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Non-invasive method for rapid bedside estimation of inotropy: theory and preliminary clinical validation

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Editor's key points

- Measurements of myocardial contractility could guide diagnosis and therapy when cardiac function is impaired.
- The authors have developed formulae for bedside assessment of inotropy and arterial impedance.
- These formulae require as inputs variables from Doppler ultrasonography, and arterial and central venous pressure.
- Retrospective analysis showed good separation of these measures in control and left ventricular failure patients.

Background. There are numerous techniques which attempt to quantify inotropy (or myocardial contractility). None has yet found general acceptance in anaesthesia and critical care as a practical method. We report a novel approach to the determination of inotropy as a bedside procedure which could identify low inotropy states in patients with clinical heart failure.

Methods. We estimated the potential and kinetic energy delivered by the left ventricle using continuous-wave Doppler ultrasound (ultrasonic cardiac output monitor, Uscom, Sydney, Australia) and data available at the point of care. A formula to calculate effective inotropy [Smith–Madigan inotropy index (SMII)] was tested against historical haemodynamic data for 250 control subjects (ASA I patients from preoperative clinic) and 83 patients with acute left ventricular failure (LVF) of New York Heart Association Grade 4 (LVF group). The ratio of potential to kinetic energy (PKR) was investigated as a measure of arterial impedance.

Results. Significant differences were found between the control and LVF groups for cardiac index, mean (range)=3.37 (2.84–5.32) vs 1.84 (1.43–2.26) litre min^{-1} m^{-2}; stroke volume index (SVI), 49.2 (39–55) vs 34.3 (23–37) ml m^{-2}; systemic vascular resistance, 893 (644–1242) vs 1960 (1744–4048) dyn s cm^{-5}; SMII, 1.78 (1.35–2.24) vs 0.73 (0.43–0.97) W m^{-2}; and PKR, 29:1 (24–35:1) vs 124:1 (96–174:1), $P<0.001$ in each case. Normal ranges were calculated for SMII and PKR as mean ($+/-1.96$) standard deviations, yielding 1.6–2.2 W m^{-2} for SMII, and 25–34:1 for PKR.

Conclusion. The method clearly identified the two clinical groups with no overlap of data points. The discriminant power of SMII and PKR may offer valuable diagnostic methods and monitoring tools in anaesthesia and critical care. This is the first report of normal ranges for SMII and PKR.

Keywords: Doppler ultrasonography; inotropism cardiac; left ventricular function; myocardial contractility; systemic vascular resistance

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While inotropy (or myocardial contractility) as a concept is well known to all clinicians, it is seldom thought of as a measurable quantity. We sought to develop a simple bedside test based on haemodynamic theory that could evaluate inotropy in a wide range of clinical conditions, and which could be performed by non-experts in a clinically timely manner. We selected left ventricular patients presenting as emergencies to the hospital as the obvious group to study.

In critical care, the diagnosis of left ventricular failure (LVF) is based on the history and clinical signs, sometimes aided by echocardiography and chest radiology. The absolute degree of inotropic failure in the overall clinical presentation is seldom if ever quantified. Commencement, dosing, and withdrawal of vasopressors, vasodilators, and inotropes is still largely based on clinical assessment, sometimes assisted by measurement of surrogates of inotropy such as ejection fraction (EF) or aortic ejection velocity, despite the well-known shortcomings of these indices in critical care. This is particularly so in complex surgical patients where vascular tone and fluid loading status are highly variable and changing.[1–5] More sophisticated echocardiographic techniques have been developed in an attempt to overcome the problems of sensitivity to preload and particularly afterload, but have achieved little penetration in critical care.[2 4 6]

Comparatively little research has been performed to evaluate methods of impedance matching of the left ventricle to the vascular tree.[7–12] Despite its fundamental physiological importance, this is seldom considered in anaesthesia or

critical care, largely because of the difficulties in assessing ventriculo-aortic coupling. A normally powered ventricle will struggle to eject a normal stroke volume (SV) against a high afterload, while a low afterload may be of considerable benefit to the failing heart. Vasodilator use in heart failure is a good example of this concept of matching or coupling the arterial impedence to the capability of the ventricle, while excessive vasodilation of the healthy circulation leads to a mismatch of ventriculo-arterial impedence with resulting hypotension.[8 10 12]

If a simple and rapid method of determining inotropy could be developed then questions regarding the usage, dosing and combination of inotropes would be greatly simplified. Ideally, for any method to gain clinical acceptance it should be simple, quick, accurate, reproducible, easily learned and taught, and applicable to the entire range of emergent patients. A simple bedside method to evaluate arterial impedance and ventriculo-aortic impedance matching (coupling) would be a desirable additional feature.

