High prevalence of recurrent nocturnal desaturations in systemic AL Amyloidosis: a cross-sectional pilot study

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Abstract

Study objectives: Cardiac involvement and/or macroglossia with soft tissue deposits are risk factors for central (CSA) and obstructive sleep apnoea (OSA), and common features of systemic AL amyloidosis. Little data exist on the occurrence of sleep disordered breathing (SDB) or recurrent nocturnal hypoxia in amyloidosis, which we sought to investigate.

Methods: 72 consecutive patients with systemic amyloidosis (mean age 69 and mean BMI 25) were evaluated for occurrence of SDB by overnight continuous pulse oximetry and completed Epworth Sleepiness Score (ESS) and STOP BANG questionnaires. Patients included: AL cardiac (AL-C), AL macroglossia (AL-M), AL both (AL-CM) and transthyretin (ATTR).

Results: Mean overnight oxygen saturations were 93% (±SD 2, 95% CI 87-96) with abnormal oximetry (4%ODI >5/hour): AC-C 84%, AL-M 57%, AL-CM 62% and ATTR - 47%. NYHA class directly correlated with a higher 4%ODI, NYHA class I versus 3, (p=0.01). Two-thirds of patients had STOP-BANG scores greater than 3 and abnormally high ESS scores (>10) were seen in up to 30% patients.

Conclusion: Recurrent nocturnal hypoxaemia, suggestive of sleep disordered breathing is frequent in systemic AL amyloidosis. The higher incidence in cardiac amyloidosis raises central CSA and recurrent hypoxia as possible mechanism for morbidity/mortality in these cases. A detailed polysomnography study is planned to clarify and investigate these findings further.

Keywords:

1. Nocturnal oxygen desaturations

2. 4% oxygen desaturation index (ODI)

3. Macroglossia and Cardiac AL amyloidosis

4. Prognostic utility of oxygen desaturations

Highlights:

1. **Sleep disordered breathing is a frequent finding in systemic light chain amyloidosis. This was equally prevalent in cardiac and soft tissue Amyloidosis patients.**
2. **Reduced heart rate variability despite frequent oxygen desaturation was associated with increased risk of death in AL Amyloid with Cardiac involvement.**
3. **Increased awareness of sleep disordered breathing in systemic AL Amyloidosis is important and further detailed studies are needed to assess its impact on mortality and identify any interventions**

Background

Systemic AL amyloidosis is a rare disorder caused by tissue deposition of misfolded immunoglobulin light chains leading to progressive organ failure. Survival of patients with amyloidosis depends predominantly on the extent of cardiac involvement. Involvement of other organs, particularly soft tissues of the oropharynx, contributes to significant symptoms and morbidity. Although cardiac deaths account for 20-40% of all deaths within a few months of diagnosis in AL amyloidosis, the terminal event and its triggers remain unclear. Bradyarrhythmias[1] or other arrhythmias may be the cause.

Central sleep apnoea (CSA), characterised by the faulty respiratory drive during sleep, is a well-recognised complication of heart failure and can lead to recurrent episodes of nocturnal hypoxemia worsening symptomatic heart failure[2], causing increased morbidity and mortality. Obstructive sleep apnoea (OSA) is now a well-recognised cause of acute and chronic adverse cardiovascular effects. In addition to cardiovascular effects, both CSA and OSA cause marked day time fatigue and/or sleepiness contributing to morbidity. Systemic AL amyloidosis is one of the few disorders which cause acquired progressive heart failure and can also be associated with marked infiltration of the oropharyngeal soft tissues – both potential risk factors for CSA or OSA, respectively, or CSA and OSA together in patients with soft tissue and cardiac disease. If SDB occurs in a patient with amyloidosis, the recurrent hypoxic episodes could have a profound deleterious effect on the cardiac function contributing to morbidity and possibly mortality.

We report here the results of a study of sleep disordered breathing as evidenced by recurrent nocturnal hypoxaemia by overnight continuous pulse oximetry in patients

with systemic amyloidosis, showing a high incidence of SDB and raise a question as to whether these desaturations may be the trigger for sudden cardiac mortality.

Methods

Study Population

This included all patients with suspected cardiac or macroglossia findings seen at the UK National Amyloidosis Centre between July 2013 and June 2014 who underwent overnight oximetry for possible sleep disordered breathing, with no patient having a prior history of sleep disordered breathing and a previous evaluation for OSA Amyloid deposition was confirmed on a tissue biopsy by the presence demonstration of Congo red positivity under cross polarise light and fibril typing was done by immunohistochemistry or mass spectrometry. All patients had a detailed assessment for organ involvement as per standard protocol at the National Amyloidosis Centre. Blood tests included a full blood count, renal, liver and bone profiles, cardiac biomarkers including N terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) and troponin T. Other investigations included an electrocardiograph (ECG), echocardiography and ^{123}I serum amyloid P component (SAP) scintigraphy. Organ involvement, haematologic and organ responses were classified according to the updated international amyloidosis consensus criteria.[3] Written consent for retrospective publication of data was obtained from all patients in accordance with the Declaration of Helsinki.

