Feeling the pressure – (Patho) Physiological mechanisms of Weight Gain and Weight Loss in Humans

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Abstract

Obesity is an ongoing global epidemic and has adverse consequences for cardiovascular health. Obesity is often associated with hypertension, which is, itself, a common condition and an important cause of morbidity and mortality worldwide. Although animal models of obesity have provided extensive data on the links between obesity and hypertension, a greater understanding of the pathways linking obesity and hypertension in humans is likely to assist translation of animal data, and may, itself, identify important treatment strategies. Ultimately, this could have a substantial impact on human health, both at an individual and population level. The current review will focus specifically on studies of experimental weight gain and weight loss *in humans* and the following key areas which are strongly related to blood pressure: cardiovascular function, autonomic nervous system function, metabolic function, and the impact of cardiorespiratory fitness.

Key words: cardiovascular, hypertension, obesity, weight gain, weight loss

Introduction

Obesity is an ongoing epidemic worldwide. Globally, obesity rates have more than tripled in men and doubled in women, since 1975 [1], with more than 1 in 3 US adults [2] and 1 in 4 UK adults being obese [3]. This is of concern because obesity has marked detrimental effects on cardiovascular (CV) health.[4, 5] It is associated with an increased risk of developing type 2 diabetes, dyslipidaemia, stroke and heart disease [6, 7]. A key factor underlying the adverse consequences of obesity on cardiovascular health is likely to be the presence of hypertension, which is, itself, a common condition. Indeed, hypertension is currently the leading risk factor for cardiovascular disease and an important cause of morbidity and mortality worldwide [8].

There is extensive evidence from cross-sectional studies that obesity and hypertension co-exist. Epidemiological evidence demonstrates a positive association between body mass index (BMI) and blood pressure (BP) [9, 10 11]. Hypertension is also more frequent in obese than lean individuals [12] and, amongst subjects in the Framingham Heart study, the prevalence of obesity was more common in subjects with borderline or established hypertension than in normotensives [13]. Moreover, calorie restriction leading to weight loss is commonly associated with a fall in BP[14], and weight loss is often encouraged as an effective, non-pharmacological strategy for preventing development of sustained hypertension.

Despite the extensive epidemiological evidence linking obesity and hypertension, the precise mechanisms of obesity-associated hypertension remain unclear. Whilst cross-sectional studies have contributed much to our understanding, longitudinal studies of weight gain and weight loss allow a much greater understanding of the relationship between obesity and BP, the direction of causality and the underlying pathophysiology. A wealth of overfeeding and calorie restriction studies have been undertaken in animals, which have contributed greatly to our understanding of some of the mechanisms involved in obesity-associated

hypertension, particularly in regard to the hypothalamic-pituitary-adrenal axis (as reviewed extensively by Kotsis et al [15] and Esler et al[16]). Moreover, animal models of obesity have been extremely useful in identifying and exploring novel targets for anti-obesity drugs [17]. However, animals are not humans, and species differences do exist in cardiovascular structure and function, which may be differentially affected by weight gain and/or loss. Indeed, a number of mechanisms identified in animal models of obesity do not translate strongly to humans[16]. Moreover, despite the success of anti-obesity therapies in preclinical models, translation into humans has been largely unsuccessful due to adverse safety profiles [18]. As such, a greater understanding of the pathways linking obesity and hypertension in humans is likely to assist translation of animal data, and may, itself, identify important treatment strategies which ultimately could have a substantial impact on health, both at an individual and population level.

A brief review of experimental weight gain studies previously examined the variation in susceptibility to gaining weight [19] but did not examine the physiological consequences. Therefore, the current review will focus specifically on studies of experimental weight gain and weight loss *in humans* and the following key areas which are strongly related to BP: cardiovascular function, autonomic nervous system (ANS) function, metabolic function, and the benefits of exercise. Weight gain studies are summarized in **Table 1** and weight loss studies are summarized in **Table 2**.

