Progressive Hypertension and severe left ventricular outflow tract obstruction

Alan C. Cameron[1], Ninian N. Lang[1], Anna F. Dominiczak[1], Garry L.R. Jennings[2], Daniel Batlle[3], Michael Bursztyn[4], Atul R. Chugh[5], John S. Floras[6], Sandra J. Taler[7], Rhian M. Touyz[1], Christian Delles[1]

[1] Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK

[2] Sydney Medical School, University of Sydney and Baker Heart & Diabetes Institute, Melbourne, Australia

[3] Department of Medicine, Division of Nephrology and Hypertension, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611-3008, USA

[4] Hypertension Unit, Department of Medicine, Hadassah-Hebrew University Medical Center, Mount-Scopus, Jerusalem, Israel

[5] Franciscan Health; Indianapolis, Indiana Heart Physicians

[6] University Health Network and Sinai Health System Division of Cardiology, University of Toronto, Toronto, Canada

[7] Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN. U.S.A.

Running Title -

Hypertension and LV outflow tract obstruction

Word Count: 7616

Figures: 4

For Correspondence:
Dr. Alan C Cameron BSc (Hons), MB ChB, MRCP
Room 238, BHF Glasgow Cardiovascular Research Centre
Institute of Cardiovascular and Medical Sciences
University of Glasgow
126 University Place
Glasgow
United Kingdom
G12 8TA

Tel: +44 (0)141 330 8271
Email: alan.cameron.2@glasgow.ac.uk

The following case was presented on September 8, 2018 as part of a Clinical-Pathological conference chaired by Anna F. Dominiczak and Garry L.R. Jennings at the AHA Council on Hypertension | AHA Council on Kidney in Cardiovascular Disease | American Society of Hypertension Joint Scientific Sessions 2018 in Chicago, USA. Alan C. Cameron and Christian Delles presented the case and led the discussion.

Case Introduction

A 73-year-old woman had been monitored in our clinic for a number of years, after being diagnosed with essential hypertension in 1994. Her background included hypercholesterolemia, hypothyroidism, obesity, and asthma.

Her anti-hypertensive regimen had included a combination of dihydropyridine calcium channel antagonists, fluctuating between amlodipine and lercanidipine over the years, as well as a thiazide. She was also taking a statin, a thyroxine replacement, and inhalers. As she had previously been troubled by a cough when using an ACE-inhibitor, we avoided that treatment.

Looking over her trajectory from 2010 to 2013, we can see that she had generally reasonable blood pressures (BP) in clinic and at home (Table 1). The key issues were that she developed ankle swelling while taking amlodipine in 2012 and was therefore converted to lercanidipine by her General Practitioner (GP). In 2012, one slightly elevated clinic reading led to an up-titration of lercanidipine. Overall, she had been relatively stable on this regimen.

I would like to take you on a journey from 2014 to 2018 to look at the changes that occurred over that period. If we focus first on 2014, her BP was above target at 152 systolic. At home, she was troubled by fatigue, with reasonable BPs.

Due to fatigue and elevated home readings, her GP changed her lercanidipine to amlodipine. Based on the clinic BP, we proceeded to arrange an electrocardiogram (ECG) and an ambulatory BP monitor. Her EKG demonstrated sinus rhythm with some ectopics, but not much else.

Moving on to look at her ambulatory BP in 2014 (Figure 1a), we can see readings that are probably reasonable. Although there may be some scope to be more aggressive, there is definitely evidence of a loss of nocturnal dips. When we followed up in clinic to review the issues, her clinic reading was satisfactory. We therefore continued the regimen, which at that time was amlodipine 10 mg and a thiazide diuretic.

At this point, I think it would be useful to stop the introduction and ask for people's thoughts on the case to date and management at that point. What are experts' opinions? Would anyone have done anything differently?

Discussion

Dr. Floras: At this point, if I were presented with a hypertensive, obese woman, who was reporting daytime fatigue, had developed a peripheral edema after starting a dihydropyridine calcium channel antagonist, and had then found that her blood pressure did not fall at night, my next step would be to schedule polysomnography.

Dr. Cameron: This is an excellent point, and we heard discussions yesterday about the importance of sleep, hypertension, and cardiovascular risk. In Glasgow, we now have much greater focus on that, as well as a specialist clinic. It may be an ideal point to consider.

Dr. Batlle: For a U.S. audience, which may not be familiar with the dosage of this diuretic, can you clarify that this is a type of hydrochlorothiazide (because a dose of 2.5 mg would be totally homeopathic)? In the U.S., we use 12.5 mg of HCTZ as a low dose.