Methods

The publication of the historical data used in this study was approved by the ethical committee of the Greater Western Area Health Service.

Inotropy calculation

We developed a formula based on haemodynamic theory, to calculate the potential and kinetic energy developed by the ventricle, which results from ventricular inotropy, which is then transferred to the aorta, using data easily obtained in the operating theatre or critical care situation. We then tested the formula using a bespoke computer program against stored data for 250 healthy subjects, the control group, and 83 patients known to have acute LVF, the LVF group (see below).

Basic theory

If we consider a simple hand-operated water pump, as shown in Fig. 1, then each time the pump handle moves through a full sweep it will generate one SV of the pump. This SV will be produced at a hydrostatic pressure (HP) and flow velocity (V) which is determined by the force on the pump handle. If we now move the handle more forcibly, the pump will still produce the same SV, but in a shorter flow time (FT) and with a greater HP and flow velocity. The differences in FT, mean velocity (Vmean) and HP are solely attributable to the increased power that was applied to the pump handle. If these variables can be measured for the heart then instantaneous output power can be calculated, which is a direct function of inotropy. Figure 2 shows a schematic Doppler ejection waveform for blood flow through the aortic valve into the aorta. The measured maximum or peak flow velocity (Vpk), and the calculated mean velocity of ejection (Vmean) (see below), and the total duration of flow in one ejection (heart beat) flow time (FT) are shown.
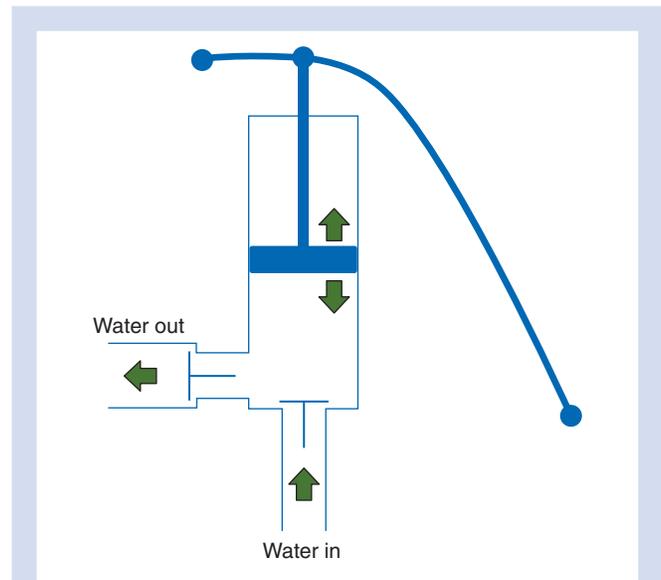
Fig 1 A simple piston water pump. With each sweep of the handle the pump will deliver one stroke volume SVol, at a flow velocity V, hydrostatic pressure HP, and in a given flow time (FT) determined by the force exerted on the handle. The parameters of SVol, V, HP, and FT can therefore be used to calculate the power transferred to the system.

When the heart contracts it follows the 'all or nothing rule', it will contract with all the power that it has available at that moment in time, which depends on its inotropy.[13] SV, FT, and Vmean [derived by integrating the area under the curve in Fig. 2 and known as the velocity–time integral (vti)] can be measured using Doppler ultrasound, and the mean arterial pressure (MAP), which equates to HP, by automated oscillometry or from arterial lines. From these, along with blood density which can be derived from haemoglobin
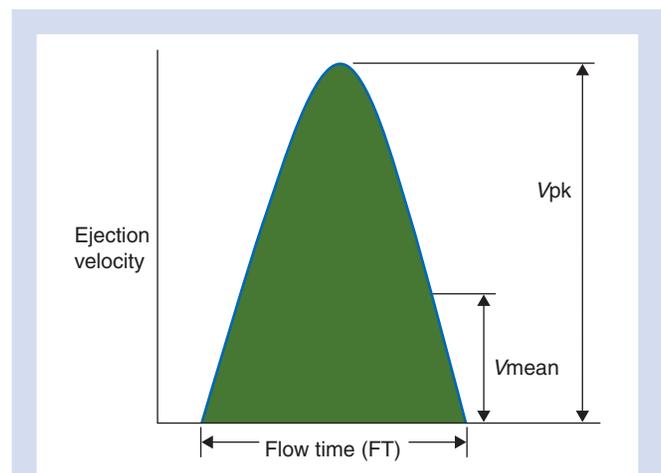
Fig 2 Diagrammatic representation of aortic transvalvular flow as measured by continuous wave Doppler ultrasound. Vmean is calculated by integration of the area under the velocity–time curve to give the velocity time integral, vti.

