Review Article

Effects of somatostatin analog treatment on cardiovascular parameters in patients with acromegaly: A systematic review

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Background: There is a belief that in patients with acromegaly, first-generation somatostatin analogs (SSAs) might improve cardiovascular (CV) structure and function. However, most published clinical trials involved only a few patients and their results are rather variable. We aimed to conduct a systematic review on available studies on the impact of these drugs on CV parameters. **Materials and Methods:** A literature search was conducted in MEDLINE (OVID), EMBase, Cochrane, and ISI Web of Science for citations published until April 30 2018 to identify studies on our objective that considered changes in CV parameters. For this search, we established a Boolean search strategy using keywords related to "acromegaly," "Somatostatin analog," and "cardiovascular diseases and parameters." All study types except for case reports or conference abstracts were included. Twenty-four studies ($n = 558$) fulfilled the inclusion criteria and were selected for final analysis. **Results:** In 12 studies ($n = 350$), decrease in heart rate (HR) and in 4 studies ($n = 128$), decrease in blood pressure (BP) was significant. In 15 studies ($n = 320$), left ventricular mass index (LVMi) changes were significant. In 9 studies ($n = 202$), the early diastole to peak velocity flow in late diastole (E/A ratio) was evaluated, and in 5 of them ($n = 141$), the improvement was significant. Eighteen studies ($n = 366$) examined changes in left ventricular ejection fraction (LVEF), 5 of which ($n = 171$) reported that these changes were significant. Decrease of left ventricular end-diastolic diameter was reported in only 2 studies ($n = 27$). **Conclusion:** We found that first-generation SSAs have a beneficial effect on cardiac parameters such as HR and LVMi. For other parameters such as LVEF, BP, LV diameter, and E/A ratio, we were not able to draw a firm conclusion.

Key words: Acromegaly, cardiomyopathy, growth hormone, receptor, somatostatin

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INTRODUCTION

Acromegaly is a rare chronic disease, characterized by excessive production of growth hormone (GH). The total prevalence ranges between 2.8 and 13.7 cases per 100,000 people, and the annual incidence rates range between 0.2 and 1.1 cases per 100,000 people.[1,2] In the vast majority of cases, it occurs as a result of a somatotroph pituitary adenoma and a consequent overproduction of insulin-like growth factor I (IGF-I) by the liver and other tissues. Due to the subtle progress of the disease, diagnosis is frequently delayed for about 8–10 years after onset of clinical manifestations, which means that patients are rarely diagnosed before the age of 40.[3-9] A vast number of clinical series have demonstrated that acromegaly is associated with increased morbidity

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and mortality, mainly due to cardiovascular (CV) complications.[10,11] GH and IGF-I excess result in arterial hypertension (HTN) in one-third of these patients. Acromegalic cardiomyopathy is one of the leading causes of death in patients with acromegaly.[12] Choice of treatment should be individualized based on biochemical and radiological features, as well as the metabolic and CV risk profile of the patients.[13-16] In practice, when transsphenoidal surgery fails to control the disease or cannot be performed, the majority of endocrinologists prescribe first-generation somatostatin analogs (SSAs), for example, octreotide and lanreotide, as an initial medical treatment.[17] To the best of our knowledge, five human somatostatin receptor (SSTR1, 2A and B, 3, 4, and 5) subtypes have been identified, and SSTR2 is the subtype expressed in more than 95% of somatotroph adenomas, followed by SSTR5, in approximately 85% of cases.[16,18] SSTR1 and SSTR3 are present in about 40% of adenomas.[19-21] First-generation SSAs are considered SSTR2 specific. The biochemical response rate of these drugs is reported to be between 20% and 70%.[19] There has been a belief that treatment with SSAs is successful in improving CV parameters, by means of their efficacy in the control of GH/IGF-I excess. However, the expression of somatostatin receptors type 1, 2, 4, and 5 on cardiac tissue and vascular bed raises the possibility of a direct effect of SSA on the heart and vessels.[22,23] In fact, based on a longitudinal study which evaluated different GH-lowering treatments, SSAs seemed to contribute to the improvement of echocardiographic parameters even in patients who had not achieved complete biochemical control of the disease.[24] Likewise, in an open-label randomized study, despite an overall similar success rate, treatment with SSAs had beneficial effects on CV parameters which were though not obvious in surgically treated patients.[22] Specifically, various studies reported that SSAs had a beneficial effect on blood pressure (BP),[25,26] heart rate (HR), systolic and diastolic function, exercise tolerance,[22,24,25,27-30] reduced left ventricular mass, QT interval duration, and the rate of arrhythmias.[31,32] To the best of our knowledge, no head-to-head comparisons are available to analyze the efficacy of lanreotide and octreotide on the CV parameters except that Auriemma *et al*. showed that there was no significant difference in the effect of two drugs on BP.[33] However, due to heterogeneity in the literature, different results were published. Furthermore, assessment with new imaging modalities such as cardiac magnetic resonance (CMR) imaging and speckle tracking echocardiography (STE) has been associated with contradictory results.[34,35] Therefore, by considering the widespread use of first-generation SSAs, our aim is to conduct a systematic review on available studies on the impact of these drugs on CV parameters.

MATERIALS AND METHODS

Database search

According to the medical liaison librarian's guide, a learning search strategy was created to identify studies. A literature search was conducted in MEDLINE (OVID), EMBase, Cochrane, and ISI Web of Science for citations published until April 30 2018. For this search, we established a Boolean search strategy using keywords related to "acromegaly," "Somatostatin analog" (lanreotide OR Sandostatin LAR Depot OR Sandostatin OR Somatuline Depot), and "cardiovascular diseases and parameters." We used MeSH terms in Medline and Cochrane and EM Tree terms in EMBase such as "Acromegaly," "cardiovascular parameters," and "cardiovascular diseases." We also used field search and truncation for more effective retrieval in aforesaid databases. For studies before June 2006, a hand searching was also performed in a meta-analysis by Maison *et al*.,[30] which analyzed suitable articles until this date. The selected publications had to report at least one of the following outcome measures: HR, systolic BP (SBP), diastolic BP (DBP), interventricular septum diameter, left ventricle end-diastolic diameter (LVEDD), left ventricle mass (LVM), LVM index (per m^2 of body surface area) (LVMi), left ventricle ejection fraction (EF), ratio of early to late mitral diastolic flow (E/A ratio), and left ventricle end diastolic volume (LVEDV). Each study was reviewed by 2 separate authors (M.H. and D.SH.) who independently screened abstracts and titles.

Inclusion and exclusion criteria

Inclusion criteria were (1) articles published in English, (2) all studies except case reports or conference abstracts, (3) treatment with first generation SSAs, and (4) including CV endpoints. Exclusion criteria were (1) failure to compare CV parameters before treatment with posttreatment and (2) use an alternative treatment such as surgery during the study period.

Data extraction

Results from all databases entered the Endnote desktops (version 7.2), and copies were identified and deleted. All the titles were reviewed by one of the authors (M. H.), and nonrelevant items were identified and removed. The studies were screened by two authors (D.SH. and M.H.) using their abstract. The remaining item was examined for the full text of the articles and the entire text was added, and the articles were re-examined using the full text and reviewed by the two authors. Data were collected and include first author, year of publication, number of patients, drug, treatment duration, dosage, GH level before and after treatment, IGF-1 level before and after treatment, and changes in CV parameters [Table 1].