Cardiovascular function

Modest weight gain in humans is associated with significant changes in cardiovascular function. In a study of normal-weight males (n=14), weight gain of 5kg was associated with increased systolic BP (5±1mmHg, P<0.01) but not diastolic BP. In addition, beta stiffness index, a commonly used measure of arterial compliance, was increased by 13±6% and, interestingly, the degree of stiffness was associated with the level of abdominal visceral fat gain [20]. This study confirmed the findings of earlier cross-sectional studies [21, 22] that visceral adiposity was an important correlate of an elevated cardiovascular disease risk profile. In a further randomised-controlled trial (RCT) in 43 subjects which consisted of weight gain or weight maintenance, an average 4.1kg weight gain was associated with impaired flow-mediated dilatation (FMD), which was reversed with weight loss [23]. The degree of FMD impairment was signficantly higher in subjects with predominantly visceral rather than subcutaneous fat accumulation. However, there were no significant changes in BP or heart rate, as a result of weight gain or loss, indicating that vascular responses are either more sensitive than, or may precede any effects on, BP. Indeed it is possible that the change in body weight, and in particular, amount of visceral fat may affect the material properties of blood vessels, independently of arterial distending pressure via mechanisms such as hyperinsulinemia [24 25], hyperleptinaemia [26 27 28 29], a greater sympathetic nervous system (SNS) activity [30, 31], and activation of the renin-angiotensin-aldosterone system [32, 33]. Such mechanisms are thought to be typical of early vascular ageing (EVA); as reviewed by Nilsson et al [34].

Many more studies have investigated the effects of experimental weight loss on blood pressure and cardiovascular function. In a meta-analysis which included 25 RCTs, 4874 subjects were assessed to identify the effects of weight loss on BP [14]. The mean age of the study populations ranged from 27-66 years and mean weight loss ranged from 0.6 to 11.9 kg. There was an average reduction in systolic BP of 4.44mmHg and in diastolic BP of 3.57mmHg, relating to a reduction in systolic BP/diastolic BP per kg of body mass of

1.05mmHg and 0.92mmHg, respectively. In a further study of 25 middle-aged and older individuals who were randomly assigned to losing weight (7.1kg) via a hypocaloric diet versus maintaining weight, brachial systolic BP and diastolic BP decreased only in the weight loss group, by 7mmHg and 5mmHg, respectively. [35]

A separate study [36] compared the impact of two weight loss interventions on BP and other CV risk factors. The interventions were; 1) a goal of 10% body weight loss and 2) 3 meetings per year focusing on social support. Significant improvements were seen in CV risk factors such as BP, glycaemia, triglycerides, and HDL cholesterol with modest weight losses of 5-10%, as well as increased odds of achieving a 5mmHg decrease in systolic BP and diastolic BP, 0.5% reduction in HbA1c, a 40mg/dL decrease in triglycerides, and a 5mg/dL increase in HDL cholesterol. The relationship between the degree of weight loss and improvement in the CV risk profile was almost exponential. In a further 344 overweight and obese males and females aged between 20 and 45 years, a mean weight loss of 6.7kg over 12 months reduced aortic, but not brachial pulse wave velocity (PWV) [37]. In linear, mixed, log-transformed models which included age, sex, race and time since baseline, reductions in weight and BMI were signficantly associated with the reduction in aortic PWV. In further models adjusting for variations in mean arterial pressure, the reduction in aortic PWV was positively associated with reduction in BMI and carotid artery diameter.

Existing intervention studies have examined the impact of weight gain or loss on novel aspects of CV function such as arterial stiffness and endothelial function. However, since the mean (arterial) BP is a function of cardiac output (CO) and peripheral vascular resistance (PVR), it is notable that the existing studies described above have not examined these key haemodynamic mechanisms. It is well-established that CO is higher in those with increased body size [38] and cross-sectional observations demonstrate a marked elevation of CO in overweight or obese subjects in the early stages of BP elevation [39-41]. Moreover, longitudinal, observational data in 351 children (aged ~10 years) demonstrate a greater increase in SBP in those with the greatest increase in BMI over a two-year follow-up, and that this was

related to increases in CO and stroke volume, rather than arterial stiffening [11]. However, recent cross-sectional data in young adults demonstrate that not all overweight and obese subjects have elevated BP *despite* having an elevated CO, and it is the level of PVR, rather than CO, which distinguishes between different levels of BP in overweight and obese individuals [42] (**Figure 1**). These data strongly suggest that the ability to modulate PVR in response to an increased CO accompanying overweight/obesity may be an important determinant of the overall level of BP. Clearly this hypothesis requires testing, and further studies in humans are required to explore potential modulatory influences on vascular structure and function during weight gain and whether these relate to measurable changes in BP.

