

DynaPulse

Physician's Reference

*Hypertension and CVD/CHF Management
with
Noninvasive Hemodynamic Profiles
(Clinical applications and Case Studies)*

By
The DynaPulse Research Team
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Introduction

Management of Hypertension as well as cardiovascular disease (CVD) and congestive heart failure (CHF) using “Hemodynamic profiles and responses” is a new trend in advanced patient monitoring and disease prevention. The basic idea of hemodynamic monitoring had been summarized by Fetnat Fouad-Tarazi and Joseph L. Izzo, Jr, in “Hypertension Primer”, 2nd ed., Chapter 45, published by American Heart Association 1999, described the classical example of applying clinical hemodynamic values in high blood pressure control. It assumed that arterial blood pressure (BP), or Mean Arterial Pressure (MAP), is a product of cardiac output (CO) and systemic vascular resistance (SVR), $MAP = CO * SVR$, and applies this relationship to better understanding of the causes of high BP, and to effective treatments, for example, with antihypertensive drugs, such as beta-blockers, ACE inhibitors, alpha and beta adrenergic blockade, etc. In the article, they also pointed out that many other factors, such as stress, vascular structure and endothelial functions, as well as age, gender, race, personal life-style, etc. may all play essential roles in hypertension, which would need further investigations.

During the past two decades, several noninvasive hemodynamic monitoring technologies, which measure CO, BP and other vascular properties, were developed and reported their clinical value of improving cares to hypertensive patients (see References for related publications). Most recently, DynaPulse, a cuff-sphygmomanometry based method, applies Pulse Dynamics waveform analysis principle, has demonstrated and validated its capability of deriving cardiac output (CO) ***simultaneously*** with BP, MAP, SVR, systemic vascular compliance (SVC), brachial artery compliance, distensibility and resistance (BAC, BAD and BAR), LV(dP/dt)Max, and other hemodynamic parameters. These ***simultaneously*** obtained hemodynamic values allows physicians to correlate the ***dynamic*** changes of each parameters for evaluation of physiological conditions of a patient’s circulation system. For over ten years, DynaPulse has been used in US on several large cohort studies, including the BOGALUSA heart study of Tulane University Hospital, SWAN study of Pittsburgh University School of Public Health, etc., which normal population were studied and the “***Normal Range***” for DynaPulse Hemodynamic parameters were established. These Normal hemodynamic values allow better evaluation and assessment of patient’s hemodynamic profiles by physicians. (See References for related publications).

In this Physician’s Reference, we summarize and define the hemodynamic parameters and their values that reported by DynaPulse hemodynamic profiling via on-line DynaPulse Analysis Center (DAC). We also summarize and share the experiences and sample hemodynamic cases, from Dr. Michael Gutkin, a hypertension specialist, how he has been using DynaPulse hemodynamic profiles in his practice to evaluate patient’s circulation system and to apply it to achieve a better anti-hypertension drug therapy. Also included in Appendix are case studies and comments from other leading physicians in the advanced hypertension and cardiovascular disease patient managements with hemodynamic values.

- Area 1:** Showed auscultatory (K-sound) equivalent Systolic, diastolic and heart rate, and the Pulse Dynamic pulse waveform for visual identification of a good pulse signal or bad signal with irregular heart beat or motion artifacts.
- Area 2:** Showed Pulse Dynamic blood pressures, systolic, diastolic and MAP that are closely related to central aortic pressures, and pulse pressure.
- Area 3:** Showed cardiac or heart functions, which include heart rate, ejection time, contractility, cardiac output, stroke volume and their indexes, according to the equations described below.
- Area 4:** Showed systemic vascular compliance and resistance as derived from cardiac output and other pressure parameters, according to the equations described below.
- Area 5:** Showed brachial artery compliance, distensibility and resistance, according to the equations described below.

** Each DynaPulse parameter value, area 2-5, is provided with (dimension) and a Normal Range for either (Male) or (Female), and graphically indicated in scale of 1 to 5 when compare to the normal range. Normal ranges for both genders were established using DynaPulse data collected in several large cohort studies in the US, age from 18 to 90 with ~70% white in population.*

*** Simultaneously obtained hemodynamic parameters are coherent to each other and make possible to correlate their directional changes or trends for evaluation the dynamics of a circulation system, which is essential and the key advantage of DynaPulse vs. other noninvasive hemodynamic monitoring methods.*

Definitions of DynaPulse Hemodynamic Parameters:

I. BLOOD PRESSURE

- **Systolic (SBP)** is the measurement of standard clinical systolic blood pressure. Measured using standard oscillometric algorithms, and closely represents values taken by auscultatory techniques using mercury cuff sphygmomanometry and Korotkoff sounds (K1).
- **Diastolic** blood pressure (DBP) is the measurement of standard clinical diastolic blood pressure. Measured using standard oscillometric algorithms, and closely represents values taken by auscultatory techniques using mercury cuff sphygmomanometry and Korotkoff sounds (K4).
- **End Systolic** blood pressure measures central arterial blood pressure at end-systole. Measured using proprietary Pulse Dynamics waveform pattern-recognition algorithms.