Table 1: Characteristics of selected studies evaluating the effects of first-generation somatostatin analogs on the cardiovascular parameters

Authors	Year	Total patients (*n*)	Treatment	Duration (months)	Dose (mg)	GH before (µg/L)	GH after (µg/L)	IGF1 before (µg/L)	IGF1 after (µg/L)	Cardiac Imaging Modality	Result (s)
Thuesen *et al* [37]	1989	9	Sandostatin	12	0.6[b]	63±51	21±21	N/D	N/D	Echocardiography	HR↓, BP↓, LVMi↕
Pereira *et al* [38]	1991	5	Sandostatin	6	0.3[b]	22.4±9	4.3±23	N/D	N/D	Echocardiography	EF↓, LVEDD↕, LVMi↕, IVS↓, E/A↓
Lim *et al*[c] [39]	1992	10	Sandostatin	2	0.15[b]	19±4	N/D	481±49	N/D	Echocardiography	HR↓, BP↕, LVEDD↕, IVS↓, LVMi↓
Lim *et al*[c] [39]	1992	6	Sandostatin	2	0.15[b]	28±9	N/D	584±53	N/D	Echocardiography	HR↕, BP↕, LVEDD↕, IVS↕, LVMi↕
Merola *et al* [40]	1993	11	Sandostatin	6	0.1 [b]	34±6.5	4.6±0.9	767±72.4	235±10.3	Echocardiography	HR↕, BP↕, EF↕, LVEDD↕, IVS↓, LVMi↓, E/A↑
Tokgozoglu *et al* [41]	1994	6	Sandostatin	6	0.3[b]	15.8±9	4±4	N/D	N/D	Echocardiography	HR↕, BP↕, EF↕, LVEDD↕
Giustina *et al* [42]	1995	10	Sandostatin	0.033	0.15[b]	19±6	8±3	584±69	491±57	Echocardiography	HR↓, BP↕, EF↑, LVEDD↕, IVS↕, LVEDV↕
Padayatty *et al* [43]	1996	10	Sandostatin	12	0.3[b]	58±60	32±71	979±375	639±314	Echocardiography	HR↓, BP↕, EF↕
Lombardi *et al* [44]	1996	26	Sandostatin	6	0.15[b]	34±6.5	4.6±0.9	767.4±72	235±10	Echocardiography	EF↓, IVS↓, LVMi↓
Hradec *et al* [50]	1999	13	Lanreotide PR	18	30[d]	86±110	33±53	1222±249	746±403	Echocardiography	HR↕, BP↕, EF↕, LVEDD↓, IVS↓, LVMi↓, E/A↕
Colao *et al* [46]	1999	30	Sandostatin	12	0.15-0.3[b]	40.9±6	5.8±1.3	672.4±32	398.5±38	Echocardiography	HR↓, BP↕, EF↑
Baldelli *et al* [51]	1999	13	Lanreotide PR	12	30[d]	10.1±2.2	3.9±0.9	511±33	305.8±34	Echocardiography	BP↕, EF↕, LVEDD↕, IVS↓, LVEDV↓, LVMi↓, E/A↑
Colao *et al* [29]	2000	15	Octreotide LAR	6	20[e]	94±24.9	12.9±2.7	757.8±66	333.7±40	Echocardiography	BP↕, EF↕, IVS↓, LVMi↓
Colao *et al* [45]	2002	25	Octreotide LAR	6	20[e]	43.8±6	5.04±1.1	772±34	422.3±5.3	Echocardiography	HR↓, BP↕, EF↕, LVMi↓
Lombardi *et al*[32]	2002	19	Lanreotide PR	6	30[d]	37.9±7.5	5.7±2.5	143.8±21.9	36.4±17	Echocardiography	HR↓, BP↕, EF↕, IVS↓, LVMi↓, E/A↕
Colao *et al*[c] [47]	2003	10	Octreotide LAR	12	20[e]	90.9±22.8	68.1±11.4	714.7±61	614±71	Echocardiography	HR↕, BP↓, EF↑, LVMi↓
Colao *et al*[c] [47]	2003	12	Octreotide LAR	12	20[e]	68.1±11.4	4.5±0.6	614.6±71	272±18.8	Echocardiography	HR↕, BP↕, EF↑, LVMi↓
Ronchi *et al* [55]	2006	36	OCT/LAN[f]	12	10-30/60[e]	16.7±18	N/D	721.4±294	N/D	None	BP↕
Colao *et al* [56]	2008	56	OCT/LAN[f]	12	10-40/30-120[e]	52.9±44	1.3±0.6	712±225	N/D	Echocardiography	HR↓, BP↓, EF↑, LVMi↓, E/A↑
Delaroudis *et al* [48]	2008	18	Octreotide	6	N/D	8.45	3.4	670±77	4473±58	None	BP↕
Colao *et al* [57]	2009	45	OCT/LANf	60	20-40/60-120[e]	44.2±39	0.88±0.4	664.9±241	185.5±57	Echocardiography	HR↓, BP ↓, EF↑, LVMi↓, E/A↑
Bogazzi *et al* [52]	2010	14	Lanreotide	6	120[e]	6.4±9.9	4.3±5.5	725±212	401±161	CMRg	EF↕, LVMi↓, RVMi↕
Melmed *et al* [53]	2010	99	Lanreotide	12	60-120[e]	19.8±29	6.6±19.7	735±240	376±172	Echocardiography	HR↓, LVEDV↓
Annamalai *et al* [54]	2013	30	Lanreotide	6	90-120[e]	21.43	N/D	N/D	N/D	Echocardiography	BP↕, LVMi↓
Silva *et al* [49]	2015	30	Octreotide LAR	12	20-30[e]	9.9±13.6	N/D	N/D	N/D	CMRg	EF↑, IVS↕, LVEDVi↕, LVMi↕
Warszawski etal [35]	2016	28	Octreotide LAR	12	20-30[e]	4.9	N/D	318.4	N/D	CMRg	HR↓, EF↕, LVMi↕

[a]Data are based on mean ± SD but in some studies, not concluded SD, [b]Daily dose, [c]In these studies, distinct populations have been analyzed separately, [d]Administered every 10.15 days, [e]Administered every 28 days, [f]Octreotide lAR in some patients and Lanreotide in others, [g]Cardiac Magnetic Resonance Imaging, N/D: Not defined ↑: Significantly Increased, ↓: Significantly Decreased, ↕: Not Significant Change

