

# Periods of low atmospheric pressure are associated with high abdominal aortic aneurysm rupture rates in Northern Ireland

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## ABSTRACT

Seasonal and circadian variation in the incidence of ruptured abdominal aortic aneurysm (RAAA) has been reported. We explored the role of atmospheric pressure changes on rupture incidence and its relationship to cardiovascular risk factors. During a three year-period, 1st April 1998 and 31st March 2001, data was prospectively acquired on 144 Ruptured Abdominal Aortic Aneurysm (RAAA) presenting to the Regional Vascular Surgery Unit at the Royal Victoria Hospital, Belfast, Northern Ireland. For each patient the chronology of acute onset of symptoms and presentation to the regional vascular unit was recorded, along with details of standard cardiovascular risk factors. During the same period meteorological data including atmospheric pressure and air temperature were recorded daily at the regional meteorological research unit, Armagh. We then analyzed the monthly mean values for daily rupture incidence in relation to the monthly values for atmospheric pressure, pressure change and temperature. Furthermore atmospheric pressure on the day of rupture, and day preceding rupture, were also analyzed in relation to days without rupture presentation and between individual ruptures for various cardiovascular risk factors. Data demonstrated a significant monthly variation in aneurysm rupture frequency, ( $p < 0.03$ , ANOVA). There was also a significant monthly variation in mean barometric atmospheric pressure, ( $p < 0.0001$ , ANOVA), months with high rupture frequency also exhibiting low average pressures in the months of April ( $0.24 \pm 0.04$  ruptures per day and  $1007.78 \pm 1.23$  mB) and September ( $0.16 \pm 0.04$  ruptures per day and  $1007.12 \pm 1.14$  mB), respectively. The average barometric pressures were found to be significantly lower on those days when ruptures occurred ( $n = 1127$ ) compared to days when ruptures

did not occur ( $n = 969$  days), ( $1009.98 \pm 1.11$  versus  $1012.09 \pm 0.41$ ,  $p < 0.05$ ). Full data on risk factors was available on 103 of the 144 rupture patients and was further analyzed. Interestingly, RAAA with a known history of hypertension, ( $n = 43$ ), presented on days with significantly lower atmospheric pressure than those without, ( $n = 60$ ), ( $1008.61 \pm 2.16$  versus  $1012.14 \pm 1.70$ ,  $p < 0.05$ ). Further analysis of ruptures grouped into those occurring on days above or below mean annual atmospheric pressure  $1013.25$  (~1 atmosphere), by Chi-square test, revealed three cardiovascular risk factors significantly associated with low-pressure rupture, ( $p < 0.05$ ). Data represents mean  $\pm$  SEM, statistical comparisons with Student t-test and ANOVA. These data demonstrate a significant association between periods of low barometric pressure and high incidence of ruptured aneurysm, especially in those patients with known hypertension. The association between rupture

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incidence and barometric pressure warrants further study as it may influence the timing of elective AAA repair.

## INTRODUCTION

Ruptured abdominal aortic aneurysm (RAAA) remains a leading cause of death in elderly males, causing 2.1 per cent of all deaths in men and 0.75 per cent of all deaths in women over the age of 65 years in England and Wales.<sup>1</sup> Autopsy studies suggest that the numbers of RAAA are increasing annually,<sup>2</sup> and despite improvements in perioperative care the mortality rates have remained fairly static over the last fifty years.<sup>3</sup>

A clear seasonal variation has been reported in the incidence of rupture in both thoracic<sup>4</sup> and abdominal<sup>5</sup> aortic aneurysms. More recently a relationship between seasonal periods of low atmospheric pressure and aneurysm rupture has been reported.<sup>6</sup> A circadian variation has also been reported which mirrors the circadian variation in systolic blood pressure and thrombotic events, respectively.<sup>7</sup> It is known that wall stresses blood vessels are exposed to are determined by the net effect of blood pressure and extra-arterial tissue pressure, and their ability to cope depends largely on the strength of the vessel wall.<sup>8,9</sup> Indeed a calculated mechanical wall stress has been suggested as a better predictor of aneurysm rupture than simply aneurysm diameter alone.<sup>10,11</sup> A number of risk factors have been identified for abdominal aortic aneurysm (AAA) rupture including aortic size, hypertension, age, gender, smoking, chronic obstructive pulmonary disease, and family history.<sup>12</sup> Yet the relationship between these risk factors and atmospheric pressure with regard to aneurysm rupture is unknown.