- **End Diastolic** blood pressure measures central arterial blood pressure at end-diastole. Measured using proprietary Pulse Dynamics waveform pattern-recognition algorithms.
- **Mean Arterial Pressure (MAP)** is the average blood pressure over time, measured using proprietary Pulse Dynamics pattern-recognition algorithms. It can also be estimated using $MAP = 1/3 \text{ Systolic} + 2/3 \text{ Diastolic}$.
- **Pulse Pressure (PP)** = Systolic – Diastolic

II. CARDIAC PARAMETERS

- **Heart Rate (HR)** is determined by the DynaPulse monitor
- **LV Ejection Time** is the duration of the systolic cycle
- **LV dP/dt max** is the maximum rate of pressure change in the LV, derived from arterial dP/dt max
- **LV Contractility** is an index of cardiac contractility derived from LV dP/dt max
- **Cardiac Output (CO)** is the volume of blood ejected by the left ventricle per minute. It is calculated using proprietary algorithms and a model based on LV dP/dt, HR, and an empirically derived scaling factor. Validation has been performed using thermo-dilution and echocardiography.
- **Cardiac Index** = CO / BSA Where, BSA = Body Surface Area
- **Stroke Volume (SV)** = CO / HR
- **Stroke Volume Index** = SV / BSA

III. SYSTEMIC VASCULAR PARAMETERS

- **Systemic Vascular Compliance (SVC)** = SV / PP
- **Systemic Vascular Resistance (SVR)** = MAP / CO

IV. BRACHIAL ARTERY PARAMETERS

- **Brachial Artery Compliance (BAC)** is defined as dV/dP , derived using a physical model of the brachial artery segment
- **Brachial Artery Distensibility (BAD)** is defined as the compliance divided by the arterial volume $[(dV/dP)/V]$, or the percentage change in volume per mmHg change in pressure
- **Brachial Artery Resistance (BAR)** = $(MAP-DBP)/(Diastolic \text{ volume flow})$

V. ANTHROPOMETRIC PARAMETERS

- **Body Surface Area (BSA)** is defined by the standard DuBois equation
- **Brachial Artery Diameter** for the reference volume was estimated using an empirically derived model based on gender, height, weight, and MAP, and validated using B-Mode ultrasound ($n = 1,250$, $r = 0.63$, $P < 0.05$)

DynaPulse Hemodynamic Values in Hypertension

Provided below is a summary of clinical evaluations and explanations of how to use the DynaPulse resting hemodynamic parameters and values in hypertension treatments, and some examples. (By Dr. M. Gutkin):

- I. What does the DynaPulse apparatus measurement that is of convenient use to the treating physicians?
 1. Central (aortic) blood pressure, the end-systolic and end-diastolic, and mean arterial pressure (MAP).
 2. Cardiac output (CO), pulse rate and stroke volume.
 3. Total peripheral resistance (SVR)
 4. Brachial (muscular) artery rigidity (BA compliance and distensibility)
 5. Pulse pressure/stroke volume rates, a measure of rigidity of aorta, femoral segments, and common carotid arterials – “Systemic vascular compliance (SVC)”
 6. Maximum left ventricular dP/dt (LV dP/dt max)

- II. What do these measurements tell us beyond our conventional measures of blood pressure, pulse pressure and pulse rate?
 1. Hypertension does not present a uniform hemodynamic pattern.
 2. Varying hemodynamic patterns have different therapeutic implications. Examples:
 - a. High cardiac output with “inappropriately normal” peripheral resistance devotes the early phase of hypertension, which have not yet developed fixed vascular change – opportunities for non-medicinal therapy. In light of the results of the TROPHY trial, the finding of normal cardiac output in this group could justify antihypertensive therapy at a blood pressure of 139/80 to 139/90.
 - b. Normal cardiac output with high peripheral resistance – a target for traditional pharmaco therapy.
 - c. Low cardiac output with high peripheral resistance – a marker of left ventricular hypertrophy with cavitory encroachment.
 - d. High systolic blood pressure with normal peripheral resistance – a marker of great vessel rigidity.
 - e. Increased dP/dt max as a marker for anxiety and treatment with anxiolytic.
 - f. Decreased dP/dt max – as a sign of effective beta-blockade.

- III. How to tell when an artery is abnormally rigid?
 1. Arteries become more rigid as they are stretched.
 - a. “Hypertension” excess tension on arterial wall.
 - b. Arteries resist excessive tension.

- c. Is the rigidity due to excessive stretch on a normal artery?
 - 2. Causes of disproportionate arterial stiffness.
 - a. In muscular (brachial) arteries.
 - b. In elastic (aorta) arteries.
- IV. Why is excess rigidity important?
- 1. Aortic rigidity predicts cardiovascular disease and stroke even better than blood pressure.
 - 2. It wastes cardiac work or energy.

