Sleep disordered breathing and its treatment in congestive heart failure

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REVIEW

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Sleep disordered breathing (SDB) is a common problem with adverse cardiorespiratory, endocrinological, and endothelial effects. Recent studies demonstrate an even higher prevalence of SDB in congestive heart failure (CHF) than in a randomly selected population, with up to 40% and 11% having Cheyne Stokes respiration–central sleep apnoea and obstructive sleep apnoea–hypopnoea syndromes, respectively. Randomised controlled trials of nocturnal respiratory support for SDB associated with CHF for up to three months demonstrate significant benefits in terms of improvements in left ventricular ejection fraction, markers of sympathetic system activity, and quality of life. Further randomised controlled trials of larger scale and longer duration are required to establish the role and benefit of this intervention for the treatment of this debilitating condition. The evidence for the higher prevalence of SDB in CHF, its pathogenesis, its pathophysiological consequences, and the emerging benefits of respiratory support are reviewed.

Congestive heart failure (CHF) remains a leading cause of morbidity and mortality worldwide.[1] Randomised controlled trials have shown significant benefits of pharmacological treatment based on the attenuation of adrenergic drive through selective β blockade[2 3] or manipulation of the renin–angiotensin–aldosterone system.[4–6] More recently cardiac resynchronisation[7] has developed as a new treatment modality for specific patients with CHF. However, the survival benefits manifested in such trials have yet to translate into a dramatic reduction in CHF mortality.[8 9]

It is therefore important to identify and explore all of the factors that may alter the prognosis of heart failure, to facilitate the development of additional treatment options.

Sleep disordered breathing (SDB) in CHF is a burgeoning field of research, which offers insight into pathophysiological mechanisms and has treatment potential.

Undiagnosed SDB is a common problem affecting up to 24% and 9% of randomly selected middle aged men and women, respectively,[10] with 4% and 2% having obstructive sleep apnoea–hypopnoea syndrome (OSAHS).[10] Prevalence data on CSA in the healthy adult population are lacking.

There is, however, evidence of a higher prevalence of SDB in the heart failure population than in the normal population.[11–13] Obstructive sleep apnoea is also associated with increased odds of developing heart failure independent of other risk factors.[14]

DIAGNOSIS AND CLASSIFICATION

The primary parameter used to quantify SDB is the apnoea–hypopnoea index (the mean number of apnoeic and hypopnoeic events an hour during a night's sleep). Five or more an hour are regarded as significant and are classified as either obstructive or central. Table 1[15] outlines the diagnostic criteria for the classification of SDB.

Obstructive apnoeas and hypopnoeas result from complete or partial collapse of a narrowed pharynx, respectively.[16] Central sleep apnoeas and hypopnoeas can result from either a reduction in central respiratory drive (as occurs in brainstem pathology or respiratory muscle weakness, thus associated with hypoventilation and hypercapnia) or an instability in feedback control of the central respiratory centre (as occurs in CHF, but it is often idiopathic and not associated with hypercapnia).[17–19] Cheyne-Stokes respiration (CSR) is a form of periodic breathing with oscillations in tidal volume associated with central apnoea and hypopnoea, often referred to as CSR-CSA. However, as the purpose of this review is to focus on SDB in CHF, because of the similarity in pathophysiology of CSR-CSA and CSA, they will be regarded as one.

Table 2 outlines a basic classification of sleep studies.[15] Attended nocturnal polysomnography is considered the ideal diagnostic modality for the diagnosis of the cause of SDB, although it is clearly not widely available.[20]

However, guidelines[15] advise that level II and III studies are acceptable for the diagnosis and assessment of treatment for SDB in the adult population. There is not yet guidance for the use of these studies on the diagnosis and assessment of SDB in the CHF population. Level IV studies, a combination of continuous pulse rate and oxyhaemoglobin saturation recording, though not recommended for the diagnosis and classification of SDB, have a role as a screening tool for SDB in an adult population. Level III studies, which can also be performed in the home, record more detailed information (pulse rate,

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Abbreviations: CANPAP, Canadian continuous positive airway pressure; CHF, congestive heart failure; CPAP, continuous positive airway pressure; CSA, central sleep apnoea; CSR, Cheyne-Stokes respiration; NYHA, New York Heart Association; OSAHS, obstructive sleep apnoea hypopnoea syndrome; P_{CO_2}, partial pressure of carbon dioxide; SDB, sleep disordered breathing

