BK plasma levels in the great cardiac vein.

The present study. In our study, the intra-arterial infusion of BK caused a painful sensation, which, in most individuals, was similar to that elicited by the infusion of adenosine, the only mediator of ischemic pain so far identified in humans (19–21,27). Furthermore, the intracoronary infusion of BK caused chest pain, which was described by all patients but one as indistinguishable from their habitual angina during everyday life. In a recent study, Schaefer et al. (17) reported that the intracoronary injection of BK in patients with coronary atherosclerosis caused chest pain that appeared to be different from angina. The different findings of the study conducted by Schaefer et al. (17) and ours are probably due to the substantially different study protocols. Indeed, in the Schaefer study repeated intracoronary bolus injections instead of graded infusion of BK were used; thus, the effective doses of BK administered in the two studies are not directly comparable. As a proof of that, in the study by Schaefer et al. (17), marked changes in blood pressure and heart rate were observed that were often associated with flushing and nausea. By contrast, in our study, no major changes in blood pressure and heart rate or systemic side effects were observed.

The possibility that the pain induced by BK might be related to its marked vasodilating effect is made unlikely by the observation that other potent vasodilators such as

nifedipine and nitrates do not cause pain when infused intra-arterially or intracoronary (19); furthermore, pain elicited by BK in our study constantly appeared later than BK-induced maximal vasodilation. Finally, in the present study, IV administration of acetylsalicylate in a dose capable to markedly inhibit cyclo-oxygenase (28) abolished or significantly reduced BK-induced pain in most subjects, but it did not affect BK-induced vasodilation.

The ability of acetylsalicylate to prevent BK-induced pain but not adenosine-induced pain suggests that BK but not adenosine acts through the release of arachidonic acid metabolites. Of note, acetylsalicylate administration could not prevent pain induced by infusion of BK in all patients both when infused intra-arterially and intracoronary, thus suggesting that, in some subjects, BK can also act through mechanisms insensitive to acetylsalicylate.

The reason why in this study acetylsalicylate abolished or reduced BK-induced pain although it does not seem to abolish pain in patients during myocardial ischemia may have different explanations. First, ischemic pain might be caused by different chemical mediators acting on different receptors through different mechanisms. Accordingly, in previous studies (20,21,29), we have shown that pretreatment with theophylline and bamiphylline, both antagonists of adenosine, reduced but did not abolish exercise-induced angina, thus suggesting that multiple mediators are involved in the pathogenesis of cardiac ischemic pain.

Second, in our study, we used a rather high IV dose of acetylsalicylate, substantially higher than the usual dose of aspirin given to patients. A randomized, placebo-controlled trial of the effects of acetylsalicylate on exercise-induced angina is warranted to establish whether prostaglandins play a role in the generation of cardiac ischemic pain.

In our study, acetylsalicylate did not prevent the marked vasodilation induced by BK, thus suggesting that the vasodilating action of BK, which is comparable to that of adenosine, is independent from arachidonic acid metabolites. This finding is consistent with the results of Pelc et al. (30), who recently showed that pretreatment with indomethacin, a potent cyclo-oxygenase blocker, does not affect BK-mediated increases in total left ventricular blood flow.

Study limitations. A critical issue in our study was the assessment of pain. To this end we used the visual analog scale, which has been extensively validated by Huskisson (11). Its reproducibility is confirmed by observations in previous studies that pain severity during infusion of adenosine before and after placebo is similar. Furthermore, testing personnel were not unaware of the nature of the infused materials, and patients themselves, who were unaware of the nature of the infused materials, marked the visual analog scale. A limitation of our study is that we cannot rule out that the attenuation of BK-induced pain after acetylsalicylate was merely due to tachyphylaxis. However, this possibility appears to be remote; indeed, previous studies failed to show tachyphylaxis for pain provoked by repeated intra-arterial injections of BK (3,26). Lack of tachyphylaxis is further supported by the observation in our study that BK-induced vasodilation was similar during the first and second infusion.

Finally, our findings suggest but do not prove that BK is a mediator of angina. The definitive answer would require the demonstration that a BK receptor antagonist prevents spontaneously occurring angina pectoris as previously done for other putative pain mediators such as adenosine (19,29).

Conclusions. This study shows that the intra-iliac infusion of BK causes muscular pain similar to that elicited by the infusion of adenosine, a known mediator of ischemic pain in humans, and that its intracoronary infusion in patients with angina and coronary artery disease causes cardiac pain similar to their habitual angina. Moreover, BK-induced pain is abolished or reduced by acetylsalicylate, thus suggesting that acetylsalicylate-sensitive mediators, such as prostaglandins, are involved in the pathogenesis of BK-induced pain. As BK is released in large amounts by the heart during ischemia, it can be a natural stimulus for causing, via arachidonic acid metabolites, excitation of the sensory receptors signaling the pain during myocardial ischemia.

Acknowledgments

We wish to thank Mrs. Maria-Teresa Palumbo, Mr. Alessandro Pesaola and Miss Paola D'Alessandro for technical assistance.

Reprint requests and correspondence: Dr. Achille Gaspardone, Divisione di Cardiochirurgia, Università di Roma Tor Vergata, European Hospital, via Portuense 700, 00149 Rome, Italy. E-mail: gaspardone@tin.it.

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