Examples: Anti-hypertension therapy for DynaPulse hemodynamic values

Blood Pressure (SBP/DBP)	Cardiac Output (CO)	Peripheral Resistance (SVR)	Brachial Rigidity Distensibility (BAD)	Systemic Vascular Compliance (SVC)	LV dP/dt Max	Implications for Therapy
150/100	Normal	High	Increased as expected	Increased as expected	Normal	Classic antihypertension Therapy
142/92	High	Normal	Normal as expected	Normal as expected	Normal	Non-medicinal therapy and close observation warranted
164/96	High	High	Increased	Normal as expected	Normal	Calculate body mass index consider ACE/ARB
183/106	Normal	High	Increased	Increased as expected	Normal	Classic antihypertension Therapy
174/82	High with high stroke output	High	Increased as expected	Increased	Normal	Loop diuretic and/or alpha blocker based therapy
182/71	Normal	Normal	Increased more than expected	Increased more than expected	Normal	Classic antihypertension Therapy to include ACE/ARB plus nitrates
154/102	High	Normal	Increased as expected	Increased as expected	High	Beta-blocker plus anxiolytic therapy

Appendix A: DynaPulse Case Studies and Other Case Reports (Clinical Utilities)

Through the efforts of numerous worldwide clinical studies, collaborations, and independent patient participation, Pulse Metric, Inc. has also identified many interesting cases in which the DynaPulse hemodynamic monitoring technology has enabled clinicians to more effectively manage and treat patients with cardiovascular disease. In this Case Studies section, we share the findings of such cases. Included below, for references, are some published case reports that applied hemodynamic monitoring in cares of hypertension and related cardiovascular diseases.

DynaPulse Case Studies

Case #1:

Patient Background & History: A 36-year-old male, Chinese, has experienced symptoms with shortness of breath and palpitations, on and off, since early February of 2000. His physician recorded the following: ECG showed left axis deviation and premature ventricular contraction. Echocardiogram examination revealed mild mitral regurgitation and mild tricuspid regurgitation. Stress test was negative. He was quite well until June 5th, when the episode of palpitations reoccurred. ECG then showed frequent PVC. Ambulatory 24 hours Holter ECG revealed 16597 isolated PVC and 20 couplets PVC but no short runs of VT. Mexitil was prescribed and the patient's condition stabilized. Since May 15th, 2000, he was further advised to monitor cardiac, blood pressure, and hemodynamic functions using DynaPulse at home. The patient is currently stable and receiving medication with propafenone (Rytmonorm) 150mg b.i.d. under diagnosis of cardiac arrhythmia. Propafenone is a class 1C drug that has sodium channel blocking activity and also beta-adrenergic blocking properties.

DynaPulse Monitoring & Data Analysis: On May 15th, 2000, patient experienced an episode of arrhythmia. His physician, then, provided (prescribed) him with a DynaPulse 200M home monitoring device, and the patient was instructed to take a series of blood pressure measurements at home for a period of 15 days. Blood pressure and waveform data were collected by DynaPulse, and then transmitted to Pulse Metric's DynaPulse Analysis Center (DAC) for hemodynamic analysis. Blood pressures, Pulse Pressures (PP), Heart Rate (HR) and other hemodynamic parameters were recorded and analyzed during the observation period. A cardiac event (angina) was captured. Trending of changes in blood pressure, cardiac function, and vascular condition were analyzed and later evaluated. When compared to their normal mean values, PP and HR percentage changes were significantly different. PP and HR (Fig.1) were then plotted. The trend of proportional changes corresponding to time and the occurrence of the cardiac event are displayed. The percentage change of the PP/HR ratio against the mean was calculated as:

$(\Delta pp / \text{mean baseline PP}) : (\Delta hr / \text{mean baseline HR})$

Results & Observations: One day before the onset of the cardiac event (angina), over 40% elevation in PP was observed. Then, at 15 minutes before patient reported angina, a significant drop (50%), which is 10% below the mean, occurred. 15 min. later after patient reported the episode of angina, PP dropped another 35%. The PP stabilized in 30 min following the medication.

Comments & Opinions: The dramatic unidirectional shifting (85%) of PP within 24 hours from positive to negative vs. mean suggested the patient went from cardiovascular compensation to decompensation. The PP was stabilized following the medication in 30 min. Fig.2 shows the trend of PP/HR ratio changes. It indicates that before onset of the cardiac event, PP/HR ratio was significantly higher than the mean value (~2 times > normal range). Using the trend ratio change as cardiac function index could objectively provide a quantified indicator for predicting an upcoming event particularly among outpatients.

Figure 1.