All patients underwent overnight pulse oximetry using a Minolta 300i pulse oximeter. An episode of significant desaturation was defined as a 4% or greater decrease in oxygen saturation from the average oxygen saturations in the preceding 120 seconds. The oxygen desaturation index (ODI), the hourly average number of

desaturation episodes over the whole night, was calculated. ODI is a standard measure used to score oxygen desaturations, but may not always show evidence of hypopnoea.[4] Heart rate (HR) variability was defined as HR change of >6 beats per minute to assess whether patient developed appropriate tachycardia as a normal physiological response to desaturation.[5]

All patients completed the Epworth Sleepiness Score (ESS) and STOP BANG questionnaires for obstructive sleep apnoea (OSA). The STOPBANG (Snoring, Tiredness during the daytime, Observed apnoea, high blood Pressure, Body mass index, Age, Neck circumference and Gender) and ESS (Epworth Sleepiness Scale) (included as supplementary data) are validated screening tools of OSA with a high sensitivity[6] but low specificity. Patients were classified as high risk of OSA if the STOP-BANG score was greater than and equal to 3 and low risk if the score was less than 3. The ESS (Epworth Sleepiness Scale) questionnaire is based on the probability to fall asleep during different situations[7] and patients were classified as being high risk if the ESS score was greater than or equal to 10.

Baseline characteristics and clinical investigations are presented as medians with minimum and maximum values for continuous variables and percentages with proportions for categorical variables. Statistical significance for comparison between groups was analysed with the one way anova variance for continuous variables and Turkey post-test analysis using the Graph pad prism version 5 software. Correlation statistics were performed using linear scatter plots and Pearson coefficients. A two-sided P value of less than 0.05 was considered as statistically significant. A univariate model was used to assess the poor prognostic features of those diagnosed with cardiac AL. Multivariate models are not presented due to instability from small patient numbers. Survival was assessed by the method of Kaplan-Meier

analysis and patients with cardiac AL amyloidosis and those with transthyretin amyloidosis were analysed separately due to a different disease natural history.

Results

Baseline Characteristics

A total of 72 patients were included in this study. The median age of all patients was 68.8 years (range 47-83 years). Eighty percent of the patients had cardiac involvement with a median NT-proBNP 2568ng/L (range 136-146203 ng/L). The median 4% ODI 7.9 (range 0.9-59). Patients were stratified as systemic AL amyloidosis with cardiac involvement (AL-C), AL amyloidosis with no cardiac involvement but only macroglossia (AL-M), AL amyloidosis with both macroglossia and cardiac involvement (AL-CM) and wild type transthyretin amyloidosis (ATTR). Table 1 illustrates the baseline presenting characteristics in each group. One patient in the AL-M group has an elevated NT-proBNP due to end stage renal impairment.

Overnight Oximetry

Overnight oximetry tracings were recorded in all 72 patients and shown for the four groups (and patients who died) in Table 2. The mean oxygen saturation of all patients in the study was 93% (±SD 1.99, range 87-96%). There was no significant difference in the mean oxygen saturations across the groups. The ATTR group had the lowest number of abnormal oximetry tracings. Figure 1A illustrates a normal tracing of overnight oxygen desaturations and pulse in a patient with cardiac amyloidosis showing repeated desaturations, with an abnormal tracing of these parameters illustrated in Figure 1B. The 4% ODI was highest in patients with cardiac

AL at a median 11 episodes (range 1-48)) compared to patients with macroglossia, cardiac and macroglossia and ATTR amyloidosis (6.02 (p=0.94), 6.03 (p=0.17) and 8.39 (p=0.34) episodes respectively, (Figure 2A). The absolute number of 4% ODI episodes per night were calculated for each group (cardiac AL, AL macroglossia, AL cardiac and macroglossia and ATTR) respectively and were: more than 15 per night – 32%, 14%, 18% and 29% respectively; and between 10-15 episodes per night in 20%, 21%, 6% and 12% respectively. Heart rate variability (a HR change of >6 beats per minute), a normal physiological response to desaturation, was seen in: cardiac AL amyloidosis - 17/25 (68%), patients with macroglossia - 10/14(71%), ATTR - 15/17(88%), and cardiac and macroglossia patients - 13/16 (81%), and in the patients who died - 8/12 (67%), (Figure 2B). The patients who died, as a group, had a lower blood pressure, more abnormal oxygen oximetry readings, a high ESS score (including proportion with ESS >10), in addition to markers of poorer cardiac function like a higher NT-proBNP and lower TAPSE.