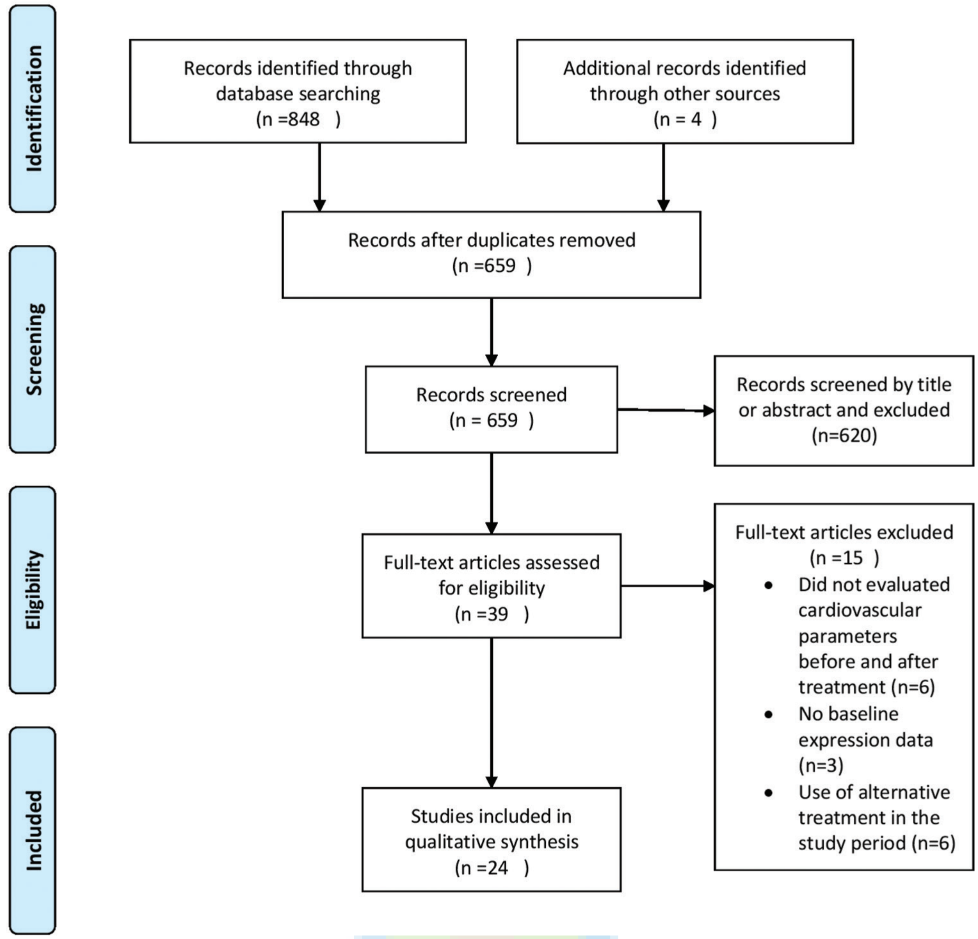

Figure 1: The search strategy and stepwise results of the literature review

Quality assessment

The methodological quality of the reviewed articles was measured using a scale of 11 items moderated from previous studies.[36] This scale focused on reporting quality (4 items) and study quality (7 items). The items were identified as positive, negative, or not sufficiently defined. The total score for "reporting quality" and "study quality" was calculated using the sum of all positive scores for each study. For negative or not sufficiently defined items, no score was taken. The score of each study was to make it possible to compare to the percentage. Therefore, a higher percentage meant a higher reading quality. Based on the quality of the study, the articles were categorized according to the midterm considerations into high- and low-quality studies. Studies that were potentially eligible were further assessed in detail by retrieving full-length articles. As a second step, references cited in selected literature, in addition to those in relevant meta-analysis published in the last 10 years, were reviewed to identify additional potential studies for inclusion. When disagreement about inclusion or exclusion of specific studies occurred, all authors met to review and reach consensus. We could not conduct meta-analysis because of the considerable heterogeneity of the data including study design, patient population, and study duration.

RESULTS

Study selection

The search strategy and stepwise results of the literature review are shown in Figure 1.

A literature search was conducted in MEDLINE (OVID), EMBase, Cochrane, and ISI Web of Science for citations published until April 30, 2018. A total of 38 articles were related to treatment with first-generation SSAs (octreotide or lanreotide) and CV effects. Of these, 24 articles met all inclusion criteria and included a total of 558 patients. In each of these studies, references cited within the articles and relevant meta-analysis studies were reviewed to determine the compliance with all criteria.[30]

Study characteristics and results

Characteristics of the 24 selected studies published between 1989 and 2016 are shown in Table 1. Of these, fifteen studies[29,35,37-49] evaluated the impact of octreotide on cardiac parameters and BP, 6 studies[32,50-54] evaluated lanreotide, and 3 studies[55-57] evaluated both octreotide and lanreotide. Treatment duration varied from day 1[42] to 5 years;[57] but in 19 studies, treatment duration was between 6 and 12 months. In 2007, Maison *et al*.[30] conducted a meta-analysis on the impact of first-generation SSAs on CV parameters in patients with acromegaly. In the meta-analysis published by Maison *et al*.,[30] 15 articles with 230 patients were evaluated, and thereafter, 9 studies[35,48,49,52-57] with 328 patients were enrolled in our systematic review. The sample size of each of the studies evaluated by Maison *et al*.[30] did not exceed 30 patients.

In 3 studies, cardiac parameters were assessed through CMR.[35,49,52] Studies performed with dos Santos Silva *et al*.[49] and Warszawski *et al*.[35] used the same patient population; therefore, we extracted the effects on the HR from the study carried out by Silva and changes in EF and LVMi from the study carried out by Worszawski.

Changes in HR were investigated in 17 studies,[29,32,35,37,39-43,45-47,50,51,53,57] and 12[29,32,35,37,39,42,43,46,53,56,57] of those (n = 350) indicated a significant reduction in HR.

In 18 studies (n = 380),[29,32,37,39-43,45-48,50,51,54-57] changes in BP were examined and 4 studies (n = 128)[37,48,56,57] reported that there was also a significant decrease in BP. In one study,[56] only changes in diastolic BP were significant.

In 15 of 18 studies (n = 320),[29,32,35,37,39-42,45,47,49,50,52,54,56,57] LVMi changes evaluated were significant. However, it should be noted that in one study,[54] including 15 men and 15 women, a significant reduction was seen only in men. In a survey of 14 patients conducted through CMR, there was no change regarding right ventricular mass index during 6 months of treatment.[52]

LVEDD was analyzed in 7 of the studies (n = 78);[39-41,50-52] in 2 of which,[50,52] a significant reduction occurred in 27 patients. Of course, LVEDV was analyzed in 4 studies (n = 152),[35,49,51,52] of which 2 (n = 112)[51,53] showed a significant reduction.

In 18 publications (n = 365),[29,32,35,38-47,50,51] changes in left ventricular ejection fraction (LVEF) were examined, 5 of which (n = 153)[42,46,54,56,57] reported that both changes and effect size were significant. In 10 studies (n = 216),[32,38,40,42,46,50-52,56,57] E/A ratio was evaluated, and in 6 of them (n = 155),[32,40,42,52,56,57] improvement was statistically significant.

DISCUSSION

This review suggests that first-generation SSAs have a beneficial effect on some cardiac parameters such as HR and LVMi. Therefore, at the outset, two points should be noted. First, the rare nature of acromegaly and patient heterogeneity contribute to a limitation in randomization. Furthermore, comorbidities such as HTN and insulin resistance can also confound the results independently, especially when concluding an overall result from all studies. Second, the absolute effect of these drugs on patients with impairment in a CV parameter can be more obvious and significantly different from those lacking this condition. In the following sections, we will discuss the impact of first-generation SSAs on different CV parameters.

