Universitat Autònoma de Barcelona

EVALUATION OF FEMORAL dP/dt_{max} AS A MARKER OF CARDIAC FUNCTION IN CRITICALLY ILL PATIENTS

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DOCTORAL THESIS

EVALUATION OF FEMORAL dP/dt $_{max}$ AS A MARKER OF CARDIAC FUNCTION IN CRITICALLY ILL PATIENTS

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To my teachers and mentors, for sharing their wisdom;

to my friends and my family, for being always there for me;

and to my wife and my daughter, for their love and unconditional support.

List of abbreviations

(in order of appearance)

dP/dt_{max}	Maximum rise of pressure over time
CO / CI	Cardiac output / Cardiac index
SV / SVI	Stroke volume / Stroke volume index
ESPVR	End-systolic pressure-volume relationship
EDPVR	End-diastolic pressure-volume relationship
ESV	End-systolic volume
EDV	End-diastolic volume
HR	Heart rate
CVP	Central venous pressure
PLR	Passive leg raising
SVR / SVRI	Systemic vascular resistance / Systemic vascular resistance index
E_a	Effective arterial elastance
E_{es}	Ventricular end-systolic elastance
TAC	Total arterial compliance
MAP	Meant arterial pressure
PP	Pulse pressure
SAP	Systolic arterial pressure
LV	Left ventricle
LVEF	Left ventricle ejection fraction
CFI	Cardiac function index
DAP	Diastolic arterial pressure
SD	Standard Deviation
DBT	Dobutamine
NE	Norepinephrine
TASi	Total arterial stiffness index
TPRi	Total peripheral resistance index

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Abstract

Femoral dP/dt_{max} (the maximum rise of pressure over time) has been considered by many as a minimally invasive, peripheral marker of left ventricle contractility. However, in contrast to left ventricular dP/dt_{max}, femoral dP/dt_{max} occurs during the ejection phase of the cardiac cycle and should therefore be subject to afterload and arterial load variations. Furthermore, similar to the left ventricle dP/dt_{max}, femoral dP/dt_{max} might be subject to preload variations through several potential mechanisms.

The objective of the present work was to elucidate the effects of left ventricle loading conditions (preload and afterload) on the measure of femoral dP/dt_{max} and to assess the reliability of this marker as an estimator of cardiac contractility.

Two studies were performed to address the hypothesis formulated for the present doctoral work. In the first, changes in femoral dP/dt_{max} were prospectively monitored during contractility (dobutamine infusion change), afterload (norepinephrine dose change) and preload (passive leg raising or volume expansion) variations in critically ill patients. In the second, a retrospective analysis of a database of critically ill patients receiving fluid infusion was analysed to evaluate the relevance of preload-dependence on the responsiveness of femoral dP/dt_{max} to preload variations.

Results suggested that although a link between femoral dP/dt_{max} and left ventricle contractility variations may exists, femoral dP/dt_{max} is highly susceptible to changes in afterload and arterial load, and varies with preload increases in preload-dependent patients. Furthermore, femoral dP/dt_{max} retained an almost direct correlation with pulse pressure in all cases, suggesting that any change in the later should also influence the former.

According to present results, it can therefore be concluded with reasonable certainly that femoral dP/dt_{max} is not an adequate marker of cardiac contractility as it is affected by left ventricular loading conditions and should not be used as such in clinical practice.

Resum

El màxim increment de pressió per unitat de temps (dP/dt_{max}) mesurat a nivell de l'arteria femoral és considerat per molts com un marcador fiable i mínimament invasiu de la contractilitat cardíaca. A diferència de la mesura del dP/dt_{max} al ventricle esquerre, el dP/dt_{max} femoral te lloc durant la fase d'ejecció ventricular del cicle cardíac i, per tant, hauria d'estar subjecte als efectes de la post-càrrega i dependre del to arterial. A demès, i de forma similar al dP/dt_{max} del ventricle esquerre, la mesura del dP/dt_{max} femoral podria estar subjecte a variacions en la pre-càrrega cardíaca a través de múltiples mecanismes.

L'objectiu de la present tesi doctoral és el d'analitzar els efectes de la pre-càrrega i la post-càrrega en la mesura del dP/dt_{max} femoral, i avaluar la seva validesa com a marcador de contractilitat cardíaca.

Es van realitzar dos estudis per respondre a les hipòtesis formulades. En el primer es van analitzar els canvis en el dP/dt_{max} femoral de manera prospectiva durant canvis en la contractilitat cardíaca (variacions en la dosi d'infusió de dobutamina), post-càrrega (variacions en la dosi d'infusió de noradrenalina) i en la pre-càrrega (mitjançant l'administració d'una càrrega de volum estàndard o una maniobra d'elevació de les cames) en pacients crítics. En el segon, es va realitzar un estudi retrospectiu en pacients crítics que havien rebut una càrrega de volum estàndard on es va analitzar la rellevància de la pre-càrrega dependència sobre la resposta del dP/dt_{max} femoral a canvis en la pre-càrrega cardíaca.

Els resultats suggereixen que, tot i que pot existir una relació entre les mesures de dP/dt_{max} femoral i ventricular, el dP/dt_{max} femoral és altament susceptible a canvis en la post-carrega ventricular i el to arterial, i canvia amb els canvis de pre-càrrega en pacients en situació de pre-càrrega dependència. Addicionalment, el dP/dt_{max} femoral va mostrar una relació quasi directe amb la pressió de pols en tots els casos, el qué suggereix que qualsevol canvi en aquesta pot influenciar la mesura del dP/dt_{max} femoral.

Basant-se en els resultats obtinguts, es pot concloure amb una raonable certesa que el dP/dt_{max} femoral no és un marcador adequat de la contractilitat cardíaca, donat que es veu influenciat pels canvis en la pre i post-càrrega ventricular, i per tant, no s'hauria d'emprar com a tal en la practica clínica habitual.

1 Introduction

The present doctoral Thesis aims at evaluating the utility of the maximum rise of pressure over time of the femoral artery pressure waveform (femoral dP/dt_{max}) as a means to estimate cardiac function in critically ill patients. In order to understand the potential utility of this marker and the factors that may influence its measure, it is necessary to first analyse the elements that determine cardiac performance and the role of the complex interaction between the heart and the arterial system. The following introductory sections will address these points, with increasing level of detail, and with the objective of providing a solid base from which a logical explanation of the observed results can be drawn.

1.1 The main function of the Cardiovascular System

Cardiovascular system's principal role is to deliver oxygen and nutrients to human body tissues. This is achieved by the close interaction between the heart and the vascular system, that enables delivery of sufficient oxygen-rich arterial blood to match oxygen consumption demands at any given time and tissue activity level (1). Failure to do so, such as in different forms of cardiovascular shock, results in microvascular dysfunction, cellular hypoxia, anaerobic metabolism and cellular function impairment (2–5). If sustained, these alterations can lead to irreversible damage and death (1,2,4,5). Furthermore, maintenance of a sufficient perfusion pressure is principal to ensure sufficient capillary flow and tissue oxygenation (1,5–7). It is therefore not surprising to observe that a lack of sufficient arterial system pressure leads to increased organ failure and mortality (8,9).

1.2 Oxygen delivery

The amount of provided oxygen to the tissues is a function of arterial blood oxygen content and cardiac output. Blood oxygen content is determined by haemoglobin concentration, its affinity for oxygen, its oxygen saturation and a small portion of plasma-dissolved oxygen according to oxygen partial pressure and temperature. Cardiac output is defined by stroke volume and heart rate (10). Tissue oxygen delivery can mathematically be expressed as follows:

Equation 1-1: Oxygen delivery determinants

$$DO_2 = \underbrace{([Hb] \cdot A \cdot SO_2 + K \cdot ppO_2)}_{CaO_2} \cdot \underbrace{SV \cdot HR}_{CO}$$

where DO_2 indicates delivery of O_2 in mL.min^{-1}, CaO_2 is the arterial oxygen content in mL.gr^{-1}.dL^{-1}, [Hb] indicates concentration of haemoglobin in gr.dL^{-1}, A is the amount of O_2 able to be bound to haemoglobin in ml.Kg^{-1}, SO_2 indicates percentage of O_2-saturated haemoglobin and K is the amount of O_2 in mL dissolved in plasma for a given temperature per each kPa of pressure, ppO_2 is the actual partial pressure of O_2 in kPa, CO is the cardiac output in litters of blood ejected by the heart per minute, SV is the amount of blood ejected in each heart beat in mL and HR is the number of heart beats per minute.

It becomes obvious that one of the main factors determining the ability of the cardiovascular system to provide sufficient oxygen to match tissue demands is related to the capacity of the heart to generate a sufficient cardiac output (CO). However, cardiac output and more specifically stroke volume (SV), result from the interaction of multiple cardiac and vascular factors that continuously interact through the cardiac cycle. Stroke volume should therefore be seen as the end product of a complex process, whose deep understanding is key for the purpose of the present work.

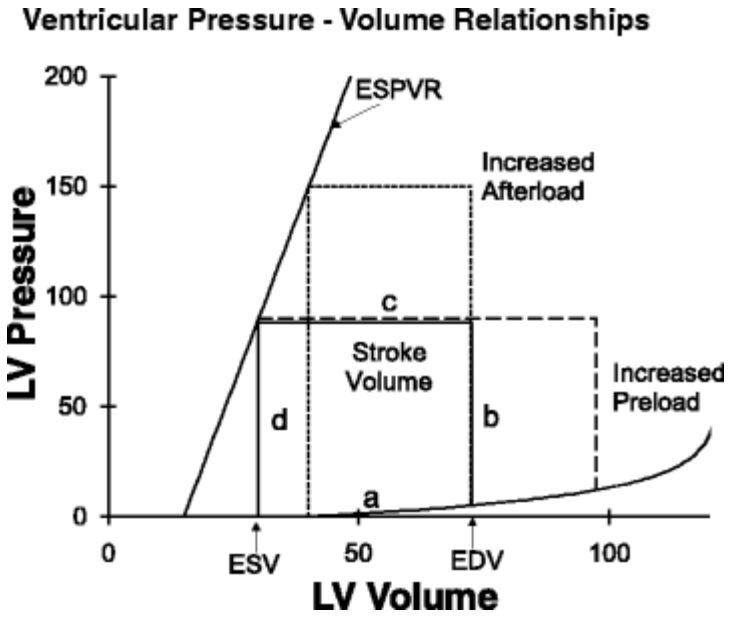
1.3 Pressure-volume loops

In order to better visualize and analyse the different phases of the cardiac cycle, the influence of changes in ventricular loading conditions and intrinsic cardiac function, and other factors affecting the generation of SV, the pressure-volume loop representation will be used (Figure 1-1). Popularised by Suga, et al in 1972, ventricular pressure-volume loops can be obtained in-vivo by the invasive measure of ventricular pressures during a cardiac cycle (11). Their use in clinical practice at the bedside is however limited, as they require placement of an intraventricular catheter. Notwithstanding their operational limitations, pressure-volume loops provide substantial information on the relation between cardiac load and contractile function, and can be used to estimate cardiac work, myocardial oxygen consumption and cardiac efficiency (12).

In pressure-volume loops four phases are depicted (Figure 1-1): diastolic filling (a), isovolumetric contraction (b), ejection (c) and isovolumetric relaxation (d). Through

modification of cardiac loading conditions, two additional relationships can be described: the end systolic pressure-volume relationship (ESPVR) and the end diastolic pressure-volume relationship (EDPVR). End-systolic volume (ESV) point represent the remaining ventricular volume the endo of ventricular contraction and the end-diastolic volume (EDV) the ventricular volume at the end of diastole.

Figure 1-1: Cardiac pressure-volume loop [1]



1.4 Determinants of cardiac output

The amount of blood expelled by the heart, or cardiac output, is a function of heart rate (HR) and SV. Heart rate is controlled through sympathetic innervation, circulating catecholamine levels and other factors that can influence the heart pacing tissue (sino-auricular node, auriculo-ventricular node, etc.) but also directly cardiac myocytes (1). Heart rate is the most adaptable response to changes in oxygen consumption demands, with increases that can reach 2 to 3-fold baseline values in some cases (1). Stroke volume on the contrary, is less adaptable (peaking at 50% increase from baseline), and determined by three main factors that inter-relate beat by beat during the cardiac cycle: preload, afterload and contractility (1). Ability to evaluate these three parameters independently from one another is a challenging but an often necessary task in the critically ill patient. The independent measure of preload, afterload and

[1] From Walley, K.R. Left ventricular function: time-varying elastance and left ventricular aortic coupling. Crit Care 20, 270 (2016). (12). Reproduced under Creative Commons CC BY license.

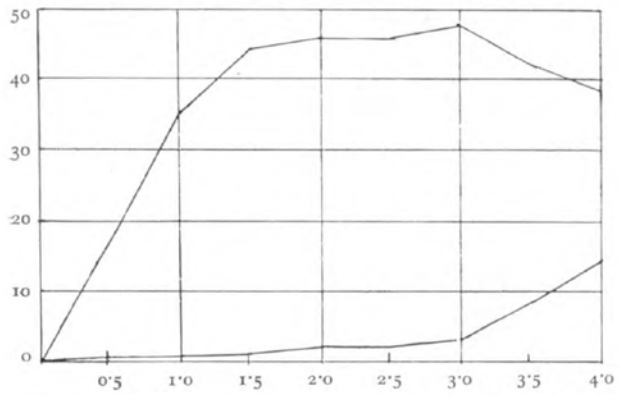
contractility in the critically ill patient is of key relevance to understand the physio-pathological processes of illness, the logic behind therapeutic targets and to measure the effects of medical interventions. The following sections will aim at describing the most up-to-date knowledge of these variables and the currently most accepted methods for their estimation.

1.4.1 Preload and its estimation

Numerous studies have demonstrated that isometric absolute tension and isotonic contraction velocity, or fibre shortening velocity, of cardiac fibres and papillary muscles depend on the longitude of the muscular fibre length at the moment of contraction initiation (1,12–17). The phenomena by which greater tension levels can be generated according to sarcomere length in cardiac myocytes is known as Preload (1). Multiple theories exist to explain the physiology behind preload, some of them pointing at enhanced troponin C sensitivity to calcium, calcium homeostasis changes due to structural fibre changes and enhanced actin-myosin binding capacity as sarcomeres elongate (1,18). The analysis of the physiology of preload is beyond the scope of the present work and will not be discussed in detail.

Although identified by others before, Starling et al. described the ability of the heart to adjust its contractile force in response to changes in ventricular volumes (1,18,19). The so-named Frank-Starling relationship is a curved relation between EDV and generated end-systolic pressure, being steep in its initial portion and flattening at higher EDV (Figure 1-2) (19) . It indicates that in the healthy heart, increases in EDV lead to more powerful and faster contractions, higher systolic ventricular pressure, longer ejection times and eventually increased SV, or in other words, that increases in preload can lead to increases in SV (12).

Figure 1-2: Startling's relation between end-diastolic volume and end-systolic pressure [2]

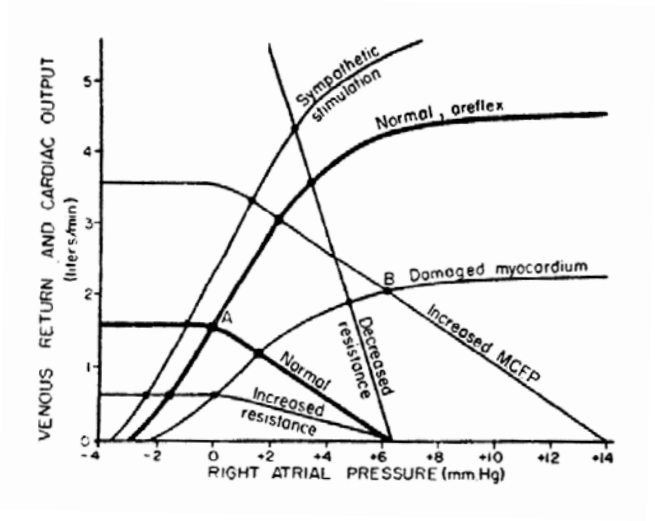


x-axis: ventricular volumes in mL / y-axis: intraventricular pressure in mmHg

Guyton et al. were able to identify that for a given contractile function of the heart, a direct relation between venous return, right atrial pressure and CO exist, and that venous return is directly linked to the difference between mean systemic filling pressure and right atrial pressure (20). By coupling venous return curves with the Frank-Starling relationship according to right atrial pressure, Guyton et al. were able to model CO production for a given contractility and venous return, linking preload-driven increases of CO to venous return (Figure 1-3) (20). However, because right atrial pressure is determined in part by venous return, but also right atrial, ventricular and pulmonary artery compliance, and the second can be influenced by ventricular intrinsic or extrinsic factors, atrial pressure may fail to estimate preload accurately and is therefore considered as an unreliable marker of preload (21).

[2] From Starling E-H. The Linacre lecture on the law of the heart. Cambridge; 1915. (19). Reproduced under public domain attribution license.

Figure 1-3: Guyton's interaction between cardiac function curves and venous return [3]



Other authors have considered the definition of preload as the passive ventricular tension exerted on the ventricular wall at the end of ventricular diastole by using the modified Laplace equation and assuming a spherical ventricle (21). By this definition, the force or tension exerted on ventricular fibres at end-diastole is a function of ventricle radius, wall thickness and intraventricular pressure. However, measures of ventricular end-diastolic tension are difficult to obtain in clinical practice as some of them (end diastolic pressure) require intraventricular catheterisation for direct measurement (22). These limitations add to the potential inaccuracies derived from the mathematical oversimplification of the ventricular three-dimensional structure. Since ventricular thickness at end-diastole does not change acutely, and considering the limitations of end diastolic pressure, it is widely accepted that the evaluation of variations in EDV is the most practical and reliable marker of changes in preload (1,22).

It must be taken into account that estimation of ventricular volumes or pressures does not imply assessment of volume responsiveness, this is, the ability to increase SV after administration of a fluid bolus. There is general consensus that the use of static markers of preload, such as right atrial pressure or EDV provide little to no ability to predict fluid responsiveness (23–26). As described by Guyton et al., changes in ventricular function curves will yield different responses in CO for the same right atrial pressure (20). It is therefore not surprising to observe a lack of ability of central venous

[3] From Guyton A. Determination of cardiac output by equating venous return curves with cardiac response curves. Physiol Rev. 1955 Jan;35(1):123–9. (20). Reproduced with permission from the American Physiologycal Society (license agreement number: 4864041055047).

pressure (CVP - here to be considered as almost equivalent to right atrial pressure and end diastolic ventricular pressure) to predict increases in CO induced by preload increases, as different patients may have the same CVP but respond very differently to fluid administration (24,27). Similarly, a single value of EDV lacks the ability to inform on whether fluid administration could induce further ventricular dilation, preload increase and consequently, more powerful contractions that result in greater SV. On the contrary, the assessment of volume responsiveness through dynamic indices, that utilise the assessment of responses in cardiac output to preload variations (i.e.: pulse pressure variation, stroke volume variation, passive leg raising manoeuvre - PLR, etc.) have demonstrated to be reliable to detect preload reserve and are currently recommended to guide fluid therapy (23,24,26,28).

