SPECIAL REPORT

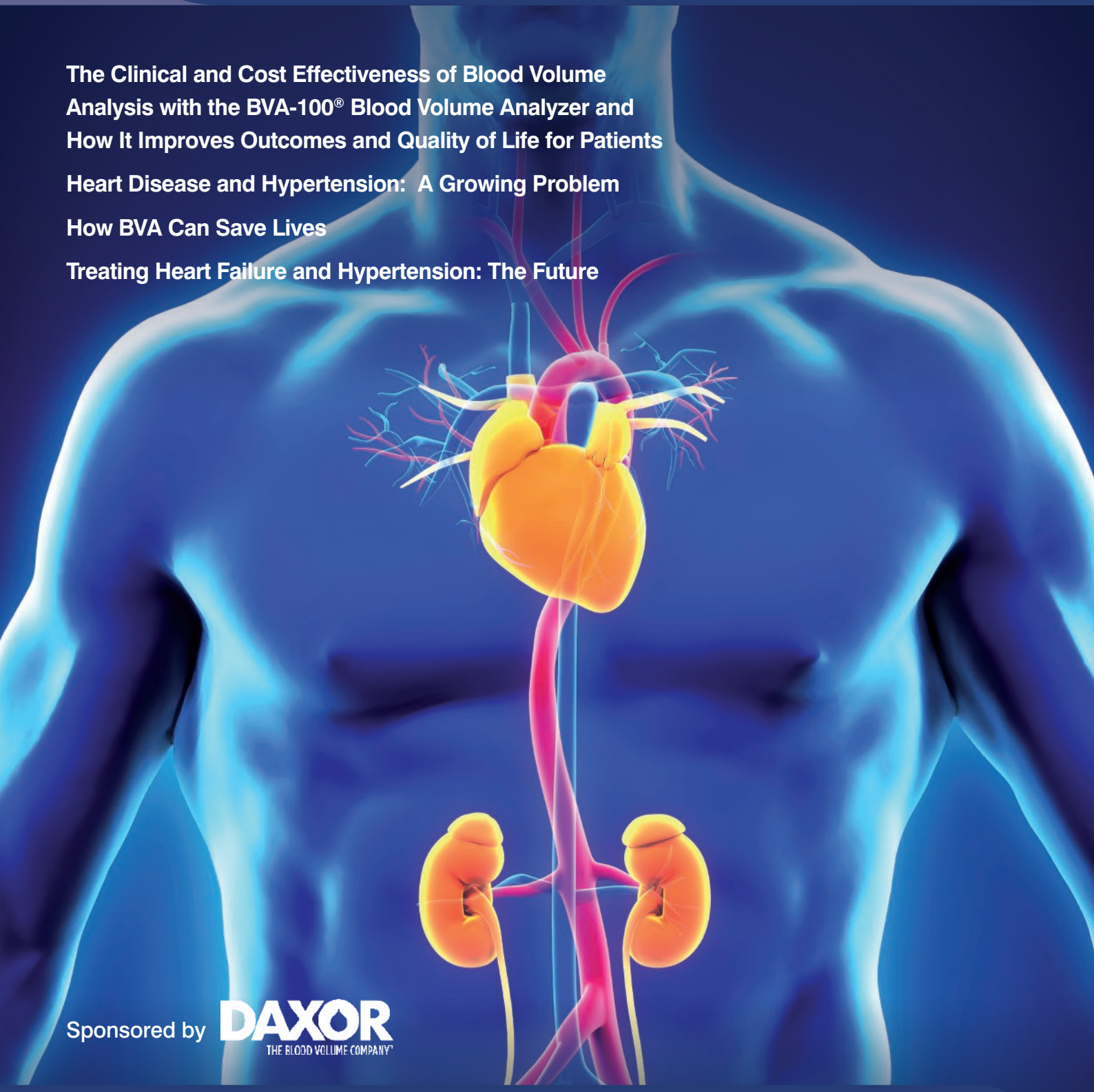
Improving Outcomes for Patients with Heart Failure and Hypertension and the Role of Blood Volume Analysis

The Clinical and Cost Effectiveness of Blood Volume Analysis with the BVA-100® Blood Volume Analyzer and How It Improves Outcomes and Quality of Life for Patients

Heart Disease and Hypertension: A Growing Problem

How BVA Can Save Lives

Treating Heart Failure and Hypertension: The Future



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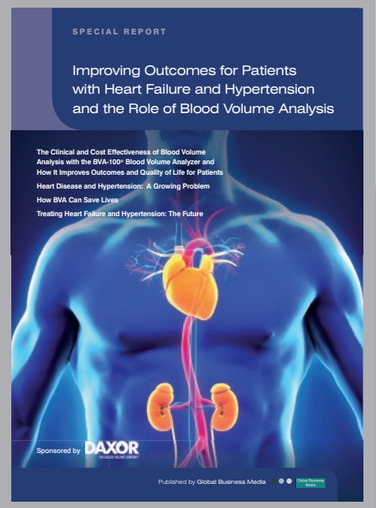

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Foreword

MILLIONS OF people suffer from heart failure worldwide and those numbers keep growing, and so does the burden on health providers. The challenge is to reduce the number of deaths, manage costs and improve patients' quality of life. For that, early intervention is critical but managing this is easier said than done.

Our opening article comes from the Daxor Corporation. The BVA-100 Blood Volume Analyzer is a one of a kind diagnostic test that measures total blood volume, calculates patient specific ideal volumes and translates that into a percentage deviation from the norm. In numerous studies it has been shown to deliver dramatic improvements in accuracy and reliability over traditional indirect methods and clinical observation.