Table 1 Diagnostic criteria for the classification of SDB (based on the American Academy of Sleep Medicine Task Force)[15] on the basis of the combination of symptoms or signs and findings on overnight monitoring

Syndrome	Symptoms and signs	Overnight monitoring
OSAHS	Excessive daytime sleepiness not explained by other factors or two or more of the following: choking or gasping during sleep; recurrent awakenings from sleep; unrefreshing sleep; daytime fatigue; impaired concentration	Five or more obstructed breathing events/hour, any combination of apnoea, hypopnoea, and respiratory effort related arousal
CSA-HS	One or both of excessive daytime sleepiness and frequent nocturnal arousals or awakenings	Five or more central apnoeic and hypopnoeic events/hour and normal daytime P_{CO_2} (<6 kPa)
CSR-CSA	CHF or cerebral neurological disease	Three or more consecutive cycles of cyclical crescendo and decrescendo change in breathing amplitude and five or more central apnoeic and hypopnoeic events/hour or a cycle of crescendo–decrescendo change in breathing amplitude lasting 10 minutes or more

CHF, congestive heart failure; CSA, central sleep apnoea; CSR, Cheyne Stokes respiration; HS, hypopnoea syndrome; OSAHS, obstructive sleep apnoea–hypopnoea syndrome; P_{CO_2}, partial pressure of carbon dioxide; SDB, sleep disordered breathing.

oxyhaemoglobin saturation, abdominal and thoracic wall movement, airflow, and sleeping position). They allow the diagnosis of disordered breathing during assumed sleep and its classification and quantification of severity. Though not necessarily validated for the assessment of SDB in the context of CHF, level III studies are more widely available than level I or II studies for the assessment of SDB at a secondary care level through sleep disorders clinics.

EPIDEMIOLOGY OF SLEEP DISORDERED BREATHING IN CONGESTIVE HEART FAILURE

In a prospective study of 81 consecutive patients with predominantly New York Heart Association class I and II heart failure (caused by ischaemia, alcohol, and idiopathic cardiomyopathy) and a mean ejection fraction of < 30%, 51% of patients had significant evidence of SDB. Of those, 78% had CSA and 22% had OSAHS.[11] In a population of 450 patients with CHF with symptoms of SDB referred for polysomnography studied retrospectively, the prevalence of SDB, CSA, and OSAHS was 61%, 29%, and 32%, respectively.[12] Similarly in a series of 35 consecutive patients with CHF, the prevalence of the same disorders was 65%, 37%, and 28%.[13]

There is some evidence that the prevalence of CSA is increased in CHF populations with increasing disease severity. In a study of consecutive patients presenting with acute left ventricular failure, the prevalence of SDB, CSR-CSA, and OSAHS was 82%, 75%, and 25%, respectively, within one month of presentation and treatment.[21] CSR-CSA syndrome affected up to 45% in a series of consecutive patients awaiting cardiac transplantation.[22] However, the strength of this relation has recently been questioned.[23]

On the other hand, prospective studies of consecutive patients who have OSAHS provide evidence of left ventricular dysfunction when all other causes of left ventricular dysfunction have been excluded (coronary artery disease, CHF caused by cardiomyopathy or valvar heart disease, hypertension, and hypertrophic cardiomyopathy).[24–25] Therefore, SDB can occur as a consequence of CHF but may also exacerbate the disease process.

However, it must be highlighted that larger epidemiological studies are required to quantify more accurately the prevalence of SDB and its subclassifications in the CHF population. Such studies will also add to our understanding of the impact of more recently introduced treatment modalities such as β blockade and biventricular pacemaker insertion on the prevalence of SDB, especially CSR-CSA, in CHF.

PATHOGENESIS

The pathogenesis of CSR-CSA in CHF has recently been elucidated.

Hyperventilation with reduction of arterial carbon dioxide pressure below a threshold is critical to the initiation of CSR-CSA independent of circulation time. However, there is a significant correlation between lung to chemoreceptor circulation time and the *length* of the CSR-CSA cycle.[18] Hyperventilation in the setting of CHF is believed to occur due to the stimulation of lung vagal irritant receptors as a consequence of pulmonary congestion as indicated by higher pulmonary capillary wedge pressure in patients with CHF associated with CSR-CSA than in those without.[26]

Hyperventilation may also occur due to increased ventilatory sensitivity to carbon dioxide, as patients with CHF associated with CSR-CSA have a greater ventilatory responsiveness to carbon dioxide than do those without.[27] Risk factors for the occurrence of CSR-CSA in a CHF population are male sex, atrial fibrillation, age greater than 60, and daytime hypocapnia.[12]

