CARDIOVASCULAR DISEASE AND SLEEP DISORDERED BREATHING IN ACROMEGALY

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Abstract

Treatment goals in acromegaly include symptom relief, tumour control and reversal of the excess morbidity and mortality associated with the disorder. Cardiovascular complications include concentric biventricular hypertrophy and cardiomyopathy, hypertension, valvular heart disease and arrhythmias, while metabolic disturbance (insulin resistance/diabetes mellitus, dyslipidaemia) further increases the risk of cardiovascular and cerebrovascular events. Sleep disordered breathing (in the form of sleep apnoea) is also common in patients with acromegaly and may exacerbate cardiovascular dysfunction, in addition to contributing to impaired quality of life. Accordingly, and in keeping with evidence that cardiorespiratory complications in acromegaly are not automatically reversed/ameliorated simply through the attainment of 'safe' growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels, recent guidelines have emphasised the need not only to achieve stringent biochemical control, but also to identify and independently treat these comorbidities. It is important therefore that patients with acromegaly are systematically screened at diagnosis, and periodically thereafter, for the common cardiovascular and respiratory manifestations, and that biochemical targets do not become the only treatment goal.

Introduction

Acromegaly is associated with an increased mortality rate [1,2], with a meta-analysis of 16 studies revealing a weighted mean of the standardised mortality ratio (SMR) of 1.72 (95% confidence interval 1.62-1.83) [3]. Variance across studies has been attributed to several factors, including differing background population mortality rates and the weighting of historical versus contemporary cases (with modern treatments for acromegaly and its associated comorbidities more effectively mitigating the adverse sequelae of this condition) [4]. The increased risk of premature death has been attributed to cardiovascular and cerebrovascular events, respiratory complications and malignant neoplasms [3,5,6]. Restoration of serum growth hormone (GH) and insulin-like growth factor 1 (IGF-1) to 'normal' or 'safe' levels remains a central goal of modern acromegaly management, although several studies have shown a continuing excess mortality when compared with the general population [3,5]. One important consideration when interpreting these data is the frequent reliance on a single GH and/or IGF-1 measurement at the end of the follow-up period which, however, may not reflect the degree of disease control throughout a treatment period [7]. These findings have prompted several workers to highlight the importance of identifying and independently treating cardiovascular and respiratory comorbidities in acromegaly [8,9,10]. In this article we review the spectrum of cardiovascular disorders that may be seen in acromegaly and draw attention to sleep disordered breathing as both an under-recognised, and often inadequately treated comorbidity, especially in patients who have achieved satisfactory biochemical control following primary therapy.

Cardiovascular complications

Cardiovascular abnormalities are common in acromegaly and may include a specific ('acromegalic') cardiomyopathy, hypertension, altered vascular function (with increased arterial stiffness and impaired endothelial relaxation), cardiac valvular dysfunction, arrhythmias and premature coronary and cerebrovascular disease [11]. Insulin

resistance/diabetes mellitus and dyslipidaemia are frequent accompaniments of GH excess and may exacerbate cardiovascular disease.

Hypertension

Hypertension affects at least one third (and possibly up to a half) of all patients with acromegaly, and is a key negative prognostic factor for mortality [1,12,13,14]. It is present from the earliest stages and is not necessarily influenced by disease duration [15], although it is more common in older subjects, as in the general population. An elevation in diastolic pressure is usually the first and predominant finding and may be heralded by changes in vascular dynamics [12]. Minimally invasive vascular studies have revealed an increase in arterial pulse wave velocity (a measure of arterial stiffness) and a reduction in flow-mediated dilatation (signifying impaired endothelial function) in newly diagnosed patients [9], which are believed to be mediated, at least in part, by direct effects of GH and IGF-1 on the vascular tree [16]. Insulin resistance and hyperinsulinism, which are common metabolic sequelae of acromegaly, may also contribute to endothelial dysfunction [17].

In addition to the direct effects of GH and IGF-1 on the vasculature, several other pathophysiological mechanisms have been postulated to contribute to hypertension in acromegaly [18], including GH-mediated increased renal tubular sodium reabsorption [19], and inhibition of atrial natiuretic peptide by IGF-1 [20]. Where present, elevated insulin levels may also lead to increased sodium reabsorption with activation of the renin-angiotensin-aldosterone system. Each of these mechanisms serves to increase circulating plasma volume and raise blood pressure. Cardiac hypertrophy can both induce and be exacerbated by hypertension, and sleep apnoea may also be contributory. Finally, secondary changes (remodelling) in the vasculature are commonly seen in response to longstanding/established hypertension.