Blood pressure

In patients with acromegaly, HTN is one of the most frequent CV complications.[58] A mean prevalence of HTN in a meta-analysis of 18 studies was 35%, varying from 18% to 60%.[59] Indeed, HTN is a determinant prognostic factor which increases mortality rates.[10] When regarding the correlation between IGF-I levels and BP, results have been mixed.[22,60] Vitale *et al*.[60] evaluated approximately 200 patients and showed that arterial hypertension predominantly involved diastolic BP and was less frequently related to IGF-I levels. However, recently, Schutte *et al*.[61] evaluated more than 11000 patients and reported a positive relationship with BP when IGF-I levels were higher than normal values, but an inverse relationship when IGF-I levels were within normal values. Systemic HTN in acromegaly is multifactorial with several possible mechanisms.[54,59,62-64] HTN can be controlled with an optimal treatment of acromegaly.[22] However, the effect of biochemical control of acromegaly on HTN is not that straightforward; for example, Sardella *et al*.[65] who reviewed a cohort of 200 acromegalic patients showed that optimal control of acromegaly did not influence BP. However, expression of somatostatin receptor subtypes has been seen in human vasculature, raising the probability of a direct effect of SSAs on the vascular system.[22,54,66,67] In addition, the effect of first-generation SSAs on glucose homeostasis may affect overall CV comorbidities.[22,57,67]

In our systematic review, 3 of the studies (n = 72)[37,48,57] reported a decrease in systolic and diastolic BP and 1 study[56] reported a decrease in diastolic BP whereas in 14 studies (n = 356),[29,32,39-43,45-47,50,51,55] there was no significant improvement in BP. Annamalai *et al*.[54] reported a significant improvement in arterial stiffness (assessed by aortic pulse wave velocity evaluation) and endothelial cell function (assessed by flow-mediated dilation measurement) despite no improvement in BP after 6 months. They found that aortic pulse wave velocity (PWV) and flow-mediated dilation did not correlate with GH/IGF-I levels, which means that first-generation SSAs may have an independent beneficial effect on the vascular bed.[54,68,69] In 2 studies by Colao *et al*. (n = 101),[56,57] significant improvement was observed only in diastolic BP. Interestingly, in a study by Delaroudis *et al*. (n = 18), a decrease in BP was recorded despite lack of biochemical control of acromegaly. At this point, it should be noted that of the 24 studies included in our systematic review, only Colao *et al*.[57] evaluated hypertensive acromegalic patients, and among these patients, mean decrease in BP was <10 mmHg. Results of an observational, retrospective, and multicenter study[70] in 105 hypertensive patients showed that an improvement in HTN in patients with controlled acromegaly was only observed in those with severe HTN compared to those with mild HTN. The authors reported that in hypertensive patients, biochemical control of acromegaly leads to better control of hypertension independent of treatment methods. Indeed, in 7 studies[29,32,40,45,47,50,51] included in our analysis, there were no changes in BP despite a decrease in myocardial thickness. Annamalai *et al*.[54] reported that PWV improved irrespective of changes in BP and independent of changes in GH/IGF-I levels. In contrast, Cansu *et al*.,[71] showed by analyzing 53 patients that there was no difference between patients with controlled or uncontrolled acromegaly. Finally, in a meta-analysis by Maison *et al*.,[30] global effect size was not significant for BP. Therefore, in total, it seems that first-generation SSAs do not decrease BP significantly in normotensive patients, but we cannot rule out the beneficial effect of these drugs in hypertensive patients, and this concept should be evaluated in large randomized trials after adjustment for confounding variables.

Heart rate

HR is modulated by the autonomic nervous system and is probably the best index of sympathovagal balance.[17,72] In patients suffering from acromegaly, a subclinical decompensated state might increase HR due to an enhanced hemodynamic response. Indeed, some degree of autonomic dysfunction has been reported in these patients.[72-74] Biventricular hypertrophy, high HR, and increased cardiac output are characteristics of the early phase of acromegalic cardiomyopathy (hyperkinetic syndrome).[73,75] First-generation SSAs can decrease sinus rate, atrioventricular conduction, and propagation velocity in the cardiac conduction system.[76] Some case reports showed asystole[76] and severe bradycardia[77] in less than a week of treatment with first-generation SSAs, but it seems that these drugs can decrease HR in the long term. Fatti *et al*. reported that first-generation SSAs reduced QT interval duration in acromegalic patients.[78] Of the 24 studies included in our review, this parameter decreased in 12 studies (n = 350);[29,32,35,37-39,42,43,46,53,56,57] but in 6 studies (n = 71),[29,40,41,47,50,51] there was no decrease in HR despite decrease in GH/IGF-I levels. In the meta-analysis by Maison *et al*.,[30] there was a significant decrease in HR and the weighted mean was −5.7 beat/min. Thereafter, all 4 studies[35,53,56,57] which evaluated HR reported a significant decrease in this parameter. In a study by Colao *et al*.,[56] decrease in HR was only reported in the SSA versus surgical group, and this result supports the independent effect of first-generation SSAs on the vascular bed. In conclusion, first-generation SSAs decrease HR modestly, resulting at least theoretically in a decrease in myocardial oxygen consumption and arrhythmia burden, but an increase in diastolic filling time and coronary perfusion.

Left ventricle mass index

Acromegalic cardiomyopathy is characterized by concentric biventricular hypertrophy without cavity enlargement, mainly involving the LV. However, with time, cardiac chamber enlargement occurs and systolic heart failure develops.[10,74,79] Severity of myocardial hypertrophy correlates with multiple factors such as patient age, disease duration, and presence of HTN, though not with IGF-I levels.[80] Two-dimensional (2D) echocardiography is the most common method for the measurement of LV mass. However, this parameter is influenced by weight and height and is therefore commonly indexed to body surface area such as LVMi. Indeed, one of the most important limitations of 2D-echocardiography is reproducibility, and in the presence of abnormal left ventricular geometry due to asymmetrical hypertrophy, valvular heart disease, and previous myocardial infarction, LVMi calculation may not be accurate. Indeed, LV mass measurement by echocardiography is highly dependent on the change in intravascular volume.[81-83] For this reason, LVMi calculation with CMR is more reliable than 2D-echocardiography.[83] Indeed, CMR is considered the gold standard for quantifications of ventricular volume and mass.[84] It has been shown that echocardiography significantly overestimates LV mass relative to CMR in the presence of left ventricular hypertrophy.[82,85,86] However, Bogazzi *et al*.[52] showed higher and dos Santos Silva *et al*.[49] showed lower prevalence of LVH by CMR compared with 2D-echocardiography; therefore, by considering different cutoffs to define LVH, patients' heterogeneity, and basic characteristics, this disparity is evident and needs to be resolved by carrying out further large scale controlled trials. In our review, changes in LVMi, after treatment with first-generation SSAs, were evaluated in 17 studies (n = 358).[29,32,35,37,39-42,44,49-52,54,57] In 15 studies (n = 320),[29,32,37,39-41,44,45,47,50-52,54,56,57] treatment with SSAs contributed to a decrease in LVMi. In the 2 remaining studies, Giustina *et al*. (n = 10)[42] reported no significant change after only 24-h treatment with octreotide infusion and Warszawski *et al*. (n = 28)[35] showed no difference in LVMi measured by CMR after 12 months' treatment. However, in the latter study, only two patients had LVH from the beginning. Therefore, we cannot rule out the beneficial effect of SSAs on LVMi due to the results of these studies. The studies by Colao *et al*.[29,57] and Annamalai *et al*.[54] reported no relationship between decreased LVMi, changes in BP and GH levels. The shortest time needed for LVMi decrease was reported to be approximately