1.4.2 Afterload and its estimation

In the isolated cardiac fibre, definition of afterload is rather straightforward, and is considered as the force opposing contraction (1,29). Logically, the higher the opposing force on the contracting myocyte, for a given preload and contractile state, the slower the contraction velocity (1,29–31).

However, estimating afterload on the living ventricle becomes a challenging task. Using a direct extrapolation from isolated muscle studies, afterload could be defined as the stress exerted on the ventricular wall during systole. As described for preload in previous sections, this can be estimated using a simplified Laplace equation, assuming a spherical ventricle, as described in Equation 1-2.

Equation 1-2: modified Laplace equation for ventricular wall tension

$$\sigma = \frac{p \cdot r}{2h}$$

where σ is the average ventricle wall stress, p is the pressure in the ventricle, r is the radius of the ventricle and h is the thickness of the ventricle wall. From the equation above, and assuming the drawbacks of its oversimplified approach for a spherical ventricle, it becomes clear that estimations made with this method will vary throughout systole, as intraventricular pressure, ventricle radius and wall thickness change during contraction (21,29,32). It has been postulated that ventricle wall stress at the end of

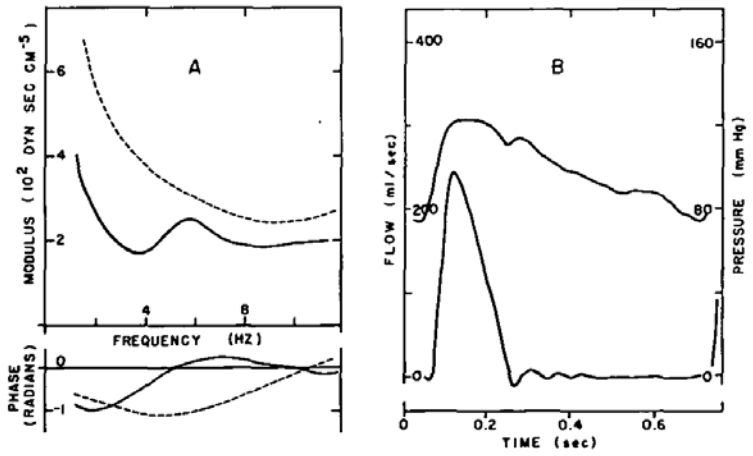
systole represents the best estimation of afterload as it defines the limiting force opposing further cardiac fibre shortening. In other words, no further ejection of blood occurs when wall stress reaches the maximal value for a given ventricle size, thickness and pressure (32). However, the measure of ventricular wall stress requires measurement of intraventricular pressures, chamber sizes and wall thickness on a beat-by-beat basis, which limits its implementation at the bedside. Furthermore, wall stress can be modified not only by interventions modifying afterload but also by variations in preload and contractility, which change end-systolic pressure (29,32).

Alternatively, several authors have considered the use of systemic vascular resistance (SVR) as ventricular afterload. In such approach, and in analogy to the Ohm's law for a direct current electrical circuit, resistance relates to static pressure and flow through the system. Resistance is, in turn, linked to the diameter of arterioles and capillaries, blood viscosity and arterial tree geometry among others (1,29,32). While SVR relates to changes in afterload induced by vasodilation and vasoconstriction it underestimates its measure when compared to end-systolic wall stress (32). The reason for this is that SVR assumes a constant flow and pressure throughout the cardiac cycle, ignoring the pulsatile component and wave reflections occurring in the cardiovascular system (29,32).

The use of aortic input impedance aims at incorporating the oscillatory component of the cardiovascular system into the estimation of afterload (29,33). In analogy to alternate current circuits, aortic input impedance is a frequency-dependent function that depends on oscillations throughout the cardiac cycle and is calculated on a frequency domain basis. Aortic input impedance reflects elastic properties of the aorta and pressure wave reflections (29,33,34), and remains stable during the cardiac cycle and independent from cardiac function or preload (29,33). Furthermore, using the model of a hydraulic conducting system, characteristic impedance of the aorta can be calculated when there are no reflected waves or when their effect is significantly attenuated. Since these exert its maximum effect at higher frequencies, elastic properties of the aorta can be estimated as an average of the moduli of oscillations in the lower frequency spectrum (29,33). Vascular resistances can also be integrated into the calculation as impedance at zero oscillatory frequency (29,33). Therefore, the total force opposing blood flow depends on a static component (SVR or non-pulsatile) and a pulsatile component in the frequency domain (arterial impedance) (Figure 1-4). Then, aortic input impedance can be considered as the external load opposing blood flow (extrinsic afterload) whereas ventricular wall tension would be the internal load against which the myocardium needs to contract during ejection (intrinsic afterload) (29). Nevertheless,

neither of the two options is readily applicable on clinical practice. Evaluation of aortic input impedance requires the use of accurate aortic invasive pressure and flow measurements, and advanced computation using Fourier analyses (35). How these two measures interact with each other on a beat-to-beat basis and how could they be combined to produce a final consolidated measure of afterload is still matter of debate (21,22).

Figure 1-4: Example of an aortic input impedance spectra [4]

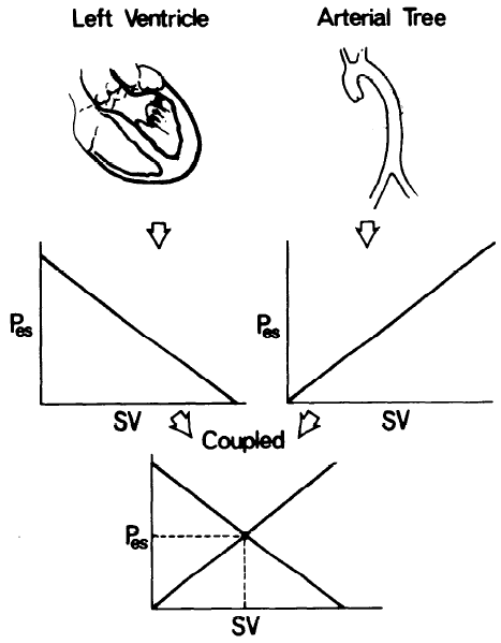


An alternative assessment of the extrinsic afterload or the so-called arterial load comes from the analysis of the effective arterial elastance (E_a). Suangawa et al. modelled the left ventricle as an elastic chamber which periodically (beat-by-beat) increases its elastance to a value equal to the slope of the ESPVR, and called it ventricular end-systolic elastance or E_{es} (36). Similarly, the arterial load property was represented as an "effective elastance" which is the slope of the arterial ESPVR. The maximal transfer of potential energy from one elastic chamber to another occurs when they have equal elastances, this is, when the ventricle and arterial system are considered to be "coupled" for an optimized stroke work (Figure 1-5) (36). Effective arterial elastance is estimated using a 3 element Windkessel model (37) and integrates characteristic impedance, SVR, total arterial compliance (TAC) and ejection times (38). Is also simplifies the measure of arterial load allowing it to be performed in the time domain without the need for advanced measures and computations. This approach has been validated in human subjects (35) and allows for a practical evaluation of extrinsic afterload or arterial load. Furthermore, as it was the case for preload and the right atrial

[4] From Milnor WR. Arterial impedance as ventricular afterload. Circ Res. 1975 May;36(5):565–70. (33). Reproduced with permission from Wolters Kluwer Health, Inc. (license agreement number: 4872401457009).

pressure in the venous return – cardiac output relation described by Guyton et al. (20), end systolic pressure can be used to relate ventricular and arterial elastance and link them with ventricular end-systolic wall stress changes for a given thickness and ventricular volume, thus joining extrinsic and intrinsic afterload measurements.

Figure 1-5: Effective arterial elastance and ventriculo-arterial coupling [5]



While the utilisation of E_a allows for a general estimation of extrinsic afterload on the ventricle, it does not inform on the relevance of its main components, those mainly being vascular resistances, compliance and reflected waves. This is especially relevant, as different therapeutic approaches may be taken for different pathophysiological reasons for altered extrinsic afterload or arteria load (39). However, the static component of arterial load can be relatively easily estimated by the calculation of SVR according to the ratio of mean arterial pressure (MAP) to CO. However the estimation in the time domain of the pulsatile component of arterial load is challenging. Accurate calculations of TAC can be performed by analysing systolic and diastolic areas under the aortic pressure waveform (40), however this requires continuous data measurements and, again, substantial computation and complex analyses. Alternatively, the ratio of pulse pressure (PP) to SV can be used and has

[5] From Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol. 1983 Nov;245(5 Pt 1):H773-80. (38). Reproduced with permission from the American Physiologycal Society (license agreement number: 4864040994123).

proven to be closely related to arterial system compliance calculated by the area method (41). Chemla et al. were able to demonstrate that E_a could also be described as a multilinear function of SVR and TAC in both normotensive and hypertensive patients (42). In their study, E_a was 2.5 times more sensitive to changes in SVR than in TAC, indicating the predominance of the former on arterial load. In addition, Chemla et al. demonstrated that end-systolic ventricular pressure can be best estimated as 90% of the aortic systolic arterial pressure (SAP), and proposed a new definition of E_a as the ratio of 0.9 x SAP over stroke volume index (SVI). The advantage of relating arterial load to SAP rather to other pressures is that it incorporates SVR, TAC and wave reflections (43). Therefore, as suggested by some authors, and in absence of significant aortic outflow tract obstruction, changes in SAP could be a practical, bedside estimate of extrinsic afterload variations (1,22).

1.4.3 Contractility and its estimation

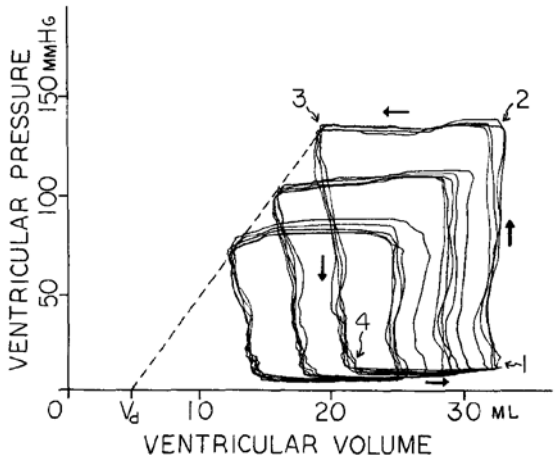
Contractility is an intrinsic property of the cardiac muscle that depends on the interaction between its different contractile elements to produce increases or decreases of generated force independently from muscle fibre loading conditions (preload and afterload) (1). Contractility, inotropy and ventricular function are used as synonyms in the present work. Any factor that ultimately increases the ability of the cardiac muscle to convert chemical into mechanical energy will, thereafter, generate more powerful contractions and increase its contractility (1,18). Contractility is mainly enhanced by increasing calcium ion influx across the sarcolema, increasing the release of calcium by the sarcoplasmatic reticulum or sensitizing troponin C to calcium (1,18). It must also be taken into account that abrupt increases in afterload can lead to increases in contractility by a mechanism not fully understood (Anrep effect) and increases in heart rate can also increase contractility (Bowditch effect, or Treppe phenomenon) (1,18).

It is widely accepted that the gold standard for estimating contractility is the slope of the ventricular ESPVR (Figure 1-1) or E_{es} (12). First described by Suga et al., E_{es} was proposed as a true load-independent marker of contractility (44), being constant through changes in preload (45), at different afterload levels (46) (Figure 1-6) and remaining stable during heart rate variations in canine models (47). The hypothesis was later confirmed in human subjects by McKay et al. (48). According to this description of the heart, the ventricle can be represented as an elastic chamber that is able to change its elastance (here the ratio of ventricular pressure over instantaneous

volume) throughout the cardiac cycle, from a very compliant / low elastance compartment in diastole, to a low compliance / high elastance chamber during systole (12). Furthermore, as described before, the combination of the ESPVR with the equivalent relation in the arterial system, through the use of the maximum value of both ventricular and arterial elastances (E_{es} and E_a), permits the coupling of the heart with the arterial system (12,49).

However, the use of E_{es} in clinical practice is limited, as it requires invasive measures of intraventricular pressures, simultaneous ventricular volume measures and interventions to modify loading conditions so the ESPVR can be determined. Therefore, E_{es} has been relegated to the physiology laboratory and is not widely applied at the bedside to estimate contractility. More recently, Chen et al. have attempted to estimate E_{es} using non-invasive methods (50). Authors developed an approach which uses systolic and diastolic arm cuff non-invasive readings, echocardiography derived SV and left ventricle ejection fraction (LVEF). Results yielded a good correlation with invasive measures at baseline and after dobutamine infusion. Since then, several other methods have been developed to estimate E_{es} non-invasively using a single beat principle. However results indicate that accuracy of these methods is insufficient for its broad implementation in clinical practice (51,52).

Figure 1-6: Effects of preload and afterload changes on pressure-volume loops and end-systolic pressure-volume relationship [6]



[6] From Suga H, Sagawa K. Mathematical interrelationship between instantaneous ventricular pressure-volume ratio and myocardial force-velocity relation. Ann Biomed Eng. 1972 Dec;1(2):160–81. (11). Reproduced with permission from Springer Nature (license agreement number: 4863660496794).

1.5 Left Ventricular dP/dt $_{max}$

The maximum value of the first derivative of left ventricular (LV) pressure over time or LV dP/dt_{max}, measured during the isovolumetric phase of the cardiac systole, before the opening of the aortic valve, has been studied for many years as a simpled method to measure changes in cardiac contractility.

Reeves et al. were the first to systematically evaluate the performance of LV dP/dt_{max} during changes in preload, afterload and contractility in open-chest dog models (53). Results indicated a strong correlation with contractility but also a clear dependence of LV dP/dt_{max} to changes in preload and afterload (53). While these results were later confirmed in similar experiments by Wallace et al. (54), it was also found that LV dP/dt_{max} could be affected by changes in HR. Therefore, early in the discovery of this parameter, its ability to purely represent contractility was challenged (54). Interestingly, some contradictory results were found in canine models with regards to the afterload dependency of LV dP/dt_{max}. Mahler et al. (55) as well as Schmidt et al. (56) presented similar preload dependence after fluid overload but did not observe a dependency of LV dP/dt_{max} to afterload (55). These findings might have helped to maintaining the believe on the validity of LV dP/dt_{max} to be a pure estimator of LV contractility.

1.5.1 Corrections on LV dP/dt_{max} to reduce the effect of loading conditions

Mason et al. proposed methods to minimize the effect of preload and afterload dependence on the measure of LV dP/dt_{max} (57). In their study on human subjects, LV dP/dt_{max} corrected by EDV and common developed isovolumetric pressure, and a combination of both, was useful to track changes in contractility without the influence of loading conditions (57). In a latter, more detailed physiological study on isolated papillary muscle, canine models and patients, Mason et al. found that the ratio of LV dP/dt_{max} to instantaneous measured ventricular pressure and to the common developed isovolumetric pressure remained unaltered to changes in afterload but were slightly sensitive to changes in preload (13). Furthermore, results also suggested that LV dP/dt_{max} was only afterload independent when it occurred before aortic valve opening, meaning that changes in arterial pressure that accelerate or delay aortic valve opening had the potential to affect LV dP/dt_{max} (13).

Quinones et al. confirmed again in humans, that LV dP/dt_{max} was sensitive to changes in contractility but it showed a clear preload dependence during acute changes in preload (31). However, normalizing measures by ventricular end-diastolic

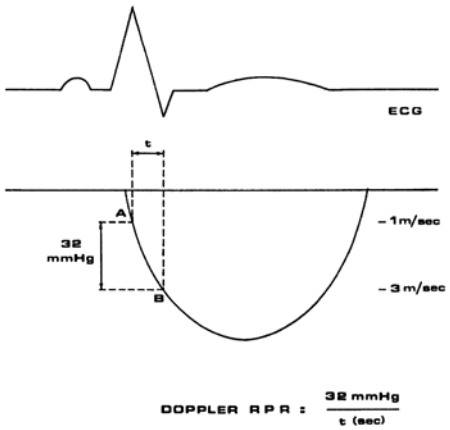
circumference nullified the effect of preload variations (31). In their study an acute increase in afterload yielded only slight elevations in LV dP/dt_{max} and no changes in the normalized estimation by LV end-diastolic circumference. Heart rate also affected LV dP/dt_{max}. Interestingly, velocity of circumferential shortening, a preload insensitive marker of cardiac performance during the LV ejection phase, was substantially decreased during afterload increases (31). This indicated that elevations in afterload affect in opposed directions isometric (increase during afterload increase) and isotonic (decrease during afterload increase) markers of cardiac contractility, resembling the effects of increased loading in the isolated cardiac fibre (1,30).

Finally, Little et al. demonstrated in dogs that the rate of LV dP/dt_{max} over EDV described a straight line relationship that was preload and afterload independent, and that resembled E_{es}, being superior to track inotropic stimulation in some circumstances (58).

1.5.2 Measuring LV dP/dt_{max} non-invasively

The main drawback of the use of LV dP/dt_{max} is that it requires an intraventricular catheter for its measure. While this may be justifiable in some clinical set-ups, such as in the cardiac catheterisation laboratory, it is not practical in the intensive care unit scenario. It is also not ethically reasonable to place an intraventricular catheter only for the purpose of the measurement of LV dP/dt_{max} in critically ill patients due to its potential iatrogenic effects. Therefore, methods to evaluate LV dP/dt_{max} non-invasively have been explored, being the method proposed by Bargiggia et al. using ultrasound the most widely applied in clinical practice (59). In this method, continuous wave Doppler is used to estimate pressure differences between the left atrium and the ventricle by the measure of flow velocity of a subjacent mitral insufficiency jet. According to the Bernouilli equation pressures are calculated at arbitrary points equivalent to 1 m/s (4 mmHg) and 3 m/s (34 mmHg) of mitral insufficiency jet flow velocities. By dividing by the time interval between these points a value of dP/dt is obtained that presents a good correlation (R=0.87) with LV dP/dt_{max} (Figure 1-7) (59).

Figure 1-7: Estimation of LV dP/dt$_{max}$ from the mitral insufficiency flow measurement using continuous flow Doppler signal [7]



However, the echocardiographic estimation of LV dP/dt$_{max}$ relies on a subjacent mitral insufficiency that is of sufficient significance to be measurable. Furthermore, it requires a good echocardiographic window that allows a correct alignment with the jet's flow direction. Unfortunately, limitations in image quality may jeopardize its measure, especially in those patients under mechanical ventilation and high positive-end-expiratory pressure levels, where the echocardiographic window is significantly limited.

1.6 Arterial dP/dt $_{max}$

Due to the limitation in the measure of LV dP/dt$_{max}$, the question whether arterial measures of dP/dt$_{max}$ could be used to estimate LV dP/dt$_{max}$ has gained popularity in recent years. While the validation of minimally invasive and non-invasive equivalent estimates of LV dP/dt$_{max}$ would be of significant value for clinicians, it must take into account not only the ability to track changes in contractility, but also evaluate their independence from arterial properties and ventricular loading conditions, so these new potential indices fulfil the basic requirement of any marker of LV contractile function.