Elsewhere in this Report, Jo Roth will look at the evolution of the BVA test – how it works and the growing body of evidence which suggests this could lead to dramatically improved outcomes for health providers and patients. Both need a new approach to treatment. Inadequacies in monitoring and diagnosis and identification of risk factors such as hypertension mean survival rates and quality of life are much lower than they should be. Many people with hypertension go undiagnosed as the specific medicine (dilator or diuretic) is not MATCHED to the cause or driver of hypertension - something that can only be done with blood volume measurement, which means many of the people most at risk of heart disease are not taking remedial action which could save their lives.

Inevitably, this means health providers will be struggling to cope with the financial burden of managing heart failure and, as we move into the future, the costs are likely to grow. As James Butler discovers in our final article, focus is growing on preventative measures which can identify symptoms sooner, improve monitoring and reduce the impact on struggling health providers. Research is driving new guidelines which, in turn, are changing treatment methods. Technology is increasing the amount of data at the hands of clinicians to make assessments. All these innovations will be crucial as health providers move to manage the growing burdens being placed upon them.

Tom Cropper
Editor

***Tom Cropper**, has produced articles and reports on various aspects of global business over the past 15 years. He has also worked as a copywriter for some of the largest corporations in the world, including ANZ Bank, ING and KPMG.*

IMPROVING OUTCOMES FOR PATIENTS WITH HEART FAILURE AND HYPERTENSION AND THE ROLE OF BLOOD VOLUME ANALYSIS

The Clinical and Cost Effectiveness of Blood Volume Analysis with the BVA-100® Blood Volume Analyzer and How It Improves Outcomes and Quality of Life for Patients

Daxor Corporation

Heart failure and hypertension are major public health concerns as well as significant financial burdens to the US healthcare system. Providing evidence-based care is crucial to improving patient outcomes and managing costs. The BVA-100® Blood Volume Analyzer test offers a major advance in informing clinicians of the patient's actual total intravascular blood volume, red blood cell volume and plasma volume vs. the patients ideal volumes based on height, weight and gender with 98% accuracy so they can optimize treatment plans and individualize care, therefore improving outcomes and reducing duration and cost of care.

The Burden of Heart Disease and Hypertension[1, 2, 3]

Over 6 million Americans have heart failure and by 2030, the prevalence is expected to increase by 46%. The lifetime risk of developing heart failure currently stands at one in five with nearly half of patients dying within five years of diagnosis. Aside from the danger to health and well being, heart failure represents a $31+ billion annual financial burden to the US healthcare system and remains the leading cause of hospital 30-day readmissions with Medicare penalties costing hospitals $564 million in 2017.

Linked to this is the fact that more and more Americans suffer from high blood pressure. About one in three adults or approximately 75 million people have high blood pressure with only about half having their high blood pressure under control. That puts them in the higher risk category for a range of health conditions. Seven out of ten people having their first heart attack also have high blood pressure. The same figures hold true for people with chronic heart failure while 80% of those having their first stroke have high blood pressure. People who have kidney disease are also significantly more likely to have problems with their blood pressure.

The Link Between Hypertension and Heart Failure

Over 70% of heart failure patients have a known history of hypertension.[4] Heart failure is a condition where the heart is unable to pump enough blood through the body. This happens when blood vessels become narrow or blocked caused by high blood pressure or hypertension therefore increasing the risk of developing heart failure. Narrowed arteries are less elastic and make it difficult for blood to flow, causing the heart to work harder. In order to cope with the increase in demand, the heart muscle thickens and become larger. The heart has to pump more but becomes less efficient.[5]

Clinicians have a choice between dilator and diuretic therapy for hypertension control. Controlling pressure the "wrong way" i.e. dilators for volume-expansive hypertension, or diuretics for vasoconstrictive hypertension could lead to poor long term results because symptom relief of excessive pressure will not mitigate the underlying volume derangement driving cardiovascular remodeling or danger of kidney damage. Chronic heart failure patients suffer from symptoms of intravascular volume overload and increased cardiac fill pressures. The mainstay of treatment remains diuresis but without knowledge of the actual intravascular blood volume, diuretic intervention could potentially lead to poor outcomes.

Heterogeneity in TBV & RBCV Status Is Common

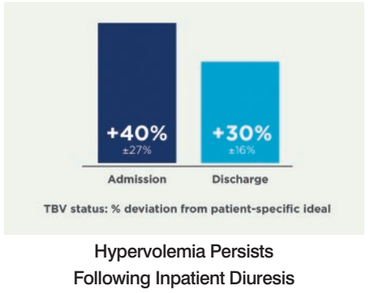
The accurate assessment of volume derangements to achieve "euvolemia" (a term

Over 70% of heart failure patients have a known history of hypertension

Being able to distinguish between dilutional versus true anemia is critical in making decisions around red cell management (such as IV Iron, transfusions, EPO use and phlebotomy), as well as getting the patient to an overall level of total ideal volume or euvolemia

used to describe a patient's' ideal volume status) remains a significant challenge as heterogeneity in total blood volume and red blood cell volume status is quite common.

In a prospective observational study from the Mayo Clinic, heart failure patients were evaluated for volume status at admission and discharge to determine the magnitude and distribution of blood volume, and body water changes following diuretic therapy. Clinicians blinded to the BVA results showed that standard care resulted in poor discharge volumes when standard assessments were used. While diuretic therapy decreased hypervolemia, many or most of the patients were still hypervolemic at discharge versus admission (30% vs. 40%) despite an average body weight loss of 6.9 kilograms. Eighty-five percent of overall fluid loss during diuresis was derived from the interstitial rather than the intravascular space.[6]



Hypervolemia Persists Following Inpatient Diuresis

The investigators concluded that the extent, composition, and distribution of volume overload in decompensated heart failure are highly variable, and this variability needs to be taken into account in the approach to individualized therapy instead of a "one size fits all" decongestion strategy.
Red blood cell volume derangements are far more prevalent that thought as shown in a study of 245 patient admissions in a published study in JACC-Heart Failure whereby true anemia was present in 62% of the cohort and 11% of the patients were identified as polycythemic through direct blood volume analysis.[7]

