Coronary flow reserve and the J curve relation between diastolic blood pressure and myocardial infarction

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Abstract

The results of several large studies of hypertension and follow up studies on insured people have indicated that the lower the blood pressure the better for longevity. These studies excluded subjects with overt ischaemia. More recently long term studies of hypertension that included patients with more severe forms of hypertension and did not exclude those with overt ischaemia have shown a J shaped relation between diastolic blood pressure during treatment and myocardial infarction; the lowest point (the J point) was at a diastolic blood pressure (phase V) between 85 and 90 mm Hg. The J curve seems to be independent of treatment, pulse pressure, and the degree of fall in diastolic blood pressure and is unlikely to be caused by poor left ventricular function. The most probable explanation is that subjects who have severe stenosis of the coronary artery as well as hypertension have a poor coronary flow reserve, which makes the myocardium vulnerable to coronary perfusion pressures that are tolerated by patients without ischaemia, particularly at high heart rates. An optimal diastolic blood pressure (phase V) for such patients is about 85 mm Hg, though particular caution is appropriate when treating very old patients (84 and over) and patients aged 60-79 who have isolated systolic hypertension.

Introduction

Follow up studies on people with life insurance have indicated that the blood pressures optimal for longevity are those below 110 mm Hg systolic and 70 mm Hg diastolic,¹ and data from the Framingham survey did not disagree with this conclusion.² The therapeutic goal of "the lower the better" was, however, questioned by Anderson, who examined unsmoothed data from the Framingham study and suggested that whereas a continuous positive relation existed between systolic blood pressure and cardiovascular events a "dog-leg" relation existed between diastolic blood pressure (measured at phase V) and cardiovascular events, with the break occurring at about 90 mm Hg.³ This dog-leg relation was also strong in the pooling project,⁴ which pooled the rates of death from all causes of men in four carefully studied

populations (in Albany and Tecumseh and two in Chicago).

Stewart, who suspected that excessive long term reduction of blood pressure caused myocardial infarctions as well as preventing them, showed that in 169 patients being treated for moderate to severe hypertension the relative risk of myocardial infarction in those whose diastolic blood pressure (phase IV) was less than 90 mm Hg was more than five times that in those whose diastolic pressure was 100-109 mm Hg.⁵⁻⁷ In three subsequent large controlled studies of patients treated for mild to moderate hypertension, which excluded patients with overt ischaemia, no U shaped or J shaped relation was found between diastolic blood pressure (phase V) and myocardial infarction.⁸⁻¹² Little or no cardiovascular benefit accrued from lowering diastolic blood pressure to less than 95 mm Hg. Recently, however, the observations of Anderson and Stewart were supported by a series of reports on treatment of hypertension, which did not exclude patients who also had ischaemia.

Six studies reported in 1987 and 1988, which included a total of 14 536 patients with mild to severe hypertension, showed a J shaped or U shaped relation between diastolic blood pressure (phase V) and myocardial infarction.¹³⁻¹⁹ The table shows the basic protocols of these studies, and figure 1 shows their J curves and J points (the J point is the point at the lower end of the range of diastolic blood pressure at which the lowest incidence of myocardial infarction occurs). The J point varied from 80 to 91 mm Hg, being 85-87 mm Hg in four studies, and was also found (at 90 mm Hg) in elderly patients with untreated hypertension.¹⁶

Cruickshank *et al* claimed that the J curve was present only in hypertensive patients who also had ischaemia (shown by previous myocardial infarction, angina, intermittent claudication, or electrocardiographic evidence of ischaemia),¹³ whereas Waller *et al* and Fletcher *et al* suggested that both patients with ischaemia and patients without ischaemia showed a J curve (though the evidence for patients without ischaemia given by Fletcher *et al* is not convincing).^{18, 19} The J curve occurred in both men and women^{18, 19}; it was independent of the size of the fall in blood pressure on treatment^{13, 18, 19} and the pulse pressure (Cruickshank *et al*, unpublished data).

