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Early appearance of 2,3-butanediol in acute myocardial infarction. A new marker for ischaemia?

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In 28 patients with acute myocardial infarction, the release pattern of 2,3-butanediol (BD), a product of intermediary metabolism, and creatine kinase activity (CK) in blood were compared. Whereas CK at entry was low in all patients, the BD level was elevated in 18 (64%). However, BD returned to normal levels during the next 24 h whereas CK increased. The BD level at entry did not allow differentiation between patients with transmural or non-transmural infarction; it was independent of clinical findings and biochemical parameters. We suggest that, in patients with acute myocardial infarction, elevated levels of BD originates from myocardial metabolism. Whether it reflects ongoing ischaemia or reperfusion of the infarcted area remains unresolved.

Introduction

In the early phase of myocardial infarction, no biochemical parameter for myocardial ischaemia is known in the peripheral venous blood. Elevation of plasma creatine kinase occurs late and indicates myocardial injury or cell necrosis. A biochemical parameter for ischaemia however could be important for stratifying patients with acute chest pain.

2,3-butanediol (BD) is a product of intermediary metabolism; its precursors are pyruvate, acetaldehyde and acetoin[1,2]. In his studies of the enzymatic synthesis and breakdown of acetoin in the animal organism, Järnefelt has shown that, under anaerobic conditions, the formation of BD is accelerated[3]. In a preliminary study we found elevated levels of BD in some patients with acute myocardial infarction.

We report a prospective study of 28 patients with acute myocardial infarction. In addition to conventional clinical, electrocardiographic and enzymatic techniques we performed frequent serial determinations of BD to assess its release pattern.

Patients and methods

Of 121 consecutive patients with chest pain who were admitted to the coronary care unit, 21 men and 7 women (age 42 to 84 years) were included in the prospective study. All 28 patients had typical chest pain of at least 30 min duration, which had occurred within the preceding 6 h. Serial electrocardiograms showed in all cases either Q wave evolution or typical S-T wave changes. Increase of CK activity during the first day was noted in 22 patients. As a reference group, we determined BD in 23 patients with stable angina pectoris (aged 29–78 years).

For the analysis of 2,3-butanediol, 10 ml samples of venous blood were taken at 2, 4, 6, 9, 12 and 24 h after the onset of pain. The blood was deproteinized immediately with sulphuric and tungstic acid. The supernatant was frozen at −20 °C and stored. The samples were analysed according to the method described by Happold and Spencer[4] and Westerfeld[5]. 2,3-butanediol in the supernatant was oxidized to diacetyl with bromide and ferrichloride; diacetyl was reacted with 2,4-dinitrophenylhydrazine. The precipitated hydrazone was filtered and determined colorimetrically. The relative coefficient of variation was less than 5%; normal levels are below 0·029 mmol l^{-1}. The results were obtainable within 8 h. CK activity was measured with a commercially available diagnostic kit (Merck); normal values are below 80 U l^{-1}.

Results are expressed as the mean ± SD (SEM where noted). Unpaired Student's *t*-test was used for statistical analysis.

Results

In a group of 28 patients with acute myocardial infarction, BD showed a release pattern contrasting to the rise of CK during the first 24 h (Fig. 1).

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At entry, 18 of 28 patients had elevated levels of BD, $0{\cdot}087 \pm 0{\cdot}036$ mmol l^{-1} (range 0·055–0·188 mmol l^{-1}), which decreased to normal levels within 24 h, $0{\cdot}025 \pm 0{\cdot}015$ mmol l^{-1}. In 10 other patients, BD was found to be normal at entry, $0{\cdot}012 \pm 0{\cdot}006$ mmol l^{-1} (range 0·006–0·026 mmol l^{-1}); in eight it remained normal during the 24 h, whereas in two minor changes were noted. No significant difference in history (unstable angina pectoris and old myocardial infarction), clinical presentation at entry (Killip), duration of chest pain or need for antiarrhythmic therapy was found between patients with high or low levels of BD. The release of BD was independent of time of admission and history of alcohol consumption. In 23 patients with stable angina pectoris the mean value of BD was $0{\cdot}015 \pm 0{\cdot}005$ mmol l^{-1} (range 0·008–0·029 mmol l^{-1}).

Twenty-one patients showed a typical rise in CK during the first 24 h; CK was higher in transmural than in non-transmural infarction. No or little rise in CK was found in four patients with low BD and in three patients with high BD at entry; they all had non-transmural infarction. There was no direct relationship between BD level and CK activity; however patients with high BD at entry showed a non-significantly higher level of CK 9 h after the onset of chest pain. In addition, patients with transmural infarction had a significantly higher BD level at 12 h than patients with non-transmural infarction ($P < 0{\cdot}02$).

Two patients died; both were in cardiogenic shock on admission and both had transmural infarction. Their BD levels were 0·017 mmol l^{-1} and 0·049 mmol l^{-1}.