The majority of ruptured AAA present de-novo and not in those previously under surveillance, but with the expansion of regional AAA screening programmes many more asymptomatic AAA shall come to under clinical supervision, making timing of repair an important consideration. Changes in atmospheric pressure may increase transmural arterial stress by transiently lowering extra-arterial pressure in respect to blood pressure, or by increasing blood pressure itself, predisposing to rupture of a weakened aneurysm wall. Alternatively altered pressure flux across the arterial wall may activate lytic factors within the aneurysm wall, which predispose to rupture. We therefore intended to explore the effects of changes in atmospheric pressure on risk of aneurysm rupture and the relationship between atmospheric pressure and known cardiovascular

risk factors, as it may have immense bearing on when and how AAA are repaired in the future.

## METHODS

### *Case identification and Data retrieval*

Prospectively acquired data between, 1998 and 2002, on the incidence of RAAA presenting to the Regional Vascular Surgery Unit at the Royal Victoria Hospital, Belfast and atmospheric pressure data retrieved from the regional meteorological research unit, Armagh, were analysed. In all cases aortic rupture was diagnosed and confirmed at surgery in 144 cases (mean age 73.4 years [range 43-92]). Ruptures occurred on 127 days within this period and presented as follows: on 112 days one rupture, on 13 days two ruptures, and on 2 days three ruptures. On arrival time of onset of acute symptoms and past medical history was determined from patients or witnesses and recorded prospectively in a computerized vascular registry (Northern Ireland Vascular Registry: NIVASC). Accuracy of prospective data was confirmed by retrospective case identification from death certificate record and the admission record of the accident and emergency department, operating room, intensive care unit and high dependency unit. All patient charts were inspected manually to confirm data accuracy. Cases were only included if the analysis of rupture was confirmed by the presence of blood outside the aorta (intra- or retroperitoneally) at laparotomy for AAA repair or at autopsy. The details of patients that had a clinical or radiological diagnosis of RAAA but not fit enough for surgery were also recorded. Patients with aorto-caval or aorto-enteric fistulas were not included in the analysis. Special attention was given to the accurate identification of time of acute onset of symptoms or rupture and the pre-morbid state of the patient regarding the presence or absence of hypertension and or treated hypertension and other cardiovascular risk factors.

### *Meteorological Data*

Belfast is located on the east coast of Northern Ireland on the western edge of Europe. The data on climate in this region were obtained from the Regional Meteorological Unit at Armagh Observatory. Daily records (high, low, and mean) of atmospheric pressure and air temperature were recorded prospectively at the regional meteorological center at Armagh Observatory, for the study period.

### *Statistical analysis.*

Data are expressed as counts of event (rupture) by month and daily rupture frequency per month

(counts of event per month divided by days), averaged over the 3-year period. Data expressed as mean  $\pm$  standard error mean. Standard univariate analysis examined the association between demographic and clinical characteristics, meteorological data and rupture presentation. Full data on risk factors was available on 103 of the 144 patients (71.5%), as such risk factor analysis was restricted to this subgroup. In these patients events (rupture) were further subcategorized into those occurring above ( $n=44$ ) and below ( $n=59$ ) mean atmospheric pressure (1013.25mB $\sim$ 1 atmosphere), to explore the effect of common cardiovascular risk factors on rupture during periods of low atmospheric pressure. Chi-squared test was used for statistical analysis. A P value less than 0.05 indicated statistical significance. Population characteristics including information on demographics, medical and family history, smoking, occupation and medication were collected prospectively in a computerized vascular registry (Northern Ireland Vascular Registry; NIVASC). Data was retrospectively checked for accuracy by manual search of all written case records, by one of the authors (MO'D). Cardiovascular risk factors were recorded prospectively into a computerized vascular registry (NIVASC) at time of patient presentation, these data included: no risk factors; cerebrovascular; TIA or CVA; diabetes; family history: cardiovascular; hyperlipidaemia; previous vascular surgery/ amputation; hypertension:

treated/ BP>160/95; tobacco: smoker or history of smoking; cardiac: CCF; MI; CABG; ECG changes; pulmonary: chronic obstructive disease; MI; renal: serum creatinine above 150 micromol/L; AF.