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Details of studies of hypertension that showed a J curve relation between diastolic blood pressure and morbidity or mortality, or both, from myocardial infarction

	Design	No and sex of patients	Age range (years)	Degree of hypertension	Treatment	Length of follow up	Remarks
Cruickshank <i>et al</i> ¹³	Open	932 (585 men, 347 women)	17-77	Moderate to severe	Atenolol ± diuretic ± vasodilator ± other	Up to 10.2 years (mean 6.1)	J curve only in patients with ischaemia (mortality)
Heart attack primary prevention in hypertension trial ^{14*}	Randomised, controlled, open	6569 men	40-64	Mild to moderate	Atenolol, metoprolol, or diuretic	Mean 3.8 years	
Samuelsson <i>et al</i> ¹⁵	Open	686 men	47-54	Mild to moderate	β-Blocker ± diuretic ± vasodilator ± other	12 Years	
Coope and Warrender ^{16, 17}	Randomised, open	884 (273 men, 611 women)	60-79	Mild to moderate	Atenolol ± diuretic or no treatment	Up to 10 years (mean 4.4)	J curve in both treated and untreated groups (mortality)
Waller <i>et al</i> ¹⁸	Open	3350 (1660 men, 1690 women)	25-84	Mild to severe	Not stated	Up to 15 years (mean 6.5)	J curve in both men and women with and without ischaemia; independent of treatment with specific drug (mortality)
Fletcher <i>et al</i> ¹⁹	Open	2145 (1075 men, 1070 women)	13-89	Mild to severe	β-Blockers, diuretics, methyldopa, hydralazine, etc	Up to 10.5 years (mean 4.3)	J curve in both men and women (mortality)

*Information on the J curve is by personal communication from L. Wilhelmsen.

Mechanism of the J curve

PULSE PRESSURE

Sleight recently suggested that patients with a wide pulse pressure (that is, poor compliance of the arterial wall) rather than patients with ischaemia might be the group at risk from myocardial infarction if diastolic blood pressure is too low.²⁰ Re-examination of the "Clatterbridge" data on 902 patients treated for moderate to severe hypertension who were followed up for a mean of 6.1 years (maximum 10.2 years)¹³ provided no evidence to suggest that the J curve relation between diastolic blood pressure during treatment and death from myocardial infarction was confined to patients with a wide pulse pressure. In the original report atheromatous narrowing of the coronary arteries had been suggested to be the underlying condition giving rise to the J curve.¹³

DEGREE OF FALL OF BLOOD PRESSURE

Neither the Clatterbridge data¹³ nor those of Waller *et al*¹⁸ or Fletcher *et al*¹⁹ provided support for the hypothesis that the patients with the greatest fall in diastolic blood pressure were at greatest risk from myocardial infarction. Moreover, the J curve relation

FIG 1—Relation of diastolic blood pressure (phase V) during treatment to mortality or morbidity from coronary heart disease. The six studies included 14 536 patients.¹³⁻¹⁹ Information on heart attack primary prevention in hypertension trial (HAPPHY) is by personal communication (L Wilhelmsen). Numbers of histogram indicate diastolic blood pressure in mm Hg at which J point (lowest incidence of myocardial infarction) occurred

FIG 2—Effect of different perfusion pressures (maximum arterial pressure) on left ventricular function in dogs ($n=10$) with no stenosis (■) and experimental moderate stenosis (▲) and severe stenosis (●) at different heart rates as measured by Buffington²¹

FIG 3—Relation of coronary flow (ratio of flow during vasodilatation to flow before vasodilatation) to pressure in the left ventricle at various degrees of stenosis (indicated by percentages) and with left ventricular hypertrophy, high heart rate, or preloading, as determined in humans by Klocke.²² Vasodilatation without stenosis: ○=under basal conditions; □=without hypertrophy, high heart rates, or preloading; △=with hypertrophy, high heart rates, or preloading. Vasodilatation at various degrees of coronary stenosis: ●=under basal conditions; ■=without hypertrophy, high heart rates, or preloading; ▲=with hypertrophy, high heart rate, or preloading — — =Maximum vasodilatation. ○○○=Maximum vasoconstriction. — — — =Flow reserve

between diastolic blood pressure and myocardial infarction does not seem to be related to treatment.^{3 17}

POOR LEFT VENTRICULAR FUNCTION

Waller *et al* suggested that the excess of deaths from myocardial infarction in patients with a low diastolic blood pressure reflects poor left ventricular function due to ischaemia,¹⁸ but no information on left ventricular function in patients with hypertension is available to prove or disprove this hypothesis. Fletcher *et al* suggested that poor left ventricular function was not important as the J curve relation between diastolic blood pressure and myocardial infarction was seen in their patients who had been treated but not in those who had not.¹⁹

DIMINISHED CORONARY BLOOD FLOW IN STENOSED VESSELS

Two recent reports support the notion that a low coronary perfusion pressure (diastolic blood pressure) in patients with critical narrowing of the coronary artery is responsible for the J curve relation between diastolic blood pressure and myocardial infarction.