Cardiomyopathy and cardiac dysfunction

Both GH and IGF-1, acting through their respective receptors, mediate direct effects on cardiac myocytes, e.g. increasing intracellular calcium content and sensitivity, and thereby altering myocardial contractility [21]. Over time, exposure to chronically raised GH and IGF-1 levels may lead to extracellular collagen deposition, myofibrillary derangement, lymphomononuclear infiltration and ultimately necrosis, resulting in a progressive change in cardiac architecture [1,22,23]. These changes are independent of, but may be exacerbated by coexistent hypertension. Classically, three stages of intrinsic heart disease are recognised in acromegaly: (i) biventricular concentric hypertrophy (**Fig. 1a**) with increased myocardial contractility and systolic output, which is typically combined with an increased heart rate to give a hyperkinetic syndrome, (ii) more pronounced hypertrophy with diastolic filling defects at rest (**Fig. 1b**) and systolic dysfunction during exertion, and (iii) end stage cardiomyopathy with diastolic and systolic dysfunction at rest manifesting as overt heart failure [24,25,26]. In addition to hypertension, arrhythmias, metabolic dysfunction and ischaemic coronary disease may all conspire to further impair cardiac performance. Screening for these complications and for other common vascular risk factors (e.g. smoking, dyslipidaemia) should therefore be performed in all patients.

Valve disease

An excess of cardiac valve disease has been reported in acromegaly [27]. It has been suggested that GH exposure mediates an increase in expression of matrix metalloproteinases, leading to matrix dysregulation and a predisposition to annular fragility and leaflet disarray [28,29]. The mitral and/or aortic valves are most commonly affected, predisposing to ventricular hypertrophy, arrhythmia and heart failure. An increase in aortic root diameter may be another important contributory factor in valve dysfunction [30,31]. The prevalence of at least mild valve disease has been reported in as many as a fifth of patients with acromegaly [32], and has been shown to be dependent on disease duration, which suggests a potentially cumulative effect of GH exposure.

Arrhythmias

Paroxysmal atrial fibrillation and supraventricular tachycardia, sick sinus syndrome, ventricular ectopic beats and ventricular tachycardia have all been linked with acromegaly, particularly during physical exertion. In one study, arrhythmias were observed in 48% of patients [33]. Myocardial hypertrophy and areas of fibrosis may be contributory, and conduction abnormalities have been reported in 41–56% of cases [34,35].

Carotid and coronary artery atherosclerotic disease

As already noted, cerebrovascular and cardiac events are among the most commonly reported causes of death in acromegaly [3,5,6]. Their aetiology is likely to be multifactorial, with important contributions from each of the specific comorbidities highlighted in this article, acting in concert with other commonly-recognised cardiovascular risk factors such as age, sex and smoking status. Interestingly, specific assessments of carotid and coronary artery disease in patients with acromegaly have yielded mixed results. For example, Kartal *et al.* (2010) [36] and Brevetti *et al.* (2002) [37] both observed an increase in carotid intima-media thickness in active acromegaly, whereas others have reported no significant increase [38]. Early post-mortem studies suggested an increase in coronary artery atherosclerosis [39,40]. More recent studies have sought to use a combination of CT-derived calcium scores and conventional risk scores (Framingham risk score, European Society of Cardiology risk score) to define risk for coronary artery atherosclerosis. Cannavo *et al.* (2006) [41] identified 41% of patients with acromegaly to be at risk of coronary atherosclerosis, with approximately half exhibiting increased calcification. However, other non-invasive studies have failed to confirm these findings, reporting low risk rates for coronary artery disease and no correlation with GH status [42,43]. A recent retrospective study of patients with acromegaly attending a tertiary clinic in Mexico identified 8% of their cohort with symptomatic coronary artery disease, defined as a history of angina or a documented myocardial infarction [10].

Metabolic risk factors

Insulin resistance, diabetes mellitus and dyslipidaemia are more prevalent in acromegaly and are independent risk factors for cardiovascular disease [1]. The insulin resistance is largely driven by GH hypersecretion, with impaired glucose tolerance or frank type 2 diabetes subsequently manifesting in 15-38% of patients [6]. The effect of elevated GH levels on lipid metabolism is more complex, and likely to be related in part to the insulin response to the counter-regulatory effects of GH. Broadly, an atherogenic profile is recognised, with reduced HDL cholesterol levels and elevated triglycerides [10]. A more detailed review of the metabolic sequelae of acromegaly is provided in the review of Colao and colleagues [1].