Indirect Measures Offer Low Clinical Utility as Indicators of True TBV and RBCV

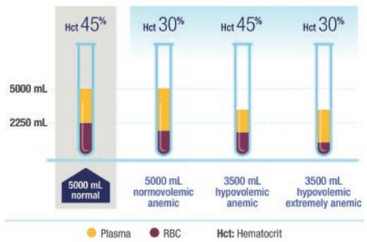
Volume management is a two-dimensional challenge: it is beyond "wet versus dry". The total blood volume must be normal and the composition of that blood must also be normal (i.e. not overly anemic or polycythemic). The literature sites that physicians currently rely on non-specific and inaccurate surrogate measures such as wedge pressure, mean arterial pressure, hematocrit, formula-based estimates, levels of brain natriuretic peptide and imperfect clinical assessment (signs of JVD or edema) to estimate blood volume. Being able to distinguish between dilutional versus true anemia is critical in making decisions around red cell management (such as IV Iron, transfusions, EPO use and phlebotomy), as well as getting the patient to an overall level of total ideal volume or euvolemia.

Clinical Assessment

Clinicians often rely on classical signs of physical congestion, including abnormal lung sounds, elevated jugular venous pressure, radiographic abnormalities and edema to assess intravascular blood volume status. Even when signs and symptoms of clinical congestion are relieved through diuresis or other therapy, patient may still have unrecognized volume overload and an increased risk for worsening prognosis and death. In a prospective study of ambulatory patients with heart failure, clinical assessment of volume status by a board-certified internist with specialty training in heart failure was correct only 51% of the time.[8]

HCT

Hematocrit (Hct) is a common indirect or surrogate measure of blood volume status. Hct is the ratio of the volume of red blood cells to the total volume of blood. It is normally 47% ±5% for men and 42% ±5% for women. It is considered to be an indirect measure because patients with the same Hct may be highly discordant in true RBCV status. The illustration shows that sample tubes 1 and 3 both have a normal Hct of 45%. However, true anemia is masked by hypovolemia in sample tube 3. Unlike Hct, direct BVA will quantify RBCV accurately and reliably even in volume deranged patients.



Volume Derangements Confounds Assessment of Anemia by Hct

Calculated Estimates

There is widespread use of formula-derived estimates of plasma volume in heart failure patients despite these methods having been proven to be inaccurate compared to measured volume. Plasma volume was measured using the BVA-100 in 110 patients with clinically stable chronic heart failure. These measurements were correlated using two different plasma volume estimation techniques. The first was the Kaplan-Hakim formula, which calculates blood volume using a formula calculating hematocrit relative to dry body weight. The second, the Strauss formula, estimates changes in plasma volume over time using hemoglobin and hematocrit measurement. The study ultimately showed neither formula demonstrated an accurate blood volume estimate compared to the BVA-100. These formulas varied in their accuracy between 16% and 68% compared to the BVA-100.[9]

"Indirect assessments of plasma volume or blood volume are limited by their inaccuracy. Our study shows that this is true for formula-based volume assessment or the measure of hemoconcentration, and similarly poor correlation has previously been shown for the physical exam and even intra-cardiac pressure assessment." – Dr. Marat Fudim, Duke University

Pressure is Not Volume and Volume is Not Pressure

A study presented at the 2018 Heart Failure Society of America (HFSA) Annual Meeting compared blood volume analysis to CVP, PCWP and dPAP. The findings revealed neither PCWP, CVP, nor dPAP accurate reflect intravascular volume as the correlation was 29%, 31% and 36% respectively. Patients with low filling pressures can have marked expansion of intravascular volume while patients with elevated filling pressures can have normal or even contracted volumes. Elevated cardiac pressures may, therefore, reflect hemodynamic congestion but not necessarily total volume overload or hypervolemia. The study concluded that while both demonstrate value, there is no substitute for direct measurement of blood volume, as pressures do not accurately reflect volume status and therefore should be an additional measure to blood volume analysis rather than a substitute when making treatment decisions in heart failure patients with potential volume overload.[10]

BNP

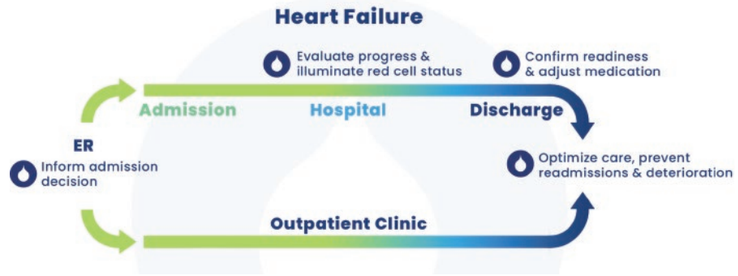
B-type natriuretic peptide (BNP) is a protein produced by the heart and is an indicator of left ventricular wall stress or myocardial stretch. High levels in the blood are indicative of diminished pumping capability of the heart and associated with a worse prognosis. BNP has been used as a noninvasive adjunct in the diagnosis of fluid overload and as a marker of the response to therapy in patient with heart failure. One study evaluated eighty-one critically-ill patients for blood volume derangements by measuring BNP levels and compared to direct blood volume measurement with the BVA-100. The results revealed that there was no relationship between BNP levels and blood volume when compared to the 98% accurate measures from the BVA-100.[11]

Another study compared blood volume and BNP in congestive heart failure patients. The data showed no relationship between changes in BNP and measured changes of blood volume which may help to explain why BNP has not proven a reliable marker to target for volume adjustment to euvolemia.[12]

The BVA-100 Solution

Clinicians have struggled to manage volume derangements because unlike the management of diabetes where blood sugar is measured, there has not been a rapid, accurate and objective way to measure blood volume abnormalities. The BVA-100 test changes that and offers an objective and reliable approach; it's a simple blood test and means clinicians can move away from subjective assessment towards more objective measurements. Education and awareness that a viable solution exists with the BVA-100 test can help to change the status quo.