Firstly, Buffington studied the effect of lowering blood pressure on ischaemic myocardial dysfunction in dogs.²¹ All the dogs initially had good left ventricular function. The circumflex artery was progressively artificially stenosed at differing perfusion pressures. Figure 2 shows that left ventricular function (systolic wall thickness) remained well preserved at all perfusion pressures when stenosis was moderate or absent, even with high heart rates. In contrast, left ventricular function deteriorated rapidly at low perfusion pressures when stenosis was severe, especially with higher heart rates.

Secondly, Klocke has measured coronary blood flow with a Doppler velocity probe in patients undergoing cardiac catheterisation.²² Figure 3 shows the relation between coronary flow and pressure. Owing to autoregulation coronary flow remains the same over a wide range of coronary pressure, and when patients are given a vasodilator (for example

dipyridamole) the coronary artery can dilate fivefold—that is, it has a coronary flow reserve of 5.0. Flow reserve decreases as coronary pressure falls and becomes exhausted when coronary pressure reaches the point at which autoregulating vasodilatation is maximal. Coronary flow reserve is virtually absent when a stenosis exceeds 85%, at which point a fall in perfusion pressure (diastolic blood pressure) will be accompanied by an equivalent fall in coronary flow. This is exacerbated by high heart rates and left ventricular hypertrophy.

Discussion

Follow up studies on insured persons are based on populations from which patients with ischaemia have been excluded (R D C Brackenridge, personal communication). The same applies to recent large, prospective, randomised studies of patients with mild to moderate hypertension.⁸⁻¹⁰ If narrowing of the coronary arteries is an important underlying factor in the J curve relation between diastolic blood pressure and myocardial infarction these populations would not be expected to show such a relation, and such was the case. In contrast, the Framingham survey, the pooling project, and six recent long term studying of hypertension did not rule out patients with ischaemia, and all showed a J shaped or U shaped relation between diastolic blood pressure and myocardial infarction.^{13-16 18 19} Moreover, untreated as well as treated populations displayed the relation^{3 16} (though not in the study of Fletcher *et al*¹⁹). Thus the J curve is probably independent of treatment, reflecting a relation between myocardial infarction and absolute diastolic blood pressure; treatment would merely shift an ischaemic, hypertensive patient from a fairly safe to a less safe part of the curve, or vice versa.

Waller *et al* claimed that the inconsistency pressure at which the J point occurs is a reason for not accepting that lowering diastolic blood pressure too far could be dangerous.¹⁸ A large part of the purported inconsistency can, however, be ascribed to the fact that diastolic blood pressure was measured at phase IV in some studies⁷ and phase V in others. The six recent studies (table) all used phase V, and four of the six had a J point of 85-87 mm Hg. The J point of course depends on how many arbitrary subdivisions of diastolic blood pressure were used when the study was analysed. The J point may be found more precisely by using more subdivisions though small numbers of deaths from myocardial infarction in each division became a problem for interpretation. Having at least two subdivisions below the J point would elucidate the pattern of increasing numbers of deaths from myocardial infarction. Two subdivisions below the J point are present in the study of Waller *et al* and show a large increase in morbidity or mortality among patients with diastolic blood pressure less than 5 mm Hg below the J point (fig 1).¹⁸ Reanalysis of the Clatterbridge data, breaking down the diastolic blood pressure of treated patients into nine subgroups, confirmed the J point of 84-85 mm Hg found with the original three subgroups—that is, most of the deaths from myocardial infarction did not occur at the very lowest diastolic blood pressures (<78 mm Hg) (fig 4).

The mechanism of the J curve relation between diastolic blood pressure and myocardial infarction has been much debated. From this has emerged the hypothesis that the J curve results solely from patients with impaired ischaemic left ventricular function, who have a poor prognosis.¹⁸ No direct measurements of left ventricular function have been made to prove or disprove this hypothesis, but if such were the case the group of patients with pressures below the J point would be expected to have a larger heart, and this was

FIG 4—Effect of subdividing diastolic blood pressure during treatment in study of Cruickshank *et al*¹³ into narrower ranges than shown in figure 1 on curve relating pressure to deaths from myocardial infarction. Vertical bars indicate 1 SE

not so in the one study in which it was measured.²³ The work of Buffington (in dogs) showed clearly that when baseline left ventricular function was normal and the left coronary artery was severely stenosed lowering coronary perfusion pressure caused ischaemic left ventricular dysfunction.²¹ Klocke developed the concept of coronary flow reserve, which reflects the ability of the coronary arteries to dilate and maintain constant coronary flow over a wide range of coronary perfusion pressures (autoregulation); in the presence of severe coronary stenosis the flow reserve is minimal or absent and a fall in perfusion pressure leads to a steep fall in coronary flow.²²

