V The Cardiovascular Effects of Caffeine

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1 Introduction

The effect of caffeine on the heart and blood vessels has attracted the attention of investigators for more than 100 years. The earliest studies are reviewed in some detail by Bock (1920) and Eichler (1938). In the second edition of his monograph on caffeine, Eichler (1976) reviewed the literature on the cardiovascular effects of caffeine up to the year 1974. Much of the available data comes from animal studies. In some cases the human pharmacology of caffeine has been inferred from studies with theophylline. The first part of this chapter will deal with in vitro and animal studies. In the last part of the chapter the effects of the drug in man will be treated.

Coffee has been shown to be made up of hundreds of chemical constituents, all with potential pharmacological effects (Vitzthum 1975). It would be remarkable if caffeine proved to be the only substance of significance. Unfortunately, the limited knowledge concerning the vast majority of these constituents prevents us from drawing firm conclusions about their contributions to the effect of coffee ingestion in man. Certainly the recent demonstration of a principle in coffee that acts as an opiate antagonist (Boublik et al. 1983), presumably at concentrations achievable with ordinary coffee consumption, provides a sobering reminder of just how much remains to be learned about the physiological effects of the beverage.

The mechanism of action of caffeine is treated in detail in Chaps. 9 and 10 of this book. Caffeine probably exerts most of its effects through antagonism of adenosine receptors (Fredholm and Persson 1982; Daly et al. 1981; Burnstock 1972), although phosphodiesterase inhibition (Beavo et al. 1971) and calcium mobilization (Guthrie and Naylor 1967) may be important at some concentrations of caffeine. The relative importance of these various mechanisms has been reviewed by Rall (1980).

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2 Myocardial Contractility

In studies in many species of animals there is usually an increase in myocardial contractility with caffeine. Thus in the superfused frog heart, tension development is enhanced by caffeine in a reversible manner (Chapman and Miller 1971). In the papillary muscle from the right ventricle of the cat, caffeine at concentrations of 0.02% elicited an increase in the amplitude of contraction (Krop 1944). Similar results have been seen in guinea pig atrium, where caffeine concentrations of 0.25–1.50 mM increased contractility, while higher concentrations had a lesser effect (De Gubareff and Sleator 1965). Pretreatment of the animals with 5 mg/kg reserpine, which reduced myocardial catecholamine content to 5% of normal, lessened but did not abolish the effect of caffeine on contractility. In general, theophylline has been shown to be more potent than caffeine in eliciting myocardial effects in virtually all species tested (Rall 1980).

3 Heart Rate

The effect of caffeine on heart rate is variable. It seems to depend not only on dose but also on route and manner of administration. Smaller doses tend to elicit a slight bradycardia in dogs, while larger doses increase heart rate. Since the bradycardia can be blocked by cutting the vagus nerve or by the administration of atropine, it is presumably mediated by parasympathetic activation (Bock and Buchholtz 1920). However this does not appear to be the sole explanation for the bradycardia, since it is also observed in isolated rabbit hearts, albeit to a lesser degree (Vittorio 1923).

An increase in heart rate following caffeine administration to dogs via the left coronary artery occurred with small doses which induced a primary hypotensive response (Raff 1971). With doses of 10 mg or greater there was no increase in heart rate. The administration of 50 mg/kg caffeine to rats also led to a transient tachycardia which was more prominent in older than younger animals (Ammon and Estler 1969).

In spite of the widespread conviction that caffeine provokes arrhythmias, there is limited animal data addressing this rather critical issue. There is a prolongation of the left atrial action potential in bullfrogs and guinea pigs with 3.0 mM caffeine (Kimoto et al. 1974). Dogs with myocardial infarctions induced by arterial ligature had lower fibrillation thresholds when given 25 mg/kg caffeine sodium benzoate intravenously (Bellet et al. 1972). Caffeine doses of 25–100 mg/kg intravenously in dogs caused the development of ventricular irregularities that could be partially attenuated by pretreatment with barbiturate, by pretreatment with reserpine, and by bilateral vagus section.

4 Blood Pressure

Caffeine doses above 10 mg/kg increase stroke volume in dogs (Pilcher et al. 1927). With the Starling heart-lung preparation, in which the complicating influence of autonomic reflexes can be removed, it is possible to observe an increase in stroke vol-