Response of cardiovascular complications to primary acromegaly therapy

Surgery remains the primary treatment modality for the majority of patients with acromegaly, with adjunctive roles for somatostatin analogues (SSAs), dopamine agonists, the GH-receptor antagonist pegvisomant and radiotherapy where surgery is not curative or possible. A key goal of treatment is to reduce serum GH and IGF-1 to 'safe' levels. Historically, post-treatment GH levels of <2.5 mcg/L were reported to correlate with a normal life expectancy [44]. However, in papers reporting SMRs for different levels of post-treatment GH and IGF-1, the lowest mortality ratios were found in patients with the lowest post-treatment GH and IGF-1 levels [3,45,46]. The recently published Endocrine Society guidelines now propose biochemical targets of a serum IGF-1 within the age-and sex-matched reference range and a random growth hormone of <1.0 mcg/L [6]. For a significant proportion of patients multimodal therapy is required to achieve these targets.

Several groups have reported improvements in different cardiovascular parameters in response to primary acromegaly treatment. For example, follow-up at six months post-transphenoidal surgery in a cohort of newly diagnosed patients revealed a reduction in left ventricular mass and an increase in diastolic function [47]. Lower diastolic blood pressure has also been reported post-surgery [48]. Similarly, somatostatin analogue (SSA) therapy has been shown to have a beneficial effects on blood pressure [49,50,51], and to bring about

significant improvements in left ventricular mass, systolic and diastolic function, and exercise tolerance [51,52,53,54]. Rhythm disturbances may improve following commencement of SSA therapy [50,55,56], but asymptomatic bradycardia is a potential side-effect. Little is known about the numbers/proportion of patients who require invasive interventions (e.g. ablation and/or permanent pacemaker). Valvular heart disease was not found to be influenced by treatment with somatostatin analogues [57]. Fewer studies have assessed cardiovascular outcomes following treatment with pegvisomant, although a reduction in diastolic and systolic blood pressure and left ventricular mass have been shown, as have improvements in cardiac and vascular dynamics [58,59].

Although biochemical targets remain central to modern acromegaly management, making the attainment of stringent biochemical thresholds the sole objective is not without its risks, especially at the level of the individual patient. For example, in the study of Ayuk and colleagues, a history of pituitary radiotherapy was independently identified as a cause of increased mortality in acromegaly [46], and the endocrinologist and oncologist must therefore carefully weigh the benefits of further lowering GH and IGF-1 levels versus the increased risk of cerebrovascular disease when deciding whether to proceed to radiotherapy.

Equally importantly, ongoing/new cardiovascular complications must not be overlooked in those who have reached biochemical treatment targets. In our own cohort of 30 newly-diagnosed, treatment-naive patients, who were studied both at baseline and following six months of SSA therapy, attainment of even stringent biochemical targets did not necessarily equate to uniform improvements in cardiovascular markers of disease activity, and in some patients a deterioration in one or more parameters was observed even when 'safe' GH and IGF-1 levels were reached [9] (**Fig. 2**). In contrast, not all patients with persistent acromegaly (raised GH and IGF-1) or 'discordant' biochemical responses (most commonly GH within target, but IGF-1 raised) exhibited ongoing complications of their acromegaly [9]. We also observed some important gender differences (e.g. left ventricular mass index improved in men

but not in women). Therefore, for the most part cardiovascular changes following SSA therapy were independent of GH and IGF-1 levels and showed considerable inter-individual variation [9].

In recognition of the importance of directly addressing those factors which contribute to the excess morbidity and mortality associated with acromegaly, the recently published guidelines of the American Endocrine Society recommend assessment for hypertension and cardiovascular disease at diagnosis, with longitudinal monitoring and rigorous management of individual complications [6]. Similarly, a consensus guideline for the diagnosis and treatment of acromegaly complications [8] advises blood pressure monitoring at baseline and at intervals of six months thereafter, with electrocardiography and echocardiography at baseline, and repeated annually thereafter. Suggested screening modalities are summarised in **Table 1**.

Specific cardiovascular risk-modifying therapies in patients with acromegaly need not differ from those used for the general population (e.g. statins, antihypertensive agents), and lifestyle modification remains an important part of any management strategy.