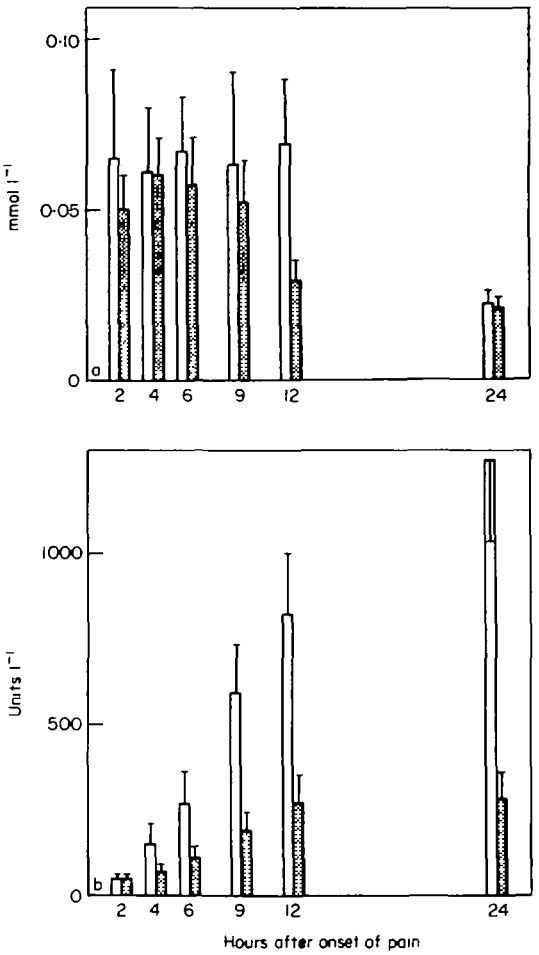

Figure 1 2,3-butanediol (a) and creatine kinase (b) during the first 24 h in 28 patients with acute myocardial infarction (mean ± SEM). Open area: transmural infarction; dashed area: non-transmural infarction.

Discussion

BD at entry in 28 patients with acute myocardial infarction was found to be significantly different from BD in a group of 23 patients with stable angina pectoris ($P < 0{\cdot}001$). However, a difference in release pattern was noted within the group of acute myocardial infarction patients. In 18 of 28 patients (64%), BD was elevated at entry and returned to normal within 24 h; in 10 patients (36%) BD remained normal during the study period. This different pattern was related neither to the localization or extent of the infarction nor to clinical parameters. However at 12 h after the onset of pain, BD was significantly higher in patients with transmural infarction (Fig. 1). We suggest that BD is a product of ischaemic myocardial metabolism which is released early into the peripheral circulation, unlike CK, which is found in blood only after some hours. This is supported by the study of Järnefelt who showed that BD is produced in heart muscle and that production is increased under anaerobic conditions[3]. We suppose that BD crosses the cellular membrane early in the course of ischaemia, as does lactate which can be found in the coronary sinus but not in the peripheral blood[6]. Both metabolites have a low molecular weight. However, it still remains unresolved whether elevated BD at entry indicates ongoing ischaemia or washout of ischaemic metabolites by natural reperfusion of the infarcted area. As evolution of a myocardial infarction is considered to be a dynamic process[7], the

explanation is even more difficult. The finding that in patients with transmural infarction BD remains elevated during the first 12 h in comparison to non-transmural infarction could however be due to dynamic alteration of myocardial metabolism and perfusion. In patients with non-transmural infarction this dynamic process would be of shorter duration with earlier reperfusion; however, one can not exclude the possibility that in these patients the ischaemic area at the onset of pain is large enough to produce substantial quantity of BD. Indeed in 11 of 19 patients with non-transmural infarction, BD was high at entry, $0{\cdot}083 \pm 0{\cdot}021$ mmol l^{-1} (range $0{\cdot}056$–$0{\cdot}114$ mmol l^{-1}).

Different patterns of BD could also be due to different metabolism and excretion of the metabolite itself. However this seems to be less likely, although little is known about metabolism and excretion. Söling *et al.* concluded from their rat study that approximately 80% of infused BD was absorbed by the peripheral tissue within 2–4 h[8]. From their cat studies, Dawson and Hullin came to the conclusion that BD was rapidly metabolized as a first step (up to 90% within the first hours); the second step would be slow[1]. According to observations by Westerfeld and Berg, urinary excretion is minor[9].

Elevated levels of BD are also found in patients with hepatic or uraemic coma[10]; rising blood glucose in diabetics is accompanied by a rising level of BD[11]. However no patient of our study had renal or hepatic insufficiency or a metabolic disorder. Elevated alcohol intake could be excluded from the patients' history. They also had no pulmonary embolism or perimyocarditis.

The findings of our study suggest that elevated BD in blood of patients with acute myocardial infarction originates from ischaemic myocardial metabolism. Whether it indicates ongoing ischaemia or reperfusion still remains unresolved. Further studies are needed to support our results and to clarify their relevance for managing patients with acute myocardial infarction. New and rapid laboratory methods are needed.

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