[7] From Bargiggia GS, Bertucci C, Recusani F, Raisaro A, de Servi S, Valdes-Cruz LM, et al. A new method for estimating left ventricular dP/dt by continuous wave Doppler-echocardiography. Validation studies at cardiac catheterization. Circulation. 1989;80(5):1287–92. (59). Reproduced with permission from Wolters Kluwer Health, Inc. (license agreement number: 4873571302548).

1.6.1 Femoral dP/dt$_{max}$

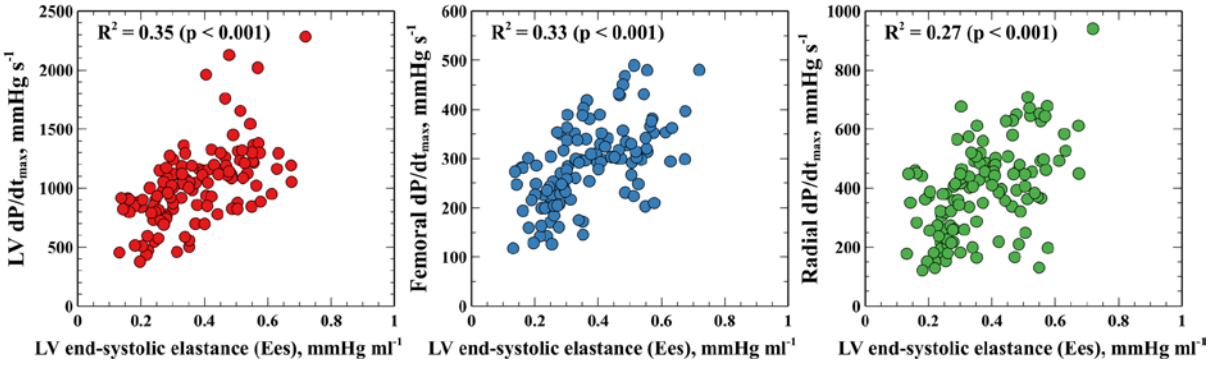
De Hert and colleagues were one of the first to evaluate the value of femoral dP/dt$_{max}$ to estimate LV dP/dt$_{max}$ and track changes is contractility (60). Authors evaluated the responses of femoral dP/dt$_{max}$ during changes in preload via PLR and contractility with dobutamine infusion. Femoral dP/dt$_{max}$ was significantly correlated with LV dP/dt$_{max}$ (R=0.82) but underestimated the measure by almost 40%. In this study, preload increases with PLR increased EDV but did not modify SV or LV dP/dt$_{max}$ which is of key relevance to explain the differences observed with present results. Conversely, dobutamine changes exerted a significant effect on both LV and femoral dP/dt$_{max}$ (60). These results suggested that femoral dP/dt$_{max}$ could be used to track changes in contractility while remaining preload independent.

On a later report, Scoletta et al. evaluated the relation between echocardiographic measures of LV dP/dt$_{max}$ and femoral artery readings. Both measure correlated well during stability periods but the limits of agreement where wide, with a percentage of error of 28% (61).

Interestingly, Morimont et al. was able to demonstrate that in anesthetized and mechanically ventilated pigs, femoral dP/dt$_{max}$ was significantly better in estimating both LV dP/dt$_{max}$ (R=0.7) and E$_{es}$ (R=0.8) when appropriate vascular filling was achieved (measured as a pulse pressure variation < 11%). This may suggest that the dependence of femoral dP/dt$_{max}$ to preload variations might only be present when preload reserve is present (62).

Up to date, the only study that evaluated the effects of changes in all determinants of cardiac performance (preload, afterload and contractility) on the measure of femoral dP/dt$_{max}$ is the study by Monge et al. (63). In their work on anesthetized pigs, the authors compared E$_{es}$, and LV, femoral and radial dP/dt$_{max}$, during increases and decreases of preload, afterload and contractility (Figure 1-8). Correlations of femoral and radial dP/dt$_{max}$ with E$_{es}$ were R^2=0.33 and 0.27, indicating that most of the variance explained was attributable to other factors other than cardiac contractility (63). The correlation between LV with femoral and radial dP/dt$_{max}$ was R^2=0.56 and 0.45, also indicating that half of the variance was due to other “non-ventricular” factors. In addition, femoral and radial dP/dt$_{max}$ were sensitive to changes in afterload (both increases and decreases) and preload decreases (63) (Figure 1-8).

Figure 1-8: Correlation between E_{es} and LV, femoral and radial dP/dt_{max} (as originally presented) [8]



1.6.2 Radial dP/dt_{max}

Results on the ability of radial dP/dt_{max} to estimate changes in contractility and reflect LV dP/dt_{max} values are conflicting. Tartiere et al. evaluated the capacity of radial dP/dt_{max} in patients with heart failure to track LV dP/dt_{max} changes measured from the mitral insufficiency flow as described by Bargiggia et al. (59,64). Results indicated that both parameters were significantly correlated (R=0.7) (64). In a later report, the same authors utilized radial measures of dP/dt_{max} to predict mortality or transplantation on heart failure patients. Results suggested that low radial dP/dt_{max} could be superior and independent from other usual predictors of poor outcome (65), such as PP (66,67) or LVEF (68). However, such results were strongly criticised and mostly attributed to a close relation between PP and radial dP/dt_{max} (69). Conversely, Sharman et al found poor correlations / explained variance (R^2=0.006) and a significant bias (almost -20% from ventricular values) between measures of radial dP/dt_{max} and LV dP/dt_{max}.

[8] From Monge Garcia MI, Jian Z, Settels JJ, Hunley C, Cecconi M, Hatib F, et al. Performance comparison of ventricular and arterial dP/dtmax for assessing left ventricular systolic function during different experimental loading and contractile conditions. Crit Care. 2018;22(1):325. (63). Reproduced under Creative Commons CC BY license.

1.7 Introduction summary

Cardiovascular system performance is determined by the beat-by-beat interaction of the heart and the vascular system. Factors affecting cardiac performance (preload, afterload and contractility) interact with each other and with the arterial and venous system to deliver sufficient oxygen to the tissues. Stroke volume is the result of the interaction of all above mentioned elements.

Estimation of the different factors affecting cardiac performance independently from one another is a challenging task, but often necessary for diagnosis and treatment in the critically ill patient. The use of LV dP/dt_{max} was popularized in the 60'-80' as a marker of contractility, however it suffers from a preload dependence and a slight afterload dependence. While attempts to normalize its measure according to preload and afterload estimates have yielded different degrees of success, its measure is unpractical in the critically ill patient, as it requires invasive LV catheterisation.

The use of arterial dP/dt_{max} has been proposed as a surrogate of LV dP/dt_{max} and as a potential estimator of contractility. However, recent results suggest that it may present a similar preload dependence as LV dP/dt_{max}. Furthermore, since it is measured during the ejection phase of the cardiac cycle, it should also be influenced by arterial loading characteristics (or extrinsic afterload). Despite these potential limitations, arterial dP/dt_{max} keeps being considered as a potential marker of contractility and presented as such in many cardiovascular monitors currently available on the market. The present work aims at elucidating whether femoral dP/dt_{max} is influenced by ventricular and arterial loading conditions, and whether it can be considered a good estimator of cardiac contractility in clinical practice.

2 Hypothesis

The driving hypothesis of the present doctoral work reads as follows:

"We hypothesise that the dP/dt_{max} measured at the femoral artery level is influenced by cardiac loading conditions (preload and afterload) and arterial load (external afterload), and is thereafter an unreliable marker of left ventricular contractility in clinical practice"

3 Objectives

3.1 Primary objective

- To measure the effect of the following cardiac performance determinants on femoral dP/dt_{max} in a representative cohort of critically ill patients with acute cardiovascular failure:
    - Contractility changes induced by changes in dobutamine infusion;
    - Afterload changes induced by changes in norepinephrine infusion;
    - Preload changes induced by PLR or standard fluid bolus.

3.2 Secondary objectives

- To determine the relevance of arterial load factors in the measure of femoral dP/dt_{max}.
- To determine the relevance of preload dependence on the response of femoral dP/dt_{max} to preload increases.

Two different studies were performed to fully address the hypothesis and objectives defined for the present work. In the first, a prospective observational study was designed to evaluate the responses of femoral dP/dt_{max} during variations in preload, afterload and contractility. The second study was designed as a retrospective analysis of a pre-existing database of controlled volume expansions, to determine the role of preload dependence status on the sensitivity of femoral dP/dt_{max} to preload variations. The results of the present doctoral work have been published in two first-quartile scientific research journals and are presented hereinafter.

4 Published Articles

4.1 Article 1

Title:

Influence of changes in ventricular systolic function and loading conditions on pulse contour analysis-derived femoral dP/dt_{max}

Authors:

Sergi Vaquer, Denis Chemla, Jean-Louis Teboul, Umar Ahmad, Flora Cipriani, Joan Carles Oliva, Ana Ochagavia, Antonio Artigas, Francisco Baigorri and Xavier Monnet.

Journal:

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RESEARCH Open Access

Influence of changes in ventricular systolic function and loading conditions on pulse contour analysis-derived femoral dP/dt_{max}

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Abstract

Background: Femoral dP/dt_{max} (maximum rate of the arterial pressure increase during systole) measured by pulse contour analysis has been proposed as a surrogate of left ventricular (LV) dP/dt_{max} and as an estimator of LV systolic function. However, femoral dP/dt_{max} may be influenced by LV loading conditions. In this study, we evaluated the impact of variations of LV systolic function, preload and afterload on femoral dP/dt_{max} in critically ill patients with cardiovascular failure to ascertain its reliability as a marker of LV systolic function.

Results: We performed a prospective observational study to evaluate changes in femoral dP/dt_{max}, thermodilution-derived variables (PiCCO2—Pulsion Medical Systems, Feldkirchen, Germany) and LV ejection fraction (LVEF) measured by transthoracic echocardiography during variations in dobutamine and norepinephrine doses and during volume expansion (VE) and passive leg raising (PLR). Correlations with arterial pulse and systolic pressure, effective arterial elastance, total arterial compliance and LVEF were also evaluated. In absolute values, femoral dP/dt_{max} deviated from baseline by 21% (201 ± 297 mmHg/s; $p = 0.013$) following variations in dobutamine dose ($n = 17$) and by 15% (177 ± 135 mmHg/s; $p < 0.001$) following norepinephrine dose changes ($n = 29$). Femoral dP/dt_{max} remained unchanged after VE and PLR ($n = 24$). Changes in femoral dP/dt_{max} were strongly correlated with changes in pulse pressure and systolic arterial pressure during dobutamine dose changes ($R = 0.942$ and 0.897, respectively), norepinephrine changes ($R = 0.977$ and 0.941, respectively) and VE or PLR ($R = 0.924$ and 0.897, respectively) ($p < 0.05$ in all cases). Changes in femoral dP/dt_{max} were correlated with changes in LVEF ($R = 0.527$) during dobutamine dose variations but also with effective arterial elastance and total arterial compliance in the norepinephrine group ($R = 0.638$ and $R = -0.689$) ($p < 0.05$ in all cases).

Conclusions: Pulse contour analysis-derived femoral dP/dt_{max} was not only influenced by LV systolic function but also and prominently by LV afterload and arterial waveform characteristics in patients with acute cardiovascular failure. These results suggest that femoral dP/dt_{max} calculated by pulse contour analysis is an unreliable estimate of LV systolic function during changes in LV afterload and arterial load by norepinephrine and directly linked to arterial waveform determinants.

Keywords: Haemodynamic monitoring, Waveform analysis, Ejection fraction, Preload, Afterload, Thermodilution

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Background

Current haemodynamic monitoring devices performing arterial pulse contour analysis can measure and monitor the maximum rate of rise of arterial pressure (dP/dt_{max}). By analogy with the left ventricle (LV) dP/dt_{max}, arterial dP/dt_{max} is supposed to reflect LV systolic function [1–8].

Several studies have suggested that measurements of arterial dP/dt_{max} obtained from radial [7, 9] and femoral [7, 10] arterial pressure waveforms were comparable to LV dP/dt_{max} and, in some cases, might be useful for predicting patient outcome [11]. However, conflicting results regarding the comparability of LV dP/dt_{max} and arterial dP/dt_{max} have also been presented in both adults and children [12, 13]. Despite these uncertainties, arterial dP/dt_{max} is most often presented as a marker of LV systolic function in many off-the-shelf haemodynamic monitoring systems. Supportive literature is based on the observed good correlation between LV and arterial dP/dt_{max} during periods of haemodynamic stability [7–9, 12]. However, these good correlations documented on stable patients do not necessarily imply that femoral dP/dt_{max} provides an adequate evaluation of changes in LV systolic function during haemodynamic challenges.

Many physiological factors other than LV systolic function may influence arterial dP/dt_{max}, including the timing of the measurement relative to aortic valve opening, and the potential influences of cardiac preload and afterload (including its resistive and pulsatile components). To be considered a reliable marker of LV systolic function, arterial dP/dt_{max} should be unaffected by changes in these variables and should consistently respond to directional changes in LV systolic function.

Therefore, to assess the validity of arterial dP/dt_{max} as an index of LV systolic function and the relative contribution of changes in cardiac preload and afterload on its measurement, we studied the responses of femoral dP/dt_{max} during changes in the dose of dobutamine and norepinephrine, during passive leg raising (PLR) manoeuvre [14] and after intravascular fluid administration in critically ill patients with circulatory shock. We also compared these changes with markers of left ventricular afterload and with left ventricle ejection fraction (LVEF) measured by transthoracic echocardiography.

Methods

We performed a prospective observational study in two adult intensive care units (Servei de Medicina Intensiva, Corporació Sanitària Universitària Parc Taulí, Sabadell, Spain, and Service de Médecine intensive-réanimation, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France). The study was approved by local ethics committees of both institutions (Comitè Ètic d'Investigació Clínica de la Corporació Sanitària Parc Taulí CEIC2013616 and Comité pour la Protection des Personnes Ile-de-France VII 2011A01696-35). All patients or next of kin gave their consent to participate to the study. Data in this manuscript are presented following the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) criteria for observational studies [15].

Patients

Inclusion criteria were age older than 18 years old and presence of at least one of the following signs of haemodynamic failure in the context of acute illness:

- Systolic arterial pressure ≤ 90 mmHg or decreases of more than 50 mmHg in the last 3 h or mean arterial pressure ≤ 65 mmHg
- Oliguria ≤ 0.5 mL/kg/h for more than 2 h
- Blood lactate ≥ 2 mmol/L (or 22 mg/dL)
- Central venous oxygen saturation ≤ 60%
- Skin mottling

Patients had to be monitored with a transpulmonary thermodilution device (PICCO2, Pulsion Medical Systems, Feldkirchen, Germany) and must present the need for a change in the dose of norepinephrine or dobutamine, or for volume expansion or a PLR test [14], as decided by the attending physicians.

Exclusion criteria were the evidence of a significant aortic stenosis with echocardiography (mean pressure gradient of the aortic valve ≥ 25 mmHg) and conditions precluding measurements of femoral dP/dt_{max} of sufficient quality such as over-damping or under-damping of the arterial pressure signal persisting after repeated flushes of the arterial line.

Recorded variables

Arterial pressure was measured through an arterial catheter inserted in the femoral artery (PV2015L20-A, Pulsion Medical Systems, Feldkirchen, Germany). The catheter was connected to a PiCCO2 device, which automatically and continuously calculated femoral dP/dt_{max}. With this device, dP/dt_{max} was obtained from the uprising portion of the arterial curve, representing the steepest incline of the arterial trace in systole, and averaged over 12 s. After zeroing the arterial pressure transducer system and before each measurement, the arterial waveform signal quality was checked visually using a fast flush test to assess the adequacy of its damping [16]. In case of damping, repeated flushes were performed until sufficient signal quality was acquired. Data were recorded automatically by the PICCO2 device, and synchronisation of measurements with interventions was performed

manually and required the presence of the investigator team.

Transthoracic echocardiography was performed with a CX 50 device (Philips Healthcare, DA Best, The Netherlands) and used to estimate LV ejection fraction (LVEF). Measurements were taken by the same observer in all cases (SV) using the Simpson's method from two- and four-chamber apical views. Endocardial contours were hand-drawn, and volumes were automatically averaged out over three consecutive cardiac cycles by the software to calculate LVEF.

All patients were equipped with a central venous catheter in the superior vena cava territory. Thermodilution measurements were taken by injection of a 15-mL cold saline bolus (< 8 °C) through the central venous catheter. The results of three consecutive thermodilution measurements were averaged [17]. Cardiac output and stroke volume were measured through transpulmonary thermodilution [18] and indexed to body surface to provide cardiac index (CI), stroke volume index (SVI) and global end-diastolic volume index (GEDVi). Cardiac function index was obtained directly from the PiCCO2 device as a calculated variable (CFI = CI/GEDVi) [19].

To evaluate the resistive component of the arterial load, we calculated the systemic vascular resistance index (SVRi) as SVRi = (mean arterial pressure − central venous pressure)/cardiac index. To evaluate the pulsatile component of arterial loading, we calculated the total arterial compliance (TAC = stroke volume/arterial pulse pressure) [20]. Pulse pressure was calculated as the systolic minus the diastolic arterial pressure. The effective arterial elastance was used as a global index of arterial load as previously described (Ea = 0.9 × systolic arterial pressure/stroke volume) [21].

Study design

Data were collected before and after haemodynamic interventions. Volume expansion was performed by infusing 500 mL 0.9% saline solution over 10 min. Although other fluids might be considered for volume expansion [22], 0.9% saline solution was used in the units at the time the study was performed. A PLR test was performed by moving the patient from the semi-recumbent position to a position where the trunk is horizontal and the legs are elevated at 45°, as previously described [14].

In patients receiving fluid, the post-intervention measurements were taken immediately after the end of volume expansion. In patients in whom a PLR test was performed, these measurements were taken at the time when the maximal PLR-induced change in CI, if any, had occurred. This usually occurs within 1 min [14]. After the change in dose of norepinephrine or dobutamine, the post-interventions recording was performed after stabilisation of pulse contour-derived CI (for dobutamine) or of mean arterial pressure (for norepinephrine).

Patients could be included in the study as many times as therapeutic interventions were indicated by the attending physicians. Multiple measurements on the same patient could only be performed after sufficient time had passed between different manoeuvres to allow for stabilisation of haemodynamic variables and provided that the haemodynamic status of the patient had significantly changed when assessing the same type of interventions.

Data analysis

During norepinephrine dose variations, changes in Ea, TAC and SVRi were used to identify changes in arterial loading properties, while changes in systolic and mean arterial pressure were used to estimate changes in LV afterload. During dobutamine dose variations, changes in LVEF, CI and CFI were used to estimate changes in LV systolic function. Finally, during PLR and volume expansion, changes in central venous pressure (CVP) and GEDVi were used to track changes in LV preload.

We considered changes in femoral dP/dt_{max} induced by dobutamine dose variations as the main study variable. Using previous published data [10] and assuming a minimum required threshold of 10%, an α risk of 5% and a β risk of 20%, we estimated that the minimum number of paired measurements required for detecting a significant change in femoral dP/dt_{max} during variations in the dose of dobutamine was seven. We continued inclusions in the other study groups (changes in the dose of norepinephrine and PLR/VE) until this number was reached in both dobutamine subgroups (dose increases and decreases).