Sleep disordered breathing

Sleep disorders are common in acromegaly, in particular obstructive sleep apnoea (OSA), which affects more than two thirds of patients [9,60,61].

Sleep apnoea

OSA has been proposed to account for up to 25% of the excess mortality seen in untreated acromegaly [1,44]. When associated with excessive daytime somnolence, the obstructive sleep apnoea syndrome is diagnosed, which has significant ramifications for both quality of life and safety, e.g. in relation to driving or operating machinery [62,63,64]. Furthermore, OSA is independently associated with hypertension and cardiovascular disease, and has been linked in some studies to the development of the metabolic syndrome (insulin resistance, type

2 diabetes, dyslipidaemia) and hypogonadism [65,66,67,68], thereby exacerbating a number of the primary complications of acromegaly.

The development of OSA in acromegaly has been linked to craniofacial, pharyngeal, laryngeal and bronchial soft tissue thickening, which all predispose to airway restriction, with further contributions in some patients from facial skeletal abnormalities and neuromuscular defects of the pharyngeal muscles [61]. As with the general population, male gender, increasing age and co-existent obesity are significant risk factors [69,70], and hypothyroidism, if present, also predisposes to OSA [71]. A small subset of patients experience central apnoeas, thought to result from modulation of central respiratory centre function, combined with an increased ventilatory threshold for carbon dioxide [72].

Assessment of sleep status in acromegaly

Screening for symptoms suggestive of excessive daytime somnolence in the general population is commonly based on a questionnaire, the Epworth Sleepiness Scale (ESS) [73], with a score of 10 or greater triggering more rigorous assessment using either pulse oximetry, which yields an oxygen desaturation index (DI), or polysomnography to derive an apnoea-hypopnoea index (AHI). The latter remains the gold-standard investigation, but is technically more demanding and often requires an overnight stay in a specialist sleep unit [74]. In our study of 30 patients with newly-diagnosed acromegaly we observed OSA in 79% of cases by AHI criteria [9]. However, although there was a modest correlation between DI and AHI (R^2 0.63, $P<0.0001$), DI tended to underestimate the severity of OSA, with AHI categorising 9 as having mild OSA, 4 as moderate and 9 as severe while, in marked contrast, DI identified 16 cases of mild OSA, 4 moderate and only 3 severe [9]. Based on these findings, and given the high prevalence of OSA in acromegaly, we recommend polysomnography as the preferred method for screening for sleep apnoea.

Response of sleep apnoea to primary acromegaly therapy

Biochemical control of acromegaly does not reliably predict reversal of sleep apnoea, whether following surgery or somatostatin analogue therapy [60,72,75,76,77]. Although many patients will demonstrate an improvement in symptoms, 40% of those with controlled acromegaly continue to suffer with sleep apnoea [61,77,78]. In our study of 30 newly diagnosed patients, there was marked variation in the response of OSA to medical treatment of acromegaly: despite clear evidence of an improvement in biochemical control in 93% of patients, only 61% demonstrated an improvement in OSA as measured by AHI, while 9% showed no change and 30% in fact manifested a significant deterioration [9] (**Fig. 3**).

Given that a significant proportion of patients with OSA may fail to respond to primary therapy for acromegaly, detection and specific targeted treatment [e.g. with continuous positive airway pressure ventilation (CPAP)] should be considered in all patients [6,79]. This is especially pertinent given the implications regarding the legal right to drive, and potential impact of coexistent OSA on other acromegaly comorbidities, although evidence for the efficacy of primary treatment of OSA in ameliorating these conditions remains mixed [61,80].

Summary

The last decade has witnessed numerous advances in the treatment of acromegaly such that it is now unusual to encounter a patient in whom multimodal therapy cannot restore GH and IGF-1 to target levels. However, the need to remain vigilant and to screen for, and independently treat the well-recognised cardiovascular and respiratory complications of acromegaly is as pertinent today as it has ever been. In so doing, the clinician can be confident that he/she is maximising the chance of reversing those comorbidities that contribute most to the excess morbidity and mortality associated with this disorder.