To summarise, the available evidence suggests that weight gain and weight loss induce changes in BP and other aspects of cardiovascular function. Interestingly, the magnitude of change is, in part, related to the extent of change in visceral fat levels**.** However, further longitudinal, interventional studies are warranted to explore, in greater detail, the association between weight gain and cardiovascular function. These studies should examine haemodynamic mechanisms directly related to BP, such as CO and PVR, as these may provide important early insights into how BP becomes elevated with weight gain in humans.

Autonomic nervous system function

Since Landsberg first proposed the involvement of the sympathetic nervous system (SNS) as an adaptive, thermogenic response to overeating [43], the role of the SNS in obesity-associated hypertension has been intensively studied and reviewed [44 45 16]. It has been speculated that the SNS is firstly downregulated, with reduced thermogenesis contributing to obesity, but eventually upregulated, contributing to hypertension [44]. However, other studies have demonstrated that SNS activation is involved in the pathophysiology of hypertension in lean individuals [46, 47]. Nevertheless, sympathetic overactivity has been widely implicated in obesity-associated hypertension, and data from animal models [48 49] (and reviewed by

Vickers et al[17]), cross-sectional studies in humans (as reviewed by Feldstein et al [44] and Kotsis et al [50]) and interventional weight gain and loss studies largely support this view.

In an observational study of 1897 Japanese males, 353 individuals (18.6%) gained weight over the 12-month study period (defined as an increase in BMI of >10%) [51]. Interestingly, a rise in BP (increase in mean BP >10%) was detected only in ~ 60% of lean subjects, despite similar increases in BMI to those in whom pressure did not rise, indicating a variable response of BP to weight gain. Levels of plasma noradrenaline, a marker of SNS activity, insulin and leptin all rose with weight gain, irrespective of the change in BP. However, significant increases in heart rate and plasma noradrenaline were detected in those individuals with accompanying BP elevation, suggesting that SNS activation is likely to be a major mechanism of BP elevation with weight gain in humans.

In 12 healthy, nonobese males [52] in whom 8 weeks of overfeeding by 4 184kJ/day (1000 Kcal/day) resulted in a mean 5kg weight gain, increased muscle sympathetic nerve activity (MSNA) was observed, together with an increase in systolic BP from 114±2mmHg to 119±2mmHg. Interestingly, the reverse pattern was observed in another study involving an acute 3 day period of semi-starvation, followed by longer-term (3-5 months) energy restriction in 30 moderately obese, borderline-hypertensive females. With longer-term energy restriction, there was a mean weight reduction of 5.8kg.The acute and long-term energy restriction resulted in a reduced body weight, diastolic BP and MSNA [53].

In 41 adults with the metabolic syndrome, a very low calorie diet (VLCD) of 800 calories per day for 9 weeks followed by maintenance of weight loss for one year [54], resulted in a mean weight loss of 14.6kg. Night-time heart rate decreased and stayed reduced after 1 year. The high frequency spectrum of heart rate variability (HRV), which represents predominantly vagal activity [55], increased during the weight loss and maintenance periods. Both clinic and ambulatory BP decreased signficantly during the VLCD period, but only clinic systolic BP remained lower at 6-months. Furthermore, a study in 18 obese, hypertensive patients

involved stress testing (cold pressor, deep breathing and hand-grip test) to assess the response of the autonomic nervous system. The effects of a short-term low calorie diet (11 days) on HRV were examined before and during each stress test. The low frequency domain of HRV, a potential [56, 57] but disputed [58, 59] marker of SNS activity was significantly lower during the deep breathing and cold pressor tests on the low-calorie versus regular-calorie diet [60]. Adaptations in sympathetic and parasympathetic activity upon weight loss may therefore be important in 'setting' the BP level.

Taken together, the data from human weight gain and weight loss studies support the contention that SNS overactivity plays a key role in driving increased BP with weight gain **(Figure 2)** although clearly, further studies in humans are required to clarify the relationship between the ANS and BP during weight gain/loss.