Normality of variables was assessed using the Kolmogorov–Smirnov test. Data are presented as mean ± standard deviation (SD) or medians and 25th–75th percentile, as appropriate. Data from norepinephrine and dobutamine dose changes were pooled (absolute values of increases and decreases were evaluated together and averaged), and absolute deviations from baseline values (called "changes" or "variations") were presented as mean differences. Statistical comparisons were made using the paired Student's *t* test or Wilcoxon rank test as appropriate. Percentages of change, rather than raw values alone, were presented in order to normalise baseline values. Correlation of changes in study variables during interventions was performed using Pearson's correlation test. In order to evaluate the potential impact of repeated measurements of the same type on a single patient, we studied changes in femoral dP/dt_{max} during interventions using only one measurement per patient. Manoeuvres with the highest norepinephrine or dobutamine dose change were selected, as well as the first volume expansion or PLR performed in each patient. All statistical

calculations were done using SPSS version 22 (International Business Machines, Armonk, NY, USA). Values of $p < 0.05$ were considered statistically significant.

Table 1 Baseline demographic and clinical characteristics of included patients

Clinical variable	All patients ($n = 19$)
Weight (kg)	81 ± 19
Height (cm)	166 ± 10
Age (years)	71 ± 9
Apache II (points)	25 ± 10
VT (mL)	406 ± 71
RR (min^{-1})	20 (18–25)
FiO_2	0.37 ± 0.08
PaO_2/FiO_2	257 ± 101
PEEP (cmH_2O)	6 (5–8)
P_{plat} (cmH_2O)	19 ± 5
NE (μg kg^{-1} min^{-1})	0.92 ± 0.93
DBT (μg kg^{-1} min^{-1})	5.39 ± 4.9)
WBC (× 10^3 dL^{-1})	18.6 (11–23)
CRP (mg dL^{-1})	24 ± 11.5
Cr (mg dL^{-1})	2.4 ± 1.2
Bil (mg dL^{-1})	1.1 (0.4–3.4)
Lactate (mg dL^{-1})	48.3 ± 30

Data are presented as mean ± SD or median (25th–75th%)

VT, tidal volume; RR, respiratory rate; FiO_2, inspired oxygen fraction; PaO_2, arterial oxygen partial pressure; PEEP, positive end-expiratory pressure; Pplat, plateau pressure; NE, norepinephrine; DBT, dobutamine; WBC, white blood cells; CRP, C reactive protein; Cr, creatinine; Bil, total bilirubin

Results

Patients

Nineteen patients were included (68% male subjects) between March 2013 and January 2015, in whom 72 therapeutic interventions were analysed (162 data points). Arterial line damping problems were observed in five patients, representing nine interventions. In all cases, repeated flushing of the arterial line led to resolution of the damping effect, so that no patient was excluded due to this problem. Two interventions had to be rejected given repeatedly doubtful validity of the data due to patient movement and incorrect acquisition procedure (Additional file 1: Figure S1). The distribution of medical interventions was as follows: norepinephrine dose increase: 9 (13%), norepinephrine dose decrease: 20 (29%), PLR: 12 (17%), volume expansion: 12 (17%), dobutamine dose increase: 7 (10%), dobutamine dose decrease: 10 (14%). On average, 3.7 ± 2.0 interventions were collected in each patient (Additional file 1: Figure S1). Case demographics and clinical characteristics are presented in Table 1 and Additional file 1: Table S1. Baseline haemodynamic characteristics are presented in Table 2. The majority of interventions occurred during septic shock (54 cases; 77%), followed by cardiogenic shock (10 cases; 14%) and hypovolemic shock (6 cases; 9%). During 55 (79%) therapeutic interventions, patients were mechanically ventilated, in 25 (45%) of which patients were not fully adapted to mechanical ventilation. In 44 cases (67%), sinus rhythm was present.

Table 2 Haemodynamic variables at baseline

Haemodynamic variable	DBT ($n = 17$)[a]	NE ($n = 29$)[a]	VE/PLR ($n = 24$)[a]	All interventions ($n = 70$)[a]
Femoral dP/dt_{max} (mmHg s^{-1})	1049 ± 347	1319 ± 371	1162 ± 336	1199 ± 365
HR (beats min^{-1})	89 ± 14	92 ± 18	90 ± 15	90 (74–104)
SAP (mmHg)	117 ± 17	137 ± 25	123 ± 14	127 ± 21
MAP (mmHg)	75 ± 7	84 ± 16	78 (75–84)	78 (70–86)
PP (mmHg)	66 ± 17	80 ± 18	70 ± 11	73 ± 17
CVP (mmHg)	9 ± 4	9 (8–12)	11 ± 4	9 (8-12)
GEDVi (mL m^{-2})	749 ± 120	773 (684–878)	773 ± 146	750 (671–846)
CI (L min^{-1} m^{-2})	2.7 ± 0.6	3.1 ± 1.2	3 (2.5–3.5)	3 (2.2–3.4)
SVI (mL m^{-2})	31 ± 9	35 ± 14	32 (24–45)	32 (25–44)
CFI (min^{-1})	3.9 ± 1.2	4.3 ± 1.6	4.4 ± 1.7	4.2 ± 1.6
LVEF (%)	43 ± 11	57 (42–61)	54 ± 17	50 ± 14
Ea (mmHg ml^{-1})	2 ± 0.5	2 (1.3–2.4)	1.9 (1.4–2.2)	1.9 (1.4–2.3)
TAC (ml $mmHg^{-1}$)	0.9 ± 0.3	0.8 (0.6–1.2)	0.8 (0.8–1.1)	0.8 (0.7–1.1)
SVRi (dynes s cm^{-5} m^{-2})	1774 (1657–2379)	2241 ± 1078	1739 (1575–2172)[b]	1775 (1627–2404)[b]

Data are presented as mean ± SD or median (25th–75th%)

NE norepinephrine, *VE/PLR* volume expansion/passive leg raising, *DBT* dobutamine, *HR* heart rate, *SAP* systolic arterial pressure, *MAP* mean arterial pressure, *PP* pulse pressure, *CVP* central venous pressure, *GEDVi* global end-diastolic volume index, *CI* cardiac index, *SVI* stroke volume index, *CFI* cardiac function index, *LVEF* left ventricle ejection fraction, *Ea* effective arterial elastance, *TAC* total arterial compliance, *SVRi* systemic vascular resistance index

[a] *n* value refers to cases

Effects of dobutamine

Changes in the dose of dobutamine ($n=17$ interventions; absolute dose variation $=4.3\pm1.3$ µg kg^{-1} min^{-1}) induced an absolute deviation from baseline in femoral dP/dt_{max} of 21% and were correlated with changes in femoral dP/dt_{max} ($R=0.62$; $p=0.008$). Changes from baseline were also observed in CFI (7%), LVEF (20%), CI (12%) and heart rate (5%) (Table 3). SVI remained unchanged. While systolic arterial pressure and mean arterial pressure values did not vary, pulse pressure changed by 20%. SVRi changed by 5%; however, Ea and TAC presented no significant change. GEDVi and CVP also remained unchanged (Table 3).

When only one intervention per patient was considered, changes in the dose of dobutamine induced an absolute deviation from baseline in femoral dP/dt$_{max}$ of 17% (1068 [748–1480] vs. 1254 [812–1672] mmHg^{-1} s^{-1}; $n=8$; $p=0.036$).

Increases in the dose of dobutamine increased femoral dP/dt_{max} by 20% (Fig. 1; Additional file 1: Table S2) and reductions in the dose led to a decrease in femoral dP/dt_{max} of 28% (Fig. 1; Additional file 1: Table S2). Additional data from haemodynamic changes obtained before and after increases and decreases in dobutamine doses are presented in Additional file 1: Table S2 in the Supplemental Material.

The dobutamine-induced per cent changes in femoral dP/dt_{max} were significantly correlated with the per cent changes in CFI, LVEF and CI, but presented the highest correlation with systolic arterial pressure and pulse pressure (Additional file 1: Table S3).

Effects of changes in norepinephrine dose

Changes in the dose of norepinephrine ($n=29$ interventions; absolute dose variation $=0.19\pm0.16$ µg kg^{-1} min^{-1}) induced an absolute change from baseline in femoral dP/dt_{max} of 15% and were correlated with changes in femoral dP/dt_{max} ($R=0.47$; $p=0.011$). Arterial systolic, mean and pulse pressure also changed from baseline by 14, 11 and 9%, respectively. There were no significant variations in heart rate, CI and CFI (Table 3). LVEF presented a 11% change from baseline. Although SVI presented a significant change of 4%, CI remained unchanged. CVP and GEDVi also remained at baseline levels. Estimated Ea, TAC and SVRi changed by 9, 17 and 5%, respectively (Table 3).

When only one intervention per patient was considered, changes in the dose of norepinephrine induced an absolute change from baseline in femoral dP/dt_{max} of 11%

Table 3 Changes in haemodynamic variables during monitored interventions

Haemodynamic variable	DBT changes		NE changes		VE/PLR	
	Mean difference ± SD	P[a]	Mean difference ± SD	P[a]	Mean difference ± SD	P[a]
Femoral dP/dt_{max} (mmHg s^{-1})	201 ± 298	*0.013*	177 ± 136	*< 0.001*	59 ± 304	0.355
CFI (min^{-1})	0.3 ± 0.4	*0.013*	0.1 ± 0.2	0.124[b]	0.2 ± 0.4	*0.042*
LVEF (%)	7 ± 5	*< 0.001*	5 ± 13	*0.025*[b]	− 1 ± 4	0.309[b]
CI (L min^{-1} m^{-2})	0.3 ± 0.5	*0.031*	0.1 ± 0.2	0.112	0.1 ± 0.4	0.153[b]
SVI (mL m^{-2})	0.7 ± 3.7	0.163[b]	1.2 ± 3	*0.040*	1.9 ± 4.1	*0.028*[b]
HR (beats min^{-1})	4 ± 8	*0.027*	1 ± 3	0.079	− 2 ± 5	*0.019*[b]
SAP (mmHg)	7 ± 15	0.065	18 ± 14	*< 0.001*	11 ± 22	*0.027*
MAP (mmHg)	3 ± 7	0.089	9 ± 7	*< 0.001*	5 ± 14	0.092[b]
PP (mmHg)	13 ± 10	*< 0.001*	6 ± 12	*< 0.001*[b]	6 ± 16	0.072
CVP (mmHg)	0 ± 2	0.748	1 ± 2	0.099[b]	3 ± 3	*0.001*
GEDVi (mL m^{-2})	61 ± 244	0.535[b]	3 ± 86	0.380[b]	− 17 ± 74	0.268
Ea (mmHg mL^{-1})	0.05 ± 0.2	0.403	0.18 ± 0.2	*< 0.001*[b]	0 ± 0.4	0.339[b]
TAC (mL mmHg^{-1})	0.01 ± 0.1	0.696	0.15 ± 0.1	*0.001*	0.03 ± 0.2	0.394[b]
SVRi (dynes s cm^{-5} m^{-2})	94 ± 157	*0.025*	109 ± 210	*0.009*	32 ± 272	0.574

In norepinephrine and dobutamine cases, absolute mean differences are presented. These were calculated as absolute results from increases and decreases in catecholamine dose

NE norepinephrine, *VE/PLR* volume expansion/passive leg raising, *DBT* dobutamine, *CFI* cardiac function index, *LVEF* left ventricle ejection fraction, *CI* cardiac index, *SVI* stroke volume index, *HR* heart rate, *SAP* systolic arterial pressure, *MAP* mean arterial pressure, *PP* pulse pressure, *CVP* central venous pressure, *GEDVi* global end-diastolic volume index, *Ea* effective arterial elastance, *TAC* total arterial compliance, *SVRi* systemic vascular resistance index

Significant results ($p<0.05$) are highlighted in italics

[a] Calculated with Student's *T* test unless indicated

[b] Calculated with Wilcoxon's rank test

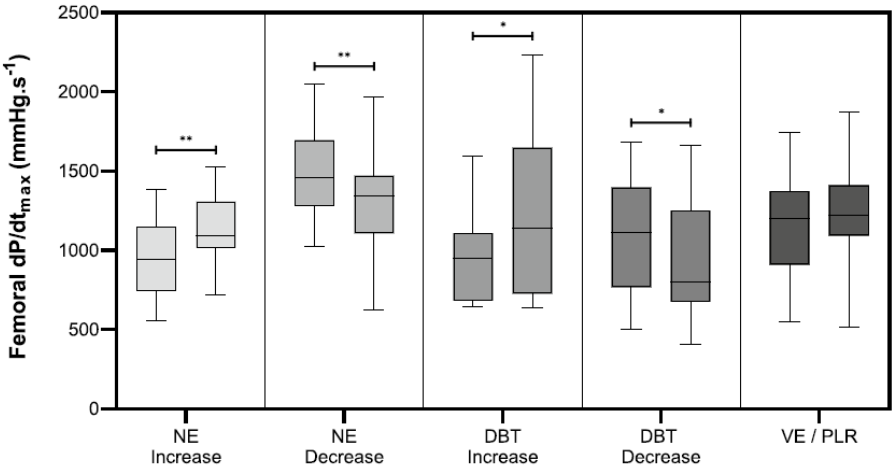

Fig. 1 Changes in femoral dP/dt_{max}. Femoral dP/dt_{max} before and after clinical interventions. Skewers indicate minimum and maximum value. *NE* norepinephrine, *DBT* dobutamine, *VE/PLR* volume expansion, passive leg raising. *$p<0.05$; **$p<0.01$

(1134 [909–1457] vs. 1265 [1028–1623] $mmHg^{-1}$ s^{-1}; $n=13$; $p=0.001$).

Increases in the dose of norepinephrine increased femoral dP/dt_{max} by 16% (Fig. 1 and Additional file 1: Table S2) and reductions in the dose led to a decrease in femoral dP/dt_{max} of 8% (Fig. 1 and Additional file 1: Table S2). Additional data from haemodynamic changes obtained before and after increases and decreases in norepinephrine doses are presented in Additional file 1: Table S2 (Fig. 2).

The norepinephrine-induced per cent changes in femoral dP/dt_{max} were correlated with per cent changes in arterial systolic pressure, arterial pulse pressure, Ea and TAC (Additional file 1: Table S3).

Effects of volume expansion and passive leg raising

The PLR test and volume expansion ($n=24$ interventions) did not induce significant changes in femoral dP/dt_{max}. Heart rate decreased by −3%, and systolic arterial pressure increased by 9%, while mean arterial pressure and pulse pressure remained unchanged. LVEF did not change, but CFI significantly increased by 4%. In this subgroup, CI did not change from baseline but SVI increased significantly by 5%. CVP increased by 30%, while GEDVi remained at baseline values. Calculated Ea, TAC and SVRi also remained unchanged (Table 3).

When only one intervention per patient was considered, PLR and volume expansion did not modify femoral dP/dt_{max} (1161 [858–1404] vs. 1218 [1105–1379] $mmHg^{-1}$ s^{-1}; $n=14$; $p=0.470$).

The PLR and volume expansion-induced changes in femoral dP/dt_{max} presented the highest correlation with changes in pulse pressure and systolic arterial pressure (Additional file 1: Table S3).

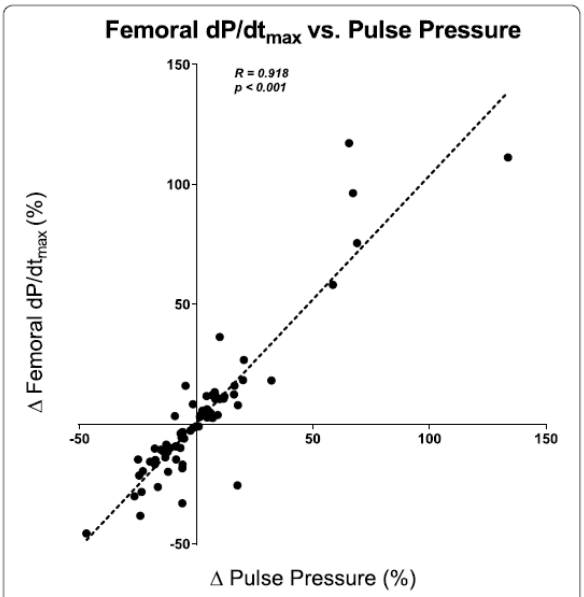

Fig. 2 Femoral dP/dt_{max} versus pulse pressure. Correlation between femoral dP/dt_{max} and pulse pressure (all interventions pooled)

Discussion

The present study evaluated changes in pulse contour analysis-derived femoral dP/dt_{max} following haemodynamic interventions aimed at modifying LV systolic function and LV loading conditions (afterload and preload)

in critically ill patients with acute circulatory failure. Changes in femoral dP/dt_{max} were strongly and consistently correlated with changes in arterial pressure waveform determinants across all interventions (arterial systolic pressure and pulse pressure). While femoral dP/dt_{max} changed during dobutamine infusion, thus suggesting a certain degree of relation with LV systolic function, femoral dP/dt_{max} also changed during norepinephrine dose variations and was correlated with changes in arterial systolic pressure, pulse pressure, TAC and Ea. Our results suggest that femoral dP/dt_{max} was mainly sensitive to ventricular loading conditions, specifically afterload, due to arterial load variations, and highly linked to changes in arterial pressure waveform, thus making it an unreliable tool to estimate LV systolic function in acute circulatory failure.

Femoral dP/dt_{max} and LV systolic function

Pulse contour analysis is used at the bedside for estimating several haemodynamic variables. In particular, the arterial dP/dt_{max} is automatically displayed and is thought by many to be an indicator of LV systolic function. As expected, femoral dP/dt_{max} changed following dobutamine increases and decreases and was related to the direction and magnitude of the dose variation. Furthermore, although LVEF and CFI are not pure estimators of LV systolic function, femoral dP/dt_{max} changed coherently with these markers during dobutamine dose variations. Note that we assessed the LV systolic function not only with CFI, which is only an estimation of LVEF and which might be mathematically coupled with GEDVi [23], but also more directly, with LVEF measured by echocardiography. These results would suggest that femoral dP/dt_{max} retains a certain degree of relationship with LV systolic function. Also, it has been previously observed in animal models that LV dP/dt_{max} reflects cardiac contractility when adequate LV filling is achieved [24, 25]. In our study, femoral dP/dt_{max} remained unchanged during VE or PLR, which could be explained by an optimised LV preload status at the time of the intervention. This finding would suggest that, similarly to what has been previously observed [24, 25], femoral dP/dt_{max} is independent from cardiac preload changes, as it would be expected from a marker of LV systolic function.

Femoral dP/dt_{max}, LV afterload and arterial load

Our results also indicated that femoral dP/dt_{max} is markedly influenced by changes in LV afterload (as estimated by changes in systolic and mean arterial pressure) during changes in the dose of norepinephrine. Unlike LV dP/dt_{max}, which is measured during the isovolumetric phase of LV contraction before aortic valve opening [2], femoral dP/dt_{max} takes place during the LV ejection phase and should therefore be more sensitive to changes in LV afterload. Our results support this hypothesis by evidencing not only significant changes in femoral dP/dt_{max} during changes in norepinephrine dose, but also significant correlations between changes in femoral dP/dt_{max} and changes in systolic and mean arterial pressure during such interventions. This demonstrates a dependence of femoral dP/dt_{max} with LV afterload, which may invalidate its utility as a marker of LV systolic function.