Dr. Delles: This is a U.K.-specific thiazide. It is like hydrochlorothiazide, and the 2.5 is equivalent to the 12.5–25 mg of hydrochlorothiazide.

Dr. Batlle: Thank you.

Dr. Bursztyn: I wonder if there is a history of frequent nocturnal urination, which may explain her nocturnal hypertension on a behavioral, rather than physiological, basis.

Dr. Cameron: Again, that is an interesting point. Perhaps it is a question we do not ask often enough in clinics and something that we should probe more deeply—an excellent point for discussion.

Follow-up of hypertensive patients

These were some of the issues we considered. We did wonder whether the ambulatory monitors that we had arranged provided enough useful information. We saw the loss of the nocturnal dip. Should we have made an adjustment at that point on the basis of the patient's current BP? We have touched upon the thiazide, which is slightly unusual but a common treatment in the U.K.

Is bendroflumethiazide, which is predominantly a U.K. drug, the most appropriate thiazide we can use, or do other agents act better? Particularly if someone is stable, should we change the treatment or continue on the current regimen? A key issue to discuss is the follow-up on this lady. We have seen that she is relatively stable, but with a loss of nocturnal dip. How frequently

should we follow up on her? What is the best setting to do that in, and what approaches should we take? I will hand over the discussion to Dr Delles and he will talk through those questions.

Thanks very much. There is not that much to discuss, because you have mentioned some of these issues; they are part of the reason why we wanted to present this case. Back in 2014, this was a very stable patient who had attended the clinic for quite a few years. I think our clinic is as busy as many of yours, so the question really is whether management would change dramatically if there were 15 or 20 patients on the list and some of them were presenting with real issues. And then you had this one, who was not actually too bad. Her blood pressure was okay; she was complaining of some fatigue but had no real red-flags. I think it was perfectly fine management, at this point in time, to say, "We are not making any major changes here." However, I take the point that sleep studies and other approaches might be appropriate, especially now in 2018.

What I want to show very briefly comes from the new guidelines: the actual recommended follow-up (Figure 2)[1]. I think you are all aware that, at the very beginning of managing hypertensive patients, we should be much more aggressive with the follow-up and see patients more frequently—at approximately monthly intervals.

Later on, three- to six-month intervals are entirely appropriate. These follow-up appointments should focus on adherence and a number of other issues, including side effects, but should also include occasional screenings for other conditions, such as target-organ damage. Of course, we should always bear in mind that somebody who is labeled primary or essential hypertensive

could, after many years, still develop a secondary form of hypertension, and we should always be alert to this.

One of the issues that Alan has kindly pointed out was the loss of nocturnal dip, which is something we can discuss later on during the presentation. Would this be a symptom that would trigger a search or investigation into secondary forms of hypertension, which could be associated with this finding?

There may be a few situations wherein we should screen for secondary hypertension, and the loss of nocturnal dip in this patient is one factor that could have triggered further investigations. It was not discussed very much, back in 2014, because everybody was so happy that she was well controlled.

Taking you now to 2015, she presented to her GP complaining of predominantly atypical chest discomfort, with no other associated symptoms, and was referred to a cardiology clinic. Her BP was elevated at 160/80 mmHg, but the cardiology examination was otherwise unremarkable. The cardiologists proceeded initially with an ECG, which was generally unchanged. An exercise-tolerance test was carried out; likely due to her body habitus, she could only exercise for three minutes out of a predicted six. Overall, it was a relatively satisfactory exercise-tolerance test.

These results, combined with her atypical symptoms, reassured the cardiologists that her symptoms overall were not suggestive of ischemia. They noticed the elevated clinic BP, which contrasted with earlier results, and arranged an ambulatory BP monitor and echocardiogram.

We will look at the echocardiogram images first. Essentially, what we see is mild concentric left ventricular hypertrophy (Figure 3a). If we were able to show all of the images, we would see that the LV function was satisfactory. Overall, there was some mild concentric LVH.

As I mentioned, they also arranged an ambulatory BP monitor (Figure 1b). We can see a marked difference compared to previous results, with readings averaging up to around 190 mmHg systolic, and the continuing loss of nocturnal dip. This was certainly more elevated than her clinic BP at that point.

On the basis of these results, I wondered what you thought of this case and what steps you would take next to manage it. She was then on amlodipine 10 mg and bendroflumethiazide 2.5 mg.