The left ventricular ejection fraction (LVEF) in all groups group (cardiac AL, AL macroglossia, AL cardiac and macroglossia and ATTR) were recorded, with a median value of 55%, 61%, 56.5% and 41% respectively. There was a significant difference between the ATTR group and cardiac AL (p=0.0004) and the ATTR group and the macroglossia groups (P<0.0001). There was no significant correlation with LVEF and 4%ODI in any amyloid type groups.

The STOP-BANG and ESS questionnaires were completed by all 72 patients. The STOP-BANG score all four groups were high (71%, 69%, 71% and 64%) and would suggest a high risk of OSA, (Figure 2C). An abnormally high ESS score (>10) was seen in 28%, 21%, 19%, 24% in patients in the four groups, (Figure 2D). It was higher in those with cardiac AL (28%) and those who died (33%).

Relationship between overnight oximetry and cardiac amyloidosis

In all patients with cardiac AL amyloidosis, increasing NYHA class directly correlated with a higher incidence of 4% ODI (NYHA 1-2 n=29, NYHA 3, n=12, NYHA 1 vs. 2 (p=0.004), NYHA 1 vs 3 (p=0.01); figure 3). A higher NT-proBNP significantly correlated with reduced heart rate variability (correlation coefficient r^2 0.185, p=0.0002) There was no correlation of 4% ODI with right ventricle Doppler imaging (RVS TDI) (r^2=0.02, p=0.4) or tricuspid annular plane systolic excursion (TAPSE) (r^2=0.02, p=0.4). There was no correlation between TAPSE and heart rate variability (r^2=0.030; p = 0.30).

The median follow up for all cardiac amyloidosis patients was 10 months (range 2-15), with 12 deaths: 11 with cardiac AL and 1 with ATTR. The overall survival for the cohort stratified by AL-C (including AL-CM), AL-M and ATTR is illustrated in figure 4, with the worst prognosis in the cardiac AL group. Higher NYHA class and NT-proBNP, well recognised markers of poorer prognosis in cardiac amyloidosis, were also markers of poorer prognosis in this study. On univariate analysis of newly diagnosed cardiac AL patients (table 3), the factors significantly impacting survival included: TAPSE (HR 0.69, p=0.01) and NT-proBNP (HR 2.79, p=0.04). Small patient numbers make a multivariate model unreliable.

Discussion

Patients with systemic AL amyloidosis present complex clinical problems due the multisystem nature of the disease and complex interaction between tissue deposition of the amyloid fibrils and organ dysfunction. Standard assessment of outcomes and symptoms has been focused on tests of organ function and is dominated by abnormal cardiac markers. Sleep disordered breathing is a well-recognised cause of

fatigue, day time sleepiness and is associated with increased cardiovascular morbidity/mortality. In this study, using overnight oximetry, we report a high incidence of repeated and significant nocturnal hypoxaemia strongly suggestive of sleep disordered breathing in patients with systemic amyloidosis. The extent of nocturnal desaturations correlated with the worsening grade of heart failure and worse right ventricular function – both markers of poor prognosis suggesting a possible role for SDB in worsening organ function in amyloidosis.

Overnight pulse oximetry is the most commonly used screening method for sleep apnoea, with the sensitivity ranging from 31 to 98% and specificity of 41-100%.[8-10] It gives a continuous recording of oxygen desaturations with a characteristic pattern of overnight oxygen desaturations as well as heart rate data. Clinical prediction models are useful with sensitivities between 76-96% and specificities 13-54% and useful in excluding a diagnosis,[11] but in conjunction with pulse oximetry can confirm the presence of sleep apnoea.[12]

Our initial hypothesis at the start of the study was that SDB would be more prevalent in patients with macroglossia or soft tissue amyloid deposits due to the severe anatomical alterations. The striking finding in our study was presence of significant overnight oxygen desaturations in all groups of patients. Although patients with macroglossia/soft tissue amyloidosis had 4% ODIs, these were less frequent than in the cardiac AL group, SDB was not seen in all cases AL-M. Collapsibility of the upper airway is hallmark of OSA. Our findings, of less than expected severe desaturations in patients with significantly narrow upper airway due to soft tissue amyloid deposits raises an interesting question whether the increased stiffness of the soft tissue, which is a hallmark of amyloid deposition, actually protects against upper airway collapse.

Central sleep apnoea (CSA) is a well-recognised complication of systolic heart failure, is worse in patients with an ejection fraction of <40% and has been reported to be associated with increase in non-sustained ventricular tachycardia as well as reduction in heart rate variability.[13] The occurrence of repeated severe nocturnal oxygen desaturations seen in patients with cardiac amyloidosis raises the possibility that CSA also occurs in AL amyloidosis – a finding that will need further investigation by polysomnography. In our study, the oxygen desaturations were greatest in those with cardiac AL and 4% ODI correlated with NYHA class and NT-proBNP – suggesting a direct correlation with worsening amyloid burden/heart failure with ODI. The small numbers of newly diagnosed patients in this study precluded any meaningful survival analysis of impact of the number of 4% ODIs. Patients with new diagnosis of AL amyloidosis, have the most unstable heart disease, with 30-40% patients dying of cardiovascular complications within 6 months. Although the exact cause of death in AL amyloidosis remains unclear, our finding of frequent nocturnal hypoxia in such cases raises an important question – does repeated hypoxemia play a role by increasing the risk of arrhythmias or worsening myocardial function or both.