Steps in calculation of SMI and PKR.

The work performed by the heart in generating arterial pressure (potential energy) is the product of change in pressure and change in volume

$$\text{Work (PE)} = \Delta P \times \Delta \text{Vol} \qquad (i)$$

The work performed by the heart in generating blood flow (kinetic energy) is the product of mass and velocity

$$\text{Work (KE)} = \tfrac{1}{2}mV^2 \qquad (ii)$$

For one stroke volume (SVol) of blood of density ρ kg m^{-3}

$$\text{Work (KE)} = \tfrac{1}{2}\text{SVol}\rho V^2 \qquad (iii)$$

The power from the ventricle that appears as arterial pressure (PE) is work (PE) per unit time (FT)

$$\text{Power (PE)} = \Delta P \times \Delta \text{Vol}/\text{FT} \qquad (iv)$$

The power from the ventricle that appears as blood flow (KE) is work (KE) per unit time (FT)

$$\text{Power (KE)} = \tfrac{1}{2}\text{SVol}\rho V^2/\text{FT} \qquad (v)$$

The total power transferred to the aorta from the left ventricle (SMI) is thus (iv)+(v) and with substitution of mean arterial pressure (BPmean) for ΔP and mean velocity (Vmean) for V results in

$$\text{SMI} = \frac{\text{BPmean} \times \text{SVol} \times 10^{-3}}{7.5 \times \text{FT}} + \frac{\text{SVol} \times 10^{-6} \times \rho \times \text{Vmean}^2}{2 \times \text{FT}}$$

where BPmean = (mean arterial pressure–central venous pressure) in mm Hg, SVol=stroke volume in ml, ρ=density in kg m^{-3}, Vmean=mean velocity in m s^{-1}, FT=systolic flow time in ms. The factors 7.5, 10^{-3} and 10^{-6} are required to convert milliseconds to seconds, millilitres to cubic metres, and millimetres of mercury to kilopascals (kPa) (1 kPa=7.5 mm Hg), to conform to SI values; see text for explanations.

Smith–Madigan inotropy index (SMII) is total inotropy, SMI, divided by body surface area, BSA

$$\text{SMII} = \frac{\text{SMI}}{\text{BSA}}$$

Potential energy to kinetic energy ratio (PKR) is (iv) over (v)

$$\text{PKR} = \frac{\text{Power (PE)}}{\text{Power (KE)}} = \frac{\Delta P \times \Delta \text{Vol}/\text{FT}}{\tfrac{1}{2}\text{SVol}\rho V^2/\text{FT}}$$

Fig 3 The derivation of the formula for SMI and SMII, and PKR, which is analogous to dynamic impedance (see text).

concentration, it is possible to calculate both the potential energy (PE) developed by the heart, which is that portion of output energy that produces arterial pressure, and also kinetic energy (KE), the energy of blood flow (see data collection below).

Energy is the capacity to perform work. For PE, the work performed is the product of change of pressure and change of volume or PE=$\Delta P \times \Delta$Vol (see Fig. 3). The change in pressure, ΔP, is the MAP-CVP, or output pressure minus input pressure. The change in volume, ΔVol, is the stroke volume, SVol. KE for any moving mass is calculated using the formula KE=$\tfrac{1}{2}mV^2$, where m is the mass of the object and V its velocity. For one SVol of blood, the mass is simply SVol× density of blood (ρ), typically 1055 kg m^{-3}, so KE=$\tfrac{1}{2}$SVolρV^2.