7 days.[39] In addition, the authors reported that a decrease in this parameter was only seen in patients with LVH. Recently, Volschan *et al*.[34] reported that in patients with active acromegaly and high LVMi measured by 2D-echocardiography, there was no impairment in strain in comparison with the matched control group. This finding can be explained by the different pathophysiology of acromegalic cardiomyopathy in comparison with other types of cardiomyopathy.[87-91] In conclusion, it seems that these drugs have a beneficial effect on patients with LVH irrespective of biochemical control of acromegaly. However, with the advent of new imaging modalities such as CMR and speckle tracking echocardiography, we need to carry out large scale prospective studies which will evaluate these changes with more sensitive and accurate technology than currently accepted as being the norm.

Left ventricular ejection fraction

The LVEF remains the most frequently used method for the measurement of systolic function. It is one of the simplest diagnostic and prognostic parameters in CV medicine.[85] In our review, increase of LVEF was reported in 5 studies (n = 153),[42,46,49,56,57] while in 14 studies (n = 212),[29,32,38-41,43-47,50-52] treatment with these drugs did not contribute to an increase in LVEF. When using CMR, Bogazzi *et al*.[52] showed no change after 6 months whereas dos Santos Silva *et al*.[49] showed a significant increase in LVEF after 12 months. In a meta-analysis by Maison *et al*.,[30] there is a trend toward an increase in LVEF, but globally no positive effect could be shown on fractional shortening and left ventricular end systolic diameter. In a study by Colao *et al*.,[56] increase in LVEF was only reported in the SSA treated versus the surgical group; this result supports the independent effect of SSAs on cardiac function. Taking these facts into consideration, we cannot decide whether this information is beneficial for patients with reduced EF or not because we have been unable to extract the necessary information for confident prescription using these studies.

Left ventricular size

Concentric hypertrophy is a common feature of acromegalic cardiomyopathy; this is why LV enlargement was seen only in advanced cardiomyopathy. Therefore, beneficial effects defined by an increase or a decrease in LV volume may vary depending on the stage of cardiomyopathy. In our systematic review, decrease of LVEDD in 2 studies (n = 27)[50,52] was reported, but in 5 studies (n = 51),[38-41,51] treatment with these drugs did not contribute to a decrease in LVEDD. In addition, 2 studies (n = 112)[51,53] reported no significant changes in LVEDD. As mentioned before, CMR is considered to be the gold standard for quantifications of ventricular size.[84] However, Bogazzi *et al*.[52] showed a decrease in LVEDD and dos Santos Silva *et al*.[49] showed no significant changes of LVEDD by CMR; therefore, this disparity is evident by considering patients' heterogeneity and basic characteristics and needs to be resolved by carrying out further large scale controlled trials.

E/A ratio

The E/A ratio is defined as the ratio of the peak early (E) ventricular filling velocity to the peak late (A) ventricular filling velocity. It is one of the simple indexes used to assess the diastolic function of the LV.[92-94] In a healthy heart, this ratio is usually between 1 and 2.[93] In patients with Grade 1 diastolic dysfunction, this ratio decreases, but with the progression of the diastolic dysfunction and subsequent elevated left atrium pressure, this ratio increases by up to over one (termed pseudonormalization). Therefore, since this pattern of diastolic dysfunction can appear to be similar to the normal pattern, this parameter isolated can be misleading.[92] In addition, this ratio depends on HR, preload alteration, patient's age, afterload, insulin resistance, and severity of mitral regurgitation. Considering the above-mentioned data, this parameter is not an accurate reflection of diastolic dysfunction, and we should interpret changes of this parameter only together with other diastolic parameters such as tissue Doppler and pulmonary venous pattern.[92,95,96] In our systematic review, E/A ratio was assessed in 10 studies (n = 216),[32,38,40,42,46,50-52,56,57] and in six (n = 155),[32,40,42,52,56,57] this ratio increased. However, in the meta-analysis by Maison *et al*.,[30] overall effect size was significant for E/A ratio, and in 3 studies[52,56,57] performed thereafter, treatment with first-generation SSAs had a significant positive effect on E/A ratio. In the study by Colao *et al*.,[56] increase in E/A ratio was only reported in the SSA treated versus the surgical group despite biochemical control in both groups. In a study by Boggazi *et al*. (n = 14),[52] diastolic dysfunction was seen in 4 patients; but after 6 months of treatment, improvement in diastolic function was seen in only 1 patient. Therefore, due to the very low sample size, we cannot rely on these results. In conclusion, although first-generation SSAs can theoretically improve diastolic dysfunction with several mechanisms, any result achieved from a single parameter, such as the E/A ratio, should be concluded with caution.