An interesting additional finding of the present study was the strong linear correlation observed between determinants of the arterial pressure waveform and femoral dP/dt_{max}. Our results indicate that femoral dP/dt_{max} maintained an almost one-to-one relationship with arterial pulse pressure and systolic arterial pressure, meaning that any change in the latter inevitably led to a change in the former. In other words, the higher the amplitude of the arterial waveform, the higher the velocity of the pressure increase, provided that heart rate remains almost constant and vice versa (constant cardiac cycle duration). As observed in our results, this relationship was strong and was observed even in cases where arterial loading conditions remained unchanged, such as during volume expansion and PLR. Therefore, any haemodynamic change affecting pulse pressure and systolic arterial pressure should, in principle, affect femoral dP/dt_{max} without any corresponding changes in LV contractility. It has been previously described that arterial system compliance, pulse wave reflection and arterial system impedance affect the peripheral arterial waveform [26–29]. We did not study pulse reflection waves in our patients, but we were able to confirm this hypothesis in our study by identifying a strong correlation of femoral dP/dt_{max} with determinants of arterial load (as estimated by Ea, TAC and SVRi) during norepinephrine dose variations.

Femoral dP/dt_{max} in clinical practice

Our study challenges the previous belief that femoral dP/dt_{max} could be used as a reliable marker of LV systolic function at the bedside. This belief was based on the observed good correlation between LV and arterial dP/dt_{max} during periods of haemodynamic stability [7, 9, 12]. However, correlations alone lack the sufficient value to inform on the responses of femoral dP/dt_{max} to treatments during cardiovascular failure. The evaluation of dynamic changes during haemodynamic challenges in our study demonstrates that although femoral dP/dt_{max} is not completely independent from changes in LV systolic function, it is significantly affected by peripheral arterial properties and waveform characteristics.

Previous reports have also identified a strong relationship between femoral dP/dt_{max} and LV dP/dt_{max} during isolated changes in LV systolic function, independently

from changes in LV loading conditions [10, 30]. In a recent study on healthy animals, Monge Garcia et al. [31] presented a thorough evaluation of arterial dP/dt_{max} and its relation to LV dP/dt_{max} and other markers of LV systolic function during changes in cardiac inotropic state, preload and afterload. Authors documented a positive relationship between femoral dP/dt_{max} and changes in LV systolic function, but also reported +24% and −33% changes in femoral dP/dt_{max} during increases or decreases in LV afterload induced by epinephrine and nitroprusside infusion, respectively, and a 20% reduction in femoral dP/dt_{max} during acute preload reductions induced by bleeding. Although authors conclude that the most relevant factor of femoral dP/dt_{max} was the change in LV systolic function, these observations also show the relevant effect of loading conditions on femoral dP/dt_{max} and corroborate our findings.

Therefore, it is only in cases in which one could reasonably expect that arterial loading properties and LV afterload are unchanged, that LV systolic function is the only factor modified and that femoral dP/dt_{max} might be used as a marker of LV systolic function. It must be admitted that such cases are uncommon in a constantly changing critically ill patient.

Limitations

The present study has some limitations that warrant further discussion. First, the number of cases was small and the inclusion rate slow due to the need for specific recording equipment and need for manual synchronisation between interventions and data acquisition. Second, we did not compare measurements of femoral dP/dt_{max} with LV dP/dt_{max}. Nevertheless, the objective of the present study was to evaluate the responses of femoral dP/dt_{max} during haemodynamic challenges, and values of LV dP/dt_{max} would not have helped to fulfil such objective. Furthermore, LV catheterisation for the only purpose of the study would not have been acceptable from an ethical point of view. Alternatively, the estimation of LV dP/dt_{max} by echocardiography could have been performed. However, such an estimation at the bedside in critically ill patients is far from easy and may have provided unreliable measurements. Third, we did not use any device to evaluate and compensate damping of the arterial pressure signal as utilised by previous authors [7]. However, such devices present their highest utility when high resolution of the arterial waveform is required, for example, for resonance wave analyses, which was not the case in our study. Furthermore, the absence of under- and over-damping phenomena was checked at the beginning of recordings. Fourth, while repetition of measurements on the same patient could be considered as a source of bias, we obtained the same pattern of responses to clinical interventions when only one measurement per patient was evaluated. Fifth, in order to obtain better information of potential causality and to homogeneously spread the interventions across patients, it would have been better to have followed a crossover interventional study design. However, this would have been unethical, since patients would have had to receive intravenous fluids, norepinephrine and dobutamine regardless of any clinical indication to receive such treatments. Sixth, respiratory cycle variations may alter LVEF. This potential source of bias was not taken into account when performing measurements. However, LVEF measurements were averaged over three cardiac cycles, which attenuated any respiratory variation. Furthermore, measurements were obtained during periods of haemodynamic stability and under controlled mechanical ventilation or non-distressed spontaneous ventilation, such that the respiratory variation of LVEF was probably negligible. Finally, a potential mathematical coupling between the measurement of femoral dP/dt_{max} and systolic arterial pressure or pulse pressure could be a point of concern. However, with the PiCCO2 device used in our study, femoral dP/dt_{max} was calculated at the moment of maximal pressure rise in the systolic phase of the arterial curve and was not averaged during a time segment of the curve. This approach likely discarded any potential mathematical coupling.

Conclusions

Femoral dP/dt_{max} calculated by pulse contour analysis is an unreliable estimate of LV systolic function as it is markedly sensitive to LV afterload variations and changes in arterial loading properties during acute changes in norepinephrine, and directly linked to arterial waveform characteristics.

Additional file

Additional file 1. This file contains a patient and interventions flow chart, additional information on population characteristics, pre- and post-intervention values of haemodynamic variables for the norepinephrine and dobutamine groups, as well as a correlation matrix between femoral dP/dt_{max} and other haemodynamic variables during studied interventions.

Abbreviations

LV: left ventricle; PLR: passive leg raising; LVEF: left ventricle ejection fraction; CI: cardiac index; SVI: stroke volume index; GEDVi: global end-diastolic volume index; SVRi: systemic vascular resistance index; TAC: total arterial compliance; Ea: effective arterial elastance; CVP: central venous pressure; SD: standard deviation.

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None.

Authors' contributions
SV designed the study, collected data, analysed results and wrote the manuscript. DC and XM analysed results and reviewed the manuscript. JLT reviewed the manuscript. UA and FC collected data and reviewed the manuscript. JCO provided statistical expertise and reviewed results and the manuscript. AO, AA and FB all reviewed the manuscript. XM and FB also oversaw the development of the study and mentored SV. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author upon request.

Ethics approval and consent to participate
This study was approved by local ethics committees of both participating institutions (Comitè Ètic d'Investigació Clínica de la Corporació Sanitària Parc Taulí CEIC2013616 and Comité pour la Protection des Personnes Ile-de-France VII 2011A01696-35). All patients or next of kin gave their consent to participate to the study.

Consent for publication
Not applicable

Competing interests
Profs. XM and JLT are members of the medical advisory board of Pulsion Medical Systems. The remaining authors declare no conflicts of interest.

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4.2 Article 2

Title:

Volume infusion markedly increases femoral dP/dt_{max} in fluid-responsive patients only.

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Running title

Femoral dP/dt_{max} during preload variations

Conflicts of Interest

Profs. Monnet and Teboul are members of the medical advisory board of Pulsion Medical Systems.
The remaining authors declare no conflicts of interest.

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Abstract

Objective: To evaluate the preload dependence of femoral dP/dt_{max} during volume expansion in preload dependent and independent critically ill patients.

Design: retrospective database analysis

Setting: Two adult polyvalent Intensive Care Units.

Patients: 25 critically ill patients with acute circulatory failure.

Interventions: 35 fluid infusions of 500 mL normal saline.

Measurements and Main Results: Changes in femoral dP/dt_{max}, systolic, diastolic and pulse femoral arterial pressure were obtained from the pressure waveform analysis using the PiCCO2 system (Pulsion Medical Systems, Feldkirchen, Germany). Stroke volume index (SVi) was obtained by transpulmonary thermodilution. Statistical analysis was performed comparing results before and after volume expansion and according to the presence or absence of preload dependence (increases in SVi≥ 15%). Femoral dP/dt_{max} increased by 46% after fluid infusion in preload-dependent cases (mean change = 510.6 $mmHg.s^{-1}$; p=0.005) and remained stable in preload-independent ones (mean change = 49.2 $mmHg.s^{-1}$; p=0.114). Fluid-induced changes in femoral dP/dt_{max} correlated with fluid-induced changes in SVi in preload-dependent cases (r=0.618; p=0.032), but not in preload-independent ones. Femoral dP/dt_{max} strongly correlated with pulse and systolic arterial pressures and with total arterial stiffness, regardless of the preload dependence status (r>0.9 and p<0.001 in all cases).

Conclusion

Femoral dP/dt_{max} increased with volume expansion in case of preload dependence but not in case of preload independence and was strongly related to pulse pressure and total arterial stiffness regardless of preload dependence status. Therefore, femoral dP/dt_{max} is not a load-independent marker of LV contractility and should be not used to track contractility in critically ill patients.

Keywords

Hemodynamic monitoring; pulse contour analysis; fluid responsiveness.

Introduction

In clinical practice, few variables are available at the bedside of critically ill patients to estimate left ventricular (LV) contractility (1). Echocardiography indices are often used (2), but their measurement is time consuming, intermittent and sometimes impeded by the poor echogenicity. Devices that perform pulse contour analysis measure the first derivative of the arterial pressure (dP/dt_{max}) (3) and this index is presumed to reflect LV systolic function in an easy and continuous way.

In fact, this arterial dP/dt_{max} is assumed to reflect the LV dP/dt_{max} (4–7), which is used in physiology for decades to assess the LV contractility but requires an LV pressure sensor. LV dP/dt_{max} reliably tracks changes in LV contractility, while being slightly affected by LV loading conditions (7–10).

Nevertheless, whether arterial dP/dt_{max} is actually an index of LV contractility is still a pending question. It would be so if it was influenced only by LV contractility and not by some confounding factors. In this regard, we recently showed that it is influenced by arterial pressure. In particular, we described a very close relationship between femoral dP/dt_{max} and arterial pulse pressure (PP = systolic minus diastolic arterial pressure) (11). This reflects that, at constant heart rate, the development of a higher PP is necessarily associated with a steeper slope of the arterial pressure curve between diastolic and systolic pressure values (11).

Another issue is the influence on arterial dP/dt_{max} of changes in cardiac preload, and the present study was thought to investigate it. If strong, arterial dP/dt_{max} would lose its value as a marker of LV contractility. Concomitant changes in arterial dP/dt_{max} and cardiac preload have not been consistently observed in animal models (5,7) or patients (11), but data on this aspect is still missing. However, analysing concomitant changes in arterial dP/dt_{max} and cardiac preload is not straightforward and should consider different points. First, LV dP/dt_{max} itself might be influenced by cardiac preload (8,12,13). As it is supposed to reflect LV dP/dt_{max}, it may be also the case for arterial dP/dt_{max}. Second, arterial dP/dt_{max} is influenced by PP (11), and PP may change along with stroke volume (14,15) when cardiac preload changes, as a result of preload responsiveness.

In the present study, we made the hypothesis that femoral dP/dt_{max} may change after volume expansion in case of preload dependence. In other words, that a presumable increase in cardiac

preload with fluid infusion should lead to significant increases in stroke volume, and hence PP and femoral dP/dt_{max}. By contrast, in case of preload independence, fluid-induced changes in cardiac preload should not lead to any change in femoral dP/dt_{max} because stroke volume and presumably PP do not change (16).

Materials and Methods

We present a retrospective analysis of a prospectively collected database of patients with acute cardiovascular failure requiring administration of a standard fluid bolus. Data collection was performed in two adult intensive care units (Servei de Medicina Intensiva, Corporació Sanitària Universitària Parc Taulí, Sabadell, Spain and Service de Médecine Intensive Réanimation, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France) and was approved by local ethics committees of both institutions (Comitè Ètic d'Investigació Clínica de la Corporació Sanitària Parc Taulí 2013632 and Comité pour la protection des personnes Ile-de-France VII 2011A00302-39 and 2011A01696-35). All patients or next of kin consented to provide their data. Both ethics committees approved the retrospective analysis of the database without the need for subject re-consent. The "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) criteria for observational studies is used to present data in this manuscript (17).

Patients

We collected data from adult patients in whom the attending physician had decided to perform a volume expansion as part of their treatment. Patients had to be monitored with transpulmonary thermodilution (PICCO2, Pulsion Medical Systems, Feldkirchen, Germany) and to present at least one of the following signs of hemodynamic failure: systolic arterial pressure ≤ 90 mmHg or decrease of more than 50 mmHg in the last 3 hours or mean arterial pressure ≤ 65 mmHg, tachycardia ≥ 100 beats/min, oliguria ≤ 0.5 mL/kg/h for more than 2 hours, blood lactate ≥ 2 mmol/L (or 22 mg/dL), central venous oxygen saturation ≤ 60%, diffuse skin mottling. Exclusion criterion was the impossibility to obtain an arterial waveform of sufficient quality.

149 ***Recorded variables***

150 Arterial pressure waveform was assessed through an arterial catheter inserted in the femoral artery
151 (PV2015L20-A, Pulsion Medical Systems, Feldkirchen, Germany). The catheter was connected to a
152 PiCCO2 device which automatically and continuously measured systolic, mean and diastolic pressure,
153 and femoral dP/dt_{max} (maximum value of the continuous measure of the relation between pressure
154 increase to time in the systolic portion of the waveform). After zeroing the arterial pressure-transducer
155 system and before each measurement, the arterial waveform signal quality was checked visually using
156 a fast-flush test to assess the adequacy of its damping (18). In case of damping, repeated flushes were
157 performed until sufficient signal quality was acquired. Data from interventions in which sufficient
158 quality of the arterial curve signal could not be achieved were rejected.

159 Cardiac index and global end diastolic volume index were measured through transpulmonary
160 thermodilution (19) using a central venous catheter placed in the superior vena cava. Thermodilution
161 measurements were performed by injection of a 15-mL cold saline bolus (<8ºC) through the central
162 venous catheter. The results of three consecutive thermodilution measurements were averaged (20).

163 We calculated PP as the difference between systolic and diastolic arterial pressure, and the Total
164 Arterial Stiffness Index (pulsatile arterial load) was estimated as the PP over stroke volume index ratio
165 (21). Total Peripheral Resistance index was calculated as TPRi = mean arterial pressure / cardiac index
166 x 80 / body surface area and was used to evaluate the resistive component of the arterial load. Central
167 venous pressure (CVP) and global end diastolic volume index (GEDVi) (22) were used as static indices
168 of cardiac preload.

169

170 ***Study design***

171 At baseline, transpulmonary thermodilution was performed and a first set of arterial pressure, CVP
172 cardiac index and GEDVi measurements was recorded. If patients received concomitant catecholamine
173 treatment, study variables were registered only if 15 minutes had passed between any dose variation
174 and the start of measurements and when cardiovascular variables were considered stable (less than
175 10% variation of systolic arterial pressure though a 1-minute observation).

Volume expansion was then performed by infusing 500 mL of normal saline in less than 30 min. Immediately after volume expansion, another transpulmonary thermodilution was performed and a new set of measurements was collected. During volume expansion, the dose of catecholamines and sedatives and, in ventilated patients, the settings of mechanical ventilation, were kept unchanged. Preload dependence was defined as the increase of ≥ 15% in stroke volume index after volume expansion as recommended (23). Synchronization of events with recorded variables was performed manually by the research team. Patients could be included in the study as many times as a volume expansion was indicated by the attending physicians.

Data analysis

Mean ± standard deviation (SD) or median and 25^{th}-75^{th} percentiles are used to present results when appropriate. Percentages of changes induced by volume expansion, rather than raw values, were compared in order to normalise for baseline values. Selection of statistical test for analysis was performed based on assessment of normality of study variables using the Kolmogorov-Smirnov test. Paired Student's t-test and Wilcoxon rank test were used as appropriate to compare pre and post intervention values and mean changes during interventions. Correlation between hemodynamic variables was assessed using the Pearson's correlation coefficient. Analysis was performed in the whole population and according to patients' preload-dependence status as defined above. In order to evaluate the effects of multiple measurements on the same subject, in those who received more than one volume expansion, we repeated the analysis using only the first volume expansion performed in each patient.

Sample size estimation was based on previously published data (11). Using an estimation based on paired measures in the same group, with an assumed SD of the differences in the volume expansion/PLR subgroup = 304 $mm.Hg^{-1}$, a minimum required threshold of 15% (174.3 $mm.Hg^{-1}$), a bilateral contrast, and an alpha risk = 0.05 / beta risk = 0.10, the minimum number of paired measures required for detecting a statistically significant difference in femoral dP/dt_{max} during volume expansion was 34 paired measurements.

Statistical calculations were performed using SPSS version 25 (International Business Machines, Armonk, NY, USA). Values of $p < 0.05$ were considered statistically significant.

Results

Patients

Data from 31 patients were available, representing 43 cases of volume expansion. Eight cases were excluded due to insufficient arterial signal quality (Figure S1 in supplementary material), leaving suitable data for analysis from 35 cases performed in 25 subjects (60% male). In the majority of cases (77%), some form of distributive shock was the reason for cardiovascular failure (septic shock: 21 (60%) cases, distributive non-septic shock: 6 (17%) cases, cardiogenic shock: 4 (11%) cases, hypovolemic shock: 4 (11%) cases). In 60% of cases, sinus rhythm was present and 74% of cases were mechanically ventilated, of which 61% had no spontaneous breathing. Fluid responsiveness was present in 12 (34%) of cases. There were no significant differences between fluid responders and non-responders in main demographic and clinical variables (Table 1). Mortality at 28th day of admission was 57%.

Effects of volume expansion in the whole population

Considering the whole population, volume expansion induced a statistically significant increase in femoral dP/dt_{max} of 18±34% (Supplementary material, Table S1). Cardiac index and stroke volume index increased both by 13±16% and 14±17%, respectively. Systolic, diastolic and mean arterial pressure increased by 18±24%, 18±15% and 13±16% respectively. PP increased by 24±34%. Total arterial stiffness index and TPRi remained unchanged.

Changes in femoral dP/dt_{max} correlated with changes in systolic, diastolic, mean and pulse arterial pressure (Table 2, Figure 1). Significant correlations were also found with changes in cardiac index, stroke volume index, TPRi and total arterial stiffness index. Changes in femoral dP/dt_{max} were also correlated with changes in GEDVi (Table 2).