The loss of autoregulatory reserve in the coronary circulation is not mitigated by enhanced extraction of oxygen as it is in the cerebral circulation.²⁴ In the coronary circulation oxygen extraction is almost maximal at rest, and an inappropriately low diastolic blood pressure can lead to myocardial ischaemia. The loss of coronary flow reserve is exacerbated by left ventricular hypertrophy and by high heart rates so the method of lowering blood pressure may be important: agents that reverse left ventricular hypertrophy or do not increase heart rate will better preserve coronary flow reserve. This might account for the excess mortality in patients receiving nifedipine, around the time of infarction, which lowers blood pressure and increases heart rate, compared with placebo²⁵ but not in those who had a β blocker added to the nifedipine regimen.²⁶

These models are compatible with the claim that the J curve relation between diastolic blood pressure and myocardial infarction is confined to hypertensive patients with accompanying overt ischaemia.¹³ Waller *et al* claimed to have found the J curve in groups of patients with and without ischaemia but did not show their data.¹⁸ Fletcher *et al* made a similar claim, but their graph of data for patients without ischaemia was unconvincing.¹⁹

Thus the available evidence supports the J curve relation between diastolic blood pressure and myocardial infarction. The J point is at a diastolic blood pressure of about 85 mm Hg (phase V), though this could be higher if the heart rate is increased. The J curve is unlikely to reflect poor left ventricular function as the evidence supports the theory that reduced coronary blood flow results from a low perfusion pressure in the presence of considerable atheromatous narrowing of the coronary arteries.

Not lowering diastolic blood pressure (phase V) below 85 mm Hg in hypertensive patients with ischaemia could prevent unnecessary deaths from myocardial infarction, the main cause of death in patients with hypertension. Such a course would be

unlikely to diminish the benefit of antihypertensive drugs in preventing stroke, as suggested by Waller *et al*,¹⁸ as little reduction in cardiovascular disease resulted from lowering diastolic blood pressure below about 95 mm Hg in the Australian mild hypertension study,¹¹ the international prospective primary prevention study in hypertension,¹⁰ and the Medical Research Council's mild hypertension study (MRC Working Party, 11th scientific meeting of the International Society of Hypertension, Heidelberg, 1986). Until more information is available particular caution is appropriate when treating hypertension in elderly patients. Mattila *et al* showed that over five years of follow up the greatest mortality in patients aged 84 and over was observed in those with the lowest systolic and diastolic blood pressures (not related to poor health) and that the lowest was in patients with a systolic blood pressure of 160 mm Hg or more and diastolic blood pressures of 90 mm Hg or more.²⁷ Patients aged 60-79 who have isolated systolic hypertension (phase V diastolic blood pressure less than 90 mm Hg) may be harmed by treatment.¹⁶

Care should be taken in extrapolating data on the J curve derived from hypertensive patients with ischaemia to normotensive patients with ischaemia as the normotensive patients may have better coronary flow reserve in the absence of left ventricular hypertrophy^{28,29} and the autoregulatory curve relating coronary flow to pressure is likely to be set at a lower level than in patients with hypertension—that is, the J point may be lower.

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Babies with spina bifida treated without surgery: parents' views on home versus hospital care

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Abstract

From 1971 to 1981, 98 babies born with meningo-myelocoele at the North Staffordshire Hospital Centre's district maternity hospital, were thought not suitable for surgery. Sixty three survived for more than one week. Over the period the hospital's policy changed: initially all such babies were kept in hospital, but later parents were given the choice of taking their baby home for palliative and terminal care. In an attempt to determine parents' views on the care of their baby the parents of 44 of the babies who survived to one week were traced in 1985-6, five to 14 years later; 80 of them were asked how they felt about the lives and deaths of their babies. Eighteen babies had been taken home, and they had lived longer than the 26 who had been cared for in hospital. Parents whose baby had remained in hospital were sadder than those who had taken their baby home when they looked back at their experiences,

and they also considered that their baby's life had been of poor quality. Most of those who had taken their baby home had a more positive view of their child's life.

The figures suggest that the bereavement process after a baby's death is longer than has been thought, but despite residual sadness just over half of the parents interviewed thought that something positive had come out of their experience.

Introduction

From 1971 to 1975 babies with a meningo-myelocoele who were considered unsuitable for an operation were kept in hospital throughout their lives. By 1981 over 90% of such babies who survived for more than a week received much of their palliative and terminal care at home, though some families still returned for hospital support when the baby was dying. We

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