Power is the rate of transfer of energy or more simply, the amount of external work performed in unit time. In the case of the left ventricle, this is the duration of ventricular ejection, the FT. The power of the ventricle that appears as PE is then $\Delta P \times \Delta$Vol/FT, and for KE, $\tfrac{1}{2}$SVolρV^2/FT. The total power delivered to the aorta is thus PE/FT+KE/FT. Millimetres of mercury (mm Hg), millilitres (ml), grammes (g) and, in the case of FT, milliseconds (ms) are not SI units, so conversion factors need to be added to the formula to correct for this, resulting in the final formula:

$$\text{Power} = \text{PE}/\text{flow time} + \text{KE}/\text{flow time}$$

$$= \frac{\text{BPmean} \times \text{SVol} \times 10^{-3}}{7.5 \times \text{FT}} + \frac{\text{SVol} \times 10^{-6} \times \rho \times \text{Vmean}^2}{2 \times \text{FT}}$$

where BPmean=(mean arterial pressure−central venous pressure) in mm Hg, SVol=stroke volume in ml, ρ=density

in kg m^{-3}, Vmean=mean velocity in m s^{-1}, FT=systolic flow time in ms. The factors 7.5, 10^{-3}, and 10^{-6} are required to convert milliseconds to seconds, millilitres to cubic metres and millimetres of mercury to kilopascals (1 kPa=7.5 mm Hg), to conform to SI values.

The power generating arterial pressure and the power generating blood flow must be the product of ventricular power, or inotropy (assuming negligible internal losses within the heart). The result of the equation appears as Joules per second or Watts, the SI unit of power. As with cardiac output and cardiac index (CI), dividing total inotropy by body surface area (BSA) yields the inotropy index. To avoid confusion with other indices of inotropy we will refer to this hereafter as the Smith–Madigan inotropy index (SMII).

Potential to kinetic energy ratio

The energies of arterial pressure and blood flow must have an optimum ratio. Pressure without flow is obviously unacceptable, but equally so is flow without pressure, as there must be adequate perfusion pressure for the tissues. There is a point at which impedance matching delivers the optimum transfer of energy from the output system to the input system.[7][8] If vascular impedance is too low, as in excessive vasodilation, then there is high blood flow but inadequate arterial pressure, but if it is too high, as with excessive vasoconstriction, then there is insufficient blood flow. PKR should, therefore, provide an indication of impedance, in the same way that instantaneous voltage and current indicate the impedance (dynamic resistance) in Ohm's law, where R=V/I.

Data collection

Haemodynamic measurements were made using the ultrasonic cardiac output monitor (Uscom, Uscom Ltd, Sydney, Australia).[14–19] This is a non-invasive continuous-wave Doppler ultrasound device which has been in routine clinical use in our operating theatres, ICU, coronary care unit, and emergency department for 6 years. It utilizes the Doppler mode of traditional echocardiography to measure SV, SVI, ejection velocity, vti, and FT, in addition to calculating cardiac output, CI, and systemic vascular resistance (SVR) amongst others. BSA is calculated from height and weight data according to the formula of Dubois and Dubois.[20] Examinations can be stored on the internal hard disk of the monitor or as hard copy printouts. For further details, see the manufacturer's website at www.uscom.com.au.

We retrospectively analysed the stored Uscom and clinical record data from two groups of patients. Group one comprised 250 ASA I healthy individuals taking no medication, who were scheduled to undergo minor elective surgery and who had been screened at the pre-anaesthetic clinic 5–15 days before admission, the control group. Group two comprised 83 patients presenting to the emergency department or the combined ICU/coronary care unit with a diagnosis of acute LVF broadly in line with the Framingham criteria,[21] the LVF group. All subjects would be classified as Grade 4

by the New York Heart Association criteria or as Stage C by the American College of Cardiology/American Heart Association criteria. Subjects with evidence of significant valvular heart disease, pericardial effusion or tamponade, cor pulmonale, or iatrogenic fluid overload were excluded from the study. Subjects were included if the initial diagnosis of LVF was subsequently corroborated by a senior physician or cardiologist, after echocardiography, and if acute pulmonary oedema was confirmed on chest radiographs by a senior radiologist. Only the initial haemodynamic measurements were used in the study to prevent reiterative feedback of data from clinical treatments based on the Uscom results to the input Uscom data. Similarly, the study was not longitudinal in design as treating clinicians were not blinded to the initial Uscom findings which could have influenced outcomes.

All Uscom measurements were made from the suprasternal notch targeting the aortic valve. MAP was obtained from automated oscillometry measurements, or arterial lines if present, in the case of the LVF group. The CVP was presumed to be zero unless actual values were known. Blood density was assumed to be 1055 kg m^{-3} or calculated from the formula 1027+(haemoglobin concentration in g litre^{-1}×0.2) kg m^{-3} if haemoglobin was known.[22][23] The Uscom data were outputted in comma-delimited format directly to Excel® spreadsheets and the data integrity checked with the original examinations stored on the internal hard disk of the Uscom. PE, KE, PKR, inotropy, and SMII were calculated using a purpose-written computer program based on the formula given above. For quality assurance, all Uscom examinations used in the analyses were examined by one of the authors (B.E.S.) with experience of several thousand Uscom examinations and only traces deemed to be of diagnostic quality with a score of 8/12 or better were included.[24]

The data were analysed using χ^2 tests with Yates correction for continuity, Levene's test for equality of variances, independent sample t-tests, and Kolmogorov–Smirnov test of normality using the Statistical Package for Social Sciences® version 18. Statistical significance was taken as $P<0.05$.