The BVA 100 provides clinicians with accurate, actionable data to optimize treatment plans and individualize care improving outcomes and reducing the duration and cost of care. The illustration represents points of contact in heart failure care at which to consider direct blood volume analysis. The BVA-100 is reimbursed by Medicare and private insurers in both the inpatient and outpatient settings.



BVA-100 Impact Points

The BVA-100 Key Features

The BVA-100 Blood Volume Analyzer is a FDA-cleared diagnostic that measures of total intravascular blood volume, red blood cell volume and plasma volume. Users of the BVA-100 who prefer a shorter test time have the option to calculate blood volume using as little as three blood draws. The five point test reports blood volume and calculates a slope to give the measure of the albumin transudation rate which is an indicator of capillary permeability. All results are calculated with patient-specific ideal volumes based on height, weight and gender.

"Indirect assessments of plasma volume or blood volume are limited by their inaccuracy. Our study shows that this is true for formula-based volume assessment or the measure of hemoconcentration, and similarly poor correlation has previously been shown for the physical exam and even intra-cardiac pressure assessment."

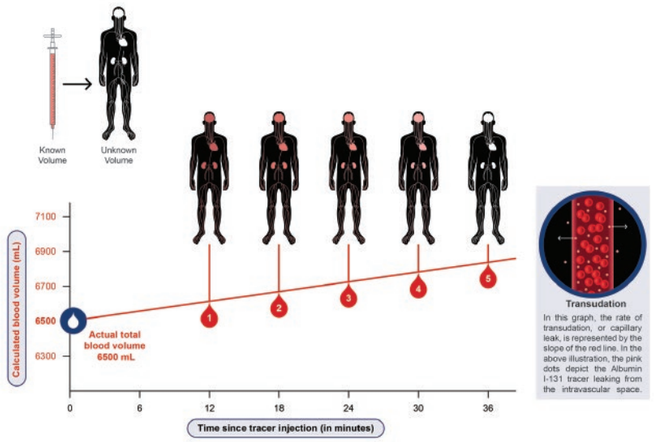
– Dr. Marat Fudim, Duke University

Saving lives and saving costs with direct blood volume analysis helps to guide individualized therapy in heart failure patients, reduces readmissions and eliminates the need for unnecessary surrogate tests

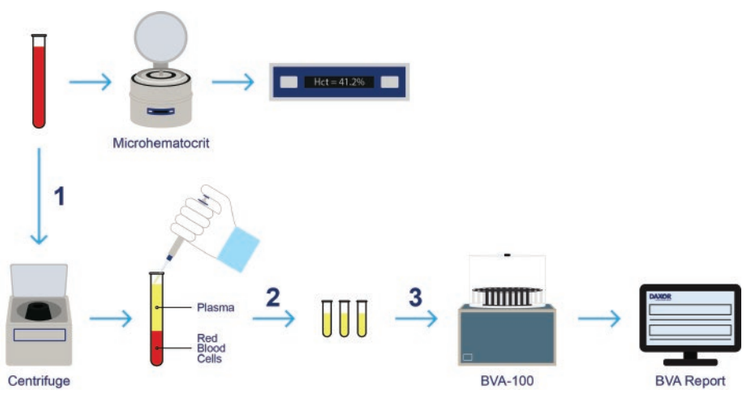
Basic Principle of Blood Volume Analysis

The BVA-100 Blood Volume Analyzer is recognized as the "gold standard" methodology in quantifying circulating blood volume. This radiolabeled albumin technique is recommended for quantitative assessment of blood volume by the International Committee for Standardization in Hematology for its precision and reproducibility compared to alternate methods. Normal values for this technique have been well established with 98% accuracy.[13, 14]

The illustration depicts the basic principle of how the BVA-100 test works. A dose of Volumex® Albumin I-131 tracer is injected intravascularly. Once the tracer has fully circulated in the bloodstream, a series of small blood samples are drawn. The BVA-100 automatically calculates patient blood volume by comparing the concentration of undiluted tracer prior to injection to the tracer concentration diluted in the patient blood samples.



The Indicator Dilution Technique



Three Easy Steps to Perform the BVA-100 Test

Blood samples are centrifuged to separate the red blood cells from the plasma and 1 cc aliquots of plasma are pipetted into counting tubes and then placed in the analyzer carousel along with corresponding standards.

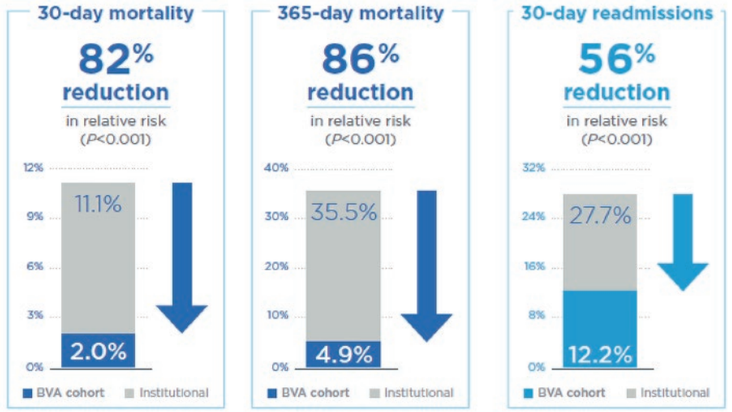
The BVA-100 generates a report that details measured, patient ideal, and deviation of measured from the patient ideal total blood volume, plasma volume, and red blood cell volume along with the rate of albumin transudation.

A Strong Body of Clinical Evidence

Since its introduction, studies have well-established the value of the BVA-100 test confirming that accurate blood volume analysis leads to better informed physicians, better treatment strategies, and improves patient outcomes and resource utilization. Highlights from a few key studies follow.