## RESULTS

### Seasonal variation in rupture rate and meteorological data

Data demonstrated a significant monthly variation in aneurysm rupture frequency, ( $p<0.03$ , ANOVA). There was also a significant monthly variation in mean barometric atmospheric pressure, ( $p<0.0001$ , ANOVA), months with high rupture frequency also exhibiting low average pressures in the months of April ( $0.24\pm 0.04$  ruptures per day and  $1007.78\pm 1.23$  mB) and September ( $0.16\pm 0.04$  ruptures per day and  $1007.12\pm 1.14$  mB), respectively, (Figure 1). There was a significant inverse correlation between the daily barometric atmospheric pressure and the daily rupture frequency, ( $r=-0.0051$ ,  $p<0.017$ ). There was also a significant inverse correlation between the monthly average daily change in barometric atmospheric pressure and the average monthly rupture frequency, ( $r=-0.25$ ,  $p<0.05$ ). Data for mean air temperature demonstrated a significant monthly variation, peak value ( $15.55\pm 0.07$  °C) in July and nadir value ( $4.40\pm 0.09$ ) in January, ( $p<0.0001$ ), ANOVA, however there was no significant correlation between temperature and number of ruptures ( $p<0.68$ ).

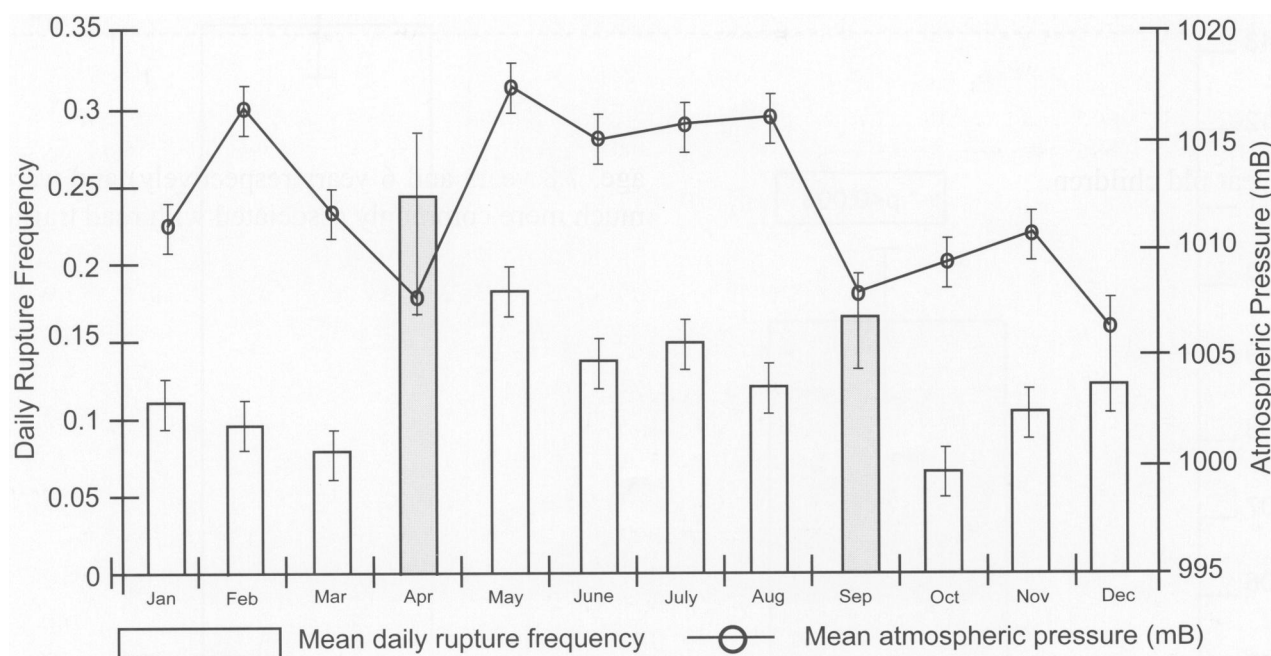


Fig 1. Monthly average of daily frequency of ruptured abdominal aortic aneurysm (bar) and monthly average of daily atmospheric pressure, shown for comparison, Mean ( $\pm$ SEM). Significant variation in monthly rupture frequency, ( $p<0.029$ ), and atmospheric pressure, ( $p<0.0001$ ), ANOVA.