Persistent and profound fatigue is a symptom in AL amyloidosis which has never been adequately explained and attributed vaguely to multifactorial organ involvement. Recurrent hypoxaemia and sleep disordered breathing may well be a substantial contributor to this symptom.

Restrictive cardiomyopathy in cardiac AL, means that cardiac output can only be increased by increase in heart rate. An interesting finding in this study was the lack of or markedly reduced heart rate variability in patients with cardiac AL amyloidosis. This lack of heart rate response to hypoxia was greater in AL amyloidosis than in the patients with ATTR cardiac amyloidosis. Cardiac autonomic dysfunction is a known

phenomenon in AL and ATTR amyloidosis as well as systolic heart failure. [14,15].[16-19] The lack of heart rate variability was most marked in the patients who died. This finding suggests that pulse oximetry could help identify patients with cardiac autonomic denervation and open a potential therapeutic avenue for consideration of device therapy to counter lack of autonomic drive.

A recent randomised study (SERV-HF) in systolic heart failure showed that controlling CSA with assisted servo ventilation (ASV) did not improve survival.[20] The restrictive cardiomyopathy in AL is however very different from systolic heart failure requiring different treatment strategies. Reducing recurrent hypoxia with simple intervention like oxygen supplementation therefore needs to be studied. The current findings also raise the possibility of using overnight pulse oximetry to provide objective data which could potentially be used to monitor disease progression or to assess response to treatment.

We recognise the limitations of this pilot study. It is a small observational cohort study and we used overnight pulse oximetry rather than formal polysomnography thereby limiting our ability to confirm the cause of the recurrent nocturnal hypoxia and clarify type of SDB. We also did not use pulse plethysmography data as the main aim was to explore and confirm the presence of oxygen desaturations in patients with systemic amyloidosis. Moreover a significant proportion of patients had cardiac dysfunction as well as the possibility of autonomic involvement which would make PPG data difficult to interpret without polysomnography. The patient cohort was heterogeneous limiting ability to assess impact of desaturations on outcomes. We intend to address these issues in future studies

Conclusions

In conclusion, recurrent nocturnal oxygen desaturations, suggestive of sleep disordered breathing, are very common in patients with cardiac amyloidosis (both AL and ATTR type) as well as in patients with soft tissue amyloid deposits affecting the oropharyngeal tract. The extent of nocturnal hypoxia correlated with worsening markers of heart failure and worse right ventricular function. Lack of heart rate variability (suggesting cardiac autonomic neuropathy) is a frequent occurrence in cardiac AL and particularly in those patients who died – findings which need further clarification. The role of hypoxia caused by SDB in precipitating cardiac arrhythmias or causing sudden death in AL needs to be clarified. Nocturnal hypoxia is a simple target for intervention in cardiac AL amyloidosis and could potentially help to reduce early mortality in AL which has remained an unmet medical need for over 25 years.

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Authorship and Contributions

SM, MS and ADW designed the study and wrote the manuscript. PS and MS performed analysis of the oximetry data. SM and ADW and MS performed the statistical analysis and critically reviewed the manuscript. All the authors SM, MS, PS, LG, CQ, SS, MF, CJW, HJL, JDG, PNH and ADW confirm they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting and revising the article; and (c) final approval of the published article.

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Table 1. Patient characteristics