Discussion

> **Dr. Taler:** I was going to say before this last part that I think it was probably not appropriate to ignore her ambulatory monitor and withhold drug treatment because her office reading was acceptable. I think that you left the door open for ongoing target-organ damage by doing that. This second monitor result is very different and her pressures are quite high now, so I think it is appropriate to look for a secondary cause, as well as assess target-organ damage. I would say there is a nocturnal fall in there, maybe not a full 20%, but that is not my major concern. I am more worried about her inadequate blood-pressure control.

Dr. Cameron: Exactly. That is one of the points that we hoped to tease out of this discussion. Was it a missed opportunity, based on the previous ambulatory monitor? We were reassured when she followed that up with a clinic BP, which we felt was satisfactory, but was there an element of masked hypertension? We have discussed this question over the past few days at the conference, as something that we need to be much more aware of and more aggressive in our management of.

Dr. Chugh: As we are trying to treat the hypertension, we are also trying to figure out what else is going on with this patient, and the one thing that keeps coming up is that the patient is fatigued. I still do not have a clear idea of the etiology of that, but I do not think it is simply a result of not sleeping well. The issue is with the echo—what was the diastolic function there? Did you get any numbers? For example, was there an elevated right atrial pressure? What were the PA pressures?

Dr. Cameron: I do not have that data, unfortunately, but the cardiologists were certainly reassured about her systolic function. Whether there was any element of diastolic dysfunction— I think that is certainly possible. Although I do not have the indices to discuss that with you, it is an important area to consider. One excellent point to establish is whether there was an element of diastolic dysfunction, perhaps even progressing to symptoms of heart failure with preserved ejection fraction (HFpEF).

Dr. Chugh: That would lead me to be slightly more aggressive with my diuretics in this situation. Was there anything in the examination, like a jugular venous dilatation (JVD) or edema? Did you see any sort of signal there?

Dr. Cameron: No, the examination was unremarkable. But one of the points that will come up as we go through the presentation is the fact that she complained of a swollen ankle, which is often attributed to amlodipine. Should we be more inquisitive when patients present with swollen ankles? Did we, perhaps inappropriately, attribute that symptom to her amlodipine—and should we have thought more about HFpEF or considered diuretic up-titration?

Dr. Chugh: If I recall correctly, your EKG may have reached the criteria for LVH, based on the Cornell Criteria. She met 20 with the V3 and aVL.

Dr. Cameron: Yes, thank you.

Dr. Batlle: You present good documentation of the progression or worsening of her hypertension over time. Often, we simply do not know that relatively rapid progression/ worsening has occurred. In this case, the differential diagnosis, given the age of the patient, would include the first renal artery stenosis. We need information on urine protein, because proteinuria is often a sign of unilateral renal artery stenosis. In other words, de novo proteinuria may be a sign of angiotensin II-dependent hypertension. Can you share this information?

Dr. Cameron: She did not have proteinuria. We did not reevaluate the ultrasound imaging. As Christian asked earlier, when we see these patients and note a change over time, should we go back to the start? She had been monitored for many years in the clinic and things seemed fairly stable until the small change in 2015. Should we have

gone back to the drawing board and started her evaluatory workup again? This is an important point.

Dr. Batlle: Well, will you tell us…

Dr. Cameron: We have not proceeded to the renal ultrasound, so I do not have that information, but she does not have proteinuria.

Dr. Batlle: Very good, thank you.

Prof. Bursztyn: I wonder about the decisions about chronic drug management. Of course, we would all sympathize with not changing a successful or apparently successful treatment. On the other hand, as every treating physician is well aware, if a patient has obstructive cardiomyopathy, dihydropyridines are usually inappropriate. Diuretics would not be recommended in this case because they can exacerbate obstruction. For these reasons, I am not all that surprised that she became symptomatic.

Prof. Bursztyn: Moreover, if you had to treat her with calcium channel blockers, high-dose verapamil would probably have been more appropriate. What was her ACE-inhibitor intolerance? How did it manifest? Was it a cough or hypotension?

Dr. Cameron: It was cough a number of years ago. You touch upon a very interesting point with verapamil that we will come back to later in the presentation.

Prof. Bursztyn: So, obviously, the alternative might have been useful.

Dr. Cameron: Exactly, yes.

Dr. Floras: We do not seem to have demonstrated left ventricular outflow-tract obstruction yet, so I think Dr. Bursztyn is ahead of us.

Dr. Cameron: Exactly, yes.

Dr. Floras: Looking at that echo, which does not demonstrate left ventricular outflow-tract obstruction, and considering the potential causes of exertional chest pain, in a hypertensive woman with a low pre-test probability of coronary artery disease, I would often recommend treadmill stress echocardiography to document estimated right ventricular systolic pressure before and at the end of exercise. In our clinical experience, the chest pain these women describe is due to high pulmonary artery pressure induced by exercise, rather than coronary artery disease. It can be attenuated by lowering exercise blood pressure.