Effects of volume expansion depending on the fluid responsiveness status

In fluid responsive cases (n = 12), volume expansion induced a statistically significant increase in femoral dP/dt_{max} of 46±46% (Table 3). Cardiac index and stroke volume index increased both by 40±19% and 46±25%, respectively. Systolic, diastolic and mean arterial pressure increased by 42±31%, 22±18% and 37±27%, respectively. PP increased by 58±44%. Total arterial stiffness index and TPRi remained unchanged (Table 3). In fluid responsive cases, changes in femoral dP/dt_{max} correlated with changes in systolic, diastolic, mean arterial pressure, PP and stroke volume index. Changes in femoral dP/dt_{max} were also correlated with changes in GEDVi (Table S2).

In fluid non-responsive cases (n = 23), volume expansion did not change femoral dP/dt_{max} statistically (Table 3, Figure 2). Systolic, diastolic, mean arterial pressure and PP also remained unchanged (Table 3). In this subgroup, changes in femoral dP/dt_{max} correlated with changes in systolic, diastolic, mean and pulse arterial pressure, but not with changes in stroke volume index, CVP and GEDVi (Table S2).

Analysis restricted to the first volume expansion

In those patients who received more than one volume expansion, when only the first volume expansion was analysed, femoral dP/dt_{max} significantly increased following volume expansion in the whole study population (median = 1104 [808 - 1544] vs. 1246 [1033 - 1679] $mmHg.s^{-1}$; p = 0.004, n = 25). When the analysis was performed in function of the presence of fluid responsiveness, femoral dP/dt_{max} significantly increased in fluid responsive cases (median = 1018 [795 - 1525] vs. 1684 [1250 - 2383] $mmHg.s^{-1}$; p = 0.028, n = 6) but remained unchanged in fluid non-responsive cases (median = 1104 [815 - 1602] vs. 1199 [915 - 1569] $mmHg.s^{-1}$; p = 0.070, n = 19).

Discussion

The present study indicates that femoral dP/dt_{max} measured by pulse contour analysis devices is sensitive to fluid-induced changes in cardiac preload when fluid responsiveness is present, but not in the absence of fluid responsiveness. These results are in accordance with previous observations in animal models (5,7), and in humans (11,24,25) and confirm that femoral dP/dt_{max} cannot be considered as a pure marker of LV contractility.

The interest in arterial dP/dt_{max}

At the bedside, the most used estimate of LV systolic function is the LV ejection fraction. Nonetheless, it has many limitations, the main being that it is influenced by cardiac loading conditions (26,27). It is less the case for LV strain and strain rate assessed through speckle tracking and tissue Doppler imaging but they require specific echocardiography software and good cardiac echogenicity (28). Therefore, the possibility to estimate LV dP/dt_{max}, a well-known physiological indicator of the contractile function, through a simple arterial catheter, is attractive. The arterial dP/dt_{max} provided by the calibrated and uncalibrated pulse contour analysis devices that are commercially available is claimed to estimate LV dP/dt_{max} reliably and to reflect LV contractility.

Femoral dP/dt_{max} and preload dependence

Using arterial dP/dt_{max} at the bedside to estimate LV contractility requires that it is reasonably independent from confounding factors, especially LV loading conditions. First of all, provided that arterial dP/dt_{max} is a reflection of LV dP/dt_{max}, it should suffer from a similar influence of cardiac preload (8,12,29,30) and, to a lesser extent, of cardiac afterload (7,12,29,31).

Moreover, arterial dP/dt_{max} should be influenced by the physiological properties of the arterial tree. Arterial compliance and resistance, and pressure wave reflections should influence the waveform of the arterial pressure and the velocity of the pressure upstroke. Changes in femoral dP/dt_{max} are correlated with arterial compliance, systemic vascular resistance and effective arterial elastance during

changes in the dose of norepinephrine (11). Also, we have previously reported (11,32) that there is a very close relationship between changes in femoral dP/dt_{max} and PP, whatever the intervention, and this was confirmed in the present study. It reflects the fact that, if the duration of the cycle is constant, a higher PP requires a faster pressure increase to reach a higher systolic pressure. This has also been observed by Sharman *et al.* at the radial artery level (24,33). In the present study, the relationship between femoral dP/dt_{max} and PP was strong in both fluid responsive and in fluid non-responsive cases; This suggests that PP is one of the main determinants of arterial dP/dt_{max}, if not the only one. Recently, a study attempted to describe the factors that influence femoral dP/dt_{max}, but the analysis did not include PP in the linear mixed-effects model analysis (7).

Given the well-known relationship between stroke volume and PP, and because stroke volume and cardiac preload are linked through the Frank-Starling relationship, we hypothesized that the effects of fluid-induced changes in cardiac preload on femoral dP/dt_{max} varied according to the fluid responsive/non-responsive status. Actually, fluid infusion increased cardiac preload in fluid responders and non-responders, as assessed by CVP and GEDVi. In response, stroke volume increased in fluid responders, while it presented a non-hemodynamically relevant increase in non-responders (3.7% from baseline). As expected, PP increased along with SV in fluid responders, and femoral dP/dt_{max} increased as well indicating a steeper slope of the ascending portion of the arterial waveform to reach a higher systolic pressure for a given heart rate.

In our previous study, we could not evidence a link between femoral dP/dt_{max} and preload changes due to the small sample size and to the proportion of fluid responsive cases, which made it markedly underpowered to detect relevant changes in stroke volume and thus variations in femoral dP/dt_{max} (11). By contrast, our present results are in full agreement with Morimont *et al.*, who showed in pigs that femoral dP/dt_{max} was better related to the end-systolic elastance (i.e., a pure marker of LV contractility) when the respiratory variation of PP was low (indicating no preload responsiveness and thus no relation to preload of femoral dP/dt_{max}) (5). Bladszun *et al.* also showed that the relationships between stroke volume and end-diastolic volume and between arterial dP/dt_{max} and end-diastolic volume were similar in rats (34) and in the study of Monge Garcia *et al. (5)*, femoral dP/dt_{max} decreased

304 during blood removal, which is again consistent with a link between arterial dP/dt_{max} and preload
305 variations.

306 Nevertheless, preload, afterload and contractility are not independent from one another and we
307 cannot exclude the possibility that the fluid-induced changes in loading conditions may have elicited
308 slight changes in LV contractility (1). However, the 46% increase in dP/dt_{max} strongly suggests a major
309 preload-dependence of this index rather than a dependence upon LV contractility in this clinical setting.

310

311 **Clinical implications**

312 Results from the present analysis suggest that femoral dP/dt_{max}, which is provided by pulse contour
313 devices as an indicator of cardiac LV contractility, is affected by preload increases in preload dependent
314 patients. Thus, if femoral dP/dt_{max} is to be used in clinical practice to estimate LV contractility, it should
315 be limited to situations in which LV contractility is the only factor being modified. As inotropic agents
316 are usually recommended after preload optimisation, conditions of preload independence are
317 generally met and any subsequent changes in dP/dt_{max}, if observed, may then indeed reflect changes
318 in LV contractility. However, as discussed elsewhere (11,32), femoral dP/dt_{max} is also highly sensitive to
319 afterload variations. These must also be excluded when considering the use of femoral dP/dt_{max} as an
320 index of LV contractility.

321

322 **Limitations**

323 The present study has a number of limitations that require further discussion. First, we present a
324 retrospective analysis of prospectively collected data of critically ill patients with acute cardiovascular
325 failure, which may rise concerns about the quality and completion of the database. Nevertheless, data
326 were collected prospectively with all the quality concern of such studies and automatically recorded
327 with the monitoring system, ensuring full data set availability. Second, certain variables that might have
328 been interesting for in-depth analysis of contractility (such as advanced echocardiographic
329 assessments) were not available. However, it is unlikely that changes in contractility occurred in the
330 present study setting, as potentially influential factors were strictly controlled during interventions and

data collection. Third, we present a cohort of predominantly septic shock patients. While this is representative of a general population of critically ill patients, it might not be transferable to other groups. Fourth, in some patients more than one volume expansion was collected and investigated. However, a *post-hoc* analysis using only one volume expansion per patient replicated the overall results of the complete dataset. Furthermore, in those in whom the measurement was repeated, this was done after a significant change in the hemodynamic status had occurred because of either changes in overall clinical status or changes in catecholamine infusion dose, representing a completely new hemodynamic situation. Fifth, we did not measure reflected pressure waves and cannot inform on its relevance on dP/dt_{max} development at the femoral level. However, it would not have changed the main outcome of the study, that femoral dP/dt_{max} closely correlates with PP and is thus related to the same factors involved in its development. Finally, we did not investigate arterial dP/dt_{max} at the radial level, which might present different characteristics from the femoral one.

Conclusion

Femoral dP/dt_{max} markedly changed along with fluid-induced changes in cardiac preload in case of fluid responsiveness, as a result of the simultaneous marked changes in PP, while it did not change in case of fluid non-responsiveness. Therefore, femoral dP/dt_{max} cannot be considered as a reliable marker of LV contractility as it depends on LV loading conditions.

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Figure captions

Figure 1

Correlation between femoral dP/dt_{max} and arterial pulse pressure (All cases n = 35)

Figure 2

Changes in femoral dP/dt_{max} following volume expansion

Table 1

Demographic and clinical variables of included patients.

Variable	Mean (SD)
Weight (kg)	79 (14)
Height (cm)	167 (9)
Age (yr)	68 (14)
BSA (m^2)	1.9 (1.5)
Vt (mL)	410 (37)
PEEP (cmH_2O)	7 (3)
P_{plat} (cmH_2O)	21 (5)
NE ($\mu g.kg^{-1}.min^{-1}$)	0.98 (0.97)
CRP ($mg.dL^{-1}$)	126 (108)
Lactate ($mmol.L^{-1}$)	4.1 (3.2)

BSA: body surface area, Vt: tidal volume, PEEP: positive end-expiratory pressure, P_{plat}: plateau pressure, NE: norepinephrine, CRP: C reactive protein.

Table 2
Correlation matrix of changes in femoral dP/dt_{max} *vs.* changes in main haemodynamic variables

Correlation coef. / Significance	**Δ HR (%)**	**Δ SAP (%)**	**Δ MAP (%)**	**Δ DAP (%)**	**Δ PP (%)**	**Δ CI (%)**	**Δ SVI (%)**	**Δ TPRI (%)**	**Δ TASI (%)**	**Δ CVP (%)**	**Δ GEDVi (%)**
R	-0.022	0.982	0.959	0.882	0.988	0.765	0.695	0.472	0.874	0.210	0.579
p	0.900	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*0.004*	*< 0.001*	0.417	*< 0.001*

HR: heart rate; SAP: systolic arterial pressure; MAP: mean arterial pressure; DAP: diastolic arterial pressure; PP: pulse pressure; CI: cardiac index; SVI: stroke volume index; TPRI: total peripheral resistance index; TASI: total arterial stiffness index; CVP: central venous pressure; GEDVi: global end-diastolic volume indexed.
Values represent the Pearson's correlation coefficients.
Δ means changes from baseline.

Table 3

Changes in haemodynamic variables following volume expansion according to preload dependence.

	Preload dependent cases			Preload independent cases		
Variable	**Pre VE mean (SD)**	**Post VE mean (SD)**	**p**	**Pre VE mean (SD)**	**Post VE mean (SD)**	**p**
Femoral dP/dt_{max} ($mmHg.s^{-1}$)	1108 (435)	1619 (576)	0.005	1087 (801 – 1602) [a]	1173 (811 – 1569) [a]	0.114 [b]
CI ($L.min^{-1}.m^{-2}$)	2.2 (0.6)	3.1 (0.8)	< 0.001	3.5 (1.2)	3.6 (1.3)	0.058
SVI ($mL.m^{-2}$)	22.8 (7.7)	33.3 (10.8)	< 0.001	37.7 (11.9)	39.1 (13)	0.011
HR ($beats.min^{-1}$)	99 (13)	95 (12)	0.046	93 (18)	92 (19)	0.053
SAP (mmHg)	95 (87 – 122) [a]	146 (125 – 173) [a]	0.002 [b]	113 (107 – 132) [a]	122 (111 – 142) [a]	0.004 [b]
DAP (mmHg)	63 (13)	86 (17)	0.001	74.8 (15)	81 (16)	0.008
MAP (mmHg)	46 (10)	56 (11)	0.001	52 (11)	57 (13)	0.003
PP (mmHg)	56 (19)	89 (23)	0.001	59 (52 – 78) [a]	60 (55 – 91) [a]	0.019 [b]
TASi ($mmHg.ml^{-1}$)	2.7 (1.1)	3.0 (1.5)	0.222	1.9 (0.6)	2 (0.7)	0.346
TPRi ($dynes.s.cm^{-5}.m^{-2}$)	2204 (1586 – 3445) [a]	2123 (1528 – 3361) [a]	0.638 [b]	1907.6 (720)	2042 (789)	0.034
GEDVi ($mL.m^{-2}$)	653 (167)	732 (132)	0.112	756 (160)	775 (140)	0.293
CVP ($mL.m^{-2}$)	9 (8)	12 (7)	0.009	8 (5)	12 (6)	< 0.001

[a] Median (25th-75th percentiles)

[b] Calculated with Wilcoxon Rank test

VE: volume expansion; CI: cardiac index; SVI: stroke volume index; HR: heart rate; SAP: systolic arterial pressure; MAP: mean arterial pressure; DAP: diastolic arterial pressure; PP: pulse pressure; TASi: total arterial stiffness index; TPRi: total peripheral resistance index; GEDVi: global end diastolic volume indexed; CVP: central venous pressure.

Figure 1

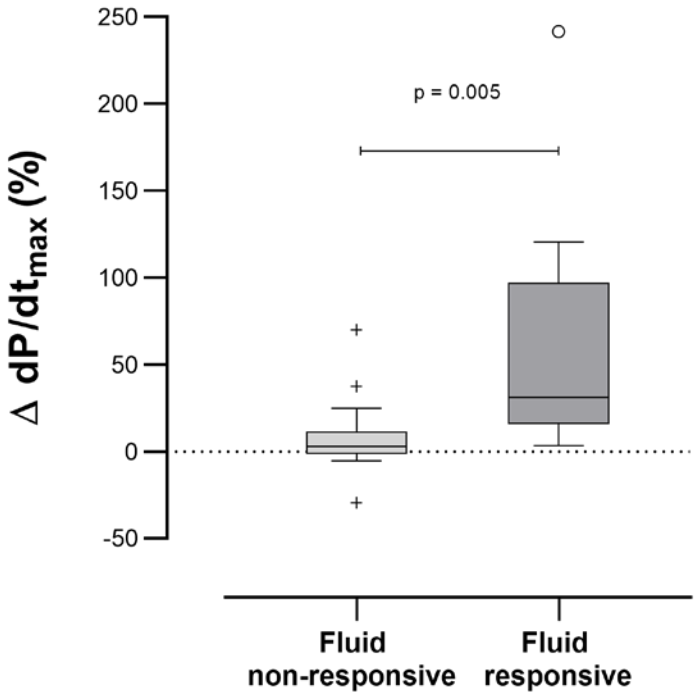
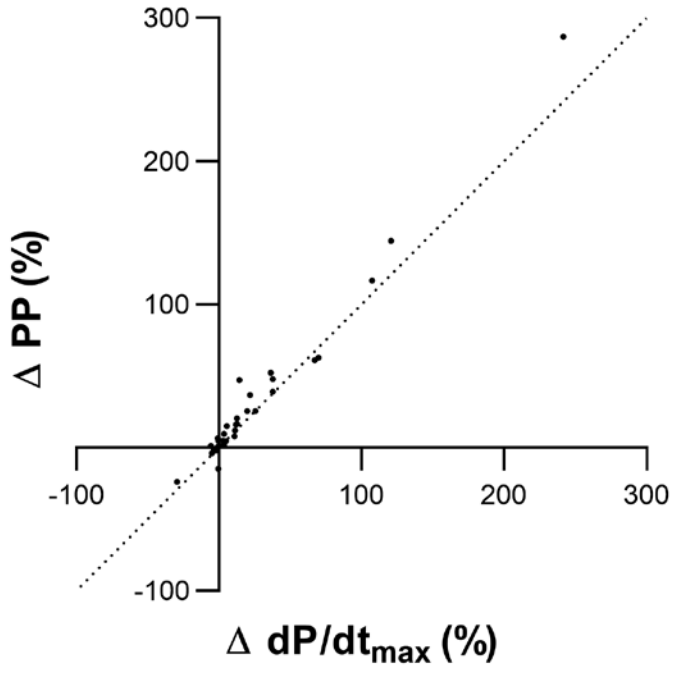


Figure 2



5 Summary of results

In response to the hypothesis formulated for the present doctoral work the following statements can be formulated:

1. Data suggests a link exists between femoral dP/dt_{max} and LV contractility variations. Femoral dP/dt_{max} is sensitive to changes in the dobutamine infusion dose. These changes averaged around 21% deviation from baseline, occur in both increases and decreases of dobutamine dose and are linked to the magnitude and direction of the dose variation.
2. Data suggests a link exists between femoral dP/dt_{max} and variations in LV extrinsic afterload or arterial load. Variations in the dose of norepinephrine induced an absolute change in femoral dP/dt_{max} of 15% from baseline. Significant changes in femoral dP/dt_{max} were observed in both increases or decreases of norepinephrine infusion and these were linked to the magnitude and direction of the dose variation.
3. Data suggests a link exists between femoral dP/dt_{max} and changes in LV preload, with the caveat that patients need to be in a preload-dependence status. Volume administration induces a 46% increase on femoral dP/dt_{max} from baseline only in cases when preload-dependence is present. Such effect is lost in preload-independent patients.

Additionally, the following key observations were made, which have significant relevance for the understanding of the present results:

1. The highest proportion of variance explained in changes of femoral dP/dt_{max} was represented by changes in PP. This is true for all subgroups and across all interventions performed.
2. During changes in norepinephrine infusion, changes in femoral dP/dt_{max} correlate with changes in markers of extrinsic LV afterload and arterial tone.
3. After administration of a standard volume expansion, changes in femoral dP/dt_{max} are correlated with changes in CVP and global end diastolic volume index in preload-dependent patients. This correlation is lost in preload-independent patients.

6 Discussion summary

Results of the present doctoral work have shown that femoral dP/dt_{max}, while being relatively sensitive to changes in LV contractile status, it is a marker susceptible to variations in LV loading conditions. These conclusions, obtained after the analysis of two independent cohorts of critical patients, challenge the reliability of femoral dP/dt_{max} to be able to truly estimate cardiac contractility at the bedside in critically patients, and provides relevant data for a long-lasting debate on the utility of this, widely believed, marker of contractility.

6.1 Clinical application

If femoral dP/dt_{max} is to be used to monitor LV contractility in critically ill patients, clinicians must pay exquisite attention to the conditions in which it is being measured due to its now evident limitations.

First, patients should be “stable” in the sense that there shall be no changes in arterial vascular tone that could influence extrinsic afterload during the measure. As our results have evidenced, femoral dP/dt_{max} is especially sensitive to changes in PP and SAP induced by variations in the dose of norepinephrine, and presents good correlations with markers of arterial load E_a, TAC / TASI and SVRi / TPRi. This means that if one wants to obtain a reliable measure of femoral dP/dt_{max}, arterial tone must be kept constant. Unfortunately, such conditions are rarely present in critically ill patients, in which arterial tone variations occur continuously, being these a consequence of a progressing underlying condition (such as sepsis) or through real-time variations of supportive medications (such as norepinephrine). Thus, it is theoretically possible but practically unlikely that femoral dP/dt_{max} can be used as a reliable real-time minimally invasive marker of cardiac contractility in critically ill patients.