Type Number	Cardiac AL n=25	Macroglossia AL n=14	Cardiac & Macroglossia AL n=16	ATTR n=17	Patients Who died n=12
Age (years)	66 (49-80)	71 (47.4-83.8)	65 (39.3-81)	75 (61-83)	69 (59-83)
Organ Involvement					
Heart	25 (100%)	0	16 (100%)	17 (100%)	12 (100%)
Kidneys	14 (56%)	4 (29%)	5 (31%)	0	7 (58%)
Liver	8 (32%)	0	0	0	3 (25%)
Macroglossia	0	14 (100%)	16 (100%)	0	3 (25%)
Mayo Disease Stage					
1	4 (16%)	7 (50%)	2 (12%)	2	1 (8%)
2	9 (36%)	6 (43%)	6 (38%)	5	1 (8%)
3	12 (48%)	1 (7%)	8 (50%)	10	10 (84%)
NT-proBNP (ng/L)	5585 (136-146203)	186 (34-11788)	1314 (136-13288)	3703 (847-12712)	6619 (424-146203)
Troponin T (ng/L)	0.1 (0-0.8)	0.02 (0.01-0.1)	0.07 (0.01-0.15)	0.083 (0.04-0.63)	0.09 (0.01-0.8)
Albumin (g/L)	42 (24-49)	40.5 (30-46)	40.5 (30-52)	46 (43-50)	36 (25-46)
Alk Phos (IU/L)	81 (37-636)	76 (59-123)	82 (49-135)	109 (69-187)	83 (64-315)
Creatinine (µmol/L)	105 (58-582)	75 (46-472)	88 (45-385)	126 (70-188)	109 (71-226)
eGFR (mls/min)	59 (10-100)	73 (10-100)	71 (10-100)	52 (31-100)	60 (26-77)
GGT (U/L)	49 (12-621)	34 (7-213)	21 (9-153)	114 (42-310)	39.5 (9-621)
Urinary protein (g/24 hours)	0.2 (0.1-6.8)	0.2 (0.1-4.8)		0.2 (0.1-0.4)	0.9 (0.1-6.8)
LVEF (%)	55 (43-70)	61 (50-69)	56.5 (38-70)	41 (30-61)	49.5 (28-70)
RV TDI (cm/s)	0.12 (0.08-0.18)	0.15 (0.09-0.21)	0.12 (0.06-0.2)	0.09 (0.05-0.17)	0.11 (0.06-0.19)
TAPSE (mm)	15 (6-27)	22 (12-31)	17.5 (7-31)	12 (7-20)	12 (6-22)
Mean pulse (bpm)	77 (60-108)	68 (55-93)	72 (56-89)	69 (53-80)	80 (61-108)
Mean systolic BP (mmHg)	109 (91-150)	117 (102-154)	120 (102-166)	123 (106-151)	102 (96-150)

AL – light chain; BMI – body mass index; ATTR – transthyretin; BP – blood pressure; 4%ODI - hourly average number of desaturation episodes defined as a 4% decrease in saturations from the average saturations in the preceding 120seconds and lasting for more than 10seconds; NT-proBNP – N terminal of the prohormone brain natriuretic peptide; eGFR – estimated glomerular filtration rate; GGT

– gamma-glutamyltransferase; LVEF – left ventricular ejection fraction; RV TDI – right ventricle tissue Doppler imaging; TAPSE – tricuspid annular pulmonary systolic excursion; cm – centimetres; bpm – beats per minute;; pMol/L – picomoles per litre; ng/L – nanograms per litre; g/L – grams per litre; IU/L – international units per litre; µmol/L – micromoles per litre; mls/min – millilitres per minute; U/L – units per litre; g – grams; cm/s – centimetres per second; mm – millilitres.

Table 2. Oximetry data in the different amyloid groups

Type Number	**Cardiac AL n=25**	**Macroglossia AL n=14**	**Cardiac & Macroglossia AL n=16**	**ATTR n=17**	**Patients Who died n=12**
BMI	25 (18-30)	25.5 (19-45)	25.3 (19-32)	26 (21-37)	23.4 (19-26)
Neck circ (cm)	39 (31-44)	39 (34.3-43)	38 (33-42)	41 (34-45)	40 (34-43)
ESS and STOP BANG scores					
ESS score	8 (0-15)	6 (2-13)	6 (1-12)	5 (2-17)	8 (0-15)
ESS>10	7/25 (28%)	3/14 (21%)	3/16 (19%)	4/17 (24%)	4/12 (33%)
STOP BANG score	3 (1-5)	3 (2-5)	3 (1-6)	4 (1-6)	3 (1-4)
STOP BANG>3	16/25 (64%)	10/14 (71%)	11/16 (69%)	12/17 (71%)	8/12 (67%)
Oxygen saturations, ODI and HR variability					
Mean oxygen saturations	93 (88.7-96)	93 (87-96)	94 (91-96)	94 (91-96)	93 (88-96)
Abnormal Oximetry	21/25 (84%)	11/14 (79%)	10/16 (63%)	9/17 (53%)	9/12 (75%)
4% ODI	11 (1-48)	6 (3-41)	6 (0.9-52.1)	8 (0.57-59)	6 (3.8-26)
Heart rate change >6bpm	12 (1.9-113)	13 (4.3-51.5)	20 (2.3-69.7)	24 (0.3-80)	10 (0.3-113)

AL – light chain; ATTR – transthyretin based disease; circ – circumference; n – number; BMI – body mass index; cm – centimetres; bpm – beats per minute; 4%ODI – hourly average number of desaturation episodes defined as a 4% decrease in saturations from the average saturations in the preceding 120seconds and lasting for more than 10 seconds; STOP BANG - Snoring, Tiredness during the daytime, Observed apnoea, high blood Pressure, Body mass index, Age, Neck circumference and Gender; ESS – Epworth Sleepiness Score; mmHg – millimetres of mercury