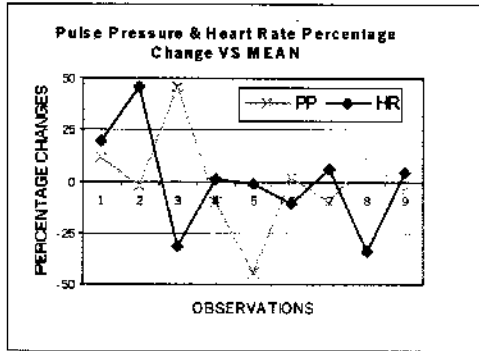
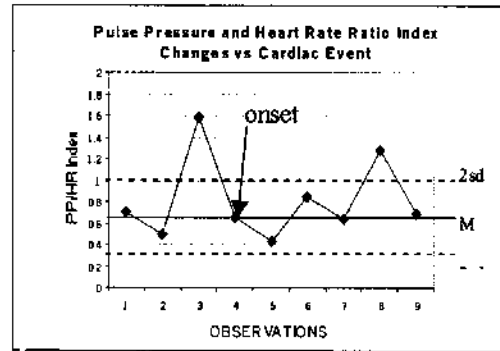


Figure 2.



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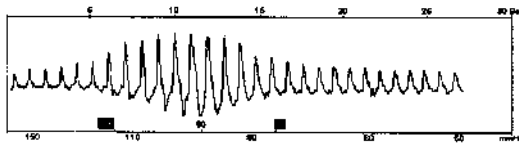
Case #2

Patient History: The patient is a 49-year-old hypertensive male who was diagnosed with paroxysmal atrial fibrillation in the fall of 1997. TEE was performed with successful DCC on December 11, 1997. However, the patient subsequently developed recurrent atrial fibrillation on December 20, 1997. Currently his symptoms persist and include occasional skipped beats, which occur mostly frequently during times of stress and fatigue. The patient experiences occasional dyspnea after the skipped beats and after climbing 2 flights of stairs. Other symptoms include fatigue, atypical left-sided chest discomfort described as a “dull ache” which is non-radiating in nature, and mild edema. Recently, persistent atrial fibrillation has occurred since August of 2000, resulting in episodes of awakening with a pause and jolt and periods of brief chest discomfort. The patient was treated with Amiodarone(800 mg/d) and Digoxin (0.25mg /qd), which was discontinued due to side-effects that included difficulty in speaking and a dramatic reduction in heart rate (40 bps).

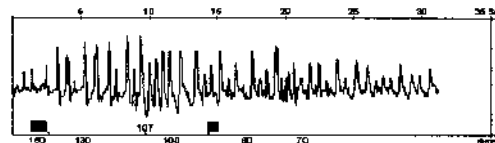
Procedure: The patient utilized the DynaPulse monitoring device to track his blood pressure and episodes of atrial fibrillation. A total of 212 DynaPulse hemodynamic measurements were obtained over a 9 month period, beginning in March of 2000. The hemodynamic measurements obtained included blood pressure (SBP, DBP, MAP, PP), cardiac function parameters (HR, LVdP/dt, LV contractility, and LV ejection time), systemic parameters (systemic vascular compliance and systemic vascular resistance), and brachial artery parameters (brachial artery compliance and brachial artery distensibility). In addition, pulse waveforms were also recorded for later morphological analysis. These data were obtained by the patient in his home and were analyzed retrospectively. A major focus of data analysis was to correlate associated hemodynamic changes with AF episodes over time. A blinded analysis of DynaPulse waveforms was performed to assess the device’s ability to detect AF episodes, and the results were then correlated with the patient’s actual documentation of such events.

Results: From a total of 212 DynaPulse measurements, 7 AF episodes were identified.

Normal Waveform



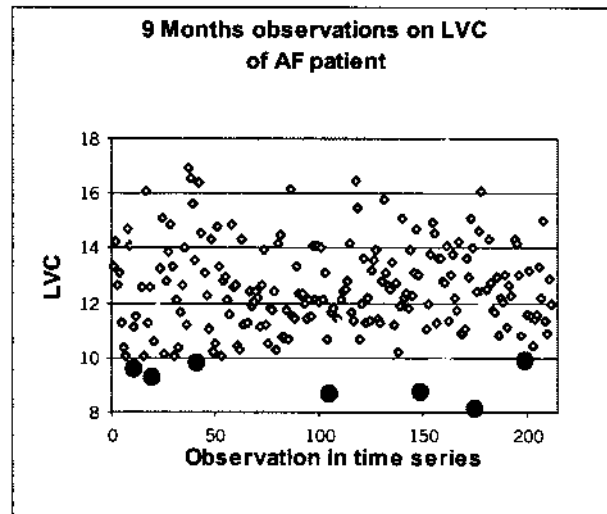
AF Waveform



Normal Waveform AF Waveform Moreover, a significant reduction in LV contractility preceded all AF episodes, which was correlated to the patient’s reported atypical left-sided discomfort that also preceded the AF episodes. In all cases, the patient’s LV contractility dropped a minimum of 2 standard deviations from the overall mean, which occurred between 3 and 8 hours prior to onset of the episode (mean = 5.5 hours prior to onset of the episode).