Results

The findings for both groups are summarized in Table 1.

The data from the control group showed normal distributions for height, weight, CI, SVI, PKR, and SMII. The mean SMII for the cohort as a whole was 1.78 W m^{-2}, with a range of 1.35–2.24 W m^{-2} (sd=0.204). SMII declined almost linearly with age (correlation coefficient $r^2=0.564$). Subjects <35 years showed a significantly greater SMII than subjects >50 years, $P=0.038$. There was no significant difference between sexes.

The normal distribution of the data enabled us to define a normal range for SMII and PKR on the basis of mean (+/−1.96) standard deviations (sd) which encompassed 238 subjects (95.2%) for SMII, and 240 subjects (96%) for PKR. This gave normal ranges of 1.6–2.2 W m^{-2} for SMII and 25:1–34:1 for PKR.

Table 1 Comparison of patient characteristics and haemodynamic parameters for control and LVF groups. PKR, potential to kinetic energy ratio (see text); SVI, stroke volume index; SMII—F/M, SMII values in females/males; NS, not significant

	Control group			LVF group		
	Mean	**Range**	**P-value**	**Mean**	**Range**	**P-value**
Age (yr)	47.7	3–74	–	64.8	16–86	0.013
Weight (kg)	68.3	13–104	–	64.3	47–98	NS
Female/male	136/114		–	35/48	–	0.02
SMII—all ages (Wm^{-2})	1.78	1.35–2.24	–	0.73	0.43–0.97	<0.001
SMII—age <35	1.87	1.83–2.27	0.038	0.79	0.68–0.97	NS
SMII—age >50	1.68	1.56–2.25		0.76	0.58–0.93	
SMII—F/M	1.75/1.83	–	NS	0.72/0.74	–	NS
CI (litre min^{-1} m^{-2})	3.37	2.84–5.32	–	1.84	1.43–2.26	<0.001
SVI (ml m^{-2})	49.2	39–55	–	34.3	23–37	<0.001
SVR (dyn s cm^{-5})	893	644–1242	–	1960	1744–4048	<0.001
PKR	29:1	24–35:1	–	124:1	96–174:1	<0.001

For the LVF group, the mean SMII was 0.73 W m^{-2}, range 0.43–0.97 W m^{-2} (sd=0.13). The difference between the groups was highly significant, $P<0.001$. No patient in the LVF group showed an SMII approaching the lowest value found in the control group 0.97 vs 1.35 W m^{-2}. This was highly significant, $P<0.001$. There was no significant relationship between age and SMII in this group. There was a statistically significant difference between the groups as regards male-to-female ratio, with a preponderance of males in the LVF group, but the clinical significance of this is unclear.

Mean CI was significantly lower in the LVF group with a mean of 1.84 vs 3.37 litre min m^{-2}, $P<0.001$. The highest value for CI in the LVF group did not approach the lowest value seen in the control group, 2.26 vs 2.84 litre min m^{-2}, $P<0.001$.

Mean SVI was significantly lower in the LVF group with a mean of 34.3 ml m^{-2} compared with 49.2 ml m^{-2} in the control group, $P<0.001$. The highest value for SVI in the LVF group did not reach the lowest value seen in the control group, 37 vs 39 ml m^{-2}, $P<0.001$.

Mean PKR showed a highly significant difference between the groups ($P<0.001$), with no patient in the LVF group showing a PKR that approached the highest figure seen in the control group at 86:1 vs 36:1, $P<0.001$. Mean SVR showed a similar pattern being significantly higher in the LVF group compared with the control group at 1960 compared with 893 dyn s cm^{-5}, $P<0.001$. The lowest value in the LVF group did not approach the highest level seen in the normal group, 1744 compared with 1292 dyn s cm^{-5}, $P<0.001$.

Discussion

The method was able to discriminate between the two study groups on the basis of SMII and PKR, with a clear separation of values. The LVF group showed a significantly lower SMII, SVI, and CI, and significantly higher vascular resistance, as indicated by SVR, and vascular impedance as shown by PKR.