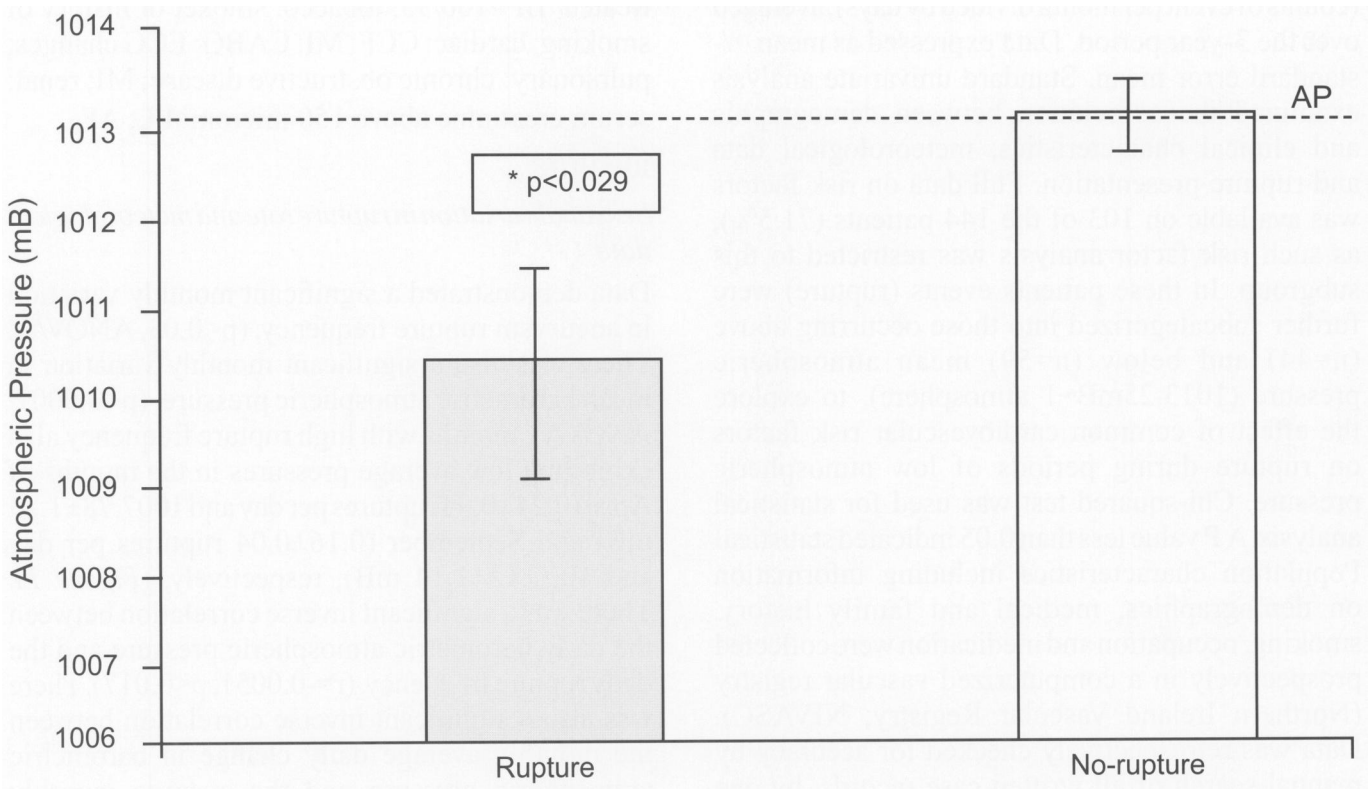


Fig 2. Histogram of average atmospheric pressure on days when ruptures occur compared to those when no ruptures occur, Mean ( $\pm$ SEM), ( $p < 0.029$ ), Students T Test. AP (1 Atmosphere pressure 1013.25 mB).