Dr. Floras: The other practical point is that, when a patient develops a gravitational edema with drugs like amlodipine, this fluid will shift over the course of the night. Our research has shown that this fluid will shift overnight to the chest and up into the neck. This leads to an increase in neck diameter, a reduction in upper-airway caliber, and an increase in upper-airway resistance. The more fluid shifts rostral, the greater the apnea-hypopnea index. I would therefore propose that, in this woman, the edema, nocturia, and fatigue were all signs of obstructive sleep apnea.

Dr. Cameron: Yes, excellent points are coming out in terms of the exercise-tolerance test. Perhaps we should have proceeded to stress imaging, and yes, we have already touched on sleep earlier in the morning. So, exactly, ideal points are coming out.

Masked hypertension

I will move on, in the interests of time. We have touched upon these issues. The overall impression was of masked hypertension. The etiology of her chest pain—should we have carried out more detailed investigations of that? Not necessarily for obstructive coronary artery disease, but for other factors that contribute to chest pain.

In terms of the management, we added an angiotensin receptor blocker (ARB), commencing Losartan 50 mg at that point. We have considered whether this lady may have had masked hypertension. We saw evidence of it earlier that perhaps was not fully understood or acted upon. We are certainly more convinced by the ambulatory monitor that we have now seen. This topic will come up again over the course of the conference. It is a common condition in our patients, with prevalence of up to 30%, and it is not a benign phenomenon.

Here, I present data on the prevalence of cardiovascular events, comparing normotensive and masked hypertensive patients; there is a two-fold increase.[2,3] In terms of cardiovascular mortality and the risk of stroke, the prevalence is comparable to that of patients with sustained hypertension, so it is not a condition to ignore. We need to be more aware of this condition and to act more aggressively when we see it. In terms of detection and management, the 2017

guidelines state that if we have patients with office BP at goal, whom we feel are at increased cardiovascular risk—or if we have evidence of target-organ damage—then we should screen them for masked hypertension and intensify treatment strategies if any is detected[1].

Moving on to 2016, the patient in question complained of further symptoms that might be considered nebulous, but could also be more significant: postural exertional lightheadedness and ankle swelling, which was a recurring theme. Her clinic and home BP readings were 143 and 135 systolic. The ankle swelling was perhaps inappropriately disregarded, due to the dihydropyridine. We reduced the dihydropyridine to 5 mg, up-titrated the Losartan, and continued the thiazide. Overall, her symptoms did improve slightly with that approach and her BP was around 140/90 both in clinic and at home.

Things took a fairly marked turn in 2017. She had been seeing her GP for a couple of weeks, with increasing dyspnea, fatigue, and peripheral edema. The GP felt that this was due to her dihydropyridine and converted the amlodipine to lercanidipine. She also had symptoms of a lower-respiratory infection with a cough, productive of a small amount of green sputum. Her BP, in contrast to earlier readings, was markedly reduced, at 106 systolic. She had a relative tachycardia, with a heart rate of 90, which had been much lower previously. She had a loud systolic murmur audible across the precordium with bi-basal crepitations and mild pedal edema.

Her ECG changed at that point. We have questioned whether the previous ECG showed features of LVH and I think there is LVH here. It also looks more tachycardic than before.

We arranged a chest X-ray to look for consolidation or any frank pulmonary edema. You can see that the cardiac size was increased. However, there was no frank edema and certainly no consolidation.

This is a more interesting echocardiogram image. We can see that there is much more impressive left ventricular hypertrophy—severe left ventricular hypertrophy on this apical four-chamber view (Figure 3b). If we move through to the parasternal short axis (Figure 3c), we can see much more marked left ventricular hypertrophy, concentric in nature.

Going back now to the four chambers, a key feature of the left ventricular outflow tract is the motion of the mitral valve. Systolic anterior motion, combined with a really chunky septum, narrows the left ventricular outflow tract and markedly impairs cardiac output. This represents a real change in the echocardiogram findings, compared to what we saw previously.

We note severe left ventricular hypertrophy, left ventricular outflow-tract obstruction (LVOT), and systolic anterior motion of the mitral valve. Importantly, we have considered whether this patient might have had masked hypertension, perhaps against a background of essential hypertension with a loss of nocturnal dip.

At this point, I would like to open this up for discussion. Given these echocardiogram findings and the patient's symptoms at this point, what are your thoughts? Do you agree with our impression so far? How would you move forward? Any suggestions?