CONCLUSION

This systematic review suggests that first-generation SSAs have a beneficial effect on some cardiac parameters such as HR and LVMi. On the other hand, since not enough literature data exist, we were not able to detect sufficient evidence to draw firm conclusions with respect to the BP and other cardiac parameters such as EF, LV size, and E/A ratio. It is therefore recommended that endocrinologists and cardiologists continue to cooperate and maintain close dialogue to ensure optimal care for their patients.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Lavrentaki A, Paluzzi A, Wass JA, Karavitaki N. Epidemiology of acromegaly: Review of population studies. Pituitary 2017;20:4-9.
2. Anagnostis P, Efstathiadou ZA, Polyzos SA, Adamidou F, Slavakis A, Sapranidis M, *et al.* Acromegaly: Presentation, morbidity and treatment outcomes at a single centre. Int J Clin Pract 2011;65:896-902.
3. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, *et al.* Guidelines for acromegaly management: An update. J Clin Endocrinol Metab 2009;94:1509-17.
4. Melmed S. Medical progress: Acromegaly. N Engl J Med 2006;355:2558-73.
5. Carmichael JD, Broder MS, Cherepanov D, Chang E, Mamelak A, Said Q, *et al.* The association between biochemical control and cardiovascular risk factors in acromegaly. BMC Endocr Disord 2017;17:15.
6. Chanson P, Salenave S. Acromegaly. Orphanet J Rare Dis 2008;3:17.
7. Gittleman H, Ostrom QT, Farah PD, Ondracek A, Chen Y, Wolinsky Y, *et al.* Descriptive epidemiology of pituitary tumors in the United States, 2004-2009. J Neurosurg 2014;121:527-35.
8. Chanson P, Salenave S, Kamenicky P, Cazabat L, Young J. Pituitary tumours: Acromegaly. Best Pract Res Clin Endocrinol Metab 2009;23:555-74.
9. Nunes VS, Correa JM, Puga ME, Silva EM, Boguszewski CL. Preoperative somatostatin analogues versus direct transsphenoidal surgery for newly-diagnosed acromegaly patients: A systematic review and meta-analysis using the GRADE system. Pituitary 2015;18:500-8.
10. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: Epidemiology, pathogenesis, and management. Endocr Rev 2004;25:102-52.
11. Sharma AN, Tan M, Amsterdam EA, Singh GD. Acromegalic cardiomyopathy: Epidemiology, diagnosis, and management. Clin Cardiol 2018;41:419-25.
12. Auriemma RS, Grasso LF, Galdiero M, Galderisi M, Pivonello C, Simeoli C, *et al.* Effects of long-term combined treatment with somatostatin analogues and pegvisomant on cardiac structure and performance in acromegaly. Endocrine 2017;55:872-84.
13. Ioachimescu AG. Impact of acromegaly treatment on cardiovascular complications. Endocrine 2017;55:659-61.
14. Somvanshi RK, Qiu X, Kumar U. Isoproterenol induced hypertrophy and associated signaling pathways are modulated by somatostatin in H9c2 cells. Int J Cardiol 2013;167:1012-22.
15. Cordelier P, Estève JP, Bousquet C, Delesque N, O'Carroll AM, Schally AV, *et al.* Characterization of the antiproliferative signal mediated by the somatostatin receptor subtype SST5. Proc Natl Acad Sci U S A 1997;94:9343-8.
16. Patel YC. Somatostatin and its receptor family. Front Neuroendocrinol 1999;20:157-98.
17. Paragliola RM, Corsello SM, Salvatori R. Somatostatin receptor ligands in acromegaly: Clinical response and factors predicting resistance. Pituitary 2017;20:109-15.
18. Reubi JC, Schonbrunn A. Illuminating somatostatin analog action at neuroendocrine tumor receptors. Trends Pharmacol Sci 2013;34:676-88.
19. Gadelha MR, Wildemberg LE, Bronstein MD, Gatto F, Ferone D. Somatostatin receptor ligands in the treatment of acromegaly. Pituitary 2017;20:100-8.
20. Ferrante E, Pellegrini C, Bondioni S, Peverelli E, Locatelli M, Gelmini P, *et al.* Octreotide promotes apoptosis in human somatotroph tumor cells by activating somatostatin receptor type 2. Endocr Relat Cancer 2006;13:955-62.
21. Cuevas-Ramos D, Fleseriu M. Somatostatin receptor ligands and resistance to treatment in pituitary adenomas. J Mol Endocrinol 2014;52:R223-40.
22. Ramos-Leví AM, Marazuela M. Cardiovascular comorbidities in acromegaly: An update on their diagnosis and management. Endocrine 2017;55:346-59.
23. Vianna CB, Vieira ML, Mady C, Liberman B, Durazzo AE, Knoepfelmacher M, *et al.* Treatment of acromegaly improves myocardial abnormalities. Am Heart J 2002;143:873-6.
24. De Marinis L, Bianchi A, Mazziotti G, Mettimano M, Milardi D, Fusco A, *et al.* The long-term cardiovascular outcome of different GH-lowering treatments in acromegaly. Pituitary 2008;11:13-20.
25. Minniti G, Moroni C, Jaffrain-Rea ML, Esposito V, Santoro A, Affricano C, *et al.* Marked improvement in cardiovascular function after successful transsphenoidal surgery in acromegalic patients. Clin Endocrinol (Oxf) 2001;55:307-13.
26. Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Della Morte AM, *et al.* Is the acromegalic cardiomyopathy reversible? Effect of 5-year normalization of growth hormone and insulin-like growth factor I levels on cardiac performance. J Clin Endocrinol Metab 2001;86:1551-7.
27. Chanson P, Timsit J, Masquet C, Warnet A, Guillausseau PJ, Birman P, *et al.* Cardiovascular effects of the somatostatin analog octreotide in acromegaly. Ann Intern Med 1990;113:921-5.
28. Bihan H, Espinosa C, Valdes-Socin H, Salenave S, Young J, Levasseur S, *et al.* Long-term outcome of patients with acromegaly and congestive heart failure. J Clin Endocrinol Metab 2004;89:5308-13.
29. Colao A, Marzullo P, Ferone D, Spinelli L, Cuocolo A, Bonaduce D, *et al.* Cardiovascular effects of depot long-acting somatostatin analog sandostatin LAR in acromegaly. J Clin Endocrinol Metab 2000;85:3132-40.
30. Maison P, Tropeano AI, Macquin-Mavier I, Giustina A, Chanson P. Impact of somatostatin analogs on the heart in acromegaly: A metaanalysis. J Clin Endocrinol Metab 2007;92:1743-7.
31. Colao A. Improvement of cardiac parameters in patients with acromegaly treated with medical therapies. Pituitary 2012;15:50-8.
32. Lombardi G, Colao A, Marzullo P, Biondi B, Palmieri E, Fazio S, *et al.* Improvement of left ventricular hypertrophy and arrhythmias after lanreotide-induced GH and IGF-I decrease in acromegaly. A prospective multi-center study. J Endocrinol Invest 2002;25:971-6.
33. Auriemma RS, Pivonello R, Galdiero M, De Martino MC, De Leo M, Vitale G, *et al.* Octreotide-LAR vs lanreotide-SR as first-line therapy for acromegaly: A retrospective, comparative, head-to-head study. J Endocrinol Invest 2008;31:956-65.
34. Volschan ICM, Kasuki L, Silva CMS, Alcantara ML, Saraiva RM, Xavier SS, *et al.* Two-dimensional speckle tracking echocardiography demonstrates no effect of active acromegaly on left ventricular strain. Pituitary 2017;20:349-57.
35. Warszawski L, Kasuki L, Sá R, Dos Santos Silva CM, Volschan I, Gottlieb I, *et al.* Low frequency of cardniac arrhythmias and lack of structural heart disease in medically-naïve acromegaly patients: A prospective study at baseline and after 1 year of somatostatin analogs treatment. Pituitary 2016;19:582-9.
36. Mansoubi M, Pearson N, Biddle SJ, Clemes S. The relationship between sedentary behaviour and physical activity in adults: A systematic review. Prev Med 2014;69:28-35.