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628 **Figure legends**

629

630 **Fig. 1** Cardiac changes in a 65-year-old woman with newly diagnosed acromegaly. **a** Two-
631 dimensional (parasternal long axis) echocardiography demonstrating increased thickness of
632 the interventricular septum [1.32 cm (RR 0.60–1.00)] and left ventricular posterior wall [1.67
633 cm (RR 0.60–1.00)]. **b** Doppler studies reveal diminished peak systolic velocity and reversal
634 of the E/A ratio [i.e. the ratio of early passive (E), to late active (A, atrial), ventricular filling
635 velocities; in a healthy heart, the E velocity is greater than the A velocity, but this ratio is
636 reversed in the presence of diastolic dysfunction with impaired ventricular filling].

637

638 **Fig. 2** Divergent cardiovascular responses in two patients with newly diagnosed acromegaly
639 treated with primary depot somatostatin analogue therapy for 6 months. **a** In Patient 1 (a 46-
640 year-old man) GH and IGF-1 were both restored to safe levels following treatment (mean GH
641 0.76 mcg/L; IGF-1 1.02 ×ULN), and accompanied by normalisation of systolic and diastolic
642 blood pressure, a reduction in arterial stiffness (as determined by aPWV) and improved
643 endothelial function (as shown by an increase in FMD); left ventricular size (measured as
644 LVMI) was normal at baseline and not significantly changed following treatment. **b** Patient 2
645 (a 51-year-old woman) exhibited comparable biochemical control to patient 1 (mean GH 0.71
646 mcg/L and IGF-1 0.60 ×ULN) post-SSA therapy but in contrast, despite improvements in
647 arterial stiffness and endothelial function, systolic and diastolic blood pressure and LVMI
648 showed an unanticipated deterioration. Key: aPWV, arterial pulse wave velocity; BP, blood
649 pressure; FMD, flow-mediated dilatation; GH, growth hormone; IGF-1, insulin-like growth
650 factor-1; LVMI, left ventricular mass index; SSA, somatostatin analogue therapy.

651

652 **Fig. 3** Sleep apnoea is a common finding in newly diagnosed acromegaly, but does not
653 necessarily improve in response to primary treatment of acromegaly. **a** Mean GH (average of
654 8-10 samples from a day profile), **b** IGF-1 (relative to the age and sex-matched reference
655 range) and **c** AHI are shown for 27 individuals pre- (circles) and post- (arrowheads) six

656 months of somatostatin analogue therapy. Green lines represent a decrease and red an increase
657 in each parameter. Despite normalisation, or near-normalisation, to GH and IGF-1 target
658 levels, patients 3, 8, 15, 16 and 24 manifest an actual worsening of sleep apnoea compared to
659 baseline and several other patients have persistent, clinically relevant, sleep apnoea (data
660 adapted from Annamalai *et al*. 2013 [7]). Key: AHI, apnoea-hypopnoea index; GH, growth
661 hormone; IGF-1, insulin-like growth factor-1.
662

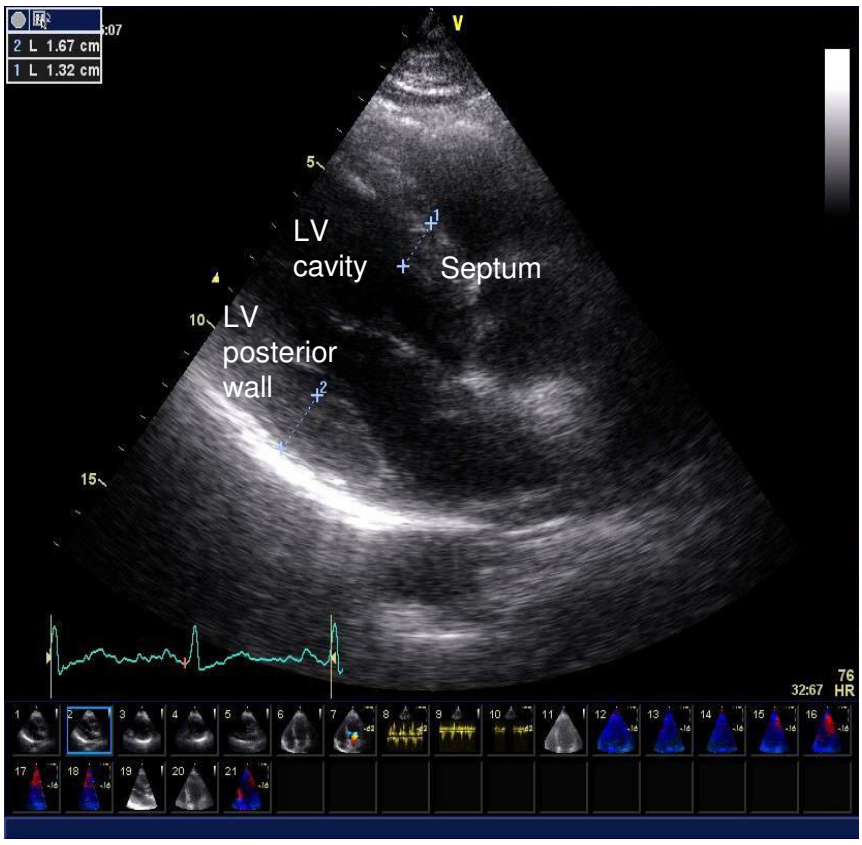
Table 1. Screening for cardiovascular and respiratory comorbidities in acromegaly.