Discussion

Dr. Chugh: Given that the cavity is so small, with a true LVOT obstruction, I would certainly think about a beta blockade in a situation like this, to try to get that heart to really slow down, give it some more filling time, and relieve that LVOT obstruction.

Dr. Chugh: By increasing the amlodipine, the GP essentially increased the gradient across the LVOT and accentuated the LVOT obstruction. So now, we should back off the dihydropyridine and really allow that LVOT to open up through all phases of systole. Could you just review the BMI of the patient one more time?

Dr. Cameron: In the region of 30.

Dr. Chugh: Okay, so a little bit on the chunkier side. Is she a small woman?

Dr. Cameron: About five foot, seven inches.

Dr. Chugh: So she is a larger woman. One challenge that we face involves women of smaller stature, who have small LVs to begin with. If their weight increases over time, what you have is a very small heart attached to a large body, which obviously exacerbates the low-output state. To those patients I would certainly want to say, "It is time to really start dialing down the pounds." That would be something to think about because it would go a long way here as well.

Dr. Jennings: We have two suggestions, a beta-blocker or verapamil. Which did you choose?

Dr. Delles: She got amlodipine and losartan. I agree that the amlodipine was not good for the gradient. The other drug introduced against the background of the mild LVH was the losartan, which had exactly the same effect, further increasing the gradient. Alan will discuss some of the details, how this patient's clinical decompensation was triggered by some of the measures taken, as well as by other precipitating factors.

Left ventricular outflow-tract obstruction

To review what we did at that point, perhaps not ideally, we stopped losartan, withheld bendroflumethiazide, and continued the dihydropyridine. On reflection, was that the most appropriate approach? Probably not. We will discuss the left ventricular outflow-tract obstruction, which often creates an impression of heart failure; traditional approaches to management can actually be deleterious. Specifically, initial management strategies for patients who appear to have heart failure can be deleterious if the patients have left ventricular outflow-tract obstruction.

We arranged an ambulatory monitor (Figure 1c) and an urgent referral to colleagues in the cardiology department. I will not dwell on the ambulatory monitor, but it looks more consistent with previous, more reasonable readings. The key point is that we managed to start some calcium channel antagonists, with verapamil, initially 40 mg three times a day, up-titrating to a more reasonable sustained release. We restarted the diuretic and discontinued lercanidipine.

Left ventricular outflow-tract obstruction is a key issue.[4,5] It is something we should be more aware of and should certainly screen for more often. The condition requires an anatomical substrate, as well as a physiological trigger (Figure 4a). Hypertension and aortic stenosis often lead to an increased afterload. Perhaps in the case of this patient, an element of masked hypertension led to left ventricular hypertrophy and some diastolic dysfunction.

With left ventricular outflow-tract obstruction, as well as the anatomical substrate, there is some form of physical trigger, which can either be a physiological response, perhaps to sepsis, with relative hypotension in this case, or vasodilators. These accentuate the problem, leading to impaired diastolic filling, left ventricular outflow-tract obstruction, and near obliteration of the LV cavity. The systolic anterior motion of the mitral valve, which then occurs, really narrows the left ventricular outflow tract and leads to the typical triad of symptoms: chest pain, breathlessness, and syncope.

To manage the condition most effectively, we need to avoid treatments such as vasodilators or positive inotropes that may be introduced if clinicians adopt the wrong strategy and fail to screen fully for LV outflow-tract obstruction. We need to think about beta-blockers or calcium channel blockers (Figure 4b). In this case, we chose a calcium channel blocker, verapamil, with subsequent up-titration. These agents improve the diastolic filling while slowing down the heart rate. They allow some reduction in the LV outflow tract, reduction of the systolic anterior motion, and improvement of symptoms. That is the approach we took with this lady.

If we fast-forward to 2018, her exercise tolerance improved; although her BP did not reach the ideal target, it was maintained on verapamil. At this point, because her symptoms and exercise

tolerance had improved, we felt that we could re-add an ARB, continue bendroflumethiazide, and achieve more satisfactory BP readings at home and in the clinic.

We updated her ambulatory monitor just a week or so ago, and can see much more satisfactory readings, again with the loss of the nocturnal dip (Figure 1d).

If we compare the echocardiogram after that period of management with verapamil, we can see marked improvement in the left ventricular hypertrophy, and a much more open left ventricular outflow tract, which has contributed to the marked improvement in symptoms (Figure 3d).