37. Thuesen L, Christensen SE, Weeke J, Orskov H, Henningsen P. The cardiovascular effects of octreotide treatment in acromegaly: An echocardiographic study. Clin Endocrinol (Oxf) 1989;30:619-25.
38. Pereira JL, Rodriguez-Puras MJ, Leal-Cerro A, Martinez A, Garcia-Luna PP, Gavilan I, *et al.* Acromegalic cardiopathy improves after treatment with increasing doses of octreotide. J Endocrinol Invest 1991;14:17-23.
39. Lim MJ, Barkan AL, Buda AJ. Rapid reduction of left ventricular hypertrophy in acromegaly after suppression of growth hormone hypersecretion. Ann Intern Med 1992;117:719-26.
40. Merola B, Cittadini A, Colao A, Ferone D, Fazio S, Sabatini D, *et al.* Chronic treatment with the somatostatin analog octreotide improves cardiac abnormalities in acromegaly. J Clin Endocrinol Metab 1993;77:790-3.
41. Tokgözoğlu SL, Erbaş T, Aytemir K, Akalin S, Kes S, Oram E, *et al.* Effects of octreotide on left ventricular mass in acromegaly. Am J Cardiol 1994;74:1072-4.
42. Giustina A, Boni E, Romanelli G, Grassi V, Giustina G. Cardiopulmonary performance during exercise in acromegaly, and the effects of acute suppression of growth hormone hypersecretion with octreotide. Am J Cardiol 1995;75:1042-7.
43. Padayatty SJ, Perrins EJ, Belchetz PE. Octreotide treatment increases exercise capacity in patients with acromegaly. Eur J Endocrinol 1996;134:554-9.
44. Lombardi G, Colao A, Ferone D, Marzullo P, Landi ML, Longobardi S, *et al.* Cardiovascular aspects in acromegaly: Effects of treatment. Metabolism 1996;45:57-60.
45. Colao A, Spinelli L, Cuocolo A, Spiezia S, Pivonello R, di Somma C, *et al.* Cardiovascular consequences of early-onset growth hormone excess. J Clin Endocrinol Metab 2002;87:3097-104.
46. Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Florimonte L, *et al.* Effects of 1-year treatment with octreotide on cardiac performance in patients with acromegaly. J Clin Endocrinol Metab 1999;84:17-23.
47. Colao A, Marzullo P, Cuocolo A, Spinelli L, Pivonello R, Bonaduce D, *et al.* Reversal of acromegalic cardiomyopathy in young but not in middle-aged patients after 12 months of treatment with the depot long-acting somatostatin analogue octreotide. Clin Endocrinol (Oxf) 2003;58:169-76.
48. Delaroudis SP, Efstathiadou ZA, Koukoulis GN, Kita MD, Farmakiotis D, Dara OG, *et al.* Amelioration of cardiovascular risk factors with partial biochemical control of acromegaly. Clin Endocrinol (Oxf) 2008;69:279-84.
49. dos Santos Silva CM, Gottlieb I, Volschan I, Kasuki L, Warszawski L, Balarini Lima GA, *et al.* Low frequency of cardiomyopathy using cardiac magnetic resonance imaging in an acromegaly contemporary cohort. J Clin Endocrinol Metab 2015;100:4447-55.
50. Hradec J, Kral J, Janota T, Krsek M, Hana V, Marek J, *et al.* Regression of acromegalic left ventricular hypertrophy after lanreotide (a slow-release somatostatin analog). Am J Cardiol 1999;83:1506-9, A8.
51. Baldelli R, Ferretti E, Jaffrain-Rea ML, Iacobellis G, Minniti G, Caracciolo B, *et al.* Cardiac effects of slow-release lanreotide, a slow-release somatostatin analog, in acromegalic patients. J Clin Endocrinol Metab 1999;84:527-32.
52. Bogazzi F, Lombardi M, Strata E, Aquaro G, Lombardi M, Urbani C, *et al.* Effects of somatostatin analogues on acromegalic cardiomyopathy: Results from a prospective study using cardiac magnetic resonance. J Endocrinol Invest 2010;33:103-8.
53. Melmed S, Cook D, Schopohl J, Goth MI, Lam KS, Marek J, *et al.* Rapid and sustained reduction of serum growth hormone and insulin-like growth factor-1 in patients with acromegaly receiving lanreotide autogel therapy: A randomized, placebo-controlled, multicenter study with a 52 week open extension. Pituitary 2010;13:18-28.
54. Annamalai AK, Webb A, Kandasamy N, Elkhawad M, Moir S, Khan F, *et al.* A comprehensive study of clinical, biochemical, radiological, vascular, cardiac, and sleep parameters in an unselected cohort of patients with acromegaly undergoing presurgical somatostatin receptor ligand therapy. J Clin Endocrinol Metab 2013;98:1040-50.
55. Ronchi CL, Varca V, Beck-Peccoz P, Orsi E, Donadio F, Baccarelli A, *et al.* Comparison between six-year therapy with long-acting somatostatin analogs and successful surgery in acromegaly: Effects on cardiovascular risk factors. J Clin Endocrinol Metab 2006;91:121-8.
56. Colao A, Pivonello R, Galderisi M, Cappabianca P, Auriemma RS, Galdiero M, *et al.* Impact of treating acromegaly first with surgery or somatostatin analogs on cardiomyopathy. J Clin Endocrinol Metab 2008;93:2639-46.
57. Colao A, Auriemma RS, Galdiero M, Lombardi G, Pivonello R. Effects of initial therapy for five years with somatostatin analogs for acromegaly on growth hormone and insulin-like growth factor-I levels, tumor shrinkage, and cardiovascular disease: A prospective study. J Clin Endocrinol Metab 2009;94:3746-56.
58. Giustina A, Casanueva FF, Cavagnini F, Chanson P, Clemmons D, Frohman LA, *et al.* Diagnosis and treatment of acromegaly complications. J Endocrinol Invest 2003;26:1242-7.
59. Bondanelli M, Ambrosio MR, degli Uberti EC. Pathogenesis and prevalence of hypertension in acromegaly. Pituitary 2001;4:239-49.
60. Vitale G, Pivonello R, Auriemma RS, Guerra E, Milone F, Savastano S, *et al.* Hypertension in acromegaly and in the normal population: Prevalence and determinants. Clin Endocrinol (Oxf) 2005;63:470-6.
61. Schutte AE, Volpe M, Tocci G, Conti E. Revisiting the relationship between blood pressure and insulin-like growth factor-1. Hypertension 2014;63:1070-7.
62. Hansen TK, Møller J, Thomsen K, Frandsen E, Dall R, Jørgensen JO, *et al.* Effects of growth hormone on renal tubular handling of sodium in healthy humans. Am J Physiol Endocrinol Metab 2001;281:E1326-32.
63. Kamenicky P, Blanchard A, Frank M, Salenave S, Letierce A, Azizi M, *et al.* Body fluid expansion in acromegaly is related to enhanced epithelial sodium channel (ENaC) activity. J Clin Endocrinol Metab 2011;96:2127-35.
64. Powlson AS, Gurnell M. Cardiovascular disease and sleep-disordered breathing in acromegaly. Neuroendocrinology 2016;103:75-85.
65. Sardella C, Urbani C, Lombardi M, Nuzzo A, Manetti L, Lupi I, *et al.* The beneficial effect of acromegaly control on blood pressure values in normotensive patients. Clin Endocrinol (Oxf) 2014;81:573-81.
66. Watson JC, Balster DA, Gebhardt BM, O'Dorisio TM, O'Dorisio MS, Espenan GD, *et al.* Growing vascular endothelial cells express somatostatin subtype 2 receptors. Br J Cancer 2001;85:266-72.
67. Tolis G, Angelopoulos NG, Katounda E, Rombopoulos G, Kaltzidou V, Kaltsas D, *et al.* Medical treatment of acromegaly: Comorbidities and their reversibility by somatostatin analogs. Neuroendocrinology 2006;83:249-57.
68. Badway AC, Blake AD. Somatostatin: A hormone for the heart? Curr Vasc Pharmacol 2005;3:125-31.
69. Smith WH, Nair RU, Adamson D, Kearney MT, Ball SG, Balmforth AJ, *et al.* Somatostatin receptor subtype expression in the human heart: Differential expression by myocytes and fibroblasts. J Endocrinol 2005;187:379-86.
70. Colao A, Terzolo M, Bondanelli M, Galderisi M, Vitale G, Reimondo G, *et al.* GH and IGF-I excess control contributes to blood pressure control: Results of an observational, retrospective,