Metabolic function

It is likely that genetic [61], lifestyle and environmental factors [15 62] interact to modulate an individual's BP and cardiovascular response to fat deposition, fat type and accumulation, [63 64] as has been demonstrated in animal models [65-69]. Subjects with high levels of visceral adipose tissue (VAT) are at higher cardiometabolic risk, including higher incidence of hypertension [70, 71]. In subjects in the Framingham Heart Study, Computed Tomography (CT) Substudy [70], 'quality of fat', thought to represent lipid density, macrophage accumulation and extent of arteriolar dysfunction was assessed in both visceral and subcutaneous regions, by CT attenuation. The odds ratio for hypertension, impaired fasting glucose, metabolic syndrome (a multiple risk factor syndrome including hypertension) and insulin resistance were all significantly greater with lower CT attenuation in visceral adipose tissue. Therefore, it may be that the quality, rather than quantity of adipose tissue is better related to metabolic health. In a study of 41 overfed 3180kJ (760 Kcal/day), nonobese males, lipid-storage related gene expression that underlies visceral fat expansion was evaluated. Diacylgerol O-acyl-tranferase 2 (DGAT2) was positively associated with increased visceral fat [72]. Metabolic

characteristics of the subcutaneous fat were related to adipose tissue (AT) expansion and resultant increased storage of fat in the visceral depot. The results of this study support the 'AT expansion theory,' which hypothesizes that there is a limited capacity for the expansion of subcutaneous fat. This capacity differs from individual to individual, and once reached, will result in lipid deposition in ectopic sites, contributing to visceral fat deposition and development of the metabolic syndrome [73].

Increased oxidative stress during fat accumulation has been established as an early initiator of metabolic syndrome in animal models [74] and cross-sectional studies in humans have demonstrated positive correlations between BMI and markers of systemic oxidative stress ([74, 75 76]). However, factors which are known to cause oxidative stress, such as angiotensin II, that induce insulin resistance within adipose tissue [77] do not necessarily cause weight gain [78]. Consequently, the direction of causality still remains unclear and the role of oxidative stress in mediating vascular dysfunction in obesity requires clarification through longitudinal and interventional trials.

In another trial of overfeeding lasting 8-weeks, 28 lean, healthy adults (15 males) gained approx. 4kg of body fat and an average 4.6±1.6kg of body weight. [79] 24-hour insulin levels (measured as area-under-curve) positively correlated with body fat measured with dual energy X-ray absorptiometry, although low insulin sensitivity was not a precursor to upper body fat gain, despite previously reported cross-sectional associations between insulin resistance and upper body obesity. [80].

The evidence from interventional studies of weight loss in humans showing an improvement in metabolic function is strong. Cardiovascular risk was assessed in 10 nondiabetic, morbidly obese women (age 38±13 years, pre-surgery weight 114±13kg) before and following 36-months post bilio-pancreatic diversion (BPD) [81]. Insulin sensitivity more than doubled after surgery and leptin, IL-6, α-defensins, and C-reactive protein were all signficantly lowered with weight loss following surgery. These findings led the study authors to suggest that

drastic weight loss via BPD demonstrates great potential in reducing the adverse inflammatory and metabolic effects of morbid obesity. These findings are supported by a meta-analysis of studies inducing weight loss via a variety of interventions [82], which demonstrated significant decreases in total cholesterol, low-density lipoprotein, very low-density lipoprotein and triglycerides. Furthermore, 845 bariatric surgery patients were analysed two years post-surgery together with 845 weight-matched controls (BMI 41.0±4.6kg/m^2), with no intervention. Bariatric surgery patients and controls lost 28±15kg and 0.5±8.9kg, respectively. Systolic BP (7mmHg), diastolic BP (5mmHg), triglycerides (0.6 mmol), glucose (1.0 mmol/l), insulin (10.7mmol/l), LDL cholesterol (0.19 mmol/l), and HDL cholesterol (0.17mmol/l) were all signficantly lower in patients versus controls [83]. Ten years following the baseline visit, it was demonstrated that, compared with conventional therapy, bariatric surgery still appeared to be a viable option for the treatment of severe obesity and improvement in CV risk factors [84]. However, it remains unclear whether a causal relationship exists between changes in metabolic parameters and changes in BP as a result of weight gain or loss. Indeed, risk factors tend to cluster and it may well be the case that metabolic BP changes occur in parallel.