The reason for the increased prevalence of OSAHS in CHF is less clear. The coexistence of both may also be a function of their respective high prevalence in the adult population.[1 10]

On the other hand, sleep onset is associated with loss of pharyngeal dilator muscle tone, which in the setting of normal pharyngeal anatomy is not associated with airway compromise. In patients with OSAHS, the pharynx is

Table 2 Types of sleep studies (based on the American Academy of Sleep Medicine Task Force)[15]

Level	Components	Location performed	Comment
I	Electroencephalogram, electro-oculogram, submental EMG, nasal/oral airflow, respiratory movement, oximetry, ECG, anterior tibialis EMG, sleeping position	Sleep laboratory	Complete attended study; facilitates determination of wake and sleep states, sleep stages, and disturbance, AHI, and detection of sleep pathology unrelated to SDB
II	Same as level I	Home	Same as level I but an unattended study
III	Partial study measuring nasal/oral airflow, respiratory movement, oximetry, pulse rate, sleep position	Home	Unattended study; allows detection of respiratory and cardiac events but no information about wake and sleep states and stages or sleep disturbance and non-SDB sleep pathology
IV	Pulse rate, oximetry	Home	Unattended study; least expensive, useful screening tool for OSAHS

AHI, apnoea–hypopnoea index; EMG, electromyogram.

anatomically narrowed and highly compliant; hence, the changes of sleep onset result in pharyngeal occlusion.[28] Obesity is a risk factor for OSAHS because of the layering of fat adjacent to the pharynx narrowing its lumen,[29] but the prevalence of obesity in the CHF populations studied was not very high. In prevalence studies, the patients studied were clinically overweight (mean body mass index 28 kg/m^2)[11] and mildly obese (mean body mass index 32.3 kg/m^2).[12] Pharyngeal muscle tone can be altered during the oscillations of ventilatory drive that accompany CSR, resulting in loss of pharyngeal dilator action,[30] in addition to increased pharyngeal oedema caused by increased fluid shift centrally from the lower limbs, which occurs while the patient is supine at night.[31] Both of these factors can compromise the patency of the upper airway.

Though SDB in patients with CHF can be classified as either CSR-CSA or OSAHS in nature,[11] there is evidence of a relation between the pathophysiology of both.

The same patient can have both OSAHS and CSR-CSA and a shift from one type to another can be observed during sleep, which is associated with a decrease in partial pressure of carbon dioxide (P_{CO_2}) and lengthening of the circulation time.[32] The reasons for such are a matter of debate. One factor that may be a determinant of apnoea type is the arterial carbon dioxide as reflected by P_{CO_2}. Hyperventilation as already mentioned occurs in CHF patients as a result of stimulation of lung vagal irritant receptors[26] and altered ventilatory responsiveness to carbon dioxide.[27] The consequent reduction of arterial P_{CO_2} below the apnoeic threshold (the level of arterial P_{CO_2} below which ventilation ceases) triggers the onset of CSR-CSA.[27] On the other hand, OSAHS is not associated with a fall in P_{CO_2}.[32] The close link between overnight lengthening of the circulation time and reductions in arterial P_{CO_2} strongly suggests that the fall in P_{CO_2} and shift in apnoea type are linked to an overnight deterioration in cardiac function.

PATHOPHYSIOLOGICAL CONSEQUENCES

The pathophysiological consequences of OSAHS in CHF are multiple.

Repeated upper respiratory obstructive events result in negative intrathoracic pressure, increased systolic transmural pressure, increased left ventricular afterload, and hence reduced stroke volume and cardiac output.[33] Increased negative intrathoracic pressure results in increased venous return, right ventricular volume overload, leftward shift of the interventricular septum, impaired left ventricular filling, and reduced stroke volume.[34]

Increased sympathetic nervous system activity is a central feature of obstructive sleep apnoea. The pulmonary stretch receptor mediated reflex, which normally suppresses central sympathetic discharge during normal breathing, ceases during apnoea, facilitating sympathetic outflow.[35] The associated hypoxia and hypercapnia further augment sympathetic activity by simulating peripheral and central chemoreceptors. The consequences are increased heart rate, vasoconstriction, and raised peripheral vascular resistance.[36 37]

The pathophysiological impact of OSAHS extends into wakefulness, with it now being recognised as an independent risk factor for hypertension[38 39] and it being associated with left ventricular hypertrophy in normotensive patients.[40]