Table 3. New Cardiac AL

Variable	HR (95% CI)	p
Univariate Analysis		
Neck circumference*	1.37 (0.31-6.13)	0.68
Body mass index*	0.81 (0.63-1.04)	0.10
Mean oximetry*	1.03 (0.7-1.52)	0.88
Abnormal pulse oximetry	0.20 (0.04-1.002)	0.05
Mean pulse*	1.05 (1.0-1.11)	0.12
Systolic blood pressure*	0.96 (0.92-1.01)	0.13
Heart rate variability>6bpm*	1.03 (0.97-1.07)	0.08
4%ODI*	0.95 (0.87-1.04)	0.28
TAPSE*	0.69 (0.51-0.92)	0.01
dFLC >180mg/L	0.14 (0.02-1.18)	0.07
NT-proBNP*	2.79 (0.54-14.38)	0.04

bpm – beats per minute; TAPSE – tricuspid annular pulmonary systolic excursion; dFLC – difference between involved and uninvolved free light chains; 4%ODI – hourly average number of desaturation episodes defined as a 4% decrease in saturations from the average saturations in the preceding 120seconds and lasting for more than 10seconds; AL – light chain.

* denotes continuous variables

Figure 1A and 1B. Overnight oximetry tracing of 2 patient with cardiac amyloidosis showing oxygen saturations (red tracing) and pulse variability (blue tracing). A normal oximetry tracing is illustrated in Figure 1B, with the mean SpO2 of 94.6% and 3% ODI of 3.6 events per hour. Figure 1C illustrates grossly abnormal oximetry findings with the mean SpO2 of 96% and 3% ODI of 46 events per hour.

Figure 2A and 2B. Relationship of 4%ODI and heart rate change greater than 6bpm in different types of amyloid respectively. This illustrates that cardiac AL patients experience the highest number of oxygen desaturations and have reduced heart rate variability.

Figure 2C and 2D STOP BANG questionnaire and ESS questionnaires in different amyloid groups respectively, showing evident elements of obstructive sleep apnoea and central sleep apnoea in these different groups. There is a relative lower risk of obstructive sleep apnoea and high risk of central sleep apnoea in cardiac AL patients.

Figure 3. Relationship between 4%ODI and NYHA class symptoms in cardiac AL patients, showing that increasing NYHA class directly correlated with higher incidence of 4% ODI; NYHA 1 vs. 2 (p=0.004), NYHA 1 vs 3 (p=0.01).

Figure 4. Kaplan Meier curves illustrating the **(A)** overall survival categorised by the type of amyloidosis: including cardiac AL (solid line), soft tissue involvement with macroglossia (dashed line) and ATTR (dotted line).