Second, femoral dP/dt_{max} cannot be used during variations of LV preload conditions, with the exception of patients with fully optimised LV preload. This imposes yet another restriction to the use of femoral dP/dt_{max} on critically ill patients, limiting it to those who have already been treated and stabilised. In other words, if one is to take the example of a patient in septic shock, femoral dP/dt_{max} would only be usable when fluid resuscitation has been completed and vasoactive medication has been fully titrated to achieve a stable haemodynamic status. Such conditions significantly limit the applicability of femoral dP/dt_{max} to a later, “post resuscitation” phase of the acute treatment of a critically ill patient, when it may actually no longer be needed.

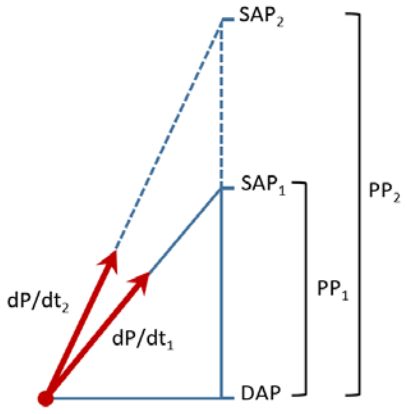
6.2 The physiology behind the results.

Present results offer a rather clear picture of the sensitivity of femoral dP/dt_{max} to changes in contractility and LV loading conditions and provide an already useful piece of information for clinicians about its reliability. However the understanding of the physiological processes behind our observations poses a much more challenging rept. It is the opinion of the Author that the incorporation of fundamental contractility, preload and afterload physiological concepts can be used to formulate sound physiological hypothesis that can offer useful explanation to the observed behaviour of femoral dP/dt_{max} and guide further research.

6.2.1 Femoral dP/dt_{max} and pulse pressure

In our results, femoral dP/dt_{max} and PP retained an almost one-to-one correlation with each other, and this relationship was observed across all patients regardless of the intervention performed and the LV loading status. This indicates a very fundamental and yet simple concept: that the higher the delta pressure to be achieved, for a given HR, the higher the $dP/dt_{max.}$ One may want to further illustrate this concept using basic trigonometry for the square triangle and apply it to the arterial waveform. For a given R-R interval, or constant HR, (in analogy to the short cathetus of the square triangle), the higher the PP (here the long cathetus of the square triangle), the greater the femoral dP/dt_{max} (in analogy to the slope of the hypotenuse) (Figure 5-1). With this analogy and following simple logic, it is possible to conclude that any phenomena that may alter PP without modifying HR will consequently affect femoral dP/dt_{max}.

Figure 5-1 Influence of changes in PP on dP/dt for a constant heart rate – square triangle theory



6.2.2 Femoral dP/dt$_{max}$ and contractility changes.

Dobutamine is a β1 agonist with strong chronotropic and inotropic effects that induce faster and more powerful ventricular contractions. As discussed in the introduction of the present doctoral work, previous research has demonstrated that a certain degree of relation exists between LV dP/dt$_{max}$ and femoral dP/dt$_{max}$. It is therefore reasonable to assume that increases in contraction velocity and force induced by dobutamine in the studied patients, and in the absence of aortic valve pathology, could be transmitted to the arterial tree and become measurable at the femoral level. Results of the present work would support such interpretation and indicate a variation in femoral dP/dt$_{max}$ in both direction and intensity following increases and decreases in dobutamine infusion.

During variations in dobutamine dose, femoral dP/dt$_{max}$ and PP remained closely related (r = 0.942) and changed in parallel with equivalent magnitudes (≈20% variation from baseline). However, there was no variation in the measure of TAC (or its inverse TASi), nor in SVi. This is an important finding, since TAC/TASI, PP and SVi are inter-related (arterial stiffness and compliance are a ratio between PP and SVi and vice-versa). In absence of changes in SVi or TAC/TASi, there is no other factor but a truly increase in contractile force that can explain the observed variations in PP. Furthermore, SAP and Ea, which are to be considered direct and calculated estimates of extrinsic afterload variations, as previously discussed, remained constant; and although one must admit that there was a change in HR and SVRi in this subgroup, the magnitude of these variations (5%) was haemodynamically irrelevant.

Therefore, one may conclude that in absence of another explanation and provided LV loading conditions remained stable (as observed in our results with no changes in GEDVi and CVP on one side, and SAP and E_a on the other), changes in dobutamine infusion dose led to variations in LV contractility, which were transmitted to the arterial tree as increases in PP and consequently detected as changes in femoral dP/dt$_{max}$. Unfortunately, due to obvious ethical reasons, we did not measure LV dP/dt$_{max}$ using an intraventricular catheter during interventions, as this would have increased the risks for the study patients with no clear therapeutic benefit. Such measures were therefore not available but would have been able to confirm the abovementioned, by evidencing a strong correlation between LV and femoral dP/dt$_{max}$ during dobutamine changes. Nevertheless, the relationship between the two variables has already been widely demonstrated in humans and animal models in the past and was considered unnecessary to repeat such observations.

6.2.3 Femoral dP/dt$_{max}$ and changes in extrinsic afterload.

During norepinephrine dose variations femoral dP/dt$_{max}$ presented significant variations and remained again closely related to PP changes, as in other subgroups. In this case, changes in SAP and E_a were evident, indicating a variation in extrinsic LV afterload. Furthermore, TAC/TASi and SVRi/TPRi changed significantly and were correlated with changes in femoral dP/dt$_{max}$ indicating that changes in norepinephrine exerted an influence in both the resistive and pulsatile elements of the arterial load. Using again the known relation between TAC/TASi, PP and SVi, for a given SVi, changes in pulsatile arterial load lead to changes in PP and consequently to femoral dP/dt$_{max}$. It is true however, that a minor change in SVi was observed in this group (4%). This variation shall be considered haemodynamically irrelevant as it lays within the coefficient of variation / percentage of error of the measurement technique.

It is to be noted that the level of correlation obtained between TAC/TASi with femoral dP/dt$_{max}$ is significant but fails to explain a substantial portion of the variance observed (R^2 = 0.47 or 47% of variance explained). In this subgroup, changes in SVRi also provided a limited explanation for the variance observed in the measure of femoral dP/dt$_{max}$ (R^2 = 0.35 or 35% of variance explained). This means that factors other than changes in pulsatile or resistive arterial load are responsible for at least 50% of the unexplained variance.

One factor with potential effects on femoral dP/dt$_{max}$ could be an increase in preload in patients with preload-dependence (as it will be discussed in the next section). However there was no association between changes in SVi, GEDVi or CVP in this subgroup, indicating no association with preload variations.

On another side, norepinephrine is known to have a small β-agonist effect and is thus capable of slight increases in contractility. In this sense, another factor that should be considered is that variations in norepinephrine dose could have caused variations in LV contractility that, as described before, could potentially affect the measure of femoral dP/dt$_{max}$ and justify a portion of the unexplained variance. Direct measurements of E_{es} through ventricular catheterisation would have offered insights on the effect of norepinephrine upon LV contractility. Unfortunately, for the same ethical reasons that prevented the direct measure of LV dP/dt$_{max}$, such measurements were not performed.

There remains another factor that could be responsible for the unexplained variance in the measure of femoral dP/dt$_{max}$ during changes in norepinephrine: the effect of arterial reflection waves on SAP and PP. By modifying arterial stiffness, pulse wave velocity is varied, leading to changes in the moment of arrival of reflected waves to the aorta. In

general, increases in arterial stiffness lead to greater SAP and PP through not only variations in arterial load but also by modifying the influence of reflection waves on the measure (i.e.: through increases in the augmentation index). In this context, increases in SAP and PP through this phenomenon would lead to greater femoral dP/dt_{max} measures. This effect may be enhanced in a population of elderly patients, where basal arterial stiffness is expected to be higher such as those in the two studied cohorts. Unfortunately, a system to measure reflection waves accurately was not available for the present doctoral work. Therefore, the effect of arterial reflection waves on the measure of femoral dP/dt_{max} will have to be elucidated in further studies.

6.2.4 Femoral dP/dt_{max} and preload variations

Following the Frank-Starling relation and Guyton's model for the interaction of the venous system and the heart's preload, administration of intravenous fluid led to increases in SVi in those patients with preload reserve. Results also indicated that fluid administration increased femoral dP/dt_{max} in preload-dependent patients. The mechanism by which optimization of preload led to changes in femoral dP/dt_{max} in these patients is, however, challenging to explain.

One possibility may rely again on the relation between TASi/TAC, SVi and PP, by which for any increase in SVi, provided arterial load is maintained constant, an increase in PP is to be expected. Due to the already mentioned almost one-to-one relationship between PP and femoral dP/dt_{max} (again observed in this subgroup of patients), any increase in PP must lead invariably to an increase in femoral $dP/dt_{max.}$ However, changes in SVi accounted for only a portion of the variance explained in femoral dP/dt_{max} ($R^2 = 0.38$ or 38% of variance explained). Thus, other factors must play a role in explaining the observed variance in the femoral dP/dt_{max} measure during preload variations.

Another possibility may be related to the transmission of greater LV dP/dt_{max} to the arterial tree due to faster LV contractions following preload optimization. Indeed, if one follows the physiology behind the Frank-Starling relationship, increases in preload lead to optimised sarcomere fibre length with a consequent increase in contractile force as described previously in many studies. This increase is independent of the intrinsic capability of the myocardium to generate force (contractility). An increase in preload-mediated contractile force would lead to a faster rise in intraventricular pressure, or higher LV dP/dt_{max}, for a constant systole duration, or in other words for a stable HR. If one accepts that in absence of aortic valve pathology, changes in LV dP/dt_{max} can be

transferred to the arterial system and measured at a femoral level, then it is possible that preload optimisation can increase femoral dP/dt_{max} when preload dependence is present without any influence of extrinsic afterload or arterial tone. This hypothesis could be partially supported by the results of a multiple regression analysis performed on the second study's population (preload dependence study). This analysis was not added to the publication and can be found in the annex of the present doctoral thesis, in section 9.3. Results indicated that both SVi and TASi can independently predict changes in femoral dP/dt_{max}. This means that regardless of the effects of arterial tone, femoral dP/dt_{max} is linked to the performance of the LV ventricle and its ability to produce SVi, or in other words, that the measure of femoral dP/dt_{max} retains certain independence of afterload during preload variations. As previously mentioned, when one considers previous literature in which LV and femoral dP/dt_{max} have been found to be linked, results may indeed support that increases in the former could be transferred to the later, and especially in cases of changes in LV dP/dt_{max} due to preload optimisation that lead to greater SVi generation. However, one must take into account that TASi is a calculated variable that contains SVi. Several analyses were performed to ensure there was independency of residuals and that no co-linearity among independent variables existed (refer to section 9.3). However, there exists a risk of mathematical coupling in the present analysis and prevents us to reach a firm conclusion on this matter. In order to avoid such risk, further research will have to focus in obtaining direct measures of extrinsic afterload and preload variations without the need for using calculated estimations.

7 Conclusions

The present doctoral work focused on the analysis of femoral dP/dt_{max} during changes in LV contractility, preload and external afterload to ascertain whether it is a reliable minimally invasive marker of cardiac contractility. Through the analysis of two independent cohorts of critically ill patients the following conclusions can be drawn:

1. Femoral dP/dt_{maxi} may be able, at least partially, to track changes in cardiac contractility,
2. However, femoral dP/dt_{max} is substantially affected by variations in LV loading conditions (preload and external afterload),
3. Such sensitivity to LV loading conditions substantially limits its clinical applicability in the ICU,
4. Femoral dP/dt_{max} presents an almost direct correlation with PP. Such strong relationship implies that factors affecting PP can also affect femoral dP/dt_{max}. These are SVi, and both pulsatile and resistive arterial load (TASi/TAC and SVRi/TPRi). Other factors such as reflection waves may also play a key role but will require further investigation.

8 Future Work

While results from the present doctoral work seem to be highly indicative of the sensibility of femoral dP/dt_{max} to changes in LV loading conditions, and thus its lack of suitability for being considered and appropriate minimally invasive real-time estimator of LV contractility, the physiological processes that explain present observations require further investigation.

As discussed previously, one of the main potential factors that could influence the measure of femoral dP/dt_{max} is the effect of arterial reflection waves. These were not evaluated in the present doctoral work for technical reasons but have the potential for influencing both SAP and PP, and therefore femoral dP/dt_{max}. Since several factors often affecting western ICU patient populations, such as advanced vascular aging of patients and common use of vasoactive medication, can exert dramatic effects on reflection waves, the study of their effect on femoral dP/dt_{max} is of clinical relevance. However their measure will require a high-fidelity arterial transducer able to provide high resolution arterial waveform tracings and advanced computational capabilities.

Another element that warrants further evaluation is the relation between LV dP/dt_{max} and femoral dP/dt_{max} during preload optimisation after volume expansion. In order to complete the physiological picture, it would be necessary to ascertain whether the observed increases in femoral dP/dt_{max} are mediated by increases in SVi (which for a given arterial tone generates higher PP and femoral dP/dt_{max} measures), or through a direct transmission of LV dP/dt_{max} to the arterial tree following increases in contractile force following the Frank-Starling relationship. Such analysis will require direct measures of LV dP/dt_{max} and the placement of a LV catheter, with its consequent ethical challenges.

Finally, the present work has not evaluated the effects of variable HR on the measure of femoral dP/dt_{max}. As previously discussed, and using the analogy of the square triangle, a reduction of the R-R interval or higher HR (here the short cathetus) could potentially influence femoral dP/dt_{max} (here the slope of the hypotenuse). In order to confirm this hypothesis, further investigations should focus in evaluating variations of femoral dP/dt_{max} during changes in HR induced by, for example, ventricular pacing.

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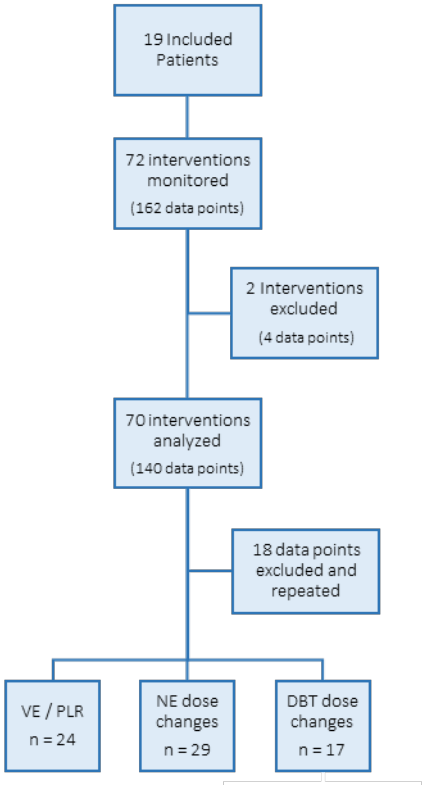
10 Annexes

10.1 Supplemental material for Article 1

Figure 9-1 Flow chart of included patients and collected interventions



NE: norepinephrine, DBT; dobutamine, VE/PLR : volume expansion, passive leg raising.

Table 1 Population characteristics - Diagnosis

Diagnosis	**n[a]**	**%**
Pneumonia	20	29
Soft Tissue	24	34
Urinary Sepsis	4	6
Colecystitis	2	3
Peritonitis	8	11
Pancreatitis	6	9
Cardiac Arrest	6	9
Total	70	100

[a] n refers to number of cases

Table 2: Before and After values of Haemodynamic Variables

	DBT up (n = 7)			**DBT down (n = 10)**		
	Pre median (25-75%)	Post median (25-75%)	p	Pre median (25-75%)	Post median (25-75%)	p
Femoral dP/dt_{max} ($mmHg.s^{-1}$)	950 (681-1107)	1140 (728-1646)	**0.043**	1114 (766-1395)	797 (677-1250)	**0.017**
CFI (min^{-1})	3.2 (2.3-4.5)	4.1 (2.5-5)	0.066	4.4 (3.5-5.1)	4 (3-4.9)	0.058
LVEF (%)	37 (30-45)	37 (34-55)	**0.043**	51 (36-53)	36 (33-46)	**0.005**
CI ($L.min^{-1}.m^{-2}$)	2.6 (1.9-2.9)	2.9 (2-3.1)	**0.027**	2.9 (2.4-3.4)	2.6 (2.3-3.1)	0.069
SVI ($mL.m^{-2}$)	26 (23-28)	28 (23-31)	0.345	29 (27-43)	31 (26-38)	0.285
HR ($beats.min^{-1}$)	94 (79-100)	96 (80-105)	**0.028**	88 (73-105)	77 (72-96)	0.059
SAP (mmHg)	108 (97-119)	116 (99-127)	0.398	123 (102-141)	111 (101-127)	0.059
PP (mmHg)	61 (49-70)	67 (51-76)	0.310	68 (52-92)	60 (49-81)	**0.047**
Ea ($mmHg.ml^{-1}$)	2.1 (1.9-2.3)	2.1 (1.7-2.3)	0.249	1.8 (1.5-2.2)	2 (1.5-2.4)	0.959
C ($ml.mmHg^{-1}$)	0.7 (0.7-1)	0.8 (0.7-1.1)	0.753	0.9 (0.7-1)	0.9 (0.8-1.1)	0.285
SVRI ($dynes.s.cm^{-5}.m^{-2}$)	1729 (1633-2867)	1697 (1516-2725)	0.128	1782 (1663-2193)	1925 (1693-2277)	**0.013**
	NE up (n = 9)			**NE down (n = 20)**		
	Pre median (25-75%)	Post median (25-75%)	p	Pre median (25-75%)	Post median (25-75%)	p
Femoral dP/dt_{max} ($mmHg.s^{-1}$)	943 (743-1148)	1093 (1013-1306)	**0.008**	1455 (1280-1696)	1341 (1106-1473)	**< 0.001**
CFI (min^{-1})	4.2 (3.2-5.4)	4.1 (3.1-5.5)	0.831	3.7 (3.3-5.2)	3.7 (3.1-5.2)	0.131
LVEF (%)	53 (47-63)	45 (39-61)	0.197	59 (39-61)	60 (43-62)	0.124
CI ($L.min^{-1}.m^{-2}$)	3.3 (2.3-4.1)	3.4 (2.3-4)	0.767	3.1 (1.9-3.6)	3.1 (1.9-3.4)	0.093
SVI ($mL.m^{-2}$)	47 (28-54)	48 (27-55)	0.678	31 (19-37)	29 (19-37)	**0.006**
HR ($beats.min^{-1}$)	75 (72-96)	75 (72-97)	0.767	97 (80-108)	97 (81-110)	0.085
SAP (mmHg)	108 (101-119)	136 (113-139)	**0.008**	147 (138-165)	127 (112-150)	**< 0.001**
PP (mmHg)	57 (54-73)	83 (63-87)	**0.008**	87 (80-100)	73 (64-86)	**< 0.001**
Ea ($mmHg.ml^{-1}$)	1.27 (0.82-2)	1.27 (1-2.2)	**0.028**	2.3 (1.6-3.5)	2 (1.5-3.5)	**0.004**
C ($ml.mmHg^{-1}$)	1.27 (0.8-1.8)	1.2 (0.7-1.5)	**0.011**	0.7 (0.4-1)	0.8 (0.4-1.1)	**< 0.001**
SVRI ($dynes.s.cm^{-5}.m^{-2}$)	1450 (958-1998)	1386 (1184-2111)	0.260	2159 (1714-3669)	2115 (1743-3573)	**0.002**

DBT: Dobutamine; NE: Norepinephrine. Calculated with Wilcoxon Rank – Test

Table 3: Correlation matrix of changes in Femoral dP/dt_{max} vs. changes in main haemodynamic variables

Intervention	ΔCFI (%)	ΔLVEF (%)	ΔCI (%)	ΔSVI (%)	ΔHR (%)	ΔSAP (%)	ΔMAP (%)	ΔPP (%)	ΔCVP (%)	ΔGEDVI (%)	ΔEa (%)	ΔTAC (%)	ΔSVRI (%)
NE change (n=29)	0.147 ns	-0.685 (2)	0.305 ns	0.312 ns	0.038 ns	0.941	0.838	**0.977**	0.174 ns (2)	0.193 ns	0.638	-0.689	0.588
VE/PLR (n=24)	0.449	0.098 ns (3)	0.599	0.625	-0.082 ns	0.897	0.786	**0.924**	0.298 ns (3)	0.484	0.299 ns	-0.514	0.234 ns
DBT change (n=17)	0.585	0.527	0.597	0.409 ns	0.147 ns	0.897	0.826	**0.942**	0.317 ns (1)	0.021 ns	-0.199 ns	-0.148 ns	0.088 ns
ALL (n=70)	0.405	0.114 ns (5)	0.522	0.488	0.009 ns	0.884	0.776	**0.918**	0.304 (4)	0.260	0.360	-0.543	0.332

NE: Norepinephrine; DBT: Dobutamine. Values represent the Pearson's correlation coefficients.