A landmark study in *JACC-HF - Outcomes with Volume-Guided Management* – is a first of its kind peer-reviewed study that showed improved outcomes when patients are treated using BVA results to guide their treatment path in heart failure. Propensity score control matching analysis was performed on a mixed (HFpEF/HFrEF) cohort of 245 serial admissions for heart failure in a community hospital. The study found that volume heterogeneity in TBV and RBCV is highly prevalent amongst HF patients which means a one-size fits all treatment strategy is inadequate. Sixty-six percent of the cohorts on admission had some degree of plasma volume expansion. Thirty-seven percent were hypervolemic (TBV > 10%) based on the BVA. True anemia (RBCV < -10% based on BVA) was present in 62% of the patients, which was surprising finding as heart failure protocols often do not address anemia. In addition, 30-day readmissions were reduced by 56% and mortality by 82%, and 365-day mortality was reduced by 86% compared to match controls. Researchers noted that the one year mortality rate was reduced from 35% to less than 5% in the BVA-guided arm.[7]

A separate observational analysis presented at the Heart Failure Society of America in 2016 examined the risk factors at discharge for 30-day readmission among 50 patients who had BVA on admission for signs and symptoms of heart failure. Only 11% of those patients discharged with normal TBV and RBCV were readmitted as compared to the Medicare HF rate of 22%, and showed a strong association of severe persistent congestion and/or anemia with 30-day readmission risk. Eighty-eight percent of patients who experienced 30-day readmission had an identifiable risk factor; 47% were anemic at discharge of which 62% were readmitted and 41% were hypervolemic of which 50% were readmitted.[15]



Outcomes Improved with Individualized Care Guided by Direct Blood Volume Analysis

Research was presented in *The American Journal of Cardiology* whereby unrecognized hypervolemia in chronic heart failure was evaluated with the BVA-100 in relation to clinical status, hemodynamics and patient outcomes. Correct clinical assessment of volume status was achieved only 51% of the time. Patients who were normovolemic or hypovolemic had a 0% risk of death during the entire study whereby hypervolemic patients had a risk of death of 39% at 1-year and 55% at 2 years. The investigators concluded that clinically unrecognized intravascular volume overload may contribute to worsening symptoms and disease progression in patients with chronic heart failure.[8]

Persistent volume overload congestion and renal dysfunction have been hallmarks of poor outcome and shown to be significant prognostic factors in patients with chronic heart failure. Whether volume interacts with renal function or markers of renal function to exacerbate or mitigate the risk associated with chronic kidney disease (CDK) in patients with heart failure remains an incompletely understood issue. Investigators from the Mayo Clinic assessed the outcomes contribution of intravascular volume status (mild-moderate vs. severe plasma volume expansion) to CKD-related risk markers such as serum creatinine, eGFR, BUN and NT-pro-BNP in patients with chronic HF. The results showed that blood volume has a direct connection with kidney function, demonstrating additional risk in patients with both heart failure and impaired kidneys. The use of the BVA-100 provided investigators with accurate plasma volume measurement in order to assess total risk.[16]

Cost Effectiveness

The reality of modern healthcare is that clinical effectiveness is only part of the story. Heart failure represents a $30+ billion US economic burden. Over 6 million patients live with heart failure with over 1 million hospitalizations annually of which greater than 25% of patients are readmitted within 30 days. Clinicians need to assess any treatment on the basis of its financial burden.[1, 2]

The average cost for a heart failure admission is $14,000 with an average per-patient readmission cost of $3,500. BVA guided care can potentially reduce readmissions by 56% generating a potential savings of $1,500 per readmitted patient based upon this cost analysis.[17, 18]

Commonly ordered in-patient surrogate tests such as pulmonary wedge pressure, echocardiogram, BNP and EKG can add up to an additional cost of $1,900 per hospitalized patient. By incorporating blood volume analysis into standard clinical practice, this cost can be reduced by $1,000 per patient.[19]

The Centers for Medicare and Medicaid (CMS) has now instituted hospital penalties up to 3% for readmissions including heart failure. In 2017, 80% of hospitals were penalized at a cost of $564 million in lost reimbursement.[1, 2]

Saving lives and saving costs with direct blood volume analysis helps to guide individualized therapy in heart failure patients, reduces readmissions and eliminates the need for unnecessary surrogate tests. The BVA-100 test is fully reimbursed by Medicare and private payers in both the inpatient and outpatient settings.

Quality of Life

Maintaining a good quality of life to perform normal physical and social activities is as important as survival to most patients living with a chronic, progressive illness such as heart failure. Patients with heart failure often experience various physical symptoms such as difficulty breathing, fatigue, edema, and chest pain which are often due to volume overload and anemia that limits their ability to perform daily activities.[20, 21] Blood volume analysis with the BVA-100 test better informs clinicians of the true blood

At Daxor Corporation, we have always been passionate about delivering innovative medical instrumentation and biotechnology advances focused on blood volume analysis to improve patient quality of life and reduce the cost of healthcare

There is widespread use of formula-derived estimates of plasma volume in heart failure patients despite these methods having proven to be inaccurate compared to measured volume

volume status enabling customization of symptom management and optimized treatment strategies so heart failure patients can live longer, more productive lives and reduce their risk of hospital readmissions.

At Daxor Corporation, we have always been passionate about delivering innovative medical instrumentation and biotechnology advances focused on blood volume analysis to improve patient quality of life and reduce the cost of healthcare. The BVA-100 Blood Volume Analyzer is a rapid, clinically-available, FDA-cleared diagnostic to provide direct measurement of a patient's blood volume in a broad range of medical and surgical conditions.

A vast library of studies have established the value of the BVA-100, confirming that accurate blood volume analysis leads to better informed physicians, better treatment strategies, and improves patient outcomes and resource utilization. As we move into the future, our goal is to partner with hospitals and physicians to integrate direct blood volume measurement into standard clinical practice.

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Heart Disease and Hypertension: A Growing Problem

Tom Cropper, *Editor*

The growing burden of hypertension is putting healthcare infrastructure under pressure. What's the solution?