Comments: The sudden onset of atrial fibrillation (AF) may cause palpitations, angina pectoris and a decrease in cardiac output. Short-term predictability of the occurrence of AF for outpatients is difficult and

has rarely been reported due to the lack of an appropriate tool to noninvasively measure hemodynamic changes. A decrease in LV contractility has been reported to occur during an AF event, and the results of this case study further indicate that a sudden decrease in LV contractility also occurs prior to the AF episode. Therefore, this study suggests that it may be possible to predict the occurrence of such cardiac events through the use of noninvasive hemodynamic monitoring technology.



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Case #3:

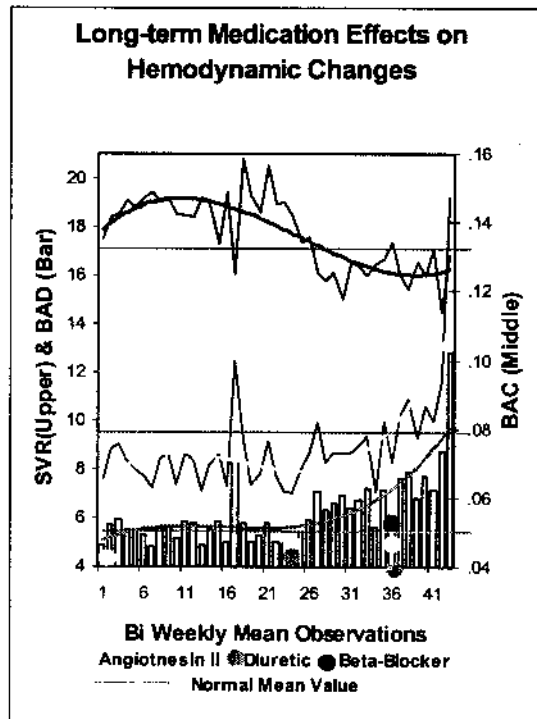
Patient History: A 72-year-old white male has been diagnosed as hypertensive for about 30 years. Medical history includes prostate surgery in 1988, kidney stone removal in 1991, mini-stroke in 1992, chest pains in 1991 and 1998, and gallbladder removed in 1998. The patient's daily medications include: Angiotensin II Inhibitor (Diovan®, Novartis 160mg/day), Diuretic (Aldactone® spironolactone 50mg/day) and beta blockade (Toprol-XL®, Zeneca) for blood pressure reduction. Other medications include: Levoxyl, Aspirin, and Zantac plus Multi-Vitamin. The blood chemistry readings were normal with the exception of a higher than normal glucose range in February of 1998 (193) and triglycerides in March of 2000 (264). Hematology and differential are normal. In addition to mild hypertension, which is now under control, the patient has also experienced irregular heartbeats since November of 2000.

Procedure: A total 372 DynaPulse measurements have been acquired over a period of 27 months, and include blood pressure (BP) other hemodynamic parameters such as Systemic Vascular Resistance (SVR), Brachial Artery Compliance (BAC), and Brachial Artery Distensibility (BAD). Measurements were collected by the patient himself at home and retrospectively analyzed. Results were compared to a normal population of males (N=877), and each individual parameter was trended and plotted against the patient's medication history.

Results: The results demonstrate an overall improvement in blood pressure and hemodynamic parameters, all of which are statistically significant. Patient reported episodes of arrhythmia as indicated by abnormal DynaPulse waveforms and verified via Holter monitoring. The patient's SVR, BAC, and BAD were compared to those obtained from the same age group within the normal population, demonstrating a lower initial BAC and higher initial SVR. The patient's Hemodynamic condition improved (as measured by SVR, BAC, and BAD), and these improvements were correlated to medication adjustments. Angiotensin II (Diovan®, Novartis 160mg/day) alone did not result in significant changes of any parameter in the early treatment stage, however Angiotensin II combined with a diuretic (Aldactone® spironolactone 50mg/day) resulted in a clear reduction of SVR and elevation of BAC and BAD. The extra addition of beta blockade (Toprol-XL®, Zeneca) to the drug treatment regime resulted in maintenance of the reduced SVR while simultaneously further improving the patient's BAC and BAD.

Comments: Demonstration of the long-term effects of drug therapy on hemodynamic parameters has been scarcely reported largely due to the lack of appropriate tools and methodology. Monitoring changes in hemodynamic parameters such as SVR, BAC and BAD in chronic Cardiovascular Disease (CVD) patients

over the course of treatment is essential for the optimization of therapy. Significant improvements in these hemodynamic parameters during the course of treatment were clearly documented in this case, demonstrating the clinical value of routine monitoring of blood pressure and hemodynamic changes.