Optimization of SV is central to haemodynamics, anaesthetics, and resuscitation. The three determinants of SV are preload, afterload, and inotropy. Essentially, clinicians need to know both where on the Starling curve their patient lies, to the left or the right of the peak, and also which Starling curve they are on. A patient with a flat Starling curve (low inotropy) cannot increase SV significantly in response to a fluid challenge. On the other hand, a patient on a healthy Starling curve with high inotropy will respond with a SV response.

Similarly, if afterload is low, as frequently happens in the hyperdynamic phase of septic shock, then SV and EF can be very high despite the underlying inotropy being severely depressed by the septic process. Failure to appreciate this can lead to the well recognized inappropriate use of vasoconstrictors to raise afterload with subsequent ventricular failure to handle the increased afterload.[7 8 12] In LVF, it is essential that we have some idea of inotropy status before we manipulate preload, inotropy, and afterload pharmacologically or physically to optimize SV.[8 12 25]

The search for an accurate index of inotropy which is independent of loading conditions has continued for decades, with many methods being suggested as possible solutions. These include maximum rate of change of ventricular pressure, dP/dt_{max},[1 3] maximum rate of change of ejection velocity, dV/dt_{max},[1 3] maximum rate of change of flow, dQ/dt_{max},[1] maximum flow acceleration, dV/dt_{max}^2,[1] end systolic ventricular elastance, Ees,[3] the myocardial performance index, MPI (or 'Tei index'),[2] ventricular wall stress and stress rate,[26] fractional shortening of cardiac myofibres,[27] and others. Many of the indices are referenced to peak or instantaneous ventricular pressures, volumes, flow velocities or time-derived ratios, or to end systolic or end diastolic volumes and pressures in the ventricle or atria.[1 3 28] To date, none has achieved significant clinical adoption, particularly because of sensitivity to changes in preload and afterload. While some indices can be derived with non-invasive

methods using echocardiography, as with the MPI,[2] and ventricular strain and strain rate,[26] these show significant sensitivity to changes in loading conditions, and even to heart rate.[3] The MPI has also been criticized as failing to reliably show changes in inotropy, particularly in low preload states as are often seen in anaesthetic and critical care practice.[4][5] Invasive methods such as dP/dt_{max} and its various derivatives require left ventricular catheterization. End systolic elastance requires several readings to be made under varying loading levels, which is impractical clinically.

Ejection fraction

EF measured echocardiographically has become commonplace in anaesthetics and critical care largely because of its simplicity as a concept. EF is SV divided by left ventricular end diastolic volume (SV/LVEDV). For any given preload, there are a number of possible EFs depending on the inotropy level. Unfortunately, while the concept is simple, the reality is that EF is a very poor indicator of inotropy being highly sensitive to changes in preload, afterload, and even heart rate.[4] This severely limits its usefulness in anaesthesia and critical care and may be dangerously misleading in septic shock and other low afterload states as detailed above, where a high EF might be interpreted erroneously as representing a high inotropy level. Indices based on ejection velocities and acceleration share this same drawback.[1][3][4]

Perhaps more fundamentally, the calculation of LVEDV and left ventricular end systolic volume (LVESV) from which SV and EF are calculated, depends on accurate measurement of the ventricular cavity and assumes symmetrical behaviour of the ventricular walls.[27] Geometric models of ventricular volume such as the Teicholz method, are unreliable in the presence of segmental ventricular wall motion abnormalities or aberrant septal motion. Simpson's method may be superior in this context, but is still based on geometric assumptions that may not be valid in any given case.[25][29] In clinical practice, EF is often assessed simply by visual inspection of the two-dimensional ultrasound image.

In our analysis, we decided to look only at the blood flow delivered to the aorta and to disregard the energy lost within the heart. We chose this approach as anaesthetists and intensivists cannot reverse the anatomical abnormalities of the heart but can manipulate the preload, inotropy, and afterload conditions. In this regard, it is unnecessary to strictly isolate inotropy from the loading conditions of the heart as fundamental physiological research has endeavoured to do. In clinical practice, we are largely concerned only with optimizing left ventricular output in terms of both volume and pressure.