IN THE quest to deliver world class healthcare, professionals can often feel as if they are facing a tough choice. On the one hand they have to manage costs, but on the other they are expected to improve care outcomes. All too often you can't do one without impacting the other. New treatments focusing on patients with hypertension and at risk from heart failure promise to do exactly that. By improving diagnosis, reducing mortality and readmission rates, they can not only save lives but ease the burden on health services.

The Rising Cost of Healthcare

Heart failure is one of the biggest health problems in the world. It affects 26 million[a] people globally with around six million of those being located in the US[b]. Around half of those diagnosed with heart failure die within five years.

It is a major cause of mortality and inevitably also has a massive drain on resources. Data from the American Heart Association (AHA) claims that heart failure costs health services in the US more than $30 billion every year[c], and that is growing and is projected to rise rapidly over the coming years. Another report from the AHA found that the number of adults living with heart failure increased from around 5.7 million in 2009-2012 to 6.5 million between 2011 and 2014. By 2030, the report predicts, heart failure rates will rise by 46% with eight million people in the US with heart failure[d].

In part, this increase may be down to improvements in healthcare delivery. If more people are surviving heart attacks, that leaves more patients with weak hearts which have a high chance of heart failure at a later date. These patients will also have a larger impact on the finances of health service providers, as they require ongoing treatment and may need hospital admissions over a longer period of time. An aging population also increases the number of people at risk of heart failure as well as those requiring long term, complicated and expensive treatment. Lifestyle issues such as obesity and diabetes also have an impact.

The challenge will be made all the worse by the rising incidents of high blood pressure and hypertension. The AHA estimates that 100 million Americans have high blood pressure[e]. This increases significantly the risk of a range of health conditions including heart failure and strokes. Seven out of ten people having their first heart attacks also have high blood pressure as do eight out of ten people having their first stroke. Additionally, 70% of people suffering with heart failure have high blood pressure[f].

Most long-standing incidents of hypertension lead to heart failure unless the sequence of events is interrupted. A Framlingham Heart Study of a population of 5,143 patients found that hypertension antedated the development of heart failure in 91% of newly diagnosed heart failure patients. The hazard for developing heart failure among hypertensive patients, compared with normal or healthy patients, was two-fold for men and three-fold for women, after adjusting for age and other heart failure risk factors[g].

Impact on Health Services

All these health problems have a significant impact on health services. A report from Ronald S Chamberlain et al found that five million people have chronic heart conditions, which lead to one million hospitalizations[h]. It is the main cause of hospitalization among people over the age of 65[i] with many patients requiring multiple admissions.

Reducing the rate of readmission is key to improving patient outcomes as well as reducing the fiscal burden on healthcare services. Under the Hospital Readmission Reduction Program of the Affordable Care Act, for example, Centers for Medicare and Medicaid Services were required to reduce payments to hospitals with excess readmissions.

Heart failure is the main cause of hospitalization among people over the age of 65 with many patients requiring multiple readmissions

A Framlingham Heart Study of a population of 5,143 patients found that hypertension antedated the development of heart failure in 91% of newly diagnosed heart failure patients

The key to doing so will be early, accurate diagnosis and prompt interventions. This could reduce mortality rates, improve outcomes for patient and limit the number of people requiring urgent readmissions and expensive ongoing treatment.

Links to Hypertension

One way to do this would be with closer examination of conditions such as hypertension and high blood pressure, which are linked to an increased risk of heart failure. As we've already seen, patients who experience heart failure are also much more likely to have had hypertension, but signs are often overlooked.

A report into the life-saving potential of early hypertension diagnosis raises this hypothetical scenario: imagine a woman who presents to a primary care provider with itching hands as a result of eczema. The chances of her having associated higher blood pressure are 50-60% but, in all probability, she will not be aware of this and doctors will not test for it[j].

Signals such as these are being missed and with them, the chance to identity patients with a higher probability of going on to develop heart failure. Identifying patients at the earliest stage with a simple diagnostic by measuring their blood volume, will make it easier for primary care providers to monitor for early onset signs of hypertension and determine the correct medication early in the cycle to correct the problem.

Unfortunately, many of the diagnostic approaches are relatively ineffective and rely on indirect observation and assessments. The ability to directly measure blood volume can improve the accuracy of assessments and arm doctors with better information to make better clinical decisions.

Reducing the rate of readmission is key to improving patient outcomes as well as reducing the fiscal burden on healthcare services

IMPROVING OUTCOMES FOR PATIENTS WITH HEART FAILURE AND HYPERTENSION AND THE ROLE OF BLOOD VOLUME ANALYSIS

How BVA Can Save Lives

Jo Roth, *Staff Writer*

Indirect or surrogate analysis has been shown to be ineffective in delivering clear and definite results. Can a blood volume test make a difference?

MAINTAINING ADEQUATE good volume blood volume is crucial to ensuring vital organs, such as the heart, continue to function normally. Volumes can be too high or too low in a range of different conditions including hypertension and congestive heart failure. However, evidence suggests that the direct measurement of blood volume is a major step forward. Blood volume measurement has shown to deliver a more accurate assessment of intravascular blood volume leading to more individualized care which, in turn, is delivering better outcomes for patients and hospitals.

The Role of BVA

Inadequacies in the effectiveness of clinical assessment have long been recognized. Clinicians may rely on clinical observation and physical signs of congestion such as abnormal sounds from the lungs, elevated jugular pressure or other anomalies to make their assessments. Unfortunately, these are vague and prone to error. The standard formula used to estimate blood volume was first presented back in 1962 and has been criticized for being inaccurate as today's population has more adiposity and fat tissue requires less vascularization. Other commonly used measures, such as central venous pressure also offer low levels of accuracy in reflecting intravascular volume status.