Figure 1A

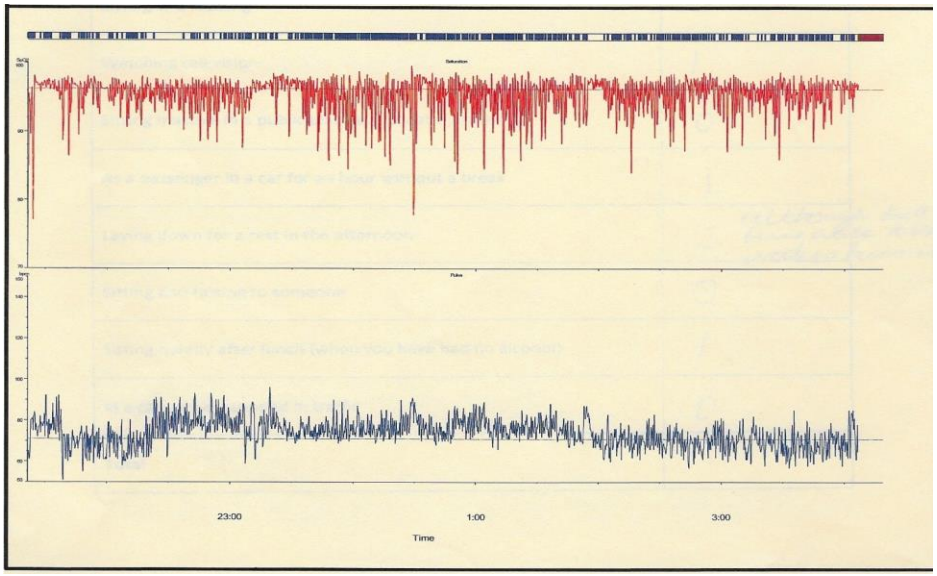


Figure 1B

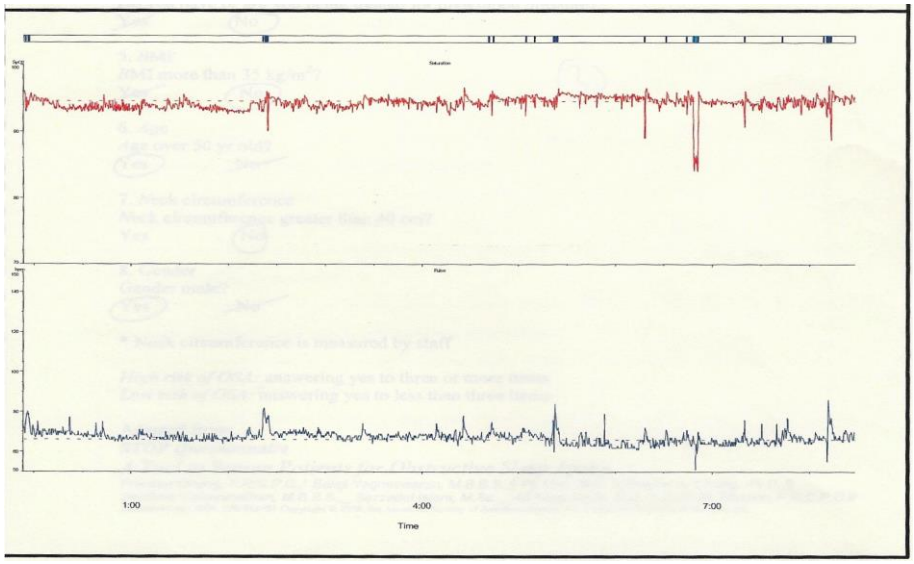


Figure 2

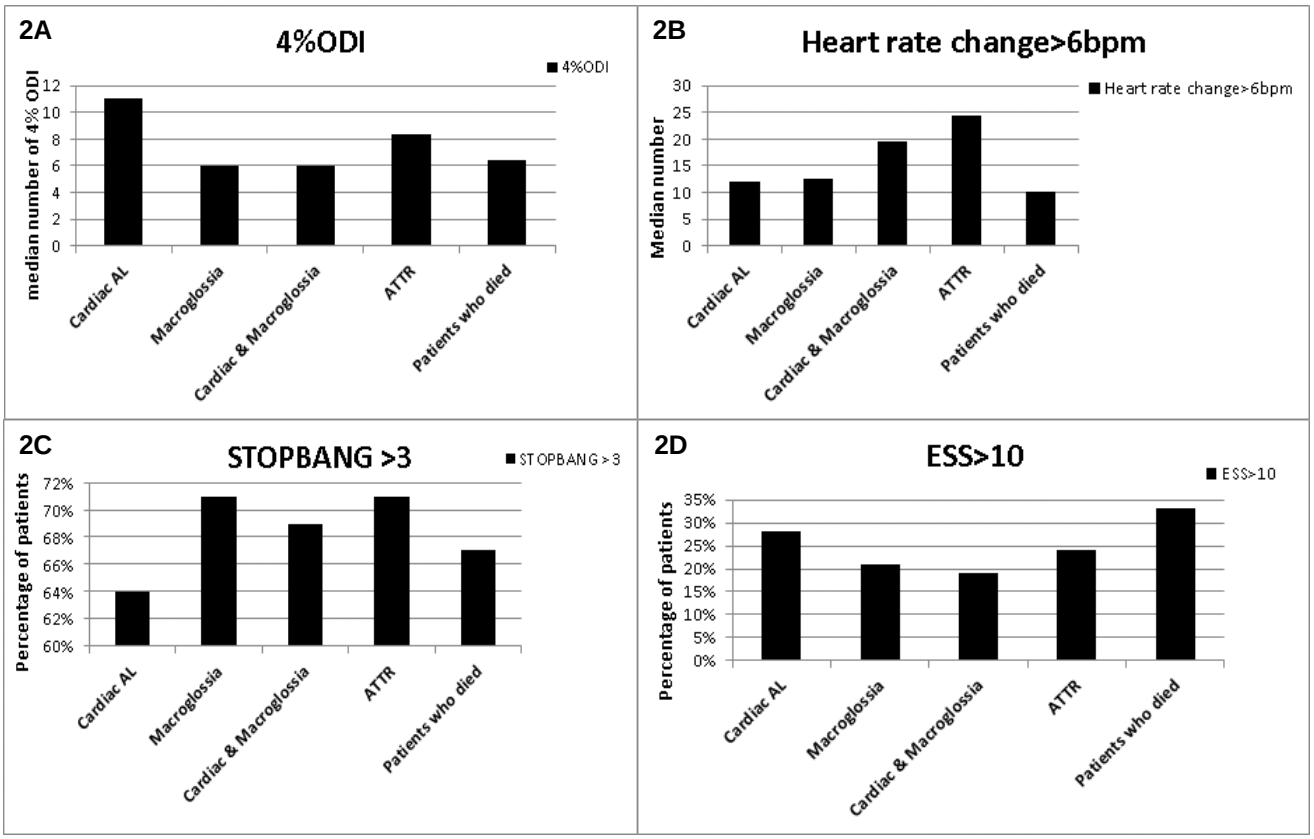

2A
4%ODI
4%ODI
median number of 4% ODI
12
10
8
6
4
2
0
Cardiac AL
Macroglossia
Cardiac & Macroglossia
ATTR
Patients who died
2B
Heart rate change>6bpm
Heart rate change>6bpm
Median number
30
25
20
15
10
5
0
Cardiac AL
Macroglossia
Cardiac & Macroglossia
ATTR
Patients who died
2C
STOPBANG >3
STOPBANG > 3
Percentage of patients
72%
70%
68%