We have now taken you on a journey that began in 2014, when a lady who had been relatively stable developed masked hypertension and a loss of nocturnal dip. She began to develop severe left ventricular hypertrophy, probably due to the masked hypertension. When we first detected the masked hypertension, we were not as aggressive in our management strategies as we could have been. Perhaps we could have prevented the progression to the anatomical substrate that, combined with the physiological trigger of relative hypotension in the context of an infection and various management strategies, may have contributed to left ventricular outflow-tract obstruction.

It is a condition to be aware of because the management implications are really important. If you adopt strategies that would be appropriate for heart failure (using diuretics in the first instance) without considering a beta blockade or a rate-limiting calcium channel blockade, then you may be going down the wrong path. You will exacerbate the symptoms and make the

situation worse. Reports from case presentations in the late 1980s have described this progression.

Fortunately, we were able to identify this patient's masked hypertension and to treat her relatively promptly with a negative inotrope that led to marked improvement in her symptoms and echocardiogram findings.

I hope that we have discussed some key features of masked hypertension, which is not a benign phenomenon. We have talked about the importance of considering and probing natriuresis at night and examining sleep studies. We have considered the use of more appropriate imaging to examine the symptoms of chest pain, perhaps with some functional imaging, and the management of left ventricular outflow-tract obstruction to improve symptoms.

I would like to thank everyone for their attention and contributions. As we still have time, we will open up the floor for discussion again.

Discussion

Dr. Jennings: Thank you. I have a comment and a question. Firstly, I would have expected her to improve with the treatment you gave her, but her response, especially with the echo, was miraculous.

Dr. Jennings: Secondly, many people have longstanding hypertension and do not follow this path. I wonder whether this lady has late-onset hypertrophic cardiomyopathy and

whether you've looked at her sarcomeric genes, particularly myosin binding protein C, which is often behind that.

Dr. Cameron: Sure. That is an important point. Is this just simple LVH due to hypertension, or could there be a more familial component? Because of its more concentric nature, it was considered more likely to be hypertensive, although a hypertrophic obstructive cardiomyopathy (HOCM) picture was not excluded. Given the improved echocardiogram findings, along with her symptoms, we have continued down that route. However, it would have been something to consider, had she not continued to improve. Should we look at these proteins or even consider MR imaging for a more detailed evaluation?

Dr. Cameron: Yes, it is important to be aware we do not attribute this fully to hypertensive LVH; we remain aware that a familial component is possible.

Dr. Jennings: Both in athletes and in hypertension, there is hemodynamic stress, but it manifests against a background of the underlying genetic or constitutional makeup. Clearly, this lady was much more prone to hypertrophy than most people.

Prof. Bursztyn: I would like to comment exactly on this point. My cardiology associates would probably have said that this was hypertrophic cardiomyopathy, with hypertension on the side. At the same time, it would actually be a bit obscene to call it familial hypertrophic cardiomyopathy, especially in a patient with hypertension or severe hypertension. I would like to add a clinical perspective. As clinicians, we ought to

seek treatable diseases. Since hypertrophic cardiomyopathy can improve symptomatically, as demonstrated here, while being false, hypertensive heart disease should be given higher consideration because it is preventable and, at least to a certain extent, reversible.

Dr. Cameron: Yes, thank you.

Dr. Tifft: Was there much discussion about the dose of verapamil? You jumped to the other drugs fairly readily. What about using higher doses, as high as 540 mg, which some people use in this kind of situation? You have treated the blood pressure beautifully, but, given that you are trying to understand what the problem is, why not use more verapamil?

Dr. Cameron: Yes, that is an interesting point. I guess we began by being a little too cautious. Perhaps caution is a recurring theme in this case. We could certainly have considered higher doses.

Dr. Tifft: Was it the fact that you had crackles or something similar? I do not think they would bother me particularly in this situation.

Dr. Cameron: The dosage was guided by our cardiology colleagues, rather than ourselves, so I do not have the background to explain why they stopped with that dose. However, it is a theme that we could have been more aggressive throughout the case.

Dr. Delles: At the same time, the other vasodilators were stopped; some drugs that were negatively influencing the gradient were stopped, and the patient received some verapamil on top of this. So she did benefit from two therapeutic approaches at the same time. However, I agree that the verapamil could have been higher.

Dr. Mihailidou: Initially, the loss of nocturnal dip is an important trigger, particularly in women. Many years ago, there was a study, which showed that a lack of nocturnal dip in females (it was not called masked hypertension in those days) led to hypertrophy. So we need to be aware that an initial ambulatory monitor is essential. The other factor is that masked hypertension can only be diagnosed by an ambulatory monitor—there is no other way to diagnose it. We have had many discussions about the lack of reimbursement, particularly in America, which impedes ambulatory monitoring. Perhaps that is something to take up with the associations, because this condition is not benign.