Impact of cardiorespiratory fitness

Regular aerobic exercise holds significant benefits for CV health. Indeed, several large outcome studies demonstrate that cardiorespiratory fitness (CRF) predicts mortality risk in the general population. The association between BMI, exercise capacity and mortality risk was assessed in 4183 hypertensive veterans (mean age 63.3±10.5 years; mean follow-up of 7.2 years) who undertook an incremental exercise test and were grouped according to body weight and level of fitness [85]. There was a strong, inverse association between mortality risk and exercise capacity. Interestingly, mortality risks for the overweight-highly fit and obese-highly fit individuals were 60% and 78% lower than normal-weight, unfit individuals, highlighting that being overweight/obese but having high CRF confers a survival advantage over those are of normal weight but unfit, particularly in older individuals. In a further large

outcome study involving 12 417 males (aged 40-70 years), CRF was assessed by a maximal exercise test. Compared to normal-weight, highly fit males, the underweight, unfit males had the highest mortality risk (4.5 [3.1-6.6]) whereas highly fit but overweight men had the lowest mortality risk (0.4 [0.3-0.6]). Taken together, these findings reflect the importance of obtaining and maintaining a high fitness level, regardless of weight status [86].

Observational data from 25 639 individuals who participated in the EPIC-Norfolk Population and were followed up for 11.4 years [87] demonstrate that physical inactivity and high abdominal adiposity independently correlate with high BP, which increased coronary heart disease (CHD) risk. A positive association existed between systolic and diastolic BP and waist circumference tertiles in both low and high fitness groups. Moreover, within each waist circumference tertile, active subjects had a lower systolic BP than inactive subjects. These data demonstrate the importance of cardiorespiratory fitness and an active lifestyle for reducing cardiovascular risk in the long-term and lend further support to the concept that CRF may counterbalance the effects of overweight and obesity.

The beneficial influence of CRF was prospectively explored in a study of experimental weight gain in 12 young males [88]. As expected, at baseline, those with a signficantly higher fitness level had lower levels of body fat (-13±1.7kg vs. 16.9±1.3kg) and abdominal fat (49±6 vs. 80±14cm^2) than their less fit counterparts. However, despite similar weight gain, fitter study participants had smaller increases in systolic BP and diastolic BP compared with less fit participants (-1±3mmHg vs. 5±1mmHg). After weight gain, an inverse correlation was demonstrated between fitness and systolic BP (r=-0.64) and diastolic BP (r=-80) with these relationships remaining significant after adjusting for the amount of visceral fat. These findings are supported by cross-sectional data in 184 males and 223 females, where those with high levels of visceral fat had higher BP, which was independent of fitness level [89].

Weight loss studies largely demonstrate the beneficial influence of exercise on CV health. A study of weight loss in 110 females was undertaken which included a dietary component

combined with either aerobic exercise, resistance exercise or a combination of both [90]. Regardless of the exercise type, in the diet-plus exercise intervention, pulse wave velocity, carotid intima-media-thickness, body weight, waist circumference, and total and low density lipoprotein cholesterol levels were significantly decreased. High density lipoprotein cholesterol levels and VO_{2max} increased over the study period. However, the combination of aerobic and resistance exercise together with the dietary intervention was the most beneficial regime in overall weight management and in the reduction of subclinical cardiometabolic and atherosclerosis risk, particularly in females with abdominal obesity.

A calorie-restricted diet, exercise and a combination of diet and exercise (D+EX) were also assessed as potential weight loss strategies in 30 obese, hypertensive men over 24-weeks [91]. The D+EX subgroup showed the most significant reductions in weight (21kg), plasma noradrenaline and insulin concentrations, versus the diet-only (16.2kg) and exercise-only (16.6kg) subgroups. In addition, after 4 weeks, subjects in the combined D+EX group had reductions in HOMA-IR (Homeostasis Model Assessment – Insulin Resistance) leptin, BMI, total body fat mass, waist-to-hip ratio and BP, which occurred earlier than the diet or exercise alone groups. After 24 weeks, BMI, total body fat mass and BP levels were significantly lower in the combined D+EX group than in the diet or exercise alone groups, with marked reductions in systolic BP (20mmHg), diastolic BP (18mmHg) and total fat mass (15.7kg).