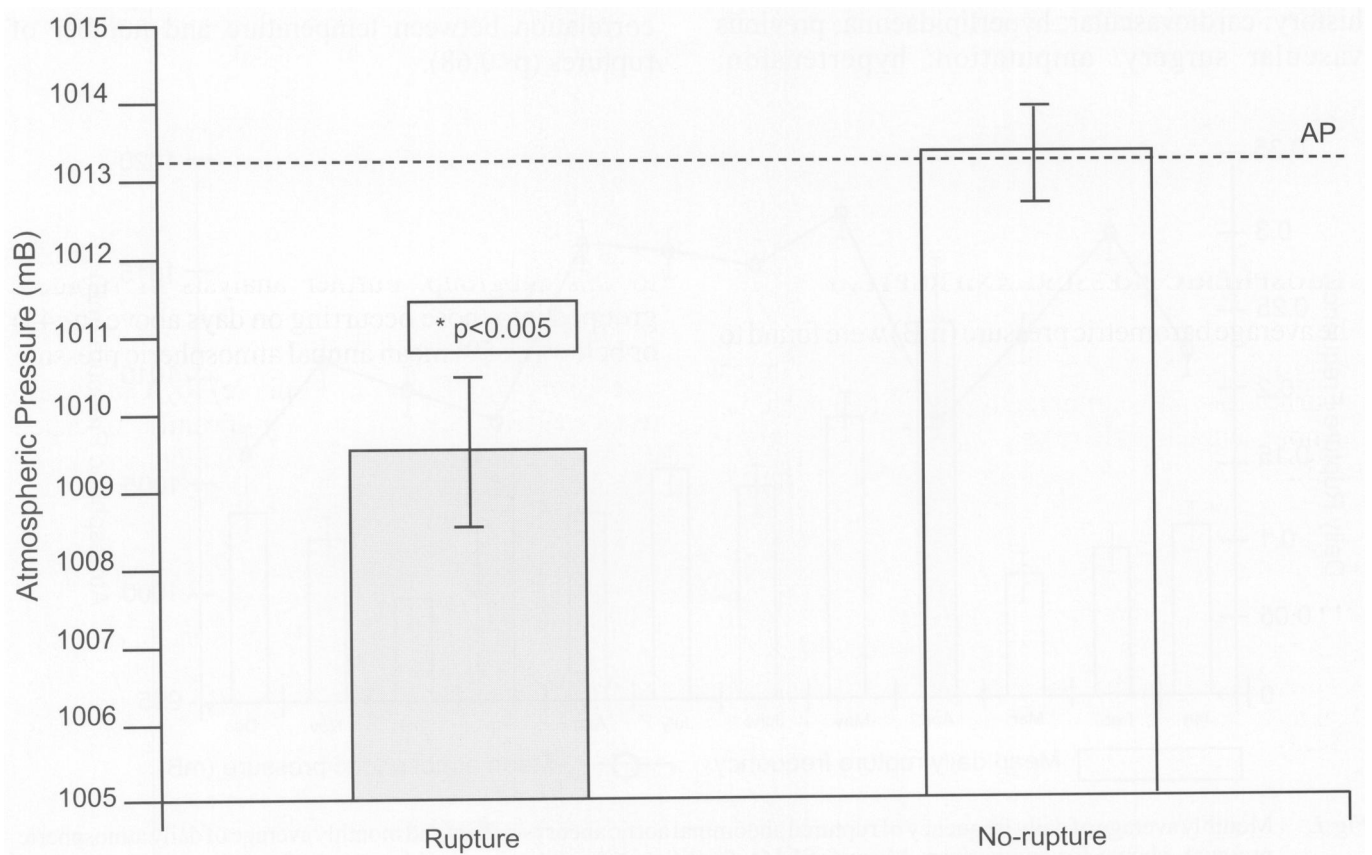


Fig 3. Histogram of average atmospheric pressure on day before rupture compared to those when no ruptures occur, Mean ( $\pm$ SEM), ( $p < 0.005$ ), Students T Test. AP (1 Atmosphere pressure 1013.25 mB).