Dr. Delles: I could not agree more. This lady probably had three or four ambulatory readings over the whole period of time, which is not too bad. However the discrepancy between clinic readings that are generally fine, but occasionally high, was confusing; the usual inertia may have led to the view that stress at home or other factors caused this condition. We have ambulatory readings as proper 24-hour readings, and we also have home BP readings.

Dr. Delles: I think what we all do, as this case highlights, is to pick the best readings and take the ones we like most and we say, well despite the absence of a dip, most of her home readings are fine, so we should not increase the treatment. You have pointed out

very rightly that the absence of dip and the slightly borderline blood pressure were observed in 2014 and should have triggered a more aggressive treatment.

Dr. Mihailidou: She still lacks a nocturnal dip. What are you doing for that?

Dr. Delles: That is quite right. We are happy to take your advice.

Dr. Batlle: I think this case should be characterized as a case of severe progressive hypertension. Masked hypertension is a term that should really be reserved for patients who have normal or close to normal blood pressure in the office, but much higher blood pressure at home with associated target damage. The high BP documented by ABPM is consistent with masked hypertension but the office BP readings are actually more variable in this case.

Dr. Batlle: I think this could be described as a case of progressive severe hypertension, rather than masked hypertension, although an element of masked hypertension could be emphasized. The lack of dip in this hypertensive patient is another sign of severe hypertension, according to the definition. You never told us what the follow-up was. Was the patient's blood pressure markedly improved after the verapamil, or did it merely improve her symptoms without fully controlling her blood pressure? I suspect that this is a case of severe hypertension and you need to add spironolactone or something else to control the blood pressure. What happened to her blood pressure at the end?

Dr. Delles: The last ABPM reading from a week ago showed much better blood-pressure control; however, it was still not quite in the optimal range and there was still a loss of nocturnal dip, so she may benefit from some changes in her treatment. Spironolactone is actually an interesting idea, especially given her history of left ventricular hypertrophy.

Dr. Peixoto: I think you have three sequential comments related to that. You have a wealth of information about her nocturnal pressure, but limited steps were taken, from both an investigative and management standpoint. I would argue that spironolactone would not only have added value in terms of overall blood pressure measurement, but also in relation to our discussion about rostral shifts, fluid shifts. If the patient is obese with a little excess aldosterone or sleep apnea (which should be investigated, as others have said), spironolactone could have a favorable effect. Now that her LVOT obstruction is gone or significantly improved, any diuretics could be used safely. If we believe in the value of spironolactone in HFpEF, it could have a double effect.

Dr. Bittman: I was going to ask about the role for spironolactone, so, thank you. I did want to raise one question about keeping the term "masked hypertension." While I agree that blood pressures should be defined as normal in clinic, one problem in this case was that we did not highlight the home blood pressures enough. Removing this term from the diagnosis or label could suggest that the patient should be tested only in the office. It is important to emphasize the need to use home blood pressures for this patient. I do not know how these considerations balance out.

Dr. Delles: One key point is that we really need to look at this patient's ambulatory profile. To come back to the term, "masked hypertension," you have seen the very bold statement in the presentation title and may also have seen Alan's small question mark on one of the slides, where he asks, "is this actually masked hypertension?" As this discussion has shown, it is defined as masked hypertension because we picked the one time point where there was a clear discrepancy between clinic blood pressure and ambulatory readings. Could this really be a case of discordant blood pressure readings over time? They occur in many patients. We may have just missed a natural progression of hypertension, indicated by a number of readings over time.

Dr. Chugh: In defense of cardiologists, I will tell you that we would not necessarily have called this patient HOCM, simply because there is such a terrible association with sudden cardiac death. Before we start telling patients that they are at higher risk for sudden cardiac death, we would want to do a bit of investigation. This may be a shameless plug for cardiac MRI, because it is my specialty, but in situations where you see a precipitous increase in the LV mass, as we saw in this case, a cardiac MRI would be helpful from both a diagnostic standpoint (to see if the patient has late-onset HOCM) and a prognostic standpoint. If you see a lot of fibrosis in the LV myocardium, then you know there is a higher risk of ventricular arrhythmias. The way you treat that patient will be different than if you had seen a low burden of fibrosis. Fibrosis can happen, not only in HOCM, but also in hypertrophic remodeling from hypertension, aortic stenosis, and a myriad of clinical issues.