This is analogous to a motor vehicle climbing a hill. The speed that the vehicle can maintain on the gradient (=afterload) depends on both the load that it is carrying (=preload) and the output power that the motor delivers to the drive wheels (=SMII). To increase the speed of the vehicle we must reduce the load it is carrying, reduce the gradient that it is working against or increase the power

delivered to the drive wheels. The true power of the motor will be somewhat higher than the output power at the drive wheels due to mechanical inefficiencies within the motor itself and the transmission system. It is the effective output or delivered power that is important. While an engineer might be able to gauge the output power of a vehicle's motor by examining its structure and the movement of its components, it would be much easier, and probably more relevant, to assess the vehicle's on-road performance. This is the approach that we have adopted.

Sensitivity of SMII to loading conditions

In our formula, the effect of preload and afterload should be largely negated. Taking preload first, at a fixed level of inotropy and afterload, FT is directly proportional to LVEDV, the preload. An increase in preload leads to an increase in SV by Starling's law, but FT will also increase in an almost linear way (the gradient of the line in the Starling curve). For PE, as SV is in the numerator (SV×MAP) but FT is in the denominator, then the fractional value will stay much the same. For KE, an increase in SV must lead to an increase in MAP assuming a fixed SVR and heart rate, as MAP=SV×HR×SVR. Ejection velocity is inversely proportional to afterload. Ejection velocity will therefore decrease and FT will increase as SV increases. Again the fractional value of the KE formula $(SV×10^{-6}×\rho×Vmean^2/2FT)$ should show reasonable constancy.

For afterload, assuming a constant preload and inotropy, an increase in MAP will increase the numerator for PE (SV×MAP). But an increase in afterload will increase FT, the denominator, offsetting overall change. As mentioned above, increased afterload will also affect the KE by decreasing ejection velocity and increasing FT, again offsetting any change in this value.

Our formula should therefore show reasonable rejection of loading values, increasing its clinical utility in haemodynamically unstable patients.

Ventriculo-aortic coupling

As with the vehicle example above, the transmission system is crucial in the transfer of power from the motor to the drive wheels. In a vehicle climbing a hill with an underpowered motor (=low inotropy), the driver can compensate by selecting a lower gear and increasing engine revolutions. In the case of the left ventricle, this would be analogous to increasing heart rate with a lower EF rather than maintaining SV. It has been shown that raising the inotropy level to a given value by using equivalent doses of different inotropes does not lead to the same haemodynamic results in the arterial tree. The peripheral effects of dopamine and dobutamine, for example, can be markedly different for a given level of inotropy, resulting in significantly different cardiac outputs and arterial pressures.[8–12] Matching the impedance of the circulation to the power of the ventricle is pivotal.[7][8][10][12] The example of excessive administration of vasopressors leading to improved arterial pressure but critical reduction

of cardiac output is well known to all.[12] The arterial impedance is raised to a level where ventricular inotropy is insufficient to maintain SV, a mismatch of output impedance of the ventricle and input impedance of the aorta. PKR may give some guidance in this situation.

Potential to kinetic energy ratio

By analogy to Ohm's law where resistance equals voltage divided by current, $R = V/I$, so SVR is MAP divided by cardiac output, $SVR = MAP/CO$. PKR may seem to be a similar concept to SVR, but SVR is a static measure; it uses overall cardiac output per minute as if flow were constant, and the average value of MAP as if the arterial tree were passive. PKR represents the dynamic relationship between the integrated values for PE and KE during the short period of systolic ejection. It will, therefore, depend upon factors such as inertance, capacitance (compliance) and reactance, as well as resistive elements. It is, therefore, indicative of dynamic impedance rather than simply passive resistance of the arterial tree.

The control group showed PKR values ~30:1, a much greater proportion of energy going towards arterial pressure than flow, with 96.8% of total energy appearing as pressure against 3.2% for flow. In the LVF group, the CI was significantly lower and the SVR considerably higher than the normal group. Vascular tone is actively increased to maintain MAP in this situation, but this can lead to a vicious circle of declining SV and cardiac output. PKR at 124:1 shows how profoundly the system changes, with 99.2% of the output energy going towards maintaining arterial pressure and only 0.8% towards blood flow. As LVF improves, so PKR trends back towards normal. A very similar situation can occur in patients under anaesthesia with haemorrhage leading to hypotension. Increasing vascular tone may increase the arterial pressure at the expense of blood flow, with PKR rising sharply (authors' own unpublished data). Conversely, in cases of septic shock with high CO and low SVR we have observed PKR values as low as 3:1. The arterial impedance in this situation is too low to allow the CO to generate adequate arterial pressure. As the patients recovered, so PKR trended upwards (authors' own unpublished data). PKR could, therefore, represent a treatment goal in haemodynamics along with CO, SV, SMII, and SVR. Further studies are needed to confirm this.