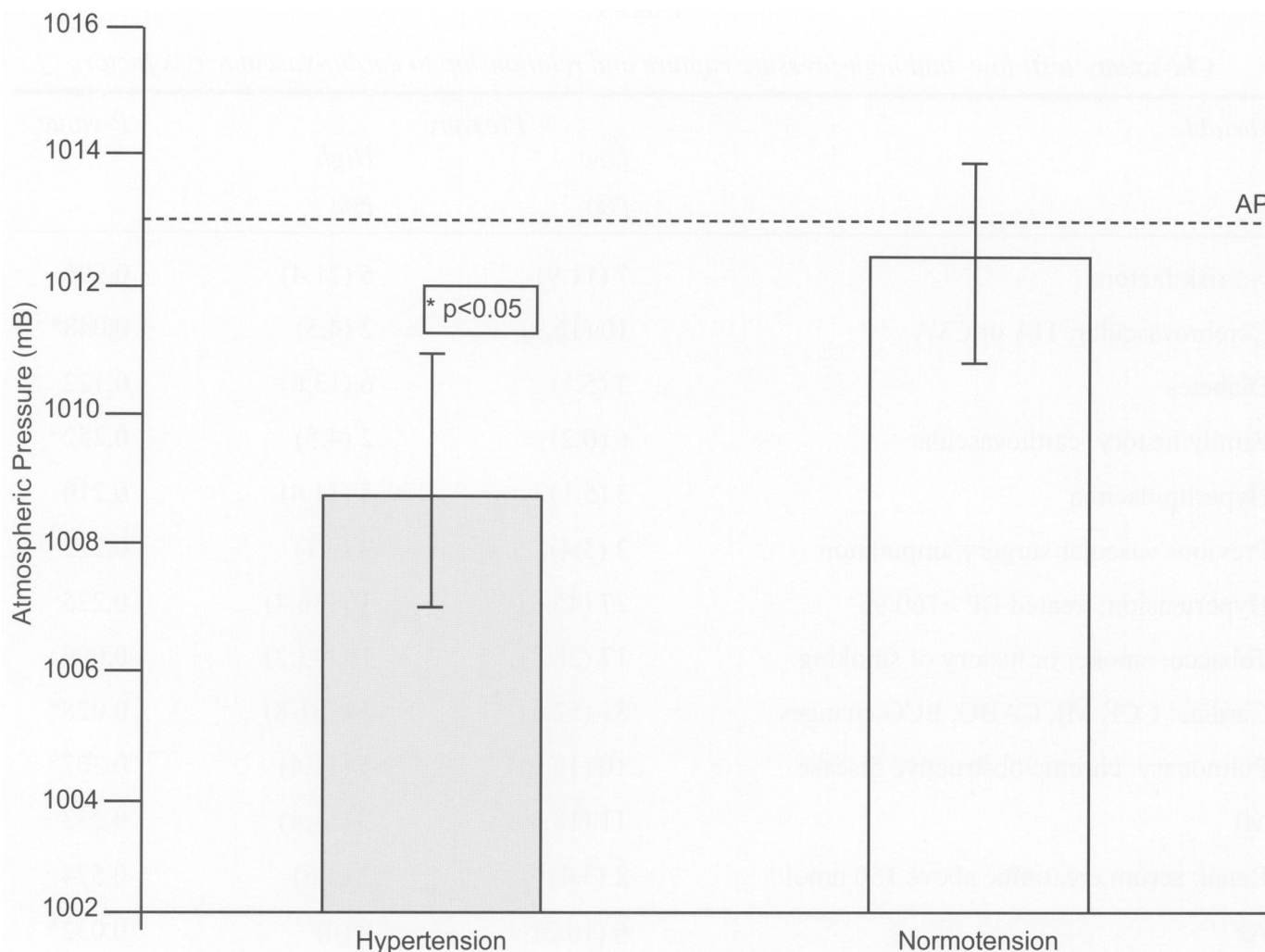


Fig 4. Histogram of average atmospheric pressure on days when ruptures with known hypertension compared to those without occur, Mean ( $\pm$ SEM), ( $p < 0.05$ ), Students T Test. AP (1 Atmosphere pressure  $\sim$ 1013.25 mB).

#### ATMOSPHERIC PRESSURE AND RUPTURE

The average barometric pressure (mB) were found to be significantly lower on those days when ruptures occurred ( $n=127$ ) compared to days when ruptures did not occur ( $n=1096$  days), ( $1010.35 \pm 1.26$  versus  $1013.24 \pm 0.35$ ,  $p < 0.029$ ), (Figure 2). Interestingly, when analyzing the preceding 24-hour period atmospheric pressure was highly significantly lower the day before rupture presentation as when not, ( $1009.58 \pm 1.25$  versus  $1013.30 \pm 0.35$ ,  $p < 0.005$ ), (Figure 3). Furthermore, the pressure change was significantly greater on days preceding rupture than days not preceding rupture, ( $7.36 \pm 0.61$  versus  $5.95 \pm 0.15$ ,  $p < 0.028$ ).

#### RISK FACTORS AND RUPTURE AT LOW-ATMOSPHERIC PRESSURE.

Full data was available on 103 of the 144 patients (71.5%), as such risk factor analysis was restricted

to this subgroup. Further analysis of ruptures grouped into those occurring on days above ( $n=44$ ) or below ( $n=59$ ) mean annual atmospheric pressure  $1013.25 \pm 0.35$  mB ( $\sim$ 1 atmosphere), by Chi-square test revealed three risk factors significantly associated with low pressure rupture, ( $p < 0.05$ ), (Table 1).