66%
64%
62%
60%
Cardiac AL
Macroglossia
Cardiac & Macroglossia
ATTR
Patients who died
2D
ESS>10
ESS>10
Percentage of patients
35%
30%
25%
20%
15%
10%
5%
0%
Cardiac AL
Macroglossia
Cardiac & Macroglossia
ATTR
Patients who died

Figure 3

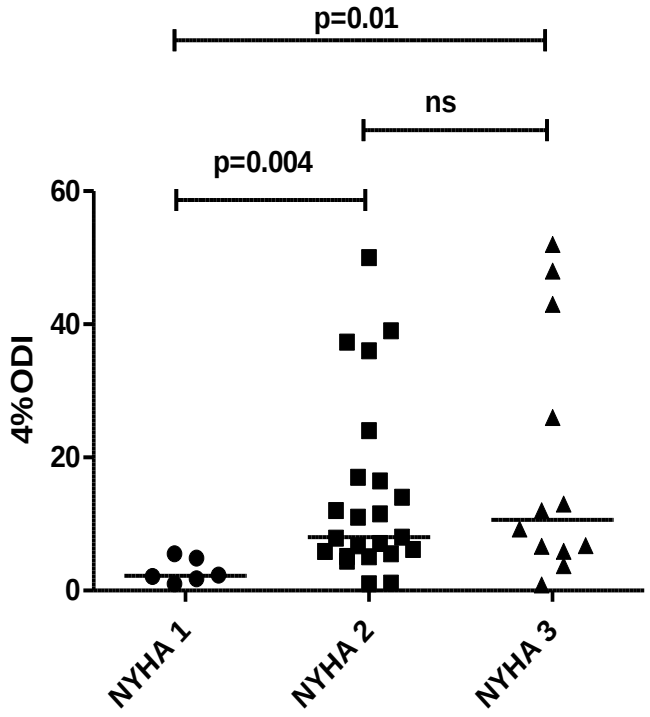
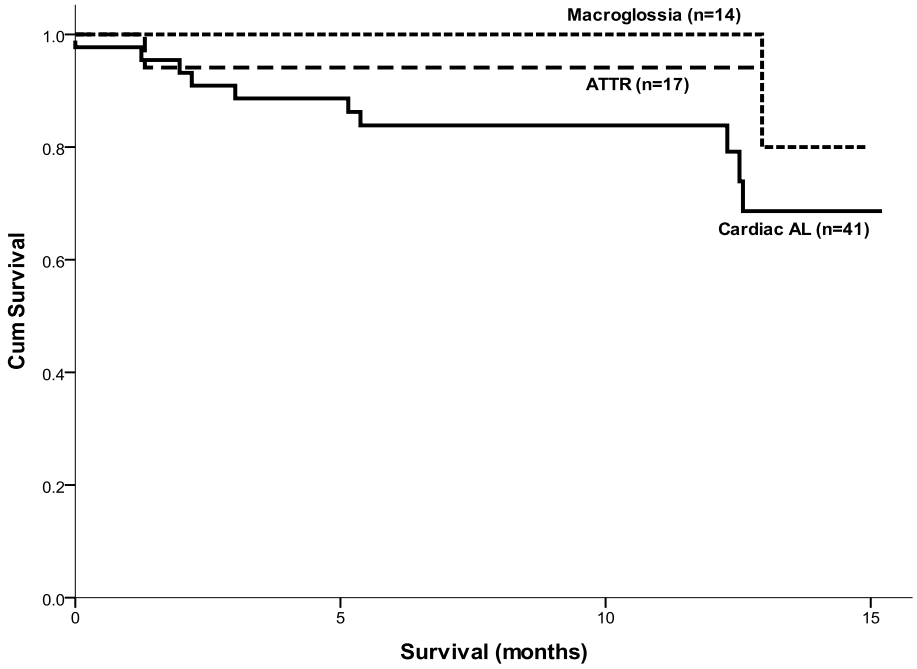

p=0.01
ns
p=0.004
60
40
20
0
4%ODI
NYHA 1
NYHA 2
NYHA 3

Figure 4


Macroglossia (n=14)
ATTR (n=17)
Cardiac AL (n=41)
1.0
0.8
0.6
0.4
0.2
0.0
Cum Survival
0
5
10
15
Survival (months)