Not all trials involving lifestyle interventions have been wholly successful in demonstrating benefits on CV outcome. The Look AHEAD trial [92] examined 5,145 type 2 diabetic patients to assess intentional weight loss on CV morbidity and mortality. Patients were randomly assigned to two groups; ‘intensive lifestyle intervention’ (ILI) which consisted of small group sessions, strict food prescriptions of 5021-7531kJ/day (1200-1800kcal/day) via meal plans/replacements, $\geq$175 minutes/week of moderate intensity physical activity and food/activity diary-recording; or ‘diabetes, support and education’ (DSE), as part of usual routine care. Patients were followed up after 13.5 years. The ILI and DSE group lost 4.7%

and 2.1% of their initial weight, respectively. However, no beneficial effects on all-cause mortality, or other CV disease outcomes were seen as a result of the intensive intervention.

Nevertheless, the majority of studies strongly support the notion that physical inactivity may be as important a risk factor for cardiovascular disease as being overweight or obese. However, there is a shortage of prospective, interventional studies examining whether CRF can prevent or attenuate the adverse physiological consequences of gaining weight.

Implications for therapy

The mechanisms of obesity-associated hypertension in humans highlighted in this review hold a number of important implications for selecting the ideal non-pharmacological or pharmacological therapies. Weight loss and, perhaps more importantly, increased levels of physical activity have beneficial effects on blood pressure, and may avoid the need for drug therapy and associated side-effects, which could become considerable over the life-course. However, in humans, weight loss programmes tend to be unsuccessful in the longer-term [93] and drug therapy is probably required in the majority of cases. Tailoring therapy towards the underlying pathophysiology would seem to be sensible and, in this regard, centrally-acting therapies targeted towards reducing SNS outflow or β-adrenoreceptor blocking drugs may be useful. They may also attenuate key haemodynamic abnormalities such as a high CO, which may be particularly beneficial in young individuals. However, there is evidence to suggest that β-adrenoreceptors are down-regulated in patients with neurogenic hypertension, presumably due to prolonged SNS activation [44]. Moreover, β-adrenoreceptors are associated with weight gain and increased insulin resistance [94] and, therefore, may not be the ideal choice in the longer term. Sympathetic de-activation with catheter-based renal denervation is an emerging therapeutic area, although with an uncertain future [95].Irrespective of the nature of therapeutic interventions, further studies in humans, which are underpinned by sound scientific rationale, are clearly required.

Summary

There is still much that we do not understand in the complex, multifactorial phenomenon of obesity. Moreover, obesity and hypertension are becomingly increasingly prevalent, although the precise mechanisms underlying obesity-associated hypertension remain relatively poorly understood. Whilst a wealth of data from animal models exists, further well-controlled mechanistic studies in humans are necessary. Unfortunately, overfeeding studies in humans are uncommon due to the adverse psychological, physiological and aesthetic associations with gaining weight. Nevertheless, the studies examined in this review have demonstrated that weight gain and weight loss are associated with significant changes in BP and associated aspects of cardiovascular function, and that activation of the SNS appears to play a key role in these changes. In addition, the type and location of fat accumulation, the type of macronutrient consumed and method of weight reduction all have significant implications for CV and metabolic function. Indeed, visceral fat accumulation, in particular, has been highlighted as a predominant factor in the obesity milieu. Finally, it appears that physical inactivity, irrespective of body weight or BMI status is an important determinant of CV risk, an effect likely to be mediated via unfavourable changes in CV function leading to elevated BP. It is clear, however, that the physiological challenge of obesity can be ameliorated by weight loss be it via dietary, lifestyle or surgical methods, and gaining physical fitness.

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Conflict of Interest/Disclosures

None

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Figure legends

Figure 1: Blood pressure (BP) is stratified by level of peripheral vascular resistance (PVR), not cardiac output (CO), in overweight/obese young adults (adapted from Middlemiss et al 2016).Therefore the ability to adapt to an elevated CO with weight gain may ultimately determine the level of blood pressure.

Figure 2: Pathophysiological mechanisms highlighted in interventional studies in humans, by which weight gain may lead to high BP and a detrimental impact on cardiometabolic health.

* Metabolic syndrome included high BP

SNS = Sympathetic nervous system; BP = Blood pressure