Comorbidity	**Preferred screening modality**
Hypertension	Clinic blood pressure readings +/- ambulatory or home blood pressure monitoring*
Cardiomyopathy	Echocardiography
Cardiac valve disease	Echocardiography
Arrhythmias	Resting 12-lead ECG +/-24 h ambulatory ECG or event recorder if symptomatic
Hyperglycaemia	Fasting plasma glucose, HbA1c
Dyslipidaemia	Fasting lipid profile
Sleep apnoea	Polysomnography

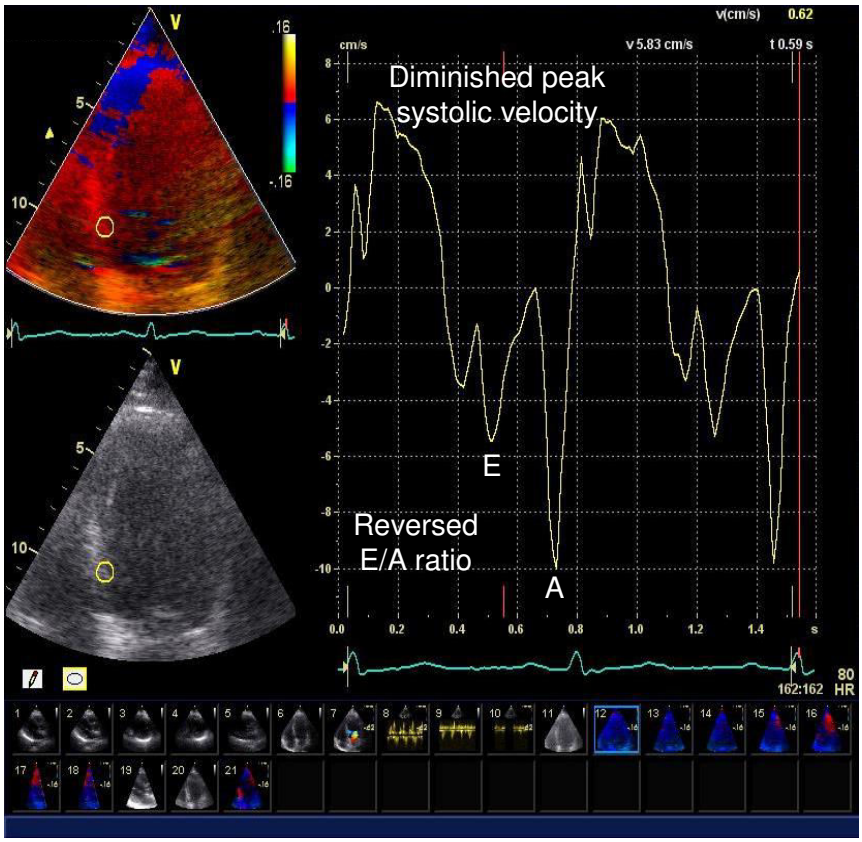
Note: Screening for each comorbidity should be undertaken at the time of diagnosis of acromegaly and on an annual basis thereafter, although more frequent monitoring may be required if symptoms and/or findings on previous investigations dictate, and less frequent screening may be appropriate in patients with well-controlled disease and no clinical features of concern.