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Other Case Reports* : Hemodynamic Clinical utilities

Case A: Determining Whether Changes in the Medical Regimen are Warranted

This 65 year old man with dilated cardiomyopathy of seven years duration, and a left ventricular ejection fraction of 12%, presented for a routine periodic evaluation. He denied any symptoms of heart failure over the preceding months, on a regimen of quinapril 20 mg bid, furosemide 80 mg qd, and digoxin 0.25 mg qd. The patient had been intolerant of beta-blockers in years past due to profound bradycardia. Physical examination was notable for a blood pressure of 120/90 mm Hg, a jugular venous pressure of 6 cm, a soft S₄ gallop, and a chronic grade I/IV mitral regurgitant murmur. Non-invasive hemodynamic analysis revealed a CI of 1.7 and an SVR of 2249. In spite of the patient's asymptomatic state, this change in his hemodynamics led to a recommendation to increase his quinapril to 40 mg bid.

Upon repeat evaluation four weeks later, the blood pressure was 108/72 mm Hg, the jugular pressure 5 cm, and the cardiac examination unchanged. Non-invasive hemodynamic analysis showed a CI of 2.4 with a SVR of 1398. In view of achievement of these normal hemodynamic values, no changes were made in his medications on this visit. With the exception of minor changes in diuretic therapy, the patient has remained asymptomatic on this stable medical regimen for over two years.

Case B: Assessing Hemodynamic Correlates of a Change in Symptoms

This 71 year old woman with idiopathic dilated cardiomyopathy, an eight year history of symptomatic congestive heart failure, and an ejection fraction of 25% presented with complaints of fatigue, lethargy, and

thirst on a regimen of lisinopril 20 mg qd, digoxin 0.125 mg qd, and bumetanide 2 mg qd. Examination showed a blood pressure of 84/60 mm Hg, a pulse in the 80s in chronic atrial fibrillation, a jugular pressure <5cm, clear lungs, no gallop, and no organomegaly or pedal edema. Non-invasive hemodynamics showed a CI of 2.5 with a SVR of 1497. As it was felt that her symptoms were likely related to volume depletion, diuretics were temporarily discontinued and she was scheduled for a follow up visit, with instructions to measure her weight daily in the interim.

Two weeks later she presented with complaints of abdominal fullness and a 1 lb weight gain, without dyspnea or peripheral edema. The blood pressure was 100/80 mm Hg, the pulse 85, and the neck veins now 12 cm in height. There was a grade I/VI mitral regurgitant murmur and moderate hepatomegaly, with no peripheral edema. Hemodynamics showed a CI of 1.6 with a SVR of 2883. Despite the minimal weight gain, it was apparent that the patient was significantly volume overloaded and bumetanide was resumed at its previous dose. She was also instructed to begin metoprolol 25 mg qd after resumption of the bumetanide.

Two weeks later a repeat evaluation revealed complaints of minimal dyspnea, with a blood pressure of 90/60 mm Hg, a heart rate of 90, a weight decrease of 1 lb down from the previous visit, and the neck veins now 8 cm in height. The CI was now 2.2 and the SVR 2710. Metoprolol was increased to 50 mg and subsequently to 100 mg daily.

Evaluation four weeks later showed a blood pressure of 96/60 mm Hg, a pulse rate of 80, a weight decrease of one more pound, and an otherwise unchanged examination. The CI at this time was 2.7 with an SVR of 1626. The patient's symptoms, physical findings, and hemodynamics remained stable over the ensuing two years on this medical regimen.

Case C: Tracking Trends in Hemodynamic Parameters After Alterations in Drug Therapy

This 79 year old man presented to the outpatient clinic on continuous home dobutamine. After a 30 year history of progressive dilated cardiomyopathy, with an ejection fraction of <15%, he was hospitalized for progressive heart failure despite aggressive outpatient medical management. Pulmonary artery catheterization revealed a CI of 1.3, which increased to 2.0 while on dobutamine. Multiple attempts at discontinuation of the drug proved futile and he was eventually discharged on an infusion of 5 mcg/kg/min of continuous dobutamine.

After six weeks of continuous home dobutamine he presented for an outpatient visit. In addition to dobutamine, he was on spironolactone 25 mg qd, lisinopril 10 mg qd, digoxin 0.25 mg qd, and furosemide 80 mg qd. He felt well, was able to walk one mile without dyspnea, and now denied any symptoms of heart failure. The blood pressure was 110/67 mm Hg, the pulse in the 80s in chronic atrial fibrillation, the central venous pressure normal, and the remaining exam notable only for a grade II/VI mitral regurgitant murmur. Non-invasive hemodynamics showed a CI of 2.8 and a SVR of 1081. In view of these excellent hemodynamics and the patient's asymptomatic status, dobutamine was discontinued in the office while undergoing continuous hemodynamic monitoring. Surprisingly, over the ensuing hours his hemodynamics remained unaltered despite discontinuation of the dobutamine infusion. The patient was sent home off IV dobutamine and on escalating doses of metoprolol.