Obstructive sleep apnoea syndrome is now recognised as an independent risk factor for increased insulin resistance. Furthermore, treatment with continuous positive airway pressure (CPAP) has been shown to increase insulin sensitivity in these patients.[41]

There is also evidence that OSAHS may have potential detrimental endothelial effects. Patients with OSAHS have higher plasma C reactive protein concentrations[42] than controls, they have signs of increased oxidative stress, such as increased reactive oxygen species production in neutrophils,[43] and they have increased serum concentrations of intracellular adhesion molecule 1 and vascular cell adhesion molecule 1.[44]

There are some reports that OSAHS alone can also act as an independent risk factor for the development of left ventricular dysfunction. In patients without a history of CHF or coronary artery disease, the presence of OSAHS is associated with evidence of left ventricular systolic[24] and diastolic dysfunction.[24 25] Nocturnal CPAP for six months results in the correction of these indices. Furthermore, normotensive patients with OSAHS have increased left ventricular wall thickness in comparison with controls.[40]

The presence of CSR-CSA additionally has an adverse prognostic impact and pathophysiological burden on patients with CHF. It is associated with a higher mortality even after adjustment for other disease severity risk factors.[45 46] The adverse effects of CSR-CSA probably arise from similar factors described for OSAHS including intermittent hypoxia, frequent arousals from sleep, sympathetic system activation, and apnoea related surges in blood pressure and heart rate, but without the effects of negative intrathoracic pressure during apnoeic events.

EVIDENCE FOR THE TREATMENT OF SDB IN CHF

There is compelling evidence for the treatment of OSAHS with CPAP irrespective of whether patients have CHF.[47 48]

The physiological benefits are reduced frequency and severity of desaturations, heart rate variability, apnoea, hypopnoeic events,[49] daytime somnolence,[50] and improved control of hypertension[51] and neuropsychological symptoms.[52]

There is also evidence that the treatment of OSAHS in CHF with CPAP has additional positive physiological and clinical benefits by abolishing apnoea related hypoxia, lowering nocturnal blood pressure, improving sleep quality[53] and ejection fraction,[54–56] and reducing catecholamine production[56] (table 3). Two randomised controlled trials of CPAP for OSAHS associated with CHF have confirmed that these improvements in ejection fraction are significant (5%[56] and 8.8%[55]) and that they are associated with improvements in symptoms.[56]

Even in the absence of evidence of CHF or a primary cardiac disease, there is some evidence (albeit from uncontrolled trials with small numbers) that the treatment of OSAHS for six months or longer results in a significant increase in left ventricular ejection fraction.[24–25]

These changes are believed to be caused by the relative increase in intrathoracic pressure due to CPAP, resulting in a reduction in cardiac transmural pressure. The reduction in transmural pressure in conjunction with the reduction of nocturnal blood pressure leads to a reduction in left ventricular afterload.[53]

However, larger and longer term randomised controlled studies recruiting treatment naive patients with OSAHS without cardiovascular morbidity at baseline are required to determine whether OSAHS can cause CHF directly.

There is also evidence from randomised controlled trials that CPAP has a significant beneficial effect on CSR-CSA caused by CHF when applied for at least 1–3 months[57–60] (table 4[57–63]). The benefits were a reduced apnoea–hypopnoea index and improved ejection fraction (6.5% to 8.6%), New York Heart Association (NYHA) functional status, and symptom score. This is postulated to be caused by reduced minute ventilation, with an increase in arterial carbon dioxide pressure (possibly above the apnoeic threshold) during sleep as a consequence of reduced lung vagal irritant

Table 3 Randomised controlled trials of nocturnal respiratory support in patients with OSAHS associated with CHF

	Patient characteristics						
Trial	CHF cause	NYHA class	Baseline LVEF (%)	Intervention	Duration of treatment	No of patients	Cardiovascular outcomes
Kaneko *et al*[55]	ICM, DCM	2.3	25.0	CPAP	1 month	24	8.8% increase in LVEF, reduced LVESD, reduced heart rate and SBP
Mansfield *et al*[56]	Not stated	2.2	37.3	CPAP	3 months	55	5% increase in LVEF, reduced fatigue and overnight urinary noradrenaline excretion, increased disease mastery and emotional wellbeing (CHFQ)

CHFQ, Guyatt chronic heart failure questionnaire; CPAP, continuous positive airway pressure; DCM, dilated cardiomyopathy; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; NYHA, New York Heart Association; SBP, systolic blood pressure.

receptor stimulation due to reduced pulmonary congestion.[64] Concern has been raised over the possible adverse haemodynamic effects of the use of CPAP in severe CHF (NYHA class III to IV) associated with atrial fibrillation in one study.[65]

Overall, the sample sizes of these studies are small,[57–60] the periods of follow up are short, and possibly as a consequence only one study has reported a reduction in mortality.[60]

Larger longer term follow up studies are required to address the mortality benefits and to clarify the subgroups of patients with CHF who are susceptible to the potential adverse haemodynamic effects of the use CPAP.