Inadequacies in existing testing methodologies can lead to severe complications. Early warning signs are missed, care plans are inadequate or wrong, which in some cases can lead to serious complications. In general, it makes it much more difficult to deliver prompt, effective and successful care and leads to increased readmission rates, higher treatment costs and a higher probability of mortality for patients.

The Role of Blood Volume Analysis

The use of indirect estimates means clinicians are working on data which is unlikely to be perfectly accurate, which makes it harder to manage early interventions or design appropriate treatments. Instead, direct analysis of blood volume using BVA-100 test provides an objective and accurate measurement of blood volume that enables clinicians to assess volume derangements and create effective treatment plans.

What's been lacking has been an easy and accurate test to measure total blood volume. The most accepted tests work with dilution indicator methodologies, but early attempts with Evans Blue and Cardiogreen were impractical thanks to their rapid clearance from the blood stream and potentially carcinogenic properties. The dual isotope technique, meanwhile, uses chromium 51 or 99mTc to label autologous red cells and radioiodine 125 or 131 to label human serum albumin (HSA). Red and plasma cells are measured separately, and their results combined. However, this approach is complex and has performance times of between six to eight hours.

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The BVA Test

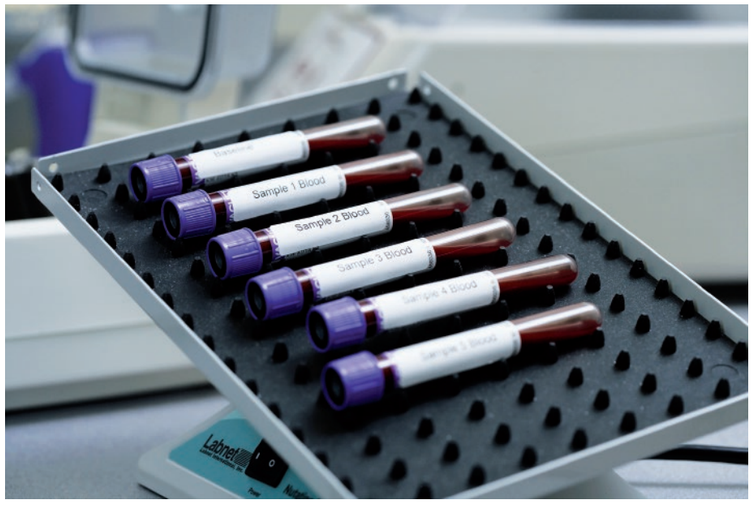
Daxor Corporation has developed a rapid, accurate and objective way to directly measure total intravascular blood volume and evidence is mounting in support of its effectiveness. Numerous studies have shown that a more precise analysis of blood volume can enable clinicians to develop more effective and individualized care plans.

In a study published in JACC Heart Failure; Strobeck et al. hypothesized that individual quantitative blood volume analysis could reduce death and rehospitalization due to heart failure. Their results showed that blood volume analysis guided care reduced heart failure 30-day readmissions by 56%, 30-day mortality by 82% and 1-year mortality by 86%[k] in a propensity-matched control group from the Centers for Medicare and Medicaid data[l].

The data showed that thirty-seven percent of the patients who were thought to be volume overloaded by clinical assessment were more than 10% over the patient norm. They also found that 62% of the patients had anemia further demonstrating that BVA differentiates between true anemia and dilutional anemia.

Each patient within the group received a minimum of one BVA test at or close to

Data showcasing individualized care guided by direct blood volume analysis revealed a reduction in heart failure readmissions by 56% and mortality by over 80% thanks to Daxor's BVA-100 simple blood test



their admission with further follow ups being conducted as and when needed. These results were integrated into each patient's decongestion strategy and outcomes for each member of this group were compared with 30-day mortality, readmission and 365-day mortality rates of ten controls from CMS data.

According to Dr Strobeck: "Directly measuring intravascular blood volume makes it possible to individualize the decongestion strategy according to the confirmed and quantified need of each patient. Based on the outcomes observed in this cohort, this may represent an important difference from the conventional approach. Effectively identifying and managing the anemia also seems to meaningfully impact outcomes."

Michael Feldschuh, CEO of Daxor was quick to highlight the role, he believes, his company's product can have in reducing the risks and incidents of heart failure. "This pioneering study confirms that Daxor's rapid diagnostic can be essential to improving outcomes and the related economic costs of hospitalized heart failure," he said. "Heart failure is one of the greatest challenges our healthcare system faces – it affects over six million Americans and is responsible for one in nine deaths. Mortality rates for heart failure have been rising and the costs to our system already exceed 30 billion dollars per year. We expect the urgent need for an effective solution will to lead to increased interest in our technology and further confirmatory studies."

The BVA-100 test works by using the gold standard methodology for quantifying circulating blood volume, the indicator tracer dilution technique. Patients are injected with a dose of Volumex® Albumin I-131 intravascularly. This tracer circulates in the bloodstream after which a series of blood samples are drawn. It can automatically calculate each patient's blood volume by comparing the concentration of the undiluted tracer prior to injection to that found in patient blood samples.

Interest is growing in this approach. It addresses the key needs of the health services to reduce the cost of health failure, to improve diagnosis and create more individualized care plans. Further studies continue to add to the weight of evidence, suggesting this could prove to be a considerable leap forward in the treatment of heart failure.

Directly measuring intravascular blood volume makes it possible to individualize the decongestion strategy according to the confirmed and quantified need of each patient

IMPROVING OUTCOMES FOR PATIENTS WITH HEART FAILURE AND HYPERTENSION AND THE ROLE OF BLOOD VOLUME ANALYSIS

Treating Heart Failure and Hypertension: The Future

James Butler, *Staff Writer*

New guidelines, innovative technology and advanced treatment techniques will combine to save lives and also reduce the strain on health services.