#### RUPTURE AND HYPERTENSION

Interestingly, RAAA with a known history of hypertension (treated hypertension or known hypertension defined as BP  $> 160/95$ ), ( $n=43$ ), presented on days with significantly lower atmospheric pressure than those without, ( $n=60$ ), ( $1008.61 \pm 2.16$  versus  $1012.14 \pm 1.70$ ,  $p < 0.05$ ), (Figure 4).

#### DISCUSSION

Ruptured abdominal aortic aneurysm rupture (RAAA) remains a major cause of death especially

TABLE I

*Chi-square test: low- and high-pressure rupture and relationship to cardio-vascular risk factors*

Variable	Pressure		P-value
	Low (%)	High (%)	
No risk factors	7 (11.9)	5 (11.4)	0.596
Cerebrovascular: TIA or CVA	10 (16.9)	2 (4.5)	0.048*
Diabetes	3 (5.1)	6 (13.6)	0.122
Family history: cardiovascular	6 (0.2)	2 (4.5)	0.252
Hyperlipidaemia	3 (5.1)	5 (11.4)	0.210
Previous vascular surgery/amputation	2 (3.4)	4 (9.1)	0.212
Hypertension: treated/BP >160/95	27 (45.8)	16 (36.4)	0.225
Tobacco: smoker or history of smoking	17 (28.8)	19 (43.2)	0.096
Cardiac: CCF, MI, CABG, ECG changes	31 (52.5)	14 (31.8)	0.028*
Pulmonary: chronic obstructive disease	10 (16.9)	5 (11.4)	0.307
MI	11 (18.6)	5 (11.4)	0.233
Renal: serum creatinine above 150 umol/l	2 (3.4)	2 (4.5)	0.574
AF	6 (10.2)	0 (0)	0.032*

among elderly men. The majority of RAAA present *de-novo* and not in those previously under surveillance, but with the expansion of regional AAA screening programs many more asymptomatic AAA shall come to under clinical supervision.<sup>1</sup> Repair by elective open technique represents a successful treatment strategy that has a very acceptable mortality rate of 2-5 per cent in specialist units.<sup>3,13</sup> With the widespread adoption of endovascular repair it may be that treatment for those deemed inoperable by open means due to co-morbid disease will also increasingly be offered treatment. The timing of elective repair in the United Kingdom has been guided by the UK small aneurysm trial<sup>14,15</sup> and a variety of studies suggesting predictive risk factors for rupture.<sup>3</sup> *Bown et al*, have recently reported an association between low atmospheric pressure and aneurysm rupture,<sup>6</sup> although in that study they made no attempt to look at other risk factors predisposing to rupture. Our study supports the role of atmospheric pressure in the seasonal variation in rupture incidence and would suggest the timing may

be critical in those awaiting elective repair, especially if they have co-existent hypertension. Unfortunately in this study, as in others, information on aneurysm size was not available in the vast majority of patients as they presented *de-novo* and were too unstable to undergo pre-operative computerized tomogram (CT) scanning. Furthermore, due to the expedient presentation of these individuals full pre-morbid health data could only be verified in 103 of the 144 patients and as such analysis was restricted to this group. The study has certain limitations inherent in the population studied, it is known that many deaths due to RAAA occur in the community and are undiagnosed, the low community post-mortem rate in our own region and the British Isles in general would make any attempt to include these deaths in the analysis unachievable at present. However, this study may stimulate such analysis in Scandinavian Countries where population post-mortem rates are considerably higher. Further study is required to assess the influence of aneurysm size and periodicity of rupture, to assess whether the larger aneurysms are

more at risk from atmospheric pressure effects.