Δ indicates changes from baseline. All correlations are significant ($p < 0.05$) unless indicated (ns).

The best correlation coefficient for each intervention is highlighted in Bold. (1): n = 11; (2): n = 19; (3): n = 17; (4) n = 47; (5): n = 53

10.2 Supplemental material for Article 2

Figure 9-2: Figure S1 – Flow chart of included patients and collected interventions

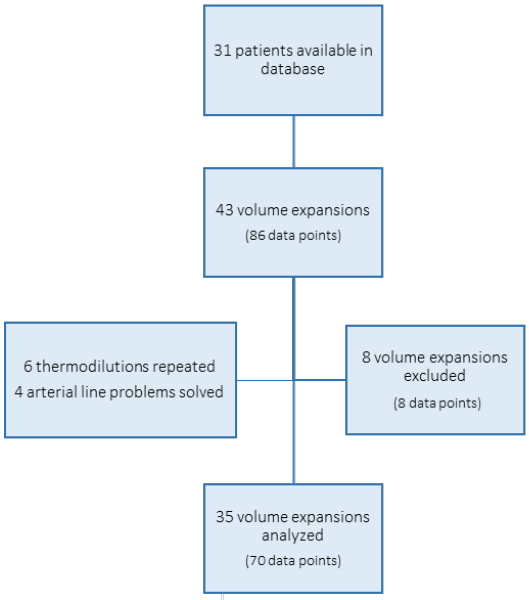


Table 4: Changes in haemodynamic variables following volume expansion.

Pooled estimations (n = 35).

	Pre VE mean (SD)	Post VE mean (SD)	Mean Difference	% of change	p
Femoral dP/dt_{max} ($mmHg.s^{-1}$)	1163 (501)	1371 (569)	207.4	17.8	**0.004**
CI ($L.min^{-1}.m^{-2}$)	3 (2.2-3.8) [a]	3.4 (2.3-4.2) [a]	0.4	13.3	**< 0.001** [b]
SVI ($mL.m^{-2}$)	32.6 (12.8)	37.1 (12.5)	4.5	13.8	**< 0.001**
HR ($beats.min^{-1}$)	95 (17)	93 (17)	-2.1	-2.2	**0.006**
SAP (mmHg)	113 (24)	133 (25)	20.2	17.9	**< 0.001**
MAP (mmHg)	50 (11)	56 (13)	6.3	12.6	**< 0.001**
DAP (mmHg)	71 (15)	83 (16)	12.5	17.6	**< 0.001**
PP (mmHg)	59 (48-75) [a]	77 (57-93) [a]	13.9	23.6	**< 0.001** [b]
TASi ($mmHg.mL^{-1}$)	1.9 (1.5 – 2.5) [a]	2.1 (1.5 – 2.8) [a]	0.16	8.4	0.116 [b]
TPRi ($dynes.s.cm^{-5}.m^{-2}$)	2120 (899)	2195 (933)	74.5	3.5	0.186
GEDVi ($mL.m^{-2}$)	721 (168)	761 (137)	40	5.5	0.053
CVP (mmHg)	9 (7)	12 (6)	3.3	36.7	**< 0.001**

[a] Median (25th-75th percentiles)
[b] Calculated with Wilcoxon Rank test

Table 5: Correlation matrix of changes in Femoral dP/dt_{max} vs. changes in main haemodynamic variables according to fluid responsiveness

Fluid responsive cases

	Δ HR (%)	Δ SAP (%)	Δ MAP (%)	Δ DAP (%)	Δ PP (%)	Δ CI (%)	Δ SVI (%)	Δ TPRI (%)	Δ TASI (%)	Δ CVP (%)	Δ GEDVi (%)
R	0.240	0.978	0.957	0.930	0.990	0.817	0.618	0.772	0.949	0.122	0.760
p	0.452	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.001**	**0.032**	**0.003**	**0.000**	**0.773**	**0.004**

Values represent the Pearson's correlation coefficients. Δ means changes from baseline.

Fluid non-responsive cases

	Δ HR (%)	Δ SAP (%)	Δ MAP (%)	Δ DAP (%)	Δ PP (%)	Δ CI (%)	Δ SVI (%)	Δ TPRI (%)	Δ TASI (%)	Δ CVP (%)	Δ GEDVi (%)
R	-0.158	0.964	0.896	0.823	0.963	-0.014	0.074	0.856	0.906	0.064	0.030
p	0.472	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.948	0.738	**<0.001**	**<0.001**	0.870	0.893

Values represent the Pearson's correlation coefficients. Δ means changes from baseline.

10.3 Regression analysis

Using data from the second study's patient population (70), a multiple regression analysis was performed to evaluate the relative contributions of SVi and TASi on the measure of femoral dP/dt_{max}. The analysis was performed following a process described elsewhere (71) and validated by expert statistical support.

Results indicated that there was linearity of the independent variables with the dependent variable, collectively and independently as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was independence of residuals, as assessed by a Durbin-Watson statistic of 2.096. There was homoscedasticity, as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values of 0.999 (greater than 0.1). There were 2 studentized deleted residuals greater than ±3 standard deviations which were excluded from the analysis as potential outliers, one additional leverage value of 0.56 (greater than 0.2), with a Cook's distance of 2.31 (above 1) was identified and further excluded as a highly influential point. The assumption of normality was met, as assessed by Q-Q and P-P Plots. The multiple regression model statistically significantly predicted femoral dP/dt_{max}, $F(2, 29) = 556.452$, $p < 0.001$, adj. $R^2 = 0.973$. Both variables added statistically significantly to the prediction, $p < 0.001$.

10.3.1 Test of linearity

Analysis of linearity was performed by evaluating a scatterplot of the studentized residuals against the (unstandardized) predicted values. Balanced distribution of residuals around the 0 value in the y-axis is highly suggestive of collective linearity of variables (Figure 9-3). Analysis of individual variable linearity was performed by evaluating partial regression plots of each independent variable against the dependent variable and calculating Pearson's correlation coefficients ($R = 0.702$, $p < 0.001$ for SVi and $R = 0.715$, $p < 0.001$ for TASi) (Figure 9-4 and Figure 9-5). Results confirmed independent linearity of variables.

Figure 9-3 Scatter plot of residuals distribution against predicted values

(collective linearity and Homoscedasticity, without outliers and leverage/high influence points)

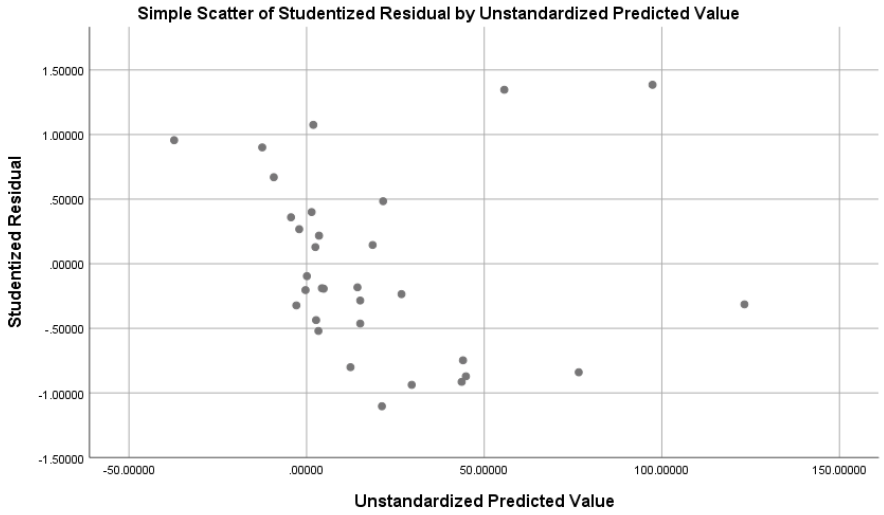


Figure 9-4 Partial regression plot of changes in SVi against changes in femoral dP/dt_{max}

(percent values in all cases)

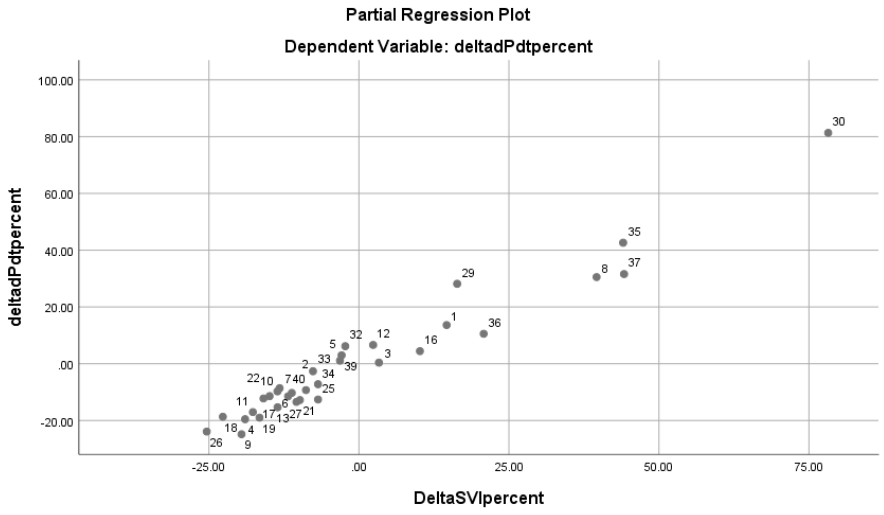
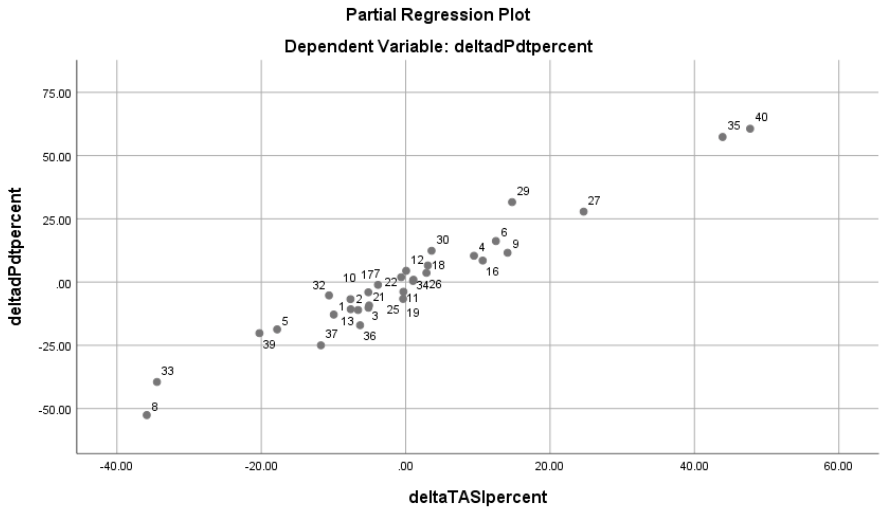


Figure 9-5 Partial regression plot of changes in TASi against changes in femoral dP/dt_{max} (percent values in all cases)



10.3.2 Testing for Homoscedasticity

Homoscedasticity is the assumption that the variance of residuals is the same for any value of the dependent variable. Analysis of homoscedasticity was performed through visual inspection of a scatter plot of studentized residuals against the unstandardized predicted values. Homogeneous distributions across the 0 value in the y-axis and that remains so across the x-axis is suggestive of homoscedasticity (Figure 9-3).

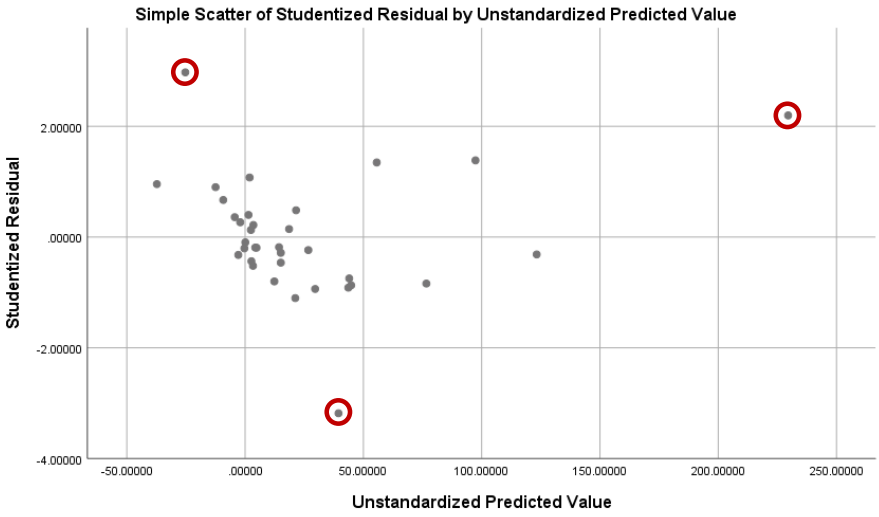
10.3.3 Testing for multi co-linearity

Multi co-linearity of independent variables implies that two or more of the variables are correlated with each other, making it difficult to understand the independent relation of each one of them with the dependent variable. It also impedes a proper estimation of the variance explained by the model and other calculations. Analysis of multi co-linearity was performed by analysing correlations between independent variables and by the estimation of tolerance values (limit at 0.1 or below as described by Hair et al. 2010) (71,72). Results indicated no co-linearity between SVi and TASi (R = 0.031, p = 0.433; tolerance = 0.999).

10.3.4 Outlier, leverage and influential point analysis

Outliers were detected by establishing a limit of ±3 standard deviations on the standardized or studenteized deleted residuals. High leverage points were identified by leverage values higher than 0.5 (as described by Huber et al. 1981) (71). Highly influential points were detected by assessing the Cook's distance and setting the threshold at a value < 1 (71). Two outliers were detected and excluded from the analysis. A third, high leverage and influence point was also detected and excluded. Identified points are presented in Figure 9-6.

Figure 9-6 Detected outliers and points with high leverage and influence



10.3.5 Assessing normality of residuals

To enable the possibility of performing inferential statistics on the relation of the independent variables with the dependent variable assessment of normality of residuals was performed. Two methods were used to this end: evaluation of an histogram with a superimposed normality curve and calculated mean and standard deviation; and assessment of normal probability (P-P) plot and quantiles (Q-Q) plots of standardized residuals. While Q-Q plots represent the quantiles or actual values against the theoretical values under the normal distribution, P-P plots, represent the corresponding areas under the curve (cumulative distribution function) for those values. P-P plot are better at finding deviations from normality in the centre of the distribution, and the normal Q-Q plot are better at finding deviations in the tails.

The histogram of standardized residuals showed a normal distribution with a mean and standard deviation close to 0 and 1 respectively (Figure 9-7). Confirmation of normality was achieved by visually analysing the distribution of points along the reference line in P-P and Q-Q plots. As presented in Figure 9-8 and , points oscillated around the reference line as expected in case of normal distribution of residuals.

Figure 9-7 Frequency histogram of residuals

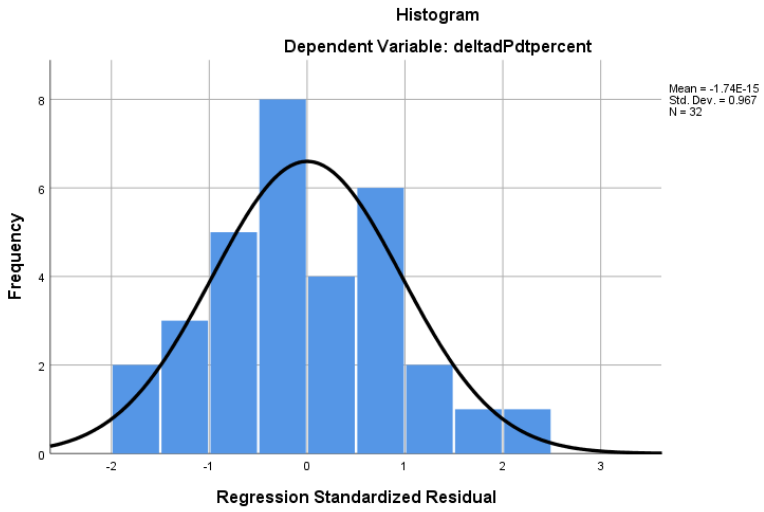


Figure 9-8 Normal probability (P-P) plot of standardized residuals

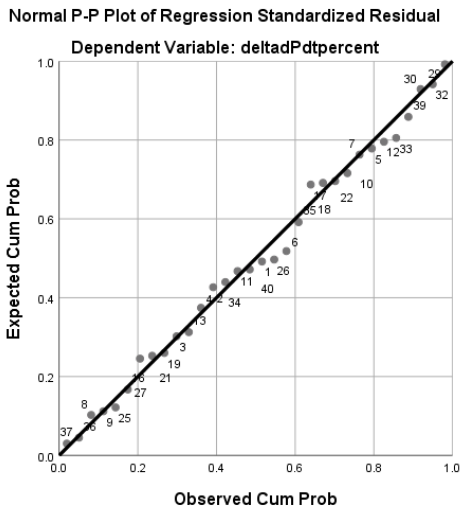


Figure 9-9 Quantile distribution (Q-Q) plot of studentized residuals