Additional forms of respiratory support have been examined in this context.

Pressure support adaptive servo- (non-invasive) ventilation, a hybrid form of respiratory support that can cycle between pressure support during hypopnoea and ventilatory support during apnoea, is as effective as CPAP for the treatment of CSR-CSA in patients with CHF in terms of indices of SDB,[61] neurohormonal activation, and reduced daytime somnolence over a period of a month.[62]

Bilevel non-invasive ventilation has also been proved to be an effective alternative to CPAP in the treatment of CSR-CSA caused by CHF.[63]

The first randomised controlled trials of respiratory support for the treatment of OSAHS associated with CHF have recently been published[55 56] (table 3). In both, patients were treated with CPAP for periods of 1–3 months. In comparison with the control groups, the CPAP treated groups exhibited an increase in left ventricular ejection fraction of 5%[56] and 8.8%.[55]

Furthermore, mean daytime systolic blood pressure (126 to 116 mm Hg), heart rate (68 to 64 beats/min), and left ventricular end systolic dimension (54.5 to 51.7 mm) changed significantly. Sympathetic nervous system activity as measured by overnight urinary noradrenaline (norepinephrine) excretion was reduced in the treatment group and indices of quality of life were improved (fatigue, disease mastery, and emotional wellbeing as measured by the chronic heart failure questionnaire).[56]

This treatment for this specific CHF patient population compares favourably with the effects of β blockade and angiotensin converting enzyme inhibition[66] in CHF as shown by randomised controlled trials.[67] However, as mentioned above, this evidence is limited by a lack of a demonstrable impact on mortality, possibly as a result of sample size and the duration of follow up.

Larger prospective trials such as the ongoing CANPAP (Canadian continuous positive airway pressure)[68] trial are required to delineate the precise benefit and roles of CPAP in the treatment of SDB in CHF.

OTHER TREATMENTS

Nocturnal supplemental oxygen in the context of CSR-CSA associated with CHF, though abolishing apnoea related hypoxia and alleviating CSR-CSA[69 70] does not cause improvements in cardiac function or quality of life over a period of one month.[71]

Oral theophylline treatment of patients with SDB associated with CHF reduces the apnoea–hypopnoea index and duration of arterial oxygen desaturation during sleep but has

Table 4 Randomised controlled (and crossover) trials of nocturnal respiratory support in patients with CSR-CSA associated with CHF

	Patient characteristics						
Trial	CHF cause	NYHA class	Baseline LVEF (%)	Intervention	Duration of treatment	No of patents	Cardiovascular outcomes
Naughton *et al*[57]	ICM, DCM	2.5	18.3	CPAP	1 month	18	6.5% increase in LVEF, reduced nocturnal urine and daytime serum noradrenaline
Naughton *et al*[58]	ICM, DCM	2.5	21.2	CPAP	3 months	29	7.7% increase in LVEF, reduced fatigue and dyspnoea, increased emotional well being and disease mastery (CHFQ)
Granton *et al*[59]	ICM, DCM	2.4	24	CPAP	3 months	17	8.6% increase in LVEF, reduced dyspnoea and fatigue (CHFQ)
Sin *et al*[60]	ICM, DCM		NA	CPAP	3 months	66	8% increase in LVEF, 81% relative risk reduction in mortality and transplantation rate
Teschler *et al*[61]	ICM, DCM	2.9	Fractional shortening 0.19	APSSV, Bi-V, CPAP, supplemental oxygen	4 nights (crossover trial)	14	APSSV reduced AHI and arousal index more than did CPAP, bilevel ventilation or oxygen supplementation; change in LVEF not measured
Pepperell *et al*[62]	ICM, DCM	2.7	36.5	APSSV	1 month	30	Reduced serum BNP, urinary metadrenaline, and daytime somnolence; change in LVEF not measured
Kohnlein *et al*[63]	ICM, DCM	2.8	23.8	Bi-V/CPAP	1 month (crossover trial)	18	Bilevel ventilation and CPAP equally improved circulation time; improved sleep quality, reduced daytime fatigue (SF-36) and NYHA class; change in LVEF not measured