Several studies have shown a seasonal variation in the presentation of AAAR with peak incidence in spring and autumn as in our series.<sup>16-20</sup> *Bown et al*, found high rupture peak incidence in the winter associated with low atmospheric pressure, which is most likely due to a regional difference in climatic condition and patient cohort.<sup>6</sup> We have also found a more direct relationship between the low atmospheric pressure on the day of and the day preceding aneurysm rupture, which would seem more relevant to a critically stressed aneurysmal arterial wall. It has been suggested that seasonal variation is related to temperature,<sup>20</sup> smoking habits,<sup>16</sup> or seasonal variation in hypertension.<sup>16</sup> *Ballaro et al*, reported a seasonal variation in the incidence of recorded deaths from abdominal aortic aneurysm in England and Wales, with a peak of deaths in the cold winter months. Winter peak of blood pressure, an independent risk factor for AAAR, in hypertensive patients was suggested as one possible cause.<sup>16</sup> In this study we have shown that those patients suffering RAAA with a known history of hypertension present on days with significantly lower atmospheric pressure than those without. Hypertension is an established risk-factor for RAAA,<sup>12,15</sup> and has also been linked to increased aneurysm growth rate.<sup>21</sup> Indeed a retrospective study has suggested that the treatment of hypertension with beta-blockade can inhibit aneurysm growth.<sup>22</sup> A circadian variation in aneurysm rupture has been reported which mirrors the circadian variation in systolic blood pressure and thrombotic events, respectively.<sup>7</sup> It is known that wall stresses that blood vessels are exposed to are determined by the net effect of blood pressure and extra-arterial tissue pressure, and their ability to cope depends largely on the strength of the vessel wall.<sup>8,9</sup> Indeed a calculated mechanical wall stress has been suggested as a better predictor of aneurysm rupture than simply aneurysm diameter alone.<sup>10,11</sup> Abdominal aortic aneurysm (AAA) rupture is believed to occur when the mechanical stress acting on the wall exceeds the strength of the wall tissue.<sup>23</sup> Changes in atmospheric pressure may increase transmural arterial stress by transiently lowering tissue pressure in respect to blood pressure creating a net expansive force, predisposing to rupture of a weakened aneurysmal wall. Alternatively atmospheric pressure may act by increasing blood pressure itself, causing increased stress across the weakened aneurysm wall. These same effects could also influence endotension and the integrity of endovascular aortic repair.

It is of interest that periodic changes in pressure

in the 24-hour period preceding rupture have been shown in our study. This may suggest that pressure related changes within the aneurysm wall induce certain factors, which subsequently predispose to aneurysm rupture. Mechanical stress has recently been reported to up-regulate genes controlling cyclooxygenase-1, tenascin-C, and plasminogen activator inhibitor-1, in human aortic smooth muscle cells by DNA microarray techniques.<sup>24</sup> Elevated barometric pressure has been shown to increase human endothelial cell secretion of pro-inflammatory cytokine interleukin-1 beta and aortic smooth muscle cell osteopontin, respectively.<sup>25,26</sup> The development of aortic aneurysms is associated with inflammation, tissue-remodelling, and upregulation of Matrix Metalloproteinases (MMP)'s. MMP's can degrade a variety of extracellular proteins such as elastin, collagen, or proteoglycans. Increased levels of MMP-2, -3, -9, and -12 have been found in the aneurysm wall.<sup>27,28</sup> Recently gene disruption of MMP-9 has been found to suppress the development of experimental abdominal aortic aneurysms.<sup>27</sup> Conversely, a decreased level of Tissue Inhibitor of MMP (TIMP) has been found in the aneurysmal wall, moreover it has been recently reported that local expression of TIMP-1 may prevent aortic aneurysm degeneration and rupture in a rat model.<sup>27,29</sup> Furthermore inactivation of TIMP-1, in a KO mice enhances aneurysm formation.<sup>29</sup> Taken together these data suggest that the proteolytic balance in the vascular wall is a key determinant of aneurysmal development and perhaps rupture. Polymorphisms in the promoter region of MMP-3 genes have recently been linked to the development of coronary artery aneurysms in humans, suggesting a genetic susceptibility to proteolysis in some patients predisposes them to aneurysmal vessel change, creating an identifiable population at risk.<sup>27</sup> The role of atmospheric pressure alone and transmural pressure changes on gene up-regulation and in particular MMP secretion remains unknown and warrants further study.

## CONCLUSION

Once again we have shown a seasonal variation in the incidence of abdominal aortic aneurysm rupture, with peak incidence in the spring and autumn months. We have shown that the barometric atmospheric pressure was significantly lower on those days when ruptures occurred compared to those days when they did not. We have shown a significant correlation between months with high rupture incidence and low barometric atmospheric pressure. The relationship between variations in

atmospheric pressure and abdominal aortic aneurysm rupture certainly warrants further evaluation, and may need to be considered in the future planning for those patients awaiting elective abdominal aortic aneurysm repair especially those with hypertension. The effects of changes in atmospheric pressure on risk of aneurysm rupture may have immense bearing on when and how AAA are repaired in the future.

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