Heart failure with preserved ejection fraction

Formerly known as diastolic heart failure, heart failure with preserved ejection fraction (HFPEF) is overall heart failure where the EF is maintained at $\geq 40\%$, although some workers have used 50% as the threshold figure. Depending on the definition used, the incidence of HFPEF is ~40% of all acute left heart failure presentations.[30-33] The LVF group should therefore have contained ~33 patients with this condition. At first sight it would seem that the data in Table 1 do not support this, seemingly showing systolic dysfunction in all patients, with SMII values < 0.97 W m^{-2} in all cases.

In fact, if we assume a normal LVEDV of 115 ml and a normal EF of 65% then normal SV would be ~75 ml. An EF of 40% would equate to a SV of just 46 ml. Assuming the same MAP and FT values for the two situations, then inserting 46 ml as the SV in the inotropy formula would yield an SMII ~40% lower than in the normal case. Similarly, for the same heart rate, both CO and CI would be 40% lower in the HFPSF subjects and SVR 40% higher as $CO = HR \times SV$, $CI = CO/BSA$, and $SVR = MAP/CO$. A reduction in EF from a normal 65% down to 40% is a reduction of ~39%. From Table 1, the reduction of SV in the LVF group is just $> 30\%$, well within the definition of HFPEF. Such patients could therefore be present in the LVF group but are not clearly identified by the pooled data. However, reduced ventricular filling attributable to HFPEF would result in a reduced SV by Starling's law, but would also result in a shorter FT than those patients with systolic failure with similar SV. In simple terms, while the SV would be the same, the patient with preserved systolic function would eject this SV more rapidly. The inotropy formula would therefore yield higher SMII values in these patients for any given SV in comparison with those with systolic failure in addition to diastolic dysfunction.

The combination of low SV, low CO and CI but apparently reasonable preservation of SMII should serve as a warning flag to clinicians that unsuspected diastolic dysfunction may be present in their patients, with significance for overzealous efforts to optimize preload. On the other hand, a reduction of SMII $> 35-40\%$ would suggest significant systolic dysfunction in addition to any diastolic dysfunction that might be present. The overall reduction in mean SMII in the LVF group was 59%, with no subject showing a reduced SMII of $< 39\%$ (0.97 vs normal ≥ 1.6 W m^{-2}) suggesting that some degree of systolic dysfunction was present in all of the LVF subjects.

Conclusion

SMII represents a novel approach to the problem of assessing inotropy status as a bedside procedure in anaesthesia and critical care. It deliberately moves away from fundamental measures of inotropy, as used in physiological research, towards a strategy of measuring what might be termed 'effective inotropy', being that energy which is delivered to the circulation by the heart, and which can be manipulated by clinicians. PKR represents a simple method for assessing vascular impedance and ventriculo-aortic impedance matching. Although we used the Uscom in this study for ease of use and simplicity, SMII and PKR can be calculated using conventional continuous-wave Doppler echocardiography (from which the Uscom was derived) and many ultrasound machines with suitable probes to fit the suprasternal notch could be used. If prospective trials confirm these results, particularly in varying conditions of ventricular loading and pharmacologically and pathologically induced myocardial depression, then SMII and PKR could have considerable utility in monitoring during surgery and in critical care, and may have diagnostic potential in cardiovascular disease.

Authors' contributions

B.E.S. performed the Uscom examinations and initial data collection, wrote the first draft and assisted with revision of the final manuscript, conducted some of the statistical analyses, wrote the inotropy calculation software, assessed the quality of the Uscom examinations and dealt with ethical committee approval. V.M.M. collected and indexed the references, performed the data integrity checking, screened the LVF group for inclusion/exclusion criteria, performed some of the statistical analyses, prepared the table and obtained copies of the references where cited. Both authors jointly formulated the concept of SMII and PKR, and prepared and authorized the final manuscript.

Declaration of interest

Neither author declares any competing interest. Specifically, neither author has any financial associations with Uscom Ltd, nor received any funding from them or any other organization, body or individual. Neither holds stock, shares or other assets in Uscom Ltd. Further, neither author has any financial associations whatsoever with any other competitor or rival company or organization. There are no patent applications in process or planned relating to this manuscript. There were no allocations of funding or grants from any organization or individual for the performance of this study or publication of this manuscript.

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