Dr. Chugh: The last point I would make is this. If you notice, this patient already has left atrial enlargement on the echo, so she is knocking on the door of atrial fibrillation, and she does have some palpitations.

Dr. Cameron: Thank you; we know what to do when those occur.

Dr. Delles: Okay. So, this is a patient who did not look too bad in 2014. Clinics are obviously under a lot of pressure to discharge patients from specialty follow-up. If we had done so at the time, leaving the patient to be seen by a GP, we might have missed even more opportunities.

Dr. Delles: Unfortunately, what we did was probably not much better. This is one of the reasons why we picked this case. Even with specialist management, we were not quite on the right track. We really must make sure that our specialist services deliver what they promise and that we take these patients and their symptoms very, very seriously. This discussion has revealed a number of moments when we could have taken a slightly different route.

Dr. Taler: I think this goes back to guidelines and targets—the higher we set the target, the more cases will pass through. If our primary care providers had used a target of less than 150 systolic, this lady would have been controlled. Instead, she developed hypertensive heart disease. If we had used the European guidelines, I think this lady would have been almost controlled. Moreover, there is a creep there. Well, she is close to the target; I do not want to hurt her; I do not want her to fall down or pass out; and

so we under-treat people. This is an educated, adherent woman, who takes her medication, and yet in front of our eyes, your eyes, she developed hypertensive heart disease. She should not have developed that. I think when we start ratcheting up the targets because we are worried, we serve the patient poorly.

Dr. Jennings: I think at this point we will stop. We have had a wonderful discussion and there is much to reflect on. It is interesting that this rather unusual case has implications for the general run of hypertensives that we treat.

Dr. Jennings: Thank you both, Alan and Christian.

Summary

Masked hypertension is not a benign phenomenon and regular ABPM should be considered in patients with masked hypertension to maintain aggressive BP control and prevent target-organ damage. Left ventricular outflow-tract obstruction should be managed with negative inotropes such as beta-blockers, or rate-limiting calcium channel blockers; vasodilators and positive inotropic drugs should be avoided.

Acknowledgments

The authors are grateful to the following session audience members for contributing to the discussion: Charles P. Tifft, Anastasia Mihailidou, Aldo J. Peixoto, Jesse Bittman.

Sources of Funding

Dr. Cameron is funded through a BHF Centre of Research Excellence Award awarded to Drs. Delles, Dominiczak and Touyz (references RE/13/5/30177 and RE/18/6/34217).

Disclosures

No relevant disclosures.

References

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun;71(6):e13-e115.

2. Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. *Journal of Hypertension*. 2007;25(11):2193-2198.

3. Ohkubo T, Kikuya M, Metoki H, et al. Prognosis of “Masked” Hypertension and ‘White-Coat’ Hypertension Detected by 24-h Ambulatory Blood Pressure Monitoring. *JACC*. 2005;46(3):508-515.

4. Wheeldon NM, Pringle TH, Lipworth BJ. Obstructive left ventricular hypertrophy. Reversibility of outflow-tract obstruction by drug therapy. *Q J Med*. 1992;84(304):629-636.

5. Pearson AC, Gudipati CV, Labovitz AJ. Systolic and diastolic flow abnormalities in elderly patients with hypertensive hypertrophic cardiomyopathy. *JACC*. 1988;12(4):989-995.

Figures

Figure 1

Ambulatory blood pressure monitors from:

(a) 2014

(b) 2015

(c) 2017

(d) 2018

Figure 2

2017 American Heart Association guidelines for the follow-up of patients with hypertension

Figure 3

Echocardiogram images from:

(a) 2015, mild concentric left ventricular hypertrophy

(b-c) 2017, severe left ventricular hypertrophy with left ventricular outflow-tract obstruction

(d) 2018, mild concentric left ventricular hypertrophy

Figure 4

Left ventricular outflow-tract obstruction:

(a) Pathophysiology

(b) Management

Tables

Table 1
Clinical trajectory from 2010 to 2013

Year	BP (mmHg)	Clinic / Home	Issues	Regimen
2010	132/80 134/81	Clinic	Nil	Amlodipine 10 mg Bendroflumethiazide 2.5 mg
2010	~ 130/80	Home	Nil	
2011	122/80	Clinic	Personal issues Fatigue	
2012	120/78	Clinic	Ankle swelling	Lercanidipine 10 mg Bendroflumethiazide 2.5 mg
2012	157/86	Clinic	Home stress	Lercanidipine 20 mg Bendroflumethiazide 2.5 mg
2013	141/77	Clinic	Nil	
2013	116/68	Clinic	Nil	