Over the ensuing weeks he remained clinically stable and repeat non-invasive hemodynamics showed a CI of 2.9 and SVR of 932, despite the reinstatement of metoprolol and the discontinuation of dobutamine.

Three months later, a periodic follow up was done with the patient on metoprolol 100 mg qd, lisinopril 20 mg qd, spironolactone 25 mg qd, digoxin 0.25 mg qd, and furosemide 80 mg qd. He complained of fatigue but was still able to walk one mile without dyspnea, and denied having orthopnea or pedal edema. Physical examination revealed no evidence of volume overload but non-invasive hemodynamics showed a CI of 1.8 and SVR of 1752. In view of the increased SVR and reduced CI, lisinopril was increased to 20 mg bid and, in hopes of achieving further sympathetic withdraw, metoprolol was increased to 150 mg qd. The patient has been stable on this clinical regimen and remains asymptomatic.

Case D: Establishing Baseline Hemodynamic Parameters After Alterations in Drug Therapy

This 37 year old woman was referred for management of chemotherapy induced dilated cardiomyopathy initially manifest as pulmonary edema and hypotension. The ejection fraction was demonstrated to be 20%. Symptomatically she improved on digoxin 0.125 mg qd, furosemide 40 mg qd, isosorbide mononitrate 60 mg qd, lisinopril 20 mg bid, and amiodarone. Physical examination revealed a blood pressure of 94/76 mm Hg with overt pulsus alternans, a pulse rate of 108 and a loud S₄ gallop, but no jugular venous distention or edema. Non-invasive hemodynamics showed a CI of 1.4 with systemic vascular resistance of 2900. Metoprolol was begun at a dose of 25 mg daily.

One week later she returned, still complaining of fatigue but with no symptoms of dyspnea. The blood pressure was 80/60 mm Hg and the pulse 84; the pulsus alternans had resolved and the S₄ gallop was unchanged. The CI was 2.1 and the SVR was 1500. Metoprolol was doubled to 50 mg daily.

Over the ensuing weeks the metoprolol was increased to 100 mg daily and the CI rose to 2.4 with a SVR of 1475. Orthostatic hypotension became problematic so lisinopril was reduced to 10 mg daily and isosorbide mononitrate was discontinued.

Over the next two months her symptoms improved and physical examination remained unremarkable except for a rise in the blood pressure to 130/60 mm Hg. At that point the CI was 2.4 with a SVR of 1338. Metoprolol was increased to 200 mg daily and digoxin was discontinued.

Over the ensuing two years the patient did well on continued medical therapy and the ejection fraction rose to 0.35. In view of this, and the fact that her hemodynamic parameters did not change, her lisinopril and furosemide doses were reduced by half. She remains clinically stable.

Case E: Measuring Hemodynamics on Periodic Follow up Visits

This 80 year old man with ischemic dilated cardiomyopathy was referred for optimal medical management because of continuing problems with fatigue despite therapy with furosemide 40 mg bid, losartan 50 mg bid, doxazosin 2 mg qd, and amiodarone. Physical examination revealed a blood pressure of 122/70 mm Hg, a pulse of 60, flat neck veins, a grade III mitral regurgitant murmur, and a S₄ gallop. There was no organomegaly or peripheral edema. Non-invasive hemodynamics showed a CI of 4.0 with a SVR of 770. It was recommended that he begin beta-blockade and in view of his low SVR, metoprolol (rather than carvedilol) was selected as the drug of choice, at an initial dose of 25 mg/day.

Two months later he returned complaining of lethargy on this new regimen. The blood pressure was 70/48 mm Hg, the pulse 58, and the cardiac exam notable only for a soft mitral regurgitant murmur and a S₄ gallop. The CI was 5.2 and the SVR was 428. Furosemide was discontinued and losartan was reduced to 50 mg qd.

On subsequent visits the blood pressure rose to 110/78 mm Hg, the pulse was 52, and the remaining cardiac exam unchanged. The CI was now 4.8 and the SVR 751. On this regimen the patient felt remarkably better.

Over the ensuing two years he remained clinically stable, on 100 mg of metoprolol daily, with unchanged hemodynamics.

Case F: Using Hemodynamic Data in Patients with AV Sequential Pacemakers to Optimize Cardiac Output