multicentre study in 105 hypertensive acromegalic patients on hypertensive treatment. Clin Endocrinol (Oxf) 2008;69:613-20.
71. Cansu GB, Yılmaz N, Yanıkoğlu A, Özdem S, Yıldırım AB, Süleymanlar G, *et al*. Assessment of diastolic dysfunction, arterial stiffness, and carotid intima-media thickness in patients with acromegaly. Endocr Pract 2017;23:536-45.
72. Chemla D, Attal P, Maione L, Veyer AS, Mroue G, Baud D, *et al.* Impact of successful treatment of acromegaly on overnight heart rate variability and sleep apnea. J Clin Endocrinol Metab 2014;99:2925-31.
73. Dural M, Kabakcı G, Cınar N, Erbaş T, Canpolat U, Gürses KM, *et al.* Assessment of cardiac autonomic functions by heart rate recovery, heart rate variability and QT dynamicity parameters in patients with acromegaly. Pituitary 2014;17:163-70.
74. Nanchen D, Leening MJ, Locatelli I, Cornuz J, Kors JA, Heeringa J, *et al.* Resting heart rate and the risk of heart failure in healthy adults: The rotterdam study. Circ Heart Fail 2013;6:403-10.
75. Thuesen L, Christensen SE, Weeke J, Orskov H, Henningsen P. A hyperkinetic heart in uncomplicated active acromegaly. Explanation of hypertension in acromegalic patients? Acta Med Scand 1988;223:337-43.
76. Yuhico LS, Gundu V, Lenox R. Octreotide-induced asystolic events in an intensive care unit patient with gastrointestinal bleeding. Heart Lung 2012;41:e18-20.
77. Erem C, Ersöz HO, Ukinç K, Avunduk AM, Hacihasanoglu A, Koçak M, *et al.* Acromegaly presenting with diabetic ketoacidosis, associated with retinitis pigmentosa and octreotide-induced bradycardia: A case report and a review of the literature. Endocrine 2006;30:145-9.
78. Fatti LM, Scacchi M, Lavezzi E, Pecori Giraldi F, De Martin M, Toja P, *et al.* Effects of treatment with somatostatin analogues on QT interval duration in acromegalic patients. Clin Endocrinol (Oxf) 2006;65:626-30.
79. Pivonello R, Auriemma RS, Grasso LF, Pivonello C, Simeoli C, Patalano R, *et al.* Complications of acromegaly: Cardiovascular, respiratory and metabolic comorbidities. Pituitary 2017;20:46-62.
80. O'Keefe J, Grant S, Wiseman J, Stiel J, Wilmshurst E, Cooper A, *et al*. Acromegaly and the heart–echocardiographic and nuclear imaging studies. Internal Med J 1982;12:603-7.
81. Mosca S, Paolillo S, Colao A, Bossone E, Cittadini A, Iudice FL, *et al.* Cardiovascular involvement in patients affected by acromegaly: An appraisal. Int J Cardiol 2013;167:1712-8.
82. Stewart GA, Foster J, Cowan M, Rooney E, McDonagh T, Dargie HJ, *et al.* Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. Kidney Int 1999;56:2248-53.
83. Rosei EA. JS ISH-ESH-2 Update on the detection and follow-up of early hypertensive heart disease. J Hypertens 2016;34:e192-3.
84. Schmid M, Daniel WG, Achenbach S. Cardiovascular magnetic resonance evaluation of the patient with known or suspected coronary artery disease. Heart 2010;96:1586-92.
85. Bottini PB, Carr AA, Prisant LM, Flickinger FW, Allison JD, Gottdiener JS, *et al.* Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient. Am J Hypertens 1995;8:221-8.
86. Missouris CG, Forbat SM, Singer DR, Markandu ND, Underwood R, MacGregor GA, *et al.* Echocardiography overestimates left ventricular mass: A comparative study with magnetic resonance imaging in patients with hypertension. J Hypertens 1996;14:1005-10.
87. Saccà L, Napoli R, Cittadini A. Growth hormone, acromegaly, and heart failure: An intricate triangulation. Clin Endocrinol (Oxf) 2003;59:660-71.
88. Fazio S, Cittadini A, Cuocolo A, Merola B, Sabatini D, Colao A, *et al.* Impaired cardiac performance is a distinct feature of uncomplicated acromegaly. J Clin Endocrinol Metab 1994;79:441-6.
89. Fazio S, Cittadini A, Biondi B, Palmieri EA, Riccio G, Bonè F, *et al.* Cardiovascular effects of short-term growth hormone hypersecretion. J Clin Endocrinol Metab 2000;85:179-82.
90. Omerovic E, Bollano E, Mobini R, Kujacic V, Madhu B, Soussi B, *et al*. Growth hormone improves bioenergetics and decreases catecholamines in postinfarct rat hearts. The study was supported by grants from the Swedish Heart and Lung Foundation, the Swedish Medical Research Council, Göteborg Medical Society, and the Medical Faculty at Göteborg University. Endocrinology 2000;141:4592-9.
91. Fazio S, Sabatini D, Capaldo B, Vigorito C, Giordano A, Guida R, *et al.* A preliminary study of growth hormone in the treatment of dilated cardiomyopathy. N Engl J Med 1996;334:809-14.
92. Lee SW, Park MC, Park YB, Lee SK. E/E' ratio is more sensitive than E/A ratio for detection of left ventricular diastolic dysfunction in systemic lupus erythematosus. Lupus 2008;17:195-201.
93. Law WG, Thong BY, Lian TY, Kong KO, Chng HH. Acute lupus myocarditis: Clinical features and outcome of an oriental case series. Lupus 2005;14:827-31.
94. Giunta A, Picillo U, Maione S, Migliaresi S, Valentini G, Arnese M, *et al.* Spectrum of cardiac involvement in systemic lupus erythematosus: Echocardiographic, echo-doppler observations and immunological investigation. Acta Cardiol 1993;48:183-97.
95. Stoddard MF, Pearson AC, Kern MJ, Ratcliff J, Mrosek DG, Labovitz AJ, *et al.* Influence of alteration in preload on the pattern of left ventricular diastolic filling as assessed by doppler echocardiography in humans. Circulation 1989;79:1226-36.
96. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, *et al.* Clinical utility of doppler echocardiography and tissue doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous doppler-catheterization study. Circulation 2000;102:1788-94.