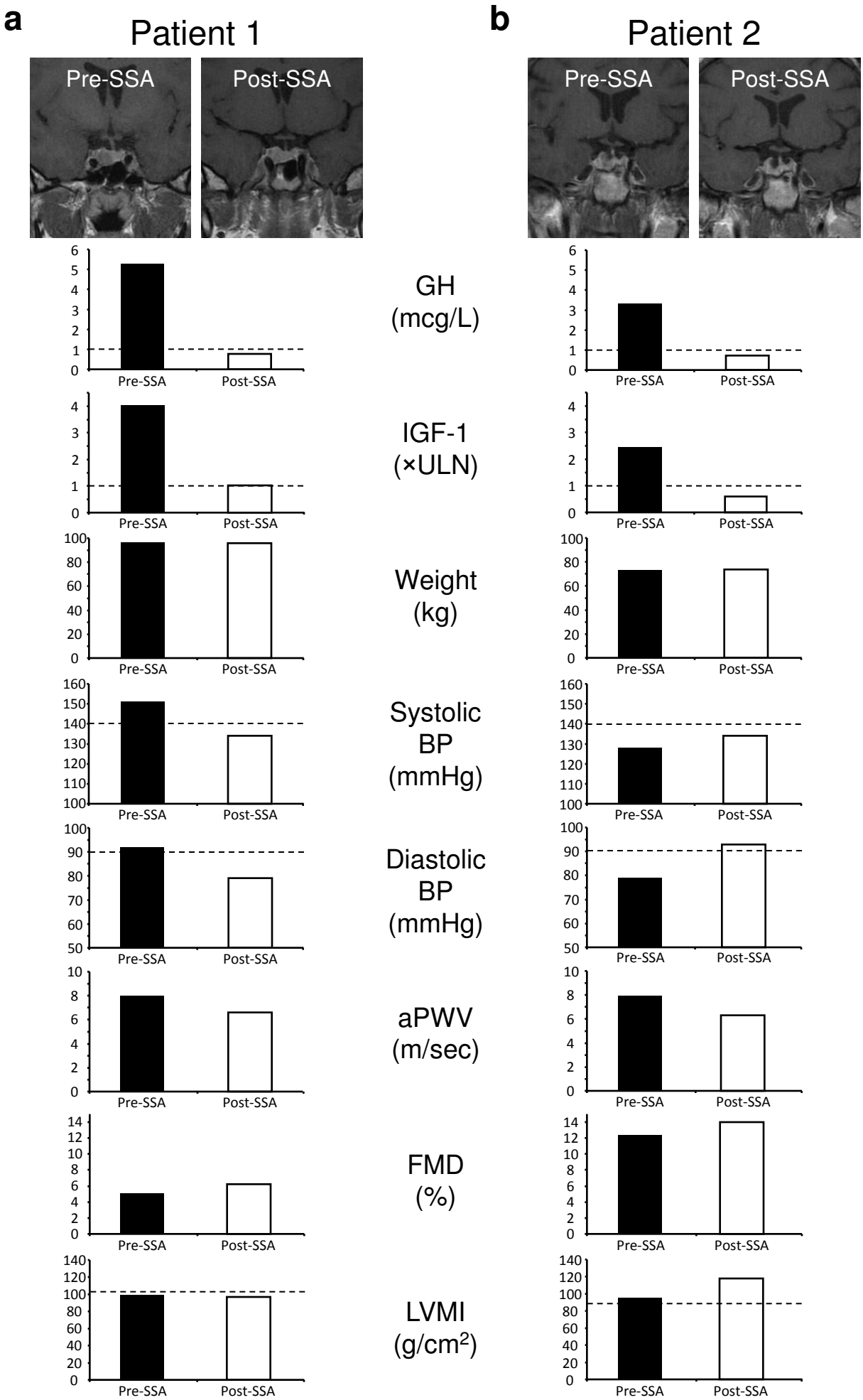
*raised values require confirmation with either 24hr ambulatory monitoring or serial home measurements [for example NICE (2011) Hypertension (update): full guideline.http://www.nice.org.uk/guidance/cg127/].

a


2 L 1.67 cm
1 L 1.32 cm
LV cavity
Septum
LV posterior wall
76 HR

b


Diminished peak systolic velocity
E
A
Reversed E/A ratio
v 5.83 cm/s
t 0.59 s
80 HR


a
Patient 1
Pre-SSA
Post-SSA
b
Patient 2
Pre-SSA
Post-SSA
GH (mcg/L)
IGF-1 (×ULN)
Weight (kg)
Systolic BP (mmHg)
Diastolic BP (mmHg)
aPWV (m/sec)
FMD (%)
LVMI (g/cm2)
Pre-SSA
Post-SSA

Powlson & Gurnell Figure 3