A 48 year old white female with a history of an aortic valve replacement and a right ventricular infarct requiring the insertion of a dual chamber pacemaker and heart failure symptoms NYHA Functional Class III-IV was evaluated for a heart transplant. Upon examination she complained of chronic dyspnea on exertion, orthopnea, and fatigue with a decrease in exercise capacity limited to 50 feet. These symptoms started after the aortic valve replacement and became progressively worse in the last two years. Reviewing

her medical records it was found that she had a right ventricular infarction secondary to a surgical sacrifice of the right coronary artery. The latter required the insertion of a dual chamber pacemaker. In addition, she previously had ventricular arrhythmias treated with amiodarone. She was admitted to the telemetry unit for evaluation. Her past medical history was also significant for hypothyroidism. Her physical examination revealed a blood pressure of 100/80 mm Hg in both arms, a heart rate of 60, a right ventricular lift, tricuspid regurgitation, jugular venous pressure of 10 cm, and bilateral lower extremity edema. Medication at the time of admission were: coumadin 5 mg/day, synthroid 0.1 mg/day, torsemide 20 mg twice a day, aldactone 100 twice a day, and cordarone 200 mg once a day. Her ECG revealed sinus rhythm with a rate of 58 and a right bundle branch block. An echocardiogram revealed a dilated right ventricle and right atrium, a normal functioning prosthetic valve in the aortic position, and a normal left ventricular function. A non-invasive assessment of hemodynamic parameters was performed and revealed a CA of 4.2 L/min and a CI of 2.1. Her laboratory tests were normal and her TSH was within the normal limits. The decision was made to non-invasively measure her hemodynamic parameters continuously and interrogate the pacemaker, to change the settings, in order to achieve a better CO. Upon interrogation of the pacemaker, several modifications in its settings were performed and hemodynamic parameters were measured at the same time. When the rate was modified to 85 bpm and the AV interval was modified to 180 msec, the CO increased to 6.0 L/min and the CI to 3.2. The changes represented a 30% increase in these hemodynamic parameters; the patient had a brief episode of flushing that abated quickly. She was discharged the next day and at the time, she was walking 250-300 feet without dyspnea or fatigue. Two months later the patient continued to do well and hemodynamic parameters remained normal (CI of 3.0).

Case G: Using hemodynamic data to help in the diagnosis of patients with “decompensated heart failure”

A 48 year old female with known history of dilated cardiomyopathy, hypertension, and an embolic stroke presented with worsening dyspnea on exertion for the previous three months. She also complained of weight loss, loose bowel movements, and occasional dizziness. In addition, she had multiple admissions in the recent past for decompensated heart failure. A previous evaluation included an echocardiogram and left heart catheterization. Both studies demonstrated an abnormal ventricular function with ejection fraction of 30% and normal coronary arteries. Despite adequate treatment for heart failure she continued to be symptomatic and, therefore, was being seen for further evaluation and treatment.

Physical examination was significant for sinus tachycardia (rate of 120), S₃ gallop, and a slightly enlarged thyroid gland. A non-invasive assessment of hemodynamics was performed, revealing a CO of 11 L/min, CI of 5.0, and SVR of 640. Blood pressure was 130/70 mm Hg. Because of her history and as a result of her abnormal hemodynamic status, thyroid function tests were performed and the results were: TSH < 0.08 mU/L (nl 0.047-5 mU/L), thyroid hormone 3 uptake (T3U) >55% (nl 24-39%), thyroid hormone 4 (T4) 22.8% (nl 5-11.4%). Based on these results and history, the diagnosis of hyperthyroidism was entertained and methimazole 10 mg per day was started. The patient was discharged home and after a three-month follow up, heart failure symptoms were resolved. Hemodynamic parameters measured non-invasively demonstrated a normalization of CO and systemic vascular resistance.

* referenced from ICD-9: 414.9 Chronic Ischemic Heart Disease; 428 Heart Failure; 786.5 Chest pain; 785.1 Palpitation, etc. sources, 2000-2003

Appendix B: Comments from physicians

Dr. E. Urbina (031908):

Hypertension experts realize that BP levels alone are insufficient in managing patients. There may be subtypes of BP (central sympathetic stimulation, renal angiotensin mediated, arterial stiffness abnormalities) and drugs affect vascular tone, stiffness and wave reflections in different manners. These observations may explain the beneficial effect on reversal of LVH seen with ACE and ARBs not seen with beta-blockers.

Dr. A. Delgado (030208):

“Dear Dr. Chio: I am very happy with your 'Clinical Assessment of Hypertension', specially because the entire literature still relies on the simple brachial measurements, while hemodynamics remain an specialized tool for basic or clinical research, rarely obtained in routine medical practice. On the other hand, I strongly support your approach, sending addition to your draft in simpler words as for GP physicians. ...”

Dr. Delgado, with his years of experiences, had suggested extending DynaPulse hemodynamic assessments with following additional clinical evaluations for advanced hypertension and CVD patient management:

- (I) *Evaluation of drug effects on cardiovascular hemodynamic, including aortic index parameters (Augmentation Index, Time of Reflection Wave, and Pulse Wave Velocity) derived from the analysis of Supra-systolic DynaPulse tracing.
- (II) ‡Evaluation of Cardiovascular Response to Isometric Hand-Grip Test (HGT), defined as changes in cardiovascular hemodynamic ($\geq 15\% \leq 25\%$) 3 minutes after starting the test in treated hypertensives.
- (III) § ECG/EKG evaluation
- (IV) **Ion Transport Studies (plasma, erythrocyte and Urine K/Na)

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