THE FUTURE of healthcare in the US and across the developed world is one of innovation and higher cost. Technology is continually advancing the boundaries of what is possible. It saves lives and extends life expectancy, but that comes at a cost. New technologies are expensive, and an aging population also means more people are presenting with long-term and complicated conditions. Healthcare costs have risen steadily as a proportion of GDP and are likely to continue to do so into the future, and that creates a fresh challenge for health services. How do they continue to deliver the best care possible while ensuring healthcare continues to be financially sustainable?

In the treatment of heart disease and other serious conditions, the focus has to be on innovations which can encourage earlier preventions and address the root causes of heart failure such as blood pressure and hypertension.

New Guidelines

This starts with looking at the guidelines for treating people with high blood pressure. In 2010, the Sprint Studies analyzed the impact that treating to a lower blood pressure target of less than 120 MM HG would have on three conditions[m]:

- **Cardiovascular:** The aim was to see if a target of less than 120mm HG would be better than the existing goal of less 140mm HG.
- **Kidneys:** To see how lower systolic blood pressure targets would affect their cardiovascular kidney function.
- **Brain:** Would treating to lower blood pressure reduce the risk of developing dementia and slow the decline in cognitive function?

The tests included 9,361 adults aged 50 or older with systolic pressures of 130mm HG or higher and at least one additional cardiovascular disease risk factor. It found that the lower target of less than 120mm HG reduced cardiovascular events by 25% and the overall risk of death by 27%. It also reduced risks and saved lives among those with chronic kidney disease.

These findings were used to inform new AHA guidelines in 2017 and American College of Cardiology (ACC) high blood pressure clinical guidelines. AHA guidelines now define high blood pressure for adults as being systolic readings of 130mm HG or higher, down from systolic readings of 140mm HG, or diastolic readings of 80mm HG or more,.

The study continues to form the basis of further scientific research. A National Heart, Lung, and Blood Institute (NHLBI) supported data challenge in 2016 saw approximately 150 teams submit new data and findings based on Sprint Data[n]. The winners included:

- An individualized decision support tool to decide on intensive hypertension treatment. This would look at predicted benefits and harms, taking into account the perceived severity of the events they represented allowing for a personalized, evidence-based decision.
- A trial into intensive blood pressure management in people with chronic kidney disease.
- The development of a clinical decision score for intensive treatment of high blood pressure.

Despite new tests, technology exists today to assist clinicians in not just controlling blood pressure, but controlling the blood pressure the right way. The BVA test is unique in that the results generated help guide which treatment path the patient would most benefit from and not rely on pressure for example, to assess blood volume. Recent data from Duke University was presented at the American Heart Association Scientific Sessions 2018 whereby the investigator looked at the three main components of blood in adults with hypertension; total blood volume (TBV), red blood cell volume (RBV) and plasma volume (PV) to test whether there is a relationship between these blood volume parameters and standard blood pressure (SBP) and to see whether there is a correlation with race. Blood volume parameters were measured with Daxor's BVA-100 and blood volumes were expressed as a percent deviation from the patient's ideal volumes. The results showed that patients with hypertension had a wide variation in TBV,

In the treatment of heart disease and other serious conditions, the focus has to be on innovations which can encourage earlier preventions and address the root causes of heart failure such as blood pressure and hypertension

As tests continue to develop and research adds to the knowledge base, we can gain new insights into the links between hypertension, blood pressure and heart disease

RBCV and PV and that SBP does not correlate with direct blood volume measurement[o].

The report's authors suggested the findings showed that blood volume measurement should play a critical role in hypertensive therapy. Blood volume analysis is not entirely new, but it has been on a path of evolution to deliver a form of test which is effective and applicable in a clinical setting. Analysis such as this has been made possible thanks to the availability of direct blood volume analysis with the BVA-100 which is discussed in more detail elsewhere in this Report.

As tests continue to develop and research adds to the knowledge base, we can gain new insights into the links between hypertension, blood pressure and heart disease. It is possible to identify at-risk individuals at a much earlier point in disease progression, and improve testing and diagnosis to ensure a better standard of treatment.

Although the BVA-100 test has been available for quite some time, awareness and utility has been expanding with new evidence. The BVA-100 test is the future as more clinicians become educated on the benefits of direct BVA. The technology has been proven. The clinical evidence is strong showing improved mortality and patient outcomes.

The Use of Data

The move towards monitoring sees a greater onus being placed on primary care and self-management. Studies comparing self-monitoring to no self-monitoring in hypertensive patients found that it appears to reduce blood pressure when used in conjunction with co-interventions[p].

Even so, there is still a significant gap in diagnosis. A global study also found that half of people around the world with hypertension do not know they have it. The problem persists in both wealthy and poor countries[q].

Technology offers a number of ways in which this gap can be plugged, by making it easier for patients to take blood pressure readings at home and also connecting them to their primary care providers.

A host of innovations are coming to market offering a various methods to improve early detection of heart disease. These include:

- **Big data:** A study from Yajuan Wang et al looked at how data from electronic health records could be used to aid earlier detection rates. As health services become better at collecting, storing and managing patient data, they have a huge amount of information about each case. If this can be analyzed effectively it can help to identify causation links and improve early detection[r].
- **Artificial Intelligence:** Researchers at Oxford University have developed an AI device capable of analyzing scans of heart disease and cancer patients picking up serious conditions at a much earlier stage[s].
- Researchers in Ireland have developed a handheld device which can detect changes in arteries to detect the early stages of heart disease and alleviate the burden on hospitals[t].

Technologies such as these increase the amount of data available to doctors and patients. As information grows in both volume and reliability, diagnosis improves and conditions are caught at a much earlier stage. This makes it easier to devise appropriate care plans, reduce mortality and ensure patients enjoy a much higher quality of life. Readmissions will be lower, hospital stays shorter and emergency cases can be avoided. Delivering the very best standard of care will become easier and more affordable. The impact on hospitals, carers and patients could be profound.

IMPROVING OUTCOMES FOR PATIENTS WITH HEART FAILURE AND HYPERTENSION AND THE ROLE OF BLOOD VOLUME ANALYSIS

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Notes:

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