APSSV, adaptive pressure support servoventilation; Bi-V, bilevel non-invasive ventilation; BNP, brain natriuretic peptide; NA, not available; SF-36, short form 36 questionnaire.

not been shown to cause improvements in ventricular function, quality of life, or clinical outcomes.[72] Atrial overdrive pacing has recently been shown by one group[73] to reduce the number of episodes of central and obstructive apnoea in a cohort of patients with SDB without CHF. The mechanism by which this occurs is a matter of debate. It may be related to the effect of an augmentation in cardiac output reducing pulmonary congestion, a stimulus for hyperventilation, and to a reduction in circulation time. Further studies are awaited to determine whether this effect can be reproduced.

Lifestyle modification resulting in weight loss reduces the severity of OSAHS,[74] possibly through a decrement in upper airway collapsibility[75] in an obese non-CHF population. Though there is no such evidence for an obese CHF population, presumably the same should occur.

CONCLUSION

The presence of SDB presents another treatment opportunity in CHF. There is now a burgeoning field of evidence that respiratory support for these patients has considerable physiological benefits. Larger longer term studies are required to determine whether these benefits have an impact on mortality. Increased awareness of the prevalence and pathophysiological implications of SDB in CHF is essential to promote and encourage the further development of this facet of treatment in CHF.

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IMAGES IN CARDIOLOGY

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Cardiac angiosarcoma: diagnosis by coronary angiography

A 55 year old man was admitted to hospital after collapsing while playing golf. During assessment in the emergency department the patient became unconscious and lost cardiac output associated with a sinus bradycardia of 40 beats/min, some non-specific changes in the inferior ECG leads, and normal myocardial injury markers. Coronary angiography demonstrated normal coronary arteries; however, a branch of the right coronary artery (RCA) supplying the right atrium (RA) was associated with a tissue blush (panel A). Transthoracic echocardiography (TTE) confirmed a mass in the RA and a global pericardial effusion (panel B). Transoesophageal echocardiography (TOE) showed a localised 3.5 × 3.5 cm tumour of the RA anterior wall (panel C). A computed tomographic (CT) scan of the chest showed no evidence of metastasis. Operative findings showed extension of the tumour to the surface of the RA and involvement of the RCA. The tumour was resected and a saphenous vein graft was anastomosed to the distal RCA. Histology confirmed angiosarcoma with a high mitotic rate and incomplete resection at the margin. A repeat operation with wider excision was performed with a clear histological margin. Five cycles of doxorubicin and ifosfamide chemotherapy were administered. Adjuvant radiotherapy to the site of the primary tumour was given. The patient died 11 months after primary diagnosis from CT proven metastatic disease.

This case demonstrates the unusual angiographic findings of a cardiac malignancy and its correlation with TTE and TOE echocardiographic images.

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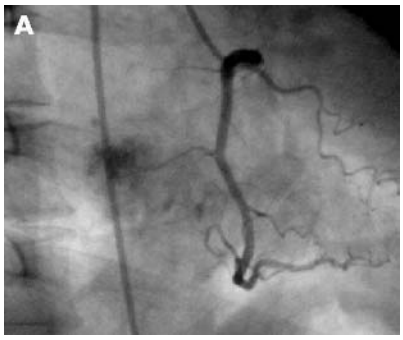
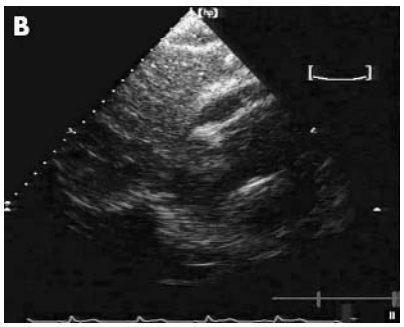
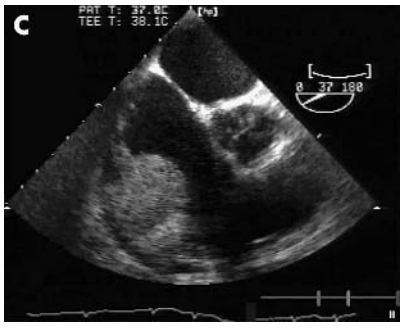


A tumour blush in the right atrium is seen during right coronary angiography.



Transthoracic echocardiogram demonstrating a mass in the right atrium.



Transoesophageal echocardiogram clearly showing the tumour and its extension.